Pergamon

Tetrahedron 57 (2001) 6181–6188

TETRAHEDRON

Acetonyltriphenylphosphonium bromide in organic synthesis: a useful catalyst in the cyclotrimerization of aldehydes

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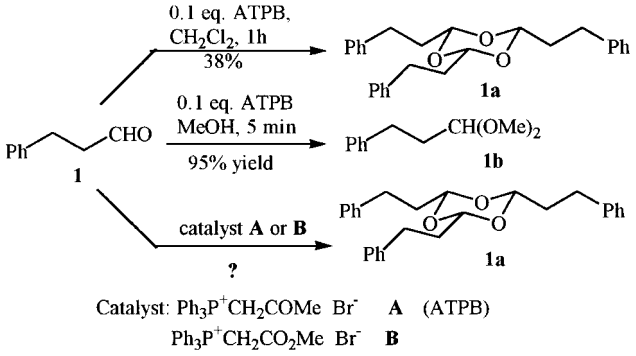
Received 30 March 2001; accepted 21 May 2001

Abstract—Acetonyltriphenylphosphonium bromide (ATPB) is a useful catalyst for the cyclotrimerization of the aliphatic aldehydes under solvent-free condition. The aldehydes tethered with a variety of functionality such as olefin, ether, ester, bromide, azide and diester could also be cyclotrimerized under the catalysis of ATPB. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The common catalysts to prepare 1,3,5-trioxanes from aldehydes are protic acids,[1] ZSM-5 zeolites,[2] bentonitic earth,[3] Lewis acids,[4] heteropoly acids such as $H_3PMo_{12}O_{40}$,[5] organic metal oxides such as $MeReO_3$,[6] and ion exchange resin.[7] Most of these reports focused on the cyclotrimerization of a few simple aldehydes and the conversion yields of the reactions were usually not high. Zhu and Espenson did a more comprehensive study on this type of reaction. However, methylrhenium trioxide (MTO) is a very effective but expensive catalyst.[6] Acetonyltriphenylphosphonium bromide (ATPB) is a precursor to prepare the corresponding phosphonium ylide, which is useful in the Wittig reaction. Interestingly, we found that ATPB is an extremely efficient catalyst for the protection and deprotection of alcohols as alkyl vinyl ethers.[8] ATPB (mp 221–223°C) can be easily and economically prepared from triphenylphosphine and bromoacetone in benzene at room temperature. It is soluble in CH_2Cl_2, $CHCl_3$, MeOH, EtOH and CH_3CN but not in THF, Et_2O, benzene and EtOAc. When aldehyde **1** was dissolved in a mixture of MeOH and CH_2Cl_2 in the presence of ATPB, dimethylacetal **1b** was formed in excellent yield in 5 min. We also found that ATPB could catalyze the cyclotrimerization of 3-phenylpropanal (**1**) in CH_2Cl_2 to give the corresponding 1,3,5-trioxane **1a** in 38% yield (Eq. (1)). Since practical applications abound for 1,3,5-trioxanes in different fields,[9] to find an economic and effective catalyst under mild preparation condition should be attractive and useful in organic synthesis. Encouraged by the result in Eq. (1), we tried to improve the reaction yield and investigate the scope of ATPB catalyst in the cyclotrimerization of aldehydes. In this report, we describe the results of our efforts in this direction.



(1)

2. Results and discussion

We tried to improve the chemical yield of the cyclotrimerization of the aldehyde by mixing and stirring the aldehyde and ATPB together with or without solvent. In order to find the optimal yield for the reaction in Eq. (1), several reaction conditions were investigated as shown in Table 1. The conclusions of these findings are described as follows: (1) the substituent on the triphenylphosphonium salts affected their catalytic activity significantly. Replacing the substituent from acetonyl (i.e. catalyst **A**) to methoxycarbonylmethyl (i.e. catalyst **B**) on the phosphine resulted in no reaction (entries 1 and 11, Table 1). Only ATPB is effective to the cyclotrimerization. (2) The use of solvents such as CH_2Cl_2 and $CHCl_3$ led to a poor conversion yield of the reaction even though the reaction time was extended to 48 h (entries 2–5, 7–10). (3) The reaction afforded a higher yield of 1,3,5-trioxane under solvent-free condition, which is a more environmentally friendly synthetic process (entries 2–5, 7–10 vs entries 12–20).[10] (4) Only 0.05–0.1 mol equiv. of ATPB was enough to achieve good

Keywords: acetonyltriphenylphosphonium bromide; cyclotrimerization; solvent-free synthesis.

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PII: S0040-4020(01)00588-9

Table 1. Cyclotrimerization of aldehyde **1** catalyzed by the triphenylphosphonium salts

