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Regioselective TEMPO oxidation of 2-alkylidene-1,3-propanediols to (*E*)-2-hydroxymethyl-2-alkenals and application to 4-alkylidene-2-penten-5-olide synthesis

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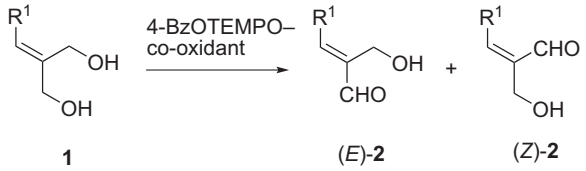
ABSTRACT

The oxidation system comprised of TEMPO and (diacetoxyiodo)benzene (stoichiometric) is enhanced during the conversion of primary alcohols to aldehydes by adding a catalytic amount of acids, *p*-TsOH and PPTS. 2-Alkylidene-1,3-propanediols, available from 1,3-dihydroxyacetone, are oxidized under the stated conditions to the corresponding (*E*)-2-hydroxymethyl-2-alkenals, which are utilized as an intermediate for the expeditious synthesis of 4-alkylidene-2-penten-5-olides.

1. Introduction

Although the Morita–Baylis–Hillman reaction,[1] a coupling reaction of alkanals and α,β-unsaturated carbonyl in the presence of base, has found wide use in producing α-alkylidene-β-hydroxyalkyl carbonyls, there are still some drawbacks including the slow reaction rate as well as the limited scope of the substrates, especially for the alkenal products. Indeed, the preparation of 2-hydroxyalkyl-2-alkenals from 2-alkenals as a nucleophilic counter part in the carbon–carbon bond making process is rare, except for the example in which the coupling of acrolein and alkanals has been realized under high pressure (1.5 kbar).[2] Therefore, we envisioned that the selective oxidation of 2-alkylidene-1,3-propanediols **1** would lead to 2-hydroxyalkyl-2-alkenals **2** that are not readily available by the Morita–Baylis–Hillman reaction (Scheme 1).[3] Meanwhile, we have developed an efficient oxidation method of alcohols, which is amenable to the demand associated with the transformation of **1** to **2**.

Among the various oxidation procedures for alcohols,[4,5] the TEMPO oxidation, categorized as non-metallic and catalytic, is less toxic and environmentally friendly.[6a] Another benefit of the TEMPO oxidation is its high selectivity in the competitive oxidation of primary alcohols in the presence of secondary ones due to the steric factor of the *N*-oxoammonium group being formed on the bulky 2,2,6,6-tetramethylpiperidine scaffold.[7] Therefore, we became interested in the application of this capability to the oxidation of 1,3-propanediols **1**, which would lead to versatile aldehydes **2** as a result of the discrimination of two sterically unequivalent primary hydroxy groups on **1**.



1 (*E*)-**2** (*Z*)-**2**

Scheme 1. Oxidation of 2-alkylidenepropane-1,3-diols **1** to either (*E*)- or (*Z*)-**2**.

Regarding the reaction conditions for the TEMPO oxidation, the method with (diacetoxyiodo)benzene[8] ($PhI(OAc)_2$, DAIB, stoichiometric) as a co-oxidant, developed by Margarita and Piancatelli et al.,[9] is highly useful in terms of the mild reaction conditions.[10,11] However, this oxidizing system was sometimes regarded as being incomplete[12a] and uses toxic methylene chloride (CH_2Cl_2) as the

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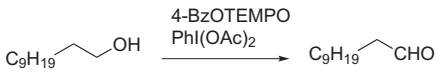
solvent. Several efforts to enhance the reaction rate of the TEMPO–hypervalent iodine systems have been made using the appropriate additives, such as water[12a] and ytterbium triflate.[12b] In our continuous study of the TEMPO oxidation,[13a,b] we examined the effect of the appropriate additive and the use of ether as the solvent instead of CH_2Cl_2.

2. Results and discussion

2.1. Optimization of TEMPO–DAIB oxidation of primary alcohols

The conditions were explored using undecanol (**3**) as a typical substrate in a 4-benzoyloxy-2,2,6,6-tetramethylpiperidine-1-oxyl (4-BzOTEMPO)[13]–DAIB system (Table 1). As shown in entries 1 and 2, the reaction rate is significantly enhanced by the addition of a small amount of *p*-toluenesulfonic acid (*p*-TsOH) in CH_2Cl_2 in order to complete it within the prescribed time (30 min, entries 1 and 2). Similar enhancements of the reaction in tetrahydropyran (THP) are also achieved by the addition of a small amount of *p*-TsOH, pyridinium *p*-toluenesulfonate (PPTS), camphorsulfonic acid (CSA) (entries 4–6), and even water (entry 7). The reaction in cyclopentyl methyl ether (CPME, entry 8) compared to THP is sluggish.[14] Thus, among the examined ether solvents, THP should be the solvent of choice in terms of not only the high yield, but also lower toxicity[15] and resistance toward peroxide formation with the oxidant during the reaction.[16]

Table 1
Effect of solvent and additive on the oxidation of **3** to **4**[a]



3 **4**

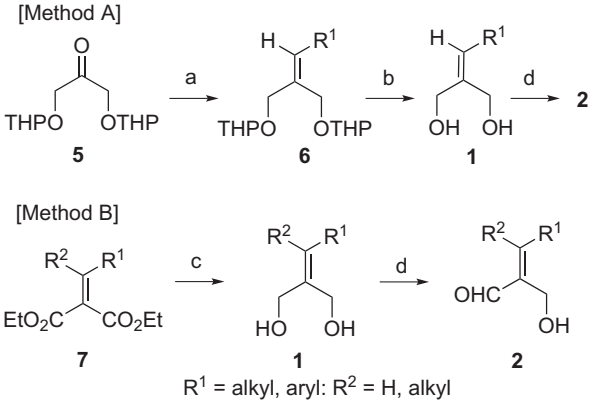
Entry	Solvent[b]	Additive[c]	Yield (%)[d] **4**	Recovery **3** (%)
1	CH_2Cl_2	None	57	20
2	CH_2Cl_2	*p*-TsOH	91	—
3	THP	None	60	32
4	THP	*p*-TsOH	97	—
5	THP	PPTS	89	7
6	THP	CSA	96	—
7	THP	H_2O	88	—
8	CPME	*p*-TsOH	54	34

[a] Carried out using **3** (1.0 mmol), 4-BzOTEMPO (0.10 mmol), $PhI(OAc)_2$ (1.2 mmol) in solvent (4 mL) at room temperature for 30 min.
[b] THP: tetrahydropyran, CPME: cyclopentyl methyl ether.
[c] Catalytic amount (1 mol %) and one drop of water.
[d] Yields are based on isolated products by LC (SiO_2).

Enhancement of the reaction rate with acid as an additive can be rationalized by taking into account its participation in the disproportionation of the TEMPO radical into the *N*-oxoammonium and *N*-hydroxyamine.[17] Furthermore, the regeneration process of the TEMPO radical or the *N*-oxoammonium from *N*-hydroxyamine with DAIB, formed after the oxidation of alcohols with the *N*-oxoammonium, would also be accelerated by the addition of an acid catalyst.[18,19] Similarly, the additive effect of water may be ascribable to the formation of acetic acid from DAIB and water.[8]

2.2. Oxidation of 2-alkylidene-1,3-propanediols and comparison of TEMPO–DAIB method with conventional ones

We examined the oxidation of 2-alkylidene-1,3-propanediols **1** under the newly developed conditions. The substrates **1** were prepared either from 1,3-dihydroxyacetone bis-THP ether **5** or the diesters **7**. Thus, the Wittig olefination of **5**, producing **6**, followed by hydrolysis of the THP protecting groups produced the trisubstituted-olefinic diols **1** in 60–75% yields (Method A).[20] On the other hand, the DIBAL-H reduction of the diester **7**, available by the Knoevenagel condensation of ketones and malonate, gave the diols **1** in about 30% yields (Method B) (Scheme 2).

