



Synthesis and diastereoselective Diels–Alder reactions of homochiral C_2 -symmetric butane-1,2-diacetal-based 1,3-dienes

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ABSTRACT

The C_2 -symmetric, butane diacetal (BDA) auxiliary-based dienes **2** and **3** are described, which display moderate to excellent diastereoselectivities in Diels–Alder reactions with a range of dienophiles under thermal and Lewis acid-catalysed conditions.

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The Diels–Alder reaction is arguably one of the most powerful synthetic transformations.¹ The quest for asymmetric protocols for this transformation has received huge attention and continues to be an active research field.² The use of both chiral catalysts and chiral auxiliaries has been described. With regard to the latter category, the synthesis and evaluation of auxiliary-based dienes is the least developed.^{2c,3,4}

Auxiliary-based dienes generally feature a single bond connecting the diene section with the auxiliary, which results in a degree of conformational flexibility. Nevertheless, it has been shown that high levels of stereinduction could be obtained in this way.^{2–4} We anticipated that if a cyclic auxiliary was connected to the diene unit through the diene C2–C3 atoms, a rigid system would result with the potential to achieve highly diastereoselective Diels–Alder reactions. To the best of our knowledge, at the outset of this work, there were no examples of 1,3-dienes with a chiral cyclic auxiliary attached to the C2–C3 position.

In designing a chiral 1,3-diene containing an auxiliary, the ease of auxiliary cleavage after its function in a diastereoselective reaction was a crucial consideration. With this in mind, we selected the 1,4-dioxane ring **1** (Fig. 1) as the parent system, with the diene present as two *exo*-methylene bonds. The diene **1**, which belongs to a subclass called ‘outer-ring dienes’, has been synthesised and used successfully in Diels–Alder reactions.⁵ There are analogous carbocyclic systems described for which it has been shown that substitution onto the ring can induce diastereoselectivity in the Diels–Alder reaction.⁶ An important design-element was to incorporate C_2 -symmetry in the auxiliary, which would lead to a simplification of the system by the resulting reduction of the number of competing diastereomeric transition states.⁷ This led us to propose the C_2 -symmetrical dienes **2** and **3**, with an auxiliary based on the butane diacetal (BDA) system.

Weavers and co-workers recently published a Letter on the use of chiral 1,3-diene **2** as a substrate in Diels–Alder reactions for the synthesis of substituted catechols,⁸ though no details regarding diastereoselectivity were included. The bis ketene acetal **4** has also been reported as a substrate for a highly diastereoselective aldol reaction as the key step in the synthesis of (+)-nephrosteranic acid.⁹ The Weavers Letter prompts us to report our results regarding the synthesis of dienes **2** and **3**, their structural analysis, and diastereoselectivities obtained in the Diels–Alder reaction of **2/3** with a set of dienophiles, including structural elucidation of a Diels–Alder adduct.

The use of 1,2-diacetal-based systems has proven to be very valuable in a variety of areas, notably in the carbohydrate field as protecting groups and for tuning anomeric reactivity, and also as a general 1,2-diol and α -hydroxy-acid-protecting group and as the basis for the synthesis of chiral building blocks and ligands.¹⁰ In addition, applications of 1,2-diacetals as chiral auxiliaries have been described, notably for glycolic acid,^{11a–i} but also in other areas,^{11j–l} including intramolecular [2+2] cycloaddition^{10a} and Diels–Alder reactions (dienophile-based).^{12a}

The synthesis of **2** and **3** (Scheme 1) was straightforward. The known diols **5** and **6**,^{12b,11} each obtained in two steps from (*R,R*)-dimethyl tartrate,¹³ were converted into the 1,4-diioidides **7** and **8** by reaction with iodine and triphenylphosphine.¹⁴ A two-step procedure towards **7** involving conversion of the diol into the

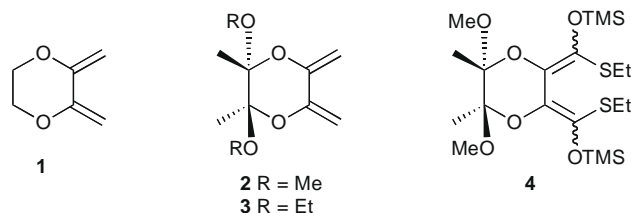
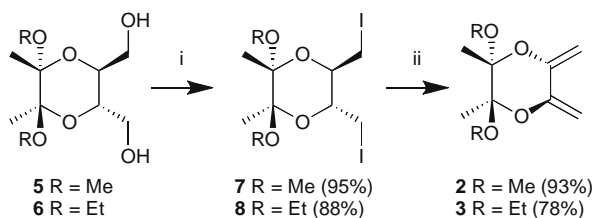


Figure 1. BDA-based chiral dienes.

