119. The Synthesis of 1,2,4-Trioxan-5-ones

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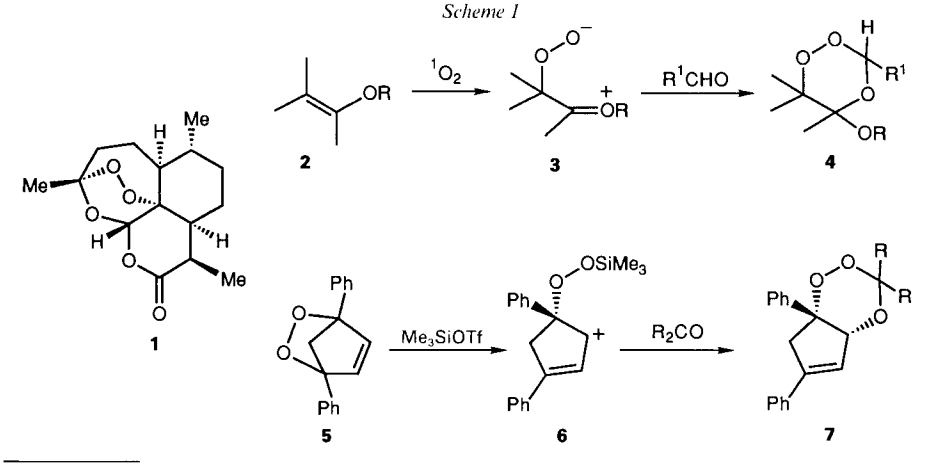
Several 3,6-substituted 1,2,4-trioxan-5-ones have been prepared in good yield by condensing aldehydes and ketones with trimethylsilyl α-[(trimethylsilyl)peroxy]alkanoates in the presence of trimethylsilyl trifluoromethanesulfonate as catalyst.

Introduction. – Interest in 1,2,4-trioxanes has been greatly stimulated by the fact that one of the few members of this class found so far in nature, artemisinine (**1**), possesses potent anti-malarial activity [1] [2]. Although sundry examples of 1,2,4-trioxanes of both monocyclic and bridged bicyclic types have been reported [3][1]), few methods of general applicability were available for their synthesis. We recently discovered that zwitterionic peroxides **3** generated by the photo-oxygenation of certain enol ethers **2** are readily captured by aldehydes (R^1CHO) to give 1,2,4-trioxanes **4** [5] (*Scheme 1*). Subsequently, this mechanistic principle has been developed into a preparative procedure. Easily accessible compounds such as 3,6-dihydro-1,2-dioxines, 1,2-dioxetanes, and allylic hydroperoxides, on acid catalysis, generate more reactive equivalents of **3** which condense with aldehydes and ketones to furnish a wide variety of 1,2,4-trioxanes in high yield [6]. Typically, the endoperoxide **5** in the presence of trimethylsilyl trifluoromethanesulfonate

Scheme 1

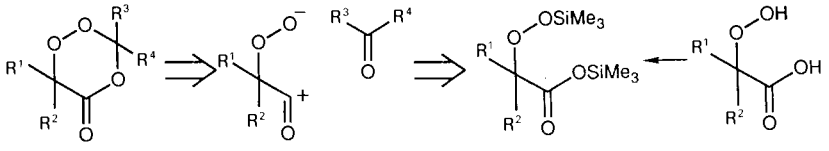


[1]) Besides the preparations cited in [3], certain cycloadditions with O_2 have furnished the 1,2,4-trioxane ring system, see *e.g.* [4].

(Me_3SiOTf) condenses with ketones (R_2CO) to give the *cis*-fused 1,2,4-trioxane **7**, presumably through the intermediacy of the allylic trimethylsilylperoxy cation **6** (*Scheme 1*). We now describe how the same mechanistic principle can be exploited for the simple and efficient synthesis of 1,2,4-trioxan-5-ones **8**, which are virtually unknown as chemical entities [7].

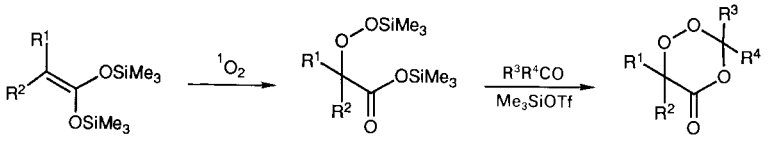
The logical disconnections reveal that the synthon required for **8** is the zwitterionic peroxide **9** (*Scheme 2*). An appropriate reagent for **9** is the trimethylsilyl α-[(trimethylsilyl)peroxy]alkanoate **10**, rather than the parent acid **11**, which is unreactive for electronic reasons. We report that such esters **10**, when allowed to react with aldehydes and ketones in the presence of Me_3SiOTf as catalyst [8], readily afford the corresponding 1,2,4-trioxan-5-ones **8**[2]).