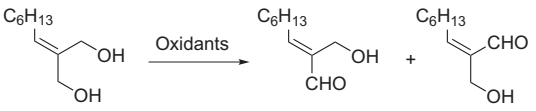


Scheme 2. Synthesis of compounds **1** and **2**. Reagents and conditions: (a) $RCH_2P^+Ph_3Br^-$, LDA, THF, 60–75%. (b) MeOH–PPTS, 98%. (c) DIBAL-H, toluene, ca. 30%. (d) 4-BzOTEMPO–$PhI(OAc)_2$, *p*-TsOH, THP.

The TEMPO oxidation of **1a** was carried out using 4-BzOTEMPO (catalytic)[13] and DAIB (stoichiometric) in THP in the presence of a small amount of acid (*p*-TsOH) to give **2a** in 86% yield as an inseparable *E*/*Z* mixture by typical column chromatography, and both the structure and the *E*/*Z* ratio of **2a** of more than 7–10:1 were determined on the basis of the ^1H NMR analysis (entry 1, Table 2). The time-course experiment for the *E*/*Z* ratio of **2a** by NMR analysis indicates that the *E*/*Z* ratio is strictly maintained for 2 h.[21,22] In addition, (diacetoxyiodo)-2,4,6-trimethylbenzene, a more hindered hypervalent iodine reagent, can be used for this purpose, but the reaction is sluggish and hence the yield of **2a** slightly decreases compared to the run using DAIB (entry 2).

Furthermore, the TEMPO oxidation is comparable to other conventional methods, notably the Dess–Martin oxidation.[23] Thus, as shown in Table 2, the oxidation of **1a** with the Dess–Martin periodinane affords ca. 1:1 *E*/*Z* mixture of **2a** in poor yield (40%) (entry 3). The PCC oxidation[24] of **1a** affords *E*-**2a** as the major isomer, but in low yield (33%, entry 4). The Parikh–Doering oxidation[25] produces the desired **2a** in 31% with an *E*/*Z* ratio of 2:1 (60% of the starting **1a** was recovered, entry 5). The Swern oxidation of **1a** was not suitable in comparison to the Parikh–Doering method. Thus, the TEMPO oxidation in combination with DAIB should be

Table 2
Oxidation of 2-heptylidene-1,3-propanediol (**1a**) to **2a**[a]



Entry	Oxidant (equiv)	Time (h)	Yield[b] (%) **2**	*E*/*Z* ratio[c]
1	4-BzOTEMPO–$PhI(OAc)_2$ (1.2)–*p*-TsOH (cat.)	4	86	7–10:1
2	4-BzOTEMPO–$(2,4,6\text{-}Me_3C_6H_2)I(OAc)_2$ (1.2)–*p*-TsOH (cat.)	16	72	8:1
3	Dess–Martin periodinane (1.2)	10	40	1:1
4	PCC (1.5)	24	33	8:1
5	DMSO–SO_3Py(**3**)[d]	4	31	2:1

[a] Carried out using **1a** (0.5 mmol).
[b] Yields are based on isolated products by LC (SiO_2).
[c] Based on NMR experiments.
[d] Recovery of **1a** (60%) and *E*/*Z* ratio after LC purification.

superior to other methods examined in this study for the oxidation of 2-alkylidene-1,3-propanediols **1** in terms of its regioselectivity, high performance, and easy operation.

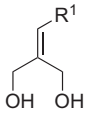
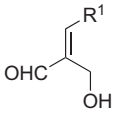
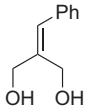
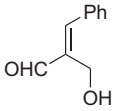
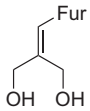
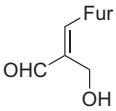
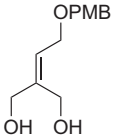
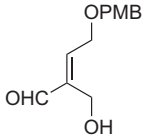
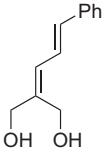
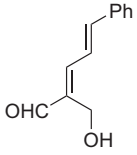
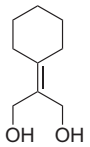
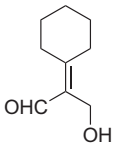
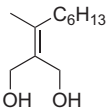
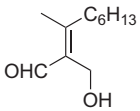
2.3. Preparation of various 2-hydroxymethyl-2-alkenals

We next attempted to prepare various 2-hydroxymethyl-2-alkenals **2** from **1** (Table 3). We were inspired by the facts that this structural motif was hardly accessible by the Morita–Baylis–Hillman procedure, present in terpenoid natural products,[26] and more importantly, highly functionalized for further elaboration. Thus, the 2-alkylidene-1,3-propanediols **1**, prepared by the above methods A (entries 1–3) or methods B (entries 4, 5, 7–9), were treated with the 4-BzOTEMPO–DAIB system in THP in the presence of *p*-TsOH, affording the corresponding 2-hydroxymethyl-2-alkenals **2** in good yields. Noteworthy is the fact that this method is smoothly applied to the oxygenated **1f**, prepared by the Horner–Emmons reaction of **5** followed by subsequent procedures consisting of the DIBAL-H reduction, 4-methoxybenzyloxylation, and THP-hydrolysis, affording the corresponding highly functionalized enal **2f** (entry 6). The dienal **2g** is now available from the diene structure **1g** based on the present protocol (entry 7). The trisubstituted-olefinic diols generally show high *E*-selectivities (entries 1–5, 7), while no *E*/*Z* selectivity was found in the oxidation of the tetrasubstituted-olefinic diol **1i** (entry 9).

2.4. Syntheses of 4-alkylidene-2-penten-5-olides

We then examined the synthesis of the 4-alkylidene-2-penten-5-olides **10** from the 2-hydroxymethyl-2-alkenals **2**, since this structural feature is one of the key elements in the bioactive 2-pentenolides, like the gelastatin analogues.[27] Thus, the Horner–Wadsworth–Emmons olefination[28] of the aldehyde **8a**, prepared by the THP protection of **2a**, by the Ando's protocol[29] with *tert*-butyl (diphenylphosphono)acetate afforded ca. 3.5:1 mixture of the corresponding 2*Z*- and 2*E*-enoates **9a**. Without separation of the geometric isomers, the dienoate **9a** was treated with PPTS at 55 °C to induce cyclization, giving 4-heptylidene-2-penten-5-olide (**10a**, 73%) and the unchanged 2*E*-dienoate **9a** (22%) as separable products. The integrity of the olefin geometry in **2a** (*E*/*Z*=10:1) changed to ca. 7:1 in the compounds **10a** during these conversions.

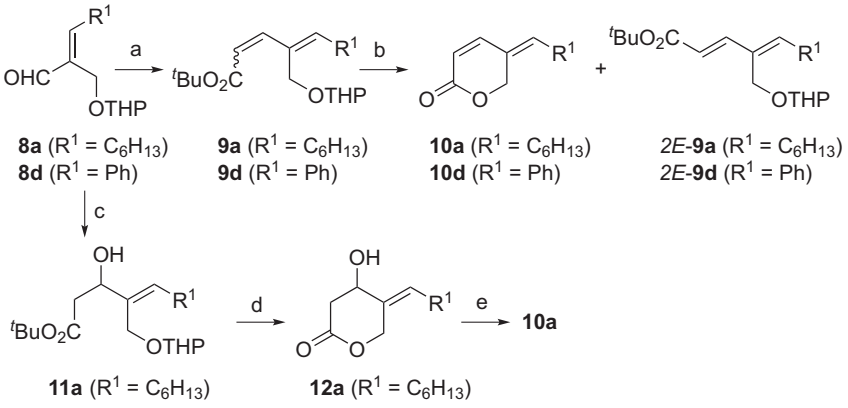
Table 3
Preparation of 2-hydroxymethyl-2-alkenals **2** by oxidation of **1** with a 4-BzOTEMPO–PhI(OAc)$_2$–*p*-TsOH system[a,b]

Entry	Diols **1**	Products **2**	Yield (%)[c]	*E*/*Z* ratio[d]
1	 **1a**, $R^1 = C_6H_{13}$; **1b**, $R^1 = C_3H_7$; **1c**, $R^1 = CH_2CH_2CO_2Et$	 **2a** **2b** **2c**	86	>10:1
2			76	12:1
3			84	12:1
4	 **1d**	 **2d**	83	12:1
5	 **1e**	 **2e**	58[e]	>10:1
6	 **1f**	 **2f**	56	3:1[f]
7	 **1g**	 **2g**	69	10:1
8	 **1h**	 **2h**	71	—
9	 **1i**	 **2i**	80	1:1

[a] Carried out by oxidation of **1** (0.5 mmol) with 4-BzOTEMPO (10 mol %) and PhI (OAc)$_2$(1.2 equiv) in THP (3 mL) in the presence of *p*-TsOH (1 mol %) at room temperature.
[b] Ph=phenyl, Fur=2-furyl, PMB=4-methoxyphenylmethyl.
[c] Yields are based on products isolated by LC (SiO_2).
[d] Determined based on ^{1}H NMR data.
[e] Dialdehyde (18%) was produced.
[f] The *E*/*Z* ratio changed to 10:1 during LC purification.