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Scheme 1. Reagents and conditions: (i) I_2 , PPh_3 , imidazole, benzene, reflux, 1 h; (ii) t -BuOK, DMF, rt, 20 min.

corresponding di-tosylate,¹⁵ followed by reaction with sodium iodide gave far inferior results. Subsequent double elimination using NaH in DMF¹⁶ only led to a 45% yield of **2**, however the use of t -BuOK^{11c,h} led to the desired dienes **2** and **3** in excellent yields on multigram scale.¹⁷ The double-iodide elimination appears more efficient for the synthesis of **2** compared to the double-mesylate elimination as reported by Weavers.

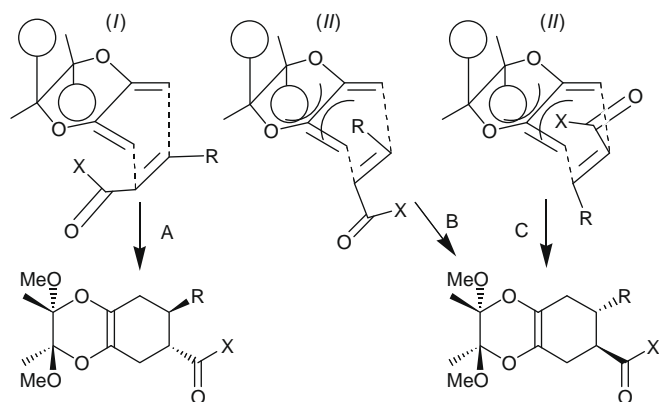
The C_2 -symmetry of the products was obvious from the structural simplicity of the 1H and ^{13}C NMR spectra.¹⁷ The λ_{max} (254 nm), as well as the molecular extinction coefficient ($\epsilon = 6543$) of **2** matched well with the reported data for 1,4-dioxane-based outer-ring diene systems such as **1**.^{5b,18} Molecular modelling (SPARTAN 04) predicted the absolute sense and the degree of diene-helicity to be 29.2° (M). This was confirmed for **2** from X-ray crystallographic analysis (Fig. 2), where both the half-chair conformation as well as the diene M -helicity are clearly observable. As expected, the OMe-groups adopt a *pseudo*-axial position. Diene **3** is an oil.

Geometry optimisation by DFT calculations (B3LYP 6-31*) shows that the corresponding ring-inverted half-chair with axial methyl groups is destabilised by 18.4 kJ/mol. Hence, the chiral auxiliary induces diene-helicity by virtue of operating anomeric

effects. For a given diene-face, the individual double bonds are diastereotopic and their faces are sterically differentiated by the *pseudo*-axial methoxy group. Hence, it was anticipated that steric hindrance would induce diastereoselectivity in cycloaddition reactions. In addition, the diene-helicity could be a contributing factor to the steric differentiation for the reaction.

The expected mode of dienophile-attack, assuming *endo*-approach (A, C), is shown in Scheme 2, and is based on steric interaction between the *pseudo*-axial methoxy group and the carbonyl group of the dienophile. Due to the diene- C_2 -symmetry, the two corresponding *exo*-approaches (e.g., B, Scheme 2) of the dienophile do not give rise to additional diastereomeric products.

In the event, the dienes **2** and **3** were reacted with a range of dienophiles under thermal conditions (Table 1). A solution of diene **2/3** and the dienophile in toluene or hexane was heated at reflux



Scheme 2. Possible *endo*-approaches (A, C) and an *exo*-approach (B).

