An enantioselective desymmetrisation approach to C9-substituted *trans*-hydrindene rings based on a diastereotopic group-selective intramolecular Diels–Alder reaction†

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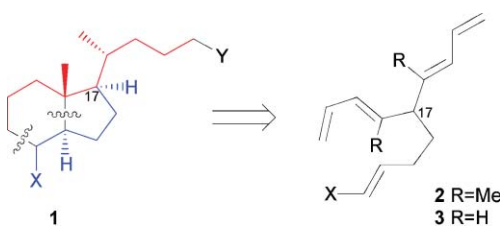
The synthesis of an achiral skipped bis(1,3-diene) substrate was achieved, which was shown to undergo an enantioselective, diastereotopic group-selective, intramolecular Diels–Alder reaction.

The formation of a hydrindene ring system *via* an intramolecular Diels–Alder reaction (IMDA) has been extensively studied.[1] The reaction with (*E*,*E*,*E*)-substrates usually affords a *trans*-fused hydrindene ring resulting from an *endo*-transition state. Several Lewis acids and organocatalysts have been shown to induce excellent enantioselectivity for the IMDA reaction towards hydrindene rings.[2] In addition, a range of chiral auxiliaries proved very efficient for inducing facial selectivity of the dienophile group.[3] Hence this particular IMDA process is very attractive for the enantioselective synthesis of hydrindene systems.

However, if the introduction of enantioselectivity is to occur through the IMDA reaction without kinetic resolution, there is an inherent limitation in that the tether connecting the diene and dienophile groups cannot contain a chiral centre. Hence, starting from an achiral substrate, this would preclude a direct enantioselective IMDA approach for the synthesis of C9-substituted (hydrindane numbering) hydrindane rings such as the C17-substituted (steroid numbering) steroid precursor **1** (Scheme 1).

We propose the achiral substrate **2** for the synthesis of the steroid CD-ring/side chain subunit **1**, by exploiting the latent structural symmetry present in **1** if the IMDA disconnection depicted in Scheme 1 is applied. Hence, despite the substitution on the tether, we envisioned that a group selective IMDA reaction would enable the enantioselective synthesis of substituted hydrindanes such as **1** because the C9 (C17) centre is only transformed into a chiral centre after the IMDA reaction, thus bypassing the structural limitation noted above.



Scheme 1 Retrosynthetic analysis revealing a structural symmetry.

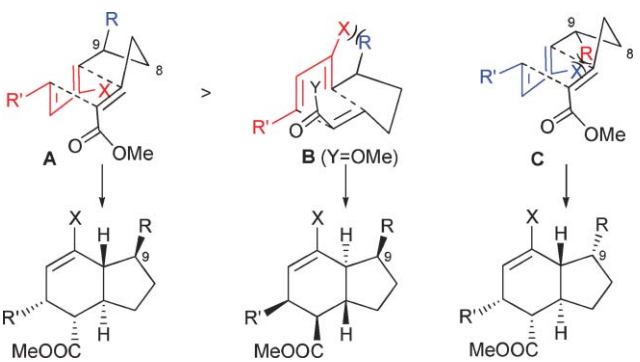
It has been shown that a substituent at the internal diene allylic position (leading to C9 hydrindene substitution after IMDA) exerts diastereofacial control to the diene group by virtue of 1,3-allylic ($A^{1,3}$) strain (Scheme 2).[1g,1h,4] Hence, the transition state **A** is preferred over **B** as $A^{1,3}$ strain is avoided, establishing the relative stereochemistry between the existing C9 stereogenic centre and the four centres formed in the IMDA process. This control element has been exploited in a number of total synthesis approaches.[5]

Crucially for our purposes, $A^{1,3}$ strain would simultaneously control the group-selectivity of the IMDA process, leading to the introduction of all stereogenic centres in a diastereoselective and potentially enantioselective fashion. Rotation along the C8–C9 bond in **A** leads to **C** (R = a 1,3-butadienyl based side chain as in **2/3**) which, being enantiomeric to **B**, is equally disfavoured.