Similarly, 4-benzylidene-2-penten-5-olide **10d** was prepared from the THP ether **9d** by the same reaction sequence as described above, involving olefination to give **9d** (*2Z*/*2E*=7:1), and cyclization to afford **10d** in 84%, which was associated with the formation of the uncyclized 2*E*-**9d** (7%). No change of the olefin geometry in **2d** (*E*-isomer) was found in compound **10d**.

Alternatively, the aldol reaction of **8a** with the lithium enolate of *tert*-butyl acetate afforded the adduct **11a** in 91% yield. Subsequently, **11a** was treated with TMSCl in CH_2Cl_2, giving the cyclized **12a** in 54% yield, which was followed by dehydration with Ac_2O/Et_3N to afford the desired **10a** in 93% yield with complete integrity of the *E*/*Z* ratio of the starting **2a** (*E*/*Z*=10:1) (Scheme 3).



Scheme 3. Syntheses of 4-alkylidene-2-pentenolides **10a** and **d**. Reagents and conditions: (a) $(PhO)_2POCH_2CO_2{}^tBu$, NaH; **9a**, 84%; **9d**, 93%. (b) PPTS, CH_2Cl_2; **10a**, 73%, 2*E*-**9a**, 22%; **10d**, 84%, 2*E*-**9d**, 7%. (c) $CH_3CO_2{}^tBu$, LDA, **11a**, 91%. (d) TMSCl, CH_2Cl_2; **12a**, 54%. (e) Ac_2O/Et_3N; **10a**, 93%.

3. Conclusion

The TEMPO oxidation of primary alcohols to aldehydes is enhanced by the addition of a small amount of acids, *p*-TsOH and PPTS. Based on this procedure, 2-hydroxymethyl-2-alkenals **2** are easily obtained from the 1,3-diol precursors **1**, prepared either by the Wittig reaction of 1,3-dihydroxyacetone THP ether **5** or by the DIBAL-H reduction of the Knoevenagel products **7**. The resulting 2-alkenals **2** are useful as precursors of the 4-alkylidene-2-penten-5-olides **10**, whose syntheses can easily be performed either by employing Ando's protocol in the Horner–Wadsworth–Emmons reaction followed by cyclization, or the aldol reaction of the lithium acetate–cyclization–dehydration sequence.

Further studies are continuing in our laboratory in order to demonstrate the applicability of this synthetic protocol to antitumor gelastatin and its analogues, which will be published in the future.

4. Experimental section

4.1. General

IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer. ^1H and ^{13}C NMR spectra were measured on either Varian INOVA-600, 400-MR or Mercury-300 spectrometer with $CDCl_3$ as a solvent unless otherwise indicated.

*4.1.1. Preparation of 2-heptylidene-1,3-propanediol (**1a**) by Wittig reaction followed by hydrolysis.* To a suspension of n-$C_6H_{13}CH_2P^+Ph_3Br^-$ (5.73 g, 13 mmol) in THF (15 mL) was added a solution of LDA (25 mmol) in THF (30 mL) at −78 °C. The mixture was allowed to warm to room temperature over 2.5 h. To the red-colored mixture was added dropwise the ketone **5** (2.07 g, 8 mmol) in THF (15 mL) at −20 °C and stirred overnight. The reaction was quenched with aq NH_4Cl at 0 °C and extracted with AcOEt. The extracts were washed with brine, and the crude products were purified by column chromatography (SiO_2; hexanes/AcOEt, 20:1 v/v) to give **6a** (R^1=C_6H_{13}) as a colorless oil (1.83 g, 67% yield): R_f=0.65 (hexane/AcOEt 3:1); ^1H NMR (600 MHz) δ 0.87 (t, J=7.2 Hz, 3H), 1.25–1.38 (m, 8H), 1.51–1.61 (m, 8H), 1.70 (m, 2H), 1.83 (m, 2H), 2.13 (q, J=7.2 Hz, 2H), 3.51 (m, 2H), 3.88 (m, 2H), 3.97 (t, J=11.4 Hz, 1H), 4.07 (d,d, J=21.6, 11.4 Hz, 1H), 4.25 (m, 2H), 4.62 (m, 2H), 5.69 (t, J=7.2 Hz, 1H); ^{13}C NMR (150.8 MHz) δ 14.1, 19.36+19.41, 19.42+19.51, 22.6, 25.48, 25.49, 27.57+27.58, 29.0, 29.6, 30.58, 30.60, 31.7, 61.96+62.00, 62.0+62.1, 62.2+62.3, 69.5+69.6, 97.4+97.5, 97.77+97.83, 132.35+132.38, 133.46+133.51. A mixture of the THP ether **6a** (0.85 g, 2.5 mmol) and PPTS (20 mg), dissolved in MeOH (15 mL), was stirred at 50–60 °C for 24 h. The mixture was neutralized with aq $NaHCO_3$ and concentrated. The crude products were purified by LC (SiO_2; hexanes/AcOEt, by increasing the gradient from 3:1 to 1:2 v/v) to give **1a** as a colorless oil (0.42 g, 98% yield): R_f=0.13 (hexane/AcOEt 1:1); IR (neat) 3341, 2957, 2926, 2857, 1665, 1466, 1379, 1217, 1107, 1011, 895, 721, 662 cm^{-1}; ^1H NMR (400 MHz) δ 0.88 (t, J=6.8 Hz, 3H), 1.24–1.38 (m, 8H), 1.98 (br, 2H), 2.08 (q, J=7.6 Hz, 2H), 4.22 (s, 2H), 4.32 (s, 2H), 5.56 (t, J=7.6 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1, 22.6, 27.4, 28.9, 29.5, 31.7, 60.2, 67.8, 131.5, 136.8; HRMS (FAB) Calcd for $C_{10}H_{20}NaO_2$ $[M+Na]^+$ 195.1356. Found 195.1316. Anal. Calcd for $C_{10}H_{20}O_2\cdot H_2O$ C, 63.12; H, 11.65. Found: C, 63.61; H, 11.56.

*4.1.2. 2-Butylidene-1,3-propanediol (**1b**).* R_f=0.10 (hexane/AcOEt 1:1); ^1H NMR (600 MHz) δ 0.91 (t, J=7.2 Hz, 3H), 1.40 (sext, J=7.8 Hz, 2H), 2.00 (br, 1H), 2.03 (br, 1H), 2.07 (q, J=7.8 Hz, 2H), 4.22 (s, 2H), 4.32 (s, 2H), 5.56 (t, J=7.8 Hz, 1H); ^{13}C NMR (150.8 MHz) δ 13.7, 22.7, 29.4, 60.1, 67.7, 131.2, 137.0; MS (FAB) m/z 154.01 $[M+Na]^+$.

