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Functionalised butanediacetal-protected 1,2-diols as suitable partners for Pd-catalysed cross-coupling reactions

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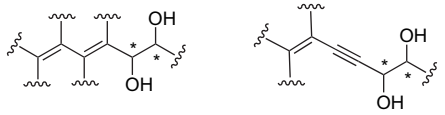
Abstract

A new method for the synthesis of dienes and enynes containing chiral 1,2-diols is described. The strategy is based on the Pd-catalysed cross-coupling reactions of a series of vinyl and alkynyl asymmetric butanediacetal-protected building blocks. After the coupling, removal of the protecting group leads to the desired functionalised dienes and enynes.

Keywords: Butanediacetal; Palladium catalysis; Dienes; Enynes; Chiral diols

1. Introduction

The presence of stereochemically defined dienes **1** or enynes **2** in chiral 1,2-diols is a common motif found in a large number of biologically active natural products, including prostaglandins,[1] leukotrienes,[2] enediyne antibiotics,[3] retinol derivatives[4] and many others[5,6] (Scheme 1).



1 2

Scheme 1. Common motifs found in many biologically active compounds. *Stereogenic centres.

Due to the prevalence of these substructures, several synthetic approaches have been used to obtain them, including, e.g., Wittig-type reactions on protected α-ketodiols,[7] enantioselective dihydroxylation of conjugated enynes,[8] enantioselective addition of Grignard-type nucleophiles to aldehydes,[9] retro-Michael reactions[10] or enantioselective reduction of conjugated ketones.[11] Although this reaction toolbox has proved to be successful in many synthetic routes, some drawbacks still arise: not all assure a perfect stereocontrol of the double bond geometry and, when the alkoxy-stereogenic centre is formed, mixtures of diastereoisomers can sometimes be formed.

Here we describe a new route to obtain chiral 1,2-diols containing dienes and enynes. This strategy is based on the use of butanediacetal (BDA) as protecting group of diols[12,13] in combination with Pd-catalysed cross-coupling reactions.[14] The use of Pd as catalyst for C–C cross-coupling reactions in organic synthesis has been well documented in recent years.[15] This well-known Pd chemistry could be combined effectively with the BDA protecting group method, thereby expanding the scope of building blocks to be used for the synthesis of natural products.

Our group has recently developed butanediacetal (BDA)-protected carbonyl-substituted building blocks from cheap chiral sources to be used in asymmetric synthesis.[16–21] This method allows access to both diastereomers from the same chiral source by equatorial–axial interconversion of the substituents (Scheme 2).[18,20,21]

We envisaged that **4** and **5** could be easily homologated by well-known reactions to obtain a series of partners for Pd-catalysed cross-coupling reactions (Scheme 3), including vinyl halides, vinyl boronates and alkynes. The enantiomeric

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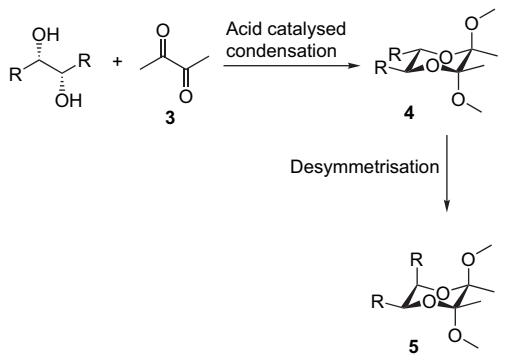
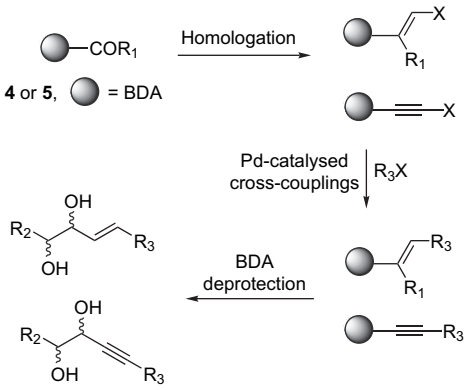


Scheme 2. Butanediacetal (BDA)-protected diols containing carbonyl functionalities. R=CO_2Me.

purity of the molecules is maintained during the process since the stereogenic centres are defined early on by the configuration of the BDA moiety. Moreover, Pd-catalysed cross-coupling reactions are reliable methods to form double bonds with defined geometry.[14] Therefore, the corresponding coupling and later deprotection of BDA will afford motifs of type **1** or **2**. In addition, further functionalisation of the intermediates could be carried out before the BDA removal.



Scheme 3. General strategy to obtain motifs **1** and **2**.

2. Results and discussion

2.1. Preparation of monosubstituted BDA-protected asymmetric building blocks for Pd-catalysed C–C cross-coupling reactions

A range of monosubstituted BDA-protected diols containing vinyl halides, vinyl boronates and alkynyl functionalities have been successfully prepared in good yield and purity (Scheme 4). Starting from D-mannitol, a set of aldehydes and methyl ketones involving both configurations (**7** and **10**–**12**) were easily obtained, which were homologated to achieve the target compounds.

Equatorial aldehyde **7** was submitted to Corey–Fuchs protocol[22] to give vinyl dibromide **13** and, subsequently, alkynes **15** and **16** in excellent yields. The *Z*-vinyl iodide **17** was obtained by diimide reduction of **16**.[23,24] The vinyl boronate **18** was obtained as pure *E*-isomer by hydroboration of **15**.[25,26] All these compounds were obtained without using any chromatographic purification. The same Corey–Fuchs sequence was applied to the axial aldehyde **10**.

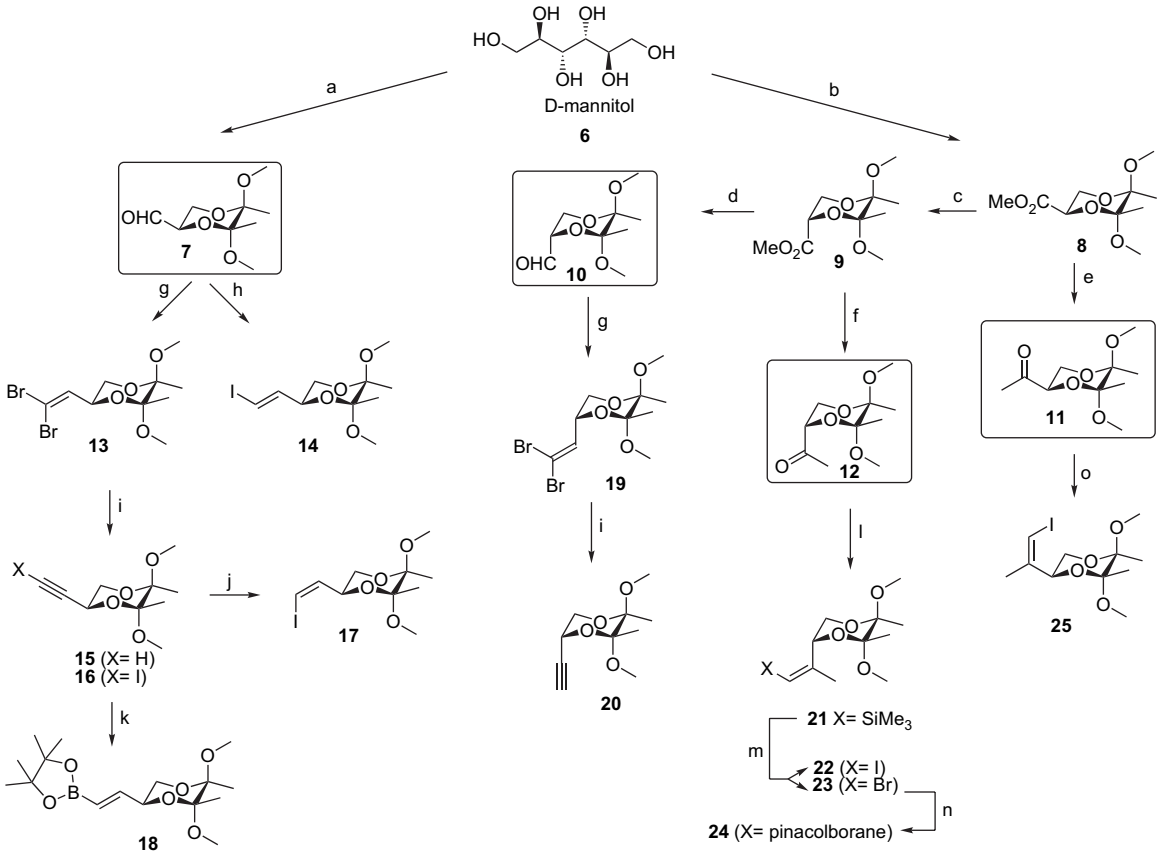
The *E*-vinyl iodide **14** was obtained directly from aldehyde **7** by Takai olefination.[27] Given the high toxicity of the reagents in this transformation, a more acceptable protocol was investigated (Scheme 5). Aldehyde **7** was homologated using the Petasis reagent $CpTi(CH_2SiMe_3)_3$[28] to give a 1:1 *E*/*Z* mixture of the corresponding vinylsilanes. Although these isomers afforded different enough R_f's to be separated on TLC, several conditions did not give any separation at all by column chromatography. Therefore, it was decided to transform the *Z* to the *E*-isomer by catalytic radical isomerisation.[29] After preparation of pure *E*-vinylsilane **26**, the desired *E*-vinyl iodide **14** (showing a similar *E*/*Z* molar ratio to that obtained in the Takai reaction) was formed using NIS as iodinating agent in hot acetonitrile. Additionally, when NBS was used as reagent instead, *E*-vinyl bromide **27** was obtained in good purity.