Scheme 2



Results and Discussion. – Three representative esters were chosen, the α-(*tert*-butyl)-, α-(adamant-1-yl)-, and α,α-(pentamethylene)-substituted derivatives **10a–c** of trimethylsilyl α-[(trimethylsilyl)peroxy]acetate. Esters **10a, b** were conveniently prepared by the photo-oxygenation of the corresponding bis(trimethylsilyloxy)ketene acetals **12a, b** [10] (*Scheme 3*). However, this method was impractical when aromatic or primary and

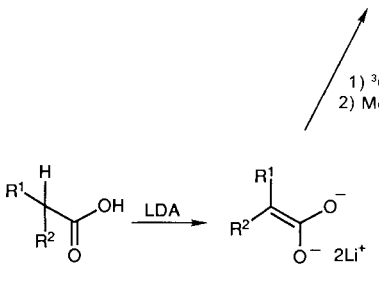
Scheme 3



12a R^1 = H, R^1 = *t*-Bu
b R^1 = H, R^2 = adamant-1-yl

10a R^1 = H, R^2 = *t*-Bu
b R^1 = H, R^2 = adamant-1-yl
c R^1–R^2 = $(CH_2)_5$

8a R^1 = H, R^2 = *t*-Bu, R^3–R^4 = 'spiro-adamantane'
b R^1 = H, R^2 = *t*-Bu, R^3–R^4 = $(CH_2)_5$
c R^1 = H, R^2 = *t*-Bu, R^3 = R^4 = Me
d R^1 = H, R^2 = *t*-Bu, R^3,R^4 = H,Me and Me,H
e R^1 = H, R^2 = *t*-Bu, R^3,R^4 = H,Ph or Ph,H (*trans*)
f R^1 = H, R^2 = *t*-Bu, R^3,R^4 = H,*t*-Bu and *t*-Bu,H
g R^1 = H, R^2 = adamant-1-yl, R^3–R^4 = 'spiro-adamantane'
h R^1 = H, R^2 = adamant-1-yl, R^3–R^4 = $(CH_2)_5$
i R^1 = H, R^2 = adamant-1-yl, R^3 = R^4 = Me
j R^1 = H, R^2 = adamant-1-yl, R^3,R^4 = H,Me and Me,H
k R^1 = H, R^2 = adamant-1-yl, R^3,R^4 = H,Ph and Ph,H
l R^1 = H, R^2 = adamant-1-yl, R^3,R^4 = H,*t*-Bu or *t*-Bu,H (*trans*)
m R^1–R^2 = $(CH_2)_5$, R^3–R^4 = 'spiro-adamantane'
n R^1–R^2 = $(CH_2)_5$, R^3–R^4 = $(CH_2)_5$
o R^1–R^2 = $(CH_2)_5$, R^3 = R^4 = Me
p R^1–R^2 = $(CH_2)_5$, R^3,R^4 = H,Me and Me,H
q R^1–R^2 = $(CH_2)_5$, R^3,R^4 = H,Ph and Ph,H
r R^1–R^2 = $(CH_2)_5$, R^3,R^4 = H,4-ClC_6H_4 and 4-ClC_6H_4,H
s R^1–R^2 = $(CH_2)_5$, R^3,R^4 = Me,COOEt and COOEt,Me



13 R^1–R^2 = $(CH_2)_5$ **14** R^1–R^2 = $(CH_2)_5$

[2]) For preliminary publication, see [9].

secondary alkyl substituents were present owing to competing [4 + 2] cycloadditions or ene-type reactions. Consequently, the cyclohexanecarboxylate **10c** was prepared by generating the dianion **14** of cyclohexanecarboxylic acid (**13**) at −78° and allowing it to react *in situ* with triplet oxygen [11] [12] (*Scheme 3*). Subsequent quenching of the resulting transient α-peroxide carboxylate with trimethylsilyl chloride gave **10c**.

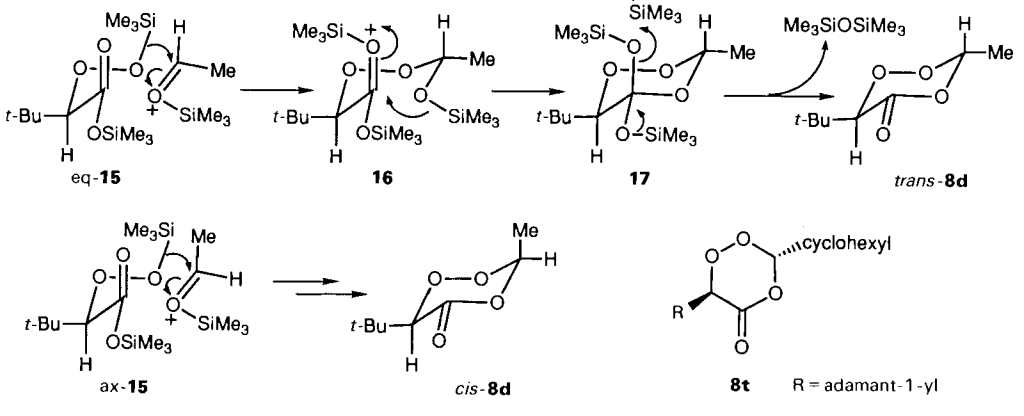
Each ester **10a–c** was allowed to react with typical aldehydes and ketones R^3R^4CO, namely acetaldehyde, benzaldehyde, pivalaldehyde, acetone, cyclohexanone, and adamantan-2-one, for several h in CH_2Cl_2 solution in the presence of a catalytic amount of Me_3SiOTf [7] (*Scheme 3*). The resulting products were the 1,2,4-trioxan-5-ones **8a–q** which were obtained in good yields.

