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A new simple and convenient method for the synthesis of substituted 2,6,9-trioxabicyclo[3.3.1]-nona-3,7-dienes from arylmalondialdehydes

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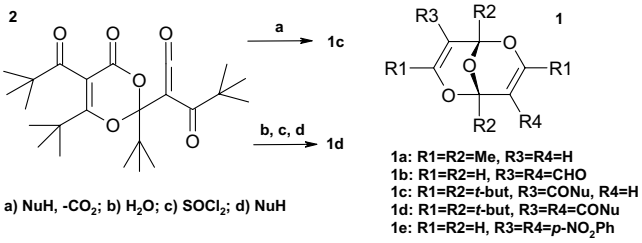
Abstract—A new convenient synthesis of substituted 2,6,9-trioxabicyclo[3.3.1]-nona-3,7-dienes is described. These new 'bridged bis-dioxines' were obtained in moderate to good yields by dimerization of the corresponding arylmalondialdehydes in the presence of 0.5 equiv of TMSOTf. The structure of the nitro derivative **1e** has been proven by X-ray crystallography. A mechanism for this reaction is proposed.

1. Introduction

Since host–guest molecular interactions have been recognised to be of fundamental importance in biological processes, the design and synthesis of novel host molecules have become an area of great interest for organic chemists. So far, many examples of synthetic ligands capable of the selective recognition of metal cations have been reported in the literature.[1] However, the synthesis of new molecular systems that exhibit improved complexation properties and especially selectively bind a given metal guest is warranted.

The uncommon 2,6,9-trioxabicyclo[3.3.1]-nona-3,7-dienes ring system ('bridged bis-dioxines') **1** (Scheme 1) has demonstrated a good ability to coordinate transition metals.[2] Recent work has shown that a series of compounds containing this bicyclic diene moiety exhibit strong complexation abilities towards various metal cations.[3] Within this framework, it seems worthwhile to explore new approaches to prepare such bridged bis-dioxines containing molecules. Indeed, surprisingly, synthetic methods leading to this diene system have received little attention and as a consequence only a few compounds possessing such a structure are currently known. To date,



Scheme 1.

except for the synthesis of the 1,3,5,7-tetramethyl derivative **1a** (R1 = R2 = Me, R3 = R4 = H)[2b,c,d] and the 4,8-dicarbaldehyde **1b** (R1 = R2 = H, R3 = R4 = CHO),[4] the elegant approach proposed by Kollenz and co-workers is the sole general synthetic method reported in the literature that has been used with success to prepare substituted trioxabicyclononadienes.[5] Thus, by addition of various nucleophiles to the stable α-oxoketene **2**, Kollenz and co-workers have synthesised functionalised bridged bis-dioxines of either type **1c** (R1 = R2 = *t*-But, R3 = CONu, R4 = H)[5a,b] or **1d** (R1 = R2 = *t*-But, R3 = R4 = CONu)[5c,d] employing the suitable one or three step strategy as depicted in Scheme 1.

We report here a novel one step procedure in order to synthesise new 2,6,9-trioxabicyclo[3.3.1]-nona-3,7-dienes ring systems from readily accessible arylmalondialdehydes.

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2. Results and discussion

In the course of our previous studies with the purpose to prepare glucuronylated anticancer prodrugs,[6] we have investigated the glycosylation of the well known 2-(4-nitrophenyl)malondialdehyde[7] **3a** (Scheme 2) in the presence of various Lewis acids. During most of these experiments, we were surprised to isolate the intriguing non-glycosylated side product **1e** (Scheme 1). Structure elucidation of this compound was initially based on the HRMS spectrum indicating the presence of a dimeric structure with the loss of 1 equiv of water. The ^{1}H and ^{13}C NMR analyses were also in good agreement with that of the structure proposed for **1e**. Indeed, apart from the signals corresponding to the aromatic protons, the ^{1}H NMR spectrum exhibited only two singlets at δ 6.08 and 7.35 ppm with an intensity of 1:1 which indicated straightforwardly the high symmetry of the molecule. The ^{13}C NMR spectrum exhibited no signal downfield from 147 ppm thus indicating the absence of any carbonyl group. However, the most important information was given by the signal at δ 88.3 ppm demonstrating the presence of a bis-oxygen bonded sp^3 tertiary carbon atom in accord with the bicyclic structure of **1e**. Finally, the confirmation of the proposed structure was obtained from an X-ray crystallographic analysis of **1e** (Fig. 1).[8]