Equatorial methyl ketone **11** was obtained in good yields from the methyl ester **8** through hydrolysis of the corresponding methyl enol ether, which was previously formed and isolated using the Petasis reagent Cp_2TiMe_2. Compound **11** was submitted to Wittig reaction conditions[30] together with the salt $(ICH_2PPh_3)I$[31] to yield *Z*-trisubstituted vinyl iodide **25** in a 8:1 *Z*/*E* molar ratio. The axial methyl ketone **12** was obtained as a crystalline solid by nucleophilic substitution on the methyl ester **9** using MeLi·LiBr.[21] Trisubstituted vinylsilanes were obtained from **12** by Petasis homologation using $CpTi(CH_2SiMe_3)_3$ as reagent in good yield as a 1.2:1 *Z*/*E* mixture, which could be this time separated by careful column chromatography, in contrast with vinylsilane **26**. Double bond geometry was confirmed by NOE experiments (see Section 4). The predominant and easy-to-separate *Z*-compound **21** was transformed into *Z*-vinyl halides **22** and **23**, using NIS and NBS, respectively. It is worth noting the milder conditions used for this transformation in contrast to those shown in Scheme 5: no epimerisation was found during the transformation of **21** to **22** or **23** at rt, while pure **26** (*E*/*Z* >20:1), when heated in acetonitrile, gave a lower *E*/*Z* molar ratio for the corresponding vinyl halides **14** and **27**. To finish, the corresponding *Z*-vinyl boronate **24** was obtained from **23** by Pd-catalysed coupling with pinacolborane dimer.[32]

In general, most compounds obtained above were easy-to-handle solids (in particular compounds **13**, **14** and **25** were obtained as crystals, see Supplementary data) and stable in a conventional fridge for at least >6 months. Having all these monofunctionalised BDA-protected diols in hand we began to explore their reactivity in Pd-catalysed cross-couplings.

2.2. Use of the BDA-protected asymmetric building blocks in different Pd-catalysed C–C cross-coupling reactions

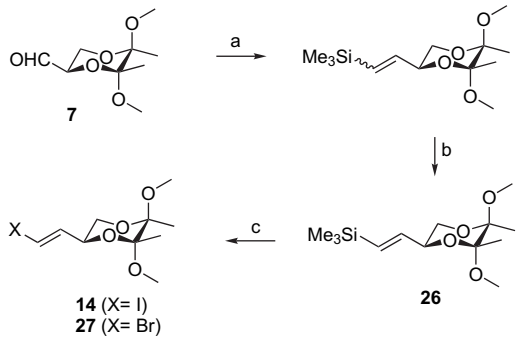
Some of the synthesised BDA-protected derivatives were examined in three of the more widespread Pd-catalysed cross-coupling reactions: Heck, Suzuki and Sonogashira cross-couplings.



Scheme 4. Synthetic route to monosubstituted BDA-protected asymmetric diols containing vinyl halides, vinyl boronates and alkynyl functionalities. *Reagents and conditions*: (a) butanedione, $HC(OMe)_3$, $BF_3\cdot Et_2O$ (cat.), MeOH, rt, 5 h; then $NaIO_4$, CH_2Cl_2, rt, 16 h, 40%; (b) butanedione, $HC(OMe)_3$, $BF_3\cdot Et_2O$ (cat.), MeOH, rt, 5 h; then $NaIO_4$, MeOH–H_2O, rt, 16 h; then Br_2, $NaHCO_3$, rt, 30 min, 46%; (c) LDA, THF, −78 °C, 30 min; then *t*-BuOH, −78 °C, 30 min, 48%; (d) $LiAlH_4$, THF; then $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 83%; (e) Cp_2TiMe_2, toluene, 65 °C, overnight; then $NH_4^+Cl^-$ (aq), 60 °C, 6 h, 70–80% over 2 steps; (f) MeLi·LiBr, CH_2Cl_2, −78 °C, 2 h, 50–71%; (g) CBr_4, PPh_3, Zn, CH_2Cl_2, rt, 2 h, 94–96%; (h) $CrCl_2$, CHI_3, THF, rt, 24 h, 45%; (i) *n*-BuLi, THF, −78 °C to rt; then NH_4Cl (aq) or I_2, 79–100%; (j) $KO_2CN{=}NCO_2K$, MeOH, AcOH, rt, 30% over 2 steps; (k) pinacolborane, 80 °C, 6 h, 70%; (l) $CpTi(CH_2SiMe_3)_3$, 1,4-dioxane, reflux, 24 h, 63%; (m) NIS or NBS, CH_3CN, darkness, rt, 16 h, 97% (iodide), 1 h, 100% (bromide); (n) pinacolborane dimer, $PdCl_2(PPh_3)_2$ (cat.), KOPh, toluene, 80 °C, 90 min, 28%; (o) ICH_2PPh_3I, NaHMDS, THF, −78 °C to rt, 3 h 30 min, 15–36%.

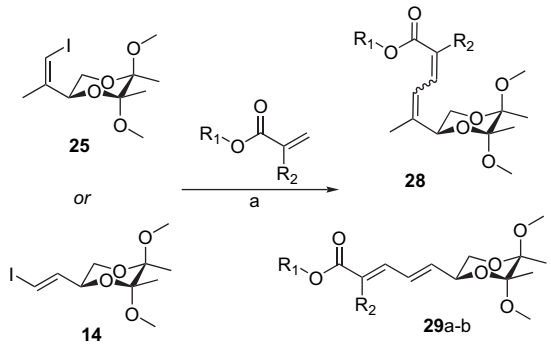
2.2.1. Heck reaction[33,34]

A typical example of a Heck reaction is the coupling of a vinyl iodide with an acrylate.[24] To investigate the reactivity of our building blocks **14** and **25**, both ethyl acrylate and the more sterically demanding methyl methacrylate were chosen as coupling partners (Scheme 6). The results are summarised in Table 1.



Scheme 5. Alternative synthetic route to obtain *E*-vinyl halides **14** and **27**. *Reagents and conditions*: (a) $CpTi(CH_2SiMe_3)_3$, 1,4-dioxane, reflux, overnight, 38%; (b) AIBN (cat.), PhSH (cat.), toluene, 80 °C, 5 h, 91%; (c) NIS or NBS, CH_3CN, darkness, 85–90 °C, 1 h, 50% (iodide), 34% (bromide).

It was observed that the Heck reaction proceeded in good yields under reasonable Pd-loadings considering the difficulty of these sterically hindered couplings. An excess of acrylates had to be added to the reaction due to both their volatility and their well-known propensity to polymerise under severe heating conditions. No racemisation or deprotection was observed by GC–MS, demonstrating the robustness of the BDA group to the reaction conditions.



Scheme 6. Heck reactions. *Reagents and conditions*: (a) 10 mol % $Pd_2(dba)_3$, 20 mol % P(*t*-Bu)$_3$, Cy_2MeN (1.5 equiv), toluene, 80–120 °C, 24 h.

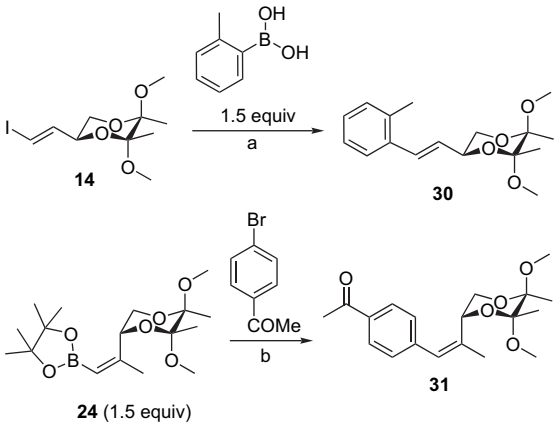
Table 1
The Heck reaction of vinyl iodides with mono- and disubstituted acrylates

	Vinyl halide	R_1	R_2	Acrylate (equiv)	Product	Conversion by GC–MS[a] (%)
1	**25**	Me	Me	1.5	**28**	>99 (90)[b]
2	**14**	Et	H	1.5	**29a**	80 (52)
3	**14**	Me	Me	3.0	**29b**	>99

[a] In brackets yield of isolated product.
[b] Mixture of isomers.