It has been remarked elsewhere that only aldehydes, and not ketones, are captured in their uncatalyzed reactions with zwitterionic peroxides [5]. In the present instance, trioxanones are formed from both aldehydes and ketones, with somewhat less selectivity being exhibited by the former. The cyclic ketones were the most efficiently incorporated into the new ring, as attested by the high yields of **8a,b**, **8g,h** and **8m,n** (81–93%). Acetone performed well in forming the 3,3-dimethyl-1,2,4-trioxan-5-ones **8c**, **8i**, and **8o** (45–78%). Acetaldehyde afforded moderate amounts of the 3-methyl-1,2,4-trioxan-5-ones **8d**, **8j**, **8p** (57–61%). When the aldehyde was bulky, incorporation was less efficient; thus, with pivalaldehyde, trioxanones **8f** and **8l** were both obtained in 42% yield. Similarly, benzaldehyde condensed less efficiently as revealed by the modest yields (25–46%) achieved for the 3-phenyl derivatives **8e**, **8k**, and **8q**. It was also found that the cyclohexanecarboxylate **10c** reacted, albeit somewhat poorly, with 4-chlorobenzaldehyde and ethyl pyruvate, producing the trioxanones **8r** and **8s** in yields of 37 and 43%, respectively.

Trial experiments revealed that certain other carbonyl partners, contrary to expectation, did not give trioxanones. For example, 4-nitrobenzaldehyde was unreactive towards **10a**; β-butyrolactone and dimethylformamide gave no isolable products with **10b**.

Catalysis was essential for reaction. No condensation occurred in the absence of Me_3SiOTf or even when Bu_4NF was used instead. How the catalyst operates is open to conjecture. A possibility is that the carbonyl partner and the ester function are successively activated by the Me_3Si cation. *E.g.*, a molecule of acetaldehyde can adopt two limiting orientations with respect to the *t*-Bu ester **10a**. In the chair-like arrangement

Scheme 4



where the *t*-Bu substituent preempts an equatorial position, the Me substituent can take up an equatorial or an axial orientation (see eq- and ax-**15**, resp., in *Scheme 4*). Silylation of the aldehydic function in eq-**15** permits the creation of the peroxide–C bond (eq-**15**→**16**). Transfer of the trimethylsilyl cation from the peroxy group to the ester carbonyl function enables the aldehydic O-atom to close the ring, so producing the trimethylsilyl acetal **17**. Finally, loss of a molecule of bis(trimethylsilyl) ether by silylation and desilylation of **17** gives the *trans*-epimer of **8d**. Similar steps operate for the axial arrangement ax-**15** and lead to the *cis*-epimer of **8d**.

According to this mechanism, pairs of *cis*- and *trans*-epimers are expected for trioxanones **8d**, **e**, **f** and **8j**, **k**, **l** and were, in fact, observed except for **8e** and **8l**. However, discrimination between the axial and equatorial transition states is not accurately reflected by the supposed bulk of the aldehyde partner. In one instance (**8k**), the Ph substituent seems to enjoy both transition states to the same degree, whereas in others (**8e** and **8l**), the *cis*-isomer does not form. If the *cis*/*trans* ratio is taken as a guide, it appears that acetaldehyde and pivalaldehyde encounter similar steric environments in the transition state leading to trioxanones **8d** and **8f**. These inconsistent ratios could also be due to some epimerization.

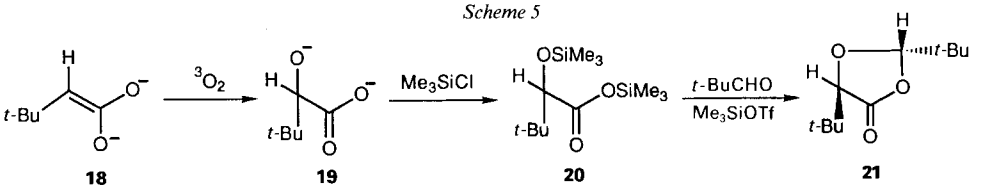
Although separable by chromatography, it was difficult to distinguish between epimers. Furthermore, for obvious reasons, proof of structure for the trioxanone entity could not be secured from the NMR spectra alone. Fortunately, several of the trioxanones were crystalline, which permitted X-ray analysis. Examination of a crystal of the doubly spirocyclic cyclohexane product **8n** established the constitution of the oxacyclic ring [13]. Similarly, identification of the *cis*- and *trans*-isomers of 6-(adamant-1-yl)-3-phenyl-1,2,4-trioxan-5-one (**8k**) was achieved by X-ray analysis [13] of *cis*-**8k** and a sample of *trans*-6-(adamant-1-yl)-3-cyclohexyl-1,2,4-trioxan-5-one (**8t**; *Scheme 4*) which was prepared from **10b** and cyclohexanecarboxaldehyde for this purpose. Consequently, the configurations of the other *cis*- and *trans*-isomers could be assigned by ^{1}H-NMR on the basis of the chemical shifts of H–C(3) and H–C(6).

