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Diastereo- and enantioselective synthesis of 1,3,5,7-tetraol structural units using a Prins cyclisation–reductive cleavage sequence†‡

Elodie Brun, Véronique Bellosta and Janine Cossy*

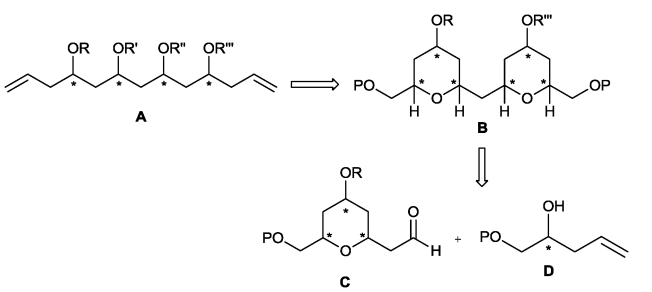
Stereocontrolled and efficient access to all the diastereomers of 1,3,5,7-tetraol structural units was developed using a Prins cyclisation–reductive cleavage sequence applied to tetrahydropyran aldehydes. Furthermore, these tetraols can be selectively functionalized.

Polyols are present in a great diversity of natural products, with different bioactive profiles.[1a] Therefore, a number of synthetic methods and strategies have been developed in the past few decades to access these scaffolds.[1] The most straightforward strategy involves an iterative sequence, including a step using chiral reagents, to access 1,3,5-triols which relies on one-directional chain elongation.[2] Desymmetrisation of *meso*-polyols and/or derivatives has also been reported.[3] For our part, we have reported the synthesis of optically active *syn*- and *anti*-1,3-polyols by using highly diastereo- and enantioselective allyltitanations[4] and we have demonstrated the utility of this method to synthesize a diversity of natural products and/or bioactive compounds.[5]

Herein, we would like to report the synthesis of 1,3,5,7-tetraol structural units **A** with excellent diastereoselectivities from bis-tetrahydropyrans **B** obtained by using a homoallylic alcohol controlled Prins cyclisation applied to tetrahydropyran aldehydes **C** (Scheme 1).

Enantiopure tetrahydropyrans **1a** and **1b**[6] were involved in a Prins cyclisation[7] with enantiopure homoallylic alcohols (+)-**2** or (−)-**2** in the presence of TFA (26 equiv., CH_2Cl_2, rt, 3 h).[8] After treatment under aqueous basic conditions (aqueous $NaHCO_3$, Et_3N), the bis-tetrahydropyrans were obtained as a mixture of diastereomers **3** and **3′**, in a ratio of around 70 : 30, with a yield in between 50% and 80% (Table 1). We have to point out that compounds **3** and **3′** were separated by column chromatography on silica gel. A good control of the stereogenic centers at C8 and C12 was observed and the ratio of the diastereomers **3** and **3′** is the result of the moderate control of the stereogenic center at C10.[9] In all cases, the substituents at C8, C10 and C12 are all *cis* in the major isomer.[10] The results are reported in Table 1.

To transform **3a–3d** and **3′a–3′d** into the corresponding tetraols **A**, the bis-tetrahydropyrans **3a–3d** and **3′a–3′d** were treated with NaI (acetone, μ-wave irradiation, 120 °C) and the obtained iodinated compounds were then treated with zinc (NH_4Cl, EtOH, 90 °C) using the conditions reported by Yadav and co-workers.[8c] The corresponding tetraols **4a–4d** and **4′a–4′d** were isolated in yields around 60% over the two steps, as single diastereomers (Table 2, entries 1–8). The hydroxyl at C10, in the bis-tetrahydropyrans **3**, can be protected with different groups such as a TBDPS group (compound **3e**) (Table 2, entry 9) and the resulting ethers were engaged in the iodination/ring-opening sequence (conditions A) to give the corresponding tetraols. It is worth noting that it is necessary to use a different sequence of reactions to introduce other protecting groups such as MOM and Boc groups, due to their instability under the iodination conditions. However, iodination of compounds **3**, followed by protection and reductive cleavage of the tetrahydropyran units (conditions B), gave the doubly protected



Scheme 1 Retrosynthetic analysis.