A synthetic approach based on group selective reactions can be very efficient,[6] and while diastereotopic group-selective cycloadditions have been reported,[7] including from achiral starting materials,[7a] to the best of our knowledge, a group-selective IMDA has not yet been described.

In this communication, we report the synthesis of a centrally substituted skipped bis(1,3-diene) substrate based on **3**, and the investigation of its group selective IMDA reaction under thermal and Lewis acid (achiral and chiral) mediated conditions.

The synthesis of the skipped bis(1,3-diene) substrate is shown in Scheme 3. Ethyl sorbate **4** was deprotonated using LDA[8] and the



Scheme 2 The $A^{1,3}$ strain control element in the IMDA reaction leading to a C9-substituted hydrindene ring. Only the *endo*-transition states are considered.

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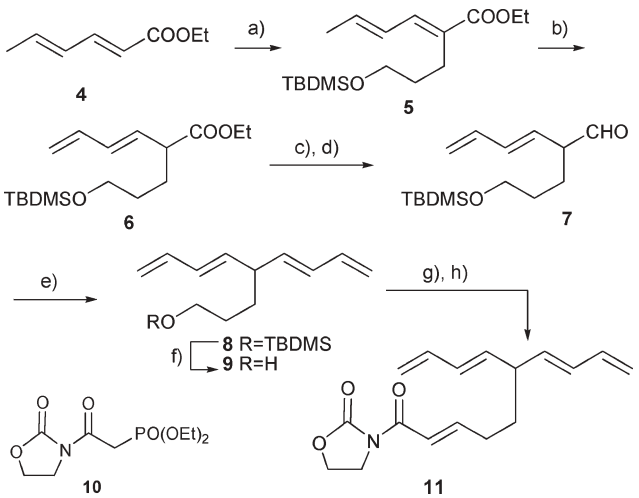
† Electronic supplementary information (ESI) available: Experimental procedures and spectral data for **11**, **12** and **13** including copies of ^{1}H and ^{13}C NMR spectra, details for determination of diastereomeric ratios and ^{19}F NMR of the Mosher ester. See DOI: 10.1039/b607488j



Scheme 3 Synthesis of the bis(1,3-diene) substrate. Reagents and conditions (a) LDA, THF, HMPA, −78 °C; $I(CH_2)_3OTBDMS$, −78 °C to 0 °C. (b) LDA, THF, −78 °C, 1 h; AcOH. (c) $LiAlH_4$, Et_2O, rt, 30 min. (d) Dess–Martin periodinane, rt, 18 h. (46% from **4**) (e) *n*-BuLi, HMPA, THF, $Ph_2P(O)CH_2CH{=}CH_2$, −78 °C to 0 °C, 1.5 h. (25%) (f) TBAF (1 equiv), THF, rt, 2.5 h. (69%) (g) $(COCl)_2$, Et_3N, DMSO, CH_2Cl_2, −78 °C, 3 h. (h) **10**, NaHMDS, rt, 2.5 h. (52%, 2 steps).

resulting anion alkylated with 1-iodo-3-[*tert*-butyldimethylsilyloxy] propane,[9] to afford the conjugated ester **5** after workup. Deconjugation to **6** was easily accomplished under kinetic conditions by deprotonation at −78 °C with LDA, followed by quenching with acetic acid.[8] Ester **6** was next transformed into aldehyde **7** *via* the corresponding (known)[10] alcohol in 46% yield overall from **4**. The aldehyde **7** was prone to oligomerisation and was used directly in the next step within the same day. Despite extensive optimisation, the Wittig–Horner olefination of **7** with the anion of allyldiphenylphosphine oxide only gave the skipped bis(1,3-diene) **8** in low yield. However, the bis(1,3-diene) moiety proved to be relatively stable, and could be obtained in pure form. Interestingly, while skipped polyene systems are known structures, to the best of our knowledge this represents the first example in which the 'skipped' position is a tertiary carbon atom.