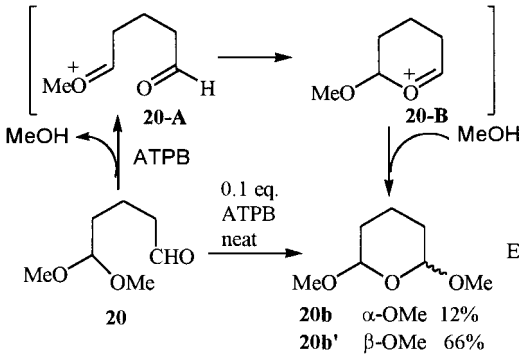
Entry	Catalyst (mol equiv.)	Solvent	Time (h)	Conversion (%)[a]
1	**A** (0.1)	CH_2Cl_2 (2 M)	1	0
2	**B** (0.1)	CH_2Cl_2 (2 M)	1	36
3	**B** (0.1)	CH_2Cl_2 (2 M)	5	44
4	**B** (0.1)	CH_2Cl_2 (2 M)	24	43
5	**B** (0.1)	CH_2Cl_2 (2 M)	48	44
6	**B** (0.1)	MeOH/CH_2Cl_2[b]	1/12	95[c]
7	**B** (0.1)	$CHCl_3$ (2 M)	1	39
8	**B** (0.1)	$CHCl_3$ (2 M)	5	42
9	**B** (0.1)	$CHCl_3$ (2 M)	24	37
10	**B** (0.1)	$CHCl_3$ (2 M)	48	36
11	**A** (0.1)	Neat	24	0
12	**B** (0.05)	Neat	1	56
13	**B** (0.05)	Neat	5	71
14	**B** (0.05)	Neat	24	74[d]
15	**B** (0.1)	Neat	1	64
16	**B** (0.1)	Neat	5	73
17	**B** (0.1)	Neat	24	80[e]
18	**B** (0.2)	Neat	1	72
19	**B** (0.2)	Neat	5	74
20	**B** (0.2)	Neat	24	74

[a] Determined by the integration of the 400 MHz ^{1}H NMR at δ 9.83 (for aldehyde **1**) and δ 4.82 (for trioxane ring protons **1a**).
[b] The volume ratio of MeOH and CH_2Cl_2 is 1:1.
[c] The corresponding dimethyl acetal **1b** is formed in 95% yield.
[d] 69% isolated yield and recovered 19% aldehyde **1**.
[e] 74% isolated yield and recovered 15% aldehyde **1**.

yield. The optimal conversion yield of the reaction was about 80% in the presence of 0.1 mol equiv. of ATPB at rt for 24 h (entry 17). More catalyst (0.2 mol equiv.) did not improve the reaction in rate and chemical yield (entry 17 vs entry 20). We could easily separate 1,3,5-trioxane **1a** from the remaining aldehyde **1** by silica gel column chromatography. The characteristic peak from the trioxane ring protons of the trimer **1a** in 400 MHz ^{1}H NMR appears at δ 4.82 (t, J=5.2 Hz). All three substituents are oriented equatorially, as confirmed by X-ray crystallography.

Based on the results in Table 1, the following typical procedure was chosen for further study. Aldehyde (5 mmol) and ATPB (0.5 mmol) were mixed together under N_2 and stirred at rt for 24 h. In general, the conversions of the reactions in Table 2 ranged from modest to good. ATPB is effective to the cyclotrimerization of the straight chain and branched-chain aldehydes (entries 1–5 and 7, Table 2). The aldehydes tethered with a variety of functionalities such as olefin (entries 8 and 9), ether (entry 10), ester (entries 11–15), bromide (entries 16–17), azide (entry 18) and diester (entry 19) could also be trimerized under the catalysis of ATPB. Interestingly, although dihydrocitronellal (**7**) underwent cyclotrimerization in 65% yield, no reaction occurred when citronellal (**6**) was used in the reaction (entries 6 and 7). We recovered about 80% of the starting material **6**. However, the double bonds on compounds **8** and **9** did not retard the reaction (entries 8–9). Comparison of the results in entries 6, 8, and 9 indicates that the spacer chain length between olefin and aldehyde is important to the cyclotrimerization. We do not have a suitable explanation to their differences in reactivity. In general, ATPB is effective to the reaction using uncojugated aliphatic aldehydes. On the other hand, ATPB is ineffective to the reactions using the conjugated aldehydes (i.e. acrolein, crotonaldehyde, benzaldehyde and cinnamaldehyde) and a sterically hindered aldehyde (i.e. pivalaldehyde).

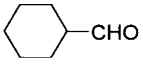
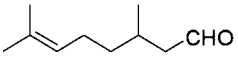
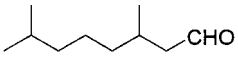
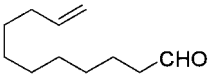
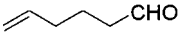
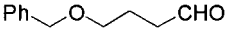
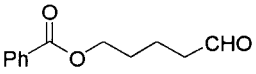
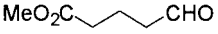
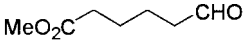
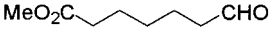
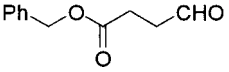
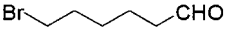
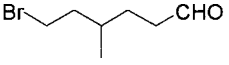
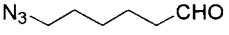
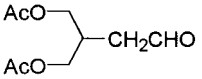
Interestingly, under the same reaction conditions, 5,5-dimethoxylpentanal (**20**)[11] undergo the intramolecular cyclization instead of cyclotrimerization. We isolated a diastereomeric mixture of 2,6-dimethoxytetrahydropyran (**20b**) and (**20b′**) (**20b**/**20b′**=1:5) in 78% yield. The formation of the tetrahydropyran products was explained as follows. The pK_a of ATPB is about 6.6.[12] Therefore, ATPB is acidic enough to protonate the dimethylacetal to give the oxonium ion intermediate **20-A**, which undergoes cyclization to give the cyclic oxonium ion intermediate **20-B**. The nucleophilic addition of methanol to the intermediate **20-B** to give two diastereomers of 2,6-dimethoxytetrahydropyran (**20b** and **20b′**) (Eq. (2)).