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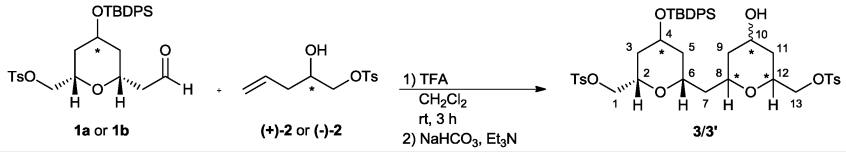
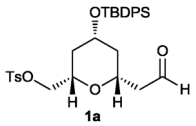
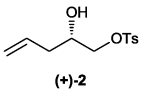
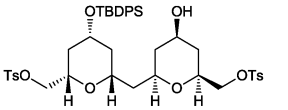
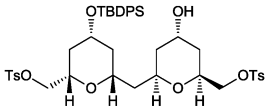
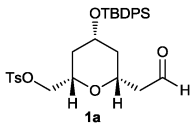
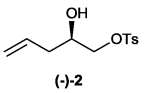
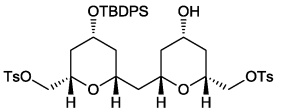
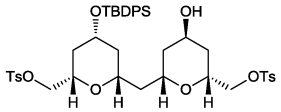
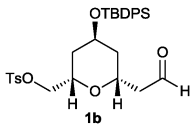
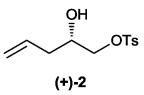
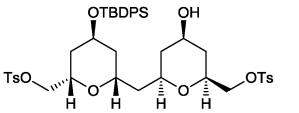
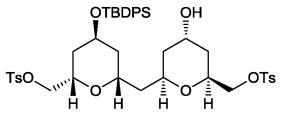
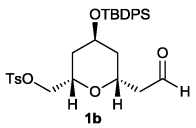
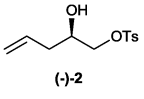
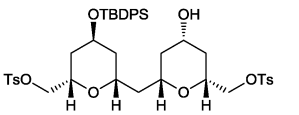
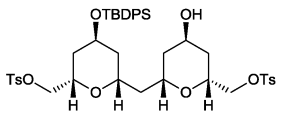
† This communication is dedicated to Prof. Taylor on the occasion of his 65th birthday.

‡ Electronic supplementary information (ESI) available. See DOI: 10.1039/c4cc02702g

Table 1 Diastereoselective Prins cyclisation



Entry	1	2	Major 3	Minor 3′	Ratio 3/3′	Yield[a] (%)
1					**3a**/**3′a** = 70 : 30	66
2					**3b**/**3′b** = 75 : 25	51
3					**3c**/**3′c** = 65 : 35	80
4					**3d**/**3′d** = 75 : 25	55

[a] Isolated yield for the mixture of diastereomers **3** + **3′**.

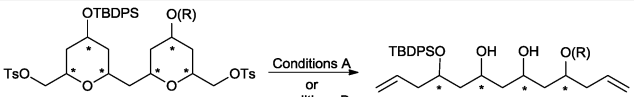
tetraols **4f**–**4i** in good yields and diastereoselectivities (Table 2, entries 10–12).

To prove the relative stereochemistry of the hydroxyl groups at C5 and C7 in the tetraols, and to confirm that the control is due to the homoallylic alcohol used, compounds **4f** and **4g** were treated with 2,2-dimethoxypropane (PPTS, acetone, rt) to form the corresponding acetonides **5f** and **5g**. The relationship between the substituents at C5 and C7 of the acetonides **5** was established by NMR analysis and was confirmed to be *trans* in compound **5f** and *cis* in compound **5g** (Scheme 2).[11]

The differentiation of the two terminal olefins can be achieved with compound **4h** by applying the Bartlett–Smith iodocarbonate cyclization.[12] After protection of **4h** as an acetonide, followed by treatment with NIS (CH_3CN, −40 °C to rt, 4.5 h), the cyclic iodocarbonate **6** was isolated in 72% yield as a mixture of two diastereomers in a ratio of 90 : 10 in favour of the *cis* isomer. After basic treatment (K_2CO_3, MeOH, rt to 40 °C, 8 h), iodocarbonate **6** was transformed to the hydroxy epoxide **7** in 76% yield in a ratio of 87 : 13 in favour of the *syn* isomer (Scheme 3).[13] As all the functionalities are orthogonally protected, this compound can be used to realize the synthesis of complex molecules.

In summary, we have developed a general and diastereoselective method to prepare functionalized 1,3,5,7-tetraol structural units, which should provide access to all the possible diastereomers, using an iterative Prins cyclisation–reductive cleavage sequence. The stereochemistry of the hydroxy groups is controlled during the Prins cyclisation and is dependent on