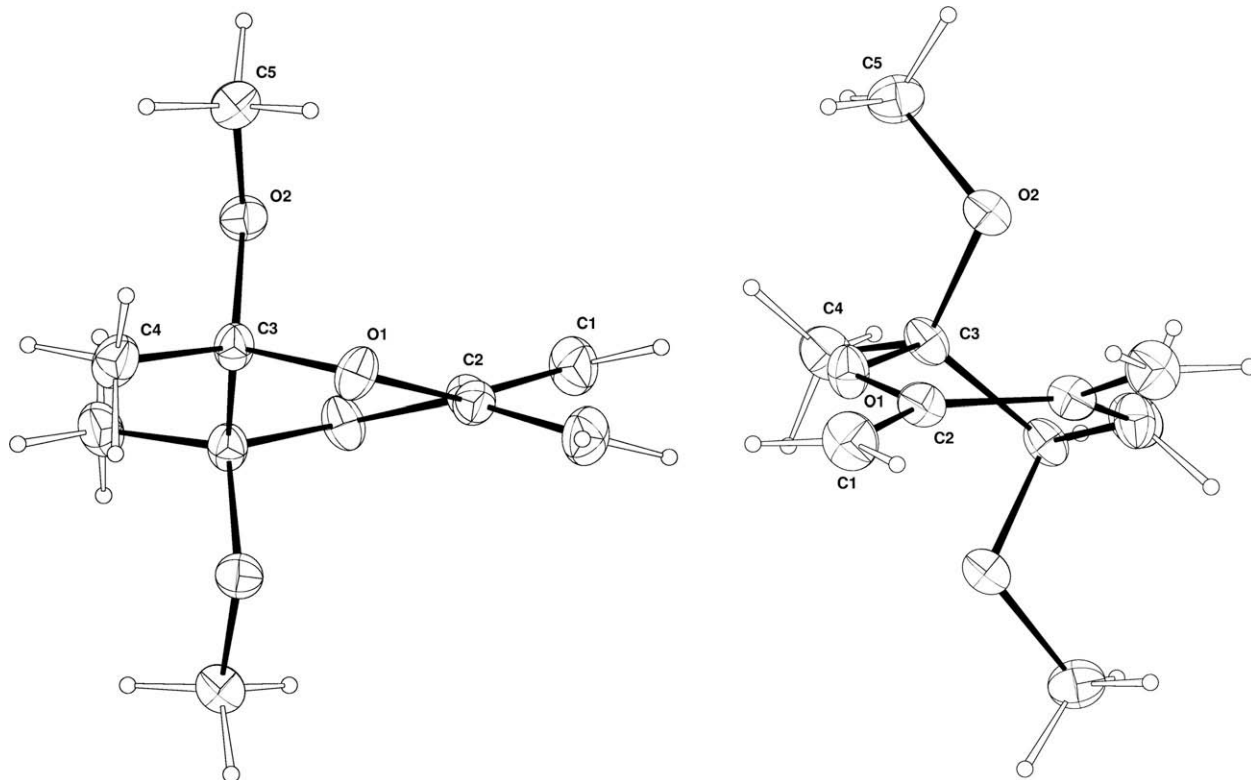
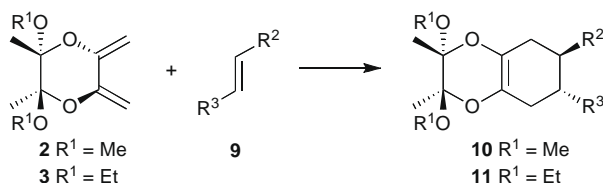


Figure 2. Crystal structure of **2**. Thermal ellipsoids drawn at the 50% probability level ($C_{10}H_{16}O_4$, tetragonal, $P4_32_12$, $a = 9.0608(8)$ Å, $b = 9.0608(8)$ Å, $c = 12.9150(9)$ Å, $V = 1060.30(15)$ Å³, $D_c = 1.254$ mg/m³, $Z = 4$, $T = 150(2)$ K.¹⁹

Table 1
Yields and diastereoselectivities of the Diels–Alder reaction between **2/3** and various dienophiles **9**



Entry	Diene	Dienophile	R ²	R ³	Adduct	Thermal (toluene or hexane)		Lewis acid catalysed ^c
						Temp (°C)	Yield ^a (ratio) ^b (%)	
1	2	9a	COOMe	COOMe	10a	111	88 (88:12)	—
2	3	9a	COOMe	COOMe	11a	70	39 (84:16)	—
3	2	9b	COOEt	COOEt	10b	111	61 (96:4)	—
4	3	9b	COOEt	COOEt	11b	70	81 (83:17)	—
5	2	9c	COOEt	CF ₃	10c	70	63 (83:17)	^d
6	2	9c	COOEt	CF ₃	10c	111	56 (82:18)	—
7	3	9c	COOEt	CF ₃	11c	111	33 (82:18)	—
8	2	9d	COOEt	Me	10d	111	75 (91:9)	^d
9	2	9e	COOMe	H	10e	111	75 (70:30)	57 (98:2)
10	3	9e	COOMe	H	11e	111	99 (69:31)	49 (>95:<5)
11	2	9f	C(O)Me	Me	10f	111	80 (89:11)	30 (94:6)
12	2	9g	C(O)Me	H	10g	111	95 (64:36)	79 (67:33)
13	3	9g	C(O)Me	H	11g	—	—	77 (62:38)

^a Isolated yield as an inseparable mixture of diastereomers. Combustion analysis returned satisfactory analysis data.