*4.1.3. Ethyl 6-hydroxyl-5-hydroxymethyl-4-hexenoate (**1c**).* R_f=0.14 (hexane/AcOEt 1:2); ^1H NMR (400 MHz) δ 1.25 (t, J=7.2 Hz, 3H), 2.30 (br, 2H), 2.43 (m, 4H), 4.13 (q, J=7.2 Hz, 2H), 4.20 (s, 2H), 4.30 (s, 2H), 5.50 (t, J=6.8 Hz, 1H); ^{13}C NMR (100.5 MHz) δ 14.2, 22.6, 33.6, 59.4, 60.7, 67.2, 128.2, 139.1, 173.4; HRMS (FAB) Calcd for $C_9H_{17}O_4$ $[M+H]^+$ 189.1121. Found 189.1088.

*4.1.4. Preparation of 2-benzylidene-1,3-propanediol (**1d**) by DIBAL-H reduction.* Dimethyl 2-benzylidenepropanedioate (**7d**, 110 mg, 0.5 mmol) was dissolved in toluene (5 mL) and cooled at −78 °C. DIBAL-H (1.0 M in toluene, 2.5 mmol) was added dropwise. The mixture was stirred at −78 °C for 5 h and quenched by adding 1.0 N HCl. The mixture was extracted with AcOEt and washed with brine. Usual work up followed by purification of the crude product on LC (SiO_2; hexanes/AcOEt, by increasing the gradient from 1:1 to 1:3 v/v) gave **1d** as white solids (25.5 mg, 31% yield): R_f=0.13 (hexane/AcOEt 1:1); IR (KBr) 3235, 2909, 2855, 2670, 1599, 1574, 1489, 1472, 1447, 1366, 1331, 1316, 1233, 1155, 1082, 1053, 1022, 947, 937, 926,

841, 795, 739, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.43 (br, 1H), 2.47 (br, 1H), 4.40 (s, 2H), 4.45 (s, 2H), 6.65 (s, 1H), 7.25–7.37 (m, 5H); ^{13}C NMR (150.8 MHz, $CDCl_3$) δ 60.8, 67.7, 127.3, 128.3 (2C), 128.8 (2C), 129.8, 136.1, 139.2. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.16; H, 7.43.

*4.1.5. 2-(2-Furylmethylene)-1,3-propanediol (**1e**).* R_f=0.21 (hexane/AcOEt 1:1); ^1H NMR (600 MHz) δ 2.28 (br, 1H), 2.41 (br, 1H), 4.36 (s, 2H), 4.64 (s, 2H), 6.31 (d, J=3.6 Hz, 1H), 6.33 (s, 1H), 6.41 (d,d, J=3.6, 1.8 Hz, 1H), 7.42 (d, J=1.2 Hz, 1H); ^{13}C NMR (150.8 MHz) δ 61.2, 67.0, 110.9, 111.5, 116.1, 137.7, 142.5, 151.7.

*4.1.6. 2-(2-(4-Methoxybenzyloxy)ethylidene)-1,3-propanediol (**1f**).* R_f=0.13 (hexane/AcOEt 1:1); IR (KBr) 3376, 2945, 2861, 1614, 1516, 1456, 1362, 1304, 1246, 1177, 1103, 1061, 1032, 1005, 941, 816, 754, 708, 667 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.04 (br, 2H), 3.80 (s, 3H), 4.07 (d, J=6.0 Hz, 2H), 4.21 (s, 2H), 4.22 (s, 2H), 4.46 (s, 2H), 5.77 (t, J=6.6 Hz, 1H), 6.88 (m, 2H), 7.26 (m, 2H); ^{13}C NMR (150.8 MHz, $CDCl_3$) δ 55.3, 59.6, 65.2, 66.5, 72.4, 113.9 (2C), 125.3, 129.6 (2C), 129.8, 142.2, 159.3. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.29; H, 7.63.

*4.1.7. 2-(3-Phenyl-2-propenylidene)-1,3-propanediol (**1g**).* R_f=0.19 (hexane/AcOEt 1:2); IR (KBr) 3271, 3174, 2903, 2849, 1487, 1447, 1398, 1364, 1236, 1213, 1165, 1130, 1063, 1003, 993, 970, 961, 870, 754, 692 cm^{-1}; ^1H NMR (400 MHz) δ 2.01 (br, 2H), 4.35 (s, 2H), 4.53 (s, 2H), 6.31 (d, J=11.2 Hz, 1H), 6.63 (d, J=15.6 Hz, 1H), 7.04 (d,d, J=15.6, 11.2 Hz, 1H), 7.23–7.44 (m, 5H); ^{13}C NMR (100.5 MHz) δ 60.2, 67.2, 123.1, 126.6 (2C), 128.0, 128.7 (2C), 129.2, 135.0, 136.9, 138.7.

*4.1.8. 2-Cyclohexylidene-1,3-propanediol (**1h**).* R_f=0.18 (hexane/AcOEt 1:1); IR (neat) 3366, 3298, 2930, 2851, 1734, 1657, 1649, 1447, 1397, 1165, 995, 853 cm^{-1}; ^1H NMR (400 MHz) δ 1.58 (m, 6H), 1.90 (br, 2H), 2.26 (m, 4H), 4.33 (s, 4H); ^{13}C NMR (100.5 MHz) δ 26.6, 28.3 (2C), 30.6 (2C), 61.8 (2C), 127.9, 142.6; MS (FAB) m/z 154.0 [M − H_2].

*4.1.9. 2-(2-Octylidene)-1,3-propanediol (**1i**).* R_f=0.26 (hexane/AcOEt 1:1); IR (neat) 3354, 2957, 2928, 2859, 1659, 1468, 1414, 1379, 1238, 1148, 999, 897, 723 cm^{-1}; ^1H NMR (400 MHz) δ 0.88 (t, J=6.8 Hz, 3H), 1.27–1.39 (m, 8H), 1.76 (s, 3H), 2.09 (m, 4H), 4.30 (s, 2H), 4.32 (s, 2H); ^{13}C NMR (100.5 MHz) δ 14.1, 18.3, 22.6, 28.7, 29.3, 31.7, 34.4, 61.9, 62.4, 130.8, 138.0; HRMS (FAB) Calcd for $C_{11}H_{22}NaO_2$ $[M + Na]^+$ 209.1512. Found 209.1471.

*4.1.10. General procedure for the TEMPO oxidation. Preparation of (E)-2-hydroxymethyl-2-nonenal (**2a**).* A mixture of the diol **1a** (86 mg, 0.5 mmol), 4-BzOTEMPO (14 mg, 0.05 mmol), $PhI(OAc)_2$ (193 mg, 0.6 mmol), and *p*-TsOH (1 mg) dissolved in THP (3 mL) was stirred at room temperature for 4 h. The reaction was quenched with a small amount of aq $Na_2S_2O_3$. The products were extracted with AcOEt and the extracts were washed with aq $NaHCO_3$. The crude products were purified by LC (SiO_2; hexanes/AcOEt, by increasing the gradient from 15:1 to 3:1 v/v) to give **2a** as a colorless oil (73 mg, 86% yield): R_f=0.67 (hexane/AcOEt 1:1); IR (neat) 3445, 2957, 2928, 2859, 2716, 1684, 1643, 1464, 1456, 1379, 1275, 1198, 1175, 1115, 1024, 901, 839, 723 cm^{-1}; ^1H NMR (400 MHz) (*E*-isomer) δ 0.89 (m, 3H), 1.26–1.39 (m, 6H), 1.52 (m, 2H), 2.43 (q, J=7.6 Hz, 2H), 2.54 (br, 1H), 4.36 (s, 2H), 6.62 (t, J=7.6 Hz, 1H), 9.42 (s, 1H); ^{13}C NMR (100.6 MHz) (*E*-isomer) δ 14.0, 22.5, 28.5, 28.8, 28.9, 31.5, 55.9, 141.3, 157.1, 196.0; HRMS (FAB) Calcd for $C_{10}H_{19}O_2$ $[M + H]^+$ 171.1380. Found 171.1285.