In general, the *trans*-isomers invariably displayed the resonances of H–C(3) and H–C(6) downfield from those of the *cis*-isomers. However, because of the magnetic anisotropy of the carbonyl group, H–C(6) showed the greatest differentiation in chemical shift and, therefore, constitutes a reliable index of configuration within a series. Regardless of the nature of the substituents at C(3) and C(6), the shift for H–C(6) was never greater than 4.25 ppm for the *cis*-isomer and never less than 4.44 ppm for the *trans*-isomer. Similar trends have been observed for the structurally related 2,5-substituted 1,3-dioxolan-4-ones [14].

The six-membered trioxanone ring was also easily recognized by the characteristic absorption band of the carbonyl group in the IR spectrum (compounds bearing aliphatic substituents: 1750–1755 cm^{-1}; compounds with aromatic or ester groups at C(3): 1760–1765 cm^{-1}) which are unmistakably different from those exhibited by the 1,3-dioxolan-4-ones (1800–1820 cm^{-1}) [14].

All 1,2,4-trioxan-5-ones proved surprisingly stable to heat. Apart from the ease of their preparation, often as crystalline solids, they survived heating in boiling toluene for several h. Contrary to previous suggestions, there was no evidence that the trioxanone ring was inherently prone to spontaneous fragmentation [15] [16].

Scheme 5



18 **19** **20** **21**

On one occasion it was noticed that an attempted preparation of 3,6-di(*tert*-butyl)-1,2,4-trioxan-5-one (**8f**) from the dianion **18** of 3,3-dimethylbutanoic acid (rather than from **12a**, see above) gave instead the corresponding *trans*-1,3-dioxolan-4-one **21** (see *Scheme 5*). This discrepancy was a consequence of the conditions used for the oxygenation of the dianion **18**: Owing to a lack of temperature control, disproportionation had evidently occurred to the anion **19** of 2-hydroxy-3,3-dimethylbutanoic acid which, on silylation, gave the trimethylsilyloxy-substituted trimethylsilyl ester **20**. Condensation of **20** with pivalaldehyde accounts for **21**. In fact, this sequence anticipated [9] similar procedures which were used for the synthesis of 1,3-dioxolan-4-ones [17] [18] and 1,3-dioxan-4-ones [19] [29]. In a future paper our own results will be fully reported [21].

Conclusion. – We have shown that 1,2,4-trioxan-5-ones can be easily prepared as stable entities from alkanoic acids. All 1,2,4-trioxan-5-ones described here were tested *in vitro* against *Plasmodium falciparum*. Despite the presence of the 1,2,4-trioxane ring, none displayed significant activity[3]). Further experiments on the chemical reactivity and potential of trioxanones as a class are under way. It has already been shown elsewhere that when a H-atom at C(6) is available, decomposition can be triggered by base so providing a new procedure for preparing α-keto acids [22].

We thank the *Swiss National Science Foundation* for supporting this research (grant No. 20–27966.89).

Experimental Part

General. HPLC: *LiChrosorb-Si-60* 10-mm column: *Waters-M-45* instrument equipped with a *R401* differential refractometer and a *Hewlett-Packard-3380S* integrator. M.p. and b.p.: uncorrected. IR spectra (in cm^{-1}): *Perkin-Elmer-681* spectrophotometer. ^{1}H-NMR spectra: *Varian-XL-200* or *Bruker-WH-360* and *-400* instruments using $CDCl_3$ as solvent; chemical shifts (δ) in ppm with reference to tetramethylsilane (TMS), *J* in Hz. MS: *Varian SM-1* spectrometer. Elemental analyses were performed by Dr. *E. Eder*, Service de Microchimie, Institut de Chimie Pharmaceutique, University of Geneva.

Trimethylsilyl 3,3-Dimethyl-2-[(trimethylsilyl)peroxy]butyrate (**10a**) *and Trimethylsilyl 2-(Tricyclo-[3.3.1.1^{3,7}]dec-1-yl)-2-[(trimethylsilyl)peroxy]acetate* (**10b**) were prepared by photo-oxygenation of the bis-(trimethylsilyl) acetals **12a** and **12b** of *tert*-butyl and tricyclo[3.3.1.1^{3,7}]dec-1-yl ketene, resp. [10].

