1,4-Dialkoxy 1,3-dienes and bis(dienes)–stereocontrolled synthesis and reactivity

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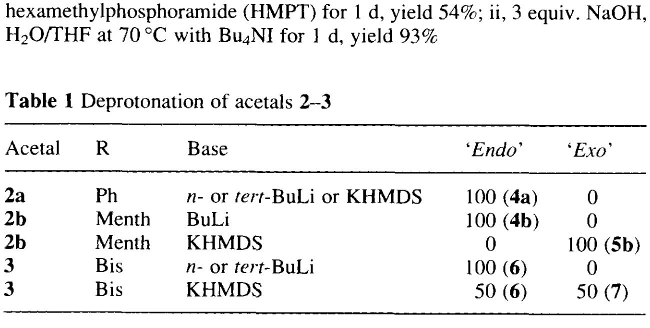
γ-Aryloxy and -alkoxy α,β-unsaturated dimethyl acetals are direct precursors to (1*Z*, 3*E*)-1,4-dialkoxy 1,3-dienes and bis(dienes) which are fine partners in cycloaddition reactions with classical dienophiles.

Although the Diels–Alder reaction remains a source of constant attention, a restricted number of functionalized dienes have found a place among the commonly used building blocks, *e.g.* Danishefsky's diene. Only a few 1,4-dialkoxydienes have been prepared before[1] and are reported to be especially fragile. Here we report a new sterocontrolled synthesis of 1,4-dialkoxy 1,3-dienes and bis(dienes) together with a few model cycloaddition reactions involving these compounds.

Halogen substitution on chloroacetal **1** by sodium phenate directly yields the corresponding ether **2a** with preservation of the original *E*/*Z* ratio, Scheme 1.[2c–d] Secondary sodium alcoholates can also be employed, such as sodium menthylate, but require harsher conditions to provide **2b**. Similarly, energetic stirring of a THF solution of acetal **1** with aqueous sodium hydroxide provides directly and in excellent yield bis(acetal) **3**. The 2*E*,2′*E*/2*E*,2′*Z* ratio is roughly 60:40.†

These acetals can be deprotonated in THF using strong bases such as *n*- or *tert*-butyllithium‡ or potassium bis(trimethylsilyl)amide KHMDS. Amide **2a** selectively gives the corresponding 1,4-dienol diether **4a** whatever the base.[2d]§ By contrast **2b** yields **4b** (100%) when treated with BuLi and **5b** (100%) with KHMDS, Table 1. The 1*Z*,3*E* to 1*E*,3*E* ratio in **4** is *ca.* 90:10, a striking result with respect to the high 1*E*,3*E* selectivity obtained in identical conditions with corresponding arylthio dimethyl acetals (**2a** with ArS instead of PhO).[2] Similarly, bis(acetal) **3** provides either bis(dienes) **6** or a mixture of bis(dienes) **6** and **7**, Scheme 2, of which the ratio depends on the base employed.¶ The yields are good to excellent.

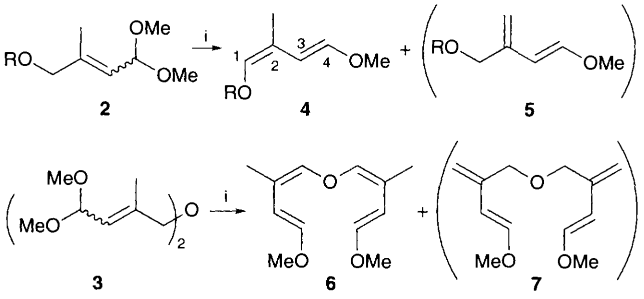


Scheme 1 *Reagents and conditions*: i, 4 equiv. PhONa, H_2O/THF at room temp. for 2 d, yield 98% or 1 equiv. sodium menthylate at 70 °C in THF/hexamethylphosphoramide (HMPT) for 1 d, yield 54%; ii, 3 equiv. NaOH, H_2O/THF at 70 °C with Bu_4NI for 1 d, yield 93%

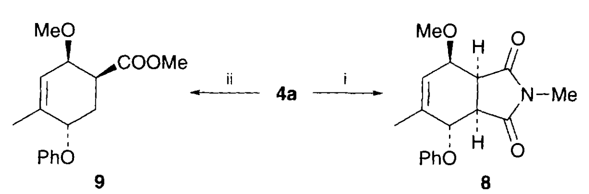
Table 1 Deprotonation of acetals 2–3

Acetal	R	Base	'*Endo*'	'*Exo*'
2a	Ph	*n*- or *tert*-BuLi or KHMDS	100 (**4a**)	0
2b	Menth	BuLi	100 (**4b**)	0
2b	Menth	KHMDS	0	100 (**5b**)
3	Bis	*n*- or *tert*-BuLi	100 (**6**)	0
3	Bis	KHMDS	50 (**6**)	50 (**7**)