*4.1.11. (E)-2-Hydroxymethyl-2-hexenal (**2b**).* Yield 76%; R_f=0.54 (hexane/AcOEt 1:1); IR (neat) 3416, 2963, 2934, 2874, 2718, 1684, 1643, 1460, 1381, 1277, 1192, 1107, 1059, 1020, 966, 910, 847 cm^{-1}; ^1H NMR (600 MHz,) δ (*E*-isomer) 0.98 (t, J=7.2 Hz, 3H), 1.55 (m, 2H), 2.40 (q, J=7.2 Hz, 2H), 2.59 (br, 1H), 4.36 (s, 2H), 6.61 (t, J=7.2 Hz, 1H), 9.42 (s, 1H); ^{13}C NMR (150.8 MHz) δ (*E*-isomer) 13.7, 21.9, 30.7, 55.8, 141.5, 156.8, 195.9; MS (FAB) m/z 129.19 $[M + H]^+$.

*4.1.12. Ethyl (E)-5-hydroxymethyl-6-oxo-4-hexenoate (**2c**).* Yield 84%; R_f=0.58 (hexane/AcOEt 1:2); IR (neat) 3476, 2984, 2942, 2359, 1732, 1684, 1645, 1418, 1375, 1252, 1192, 1155, 1022, 858 cm^{-1}; ^1H NMR (600 MHz) δ (*E*-isomer) 1.25 (m, 3H), 1.73 (br, 1H), 2.57 (t, J=7.2 Hz, 2H), 2.75 (q, J=7.2 Hz, 2H), 4.14 (m, 2H), 4.38 (s, 2H), 6.56 (t, J=7.8 Hz, 1H), 9.43 (s, 1H); ^{13}C NMR (150.8 MHz) δ (*E*-isomer) 14.1, 23.9, 32.6, 55.3, 60.9, 142.3, 153.8, 172.3, 195.2; HRMS (FAB) Calcd for $C_9H_{15}O_4$ $[M + H]^+$ 187.0965. Found 187.0980.

*4.1.13. (E)-2-Hydroxymethyl-3-phenyl-2-propenal (**2d**).* Yield 83%; R_f=0.60 (hexane/AcOEt 1:1); IR (neat) 3437, 3065, 2949, 2889, 2828, 2718, 1682, 1626, 1574, 1451, 1410, 1368, 1329, 1296, 1213, 1169, 1080, 1018, 936, 897, 864, 827, 760, 700 cm^{-1}; ^1H NMR (400 MHz) δ (*E*-isomer) 2.64 (br, 1H), 4.56 (s, 2H), 7.41–7.49 (m, 4H), 7.57 (m, 2H), 9.62 (s, 1H); ^{13}C NMR (100.6 MHz) δ 55.8, 128.9 (2C), 130.0 (2C), 130.4, 133.8, 140.1, 152.5, 195.8; MS (FAB) m/z 163 $[M + H]^+$.

*4.1.14. (E)-2-Hydroxymethyl-3-(2-furyl)-2-propenal (**2e**).* Yield 58%; R_f=0.43 (hexane/AcOEt 1:1); IR (neat) 3431, 3127, 2947, 2888, 2835, 2727, 1670, 1624, 1470, 1389, 1364, 1281, 1258, 1161, 1144, 1076, 1020, 941, 930, 885, 853, 760, 687 cm^{-1}; ^1H NMR (600 MHz) δ 2.79 (br, 1H), 4.77 (s, 2H), 6.58 (m, 1H), 6.91 (d, J=3.6 Hz, 1H), 7.03 (s, 1H), 7.67 (d, J=1.2 Hz, 1H), 9.51 (s, 1H); ^{13}C NMR (150.8 MHz) δ 56.1, 113.0, 119.2, 135.9, 136.2, 146.6, 150.4, 194.6; MS (FAB) m/z 154 $[M + H]^+$.

*4.1.15. (E)-2-Hydroxymethyl-4-(4-methoxyphenylmethoxy)-2-butenal (**2f**).* Yield 56%; R_f=0.65 (hexane/AcOEt 1:2); IR (neat) 3430, 2934, 2837, 1684, 1613, 1586, 1514, 1464, 1362, 1302, 1248, 1175, 1099, 1071, 1032, 820, 758 cm^{-1}; ^1H NMR (300 MHz) δ (*E*-isomer) 3.81 (s, 3H), 4.35 (s, 2H), 4.41 (d, J=5.4 Hz, 2H), 4.53 (s, 2H), 6.66 (t, J=5.4 Hz, 1H), 6.90 (d, J=8.7 Hz, 2H), 7.27 (d, J=8.7 Hz, 2H), 9.44 (s, 1H); ^{13}C NMR (150.8 MHz) δ (*E*-isomer) 55.3, 55.8, 66.3, 73.1, 114.0 (2C), 129.0, 129.6 (2C), 141.9, 151.5, 159.6, 194.6; MS (FAB) m/z 235.10 $[M - H]^-$.

*4.1.16. (E)-2-Hydroxymethyl-5-phenylpenta-2,4-dienal (**2g**).* Yield 69%; R_f=0.29 (hexane/AcOEt 3:1); IR (KBr) 3331, 2843, 1674, 1653, 1614, 1591, 1450, 1281, 1188, 1175, 1132, 1013, 974, 874, 826, 754, 694 cm^{-1}; ^1H NMR (600 MHz) δ (*E*-isomer) 2.62 (br, 1H), 4.56 (s, 2H), 7.08 (d, J=6.6 Hz, 1H), 7.10 (d, J=3.6 Hz, 1H), 7.30–7.41 (m, 4H), 7.54 (d, J=3.6 Hz, 2H), 9.52 (s, 1H); ^{13}C NMR (150.8 MHz) δ 56.0, 122.5, 127.7 (2C), 128.9 (2C), 129.9, 135.5, 138.8, 143.7, 150.4, 195.1; HRMS (FAB) Calcd for $C_{12}H_{13}O_2$ $[M + H]^+$ 189.0910, Found 189.0947.

*4.1.17. 2-Cyclohexylidene-3-hydroxypropanal (**2h**).* Yield 71%; R_f=0.44 (hexane/AcOEt 1:1); IR (neat) 3430, 2932, 2857, 1717, 1667, 1620, 1447, 1402, 1352, 1337, 1312, 1292, 1260, 1175, 1013, 891, 856, 829, 756 cm^{-1}; ^1H NMR (400 MHz) δ 1.64–1.69 (m, 2H), 1.71–1.78 (m, 4H), 2.43 (br, 1H), 2.49 (t, J=6.0 Hz, 2H), 2.75 (t, J=6.0 Hz, 2H), 4.36 (s, 2H), 10.15 (s, 1H); ^{13}C NMR (100.6 MHz) δ 26.2, 28.5, 28.7, 29.5, 32.9, 56.2, 133.0, 166.8, 191.3; MS (FAB) m/z 154.0 [M].

*4.1.18. (E)- and (Z)-2-Hydroxymethyl-3-methyl-2-nonenal (**2i**).* Yield 80%; R_f=0.70 (hexane/AcOEt 1:1); IR (neat) 3439, 2957, 2928, 2859, 1668, 1626, 1466, 1377, 1304, 1157, 1017, 905, 787, 725 cm^{-1}; ^1H NMR (400 MHz) δ (*E*/*Z* isomer) 0.89 (t, J=6.8 Hz, 3H), 1.31 (m, 6H), 1.52 (m, 2H), 2.06 (br, 1H), 2.07+2.23 (s, 3H), 2.35+2.59 (t, J=8.0 Hz, 2H), 4.34+4.35 (s, 2H), 10.09+10.13 (s, 1H); ^{13}C NMR (100.6 MHz) δ (*E*/*Z* isomer) 14.0, 17.9, 21.2+22.5, 28.3, 29.2+29.4, 31.5+31.6, 33.2+36.7, 56.9+57.2, 135.5+135.7, 162.6+163.2, 191.7+192.6; HRMS (FAB) Calcd for $C_{11}H_{21}O_2$ $[M + H]^+$ 185.1536. Found 185.1492.