(2)

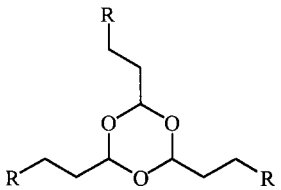
Alkaline hydrolysis of the triester **13a** gave the corresponding tricarboxylic acid **13b** in 52% yield. Since the product is very soluble in water, its isolation procedure is tedious. On the other hand, Pd/C catalyzed hydrogenolysis of the tribenzyl ester **15a** gave the corresponding tricarboxylic acid

Table 2. Cyclotrimerization of aldehyde catalyzed by ATPB under solvent-free condition at rt

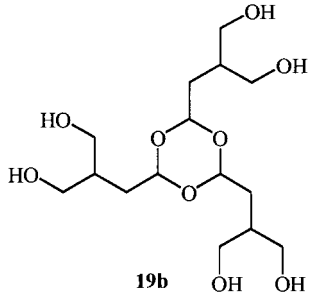
Entry	Reactant		Product	Yield[a] (%)
1	$Ph(CH_2)_2CHO$	**1**	**1a**	78[b]
2	$MeCH_2CHO$	**2**	**2a**	70
3	$Me(CH_2)_7CHO$	**3**	**3a**	69
4	Me_2CHCHO	**4**	**4a**	72[c]
5		**5**	**5a**	76[d]
6		**6**	**6a**	0[e]
7		**7**	**7a**	65
8		**8**	**8a**	77
9		**9**	**9a**	61
10		**10**	**10a**	68
11		**11**	**11a**	63
12		**12**	**12a**	74
13		**13**	**13a**	73
14		**14**	**14a**	71
15		**15**	**15a**	74
16		**16**	**16a**	72
17		**17**	**17a**	70
18		**18**	**18a**	68
19		**19**	**19a**	16

[a] The isolated yields were reported. All products were characterized by ^1H-, ^{13}C-, MS, HRMS and/or elemental analysis.
[b] Mp 65–66°C.
[c] Mp 59–60°C.
[d] Mp 196–198°C.
[e] Recovered 79% of the aldehyde **6**.

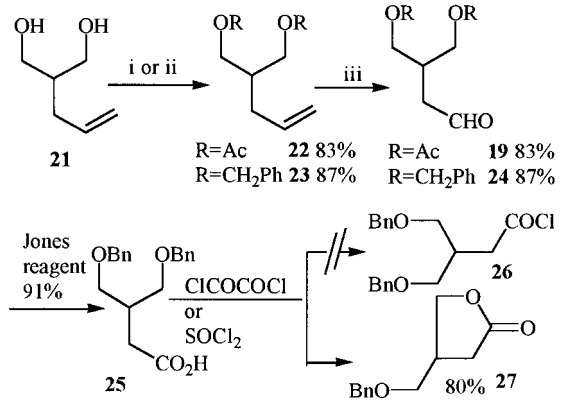
15b in excellent yields. The spectroscopically pure product can be obtained simply by filtration through Celite to remove the catalyst and then subsequent concentration. Similarly, the triol **10b** can be formed from compound **10a** under the Pd/C catalyzed hydrogenolysis in excellent yield. We believe that compounds **18b** and **19b** should be able to be prepared from their precursor **18a** and **19a**, respectively. Since these compounds are easily prepared in two steps from the corresponding aldehyde in good yields, we believe that they should be the potential core structures for the preparation of the dendritic molecules.[13]



R= $-CH_2OH$ **10b**
R= $-(CH_2)_4CO_2H$ **13b**
R= $-(CH_2)_2CO_2H$ **15b**
R= $-(CH_2)_5NH_2$ **18b**

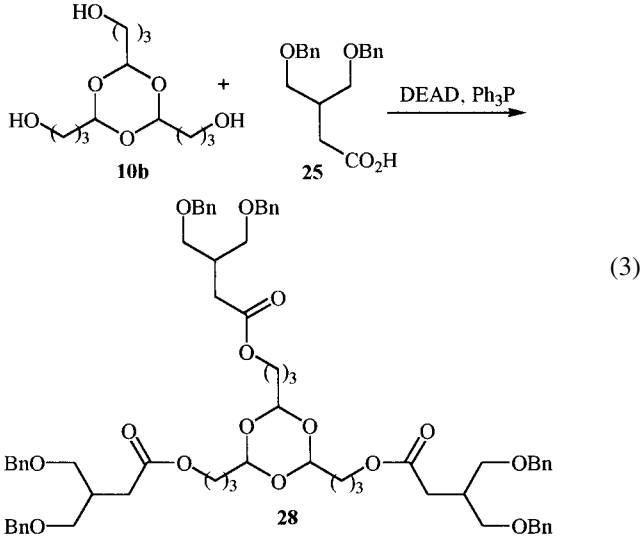


19b



Scheme 1. *Reagents*: (i) Ac_2O, Pyridine; (ii) NaH, $PhCH_2Br$, THF, DMF; (iii) (a) O_3, CH_2Cl_2; (b) Et_3N.

2-Allyl-1,3-propanediol (**21**)[14] was protected as dibenzyl ether **23**, which was subjected to the ozonolysis and subsequently treated with Et_3N[15] to give the corresponding aldehyde **24**. Oxidation of aldehyde **24** with Jones reagent gave the corresponding carboxylic acid **25** in 91% yield. Compound **25** failed to react with oxalyl chloride to give the corresponding acyl chloride **26**. To our surprise, we obtained γ-butyrolactone **27** in 80% yield. Similar result was obtained when thionyl chloride was used (Scheme 1). Therefore, carboxylic acid **25** was used directly to react with triol **10b** by Mitsunobu reaction condition. Triol **10b** reacted with 3,5-dibenzyloxybenzoic acid (**25**) in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) to give the corresponding tri-ester **28** in 25% yield (Eq. (3)). There are six benzyl ethers at the periphery of compound **28**. These six benzyl ethers are the potential useful precursors to buildup more complex dendritic molecules. Further work to prepare the dendrimers from our cyclotrimerization products is under investigation in our laboratory now.