Trimethylsilyl 1-[(Trimethylsilyl)peroxy]cylohexane-1-carboxylate (**10c**) [11] [12]. BuLi (1.65M in hexane, 79 mmol) was added at 22° under Ar to a soln. of (i-Pr)$_2$NH (7.98 g, 78 mmol) in dry tetrahydrofuran (THF, 80 ml). The mixture was stirred for 20 min and then cooled to −20° whereupon a soln. of cyclohexane-carboxylic acid (5 g, 39 mmol) in dry THF (20 ml) was added by syringe. The soln. was allowed to warm to 22° and then heated at 50° for 3 h. After cooling to 0°, the solvent and (i-Pr)$_2$NH were evaporated to yield a colorless solid which was dissolved in THF (100 ml). A portion (20 ml) was added dropwise by syringe over 3 h to dry THF (40 ml), saturated with O_2 at −78° (flame-dried flask). The soln. was stirred a further 30 min, while a stream of O_2 was passed through the soln. The atmosphere in the flask was then replaced by Ar. Me_3SiCl (2 g, 18.4 mmol) was added at −78° and the mixture allowed to warm to 22°. The solvent was evaporated, pentane (30 ml), added, and the mixture filtered. The solvent was again evaporated to yield a yellow liquid (1.38 g, 64%) which was used immediately since it decomposed

[3]) We thank Dr. *W. Milhous* and his coworkers at the Division of Experimental Therapeutics, *Walter Reed Army Institute of Research*, Washington, D.C., for performing the antimalarial tests.

rapidly. An attempt to distill the product led only to violent decomposition. IR (CCl_4): 2930, 2850, 1720, 1445, 1285, 1250, 1215, 1155, 1060, 845. ^{1}H-NMR (CCl_4): 0.3 (*s*, 9 H); 0.45 (*s*, 9 H); 1.4–2.2 (*m*, 10 H).

1,2,4-Trioxan-5-ones: General Procedure. A soln. of the trimethylsilyl α-([trimethylsilyl)peroxy]alkanoate **10** (1.35 mmol) in dry CH_2Cl_2 (1 ml) was injected by syringe under N_2 into a flame-dried 10-ml flask and cooled to −78°. Then, the carbonyl compound (1.34 mmol) and trimethylsilyl trifluoromethanesulfonate (30 µl, 0.165 mmol) were added. The mixture was stirred at the temp. and periods of time indicated below. Dry pyridine (200 µl) was added to quench the reaction. The mixture was allowed to warm to 22° and then extracted with Et_2O/hexane 1:1 (15 ml). The extracts were washed (H_2O), dried (K_2CO_3), filtered, and evaporated. The crude product so obtained was purified as indicated. Chromatography was performed on a silica-gel column in all cases. Yields are based on the carbonyl partner.

*6′-(*tert*-Butyl)spiro[tricyclo[3.3.1.1^{3,7}]decane-2,3′-1′,2′,4′-trioxan]-5′-one* (**8a**). Ester **10a** was allowed to react with tricyclo[3.3.1.1^{3,7}]decan-2-one at −40° for 4 h. Chromatography at −20° (Et_2O), yield 81%. Further purified by recrystallization (pentane/AcOEt 10:1) at −78°. Colorless crystals. M.p. 40–42°. IR (CCl_4): 2960, 1755, 1235, 1070, 1030. ^{1}H-NMR: 1.13 (*s*, 9 H); 1.5–2.5 (*m*, 14 H); 4.41 (*s*, 1 H). MS: no M^+, 150 (100). Anal. calc. for $C_{16}H_{24}O_4$: C 68.55, H 8.63; found: C 68.53, H 8.46.

*6′-(*tert*-Butyl)spiro[cyclohexane-1,3′-1′,2′,4′-trioxan]-5′-one* (**8b**). Ester **10a** was allowed to react with cyclohexanone at −20° for 4 h. Chromatography (Et_2O) gave **14b** as a colorless oil, yield 90%. IR (CCl_4): 2940, 1755, 1450, 1365, 1295, 1225, 1050, 985. ^{1}H-NMR: 1.10 (*s*, 9 H); 1.30–2.10 (*m*, 10 H); 4.35 (*s*, 1 H). MS: no M^+ 45 (100). Anal. calc. for $C_{12}H_{20}O_4$: C 63.14, H 8.83; found: C 63.05, H 8.87.

