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CHEMISTRY OF 2,5-BIS(TRIMETHYLSILOXY)FURANS.[1] II: REACTIONS WITH CARBONYL COMPOUNDS AND THE SYNTHESIS OF 2,6-DIARYL-3,7-DIOXABICYCLO[3.3.0]OCTANE-4,8-DIONES

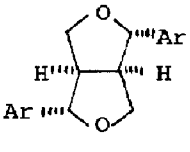
Peter Brownbridge and Tak-Hang Chan*

Department of Chemistry, McGill University,
Montreal, Quebec, Canada, H3A 2K6.

Abstract: 2,5-Bis(trimethylsiloxy)furan reacted with a number of substituted benzaldehydes under activation of titanium tetrachloride to give 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane-4,8-diones.

Natural lignans with the 2,6-diaryl-3,7-dioxabicyclo[3,3.0]octane structure are fairly well known. Fused bis-ethers[2] of type 1 were found as constituents in the Chinese drug[3] 'shin-i' and in a Nigerian bark extract.[4] Lactones of type 2 have been shown to be plant germination inhibitors.[5] Several bis-lactones of structure 3 have been isolated from a cultured mushroom, *Inonotus* sp. K-1410, and are reported to show interesting biological activities.[6]

Biogenetically, they are all derived from the coupling of two Ar-C_3 units. Recently, a number of syntheses of these compounds have been reported.[7,8] All have as the critical step the synthesis of the bis-lactones 3. The only method so far available for the synthesis of 3 involves the oxidative coupling of cinnamic acid derivatives with ferric chloride and oxygen[8] or with thallium trifluoroacetate (TTFA)[7]. However, even with the TTFA method, the yield of 3 was moderate.



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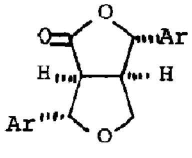

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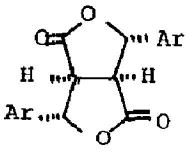

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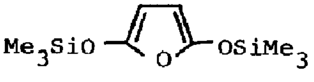

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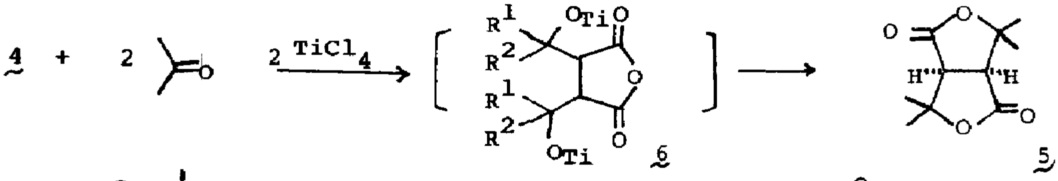
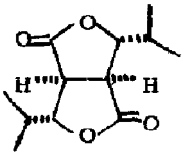
It seems to us that an alternative approach to 3 is to start from succinic acid or its equivalents. The ready preparation of 2,5-bis(trimethylsiloxy)furan (4)[1] from succinic anhydride allows us to examine the construction of 3 from the reaction of 4 with a number of carbonyl compounds.

We were pleased to find that 4 reacted with acetone under activation of titanium tetrachloride to give 5 directly in 72% yield.[9] Compound 5 has mp 104-5°; ν_{max} 1770 cm^{-1} (CH_3CN); ^1H nmr $\delta[(CD_3)_2CO]$ 1.51 (12 H,s) and 3.63 (2H,s). Presumably the initial reaction product is 6 ($R^1=R^2=Me$) which then undergoes lactonization under the reaction conditions to give 5.





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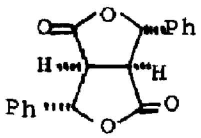

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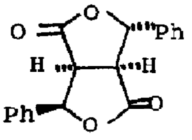

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A similar product was obtained in the reaction of 4 with i-butanal. The major product, mp 241-3°, ν_{max} 1776 cm^{-1} ($CHCl_3$), was assigned structure 7. Whilst the stereochemistry of 7 has not been rigorously ascertained, it is assumed to be the all-cis compound from the small H_A-H_B coupling constant (1.5 Hz) in the proton nmr. The all-cis structure is likely the thermodynamically most stable.

The reaction of 4 with benzaldehyde proceeds likewise[9] to give compound 8 (70%), mp 181-3°, ν_{max} 1780 cm^{-1} ($CHCl_3$), whose nmr also indicates the all-cis structure [δ 4.03 (2H,s,H_B), 5.87 (2H,s,H_A), 7.38 (10H,s,Ph) in $(CD_3)_2CO$]. We were surprised to find, however, that if one (rather than 2) mole of $TiCl_4$ was used to activate the reaction, only 12% of 8 was formed along with 58% of the trans-product 9. Compound 9, mp 178-180°, ν_{max} 1782 cm^{-1} ($CHCl_3$) was easily differentiated from 8 by its proton nmr spectrum, which shows different signals for all four aliphatic protons and two differentiated phenyl groups: $\delta[(CD_3)_2CO$ 3.94 (1H,dd,J 2.5, 10 Hz, H_B), 4.33 (1H,dd, J 8, 10 Hz, H_C), 5.80 (1H,d, J 2.5 Hz, H_A), 6.08 (1H,d, J 8 Jz, H_D), 7.39 (5H,s,Ph) and 7.44 (5H,s,Ph). There are two possible explanations for this behaviour: one is that different intermediat are formed depending on the amount of $TiCl_4$ present; alternatively the second mole of $TiCl_4$ might cause isomerization of 9 to the more stable 8 under the reaction conditions.[10]