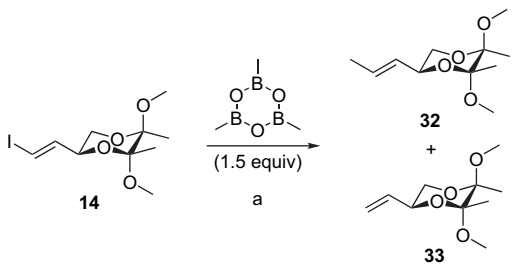
2.2.2. *Suzuki reaction*[35]

Aromatic and vinyl substrates typically react well in the Suzuki cross-coupling reaction and even sterically demanding aryl groups are also tolerated.[36,37] Firstly, the Suzuki cross-coupling reactions of **14** and **24** with *o*-tolylboronic acid and 4-bromoacetophenone, respectively, were investigated using $Pd(OAc)_2$/SPhos as the catalytic system (Scheme 7).[37]



Scheme 7. Suzuki reactions. *Reagents and conditions*: (a) 5 mol % $Pd(OAc)_2$, 7.5 mol % SPhos, K_3PO_4 (2 equiv), toluene, 110 °C, 70%; (b) 20 mol % $Pd(OAc)_2$, 20 mol % SPhos, K_3PO_4, THF, rt, 24 h, 65%.

The results shown above demonstrate the flexibility of the BDA-building blocks as partners in the Suzuki reaction, as they are able to act either as the vinyl halide or as the boronate. In order to examine the scope of our building blocks under Suzuki conditions, we investigated the coupling between **14** and some of the most demanding boronic partners, methylboronic derivatives (Scheme 8).[38]



Scheme 8. Suzuki reaction with trimethylboroxine. *Reagents and conditions*: (a) $PdCl_2(dppf)\cdot CH_2Cl_2$, K_2CO_3 (3 equiv), 1,4-dioxane, 110 °C.

Previous studies were carried out with methylboronic acid $CH_3B(OH)_2$ instead of trimethylboroxine, showing that, after complete conversion of **14**, more than twice of the reduced product **33** than of desired *E*-product **32** was formed. Furthermore, homocoupling of **14** was also observed. It was thought that the acidic protons on the boronic acid may be the cause of the hydrogen insertion on **14** in the reductive elimination step of the catalytic cycle. To prevent this reduction, the reaction was repeated with trimethylboroxine as this possesses no acidic protons. The reaction was complete after 6 h and only 12% of reduced product was observed (Fig. 1). A kinetic study was undertaken in order to optimise these conditions, whereupon it was found that the selectivity for the coupling product increased as the Pd-loading decreased. Indeed, after 48 h and with only 1.0 mol % of catalyst, 95% of ***E*-32** and 0.5% of **33** were formed (Fig. 1 and entry 1 in Table 2), obtaining the pure product after column chromatography.

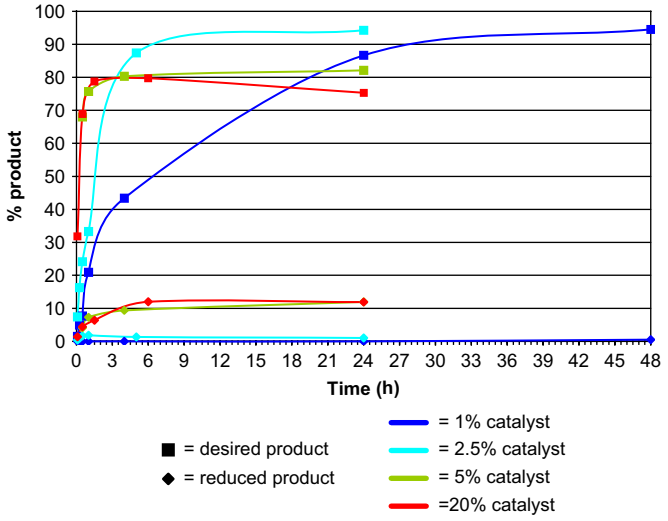


Figure 1. Kinetic study of the Suzuki reaction between **14** and trimethylboroxine using different catalyst loading.

2.2.3. *Sonogashira reaction*[39]

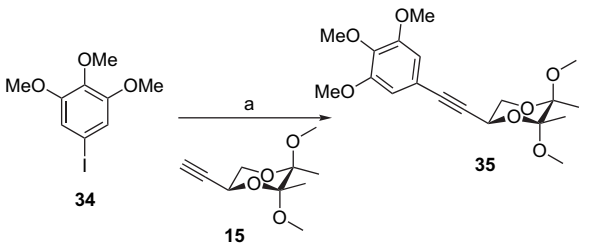
As a typical example of Sonogashira cross-coupling reaction, the aryl iodide **34** was reacted with the BDA-protected alkyne **15** under the conditions shown in Scheme 9 and Table 3.

It was eventually found that using 2 equiv of **15** at rt gave the coupling product **35** in 73% yield (entry 3) with an improved isomeric ratio eq./ax. of 7:1.

To investigate the chemoselectivity of the chiral building block **15** in the Pd-catalysed Sonogashira reaction, the chloroiodide **36** was reacted with **15** (Scheme 10 and Table 4). It

Table 2
Comparison of desired and reduced product formation

Entry	Catalyst (mol %)	Final *E*/*Z* ratio	Time (h)	Product yield (%)	
				Desired ***E*-32**	Reduced **33**
1	1	65:1	48	95	0.5
2	2.5	11:1	24	94	1.0
3	5	7:2	24	82	12
4	20	7:2	24	77	12



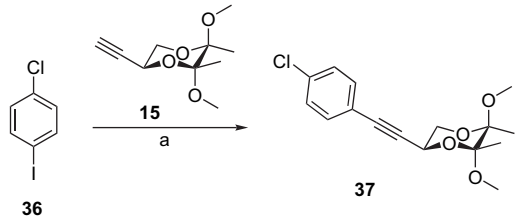
Scheme 9. Sonogashira reaction of **34** with BDA-protected alkyne **15**. *Reagents and conditions*: $Pd(PPh_3)_2Cl_2$, CuI, Hünig's base (1.5 equiv), toluene.

Table 3
Sonogashira cross-coupling of **34** with **15**

	34 (equiv)	**15** (equiv)	Pd–CuI (mol %)	Temp (°C)	Time (h)	Yield[a] (%)	**35** eq./ax.
1	1.2	1.0	5	rt	24	75	5:1
2	1.0	1.0	1	60	28	60	5:1
3[b]	1.0	2.0	5	rt	22	73	7:1

[a] Yields shown correspond to the equatorial isomer only.
[b] Performed on 0.5 g scale.

was expected that the C–I bond would be the only reactive position, leaving the chloride available for further functionalisation. At high temperature (entry 1) no product was obtained and it was inferred that volatile acetal **15** may have been lost. A further reaction with **36** was performed at rt using 2 equiv of **15** and then the desired product **37** was isolated in a moderate yield of 43%. The crude isomeric ratio eq./ax. was 5:1. The isomerisation of the BDA-building blocks observed in both cases might be explained by the presence of high amounts of base in the reaction conditions.



Scheme 10. Chemoselective Sonogashira reaction of **36** with **15**. *Reagents and conditions*: (a) 5 mol % $Pd(PPh_3)_2Cl_2$, 5 mol % CuI, Hünig's base (DIPEA), toluene, 24 h.

Table 4
Sonogashira coupling between **36** and **15**

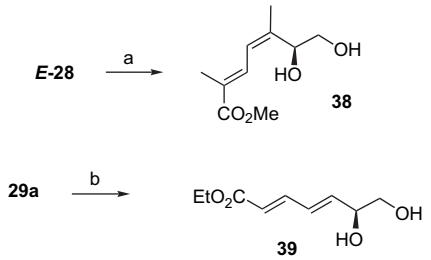
	36 (equiv)	**15** (equiv)	DIPEA (equiv)	Temp (°C)	**37**[a] (%)	eq./ax.
1	1.2	1.0	1.5	110	—	—
2	1.0	2.0	3.0	rt	43	5:1

[a] Yields shown correspond to the equatorial isomer only.

2.3. BDA deprotection

A relevant issue not always addressed in reactivity studies is the final removal of the protecting groups. In our particular case we tested deprotection conditions for two of our more highly conjugated coupling products (Scheme 11).

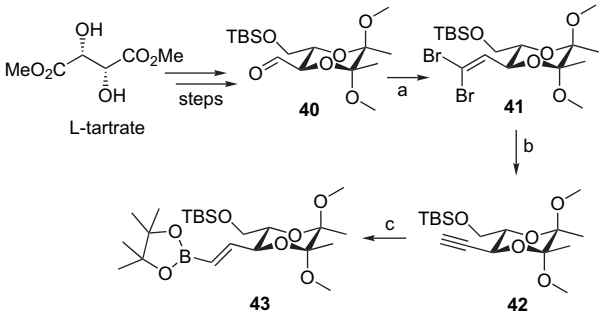
High yielding deprotections were achieved under standard conditions,[40] and no undesired dehydration or double bond isomerisation was observed. Interestingly, when the *Z*-enantiomer of **28** (obtained by column chromatography after the coupling) was deprotected under the same conditions of the *E*-isomer, the corresponding *Z*-diene was obtained, therefore maintaining the stereochemical integrity of the dienes and demonstrating the reliability of the deprotection conditions.



Scheme 11. BDA deprotection. (a) 2 N HCl (aq), MeOH, 65 °C, 2 h, 86% (0.5 g scale); (b) 2 N HCl (aq), EtOH, 80 °C, 90 min, 73%.