*6-(*tert*-Butyl)-3,3-dimethyl-1,2,4-trioxan-5-one* (**8c**). Ester **10a** was allowed to react with acetone at −30° for 18 h. Purification by bulb-to-bulb distillation at 25°/0.01 Torr gave a colorless oil, yield 45%. IR (CCl_4): 2960, 1755, 1260, 1125, 990. ^{1}H-NMR: 1.15 (*s*, 9 H); 1.60 (*s*, 3 H); 1.72 (*s*, 3 H); 4.43 (*s*, 1 H). MS: 57 (100), 86, 188 (M^+). Anal. calc. for $C_9H_{16}O_4$: C 57.43, H 8.57; found: C 57.18, H 8.33.

cis- *and* trans-*6-(*tert*-Butyl)-3-methyl-1,2,4-trioxan-5-one* (**8d**). Ester **10a** and acetaldehyde were allowed to react at −70° for 24 h. Flash chromatography (FC) [23] (5% AcOEt/hexane) gave a colorless oil, yield 81%. Separation by HPLC (5% AcOEt/hexane) gave two isomers in a ratio of 1:5.

cis-*Isomer* (minor): t_R 22 min. IR ($CDCl_3$) 2960, 1750, 1235, 1080. ^{1}H-NMR: 1.09 (*s*, 9 H); 1.44 (*d*, J = 5.6, 3 H); 4.22 (*s*, 1 H); 5.95 (*q*, J = 5.6, 1 H).

trans-*Isomer* (major): t_R 18.85 min. ^{1}H-NMR: 1.05 (*s*, 9 H); 1.41 (*d*, J = 5.2, 3 H); 4.54 (*s*, 1 H); 6.06 (*q*, J = 5.2, 1 H). IR ($CDCl_3$): 2960, 1760, 1480, 1385, 1230, 1080. MS: no M^+, 41 (100), 44, 57. Anal. calc. for $C_8H_{14}O_4$: C 55.16, H 8.10; found: C 54.92, H 8.30.

trans-*6-(*tert*-Butyl)-3-phenyl-1,2,4-trioxan-5-one* (**8e**). The reaction of **10a** and benzaldehyde was carried out at −80° overnight. Purification by column chromatography (CH_2Cl_2), yield 25%. Colorless crystals. M.p. 50–51°. IR (CCl_4): 2960, 1765, 1455, 1340, 1210, 1020, 690. ^{1}H-NMR: 1.11 (*s*, 9 H); 4.67 (*s*, 1 H); 6.84 (*s*, 1 H); 7.39 (*s*, 5 H). MS: 104 (100), 204 ([M − 32]$^+$), 236 (M^+). Anal. calc. for $C_{13}H_{16}O_4$: C 66.09, H 6.82; found: C 66.31, H 7.03.

cis- *and* trans-*3,6-di(*tert*-Butyl)-1,2,4-trioxan-5-one* (**8f**). The reaction of **10a** and pivalaldehyde was performed at −78° for 24 h. FC gave a colorless oil, yield 42%. Separation by HPLC (5% AcOEt/hexane) gave two isomers, ratio 1:4.

cis-*Isomer* (minor): t_R 15.37 min. IR ($CDCl_3$): 2980, 1750, 1470, 1380, 1100, 1040. ^{1}H-NMR: 0.94 (*s*, 9 H); 1.08 (*s*, 9 H); 4.12 (*s*, 1 H); 5.49 (*s*, 1 H).

trans-*Isomer* (major): t_R 11.33 min. IR ($CDCl_3$): 2980, 1755, 1470, 1370, 1215, 1100. ^{1}H-NMR: 0.93 (*s*, 9 H); 1.05 (*s*, 9 H); 4.52 (*s*, 1 H); 5.57 (*s*, 1 H). Anal. calc. for $C_{11}H_{20}O_4$: C 61.09, H 9.32; found: C 60.72, H 9.13.

6′-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)spiro[tricyclo[3.3.1.1^{3,7}]decane-2,3′-1′,2′,3′-trioxan]-5′-one (**8g**). Ester **10b** and tricyclo[3.3.1.1^{3,7}]decan-2-one reacted at −50° for 3 h. Purification by chromatography (Et_2O/pentane 1:1), yield 81%. Colorless crystals. M.p. 180°. IR (CCl_4): 2910, 1750, 1450, 1215, 1067, 1010. ^{1}H-NMR: 1.6–2.6 (*m*, 29 H); 4.27 (*s*, 1 H). MS: no M^+, 135 (100), 150. Anal. calc. for $C_{22}H_{30}O_4$: C 73.70, H 8.44; found: C 73,47, H 8.36.

6′-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)spiro[cyclohexane-1,3′-1′,2′,4′-trioxan]-5′-one (**8h**). Ester **10b** was reacted with cyclohexanone at −50° for 16 h. Purification by chromatography (pentane), yield 90%. Colorless crystals. M.p. 76–78°. IR (CCl_4): 2910, 1755, 1450, 1295, 1211, 1050, 905. ^{1}H-NMR: 1.2–2.15 (*m*, 25 H); 4.26 (*s*, 1 H). Anal. calc. for $C_{18}H_{26}O_4$: C 70.56, H 8.55; found: C 70.26, H 8.27.

