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Lucie Grand, Marian Powderly, Florence Popowycz, Maiwenn Jacolot. 1,4-D-Sorbitan: A Promising Biobased-Platform for the Synthesis of Chiral Amines. *Journal of Organic Chemistry*, 2023, 10.1021/acs.joc.2c02827 . hal-03967596

HAL Id: hal-03967596

<https://hal.science/hal-03967596>

Submitted on 3 Feb 2023

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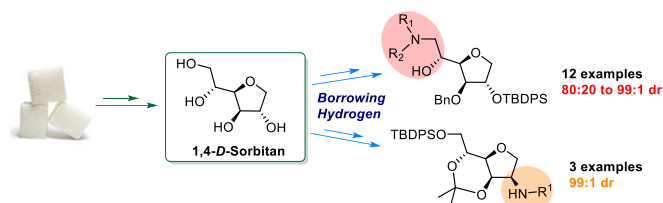
1,4-*D*-sorbitan: a promising biobased-platform for the synthesis of chiral amines

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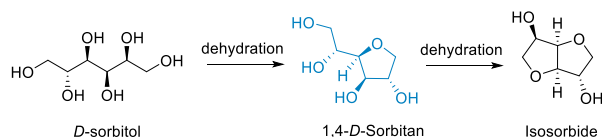
ABSTRACT: The regio- and diastereoselective synthesis of chiral amines derived from 1,4-*D*-sorbitan has been developed *via* the borrowing hydrogen (BH) reaction using a cooperative catalysis between an achiral iridium catalyst and diphenylphosphoric acid. The different reactivities of the four hydroxyl groups on 1,4-*D*-sorbitan scaffold have also been highlighted.



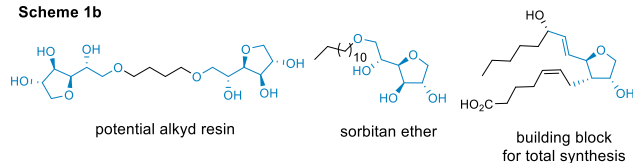
Renewable building blocks such as sugars and polyols have attracted much attention over the last decades for the synthesis of highly functionalized molecules such as amino sugar and amines.¹ In particular, sorbitol has been listed among the top 12 high value –added building block intermediate chemicals with the majority of applications found in food industry.² The chemical synthesis of sorbitol has been reported from glucose by catalytic hydrogenation, or from the fermentation of fructose. Sorbitol is particularly involved in the conversion to glycols as well as lactic acid. Further double cyclodehydration of sorbitol can generate isosorbide *via* the 1,4-*D*-sorbitan intermediate (Scheme 1a).³

Scheme 1a. Obtention of isosorbide and 1,4-*D*-sorbitan from *D*-sorbitol; 1b: Application of 1,4-*D*-sorbitan

Scheme 1a



Scheme 1b



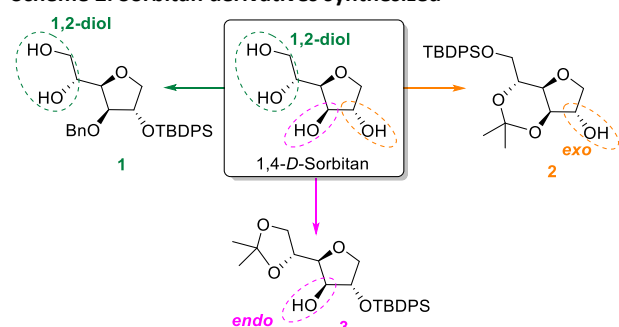
Unlike isosorbide which has been extensively studied for various purposes (polymers, medicinal chemistry, asymmetric induction...),⁴ sorbitan has mainly been used as raw material for surfactants such as Span and Tween.⁵ Lemaire reported the preparation of amphiphilic sorbitan monoethers as a replacement of their ester congeners usually more sensitive to hydrolysis.⁶ Interestingly, dodecyl sorbitan ethers were also evaluated as antimicrobials against Gram (+) bacteria.⁷ Due to a close structural similarity with dipentaerythritol, 1,4-*D*-sorbitan was also used for the formation of alkyd resin.⁸ It was also reported as a chiral template for the total synthesis of Avermectin B_{1a}⁹ and 11-oxaprostaglandin (Scheme 1b).¹⁰