2.4. Expanding the scope of precursors: preparation of bifunctionalised BDA-protected asymmetric building blocks

After having addressed the feasibility of the methodology, and in order to expand the range of structures that ultimately could be reached, it would be of great interest to obtain bifunctionalised BDA-protected vinyl and alkynyl derivatives since it would allow modification on both sides of the protected diol before or after the coupling. By way of illustration, the same synthetic sequence used for aldehyde **7** was applied to the related bifunctionalised BDA-protected aldehyde **40**, obtained by Swern oxidation of the reported corresponding alcohol[17] (Scheme 12). Thus, Corey–Fuchs reaction followed by hydroboration led consistently to the formation of the vinyl bromide **41**, alkyne **42** and vinyl boronate **43** in very high yields and without using any chromatographic purification.



Scheme 12. Applying the methodology in bisubstituted BDA-protected asymmetric diols. *Reagents and conditions*: (a) CBr_4, PPh_3, Zn, CH_2Cl_2, rt, 2 h, 84%; (b) *n*-BuLi, THF, −78 °C to rt; then NH_4Cl (satd), 100%; (c) pinacolborane, 100 °C, 24 h, 100%.

3. Conclusions

A new approach for the synthesis of dienes and enynes containing chiral 1,2-diols based on BDA-protected building blocks has been developed. A set of BDA-protected

asymmetric precursors for Pd-catalysed cross-coupling reactions has been synthesised, and their reactivity demonstrated. BDA removal is feasible even in highly conjugated systems. The method has been already used in the synthesis of the phytotoxic metabolite epipyriculol[41] and should prove useful in many different synthesis programmes.

4. Experimental

4.1. General methods

All reactions were performed in oven-dried glassware, under an inert argon atmosphere. All solvents used were reagent grade and distilled by standard procedures. All aqueous solutions were saturated and all reactions were magnetically stirred unless otherwise indicated, and monitored by GC–MS, on a Perkin–Elmer AutoSystem XL GC/TurboMass GC–MS spectrometer. Where sealed microwave tubes were used, these were sealed with Suba-Seal septa. Analytical TLC was carried out with precoated glass-backed plates (Merck Kieselgel 60 F_{254} plates), visualised by UV fluorescence (λ=254 nm) and stained with aq acidic ammonium molybdate(IV). Flash column chromatography and purification through silica pads were carried out using Merck Kieselgel (230–400 mesh). P.E. refers to petroleum ether, 40–60 °C boiling point.

Optical rotations were measured, unless the compound could not be isolated in sufficient purity, on a Perkin–Elmer Model 343 Polarimeter with a sodium lamp at 25 °C. $[\alpha]_D^{25}$ are given in 10^{-1} deg cm^2 g^{-1} and concentrations, c, are reported in g/100 mL. IR spectra were recorded on a Perkin–Elmer Spectrum One FT-IR Spectrometer and selected characteristic absorbances are reported neat, in cm^{-1} (abs). Proton magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz on a Bruker DPX-400 and are reported as follows: chemical shift δ in parts per million (number of protons, multiplicity, coupling constant J in hertz). Residual protic solvent was used as the internal reference, setting chloroform to δ 7.26. Carbon magnetic resonance spectra (^{13}C NMR) were recorded at 100 MHz on a Bruker DPX-400. Chemical shifts are quoted in parts per million, referenced to the appropriate solvent peak, taking chloroform as δ 77.0. Assignments were made using DEPT 135 experiments. Elemental analysis was carried out, unless the compound could not be isolated in sufficient purity, at the Department of Chemistry, University of Cambridge. High-resolution mass spectrometry (HRMS) was carried out on a Waters LCT Premier XE Spectrometer using electrospray ionisation (ESI) at the Department of Chemistry, University of Cambridge. X-ray crystal structures were recorded by the X-ray crystallography service at the Department of Chemistry, The University of Cambridge.

4.1.1. 1-((2R,5R,6R)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)ethanone (*11*)

Equatorial ester **8** (12.5 g, 53 mmol) and a solution of $Cp_2Ti(CH_3)_2$ in toluene–THF[42,43] (167 mL, 0.8 mmol g^{-1}, 1:1 in volume) were placed in a round-bottomed flask under argon and then additional toluene (53 mL) was added. The mixture was heated to 65 °C during 24 h. After that time the mixture was cooled and, following a reported procedure,[42,43] the reaction was quenched by careful addition of $NaHCO_3$ (6.4 g), MeOH (100 mL) and water (4 mL), and the resulting slurry was heated to 40 °C for 48 h. After cooling, solids were filtered off and the filtrates were concentrated under reduced pressure. The resulting crude was purified by column chromatography (pure P.E. to remove the cyclopentadienyl dimer and then 2% Et_2O in P.E.) to obtain the corresponding vinyl methyl ether of **8** (8.9 g, 71%, in <1 g scale the yields were >90%). This vinyl methyl ether (2.32 g, 10 mmol) was heated to 60 °C for 6 h in a saturated solution of ammonium chloride (100 mL). The mixture was extracted with Et_2O (100 mL) and the aqueous phases were further extracted with Et_2O (70 mL). The combined organic phases were dried over Na_2SO_4, filtrated and the volatiles removed under reduced pressure to obtain ketone **11** as an oil (1.7 g, 78%).

$[\alpha]_D^{25}$ −104 (*c* 0.85, $CHCl_3$). IR (neat, cm^{-1}): 2950, 1718, 1374, 1356, 1141, 1116, 1035. ^{1}H NMR δ: 4.27 (1H, dd, J= 10, 4), 3.66 (2H, m), 3.28 (3H, s), 3.22 (3H, s), 2.21 (3H, s), 1.32 (3H, s), 1.25 (3H, s). ^{13}C NMR δ: 206.9, 99.7, 98.0, 72.8, 59.4, 48.2, 48.0, 26.2, 17.5, 17.4. E.A. Calcd for $C_{10}H_{18}O_5$: C 55.03, H 8.31. Found: C 55.19, H 8.06. HRMS (ESI) *m/z* 241.1047 [(M+Na)$^+$; calcd for $C_{10}H_{18}O_5Na$: 241.1052].

4.1.2. 1-((2S,5R,6R)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)ethanone (*12*)

Methyllithium–lithium bromide complex (1.4 M solution in diethyl ether, 0.45 mL, 0.63 mmol) was added to a stirred solution of ester **9** (100 mg, 0.43 mmol) in dichloromethane (5 mL) at −78 °C. The mixture was stirred for 2 h then satd aq ammonium chloride (5 mL) was added and the mixture was allowed to return to rt. The layers were separated and the aqueous layer was extracted with Et_2O (10 mL×2). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed (Et_2O–P.E. 1:9) to give the title compound (66 mg, 71%).

R_f (10% Et_2O in P.E.): 0.17. IR (neat, cm^{-1}): 2931, 1711. ^{1}H NMR δ: 4.13 (1H, dd, J=6.0, 4.4), 4.01 (1H, dd, J=11.4, 6.0), 3.31 (6H, s), 2.28 (3H, s), 1.38 (3H, s), 1.29 (3H, s). ^{13}C NMR δ: 207.0, 100.5, 99.5, 74.9, 59.0, 50.0, 48.5, 26.4, 18.1, 18.0. HRMS (ESI) *m/z* 241.1057 [(M+Na)$^+$; calcd for $C_{10}H_{18}O_5Na$: 241.1052].

4.1.3. (2R,3R,5S)-5-(2,2-Dibromovinyl)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane (*13*)

Zn dust (1.96 g, 30 mmol) was added to a solution of triphenylphosphine (7.87 g, 30 mmol) in CH_2Cl_2 (100 mL) and the mixture was cooled to 0 °C. Carbon tetrabromide (9.95 g, 30 mmol) was added and the green mixture was stirred for 15 min. The ice-bath was removed and, after stirring for another 15 min, a solution of **7** (2.04 g, 10 mmol) in CH_2Cl_2 (40 mL) was added. The mixture was stirred for 2 h turning from green to grey to brown. After this time, pentane (120 mL) was added whereupon a precipitate was formed. The mixture was filtered and the filtrate was washed again with

pentane (120 mL) and refiltered. The solvent was removed in vacuo and the resulting crude was redissolved in pentane (120 mL) and placed in the fridge overnight, after which the mixture was filtered once more and the solvent removed again in vacuo to yield pure **13** as a pale yellow solid (3.40 g, 94%). A sample was further purified by column chromatography (P.E., then 4% Et_2O in P.E.) that, upon storage in the fridge, afforded crystals of **13**.

R_f (5% Et_2O in P.E.): 0.37. $[\alpha]_D^{25}$ −77.6 (*c* 1.05, $CHCl_3$). IR (neat, cm^{-1}): 2952, 1612, 1142, 1119. ^1H NMR δ: 6.52 (1H, d, *J*=15), 6.46 (1H, dd, *J*=15, 5), 4.35 (1H, ddd, *J*=11, 5, 3), 3.60 (1H, t, *J*=11), 3.43 (1H, dd, *J*=11, 3), 3.26 (3H, s), 3.25 (3H, s), 1.30 (3H, s), 1.28 (3H, s). ^{13}C NMR δ: 141.2, 99.4, 97.9, 80.2, 70.1, 62.0, 48.1, 48.0, 17.8, 17.5. E.A. Calcd for $C_{10}H_{16}Br_2O_4$: C 33.36, H 4.48. Found: C 33.41, H 4.40.