(3)

3. Conclusions

In summary, ATPB is an economic, effective and easily available catalyst, which is useful to the cyclotrimerization of aldehydes at room temperature under solvent-free condition. Many functional groups on the aldehydes were compatible with our reaction condition.

4. Experimental

All reactions were carried out under nitrogen. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were determined by using a Thomas–Hoover melting point apparatus and were uncorrected. The ^{1}H- and ^{13}C NMR spectra were recorded on a Bruker Avance APX-400 and a Varian Gemini-200 spectrometers, and chemical shifts were given in ppm downfield from tetramethylsilane (TMS). IR spectra were taken with a Perkin–Elmer 682 spectrophotometer and only noteworthy absorption was listed. Mass spectra were measured on a VG-Trio-2000GC/MS spectrometer by electronic impact at 70 eV (unless otherwise indicated). High Resolution Mass Spectroscopy (HRMS) was measured on a JEOL JMS-HX 110 (National Hsing-Hua University) or VG-11-250J (Academia Sinica) Mass Spectrometer. The elemental analyses were measured on Heraeus NCH-RAPID and Perkin–Elmer 2400 CHN analyzer.

4.1. Typical procedure for the cyclotrimerization of aldehyde

A mixture of the 3-phenylpropionaldehyde (**1**) (385 mg, 2.87 mmol) and ATPB (115 mg, 0.287 mmol) was stirred at rt for 24 h. The crude mixtures were subjected to silica gel column chromatography to isolate the desired product **1a** (300 mg) in 78% yield.

4.1.1. 2,4,6-Tri-(2-phenylethyl)-1,3,5-trioxane (1a). White solid, mp 65–66°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.00–2.06 (m, 6H, $-CHCH_2CH_2Ph$), 2.74–2.78 (m, 6H, $-CHCH_2CH_2Ph$), 4.81 (t, J=5.3 Hz, 3H, $-OCHO$), 7.19–7.30 (m, 15H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.6, 35.6, 100.6, 125.9, 128.3, 128.4, 141.3; IR (KBr) 3022, 2930, 1604, 1498, 1457, 1365 cm^{-1}; MS m/z (relative intensity): 402 (M^+, 2), 134 (100), 117 (35), 91 (88); Anal. Calcd for $C_{27}H_{30}O_3$: C, 80.56; H, 7.51, found: C, 80.62; H, 7.55.

4.1.2. 2,4,6-Triethyl-1,3,5-trioxane (2a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, J=7.6 Hz, 9H, $-CH_3$), 1.66–1.72 (m, 6H), 4.79 (t, J=5.3 Hz, 3H, $-OCHO$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.8, 27.6, 102.4; IR (KBr) 2958, 1461, 1360, 1272 cm^{-1}; MS m/z (relative intensity): 174 (M^+, 2), 145 (31), 117 (41), 58 (100).

4.1.3. 2,4,6-Trioctyl-1,3,5-trioxane (3a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J=7.0 Hz, 9H, $-CH_3$), 1.27–1.41 (m, 36H), 1.64–1.69 (m, 6H), 4.83 (t, J=5.3 Hz, 3H, $-OCHO$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 22.6, 23.6, 29.2, 29.4, 29.5, 31.9, 34.4, 101.7; IR (KBr) 2921, 2847, 1466, 1355, 1148 cm^{-1}; MS m/z (relative intensity): 409 (M^+-OH, 22), 267 (100), 141 (57), 83 (47); HRMS Calcd for $C_{27}H_{53}O_2$ (M^-−OH): 409.4048, found: 409.4044.

4.1.4. 2,4,6-Triisopropyl-1,3,5-trioxane (4a). White solid,

mp 59–60°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (d, J=6.8 Hz, 18H, –CH_3), 1.83–1.88 (m, 3H), 4.50 (d, J=5.5 Hz, 3H, –OCHO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ16.7, 32.4, 104.7; IR (KBr) 2958, 1470, 1355, 1263 cm^{-1}; MS m/z (relative intensity): 216 (M^+, 1), 199 (94), 127 (100), 98 (55), 81 (83); Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18, found: C, 66.59; H, 11.14.

4.1.5. 2,4,6-Tricyclohexyl-1,3,5-trioxane (5a). White solid, mp 196–198°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01–1.24 (m, 15H), 1.58–1.83 (m, 18H), 4.49 (d, J=5.6 Hz, 3H, –OCHO–); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.6, 26.5, 27.0, 41.9, 104.3; IR (KBr) 2921, 1466, 1351, 1231 cm^{-1}; MS m/z (relative intensity): 336 (M^+, 2), 225 (79), 113 (92), 95 (100); Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78, found: C, 74.87; H, 10.78.

4.1.6. 2,4,6-Tri(2,6-dimethylheptyl)-1,3,5-trioxane (7a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (d, J=6.6 Hz, 18H, –CH_3), 0.91 (d, J=6.5 Hz, 9H, –CH_3), 1.12–1.31 (m, 18H), 1.47–1.53 (m, 6H), 1.68–1.69 (m, 6H), 4.94 (t, J=5.0 Hz, 3H, –OCHO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.8, 22.6, 22.7, 24.5, 28.2, 37.3, 39.2, 41.4, 100.8; IR (KBr) 2921, 1466, 1369 cm^{-1}; MS m/z (relative intensity): 468 (M^+, 2), 313 (46), 155 (84), 83 (69), 69 (100); HRMS Calcd for $C_{30}H_{60}O_3$: 468.4545, found: 468.4533.