We have also treated a number of other aromatic aldehydes with 4 and two equivalents of titanium tetrachloride;[9] the results are presented in the table. As expected, the rate of reaction decreases with increasing electron donation the aldehyde. This is in contrast to the oxidative routes to 10.[7,8]

The ready availability of these aldehydes and bis-siloxyfuran **4** make this reaction a competitive method for the synthesis of the bis-lactone lignans.

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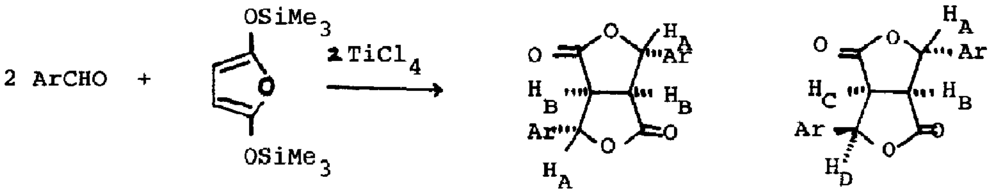

10 **11**

Ar		yield %	mp	ν_{max} (CHCl$_3$) cm^{-1}	^{1}H nmr (δ in CDCl$_3$) H_A	H_B	H_C	H_D
4-MeOC$_6$H$_4$	**10**	52	153.5-154^{a,k}	1775	5.85(s)	3.56(s)	-	-
	11	-^{b}						
3,4-(MeO)$_2$C$_6$H$_3$	**10**	57	208.5-209^c	1777	5.82(s)	3.63(s)	-	-
	11	-^{b}						
2,5-(MeO)$_2$C$_6$H$_3$	**10**	14^d	179-180	1778	5.83(s)	3.61(s)	-	-
	11	26^d	157-8	1780	5.72(d,*J* 2)	e	e	5.86(d, *J* 7.5)
2,3,4-(MeO)$_3$C$_6$H$_2$	**10**	36^f	138-9^{g,k}	1774^h	5.70(s)	3.70(s)	-	-
	11	29^f	146-7	1777^h	5.61(d,*J* 2.5)	e	e	5.83(d, *J* 8)
3,4,5-(MeO)$_3$C$_6$H$_2$	**10**	-^{b}						
(See note 11)	**11**	37	199.5-200	1786^i	5.72(d, *J* 2.5)^j	e	e	5.99(d, *J* 8)^j

[a] lit.[7] 128-130° [b] small amount (<10%) present in reaction mixture was not isolated [c] lit.[8] 207-8° [d] separated by fractional crystallization from acetone [e] obscured by the MeO-signals [f] separated by column chromatography on silica gel [g] lit.[7] 133-5° [h] film [i] in CH$_3$CN [j] in (CD$_3$)$_2$CO. [k] We have kindly been informed by Professor E.C. Taylor that in Table I of reference 7 compounds **1a** and **1b** were inadvertently interchanged, and that their compound **1e** has the same nmr spectrum as our **10** (Ar = 4-MeOC$_6$H$_4$).

References and Notes

1. Part VII of a series on the Chemistry of enol silyl ethers. For part VI see P. Brownbridge and T.H. Chan, preceeding communication.
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9. Typical experimental procedure: to a mixture of 1.66 g veratraldehyde and 1.3 g 2,5-bis(trimethylsiloxy)furan in 8 ml dry CH_2Cl_2 under nitrogen at -78°, 1.1 ml titanium tetrachloride was added with vigorous stirring. The dark red mixture was stirred at -78° for 3h then allowed to warm to 0°, poured into aqueous $KHCO_3$ and extracted with ether. The extracts were dried ($MgSO_4$), evaporated and the resulting solid (1.60 g) recrystallized from acetonitrile to give colourless needles of **10** [Ar = $3,4\text{-}(MeO)_2C_6H_3$] (1.17 g, 57%).
10. However, treatment of isolated **9** with excess $TiCl_4$ does not cause isomerization to **8**.
11. Reaction of **4** with 2 equiv. of $3,4,5\text{-}(MeO)_3C_6H_2CHO$ and 5 equiv. of $TiCl_4$ gives 12% of **11** [Ar = $3,4,5\text{-}(MeO)_3C_6H_2$] and 45% of the cis isomer **10** [Ar = $3,4,5\text{-}(MeO)_3C_6H_2$], mp 193-5° (lit.^{12} 195-6°), ν_{max} 1784 cm^{-1}, δ ($CDCl_3$) 3.57 (2H, s, H_B) and 5.86 (2H, s, H_A).
12. Y. Kumada, H. Naganawa, T. Takeuchi, H. Umezawa, K. Yamashita and K. Watanabe, J. Antibiotics, 31, 105 (1978).

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