*4.1.19. Preparation of (E)-2-((tetrahydro-2H-pyran-2-yloxy)methyl)-2-nonenal (**8a**).* A mixture of **2a** (170 mg, 1.0 mmol), dihydropyran

(252 mg, 3.0 mmol), PPTS (25 mg, 0.1 mmol) dissolved in CH_2Cl_2 (5 mL) was stirred at room temperature for 4 h. The reaction was quenched with aq $NaHCO_3$ and concentrated. The crude product was purified by LC (SiO_2; hexanes/AcOEt, by increasing the gradient from 7:1 to 3:1 v/v) to give **8a** as a colorless oil (254 mg, 100% yield): R_f=0.71 (hexane/AcOEt 3:1); IR (neat) 2930, 2857, 2710, 1692, 1643, 1468, 1454, 1368, 1354, 1261, 1202, 1182, 1134, 1119, 1078, 1055, 1028, 976, 907, 870, 816, 725 cm^{-1}; ^1H NMR (600 MHz) (*E*-isomer) δ 0.89 (t, *J*=7.2 Hz, 3H), 1.29–1.35 (m, 8H), 1.50–1.60 (m, 6H), 2.50 (q, *J*=7.2 Hz, 2H), 3.53 (m, 1H), 3.88 (m, 1H), 4.17 (d, *J*=11.4 Hz, 1H), 4.42 (d, *J*=10.8 Hz, 1H), 4.66 (t, *J*=3.6 Hz, 1H), 6.72 (t, *J*=7.8 Hz, 1H), 9.44 (s, 1H); ^{13}C NMR (150.8 MHz) (*E*-isomer) δ 14.0, 19.3, 22.5, 25.4, 28.6, 29.0, 29.2, 30.5, 31.6, 58.3, 62.1, 98.6, 139.4, 159.3, 193.9; HRMS (FAB) Calcd for $C_{15}H_{27}O_3$ $[M+H]^+$ 255.1955. Found 255.1964.

*4.1.20. (E)-3-Phenyl-2-((tetrahydro-2H-pyran-2-yloxy)methyl)-2-propenal (**8d**).* Yield 91%; R_f=0.68 (hexane/AcOEt 3:1); IR (neat) 2943, 2872, 2716, 1684, 1630, 1574, 1466, 1454, 1441, 1370, 1352, 1323, 1285, 1260, 1202, 1180, 1155, 1119, 1076, 1055, 1026, 972, 936, 907, 870, 816, 760, 700 cm^{-1}; ^1H NMR (600 MHz) (*E*-isomer) δ 1.53–1.64 (m, 4H), 1.72–1.84 (m, 2H), 3.56 (m, 1H), 3.93 (m, 1H), 4.32 (d, *J*=10.8 Hz, 1H), 4.58 (d, *J*=10.8 Hz, 1H), 4.81 (t, *J*=3.6 Hz, 1H), 7.46 (m, 4H), 7.70 (m, 2H), 9.64 (s, 1H); ^{13}C NMR (150.8 MHz) (*E*-isomer) δ 19.4, 25.4, 30.6, 58.9, 62.3, 99.3, 128.8 (2C), 130.3 (2C), 130.4, 134.0, 138.0, 153.7, 194.2; HRMS (FAB) Calcd for $C_{15}H_{19}O_3$ $[M+H]^+$ 247.1329. Found 247.1313.

*4.1.21. Preparation of tert-butyl 4-(2-tetrahydropyranoxymethyl)undec-2Z,4Z-dienoate (**9a**) by Horner–Wadsworth–Emmons reaction.* To a solution of $(PhO)_2POCH_2CO_2{}^tBu$ (261 mg, 0.75 mmol) in THF (4 mL) was added NaH (28 mg, 0.7 mmol) at −78 °C. After being stirred for 15 min, **8a** (127 mg, 0.5 mmol) in THF (2 mL) was added, and the resulting mixture was gradually warmed to 0 °C over 1–2 h. The reaction was quenched with aq NH_4Cl at 0 °C and the mixture was extracted with AcOEt. The extracts were washed with brine, and the crude product was purified by LC (SiO_2; hexanes/AcOEt, 15:1 v/v) to give **9a** as a colorless oil (148 mg, 84% yield), the 2*Z*/2*E* ratio of 3.5/1 was determined on the basis of ^1H NMR (600 MHz): R_f=0.74 (hexane/AcOEt 5:1); IR (neat) 2955, 2928, 2857, 2359, 1713, 1630, 1456, 1391, 1368, 1314, 1285, 1256, 1223, 1202, 1152, 1119, 1078, 1053, 1024, 980, 953, 905, 870, 816, 723 cm^{-1}; ^1H NMR (600 MHz) (2*Z*-isomer) δ 0.88 (t, *J*=7.2 Hz, 3H), 1.25–1.42 (m, 8H), 1.46–1.60 (m, 13H), 1.62–1.83 (m, 2H), 2.17–2.30 (m, 2H), 3.50 (m, 1H), 3.86 (m, 1H), 4.20–4.41 (m, 2H), 4.58 (m, 1H), 5.63 (d, *J*=12.6 Hz, 1H), 5.88 (t, *J*=7.8 Hz, 1H), 6.35 (d, *J*=12.6 Hz, 1H); ^{13}C NMR (150.8 MHz) (2*Z*-isomer) δ 14.1, 19.4, 22.6, 25.5, 28.1 (3C), 28.3, 29.0, 29.3, 30.5, 31.7, 62.1, 63.1, 80.2, 97.0, 120.5, 132.8, 141.8, 146.2, 166.1; HRMS (FAB) Calcd for $C_{21}H_{36}O_4$ [M] 352.2614. Found 352.2651.

*4.1.22. tert-Butyl 5-phenyl-4-(2-tetrahydropyranoxymethyl)penta-2Z,4Z-dienoate (**9d**).* The 2*Z*/2*E* ratio of 7/1 was determined on the basis of ^1H NMR (400 MHz). Yield 93%; R_f=0.64 (hexane/AcOEt 5:1); IR (neat) 2942, 2870, 1715, 1622, 1456, 1393, 1368, 1285, 1256, 1215, 1150, 1078, 1055, 1028, 974, 907, 870, 816, 754, 700 cm^{-1}; ^1H NMR (400 MHz) (2*Z*-isomer) δ 1.45 (s, 9H), 1.48–1.83 (m, 6H), 3.45 (m, 1H), 3.81 (m, 1H), 4.46 (d, *J*=12.0 Hz, 1H), 4.57 (d, *J*=11.6 Hz, 1H), 4.63 (t, *J*=3.6 Hz, 1H), 5.79 (d, *J*=12.4 Hz, 1H), 6.57 (d, *J*=12.4 Hz, 1H), 6.85 (s, 1H), 7.24–7.39 (m, 5H); ^{13}C NMR (100.6 MHz) (2*Z*-isomer) δ 19.3, 25.4, 28.1 (3C), 30.6, 62.1, 64.6, 80.5, 97.6, 122.3, 127.6, 128.2 (2C), 129.3 (2C), 134.9, 135.2, 136.1, 141.7, 166.1; HRMS (FAB) Calcd for $C_{21}H_{29}O_4$ $[M+H]^+$ 345.2060. Found 345.2055.

*4.1.23. Preparation of (5Z)-5,6-dihydro-5-heptylidene-2H-pyran-2-one (**10a**).* A mixture of **9a** (71 mg, 0.2 mmol), PPTS (5 mg, 0.02 mmol) dissolved in CH_2Cl_2 (4 mL) was stirred at 55 °C for 12 h. The mixture was neutralized with aq $NaHCO_3$ and concentrated. The crude product was purified by LC (SiO_2; hexanes/AcOEt, by increasing the gradient from 10:1 to 3:1 v/v) to give **10a** as a colorless oil (29 mg, 73% yield) and the unchanged *E*-enoate **9a** (22%) as a separable stuff. Compound **10a**: R_f=0.30 (hexane/AcOEt 5:1); IR (neat) 2957, 2928, 2859, 1728, 1641, 1559, 1458, 1408, 1375, 1223, 1130, 1103, 1051, 1028, 910, 820, 723 cm^{-1}; ^1H NMR (600 MHz) δ 0.88 (t, *J*=7.2 Hz, 3H), 1.25–1.33 (m, 6H), 1.43 (m, 2H), 2.11 (q, *J*=7.2 Hz, 2H), 5.07 (s, 2H), 5.81 (m, 2H), 6.94 (d, *J*=9.6 Hz, 1H); ^{13}C NMR (150.8 MHz) δ 14.0, 22.5, 28.3, 28.8, 28.9, 31.6, 66.6, 116.3, 127.2, 137.7, 145.3, 163.9; HRMS (FAB) Calcd for $C_{12}H_{19}O_2$ $[M+H]^+$ 195.1380. Found 195.1398.