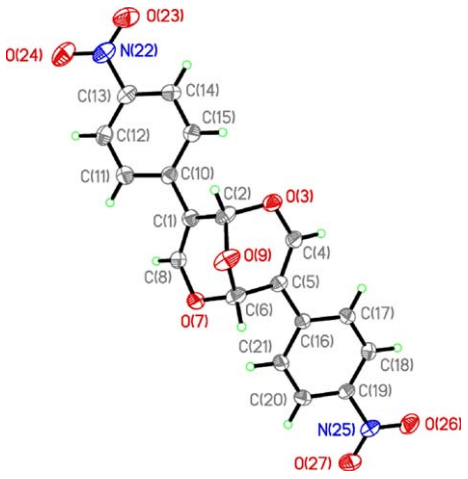


Figure 1. The molecular structure of **1e**.

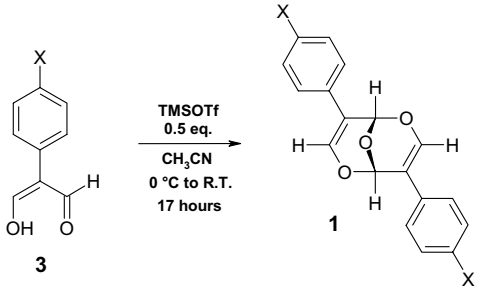
In the light of these results, we investigated the synthesis of **1e** starting from **3a** in the presence of various acid catalysts over a period of 17 h in acetonitrile. The formation of **1e** was observed using 0.5 equiv of $ZnCl_2$, $BF_3{\cdot}Et_2O$, CF_3SO_3H or TMSOTf (Table 1). All the other tested acids such as TFA, H_2SO_4, $TiCl_4$ or $SnCl_2$ were found to be inefficient to catalyse this reaction. The best result was obtained with the use of TMSOTf leading to the formation of **1e** in good yield after purification by flash column chromatography (84%, entry 4). We examined next the effect of various amounts of TMSOTf on the formation of **1e**. However, as illustrated in Table 1, every further attempt to optimise the yield of this reaction, using different amounts of the acid catalyst (entries 5–7) failed.

Table 1.

Entry	Acid catalyst	Equivalent	Yield of **1e** (%)
1	$BF_3{\cdot}Et_2O$	0.5	28
2	$ZnCl_2$	0.5	Traces
3	CF_3SO_3H	0.5	65
4	TMSOTf	0.5	84
5	TMSOTf	1	55
6	TMSOTf	0.3	61
7	TMSOTf	<0.3	—