*4.1.4. (2R,3R,5S)-5-((E)-2-Iodovinyl)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane (**14**)*

(i) From aldehyde **7** (Takai reaction): aldehyde **7** (612 mg, 3 mmol) and CHI_3 (4.73 g, 12 mmol, 4 equiv) were dissolved in THF (15 mL) under argon. This solution was added dropwise to a magnetically stirred dispersion of $CrCl_2$ (4.43 g, 36 mmol, 12 equiv) in THF (45 mL) at rt and the mixture was stirred for 24 h. After this time the mixture was poured into water (200 mL) and extracted with ether (200 mL). The aqueous phase was further extracted with ether (200 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuo. The remaining crude was purified by column chromatography (3% Et_2O in P.E., then 8% and 15%) to give the vinyl iodide **14** as a 9:1 (*E*/*Z* ratio) mixture (442 mg, 1.35 mmol, 45%). (ii) From vinylsilane **26**: vinylsilane (1.5 g, 5.48 mmol) was dissolved in acetonitrile (20 mL) under argon, NIS (2.96 g, 13.14 mmol) was added and the tube flushed again with argon. The mixture was heated to 85 °C for 1 h after which it was cooled to rt. Then P.E. (50 mL) was added and the whole mixture was passed through a pad of silica, washed with 20% ether in P.E. (300 mL) and concentrated in vacuo to yield **8** as a yellow oil, which solidified to a gum on cooling at −10 °C (0.90 g, 2.74 mmol, 50%), *E*/*Z* 8:1. Compound **8** was recrystallised from hexane at −20 °C.

R_f (10% Et_2O in P.E.): 0.28. $[\alpha]_D^{25}$ −146.2 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2950, 2832, 1372, 1142, 1116, 1037. ^1H NMR δ: 6.38 (1H, d, *J*=8), 4.61 (1H, ddd, *J*=11, 8, 4), 3.57 (1H, t, *J*=11), 3.45 (1H, dd, *J*=11, 4), 3.29 (3H, s), 3.23 (3H, s), 1.25 (6H, s). ^{13}C NMR δ: 134.1, 98.8, 97.4, 93.4, 68.5, 59.7, 47.9, 47.6, 17.2, 17.1. HRMS (ESI) *m*/*z* 351.0065 [$(M+Na)^+$; calcd for $C_{10}H_{17}IO_4Na$: 351.0069].

*4.1.5. (2R,3R,5S)-5-Ethynyl-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane (**15**)*

n-BuLi (24.4 mL, 39.07 mmol, 1.6 M in hexanes) was added dropwise over 15 min to a solution of **13** (5.0 g, 13.89 mmol) in THF (140 mL) at −78 °C. The solution was allowed to return to rt over 30 min, after which NH_4Cl (aq) (90 mL) was added and the aqueous layer was extracted with ether (2×130 mL). The organic fractions were combined and washed with water (2×100 mL) and brine (100 mL), then dried over $MgSO_4$, filtered and concentrated in vacuo to give **15** as a yellow oil (2.78 g, 13.89 mmol, 100%).

R_f (5% Et_2O in P.E): 0.32. $[\alpha]_D^{25}$ −154.4 (*c* 1.13, $CDCl_3$). IR (neat, cm^{-1}): 3259, 2951, 2123, 1141, 1115. ^1H NMR δ: 4.58 (1H, ddd, *J*=11, 3, 2), 3.76 (1H, t, *J*=11), 3.48 (1H, dd, *J*=11, 3), 3.25 (3H, s), 3.21 (3H, s), 2.42 (1H, d, *J*=2), 1.26 (3H, s), 1.20 (3H, s). ^{13}C NMR δ: 99.4, 97.9, 79.0, 74.7, 62.4, 58.7, 48.2, 47.9, 17.6, 17.4. E.A. Calcd for $C_{10}H_{16}O_4$: C 59.98, H 8.05. Found: C 62.14, H 8.65.

*4.1.6. (2R,3R,5S)-5-(Iodoethynyl)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane (**16**) and (2R,3R,5S)-5-((Z)-2-iodovinyl)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane (**17**)*

n-BuLi (1.38 mL, 2.2 mmol, 1.6 M in hexane) was added dropwise to a solution of **13** (360 mg, 1.0 mmol) in THF (8 mL) at −78 °C. The mixture was stirred for 15 min then allowed to return to rt over 30 min. After cooling again to −78 °C, iodine (305 mg, 1.2 mmol) was added and the bath allowed to warm gradually to rt over 2 h. The reaction was stirred overnight at rt. Water (11 mL) was added and the phases were separated. The aqueous phase was extracted with ether (2×2 mL). The ether phases were combined, washed with sodium thiosulfate (aq, 6 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to yield **16**. Crude **16** was used directly in the next step.

Dipotassium azodicarboxylate was prepared according to the literature procedure[24] by adding azodicarbonamide (1.16 g, 10 mmol) to a 40% aq potassium hydroxide solution (1.344 g, 24 mmol in 2 mL H_2O) at 10 °C. After addition, the mixture was stirred for 45 min at 10 °C, then filtered, precipitated with cold methanol (4 mL), filtered again and washed with further cold methanol (4 mL). The solid potassium salt (580 mg) was added to **16** (326 mg, 1 mmol) in methanol (4 mL). A solution of acetic acid (429 μL, 7.5 mmol) in methanol (20 mL) was added at such a rate as to cause gentle boiling, whereupon the solution turned colourless. Water (50 mL) was added and the aqueous layer was extracted with petroleum ether (3×30 mL). The organic fractions were combined and washed with water (2×25 mL), then dried over $MgSO_4$, filtered and concentrated in vacuo to give **17** as a yellow oil (97.9 mg, 0.30 mmol, 30% over 2 steps).

17: $[\alpha]_D^{25}$ −159.1 (*c* 1.0, $CDCl_3$). IR (neat, cm^{-1}): 2954, 1617, 1141, 1118. ^1H NMR δ: 6.47 (1H, d, *J*=8), 6.21 (1H, t, *J*=8), 4.71 (1H, ddd, *J*=11, 8, 3), 3.59 (1H, t, *J*=11), 3.48 (1H, dd, *J*=11, 3), 3.33 (3H, s), 3.26 (3H, s), 1.29 (3H, s), 1.28 (3H, s). ^{13}C NMR δ: 137.3, 99.0, 97.9, 85.1, 71.2, 60.2, 48.4, 48.0, 17.8, 17.5. E.A. Calcd for $C_{10}H_{17}IO_4$: C 36.60, H 5.22. Found: C 41.03, H 5.90.

*4.1.7. ((E)-2-((2S,5R,6R)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**18**)*

Alkyne **15** (300 mg, 1.5 mmol) and pinacolborane (435 μL, 3 mmol, 2 equiv) were placed in a sealed tube under argon and the mixture was heated at 80 °C for 6 h. Then, the crude mixture was heated at 100 °C under high vacuum (<2 Torr) for 6 h

using a trap cooled at −78 °C to resolidify the removed pinacol. After this treatment, pure **18** was obtained in the flask (345 mg, 1.05 mmol, 70%).

R_f (50% Et_2O in P.E.): 0.17. ^1H NMR δ: 6.48 (1H, dd, J=18, 5), 5.76 (1H, dd, J=18, 2), 4.44 (1H, dddd, J=11, 5, 4, 2), 3.61 (1H, t, J=11), 3.47 (1H, dd, J=11, 4), 3.26 (3H, s), 3.25 (3H, s), 1.30 (3H, s), 1.29 (3H, s), 1.25 (12H, s).

*4.1.8. (2R,3R,5R)-5-(2,2-Dibromovinyl)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane (**19**)*

Zinc dust (0.96 g, 14.7 mmol) was added to a solution of triphenylphosphine (3.86 g, 14.7 mmol) in dichloromethane (50 mL). The mixture was cooled to 0 °C and carbon tetrabromide (4.88 g, 14.7 mmol) was added. The mixture was stirred for 15 min, then removed from the ice-bath and stirred a further 15 min. A solution of aldehyde **10** (1 g, 4.9 mmol) in dichloromethane (20 mL) was added and the mixture was stirred for 2 h. Pentane (50 mL) was added and the mixture was filtered, then the residue was redissolved in dichloromethane (30 mL) and this solution was diluted with pentane (30 mL) and filtered again. This procedure was repeated for a total of four filtrations. The combined filtrates were concentrated in vacuo and the residue chromatographed (petroleum ether then Et_2O–P.E. 4:96) to give **19** (1.69 g, 96%).

R_f (50% Et_2O in P.E.): 0.73. $[\alpha]_D^{25}$ −110 (c 0.82, $CHCl_3$). IR (neat, cm^{-1}): 2992, 2948, 2832, 1609. ^1H NMR δ: 7.08 (1H, d, J=9), 4.28 (1H, ddd, J=8, 4, 1), 4.06 (1H, dd, J=12, 4), 3.39 (1H, dd, J=12, 1), 3.28 (3H, s), 3.22 (3H, s), 1.30 (3H, s), 1.26 (3H, s). ^{13}C NMR δ: 138.3, 99.2, 98.9, 92.9, 70.1, 60.8, 48.7, 48.3, 18.3, 17.8. HRMS (ESI) m/z 380.9308 [(M+Na)$^+$; calcd for $C_{10}H_{16}Br_2O_4Na$: 380.9313].