*4.1.24. (5Z)-5,6-Dihydro-5-(phenylmethylene)-2H-pyran-2-one (**10d**).* Yield 84%, along with the unchanged *E*-enoate **9d** (7%) as a separable stuff; R_f=0.17 (hexane/AcOEt 5:1); IR (KBr) 3048, 1966, 1836, 1811, 1722, 1715, 1695, 1668, 1622, 1487, 1447, 1404, 1261, 1225, 1204, 1126, 1078, 1051, 1007, 934, 903, 854, 826, 799, 743, 704 cm^{-1}; ^1H NMR (600 MHz) δ 5.40 (d, *J*=2.4 Hz, 2H), 5.96 (d, *J*=9.6 Hz, 1H), 6.78 (s, 1H), 7.14 (d, *J*=10.2 Hz, 1H), 7.20 (d, *J*=7.8 Hz, 2H), 7.36 (t, *J*=7.2 Hz, 1H), 7.43 (t, *J*=7.2 Hz, 2H); ^{13}C NMR (150.8 MHz) δ 67.6, 117.6, 128.0, 128.8 (2C), 128.9, 129.1 (2C), 134.5, 134.8, 145.7, 163.0. Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.44; H, 5.28.

*4.1.25. Preparation of tert-butyl (E)-3-hydroxy-4-(2-tetrahydropyranoxymethyl) undec-4-enoate (**11a**).* To a solution of LDA (2.0 mmol) in THF (4 mL) was added *tert*-butyl acetate (349 g, 3.0 mmol) in THF (3 mL) at −78 °C. After being stirred for 20 min, **8a** (127 mg, 0.5 mmol) in THF (1 mL) was added. The mixture was stirred at −60 °C for 3 h, quenched with aq NH_4Cl, and the products were extracted with AcOEt. The extracts were washed with brine and the crude product was purified by LC (SiO_2; hexanes/AcOEt, by increasing the gradient from 10:1 to 3:1 v/v) to give **11a** as a colorless oil (168 mg, 91% yield): R_f=0.64 (hexane/AcOEt 3:1); IR (neat) 3458, 2957, 2928, 2857, 1732, 1454, 1393, 1368, 1258, 1202, 1152, 1117, 1076, 1053, 1022, 978, 955, 907, 870, 845, 816, 766, 723 cm^{-1}; ^1H NMR (600 MHz) δ 0.87 (t, *J*=7.2 Hz, 3H), 1.24–1.36 (m, 8H), 1.44 (s, 9H), 1.51–1.81 (m, 6H), 2.10 (m, 2H), 2.57 (m, 2H), 3.38 (d,d, *J*=12.6, 5.4 Hz, 1H), 3.54 (m, 1H), 3.86 (m, 1H), 4.12 (m, 1H), 4.35 (m, 1H), 4.52 (m, 1H), 4.63 (m, 1H), 5.70 (q, *J*=7.2 Hz, 1H); ^{13}C NMR (150.8 MHz) δ 14.1, 19.3+19.4, 22.6, 25.3, 27.51+27.54, 28.1 (3C), 28.9, 29.51+29.53, 30.5, 31.7, 42.1+42.2, 62.1+62.2, 62.5+62.9, 71.9+72.2, 80.8+80.9, 97.8+98.2, 132.1+132.2, 135.3+135.5, 171.6+171.7; HRMS (FAB) Calcd for $C_{21}H_{39}O_5$ $[M+H]^+$ 371.2792, Found 371.2838.

*4.1.26. (5E)-Tetrahydro-4-hydroxy-5-heptylidene-2H-pyran-2-one (**12a**).* To a solution of **11a** (74 mg, 0.2 mmol) in CH_2Cl_2 (3 mL) was added TMSCl (cat. one drop) at 0 °C for 30 min. Then, the reaction was warmed to room temperature for 3 h, quenched with aq $NaHCO_3$, and concentrated. The crude product was purified by LC (SiO_2; hexanes/AcOEt, by increasing the gradient from 3:1 to 1:1 v/v) to give **12a** as a colorless oil (23 mg, 54% yield): R_f=0.10 (hexane/AcOEt 3:1); IR (neat) 2955, 2926, 2857, 2357, 1736, 1466, 1397, 1337, 1260, 1221, 1177, 1140, 1049, 895, 723 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) (*anti* isomer) δ 0.88 (t, *J*=7.2 Hz, 3H), 1.25–1.41 (m, 8H), 1.93 (br s, 1H), 2.05 (q, *J*=7.8 Hz, 2H), 2.79 (d,d, *J*=4.8, 1.8 Hz, 2H), 4.56 (t, *J*=4.8 Hz, 1H), 4.86 (d, *J*=14.4 Hz, 1H), 5.04 (d, *J*=14.4 Hz, 1H), 5.75 (t, *J*=7.8 Hz, 1H); ^{13}C NMR (150.8 MHz, $CDCl_3$) (*anti* isomer) δ 14.0, 22.5, 27.4, 28.9, 29.1, 31.6, 39.4, 65.6, 68.1, 130.9, 131.4, 170.1; HRMS (FAB) Calcd for $C_{12}H_{21}O_3$ $[M+H]^+$ 213.1485. Found 213.1449.

*4.1.27. Preparation of **10a** from **12a**.* To a solution of **12a** (43 mg, 0.2 mmol) in THP (3 mL) was added Ac_2O (60 μL, 0.6 mmol) and Et_3N (80 μL, 0.6 mmol) at 0 °C for 30 min. Then, the reaction was heated at 65 °C for 24 h, quenched with aq NH_4Cl, and concentrated. The crude

product was purified by LC (SiO_2; hexanes/AcOEt, by increasing the gradient from 10:1 to 3:1 v/v) to give **10a** as a colorless oil (36 mg, 93% yield).

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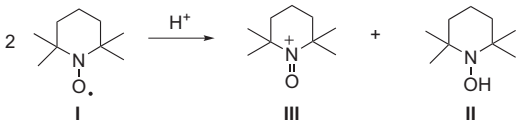
Supplementary data

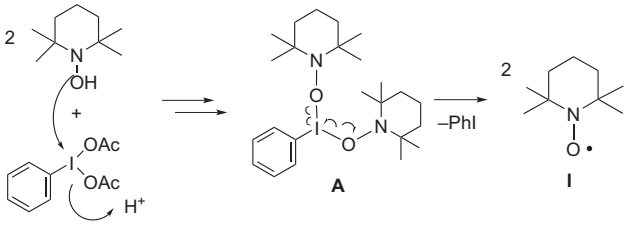
Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.10.034. These data include MOL files and InChIKeys of the most important compounds described in this article.