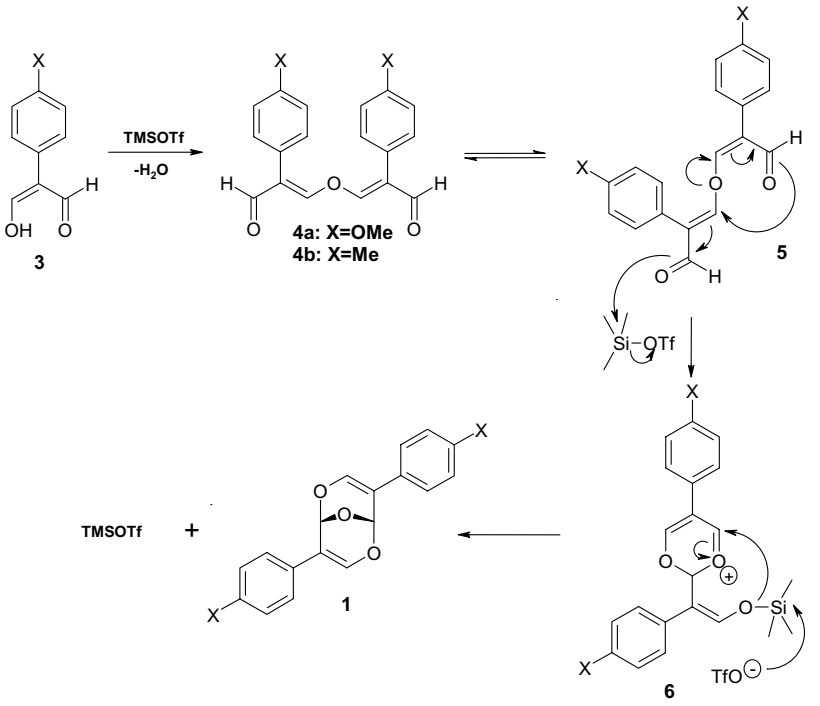
We have then applied the optimal conditions described above to the synthesis of the new 2,6,9-trioxabicyclo-[3.3.1]-nona-3,7-dienes containing molecules **1e**–**j**[9] using the corresponding arylmalondialdehydes **3a**–**f**[7] as the starting materials (Scheme 2). Except for the bridged bis-dioxine **1j** (X = H), all the expected bicyclic products were isolated in moderate to good yields after purification by flash column chromatography (42–84%). Since in each experiment, various amounts of the starting material were recovered after 17 h under these conditions, it should be noticed that an increased reaction time did not lead to higher yields but rather to the formation of unidentified degradation products.

In the course of the studies conducted with arylmalondialdehydes bearing electron-donating groups such as **3d** and **3e**, we were able to isolate compounds **4a** and **4b**,[10] respectively (Scheme 3). NOESY experiments allowed the determination of the *E* configuration of both double bonds. When placed in the presence of a catalytic amount of TMSOTf, intermediates **4a** and **4b**



3	X	1	yield of 1 (%)
3a	NO_2	**1e**	84
3b	Cl	**1f**	71
3c	F	**1g**	65
3d	OMe	**1h**	50
3e	CH_3	**1i**	42
3f	H	**1j**	traces

Scheme 2.



Scheme 3.

led to the formation of the corresponding trioxabicyclononadienes **1h** and **1i**. Such a finding allows to propose the reasonable reaction pathway described in Scheme 3 for the transformation of **3** to **1**. Thus, in the first step TMSOTf catalyses the dimerization of **3** concomitantly with the loss of one molecule of water to afford intermediate **4**. The latter must undergoe *E*–*Z* isomerisation of one double bond to allow subsequent cyclisation via intramolecular Michael addition leading to the oxonium ion **6** which is then trapped by the hydroxyl group to give the final product **1**. Since no intermediate **4** has been detected when using arylmalondialdehydes **3a**–**c** (X = NO_2, Cl and F) it may be postulated that the presence of electron-withdrawing para-substituents on the aromatic ring favoured the double bond isomerisation as well as the intramolecular Michael addition and consequently increased the rate of formation of the corresponding products **1e**–**g**. This may explain the higher yields obtained with arylmalondialdehydes **3a**–**c**.

3. General procedure for the preparation of substituted 2,6,9-trioxabicyclo[3.3.1]-nona-3,7-dienes

In a typical procedure, the arylmalonaldehyde **3** was placed in CH_3CN (0.2 mmol/mL) and the slurry cooled to 0 °C. TMSOTf (0.5 equiv) was then added dropwise and the stirred mixture was slowly allowed to reach room temperature. Stirring was continued at room temperature for 17 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and the aqueous layer was extracted 3 times with ethyl acetate. The combined organic extracts were washed twice with a saturated aqueous solution of $NaHCO_3$, dried ($MgSO_4$), evaporated and concentrated in vacuo. Purification by flash column chromatography afforded the corresponding substituted 2,6,9-trioxabicyclo[3.3.1]-nona-3,7-diene **1** (petroleum ether/ethyl acetate 8:2).