*4.1.9. 2R,3R,5R-5-Ethynyl-2,3-dimethoxy-2,3-dimethyl-[1,4]dioxane (**20**)*

n-Butyllithium (1.5 M solution in hexane, 2.89 mL, 4.20 mmol) was added dropwise to a solution of vinyl dibromide **19** (0.69 g, 1.90 mmol) in THF (15 mL) at −78 °C. The mixture was stirred for 15 min then allowed to return to rt over 30 min. Ammonium chloride (aq, 10 mL) was added and the layers were separated. The aqueous layer was further extracted with Et_2O (15 mL×2) then the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (Et_2O–P.E. 3:97 then 15:85) to give **20** (0.30 g, 79%).

R_f (50% Et_2O in P.E): 0.47. $[\alpha]_D^{25}$ −149 (c 0.23, $CHCl_3$). IR (neat, cm^{-1}): 3253, 2953, 2330. ^1H NMR δ: 4.49 (1H, m), 4.08 (1H, dd, J=11, 5), 3.67 (1H, dd, J=11, 2), 3.37 (3H, s), 3.29 (3H, s), 2.43 (1H, d, J=2.5), 1.36 (3H, s), 1.29 (3H, s). ^{13}C NMR δ: 99.0 (2C), 83.0, 72.0, 62.2, 59.6, 49.7, 48.4, 18.6, 18.0. HRMS (ESI) m/z 223.0940 [(M+Na)$^+$; calcd for $C_{10}H_{16}O_4Na$: 223.0946].

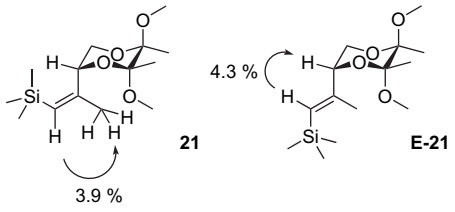
*4.1.10. ((Z)-2-((2R,5R,6R)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)prop-1-enyl)trimethylsilane (**21**) and (E)-isomer (**E-21**)*

Ketone **12** (5.2 g, 23.85 mmol) and $CpTi(CH_2SiMe_3)_3$[28] (10.705 g, 28.62 mmol, 1.2 equiv) were placed in a round-bottomed flask and purged with argon. 1,4-Dioxane (125 mL) was added and the solution was magnetically stirred at reflux temperature for 24 h. After that time the dioxane was removed under reduced pressure, the resulting mixture was dissolved in 4% Et_2O–P.E., filtered through filter paper, concentrated under reduced pressure and purified by careful column chromatography (2% Et_2O in P.E.) to obtain neat **21** (1.9 g), a mixture of **21** and ***E*-21** (1.8 g, major ***E***) and ***E*-21** (9:1 *E*/*Z*, 550 mg), total yield: 63%. Equatorial ketone **11** (200 mg) was also recovered as by-product.

21: R_f (6% Et_2O in P.E.): 0.38. $[\alpha]_D^{25}$ −63 (c 1.19, $CHCl_3$). IR (neat, cm^{-1}): 2950, 2831, 1618. ^1H NMR δ: 5.42 (1H, q, J=1), 4.95 (1H, dd, J=12, 4), 3.98 (1H, t, J=11), 3.47 (1H, dd, J=11, 4), 3.34 (3H, s), 3.30 (3H, s), 1.82 (3H, d, J=1), 1.32 (6H, s), 0.08 (9H, s). ^{13}C NMR δ: 150.7, 130.3, 100.2, 99.5, 72.6, 64.3, 48.0, 47.2, 21.0, 17.8, 17.5, −0.7 (3C). HRMS (ESI) m/z 311.1663 [(M+Na)$^+$; calcd for $C_{14}H_{28}O_4SiNa$: 311.1655].

***E*-21**: R_f (6% Et_2O in P.E.): 0.34. $[\alpha]_D^{25}$ −96.6 (c 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2951, 1620, 1372, 1248, 1141, 1114, 1041, 836. ^1H NMR δ: 5.56 (1H, s), 4.47 (1H, dd, J=11, 4), 3.77 (1H, t, J=11), 3.62 (1H, dd, J=11, 4), 3.34 (3H, s), 3.29 (3H, s), 1.74 (3H, s), 1.37 (3H, s), 1.33 (3H, s), 0.07 (9H, s). ^{13}C NMR δ: 150.0, 125.5, 100.3, 99.5, 76.2, 64.9, 48.2, 47.8, 17,7, 17.5, 17.4, −0.5 (3C). E.A. Calcd for $C_{14}H_{28}O_4Si$: C 58.29, H 9.78. Found: C 58.40, H 9.61. HRMS (ESI) m/z 311.1654 [(M+Na)$^+$; calcd for $C_{14}H_{28}O_4SiNa$: 311.1655].

Significant results from NOE experiments are shown below.



*4.1.11. (Z)-2R,3R,5R-5-(2′-Iodo-1′-methyl-vinyl)-2,3-dimethoxy-2,3-dimethyl-[1,4]dioxane (**22**)*

N-Iodosuccinimide (125 mg, 0.56 mmol) was added to a solution of vinylsilane **21** (80 mg, 0.28 mmol) in acetonitrile (2 mL) in a flask protected from light. The mixture was stirred for 16 h then sodium sulfite (aq, 5 mL) was added and the mixture stirred vigorously for 5 min until colourless. The layers were separated and the aqueous layer was extracted with Et_2O (10 mL×2). The combined organic extracts were washed with 1 M sodium hydroxide (10 mL) and brine (10 mL), then dried (Na_2SO_4) and concentrated in vacuo to afford the vinyl iodide **22** (92 mg, 97%) as prisms, mp 53–56 °C.

R_f (10% Et_2O in P.E): 0.22. $[\alpha]_D^{25}$ −47 (c 0.77, $CHCl_3$). IR (neat, cm^{-1}): 2958, 2831. ^1H NMR δ: 6.04 (1H, m), 5.02 (1H, dd, J=10, 4), 3.78 (1H, J=11), 3.74 (1H, dd, J=10.8, 4.3), 3.38 (3H, s), 3.35 (3H, s), 1.94 (3H, d, J=1), 1.42 (3H, s), 1.38 (3H, s). ^{13}C NMR δ: 144.8, 100.8, 100.1, 76.5, 75.2, 62.1, 49.0, 48.5, 20.5, 18.1, 17.9. HRMS (ESI) m/z 365.0232 [(M+Na)$^+$; calcd for $C_{11}H_{19}O_4INa$: 365.0226].

*4.1.12. (Z)-2R,3R,5R-5-(2′-Bromo-1′-methyl-vinyl)-2, 3-dimethoxy-2,3-dimethyl-[1,4]dioxane (**23**)*

N-Bromosuccinimide (579 mg, 3.25 mmol, 1.05 equiv) was added to a solution of vinylsilane **21** (890 mg, 3.1 mmol) in acetonitrile (12 mL) in a flask protected from light. The mixture was stirred for 1 h, then a hexane–ether solution (95:5 in volume) was added to the yellow concentrated mixture, observing the precipitation of a brown solid. This mixture was passed through a pad of silica and washed with the same solvent mixture to afford, after concentration in vacuo, the vinyl bromide **23** (910 mg, quantitative) as an oil that solidified to a white solid on cooling.

R_f (10% Et_2O in P.E.): 0.35. $[\alpha]_D^{25}$ −63.7 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2949, 2832, 1456, 1373, 1142, 1114, 1059, 1040, 1020. ^1H NMR δ: 5.96 (1H, m), 5.12 (1H, dd, *J*=10, 5), 3.72 (2H, m), 3.33 (3H, s), 3.32 (3H, s), 1.83 (3H, d, *J*=1), 1.38 (3H, s), 1.34 (3H, s). ^{13}C NMR δ: 138.9, 102.6, 100.1, 99.4, 70.5, 61.3, 48.3, 47.9, 18.2, 17.4, 17.3. E.A. Calcd for $C_{11}H_{19}BrO_4$: C 44.76, H 6.49. Found: C 44.72, H 6.36.

*4.1.13. 2-((Z)-2-((2R,5R,6R)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)prop-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**24**)*

Vinyl bromide **23** (236 mg, 0.8 mmol), pinacolborane dimer (244 mg, 0.96 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (16.8 mg, 0.024 mmol, 3%) and KOPh[44] (158 mg, 1.2 mmol, 1.5 equiv) were placed in a round-bottomed flask and purged with argon. Toluene (10 mL) was added and the resulting mixture was heated at 80 °C for 90 min. The reaction was quenched with water and extracted with ether. The organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The remaining crude was purified by column chromatography to give pure vinyl boronate **24** (21 mg) as first elution and a mixture of **24** with phenol (90 mg) secondly. This mixture was dissolved in ether and extracted with a 10 wt % NaOH aqueous solution (×2), water (×2), brine, dried over Na_2SO_4 and concentrated to give additional **24** (55 mg, combined yield 28%).