3,3-Dimethyl-6-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1,2,4-trioxan-5-one (**8i**). Reaction of **10b** and acetone effected at −50° for 16 h. Purification by chromatography (Et_2O/hexane 1:4), yield 76%. Colorless oil. IR (CCl_4): 2910, 1755, 1455, 1265, 1130, 990. ^{1}H-NMR: 1.6 (*s*, 3 H); 1.7 (*s*, 3 H); 1.66–2.05 (*m*, 15 H); 4.27 (*s*, 1 H). MS: 135 (100), 266 (M^+). Anal. calc. for $C_{15}H_{22}O_4$: C 67.64, H 8.33; found: C 67.39, H 8.44.

cis- *and* trans-*3-Methyl-6-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1,2,4-trioxan-5-one* (**8j**). Reaction of **10b** and acetaldehyde at −40° for 18 h afforded the *cis*- and *trans*-isomers (3:7) as an oil, 57% yield. B.p. 130°/0.005 Torr. IR (CCl_4):

2910, 1755, 1450, 1210, 1180, 960. ^{1}H-NMR: 1.44, 1.48 (2*d*, *J* = 6, 3 H); 1.6–2.1 (*m*, 15 H); 4.10, 4.45 (2*s*, 1 H, *cis* and *trans*, resp.); 6.0, 6.1 (2*q*, *J* = 6, 1 H, *cis* and *trans*, resp.). MS: 135 (100), 252 (M^+). Anal. calc. for $C_{14}H_{20}O_4$: C 66.64, H 7.99; found: C 66.39, H 7.71.

cis- *and* trans-*3-Phenyl-6-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1,2,4-trioxan-5-one* (**8k**). Ester **10b** and benzaldehyde were allowed to react at −50° for 16 h. Initial partial purification was effected by chromatography (Et_2O/pentane 1:1). Repurification by chromatography (toluene/pentane 1:1) gave the *cis*- and *trans*-isomers 1:1, 46.5% yield. IR (CCl_4): 2905, 1765, 1455, 1210, 695. ^{1}H-NMR: 1.5–2.2 (*m*, 15 H); 4.24, 4.6 (2*s*, 1 H, *cis* and *trans*, resp.); 6.8, 6.9 (2*s*, 1 H, *cis* and *trans*, resp.); 7.44 (br. *s*, 5 H). MS: 135 (100), 314 (M^+). Anal. calc. for $C_{19}H_{22}O_4$: C 72.59, H 7.05; found: C 72.21, H 6.76.

Recrystallization (pentane) at −30°, passage over activated charcoal, FC (silica gel, $CHCl_3$), and further recrystallization (MeCN) gave the *cis*-isomer as colorless crystals. M.p. 98–102°. The structure of *cis*-**8k** was determined by X-ray [13].

trans-*3-(*tert*-Butyl)-6-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1,2,4-trioxan-5-one* (**8l**). Reaction of **10b** with pivalaldehyde at −50° for 16 h gave, after chromatography (CH_2Cl_2) and recrystallization (hexane), **8l** as colorless crystals, m.p. 128–129°, in 42% yield. IR (CCl_4): 2910, 1760, 1208, 1040, 1030, 1000. ^{1}H-NMR: 1.00 (*s*, 9 H); 1.5–2.1 (*m*, 15 H); 4.44 (*s*, 1 H); 5.61 (*s*, 1 H). MS: no M^+, 57, 79, 93, 135 (100). Anal. calc. for $C_{17}H_{26}O_4$: C 69.35, H 8.92; found: C 69.09, H 8.88.

Dispiro[cyclohexane-1,6′-1′,2′,4′-trioxane-3′,2″-tricyclo[3.3.1.1^{3,7}]decan]-5′-one (**8m**). Reaction of **10c** with tricyclo[3.3.1.1^{3,7}]decan-2-one at −40° for 16 h. Purification by chromatography (Et_2O/hexane 1:10), then recrystallization (hexane/Et_2O 5:2), yield 91%. Colorless crystals. M.p. 87–88°. IR (CCl_4): 2930, 2860, 1750, 1450, 1290, 1240, 1060, 1015. ^{1}H-NMR: 1.3–2.8 (*m*, 24 H). MS: no M^+, 150 (100), 260 ($[M-32]^+$). Anal. calc. for $C_{17}H_{24}O_4$: C 69.84, H 8.27; found: C 69.60, H 8.29.

7,8,16-Trioxadispiro[5.2.5.2]hexadecan-15-one (**8n**). Reaction of **10c** with cyclohexanone at −40° for 16 h. Purification by chromatography (Et_2O/hexane 1:10), yield 93%. Colorless crystals, m.p. 93–94°, by recrystallization (Et_2O/hexane 1:5). IR (CCl_4): 2930, 2850, 1755, 1440, 1295, 1060, 960. ^{1}H-NMR: 1.25–2.4 (*m*, 20 H). MS: no M^+, 55, 99 (100), 110, 208 ($[M-32]^+$). Anal. calc. for $C_{13}H_{20}O_4$: C 64.98, H 8.39; found: C 64.88, H 8.47. The structure was confirmed by X-ray [13].