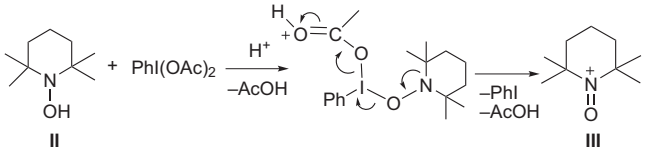
References and notes

1. (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811; (b) Iwabuchi, Y.; Hatakeyama, S. *Yuki Gosei Kagaku Kyokaishi* **2002**, *60*, 2; (c) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049; (d) Ciganek, E. *Org. React.* **1997**, *51*, 201; (e) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001.
2. Hill, J. S.; Isaacs, N. S. *Tetrahedron Lett.* **1986**, *41*, 5007.
3. For example, (*E*)-2-hydroxymethyl-3-phenylpropenal was used for various transformations: (a) Doi, T.; Hirabayashi, K.; Kokubo, M.; Komagata, T.; Yamamoto, K.; Takahashi, T. *J. Org. Chem.* **1996**, *61*, 8360; (b) Gilley, C. B.; Buller, M. J.; Kobayashi, Y. *Org. Lett.* **2007**, *9*, 3631; (c) Campi, E. M.; Dyall, K.; Fallon, G.; Jackson, W. R.; Perlmutter, P.; Smallridge, A. J. *Synthesis* **1990**, 855 Related compounds: (d) Habib-Zahmani, H.; Hacini, S.; Bories, C.; Faure, R.; Rodriguez, J. *Synthesis* **2005**, 2151.
4. (a) Tojo, G.; Fernández, M. *Oxidation of Alcohols to Aldehydes and Ketones, A Guide to Current Common Practice*; Springer: New York, NY, 2006; (b) Hudlicky, M. *Oxidation in Organic Chemistry; ACS Monograph 186*; American Chemical Society: Washington DC, 1990; p 114.
5. Reviews; Chromium reagent: (a) Ley, S. V.; Madin, A. *Comprehensive Organic Synthesis*; Pergamon: New York, NY, 1991; Vol. 7; p 251. Other Metallics: (b) Procter, G. *Comprehensive Organic Synthesis*; Pergamon: New York, NY, 1991; Vol. 7; p 305. DMSO: (c) Lee, T. V. *Comprehensive Organic Synthesis*; Pergamon: New York, NY, 1991; 7; p 291.
6. TEMPO oxidation, reviews: (a) Vogler, T.; Studer, A. *Synthesis* **2008**, 1979; (b) Bragd, P. L.; van Bekkum, H.; Besemer, A. C. *Top. Catal.* **2004**, *27*, 49; (c) Adam, W.; Saha-Möller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499; (d) Inokuchi, T.; Matsumoto, S.; Torii, S. *J. Synth. Org. Chem. Jpn.* **1993**, *51*, 910.
7. Kinetic study on steric effect of TEMPO: (a) de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Tetrahedron* **1995**, *51*, 8023; (b) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8412.
8. Moriarty, R. M.; Chany, C. J., II; Kosmeder, J. W., II. *Encycl. Reagents Org. Synth.* **1995**, *2*, 1479.
9. Mico, A. D.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.
10. Applications in natural products syntheses: (a) Looper, R. E.; Runnegar, M. T. C.; Williams, R. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3879; (b) Merten, J.; Fröhlich, R.; Metz, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 5991; (c) Looper, R. E.; Williams, R. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2930; (d) Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; Scott, J. P.; Sereinig, N. *Org. Lett.* **2003**, *5*, 35.
11. For the oxidative rearrangement of tertiary allylic alcohols mediated by TEMPO: (a) Vatèle, J.-M. *Tetrahedron* **2010**, *66*, 904; (b) Shibuya, M.; Tomizawa, M.; Iwabuchi, Y. *J. Org. Chem.* **2008**, *73*, 4750.
12. (a) Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Schuerch, F.; Seger, M.; Schreiner, K.; Daeffler, R.; Osmani, A.; Bixel, D.; Loiseleur, O.; Cercus, J.; Stettler, H.; Schaer, K.; Gamboni, R.; Bach, A.; Chen, G.-P.; Chen, W.; Geng, P.; Lee, G. T.; Loeser, E.; McKenna, J.; Kinder, F. R., Jr.; Konigsberger, K.; Prasad, K.; Ramsey, T. M.; Reel, N.; Repic, O.; Rogers, L.; Shieh, W.-C.; Wang, R.-M.; Waykole, L.; Xue, S.; Florence, G.; Paterson, I. *Org. Process Res. Dev.* **2004**, *8*, 113; (b) Vatèle, J.-M. *Synlett* **2006**, 2055.
13. 4-BzOTEMPO is inductively activated for oxidation compared with TEMPO: (a) Mei, Z.-W.; Ma, L.-J.; Kawafuchi, H.; Okihara, T.; Inokuchi, T. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 1000; (b) Mei, Z.-W.; Omote, T.; Mansour, M.; Kawafuchi, H.; Takaguchi, Y.; Jutand, A.; Tsuboi, S.; Inokuchi, T. *Tetrahedron* **2008**, *64*, 10761.
14. This reaction can be performed in a scale of 15 mmol of **3** in THP (30 mL) in the presence of *p*-TsOH (cat.) at room temperature for 1.5 h, giving **4** in 88% yield, with quantitative recovery of **3** (9%), THP used as a solvent.
15. Yamagami, I.; Yasuda, H. PCT Int. Appl. 2006, 38: WO 2006062211; CAN 145: 62784.
16. Yasuda, H.; Uenoyama, Y.; Nobuta, O.; Kobayashi, S.; Ryu, I. *Tetrahedron Lett.* **2008**, *49*, 367.
17. Ma, Z.; Bobbitt, J. M. *J. Org. Chem.* **1991**, *56*, 6110 .

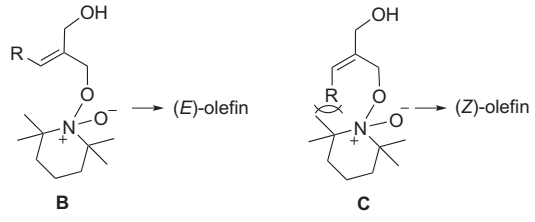


18. Formation of the acetoxy(2,2,6,6-tetramethylpiperidine-1-oxy)iodobenzene intermediate **A** by the reaction of **II** and DAIB and the subsequent decomposition to **III** would be assisted with acid catalyst.





19. Acid catalysis in the reactions of DAIB: (a) Liang, H.; Ciufolini, M. A. *J. Org. Chem.* **2008**, *73*, 4299; (b) Kitamura, T.; Inoue, D.; Wakimoto, I.; Nakamura, T.; Katsuno, R.; Fujiwara, Y. *Tetrahedron* **2004**, *60*, 8855; (c) Kryska, A.; Skulski, L. *J. Chem. Res., Synop.* **1999**, 590; (d) Varma, R. S.; Kumar, D. *J. Heterocycl. Chem.* **1998**, *35*, 1533.
20. Takaya, H.; Onodera, K.; Toyabe, Y.; Mase, N.; Yoda, H.; Takabe, K. *Tetrahedron Lett.* **2005**, *46*, 6293.
21. Selective formation of *E*-isomer can be explained by taking into the account of steric reason. Thus, the intermediate **C**, leading to (*Z*)-olefin, is affected by steric repulsion between the bulky TEMPO moiety and the R substituent, while the intermediate **B**, leading to (*E*)-olefin, undergoes no such effect. In ^{1}H NMR spectrum, *E*-isomer **2a** showed absorptions at 9.42 and 6.62 ppm due to formyl and vinylic protons, respectively, while *Z*-isomer **2a** showed at 10.14 and 6.70 ppm.
22. Further oxidation of the aldehyde **2a** with a 4-BzOTEMPO–DAIB system resulted in a complicated mixture of products.



23. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155; (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
24. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
25. Parikh, J. P.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *84*, 5505.
26. (a) Balsevich, J. *Can. J. Chem.* **1983**, *61*, 1053; (b) Uesato, S.; Matsuda, S.; Inouye, H. *Yakugaku Zasshi* **1984**, *104*, 1232.
27. (a) Lee, H.-Y.; Tae, H. Y.; Kim, B. G.; Choi, H.-M. *Tetrahedron Lett.* **2003**, *44*, 5803; (b) Pavlők, J.; Snajdr, I.; Kunes, J.; Spulák, M.; Pour, M. *J. Org. Chem.* **2009**, *74*, 703; (c) Jiang, X.; Ma, S. *J. Am. Chem. Soc.* **2007**, *129*, 11600.
28. Reviews: (a) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73; (b) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87.
29. (a) Ando, K. *J. Org. Chem.* **1999**, *64*, 8406; (b) Ando, K. *J. Org. Chem.* **1998**, *63*, 8411; (c) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934; (d) François, P. T. *Eur. J. Org. Chem.* **2005**, 1790.