4.1.7. 2,4,6-Tri(9-decenyl)-1,3,5-trioxane (8a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28–1.39 (m, 36H), 1.63–1.69 (m, 6H), 2.01–2.06 (m, 6H), 4.83 (t, J=5.3 Hz, 3H, –OCHO), 4.91–5.01 (m, 6H, –CHCH_2), 5.77–5.86 (m, 3H, –CHCH$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.5, 28.9, 29.1, 29.3, 29.4, 29.5, 33.8, 34.4, 101.7, 114.1, 139.2; IR (KBr) 3068, 2921, 1641, 1466, 1355 cm^{-1}; MS m/z (relative intensity): 504 (M^+, 1), 335 (12), 149 (43), 95 (100); Anal. Calcd for $C_{33}H_{60}O_3$: C, 78.51; H, 11.98. Found: C, 78.56; H, 12.06.

4.1.8. 2,4,6-Tri(4-pentenyl)-1,3,5-trioxane (9a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49–1.53 (m, 6H), 1.66–1.71 (m, 6H), 2.05–2.10 (m, 6H), 4.85 (t, J=5.3 Hz, 3H, –OCHO), 4.94–5.03 (m, 6H, –CHCH_2), 5.76–5.80 (m, 3H, –CHCH$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.8, 33.4, 33.8, 101.4, 114.7, 138.4; IR (KBr) 3068, 2930, 1641, 1443, 1355 cm^{-1}; MS m/z (relative intensity): 294 (M^+, 10), 252 (22), 197 (100), 154 (50), 137 (57); HRMS Calcd for $C_{18}H_{30}O_3$: 294.2196, found: 294.2192.

4.1.9. 2,4,6-Tri(3-benzyloxypropyl)-1,3,5-trioxane (10a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.72–1.77 (m, 12H), 3.48 (t, J=5.6 Hz, 6H, –OCH_2–), 4.49 (s, 6H, –OCH_2Ph), 4.83 (t, J=4.8 Hz, 3H, –OCHO), 7.26–7.33 (m, 15H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 31.1, 69.9, 72.8, 101.1, 127.4, 127.5, 128.3, 138.5; IR (KBr) 3032, 2857, 1682, 1447, 1360 cm^{-1}; MS m/z (relative intensity): 534 (M^+, 39), 358 (10), 249 (10), 179 (100); HRMS Calcd for $C_{32}H_{41}O_6$ (M^+–H): 533.2903, found: 533.2909.

4.1.10. 2,4,6-Tri(3-hydroxypropyl)-1,3,5-trioxane (10b). Compound **10a** (471 mg, 0.88 mmol) in 20 mL of EtOAc was added 10% Pd/C (9.3 mg, 0.088 mmol). The reaction mixtures were shaked under the Parr hydrogenation apparatus under 50 psi H_2 at rt for 24 h. The reaction mixtures were filtered through Celite and concentrated in vacuo to give the desired product **10b** in 87% yield. Needless to purify, this product can be used for the further reaction. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.61–1.73 (m, 12H), 3.55–3.58 (m, 6H), 4.98 (t, J=4.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.6, 32.0, 62.6, 102.4; IR (KBr) 3372, 1447, 1360 cm^{-1}; MS m/z (relative intensity): 265 (M^++1, 2), 229 (22), 159 (43), 71 (100); HRMS Calcd for $C_{12}H_{25}O_6$ (M^++H): 265.1652, found: 265.1651.

4.1.11. 2,4,6-Tri(4-benzoxybutyl)-1,3,5-trioxane (11a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55–1.60 (m, 6H), 1.72–1.82 (m, 12H), 4.30–4.33 (m, 6H), 4.89 (t, J=5.2 Hz, 3H, –OCHO), 7.26–7.56 (m, 9H, Ar–H), 8.02–8.04 (m, 6H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.1, 28.5, 33.9, 64.7, 101.2, 128.3, 129.5, 130.4, 132.8, 166.6; IR (KBr) 3059, 2949, 1724, 1599, 1452, 1365 cm^{-1}; MS m/z (relative intensity): 617 (M^+, 5), 414 (17), 273 (10), 207 (100), 154 (16); HRMS Calcd for $C_{36}H_{41}O_9$ (M^+–H): 617.2745, found: 617.2751; Anal. Calcd for $C_{36}H_{42}O_9$: C, 68.74; H, 6.29. Found: C, 68.77; H, 6.32

4.1.12. 2,4,6-Tri(3-methoxycarbonylpropyl)-1,3,5-trioxane (12a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.69–1.77 (m, 12H), 2.35 (t, J=7.2 Hz, 6H), 3.67 (s, 9H, –CH_3), 4.87 (t, J=4.8 Hz, 3H, –OCHO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.0, 33.5, 33.6, 51.5, 100.9, 173.8; IR (KBr) 2940, 1738, 1443, 1360 cm^{-1}; MS m/z (relative intensity): 391 (M^++1, 3), 261 (15), 131 (100), 99 (84).

4.1.13. 2,4,6-Tri(4-methoxycarbonylbutyl)-1,3,5-trioxane (13a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40–1.46 (m, 6H), 1.61–1.69 (m, 12H), 2.31 (t, J=7.6 Hz, 6H), 3.66 (s, 9H, –CH_3), 4.83 (t, J=5.2 Hz, 3H, –OCHO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.0, 24.6, 33.8, 33.9, 51.4, 101.2, 174.0; IR (KBr) 2940, 1738, 1438, 1365 cm^{-1}; MS m/z (relative intensity): 432 (M^+, 1), 289 (14), 145 (100), 113 (56); HRMS Calcd for $C_{21}H_{37}O_9$ (M^++H): 433.2438, found: 433.2443.