$[\alpha]_D^{25}$ −43.9 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2979, 1636, 1447, 1372, 1141, 1116. ^1H NMR δ: 5.56 (1H, dd, *J*=12, 4), 5.27 (1H, s), 3.85 (1H, dd, *J*=11, 10), 3.61 (1H, dd, *J*=10, 4), 3.40 (3H, s), 3.39 (3H, d, *J*=1), 1.93 (3H, s), 1.42 (3H, s), 1.38 (3H, s), 1.24 (12H, m). ^{13}C NMR δ: 159.1, 100.6, 99.9, 83.0 (2C), 72.2, 65.1, 48.7, 48.3, 24.9 (4C), 22.0, 18.2, 18.0. E.A. Calcd for $C_{17}H_{31}BO_6$: C 59.66, H 9.13. Found: C 59.85, H 9.11.

*4.1.14. (2R,3R,5S)-5-((Z)-1-Iodoprop-1-en-2-yl)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane (**25**)*

A 1 M solution of NaHMDS in THF (8.3 mL, 1.2 equiv) was added over a suspension of $(Ph_3PCH_2I)I$ (see preparation below) in THF (10 mL). The mixture was stirred for 1 min at rt observing the dissolution of the salt. After rapid cooling at −78 °C, a solution of ketone **11** (1.5 g, 6.9 mmol) in THF (4 mL) was added dropwise at −78 °C and the mixture was stirred for 30 min, then allowed to reach rt. The mixture was stirred at rt for additional 3 h and then ether and ammonium chloride (aq) were added. The aqueous phase was extracted with additional ether and the combined organic phases were washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified by column chromatography (4% Et_2O in P.E.) to give vinyl iodide **25** (*E*/*Z* molar ratio=1:8, 708 mg, 30%).

R_f (5% Et_2O in P.E.): 0.23. $[\alpha]_D^{25}$ −189 (*c* 0.97, $CHCl_3$). IR (neat, cm^{-1}): 2953, 1374, 1140, 1120, 1039. ^1H NMR δ: 6.02 (1H, m), 4.84 (1H, dd, *J*=11, 3), 3.61 (1H, t, *J*=11), 3.39 (1H, dd, *J*=11, 4), 3.30 (3H, s), 3.25 (3H, s), 1.88 (3H, d, *J*=1.5), 1.29 (3H, s), 1.26 (3H, s). ^{13}C NMR δ: 143.8, 99.0, 97.8, 76.1, 70.2, 59.2, 48.2, 48.0, 19.9, 17.7, 17.6. E.A. Calcd for $C_{11}H_{19}IO_4$: C 38.61, H 5.60. Found: C 40.67, H 5.73.

Preparation of the salt $(Ph_3PCH_2I)I$: following the reported procedure,[31] but changing benzene for toluene as solvent, PPh_3 (13.11 g, 50 mmol) and diiodomethane (17.41 g, 65 mmol, 1.3 equiv) were dissolved in toluene (15 mL) and the mixture heated at 50 °C overnight. The product was formed as a precipitate from the reaction mixture. The salt was filtered off, washed thoroughly with toluene and then with P.E. (40:30) and dried in vacuo. The yield was consistent with the reported example.[31] The salt was immiscible in all deuterated solvents tested. E.A. Calcd for $C_{19}H_{17}I_2P$: C 43.04, H 3.23, P 5.84. Found: C 42.98, H 3.16, P 5.80.

*4.1.15. ((E)-2-((2S,5R,6R)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)vinyl)trimethylsilane (**26**)*

Aldehyde **7** (7.0 g, 34.3 mmol) and $CpTi(CH_2SiMe_3)_3$[28] (15.4 g, 41.2 mmol, 1.2 equiv) were placed in a round-bottomed flask and purged with argon. 1,4-Dioxane (175 mL) was added and the solution was magnetically stirred at reflux temperature overnight, the starting material being consumed at this time as monitored by TLC. The dioxane was removed under reduced pressure, the resulting mixture was dissolved in 4% Et_2O–P.E. and the slurry was purified by column chromatography, both *E* (R_f in 10% Et_2O in P.E.: 0.62) and *Z* (R_f in 10% Et_2O in P.E.: 0.50) isomers of **26** coming out together under different elution conditions. After solvent removal under reduced pressure, a mixture of isomers 1.2:1 (*Z*/*E*, 3.6 g, 38% yield) was obtained as a yellow oil.

This mixture of isomers (3.014 g, 11 mmol) was treated with azaisobutyronitrile (AIBN, 90.3 mg, 5 mol %) and thiophenol (56.5 μL, 5 mol %) in toluene (28 mL) at 80 °C for 5 h, monitoring the reaction by GC. At this time the solution was cooled and passed through a pad of silica and eluted with 10% Et_2O in P.E. (600 mL), then washed with 10 wt % NaOH aqueous solution (500 mL), water (500 mL×2) and brine (500 mL). After drying over Na_2SO_4, filtration and removal of the solvents under reduced pressure, pure ***E*-26** was obtained as an oil (2.74 g, 91%).

***E*-26**: R_f (10% Et_2O in P.E.): 0.50. $[\alpha]_D^{25}$ −116.6 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2952, 2831, 1622, 1373, 1249, 1141, 1120, 1038, 862, 839. ^1H NMR δ: 5.92 (2H, m), 4.35 (1H, dtd, *J*=11, 3, 1), 3.58 (1H, t, *J*=11), 3.42 (1H, dd, *J*=11, 4), 3.28 (3H, s), 3.27 (3H, s), 1.31 (3H, s), 1.29 (3H, s), 0.05 (9H, s). ^{13}C NMR δ: 141.2, 133.4, 99.1, 97.8, 70.3,

62.7, 48.0, 47.9, 17.9, 17.6, −1.4 (3C). E.A. Calcd for $C_{13}H_{26}O_4Si$: C 56.90, H 9.55. Found: C 57.97, H 9.43.

*4.1.16. (2R,3R,5S)-5-((E)-2-Bromovinyl)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane (**27**)*

Vinylsilane **26** (54.8 mg, 0.2 mmol) was dissolved in acetonitrile (1 mL) under argon in a flask protected from light. NBS (71.2 mg, 0.4 mmol) was added and the tube flushed again with argon. The mixture was heated to 90 °C for 1 h. Flash chromatography (5% ether in P.E.) yielded **27** as a brown oil (*E*/*Z* 15:1, 19.1 mg, 0.07 mmol, 34%).

R_f (10% Et_2O in P.E.): 0.56. $[\alpha]_D^{25}$ −107.3 (*c* 0.34, $CDCl_3$). IR (neat, cm^{-1}): 2782, 1630, 1142, 1117. ^1H NMR δ: 6.46 (1H, dd, *J*=14, 1), 6.12 (1H, dd, *J*=14, 6), 4.36 (1H, dddd, *J*=11, 6, 3, 1), 3.60 (1H, t, *J*=11), 3.42 (1H, dd, *J*=11, 3), 3.36 (3H, s), 3.35 (3H, s), 1.29 (3H, s), 1.27 (3H, s). ^{13}C NMR δ: 133.1, 109.8, 99.3, 97.9, 68.2, 62.2, 48.1, 48.0, 17.7, 17.5. E.A. Calcd for $C_{10}H_{17}BrO_4$: C 42.72, H 6.09, Br 28.42. Found: C 43.36, H 6.21, Br 28.36.

*4.1.17. (2E,4E)-Ethyl-5-((2S,5R,6R)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)penta-2,4-dienoate (**29a**)*

Ethyl acrylate (97.5 μL, 0.9 mmol), P(*t*-Bu)$_3$ (60 μL of a 1 M solution in toluene, 0.06 mmol, 10 mol %) and dicyclohexylmethylamine (192.6 μL, 0.9 mmol) were added to Pd_2dba_3 (27.6 mg, 0.03 mmol, 10 mol %) and **14** (196.8 mg, 0.6 mmol) in toluene (6 mL) under argon and heated to 120 °C in a sealed tube for 24 h. The mixture was then passed through a pad of silica, eluted with CH_2Cl_2 (600 mL) and the solvents were removed in vacuo. The crude was purified by column chromatography (P.E.−Et_2O 4:1) to yield **29a** as yellow oil (93 mg, 0.31 mmol, 52%).

R_f (50% Et_2O in P.E.): 0.36. $[\alpha]_D^{25}$ −91.3 (*c* 0.665, $CDCl_3$). IR (neat, cm^{-1}): 2957, 1714, 1649, 1619, 1142, 1116. ^1H NMR δ: 7.20 (1H, dd, *J*=15, 11), 6.43 (1H, dd, *J*=15, 11), 5.94 (1H, dd, *J*=15, 6), 5.89 (1H, d, *J*=15), 4.50 (1H, ddd, *J*=11, 6, 3), 4.19 (2H, q, *J*=7), 3.59 (1H, t, *J*=11), 3.44 (1H, dd, *J*=11, 3), 3.27 (3H, s), 3.25 (3H, s), 1.31 (3H, s), 1.28 (3H, s), 1.23 (3H, t, *J*=7). ^{13}C NMR δ: 166.7, 143.3, 136.8, 129.8, 122.3, 99.2, 97.9, 67.7, 62.5, 60.3, 48.1, 48.0, 17.8, 17.5, 14.2.