After alcohol deprotection and oxidation to the corresponding aldehyde, Horner–Emmons olefination[2b] afforded the key IMDA precursor **11**. Analysis of the vinylic region by ^{1}H NMR unambiguously showed the symmetry of the skipped bis(1,3-diene) group (Fig. 1) which proved that no isomerisation had occurred.

With the bis(1,3-diene) **11** in hand, we were able to start the IMDA study (Scheme 4). The IMDA reaction was first performed under thermal conditions with a small amount of added BHT (1 mol%), used as a radical inhibitor to limit possible polymerisation side-reactions.

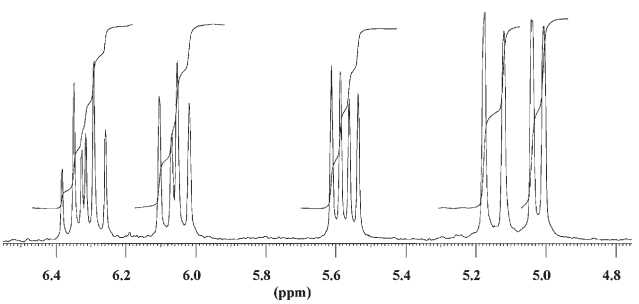
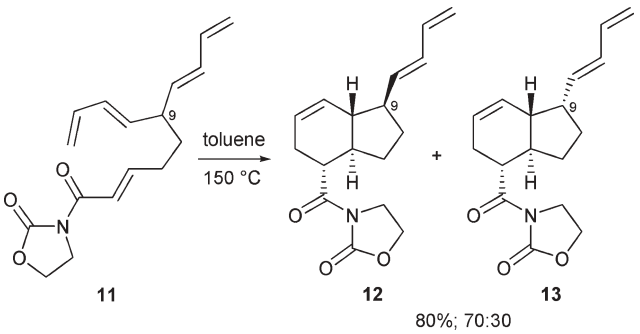


Fig. 1 ^{1}H NMR of the bis(1,3-diene) vinylic protons of **11**.



Scheme 4 The group selective IMDA under thermal conditions.

Thus, a solution of **11** in degassed toluene was heated in a sealed tube at 150 °C for 24 h leading to a 70 : 30 product mixture of the two diastereoisomers **12** and **13** (determined by ^{1}H NMR) in a 80% combined yield . The isomers could be separated by reversed phase HPLC allowing the structure of **12** to be unambiguously determined by X-ray crystallographic analysis (Fig. 2). This showed that the major product had the *trans*-hydrindene ring junction with the desired C9 relative stereochemistry implicating the predicted *endo* transition state with reduced $A^{1,3}$ strain as indicated in Scheme 2.

Given the precedence of (*2E*,*7E*)-trienimides undergoing IMDA selectively *via* an *endo*-transition state,[2d,3b] it is assumed that the minor product **13** was also formed through an *endo*-transition state though its relative stereochemistry has yet to be unambiguously established. ^{1}H NMR analysis implicated the *trans*-fused hydrindene ring system (see ESI†), suggesting the stereochemistry depicted in **13**.

In an attempt to improve the diastereoselectivity, the IMDA process was attempted at lower temperature under Lewis acid catalysis (Table 1).[3b,11] Reactions were performed using a 0.03 M solution of IMDA precursor **11** in CH_2Cl_2 with 1.4 equiv of various aluminium based Lewis acids as indicated (BEt_3, $ZnEt_2$, $ZnCl_2$, $TiCl_4$, $InBr_3$, $B(C_6F_5)_3$, $MgBr_2$, $LiClO_4$ promoted substrate decomposition). In general, the group selectivity was similar or slightly higher than the thermal IMDA reaction. Although complete consumption of starting material was indicated by TLC analysis, the isolated yields were lower compared to when no Lewis acid was used. The best group selectivity at −30 °C was obtained with Me_3Al (77 : 23, entry 4) which was similar to the outcome of the $EtAlCl_2$-catalysed reaction at −78 °C (79 : 21, entry 5). The Lewis acid catalysed IMDA reaction was also carried out at room temperature but without an improvement in yield (not