^b Determined by GC of the crude reaction mixture.

^c Et₂AlCl (20 mol %) at –78 °C in CH₂Cl₂ (0.5 M).

^d Reaction failed.

temperature for 18–24 h. The isolated yield of the products ranged from moderate to excellent. The diastereomeric ratios varied from moderate (2:1, entry 12) to good (91:9, entry 8). The reaction temperature does not significantly influence selectivity. Disappointingly, increasing the steric bulk of the axial alkoxy group did not improve the selectivity, with **2** and **3** giving comparable product ratios. As the isomers could not be separated by preparative HPLC, the ratio was determined by GC/MS analysis of the crude reaction mixture. In all cases, the retention times of the diastereomers were verified by comparison with a 'pure' sample of the diastereomeric mixture, obtained after chromatography. In all cases, these 'pure' mixtures returned satisfactory combustion analysis data.

The relative configuration of the Diels–Alder adduct **10a** was determined by X-ray crystallographic analysis (Fig. 3), and suggests that, as expected, approach A (Scheme 2) is occurring. It is surmised that when R = H, the corresponding *exo*-approach B competes,

leading to decreased levels of diastereoselectivity. However, when R ≠ H, steric hindrance occurs between the R-group and the diene-methoxy group, leading to an increase in selectivity.

The diastereoselectivity of the Diels–Alder reaction of both dienes **2/3** was also investigated under Lewis acid-catalysed conditions (Et₂AlCl, 20 mol %, –78 °C, CH₂Cl₂). Though the yield of the adducts was only moderate, the selectivity was markedly increased with methyl acrylate and 3-penten-2-one as dienophiles, reaching synthetically useful levels (entries 9–11). However, the diastereoselectivity remained moderate with the monosubstituted 3-buten-2-one (entries 12 and 13).

Auxiliary removal from the cycloadduct has not yet been achieved in acceptable yields, and further work to that effect is in progress.

In summary, a homochiral auxiliary-based diene is described, which reacts with moderate to excellent diastereoselectivities with

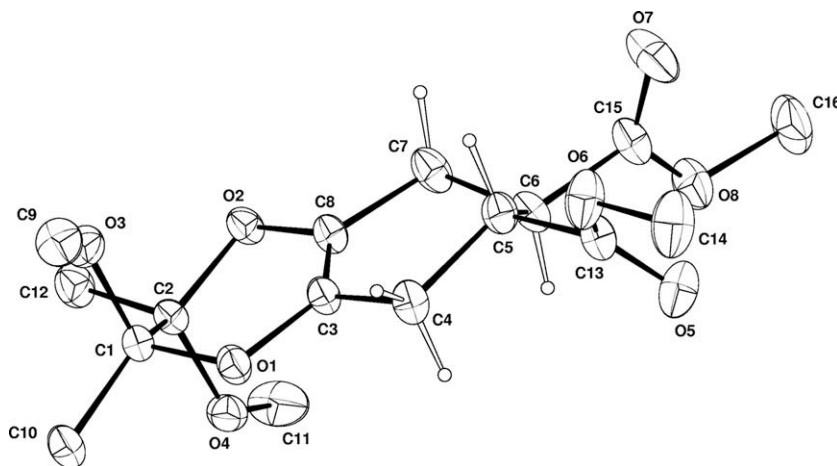


Figure 3. Crystal structure of **10a**. Thermal ellipsoids drawn at the 30% probability level, methyl hydrogens omitted for clarity (C₁₆H₂₄O₈, Monoclinic, *P*2₁, *a* = 11.4457(8) Å, *b* = 7.1306(6) Å, *c* = 12.2987(12) Å, $\alpha = 90^\circ$, $\beta = 116.005(3)^\circ$, $\gamma = 90^\circ$, *V* = 902.13(13) Å³, *D*_c = 1.268 mg/m³, *Z* = 2, *T* = 566(2) K).¹⁹

a range of dienophiles under thermal and Lewis acid-catalysed conditions. The sense of diastereoselection was proven by X-ray crystallographic analysis of an adduct.

Acknowledgements

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