*4.1.18. (2R,3R,5S)-2,3-Dimethoxy-2,3-dimethyl-5-(2-methylstyryl)-1,4-dioxane (**30**)*

Vinyl iodide **14** (32.8 mg, 0.10 mmol), *o*-tolylboronic acid (20.39 mg, 0.15 mmol), $Pd(OAc)_2$ (1.12 mg, 0.005 mmol), SPhos (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, 2.63 mg, 0.0075 mmol) and K_3PO_4 (42.4 mg, 0.20 mmol) were dissolved in toluene (0.5 mL) under argon and heated at 110 °C in a sealed tube for 4 h. The mixture was then passed through a pad of silica and eluted with CH_2Cl_2 (50 mL). Water (50 mL) was added to the filtrate and the aqueous phase was further extracted with ether (2×25 mL). The organic fractions were combined and washed with water (2×25 mL) and brine (25 mL), then dried over Na_2SO_4, filtered and concentrated in vacuo to give **30** as a brown oil (22.46 mg, 0.077 mmol, 77%).

R_f (20% Et_2O in P.E.): 0.37. ^1H NMR δ: 7.44 (1H, m), 7.14 (3H, m), 6.86 (1H, d, *J*=16), 6.02 (1H, dd, *J*=16, 7), 4.56 (1H, ddd, *J*=11, 7, 3), 3.73 (1H, t, *J*=11), 3.50 (1H, dd, *J*=11, 3), 3.34 (3H, s), 3.30 (3H, s), 2.34 (3H, s), 1.34 (3H, s), 1.32 (3H, s). HRMS (ESI) *m*/*z* 315.1591 [(M+Na)$^+$; calcd for $C_{17}H_{24}O_4Na$: 315.1573].

*4.1.19. (2R,3R,5S)-2,3-Dimethoxy-2,3-dimethyl-5-((E)-prop-1-enyl)-1,4-dioxane (**32**)*

Trimethylboroxine (99.0 μL, 0.71 mmol) was added to $PdCl_2(dppf)\cdot CH_2Cl_2$ (3.87 mg, 0.005 mmol), **14** (155.6 mg, 0.47 mmol) and potassium carbonate (196.7 mg, 1.42 mmol) in 1,4-dioxane (2 mL) under argon and heated to 110 °C in a sealed tube for 48 h. The mixture was then passed through a pad of silica and eluted with CH_2Cl_2 (100 mL). Water (100 mL) was added to the filtrate and the aqueous phase was further extracted with ether (2×50 ml). The organic fractions were combined and washed with water (2×50 mL) and brine (50 mL), then dried (Na_2SO_4), filtered and concentrated in vacuo to give **32** as a yellow oil (96.4 mg, 0.45 mmol, 95%).

R_f (10% Et_2O in P.E.): 0.29. $[\alpha]_D^{25}$ −139.3 (*c* 1.115, $CDCl_3$). IR (neat, cm^{-1}): 2949, 1730, 1140, 1118. ^1H NMR δ: 5.77 (1H, dd, *J*=15, 7), 5.38 (1H, ddd, *J*=15, 7, 1), 4.26 (1H, ddd, *J*=11, 7, 3), 3.58 (1H, t, *J*=11), 3.36 (1H, dd, *J*=11, 3), 3.26 (3H, s), 3.24 (3H, s), 1.68 (3H, dd, *J*=6, 1), 1.28 (3H, s), 1.26 (3H, s). ^{13}C NMR δ: 130.4, 127.0, 99.0, 97.7, 68.7, 63.0, 47.9, 47.9, 17.9, 17.9, 17.6. E.A. Calcd for $C_{11}H_{20}O_4$: C 61.09, H 9.32. Found: C 60.66, H 8.96.

*4.1.20. (2R,3R,5S)-2,3-Dimethoxy-2,3-dimethyl-5-((3,4,5-trimethoxyphenyl)ethynyl)-1,4-dioxane (**35**)*

Hünig's base (543 μL, 3.12 mmol) was added to **15** (832 mg, 4.16 mmol), **34** (612.5 mg, 2.08 mmol), $Pd(PPh_3)_2Cl_2$ (73.0 mg, 0.104 mmol) and CuI (19.8 mg, 0.104 mmol) in toluene (12.5 mL) under argon, and stirred at rt for 24 h. The mixture was then passed through a pad of silica and eluted with ether (500 mL). Water (500 mL) was added to the filtrate and the aqueous phase was further extracted with ether (2×500 mL). The organic fractions were combined and washed with water (2×500 mL) and brine (500 mL), then dried (Na_2SO_4), filtered and concentrated in vacuo to give **35** as a brown oil (556 mg, 1.52 mmol, 73%, eq./ax. ratio 7:1).

IR (neat, cm^{-1}): 2950, 2248, 1577, 1115. ^1H NMR δ: 6.66 (2H, s), 4.83 (1H, dd, *J*=11, 3), 3.88 (1H, t, *J*=11), 3.80 (s, 3H), 3.78 (6H, s), 3.59 (1H, dd, *J*=11, 3), 3.32 (3H, s), 3.26 (3H, s), 1.32 (3H, s), 1.25 (3H, s). ^{13}C NMR δ: 152.9, 139.1, 117.1, 109.2, 99.4, 97.9, 86.4, 83.1, 62.6, 60.8, 59.4, 59.1, 48.4, 48.0, 17.7, 17.5. HRMS (ESI) *m*/*z* 367.1773 [(M+H)$^+$; calcd for $C_{19}H_{27}O_7$: 316.1757].

*4.1.21. (2R,3R,5S)-5-((4-Chlorophenyl)ethynyl)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane (**37**)*

Hünig's base (105 μL, 0.60 mmol) was added to **15** (80 mg, 0.40 mmol), **36** (427.7 mg, 0.20 mmol), $Pd(PPh_3)_2Cl_2$ (14.0 mg, 0.02 mmol) and CuI (3.8 mg, 0.02 mmol) in toluene (1 mL) under argon, and stirred at rt for 24 h. The mixture was

then passed through a pad of silica and eluted with ether (100 mL). Water (100 mL) was added to the filtrate and the aqueous phase was further extracted with ether (2×50 mL). The organic fractions were combined and washed with water (2×50 mL) and brine (50 mL), then dried over Na_2SO_4, filtered and concentrated in vacuo to give **37** as a brown oil (70 mg, 0.225 mmol, 56%, eq./ax. ratio 5:1).

IR (neat, cm^{-1}): 2950, 2248, 1593, 1141, 1114. ^1H NMR δ: 7.37 (2H, d, J=9), 7.25 (2H, d, J=9), 4.86 (1H, dd, J=11, 3), 3.92 (1H, t, J=11), 3.62 (1H, dd, J=11, 3), 3.35 (3H, s), 3.29 (3H, s), 1.35 (3H, s), 1.29 (3H, s). ^{13}C NMR δ: 134.7, 133.2, 128.6, 120.7, 99.5, 98.0, 85.3, 85.1, 62.5, 59.4, 48.4, 48.1, 17.8, 17.5.

*4.1.22. (S,2E,4E)-Ethyl 6,7-dihydroxyhepta-2,4-dienoate (**39**)*

BDA-protected diene **29a** (60 mg, 0.2 mmol) was placed in a sealed tube under argon. Then, EtOH (0.6 mL) and 2 N HCl (aq, 0.4 mL, 0.8 mmol, 4 equiv) were added and the mixture was heated at 80 °C for 90 min, observing the consumption of the starting material on TLC. After cooling, $NaHCO_3$ (67 mg, 0.8 mmol) was added. The resulting mixture was directly purified by column chromatography (60% Et_2O in P.E., then 100% Et_2O) to obtain diol **39** as an oil (27 mg, 0.145 mmol, 73%).

R_f (100% Et_2O): 0.25. $[\alpha]_D^{25}$ −2.2 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3382 (br s), 2934, 1693, 1644, 1618, 1231, 1139, 1030, 998. ^1H NMR δ: 7.25 (1H, dd, J=15, 11), 6.47 (1H, dd, J=15, 11), 6.08 (1H, dd, J=15, 5.5), 5.90 (1H, d, J=15), 4.37 (1H, m), 4.20 (2H, q, J=7), 3.71 (1H, dd, J=11, 3), 3.53 (1H, dd, J=11, 7), 1.29 (3H, t, J=7). ^{13}C NMR δ: 166.9, 143.3, 140.0, 129.2, 122.2, 72.3, 66.0, 60.4, 14.2. HRMS (ESI) *m/z* 209.0799 [$(M+Na)^+$; calcd for $C_9H_{14}O_4Na$: 209.0790].

5. Supplementary data

X-ray crystallographic data for compounds **13**, **14** and **25** can be found in the database of the X-ray Service of the Department of Chemistry, The University of Cambridge, references: SL0744 (**13**), SL0712 (**14**) and SL0702 (**25**).

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