4.1.14. 2,4,6-Tri(4-carboxybutyl)-1,3,5-trioxane (13b). A solution of compound **13a** (261 mg, 0.603 mmol) in 6 mL of MeOH was added to a solution of KOH (118 mg, 2.11 mmol) in 3 mL of water. The reaction mixtures were heated up to reflux for 30 min. Subsequently, the reaction mixture was cooled down to room temperature, neutralized by 1N HCl until the pH was between 4–5 and then extracted with CH_2Cl_2 three times. The organic layer was dried over $MgSO_4$ and concentrated to give compound **13b** (123 mg) in 52% yield. ^{1}H NMR (D_2O, 400 MHz) δ 1.46–1.48 (m, 6H), 1.62–1.73 (m, 12H), 2.29 (t, J=7.4 Hz, 6H), 5.18 (t, J=5.1 Hz, 3H); ^{13}C NMR (D_2O, 100 MHz) δ 22.8, 25.2, 33.3, 36.5, 1.2.2, 182.3; IR (KBr) 2949, 1710, 1415, 1369, 1300 cm^{-1}

4.1.15. 2,4,6-Tri(5-methoxycarbonylpentyl)-1,3,5-trioxane (14a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27–1.39 (m, 12H), 1.55–1.64 (m, 12H), 2.26 (t, J=7.6 Hz, 6H), 3.61 (s, 9H, –CH_3), 4.78 (t, J=5.3 Hz, 3H, –OCHO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.0, 24.7, 28.7, 33.8, 34.1, 51.3, 101.3, 174.0; IR (KBr) 2930, 2857, 1738, 1438, 1360 cm^{-1}; MS m/z (relative intensity): 475 (M^++1, 1), 285 (20), 159 (100), 81 (43); HRMS Calcd for $C_{24}H_{41}O_9$ (M^+-H): 473.2751, found: 473.2758

4.1.16. 2,4,6-Tri(2-benzoxycarbonylethyl)-1,3,5-trioxane (15a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.96–2.01 (m, 6H), 2.48 (t, J=7.5 Hz, 6H), 4.91 (t, J=4.8 Hz, 3H, –OC*H*O), 5.11 (s, 6H), 7.26–7.35 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.9, 29.2, 66.3, 99.5, 128.2, 128.5, 135.9, 172.8; IR (KBr) 3022, 2930, 1728, 1503, 1452, 1355 cm^{-1}; MS *m/z* (relative intensity): 577 (M^++1, 4), 385 (12), 193 (47), 91 (100); HRMS Calcd for $C_{33}H_{37}O_9$ (M^++H): 577.2438, found: 473.2469

4.1.17. 2,4,6-Tri (2-carboxylethyl)-1,3,5-trioxane (15b). Compound **10a** (273 mg, 0.47 mmol) in 20 mL of EtOAc was mixed with 10% Pd/C (5 mg, 0.05 mmol). The reaction mixture was shaked under the Parr hydrogenation apparatus under 50 psi H_2 at rt for 10 h. The reaction mixture was filtered through Celite and concentrated in vacuo to give the desired product **15b** in 81% yield. Needless to purify, this product can be used for the further reaction. ^{1}H NMR (CD_3OD, 400 MHz) δ 1.92–1.95 (m, 6H), 2.41 (t, J=7.5 Hz, 6H), 5.02 (t, J=5.4 Hz, 3H, –OC*H*O); ^{13}C NMR (CD_3OD, 100 MHz) δ 28.7, 30.6, 101.1, 176.9; IR (KBr) 3032, 2930, 1705, 1438, 1365 cm^{-1}; MS *m/z* (relative intensity): 307 (M^++1, 15), 205 (56), 154 (51), 85 (96); Anal. Calcd for $C_{12}H_{18}O_6$: C, 47.06; H, 5.92. Found: C, 46.59; H, 6.00

4.1.18. 2,4,6-Tri(5-bromopentyl)-1,3,5-trioxane (16a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39–1.48 (m, 12H), 1.63–1.68 (m, 6H), 1.81–1.88 (m, 6H), 3.38 (t, J=6.8 Hz, 6H), 4.83 (t, J=5.2 Hz, 3H, –OC*H*O); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.5, 27.8, 32.5, 33.7, 34.0, 101.2; IR (KBr) 2930, 2857, 1457, 1360 cm^{-1}; MS *m/z* (relative intensity): 535 (M^++1, 0.3), 359 (34), 137 (32), 69 (100); HRMS Calcd for $C_{18}H_{33}O_3$ $^{79}Br_2$ ^{81}Br: 534.9862, found: 534.9881

4.1.19. 2,4,6-Tri(5-bromo-3-methylpentyl)-1,3,5-trioxane (17a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (d, J=6.3 Hz, 9H, –C*H*$_3$), 1.25–1.28 (m, 3H), 1.43–1.45 (m, 3H), 1.65–1.74 (m, 12H), 1.86–1.90 (m, 3H), 3.39–3.47 (m, 6H), 4.84 (t, J=5.3 Hz, 3H, –OC*H*O); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.7, 29.7, 31.2, 31.6, 31.9, 39.7, 101.5; IR (KBr) 2940, 1461, 1360, 1259 cm^{-1}; MS *m/z* (relative intensity): 578 (M^++2, 2), 387 (9), 193 (100), 154 (39), 113 (94); HRMS Calcd for $C_{21}H_{38}O_3Br_3$ (M^+−H): 575.0371, found: 575.0408.