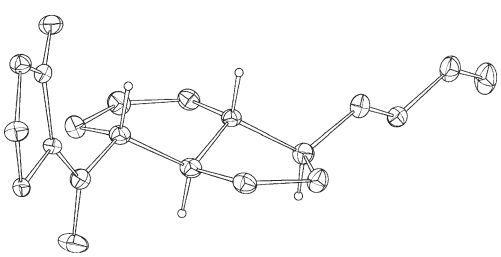
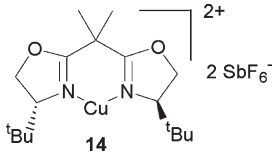


Fig. 2 ORTEP representation of the crystal structure of (racemic) **12**. The asymmetric unit contains both enantiomers, only one of which is shown. Thermal ellipsoids are drawn at the 35% probability level. Only hydrogen atoms of interest are shown.‡

Table 1 Lewis acid catalysed IMDA reaction of **11**

Entry	Lewis acid	Conditions	Yield (%)[a]	d.r.[b] **12** : **13**
1	Me_2AlCl	−30 °C, 4 h	59	69 : 31
2	Et_2AlCl	−30 °C, 4.5 h	47	70 : 30
3	$MeAlCl_2$	−30 °C, 4 h	47	73 : 27
4	Me_3Al	−30 °C, 2 h	55	77 : 23
5	$EtAlCl_2$	−78 °C, 5 h	54	79 : 21
6	 **14**	23 °C, 24 h	56	82 : 18

[a] Isolated yield. [b] Ratio determined by ^{1}H NMR in C_6D_6.

shown) and moreover, a lower selectivity was always obtained compared to the reactions at low temperature.

Importantly, the group selective IMDA reaction was also catalysed by the bis(oxazoline) catalyst **14**, developed by Evans (entry 6).[2b,2d,12] This led to an 82 : 18 mixture of diastereomers **12/13** in 56% yield.

The enantiomeric excess was estimated using Mosher's ester derivatisation method[13] on the C9 mixture§ (see ESI†) after reductive removal of the auxiliary. Pleasingly, it was found that the reaction proceeded with an enantioselectivity of approximately 90% ee (for the major diastereomer), which is a typical value for IMDA processes of substrates containing a terminal diene unit, with this chiral catalyst.[2b,2d]

In conclusion, we have developed a synthesis of a skipped bis(1,3-diene) system with substitution on the skipped position, which allowed us to demonstrate, for the first time, the viability of group selective IMDA reactions. *trans*-Hydrindene rings were obtained with excellent *endo*-selectivity and moderate to good C9 diastereoselectivity. More importantly, the use of a chiral bis(oxazoline) derived catalyst led to very good levels of enantioinduction. This experiment demonstrates that the structural limitation inherent to enantioselective IMDA reactions with regard to tether substitution can be successfully circumvented, which considerably expands the scope of this process. The synthesis of the skipped bis(1,3-diene) system **3**, and of similar IMDA precursors containing other dienophile groups,[3g] is still under investigation as is the functionalisation of the C9 dienyl group of the adducts towards steroid side chains. We thank AstraZeneca for support of this research.

Notes and references

§ We do not have a control spectrum of the individual C9 diastereomer Mosher esters, only of the racemic C9 mixture.

‡ Data were collected on a Brüker Nonius molybdenum rotating anode following standard procedures. Crystal data for **12** $C_{17}H_{21}NO_3$, M_r = 287.35, T = 120(2) K, monoclinic, space group *Pc*, a = 5.0398(17), b = 10.910(4), c = 27.268(7) Å, β = 90.36(2)°, V = 1499.3(8) Å^3, ρ_{calc} = 1.273 g cm^{-3}, μ = 0.087 mm^{-1}, Z = 4, reflections collected: 18459, independent reflections: 3464 (R_{int} = 0.0879), final R indices [$I > 2\sigma I$]: $R1$ = 0.0654, $wR2$ = 0.1119, R indices (all data): $R1$ = 0.0924. $wR2$ = 0.1197. CCDC 609533. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b607488j

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