Beyond the valorization of 1,4-*D* sorbitan as chiral polyol raised from renewable resources, we were interested in its direct amination due to the high interest of amines in polymer and pharmaceutical industries. Amongst the top reactions surveyed in pharmaceutical industries in the year 2008, reductive amination appeared with an occurrence of 5.3% on 139 publications (top 1 reaction was amide formation at 16%).¹¹ In 2018, a consortium of pharmaceutical industries co-signed a paper on the importance of developing new opportunities in organic synthesis to be compatible with the drug-discovery process, insisting on the nitrogen-containing molecules reported to display high-affinity binding interactions with proteins.¹² Among the different methods for the obtention of nitrogen-containing sugars, reductive amination of glucose,¹³ galactose,¹⁴ isomaltulose¹⁶ or agarose¹⁶ has been reported as one of the most efficient and promising.

The objective of this project was thus to take advantage of the 1,4-*D*-sorbitan scaffold bearing four hydroxyl groups for the synthesis of highly functionalized chiral amino alcohols. From our previous papers, the complexity of functionalization of isosorbide through borrowing hydrogen reaction was justified mainly from the presence of 2 hydroxyl groups, even if there were in different spatial environments.¹⁷ The borrowing hydrogen reaction, considered as a green and sustainable alternative to reductive amination, is an atom economy strategy proceeding in three sequential *in situ* steps: (i) catalytic dehydrogenation of an unreactive alcohol into the carbonyl compound (ii) condensation of the so-formed carbonyl compound with an amine generating *in situ* the corresponding imine (iii) hydrogenation of the imine using the hydrogen stored by the metal catalyst. This reaction was first discovered by Winans and Adkins in 1932¹⁸ using a heterogeneous nickel catalyst and has then been extensively used both in heterogeneous and homogeneous catalysis.¹⁹ Switching the study to sorbitan bearing 4 hydroxyl groups appeared to us as not a simple extension of the previous

contribution, but also an evaluation of the versatility of the conditions optimized in our group.

Scheme 2. Sorbitan derivatives synthesized



The stereoselective and regioselective issues for borrowing hydrogen reaction on such substrates deserve to be addressed but in an effort of simplification of the model substrate, in our first attempts, we prepared protected sorbitan derivatives **1-3** (Scheme 2).

Naturally, as regioselective amination of 1,2-diols using the BH strategy had already been reported either in racemic²⁰ and in asymmetric version,²¹ we first envisioned the direct and regioselective amination of sorbitan derivative **1**. We initiated our investigation by testing efficient catalytic systems used for the amination of alcohols and 1,2-diols by borrowing hydrogen methodology.^{20b,22} The use of a ruthenium catalyst in combination with a phosphine ligand led to the formation of **4a** within 37 to 55% yield as a 1:1 mixture of diastereoisomers with loss of chiral information on C_{1'} (entries

1-2). This observation was consistent with the results obtained by Williams on enantiopure (*R*)-1-phenyl-1,2-ethanediol with dimethylamine leading to the formation of the racemic amino-alcohol.^{22b}

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Table 1 Optimisation of the amination of sorbitan derivative 1

Entry	Cat (mol %)	Additive (mol %)	Solvent	t (h)	Conv (%) ^a	NMR yield 4a % ^a - dr ^a	Isolated yield 4a % (dr)
1	RuClH(CO)(PPh ₃) ₃ (5)	Xantphos (5)	Toluene	24	100	nd - 50:50	37 (50:50)
2	[RuCl ₂ (<i>p</i> -cymene)] ₂ (2.5)	DPE-Phos (10)	Toluene	24	100	nd - 60:40	55 (50:50)
3	[RuCl ₂ (<i>p</i> -cymene)] ₂ (2.5)	(<i>S</i>)-Josiphos (5)+PhCOOH (20)	Toluene	24	74	56 - 52:48	nd
4	RuClH(CO)(PPh ