Synthesis of 1,3,5–Trioxanes: Catalytic Cyclotrimerization of Aldehydes

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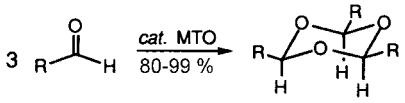
Abstract: A series of 1,3,5-trioxanes derived from a single aldehyde, or from two aldehydes, were synthesized with methylrhenium trioxide as a catalyst. Cyclotrimerization of the aldehydes gave excellent yields under proper conditions, as did diethyl ketomalonate. A possible intermediate in the case of propionaldehyde was observed using ^{1}H NMR spectroscopy. Water inhibits both forward and reverse reactions.

Key words: methylrhenium trioxide (MTO), 1,3,5-trioxane, catalytic cyclotrimerization

Practical applications abound for 1,3,5-trioxanes[1] in different fields: as constituents of a stabilizing solution in color photography, as burning regulators in fumigants for potato tuber sprouting inhibition and as the basis for many polymers and co-polymers reported in the patent literature.[2,3] Relatively few reports have dealt with the trimerization of aldehydes to form 1,3,5-trioxanes, limited to the following: acetaldehyde, propionaldehyde, isobutyraldehyde, isovaleraldehyde, and 4-*tert*-butylbenzaldehyde.[1,4–6] The reported methods require pretreatment of the catalyst,[1] the use of a catalyst insoluble in the nonpolar solvent,[6] or result in a reaction that gives rise to several byproducts.[4–6] Here we report a new method, based on the catalyst methylrhenium trioxide ($MeReO_3$, abbreviated as MTO), that does not suffer from these limitations.We have undertaken research to describe the synthesis of 1,3,5-trioxanes from a series of aldehydes and from one keto ester (Scheme 1).



Scheme 1 **1-19** **20-38**

The 1,3,5-trioxanes were prepared by the catalytic cyclotrimerization of aldehydes (Scheme 1). Acetaldehyde, propionaldehyde, and diethyl ketomalonate were used neat or as solutions in chloroform or benzene; the other aldehydes were used as neat liquids. Nearly all of the aldehydes gave high yields of the trimeric product, although the yields were lower for large R groups. No other products were observed: dimers, tetramers, and aldol condensation products were absent. The data for the 1,3,5-trioxanes are summarized in Table 1. No difference in the reaction time or the product yield was observed for purified butyraldehyde as compared to the commercial material. Diethyl ketomalonate is the only non-aldehyde carbonyl compound found that undergoes this reaction, although many others were tried; it provides a 1,3,5-trioxane with six substituents at the 2, 4 and 6-positions.

Scheme 1 shows the R groups of the trioxanes in equatorial positions,[7] the more thermodynamically stable isomer.[8] An MM2 calculation on 1,3,5-trioxanes was performed using the CAChe system with a conjugate gradient optimization method. Each optimized structure found the R groups of the trioxanes were preferred in equatorial positions. The NMR spectra of the isolated products support the all-equatorial configuration. A single-crystal X-ray determination was carried out to confirm this point, and also to show definitively that a trimer was formed. The ORTEP diagram is displayed in the Figure. The structure is characterized by bond distances and angles that are all within the normal ranges; for example: d(O–C1) = 142.1 pm, d(C1–C2) = 150.6 pm, d(C2–C3) = 149.6 pm, ∠(C2–C1–O1) = 109.4°, ∠(C3–C2–C1) = 113.1°, and ∠(O1–C1–O1b) = 109.5°.

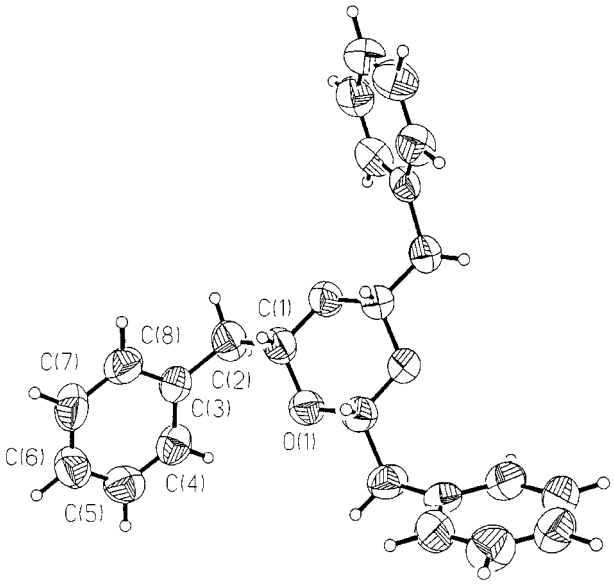
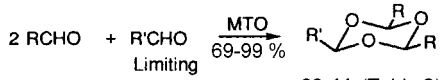


Figure: ORTEP Diagram for the 1,3,5-Trioxane Prepared from Phenylacetaldehyde (**12**), Showing the All-Equatorial Stereochemistry

Mixed 1,3,5-trioxanes can be obtained from one aldehyde taken in limiting amount, the other as the solvent, with a catalytic concentration of MTO (Scheme 2). As shown in Table 2, the mixed trioxanes contain one R group from the limiting compound, two from the other.



Scheme 2 **39-44** (Table 2)

Although a good yield of the 1,3,5-trioxane was obtained from $PhCH_2CHO$, no reaction was found for Ph_2CHCHO or PhCH(Me)CHO. The introduction of a bulky or electron-withdrawing substituent at the α-position of the aldehyde inhibited the reaction. No trioxane or other product was obtained from PhCHO, $BrCH_2CHO$, CH_2ClCHO, CBr_3CHO, CCl_3CHO, or RCH=CHCHO (R = H, alkyl, aryl), 2-ethylhexanal. It was suggested[16] that the failure of

Table 1. 1,3,5-Trioxanes **20–38** obtained from the Trimerization of Aldehydes **1–19**[b]

Aldehyde (RCHO)	Reaction Conditions		Product	Yield[b]
	Time (d)	Temp (°C)		(%)
MeCHO (**1**)	1	r.t.	**20**	> 99
EtCHO (**2**)	1	r.t.	**21**	> 99
PrCHO (**3**)	1	r.t.	**22**	> 98
BuCHO (**4**)	2	< –10	**23**	> 99
$C_5H_{11}CHO$ (**5**)	2	< –10	**24**	> 92
$C_6H_{13}CHO$ (**6**)	2	< –10	**25**	> 95
$C_7H_{15}CHO$ (**7**)	3	< –30	**26**	> 95
$C_8H_{17}CHO$ (**8**)	4	< –30	**27**	90
c-$C_6H_{11}CHO$ (**9**)	1	r.t.	**28**	87
i-PrCHO (**10**)	1	r.t.	**29**	> 88
(*E*)-$Me(CH_2)_4CH=CH(CH_2)_2CHO$ (**11**)	4	< –10	**30**	> 92
$PhCH_2CHO$ (**12**)	4	< –30	**31**	82
$PhCH_2CH_2CHO$ (**13**)	5	< –30	**32**	80
$MeCH(Me)CH_2CHO$ (**14**)	3	< –30	**33**	85
$MeCH_2CH(Me)CHO$ (**15**)	4	< –30	**34**	90
$MeCH_2CH_2CH(Me)CHO$ (**16**)	6	< –50	**35**	90
t-BuCHO (**17**)	3	r.t.	**36**	82
$CH_2=CH(CH_2)_8CHO$ (**18**)	3	< 0	**37**	90
EtO_2CCOCO_2Et (**19**)	2	r.t.	**38**	84

[a] Analytical and spectroscopical data are given in the experimental section.
[h] A specified yield of < 100% implies that some starting material remained and was separated. A yield designated with the symbol > implies some trioxane was detected in the filtrate.

certain compounds to react, CCl_3CHO for example, might derive from an inhibiting amount of water present in a hydroscopic compound. It seems to us that two other effects are more likely in operation: (1) the electron-attracting α-substituents significantly reduce the electron density on the carbonyl oxygen, reducing the extent of its coordination to rhenium; and, (2) three large substituents such as the chlorine atoms pose a barrier to coordination to MTO.

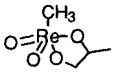
The catalytic role of MTO was analysed by ^{18}O tracer studies. In one experiment, propionaldehyde was treated with well above the usual catalytic level of ^{18}O-labeled MTO. The isolated 1,3,5-trioxane was studied by high resolution MS. In addition to the parent peak with a mass of 174.2399, the product showed a peak at 176.2404. That compares well with 176.2399 calculated for the product containing one ^{18}O. This result also suggests that only one oxygen in 1,3,5-trioxane is derived from the ^{18}O-label of MTO and further supports the catalytic role assigned to MTO.

This experiment is not without its difficulties, however, in that a number of peaks were detected. If the parent peak is set at 100%, then no other peak rises above 5%. This allows us to report that no molecule with two ^{18}O's rises much above background level.

For several of the aldehydes it proved feasible to observe but not to isolate an intermediate. In the ^1H NMR spectra, these species had spectra similar to that of related, independently characterized bis(alkoxy)rhenium compounds,[9] prepared from an epoxide and MTO. The methyl group labeled as being attached to rhenium has a chemical shift

Table 3. Comparison of the ^1H NMR spectra [$CDCl_3$/TMS, δ, J (Hz)] of the Rhenium Intermediates from Propylene Oxide and Propionaldehyde

From MTO+Propylene Oxide[a]	From MTO+Propionaldehyde[b]
2.48 (s, 3H, Re-**CH_3**), 1.43 (d, 3H, J=6), 4.55 (dd, 1H, J=6.6, 9.3), 5.08 (dd, 1H, J=5.4, 9.3), 5.29 (m, 1H)	2.37 (s, 3H, Re-**CH_3**), 0.93 (t, 3H, J=7.2), 1.91 (m, 2H), 5.08 (t, 1H, J=5.1)

[a] 

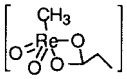
[b] 

Table 4. Effect of Water on the Formation of the 1,3,5-Trioxane **23** from Butyraldehyde[a]

Mol % of H_2O to Aldehyde	Yield[b] (%)
0	> 99
1	79
5	46
10	~ 1
20	0

[a] In the neat aldehyde, after 2 d with 1 mol% MTO at r.t.
[h] Measurement of the yield is simply carried out by taking the ^1H NMR spectrum of the reaction mixture in $CDCl_3$.

Table 2. Mixed 1,3,5-Trioxanes **39–44** Prepared by the Trimerization of 2 Different Aldehydes

Aldehydes		Reaction Conditions		Product	Yield[a] (%)
R′CHO (limiting)	RCHO (excess)	Time (d)	Temp (°C)		
c-$C_6H_{11}CHO$ (**9**)	MeCHO (**1**)	2	r.t.	**39**	> 99
c-$C_6H_{11}CHO$ (**9**)	$MeCH_2CH(Me)CHO$ (**15**)	1	< 0	**40**	85
c-$C_6H_{11}CHO$ (**9**)	$MeCH(Me)CH_2CHO$ (**14**)	1	< 0	**41**	87
c-$C_6H_{11}CHO$ (**9**)	$PhCH_2CHO$ (**12**)	2	< 0	**42**	69
MeCHO (**1**)	*c*-$C_6H_{11}CHO$ (**9**)	2	r.t.	**43**	87
PhCHO (**45**)	PrCHO (3)	6	< –50	**44**	–[b]

[a] Isolated yield after 100% conversion of limiting aldehyde.
[b] The product **44** was detected by ^1H NMR spectroscopy at < –25°C, which reverts to the starting aldehydes within 30 min in $CHCl_3$ in the presence of 1 mol% MTO at ≥ –25°C.

downfield to the one attached to carbon, as expected. A comparison to the intermediate formed from propionaldehyde is shown in Table 3.

Water inhibits the rate of formation of the 1,3,5-trioxane and reduces its yield. The variation of the product yields with water concentration is given in Table 4. At ≥ 20 mol% H_2O relative to aldehyde, no trioxane was formed. On the other hand, addition of MTO to the trioxane catalyzed the reverse reaction quite slowly: in chloroform, tribenzyl-1,3,5-trioxane with 5 mol% MTO yielded 50% phenyl acetaldehyde in 10 days. When 5 mol% water was added, however, no decomposition of the trioxane was noted within 10 days. Since the entropy change for forming the trioxane is clearly unfavorable, these observations taken together suggest that the reaction depicted in Scheme 1 represents a negative standard Gibbs energy arising from the enthalpic contributions.

In conclusion, it can be stated that some of the trimerization reactions of aldehydes are inefficient: bulky substituents and electron-withdrawing substituents inhibit the reaction. In the course of these reactions an intermediate was observed; a four-membered ring species may reasonably be an intermediate. Although there is certainly a stage in the reaction at which two aldehydes have been coupled, it is not likely that an independent 1,3-dioxetane exists, at least at an easily detected concentration, in that it appears to be unstable with respect to the parent aldehyde and the trioxane.[10] More plausibly, each aldehyde in succession interacts with MTO, building the product within the coordination sphere of the rhenium. The concentration of the intermediate is comparable to that of MTO, but much lower than that of the aldehyde; we thus infer that the intermediate is a rhenium-containing species, an assignment supported by the ^{1}H spectrum. This may also explain why benzaldehyde itself yields a cross-linked trimer when benzaldehyde was used as limiting with respect to propionaldehyde.

The aldehydes, diethyl ketomalonate, and solvents are commercially available. They were purified by shaking with $NaHCO_3$ for ca. 1 h to remove the carboxylic acid, and then dried with anhyd $CaSO_4$. The pure aldehyde was obtained by distillation, or, if necessary, by distillation at reduced pressure under argon.[11] MTO was either prepared from Rh^2O_7 and $SnMe_4$[12] or purchased.

^{18}O-Labeled MTO was prepared under argon as follows: MTO was dissolved in anhyd MeCN, then > 4 × mole ratio of H_2 ^{18}O was added. The solvents were removed under vacuum after 30 min. Then ^{18}O-labeled MTO was sublimed under vacuum at about 40 °C.

HRMS were performed on a Kratos MS 50 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained at 300 MHz in $CDCl_3$ solution unless otherwise noted; chemical shifts are relative either to internal TMS (^{1}H NMR) or to the solvent resonance (^{13}C NMR). GC/MS was performed on Magnum GC/MS from Finnegan with temperature programming: 60 °C, 2 min; 10 °C/min to 260 °C; 260 °C for 20 min. CAChe calculations were performed on a Power Macintosh 8500/120. IR spectra were recorded neat using 3M disposable IR cards, Type 61. The melting points of all products which were recrystallized from $CHCl_3$ were recorded on a Fisher Digital Melting Point Analyzer Model 355. Separations by HPLC were performed with a Waters 501 HPLC system equipped with an Econosil C18 column. The yields reported are isolated yields unless otherwise noted.

Fully Symmetric 1,3,5-Trioxanes; General Procedure:
The appropriate neat aldehyde **1–19** (5 mL) was allowed to stand with 1% MTO for 1–5 d at r.t., the reaction progress being monitored intermittently by GC/MS. Products were isolated by vacuum distillation or often by simple filtration in those cases where the reaction mixture solidifies on standing. In the latter cases, the solid was filtered under vacuum to remove the last few drops of aldehyde, and then rinsed with ice-cold water to remove the MTO (Table 1). The products were identified by their mass spectra and by comparison of their ^{1}H and ^{13}C NMR spectra with the values reported in the literature.[1,4–6,13–15]

2,4,6-Trimethyl-1,3,5-trioxane **(20)**:[5] This compound was prepared by two methods: by reacting the aldehyde **1** (5 mL) with MTO in chloroform (20 mL) or as neat at r.t. for 1 d. The product was isolated by vacuum distillation.
^{1}H NMR: δ = 1.38 (d, J = 5.1 Hz, 9 H), 5.04 (q, J = 5.1 Hz, 3 H).
^{13}C NMR: δ = 20.61, 98.47.
IR (neat): ν = 1166 (s), 1104 (s), 1055 cm^{-1} (s) (C–O–C).

2,4,6-Triethyl-1,3,5-trioxane **(21)**:[5] Prepared in the same manner as above from **2** (5 mL) and MTO in $CHCl_3$ (20 mL) or as neat at r.t. for 1 d. The product was isolated by vacuum distillation.
^{1}H NMR: δ = 0.95 (t, J = 7.5 Hz, 9 H), 1.70 (m, 6 H), 4.79 (t, J = 5.1 Hz, 3 H).
^{13}C NMR: δ = 7.82, 27.53, 102.40.
IR (neat): ν = 1171 (s), 1099 cm^{-1} (s) (C–O–C).

2,4,6-Tripropyl-1,3,5-trioxane **(22)**: Obtained by reacting the neat **3** with MTO at r.t. for 1 d. The product was isolated by vacuum distillation.
^{1}H NMR: δ = 0.93 (t, J = 5.4 Hz, 9 H), 1.42 (m, 6 H), 2.25 (m, 6 H), 4.86 (t, J = 5.1 Hz, 3 H).
^{13}C NMR: δ = 13.91, 16.96, 36.51, 101.49
IR (neat): ν = 1156 (s), 1104 (s), 1064 cm^{-1} (s) (C–O–C).
Anal. Found: C, 66.71; H, 11.13. $C_{12}H_{24}O_3$ requires: C, 66.63; H, 11. 18.

2,4,6-Tributyl-1,3,5-trioxane **(23)**: This compound was prepared by reacting the neat **4** and MTO at < –10 °C for 2 d. The product was isolated by filtration at < –10 °C; mp 5–6 °C.
^{1}H NMR: δ = 0.90 (t, J = 7.8 Hz, 9 H), 1.36 (m, 12 H), 1.67 (m, 6 H), 4.84 (t, J = 5. 1 Hz, 3 H).
^{13}C NMR: δ = 13.89, 22.42, 25.65, 34.11, 101.64.
IR (neat): ν = 1162 (s), 1107 (s), 1074 cm^{-1} (s) (C–O–C).
Anal. Found: C, 69.64; H, 11.82. $C_{15}H_{30}O_3$ requires: C, 69.72; H, 11.70.

2,4,6-Tripentyl-1,3,5-trioxane **(24)**: From the neat aldehyde **5** and MTO at < –10 °C for 2 d. The product was isolated by filtration at < –10 °C; mp 9–10 °C.
^{1}H NMR: δ = 0.89 (t, J = 8.4 Hz, 9 H)), 1.38 (m, 18 H), 1.66 (m, 6 H), 4.84 (t, J = 5.1 Hz, 3 H).
^{13}C NMR: δ = 13.92, 22.47, 25.19, 31.53, 34.33, 101.63.
IR (neat): n = 1152 (s), 1109 (s), 1050 cm^{-1} (s) (C–O–C).
Anal. Found: C, 72.04; H, 11.94. $C_{18}H_{36}O_3$ requires: C, 71.95; H, 12.08.

2,4,6-Trihexyl-1,3,5-trioxane **(25):** From the neat aldehyde **6** and MTO at <–10 °C for 2 d. The product was isolated by filtration at <0 °C; mp 6–7 °C.
^{1}H NMR: δ = 0.88 (t, J = 5.4 Hz,9 H), 1.33 (m, 24 H), 1.66 (m, 6 H), 4.84 (t, J = 5.1 Hz, 3 H).
^{13}C NMR: δ = 14.02, 22.53, 23.49, 29.01, 31.68, 34.40, 101.65.
IR (neat): ν = 1150 (s), 1112 (s), 1052 cm^{-1} (s) (C–O–C).
Anal. Found: C, 73.64; H, 12.39. $C_{21}H_{42}O_3$ requires: C, 73.63; H, 12.35.

2,4,6-Triheptyl-1,3,5-trioxane **(26)**: From the neat aldehyde **7** and MTO at <–30 °C for 3 d.The product was isolated by filtration at r.t.; mp 36–37 °C.

^{1}H NMR: δ = 0.88 (t, J = 5.1 Hz, 9 H), 1.39 (m, 30 H), 1.65 (m, 6 H), 4.83 (t, J = 5. 1 Hz, 3 H).
^{13}C NMR: δ = 14.04, 22.62, 23.55, 29.15, 29.32, 31.75, 34.40, 101.7.
IR (neat): ν = 1148 (s), 1114 (s), 1061 cm^{-1} (s) (C–O–C).
Anal. Found: C, 75.02; H, 12.51. $C_{24}H_{48}O_3$ requires: C, 74.94; H, 12.58.

2,4,6-Trioctyl-1,3,5-trioxane **(27)**: From the neat aldehyde **8** and MTO at <–30 °C for 4 d. The product was isolated by filtration at r.t.; mp 63–64 °C.
^{1}H NMR: δ = 0.88 (t, J = 6.9 Hz, 9 H), 1.39 (m, 36 H), 1.68 (m, 6 H), 4.84 (t, J = 5.1 Hz, 3 H).
^{13}C NMR: δ = 14.06, 22.64, 23.54, 29.20, 29.36, 29.44, 31.85, 34.40, 101.67.
IR (neat): ν = 1147 (s), 1115 (s), 1071 cm^{-1} (m) (C–O–C).
Anal. Found: C, 76.10; H, 12.86. $C_{27}H_{54}O_3$ requires: C, 76.00; H, 12.75.

2,4,6-Tricyclohexyl-1,3,5-trioxane **(28)**: From the neat aldehyde **9** and MTO at r.t. for 1 d. The product was isolated by filtration at r.t.; mp 204–205 °C.
^{1}H NMR: δ = 0.99 (m, 6 H), 1.73 (m, 27 H), 4.47 (d, J = 6 Hz, 3 H).
^{13}C NMR: δ = 25.65, 26.46, 27.03, 41.95, 104.28.
IR (neat): ν = 1164 (s) 1127 (s), 1071 cm^{-1} (m) (C–O–C).
Anal. Found: C, 74.92; H, 10.70. $C_{21}H_{36}O_3$ requires: C, 74.95; H, 10.78.

2,4,6-Tri(isopropyl)-1,3,5-trioxane **(29)**:[1,4] From the neat aldehyde **10** and MTO at r.t. for 1 d. The product was isolated by filtration at r.t.; mp 59–60 °C (Lit.[4] mp 60 °C).
^{1}H NMR: δ = 0.93 (d, J = 6.9 Hz, 18 H), 1.85 (m, 3 H), 4.49 (d, J = 5.7 Hz, 3 H).
^{13}C NMR: δ = 16.68, 32.40, 104.75.
IR (neat): ν = 1161 (s), 1102 (s), 1048 cm^{-1} (m) (C–O–C).

2,4,6-Tri-[(E)-non-3-enyl]-1,3,5-trioxane **(30)**: From the neat aldehyde **11** and MTO at < –10 °C for 4 d. The product was isolated by filtration at r.t.; mp 19–20 °C.
^{1}H NMR: d = 0.88 (t, J = 6.6 Hz, 9 H), 1.23 (m, 18 H), 1.74 (m, 6 H), 1.96 (m, 6 H), 2.10 (m, 6 H), 5.40 (m, 6 H), 4.83 (t, J = 5.4 Hz, 3 H).
^{13}C NMR: d = 14.05, 22.51, 26.53, 29.20, 31.34, 32.49, 34.12, 101.00, 131.2, 128.8
IR (neat): ν = 1161 (s), 1140 (s), 1065 cm.$^{-1}$ (m) (C–O–C).
Anal. Found: C, 77.96; H, 11.76. $C_{30}H_{54}O_3$ requires: C, 77.87; H, 11.76.

2,4,6-Tribenzyl-1,3,5-trioxane **(31)**: From the neat aldehyde **12** and MTO at < –30 °C for 4 d. The product was isolated by filtration at <0 °C and washed with cold acetone; mp 151–152 °C.
^{1}H NMR: δ = 2.99 (d, J = 5.4 Hz, 6 H), 4.93 (t, J = 5.4 Hz, 3 H), 7.22 (m, 15 H).
^{13}C NMR: δ = 40.99, 101.68, 126.6, 128.12, 129.9, 135.49.
IR (neat): ν = 1126 (s), 1079 (s), 1055 cm^{-1} (s) (C–O–C).
Anal. Found: C, 79.92; H, 6.74. $C_{24}H_{24}O_3$ requires: C, 79.97; H, 6.71.
X-Ray Data: Summary of data collection, structure solution, and refinement details are listed in Table 5.

2,4,6-Tris(2-phenylethyl)-1,3,5-trioxane **(32)**: From the neat aldehyde **13** and MTO at < –30 °C for 5 d. H_2O was then added to the reaction mixture to deactivate MTO. After a further period of stirring, the product was filtered at r.t.
^{1}H NMR: δ = 2.03 (m, 6 H), 2.76 (m, 6 H), 4.81 (t, J = 5.4 Hz, 3 H), 7.21 (m, 15 H).
^{13}C NMR: δ = 29.56, 35.60, 100.59, 125.9, 128.38, 128.43, 141.29.
IR (neat): ν = 1195 (s), 1130 (s), 1062 (s), 1050 cm^{-1} (s) (C–O–C).
Anal. Found: C, 80.54; H, 7.61. $C_{27}H_{30}O_3$ requires: C, 80.56; H, 7.51.

2,4,6-Tris(2-methylpropyl)-1,3,5-trioxane **(33)**: From the neat aldehyde **14** and MTO at <–30 °C for 3 d. The product was isolated by filtration at < –30 °C; mp 11–12 °C.

Table 5. Summary of Data Collection, Structure Solution and Refinement Details for 2,4,6-Tribenzyl-1,3,5-trioxane (**31**)

Crystal Data		Data Acquisition		Structure Solution and Refinement	
Empirical formula	$C_{24}H_{24}O_3$	Diffractometer used	Siemens P4RA	System used	SHELXL-93 (Sheldrick, 1993)
Color, habit	clear, triangular chip	Radiation	CuKα (λ = 1.54178 Å)	Solution	direct
Crystal size (mm)	0.5 × 0.2 × 0.1	Temperature (K)	293 (2)	Refinement method	full-matrixleast-squares in F^2
Crystal System	Cubic	Monochromator	graphite	Absolute structure	0.10 (34)
Space Group	I43d	θ Range	5.40 to 56.59°	Extinction correction	0.00029 (5)
a, Å	20.064 (2)	Scan type	ω-scan	Extinction expression	$Fc^* = kFc\,[1 + 0.001 \times Fc^2\lambda^3/\sin(2\theta)]^{-1/4}$
b, Å	20.064 (2)	Standard reflections	3 measured every 97 reflections	Hydrogen atoms	riding
c, Å	20.064 (2)	Index ranges	$-18 \le h \le 15$	Weight scheme	$w = \text{calc } w = 1/[\sigma(Fo^2) + (0.0800P)^2 + 0.00]$ where $P = (Fo^2 + 2Fc^2)/3$
α, deg	90°		$-18 \le k \le 21$		
β, deg	90°		$-21 \le l \le 10$	Parameters refined	83
γ, deg	90°	Reflections collected	5810	Final R indices [I ≥ 25 (I)]	R1 = 0.0326, wR2 = 0.0741
V, Å^3	8077.0 (14)	Independent reflections	905 (R_{int} = 0.0746)	R indices (all data)	R1 = 0.0380, wR2 = 0.0766
Z	16	Observed reflections	790 ($I \ge 2\sigma$ (I))	GooF, observed and all data	1.043, 1.000
FW	360.43	Absorption correction	none applied	Largest and mean Δ/σ	0.000, 0.000
Density (calc.)	1.186 Mg/m^3			Largest differences peak, e/Å^{-3}	0.135
Absorption coefficient	0.611 mm^{-1}			Largest difference hole, e/Å^{-3}	–0.142
F (000)	3072				

^{1}H NMR: δ = 0.91 (d, J = 6.6 Hz, 18 H), 1.56 (dd, J = 5.7, 7.2 Hz, 6 H), 1.83 (m, 3 H), 4.92 (t, J = 5.7 Hz, 3 H).
^{13}C NMR: δ = 22.71, 22.46, 43.05, 100.68
IR (neat): ν = 1162 (s), 1115 (s), 1045 cm^{-1} (s) (C–O–C).
Anal. Found: C, 69.69; H, 11.71. $C_{15}H_{30}O_3$ requires: C, 69.72; H, 11.70.

2,4,6-Tri(isobutyl)-1,3,5-trioxane **(34)**:[1] From the neat aldehyde **15** and MTO at <–30 °C for 4 d. The product was isolated by filtration at <–30°C; mp 6–7 °C.
^{1}H NMR: δ = 0.90 (m, 9 H), 1.21 (m, 15 H), 1.63 (m, 3 H), 4.60 (d, J = 4.8 Hz, 3 H).
^{13}C NMR: δ = 11.33, 13.33, 23.79, 38.88, 104.01.
IR (neat): ν = 1162 (s), 1115 (s), 1045 cm^{-1} (s) (C–O–C).

2,4,6-Tri(isopentyl)-1,3,5-trioxane **(35)**: From the neat aldehyde **16** and MTO at < –50 °C for 6 d. The product was isolated by filtration at < –50 °C; mp –7 to –9 °C.
^{1}H NMR: δ = 0.89 (m, 9 H), 1.38 (m, 21 H), 1.72 (m, 3 H), 4.58 (d, J = 4.8 Hz, 3 H).
^{13}C NMR: δ = 14.20, 19.90, 33.20, 36.97, 104.03.
IR (neat): ν = 1180 (s), 1104 (s), 1062 cm^{-1} (s) (C–O–C).
Anal. Found: C, 71.86; H, 12.27. $C_{18}H_{36}O_3$ requires: C, 71.95 ; H, 12.07.

2,4,6-Tri(tert-butyl)-1,3,5-trioxane **(36)**: From the neat aldehyde **17** and MTO at r.t. for 3 d. The product was isolated by filtration at r.t.; mp 66–67 °C.
^{1}H NMR: δ = 0.91 (s, 27 H), 4.36 (s, 3 H).
^{13}C NMR: δ = 24.21, 35.32, 105.41.
IR (neat): ν = 1210 (s), 1116 (s), 1060 cm^{-1} (s) (C–O–C).
Anal. Found: C, 69.68; H, 11.74. $C_{15}H_{30}O_3$ requires: C, 69.72; H, 11.70.

2,4,6-Tri(8-decenyl)-1,3,5-trioxane **(37)**: From the neat aldehyde **18** and MTO at <0 °C for 3 d. The product was isolated by filtration at < 0 °C; mp 47–48 °C.
^{1}H NMR: δ = 1.33 (m, 36 H), 1.65 (m, 6 H), 2.02 (m, 6 H), 4.83 (t, J = 5.1 Hz, 3 H), 4.94 (m, 6 H), 5.81(m, 3 H).
^{13}C NMR: δ = 23.49, 28.87, 29.05, 29.30, 29.33, 29.38, 33.76, 34.36, 101.62, 114.07, 139.11.
IR (neat): ν = 1124 (s), 1062 (s), 993 cm^{-1} (s) (C–O–C).
Anal. Found: C, 78.48; H, 12.09. $C_{33}H_{60}O_3$ requires: C, 78.51; H, 11.98.

2,2,4,4,6,6-Hexa(ethoxycarbonyl)-1,3,5-trioxane **(38)**: From the neat diethyl ketomalonate (**19**) and MTO or in solution in $CHCl_3$ or benzene at r.t. for 2 d. The product was isolated by preparative HPLC with MeCN as eluent at 4 mL/min. The product decomposes slowly even at –70°C, however, it gave acceptable elemental analyses; bp 166 °C/60 Torr (dec).
^{1}H NMR: δ = 1.32 (t, J = 7.2 Hz, 18 H), 4.34 (q, J = 7.2Hz, 12 H).
^{13}C NMR: δ = 14.08, 63.72, 90.20, 168.58.
Anal. Found: C, 48.25; H, 5.84. $C_{21}H_{30}O_{15}$ requires: C, 48.28; H, 5.78.

Mixed 1,3,5-Trioxanes 39–44; General Procedure:
The appropriate limiting aldehyde (16 mmol) and the aldehyde in excess were mixed in a 1:5 ratio; MTO (1%) was then added and the solution allowed to stand for 1–6 d at the specified temperature, the reaction progress being monitored intermittently by GC/MS (Table 2). Along with the mixed trioxane, the excess aldehyde used was converted to its fully-symmetric trioxane. The products were isolated by filtration when the mixed trioxane is a solid and the fully-symmetric one a liquid at the temperature used; if not, they were separated by preparative HPLC.

2-Cyclohexyl-4,6-dimethyl-1,3,5-trioxane **(39)**: From the limiting aldehyde **9** and the excess aldehyde **1**.The reaction was carried out for 2 d at r.t. and the product was isolated by filtration; mp 46–47 °C.
^{1}H NMR: δ = 1.06 (m, 2 H), 1.37 (d, J = 3.9 Hz, 6 H), 1.64 (m, 9 H), 4.57 (d, J = 4.2 Hz, 1 H), 5.00 (q, J = 3.9 Hz, 2 H).
^{13}C NMR: δ = 20.55, 25.60, 26.32, 26.96, 41.70, 98.46, 104.39.
IR(neat): ν = 1176 (s), 1156 (s), 1105 (s), 1051 cm^{-1} (s) (C–O–C).
Anal. Found: C, 66.04; H, 10.06. $C_{11}H_{20}O_3$ requires: C, 65.97; H, 10.06.