3′,3′-Dimethylspiro[cyclohexane-1,6′-1′,2′,4′-trioxan]-5′-one (**8o**). Reaction of **10c** with acetone effected at −40° for 16 h. Purification by chromatography (Et_2O/hexane 1:4), yield 78%. Colorless crystals, m.p. 50–52°, by recrystallization (Et_2O/hexane 1:5). IR (CCl_4): 2940, 1750, 1290, 1250, 1165, 1050. ^{1}H-NMR: 1.54 (*s*, 3 H); 1.75 (*s*, 3 H); 1.2–2.4 (*m*, 10 H). MS: no M^+, 69, 98 (100), 110. Anal. calc. for $C_{10}H_{16}O_4$: C 59.98, H 8.06; found: C 60.17, H 8.34.

3′-Methylspiro[cyclohexane-1,6′-1′,2′,4′-trioxan]-5′-one (**8p**). Reaction of **10c** with acetaldehyde effected at −40° for 16 h. The oil so obtained was purified by distillation at 50°/0.01 Torr, yield 61%. IR (CCl_4): 2937, 1755, 1450, 1385, 1360, 1270, 1230, 1075, 945. ^{1}H-NMR: 1.48 (*d*, *J* = 6, 3 H); 1.30–2.30 (*m*, 10 H); 6.08 (*q*, *J* = 6, 1 H). MS: no M^+, 55, 98, 126 (100). Anal. calc. for $C_9H_{14}O_4$: C 58.05, H 7.58; found: C 57.94, H 7.42.

3′-Phenylspiro[cyclohexane-1,6′-1′,2′,4′-trioxan]-5′-one (**8q**). Reaction of **10c** with benzaldehyde effected at −40° for 16 h. Purification by chromatography (Et_2O/hexane 1:1) gave a colorless oil, yield 46%. Colorless crystals, m.p. 56–58°, by recrystallization (Et_2O/hexane 1:4). IR (CCl_4): 2940, 1760, 1450, 1340, 1270, 1225, 1020, 690. ^{1}H-NMR: 1.35–2.45 (*m*, 10 H); 6.90 (2*s*, 1 H); 7.50 (*m*, 5 H). MS: 98, 105 (100), 122, 189, 216 ($[M-32]^+$), 248 (M^+). Anal. calc. for $C_{14}H_{16}O_4$: C 67.72, H 6.50; found: C 67.81, H 6.45.

3′-(4-Chlorophenyl)spiro[cyclohexane-1,6′-1′,2′,4′-trioxan]-5-one (**8r**). Reaction of **10c** with 4-chlorobenzaldehyde effected at −40° for 16 h. Purification by chromatography (Et_2O/hexane 1:4), then recrystallization (Et_2O/hexane 1:10), yield 37%. Colorless crystals, m.p. 42–43°. IR (CCl_4): 2940, 1760, 1225, 1090, 1015. ^{1}H-NMR: 1.3–2.4 (*m*, 10 H); 6.9 (*s*, 1 H); 7.6 (*s*, 4 H). MS: 125, 139 (100), 159, 282, 284 (M^+). Anal. calc. for $C_{14}H_{15}ClO_4$: C 59.48, H 5.35, 12.54; found: C 59.67, H 5.55, Cl 12.80.

Ethyl 3′-Methyl-5′-oxospirocyclohexane-1,6′-1′,2′,4′-trioxan]-3′-carboxylate (**8s**). Reaction of **10c** with ethyl pyruvate was effect at −40°, then 3 days at −20°. Purification by chromatography (Et_2O/hexane 1:1), yield 43%. IR (CCl_4): 2940, 1765, 1450, 1445, 1270, 1240, 1145, 1115, 1040. ^{1}H-NMR: 1.38 (*t*, *J* = 7, 3 H); 1.6–1.9 (*m*, 8 H); 1.72 (*s*, 3 H); 2.1 (*m*, 1 H); 2.3 (*m*, 1 H); 4.35 (*m*, 2 H). MS: no M^+, 98, 157 (100). Anal. calc. for $C_{12}H_{18}O_6$: C 55.80, H 7.02; found: C 55.77, H 6.77.

trans-*3-Cyclohexyl-6-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1,2,4-trioxan-5-one* (**8t**). Reaction of **10b** with cyclohexanecarboxaldehyde at −50° for 2 h. Purification by chromatography (CH_2Cl_2), yield 28%. Recrystallization (MeCN) at 0° gave colorless crystals. M.p. 122°. IR (CCl_4): 2940, 1763, 1455, 1248, 1212, 1015. ^{1}H-NMR: 0.8–2.2 (*m*, 26 H); 4.44 (*s*, 1 H); 5.72 (*d*, *J* = 5, 1 H). MS: no M^+, 135 (100). Anal. calc. for $C_{19}H_{28}O_4$: C 71.22, H 8.81; found: C 71.00, H 8.89. The *trans*-configuration was determined by X-ray [13].

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