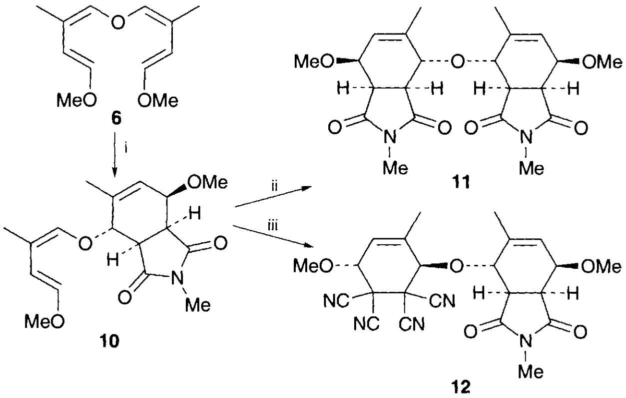
It was then interesting to assess the synthetic potential of these compounds in classical [4 + 2] cycloaddition reactions. Our method provides dienes **4**–**7** of sufficient purity and stereohomogeneity to be used as crude starting materials, Scheme 3. We first condensed **4a** with *N*-methyl maleimide (NMM). Adduct **8** was obtained with total *endo* selectivity. As expected, the 1*Z*,3*E* configuration of the starting diene leads to 3,6-*trans* disubstituted cyclohexenyl structures. The conformation of the bicyclic compounds is of the 'convex-boat type',



Scheme 2 *Reagents and conditions*: i, BuLi −40 °C for 15 min. or KHMDS at room temp. in THF for 1 h., 1 equiv. per acetal, yield 88–99%



Scheme 3 *Reagents and conditions*: i, 1 equiv. *N*-methylmaleimide in toluene at 110 °C for 6 h; ii, neat methyl acrylate at 80 °C for 5 d or 3 equiv. methyl acrylate in MeOH for 1 d under 12 kbar, yield 71–73%

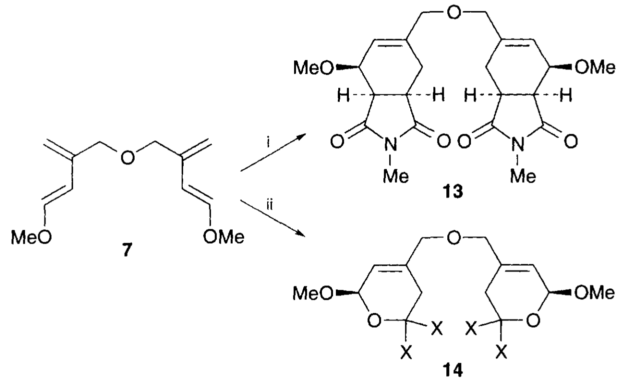


Scheme 4 *Reagents and conditions*: i, 1 equiv. *N*-methylmaleimide in THF at room temp. for 1 d; ii, 1 equiv. *N*-methylmaleimide in THF at 40 °C in the same pot for 2 d, yield 59%; iii, 1 equiv. tetracyanoethylene in THF at −40 °C in the same pot for 15 min, yield 57%

the methoxy group occupying an axial position. Both menthoxy ethers **4b** and **5b** also react with NMM with 42 and 32% de, respectively. The regioselectivity has been tested on **4a** with respect to methyl acrylate under thermal or high-pressure (12 kbar) activation conditions. The single *endo* adduct **9** is recovered in both cases, Scheme 3.

The reactivity of bis(diene) **6** has then been considered, Scheme 4. It adds onto NMM at room temperature in THF to provide intermediate monoadduct **10**, which on slight warming (40 °C) gives the double adduct **11**. Compound **10** also reacts with other dienophiles to yield mixed adducts. For instance using NMM and then tetracyanoethylene at −40 °C gives **12** in a one pot reaction. The second addition takes place with some diastereoselectivity with respect to the first. In the cases represented here, the de of **11** is almost zero while it reaches 80% in the case of **12**.

The '*exo*' bis(diene) **7** adds easily to NMM at room temperature to provide almost instantaneously double adduct **13**, Scheme 5. Advantage has been taken of this very high reactivity to prepare bis(heterocycle) **14**, a potential precursor of pseudo-disaccharides, applying **7** in a hetero-Diels–Alder reaction with diethyl 2-oxomalonate at room temperature in THF. Yield of **14** is 87% after flash chromatography.



Scheme 5 *Reagents and conditions*: i, 2 equiv. *N*-methylmaleimide in THF at room temp. yield 83%; ii, 2 equiv. diethyl 2-oxomalonate at room temp. in THF (X = CO$_2$Et), yield 87%

In conclusion, these results indicate that 1,4-dialkoxydienes **4** and **6** are easily accessible from acetals **2–3**. The configuration of the dienes thus prepared is largely in favour of the ZE-isomer. Depending on the substituent, '*exo*' (**5b** and **7**) dienes may also be obtained. The reactivity of all these compounds in [4 + 2] cycloaddition reactions is satisfactory under thermal and high-pressure conditions.

Footnotes

† Corresponding to the statistical combination of two *E*/*Z* = 80 : 20 units of **1** which is an industrial intermediate (Rhône-Poulenc Chimie).

‡ As first described for crotonaldehyde and senecialdehyde diethyl acetal.[3,4]

§ '*Exo*' diene **5a** is not obtained in these basic conditions but can be prepared as a mixture with **5a** by Me$_3$SiOTf catalysis as described for saturated acetals.[5]

¶ For **6**, 1*Z*,3*E*, 1′*Z*,3′*E* : 1*E*,3*E*, 1′*Z*,3′*E* ratio = 90 : 10 while '*exo*' **7** is obtained as a single 1*E*, 1′*E* isomer.

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