In summary, we have developed a simple method for the preparation of new substituted 2,6,9-trioxabicyclo[3.3.1]-nona-3,7-dienes starting from readily accessible para-substituted arylmalonaldehydes. The structure of these novel bridged bis-dioxines has been proven by the X-ray crystallographic analysis of the nitro derivative **1e**. Further studies are currently underway to extend the scope of this reaction to the synthesis of other trioxabicyclononadienes as well as to evaluate host–guest abilities of molecules containing such a structure.

Acknowledgement

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7. The starting arylmalondialdehydes **3a**–**f** were either commercially available (**3b**, **3e**) or prepared in two steps from the corresponding arylacetic acid (**3a**,[6b] **3c**,[6b] **3d**, **3f**) according to the method of Arnold: Arnold, Z. *Collect. Czech. Chem. Commun.* **1961**, *26*, 3051.
8. CCDC-607159 contains the supplementary crystallographic data for this letter. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
9. Compound **1e**: ^{1}H NMR ($CDCl_3$) δ (ppm): 6.08 (s, 1H) 7.35 (s, 1H) 7.45 (d, 2H, $J = 9.3$ Hz) 8.14 (d, 2H, $J = 9.3$ Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 88.3, 111.8, 124.4, 124.6, 140.5, 143.1, 146.6; HRMS (EI): calcd for $C_{18}H_{12}N_2O_7$($M^{+\cdot}$) 368.0645, found 368.0646.
   Compound **1f**: ^{1}H NMR ($CDCl_3$) δ (ppm): 5.93 (s, 1H) 7.00 (s, 1H) 7.18–7.24 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm): 88.6, 112.5, 126.0, 129.4, 133.0, 133.8, 140.6; HRMS (EI): calcd for $C_{18}H_{12}O_3Cl_2$ ($M^{+\cdot}$) 346.0163, found 346.0159.
   Compound **1g**: ^{1}H NMR ($CDCl_3$) δ (ppm): 5.99 (s, 1H) 7.00–7.06 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (ppm): 88.4, 112.3, 114.4, 126.4, 130.1, 139.7, 160.12; HRMS (EI): calcd for $C_{18}H_{12}O_3F_2$ ($M^{+\cdot}$) 314.0755, found 314.0755.
   Compound **1h**: ^{1}H NMR ($CDCl_3$) δ (ppm): 3.73 (s, 3H) 5.94 (s, 1H) 6.81 (d, 2H, $J = 8.4$ Hz) 6.91 (s, 1H) 7.21 (d, 2H, $J = 8.4$ Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 55.5, 88.9, 113.1, 114.4, 126.2, 127.1, 139.1, 158.9; HRMS (EI): calcd for $C_{20}H_{18}O_5$ ($M^{+\cdot}$) 338.1154, found 338.1149.
   Compound **1i**: ^{1}H NMR ($CDCl_3$) δ (ppm): 2.26 (s, 3H) 5.97 (s, 1H) 6.97 (s, 1H) 7.07 (d, 2H, $J = 8.3$ Hz) 7.17 (d, 2H, $J = 8.3$ Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 21.2, 88.8, 113.3, 124.8, 129.7, 131.7, 137.0, 139.8.
   Compound **1j**: ^{1}H NMR ($CDCl_3$) δ (ppm): 6.01 (s, 1H) 7.03 (s, 1H) 7.18 (ls, 1H) 7.29 (ls, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm): 88.8, 113.3, 124.9, 127.4, 128.2, 129.0, 129.3, 134.5, 140.3.
10. Compound **4a**: ^{1}H NMR ($CDCl_3$) δ (ppm): 3.75 (s, 3H) 6.80 (d, 2H, $J = 7.9$) 7.30–7.32 (m, 3H) 9.49 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 55.2, 113.5, 120.6, 126.1, 130.0, 159.6, 160.4, 190.1.
    Compound **4b**: ^{1}H NMR ($CDCl_3$) δ (ppm): 2.40 (s, 3H) 7.17 (d, 2H, $J = 8.2$ Hz) 7.33 (d, 2H, $J = 8.2$ Hz) 7.44 (s, 1H) 9.61 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 21.5, 125.6, 126.7, 129.0, 129.4, 138.7, 160.6, 190.2.