4.1.20. 2,4,6-Tri(5-azidopentyl)-1,3,5-trioxane (18a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37–1.43 (m, 12H), 1.57–1.66 (m, 12H), 3.24 (t, J=7.0 Hz, 6H), 4.82 (t, J=5.2 Hz, 3H, –OC*H*O); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.9, 26.3, 28.6, 34.0, 51.2, 101.2; IR (KBr) 2930, 2101, 1457, 1351, 1254 cm^{-1}; MS *m/z* (relative intensity): 423 (M^+, 0.3), 409 (16), 267 (77), 238 (9), 141 (100); HRMS Calcd for $C_{18}H_{33}O_3N_9$ (M^++H): 424.2785, found: 424.2783.

4.1.21. 2,4,6-Tri[(1,1-diacetoxymethyl)ethyl]-1,3,5-trioxane (19a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.71–1.74 (m, 6H), 2.02 (s, 18H, –CH_3), 2.03–2.06 (m, 3H), 3.99–4.09 (m, 12H), 4.98 (t, J=5.2 Hz, 3H, –OC*H*O); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 32.6, 63.9, 99.6, 170.8; IR (KBr) 2949, 1742, 1443, 1378 cm^{-1}; MS *m/z* (relative intensity): 607 (M^++1, 1), 405 (10), 279 (42), 143 (100); HRMS Calcd for $C_{27}H_{43}O_{15}$ (M^++H): 607.2602, found: 607.2602.

4.1.22. 2,6-Dimethoxytetrahydropyran. A mixture of aldehyde **20** (532 mg, 3.64 mmol) and ATPB (145 mg, 0.364 mmol) was stirred at rt for 24 h. The crude mixture was subjected to silica gel column chromatography to isolate compounds **20b** (353 mg, 66% yield; R_f=0.52 (Hexane/EtOAc=5:1)) and **20b′** (62 mg, 12% yield; R_f=0.45 (Hexane/EtOAc=2:1)).

4.1.23. *trans*-2,6-Dimethoxytetrahydropyran (20b). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51–1.57 (m, 2H), 1.70–1.73 (m, 4H), 3.45 (s, 6H), 4.76 (2H, t, J=4.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.2, 29.9, 55.2, 98.4; IR (KBr) 2930, 1457, 1392, 1171 cm^{-1}; MS *m/z* (relative intensity): 146 (M^+, 5), 145 (29), 115 (63), 86 (60), 58 (100).

4.1.24. *cis*-2,6-Dimethoxytetrahydropyran (20b′). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46–1.49 (m, 3H), 1.72–1.77 (m, 2H), 1.85–1.86 (m, 1H), 3.50 (s, 6H), 4.45 (2H, t, J=2.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.2, 30.2, 55.8, 100.9; IR (KBr) 2940, 1452, 1392 cm^{-1}; MS *m/z* (relative intensity): 146 (M^+, 0.1), 145 (1), 115 (4), 86 (13), 71 (20), 58 (100).

4.1.25. 2-Allyl-propane-1,3-diol (21). It was prepared according to the literature procedure in 88% yield.[14] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.78–1.82 (m, 1H), 2.01 (t, 2H, J=7.1 Hz), 3.57–3.61 (m, 4H), 3.70–3.74 (m, 2H), 5.00–5.06 (m, 2H), 5.70–4.79 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.4, 41.7, 64.9, 116.5, 136.1; IR (KBr) cm^{-1} 3326, 2921, 1645, 1443.

4.1.26. 1,3-Diacetoxy-2-allylpropane (22). It was prepared according to the literature procedure in 88% yield.[14] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.02 (s, 6H), 2.05–2.13 (m, 3H), 3.97–4.07 (m, 4H), 5.02–5.06 (m, 2H), 5.67–5.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 32.6, 36.9, 63.8, 117.4, 134.8, 170.8; IR (KBr) 2940, 1738, 1443, 1369, 1245 cm^{-1}.

4.1.27. 2-Allyl-1,3-benzyloxypropane (23). To a suspension solution of NaH (312 mg, 130 mg) in a mixture of THF (10 mL) and DMF (2 mL) was added a solution of 2-allyl-propane-1,3-diol (**21**) (503 mg, 4.34 mmol) in 5 mL of THF at 0°C. To the resulted mixture was added a solution of benzyl bromide (1.63 g, 9.54 mmol) in 3 mL of THF at room temperature and the reaction was stirred at rt for 24 h. The reaction was quenched with water and extracted with ether. The organic layer was dried over $MgSO_4$ and concentrated to give the crude residue. It was purified by silica gel column chromatography to give compound **23** (1.12 g) in 87% yield. R_f=0.6 (Hexane/EtOAc=10:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.09–2.12 (m, 1H), 2.26–2.30 (m, 2H), 3.52–3.60 (m, 4H), 4.55 (s, 2H), 5.05–5.12 (m, 2H), 5.82–5.86 (m, 1H), 7.31–7.41 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.1, 39.3, 70.4, 73.0, 116.2, 127.4, 127.5, 128.2, 136.6, 138.6; IR (KBr) 3068, 2857, 1641, 1457, 1365 cm^{-1}; MS *m/z* (relative intensity): 205 (8), 107 (34), 91 (100).

4.1.28. 4-Acetoxy-4-acetoxymethylbutanal (19). In a 250 mL of two-neck flask, which was equipped with a magnetic stirrer, a drying tube and a gas dispersing tube (with porous fritted tip), were placed 100 mL of CH_2Cl_2

and 1,3-diacetoxy-2-allylpropane (**22**) (571 mg, 2.86 mmol). A stream of ozone was bubbled through the solution at −78°C. Ozone treatment was terminated when the mixture assumed a blue color. A stream of nitrogen was used to remove excess ozone. Et_3N (0.52 mL, 3.72 mmol) was added to the solution at −78°C. The reaction was warmed slowly to room temperature and stirred for 12 h. The reaction mixture was concentrated and chromatographed on a silica gel column to give compound **19** (421 mg) as a colorless oil in 73% yield.[15] ^1H NMR ($CDCl_3$, 400 MHz) δ 1.97 (s, 6H), 2.47–2.49 (m, 2H), 2.61–2.64 (m, 1H), 3.96–4.06 (m, 4H), 9.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5, 31.9, 42.6, 63.6, 170.6, 199.7; IR (KBr) 2949, 2893, 2829, 2718, 1742, 1369 cm^{-1}.