Table 2 Access to 1,3,5,7-tetraols



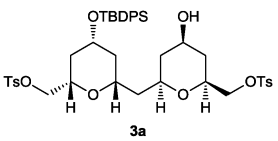
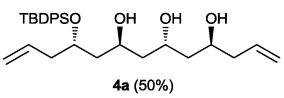
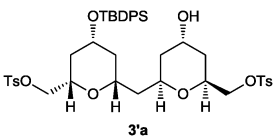
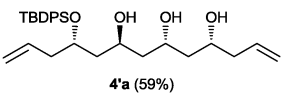
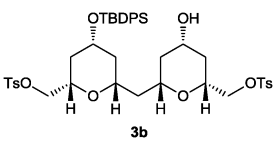
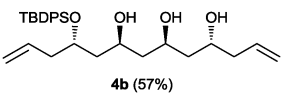
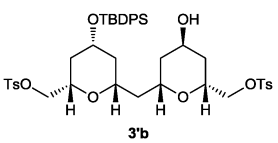
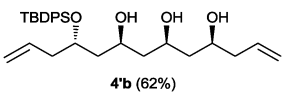
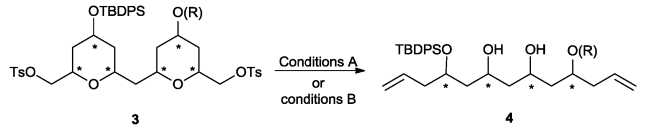
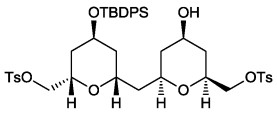
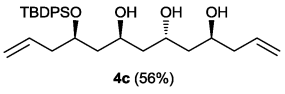
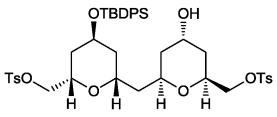
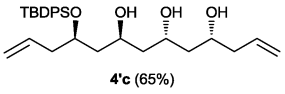
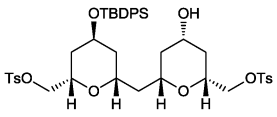
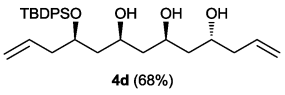
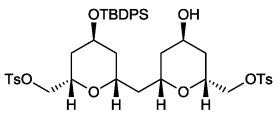
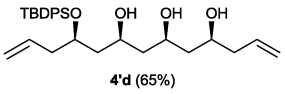
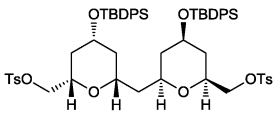
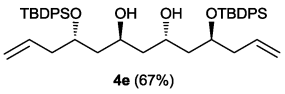
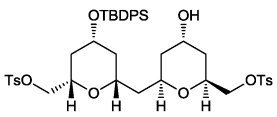
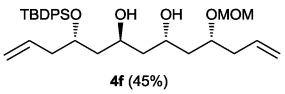
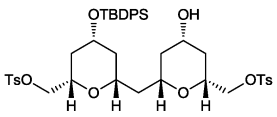
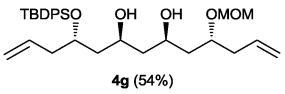
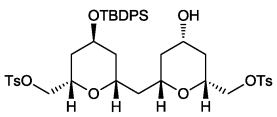
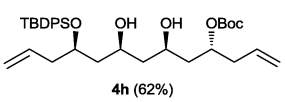
Entry	3	4 (yield %)[a]
1[b]		 **4a** (50%)
2[b]		 **4′a** (59%)
3[b]		 **4b** (57%)
4[b]		 **4′b** (62%)

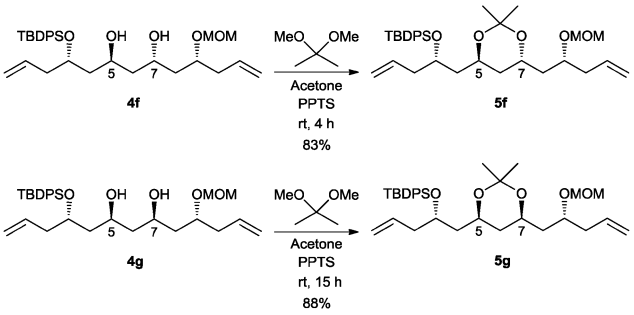
Table 2 (*continued*)



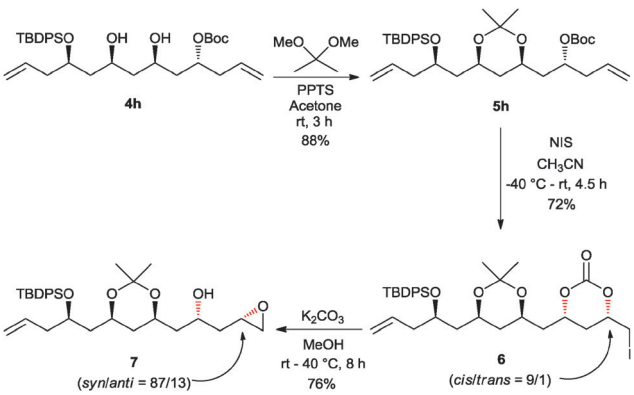
Entry	3	4 (yield %)[a]
5[b]	 3c	 4c (56%)
6[b]	 3'c	 4'c (65%)
7[b]	 3d	 4d (68%)
8[b]	 3'd	 4'd (65%)
9[b]	 3e	 4e (67%)
10[c]	 3'a	 4f (45%)
11[c]	 3b	 4g (54%)
12[c,d]	 3d	 4h (62%)

[a] Overall isolated yields from **3** or **3′**. [b] Conditions A. [c] Conditions B. [d] Reductive cleavage was performed using zinc in a THF–H_2O mixture to prevent Boc migration.

the configuration of the homoallylic alcohol involved. In addition, as the unsaturated Boc-protected 1,3,5,7-tetraols can be selectively functionalized, the use of these tetraols in the synthesis of polyketide natural products is ongoing in our laboratory and will be reported in due time.



Scheme 2



Scheme 3

Notes and references

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6 See ESI‡ for the synthesis and characterization of **1a** and **1b**.

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9 A better yield for **3** and **3′** was obtained by applying an oxidation/stereoselective reduction sequence to the mixture of diastereoisomers **3** + **3′**.
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