2-Cyclohexyl-4,6-di(isobutyl)-1,3,5-trioxane **(40)**: From the limiting aldehyde **9** and the excess aldehyde **15**. The reaction required 1 d at <0 °C for the complete conversion of **9**. The product was isolated by filtration at <0 °C; mp 79–80 °C.
^{1}H NMR: δ = 0.78 (m, 12 H), 1.06 (m, 6 H), 1.47 (m, 11 H), 4.37 (d, J = 4.8 Hz, 2 H), 4.48 (d, J = 4.2 Hz, 1 H).
^{3}C NMR: δ = 11.53, 13.55, 24.00, 25.88, 26.68, 27.21, 39.08, 42.06, 99.12, 104.29.
IR(neat): ν = 1168 (s), 1126 (s), 1096 (s), 1080 cm^{-1} (s) (C–O–C).
Anal. Found: C, 71.69; H, 11.54. $C_{17}H_{32}O_3$ requires: C, 71.78; H, 11.34.

2-Cyclohexyl-4,6-bis(3-methylbutyl)-1,3,5-trioxane **(41)**: The reaction of the limiting aldehyde **9** and the excess aldehyde **14** required 1 d at <0 °C for the complete conversion of **9**. The product was isolated by filtration at <0 °C; mp 49–50 °C.
^{1}H NMR: δ = 0.90 (d, 12 H), 1.15–1.83 (m, 21 H), 4.47 (t, J = 4.8 Hz, 2 H), 4.89 (d, J = 4.2 Hz, 1 H).
^{13}C NMR: δ = 12.63, 15.76, 22.85, 23.63, 25.73, 26.54, 27.11, 41.86, 100.81, 104.56.
IR (neat): ν = 1183 (s), 1162 (s), 1001 (s), 1069 cm^{-1} (s) (C–O–C).
Anal. Found: C, 72.02; H, 11.66. $C_{19}H_{36}O_3$ requires: C, 73.02; H, 11.61.

2-Cyclohexyl-4,6-bis(2-phenylethyl)-1,3,5-trioxane **(42)**: The reaction of the limiting aldehyde **9** and the excess aldehyde **12** required 2 d at <0°C for the complete conversion of **9**. The reaction mixture was poured into H_2O containing a little base to decompose MTO. After continued stirring for 30 min, the solution was extracted with Et_2O. The Et_2O layer was dried (Na_2SO_4) and the solvent evaporated. The product was isolated by preparative HPLC with MeCN as eluent at a rate of 4mL/min; mp 112–113 °C.
^{1}H NMR: δ = 1.01–2.89 (m, 19 H), 4.49 (d, J = 4.2 Hz, 1 H), 4.81 (t, J = 3.9 Hz, 2 H).
^{13}C NMR: δ = 25.08, 26.52, 27.11, 29.67, 35.69, 45.34, 100.64, 104.56, 125.98, 128.37, 128.69, 141.39.
IR (neat): ν = 1179 (s), 1148 (s), 1106 (s), 1038 cm^{-1} (s) (C–O–C).
Anal. Found: C, 78.82; H, 8.54. $C_{25}H_{32}O_3$ requires: C, 78.91; H, 8.47.

*2,4-Dicyclohexyl-6-methyl-1,3,5-trioxane***(43)**: The reaction of the limiting aldehyde **1** and the excess aldehyde **9** required 1 d at r.t. for the complete conversion of **1**. The product was isolated by preparative HPLC with MeCN as eluent at a rate of 4mL/min; mp 106–107°C.
^{1}H NMR: δ = 1.03 (m, 4 H), 1.38 (d, J = 3.9 Hz, 3 H), 1.66 (m, 18 H), 4.54 (d, J = 4.2 Hz, 2 H), 5.00 (q, J = 3.9 Hz, 1 H).
^{13}C NMR: δ = 20.45, 25.37, 26.12, 26.76, 41.70, 98.76, 104.48.
IR (neat): ν = 1181 (s), 1161 (s), 1106 (s), 1049 cm^{-1} (s) (C–O–C).
Anal. Found: C, 71.51; H, 10.66. $C_{11}H_{20}O_3$ requires: C, 71.60; H, 10.51.

2,4-Dipropyl-6-phenyl-1,3,5-trioxane **(44)**: The reaction of the limiting aldehyde **45** and the excess aldehyde **3** required 6 d at <–50°C for the complete conversion of **45.** The product could not be isolated and was only observed by NMR spectroscopy. All of the trioxane reverted to the aldehyde within 30 min at ≥25 °C.
^{1}H NMR: δ = 0.95 (t, J = 3 H), 1.57 (m, 4 H), 5.12 (t, J = 5.4 Hz, 1 H), 5.85 (s, 1 H).
^{13}C NMR: δ = 213.94, 17.83, 37.34, 100.51, 104.5, 126.02, 128.2, 129.06, 135.82.

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