4.1.29. 4-Benzyloxy-3-benzyloxymethylbutyraldehyde (24). In a 250 mL of two-neck flask, which was equipped with a magnetic stirrer, a drying tube and a gas dispersing tube (with porous fritted tip), were placed 150 mL of CH_2Cl_2 and 2-allyl-1,3-benzyloxypropane (**23**) (972 mg, 3.28 mmol). A stream of ozone was bubbled through the solution at −78°C. Ozone treatment was terminated when the mixtures assumed a blue color. A stream of nitrogen was used to remove excess ozone. Et_3N (0.60 mL, 4.24 mmol) was added to the solution at −78°C. The reaction was warmed slowly to room temperature and stirred for 12 h. The reaction mixture was concentrated and chromatographed on a silica gel column to give compound **24** (421 mg) as a colorless oil in 87% yield.[15] R_f=0.19 (Hexane/EtOAc=10:1). The spectral data is identical to that reported in the literature.[16] ^1H NMR ($CDCl_3$, 400 MHz) δ 2.53–2.55 (m, 2H), 2.62–2.65 (m, 1H), 3.43–3.57 (m, 4H), 4.48 (s, 4H), 7.25–7.36 (m, 10H), 9.77 (t, 1H, J=1.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 43.9, 70.6, 73.1, 127.5, 127.6, 128.4, 138.1, 201.9; IR (KBr) 3032, 2857, 2718, 1724, 1452, 1365 cm^{-1}.

4.1.30. 4-Benzyloxy-3-benzyloxymethylbutanoic acid (25). The oxidation is carried out by titrating a stirred solution of aldehyde **24** (811 mg, 2.72 mmol) in 15 mL of acetone at 0°C with Jones reagent[17] until the brown color persist. The excess Jones reagent was quenched with 2-propanol. The reaction mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, concentrated and chromatographed on a silica gel column to give the desired product **25** (778 mg) in 91% yield. R_f=0.40 (Hexane/EtOAc=2:1). ^1H NMR ($CDCl_3$, 400 MHz) δ 2.50–2.57 (m, 3H), 3.48–3.58 (m, 4H), 4.50 (s, 4H), 7.21–7.47 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.7, 36.2, 70.2, 73.0, 127.5, 128.3, 138.2, 178.9; IR (KBr) 3022, 2857, 1710, 1452 cm^{-1}; MS *m/z* (relative intensity): 315 (M^++1, 16), 298 (11), 199 (48), 131 (100), 91 (57).

4.1.31. 4-Benzyloxymethyldihydrofuran-2-one (27). A mixture of compound **25** (500 mg, 1.59 mmol) and oxalyl chloride (0.42 mL, 0.61 g, 4.77 mmol) in 3 mL of THF was stirred at room temperature for 2 h. The reaction mixture was concentrated and chromatographed by silica gel column chromatography to give compound **27** in 80% yield as a colorless oil. Its polarity is identical to the starting material **25**. R_f=0.40 (Hexane/EtOAc=2:1). Its spectral data is identical to that reported in the literature.[18] ^1H NMR ($CDCl_3$, 200 MHz) δ 2.37 (dd, J=17.6 and 6.4 Hz, 1H), 2.61 (dd, J=17.6, 8.8 Hz, 1H), 2.77–2.91 (m, 1H), 3.41–3.51 (m, 2H), 4.18 (dd, J=9.4 and 5.4 Hz, 1H), 4.40 (dd, J=9.4 and 7.4 Hz, 1H), 4.52 (s, 2H), 7.26–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 31.0, 35.3, 70.3, 70.7, 73.2, 127.5, 127.8, 128.4, 137.5, 176.7; IR (KBr) 3022, 2847, 1774, 1456, 1369, 1175 cm^{-1}.

4.1.32. 1,3,5-Trioxane[3]:(4-oxa-3-oxo-heptylidene):2-oxa-1-phenylpropane (28). To a stirring solution of triol **10b** (91 mg, 0.36 mmol), 3,5-dibenzyloxybenzoic acid (**25**) (392 mg, 1.25 mmol) and Ph_3P (327 mg, 1.25 mmol) in 5 mL of THF, a solution of 40% of DEAD in THF was added dropwise until the yellow color persisted. The reaction was then stirred at room temperature for 24 h. The reaction mixture was concentrated and the crude products were separated by silica gel column chromatography to give the desired product **28** (397 mg) in 25% yield. R_f=0.71 (Hexane:EtOAc=2:1); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.70–1.78 (m, 9H), 2.45–2.52 (m, 12H), 3.48–3.57 (m, 12H), 4.01–4.08 (m, 6H), 4.49 (s, 12H), 4.84 (s, 3H), 7.26–7.36 (m, 30H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.7, 30.8, 33.9, 36.5, 63.9, 70.5, 73.1, 100.7, 127.5, 128.3, 138.5, 172.8; IR (KBr) 3031, 1733, 1457, 1365 cm^{-1}; MS *m/z* (relative intensity): 1152 (M^+, 10), 475 (100), 475 (100), 405 (38); HRMS Calcd for $C_{69}H_{84}O_{15}$: 1152.5896; found: 1152.5818.

Acknowledgements

We are grateful to the National Science Council and National Chung Cheng University, Republic of China for financial support.

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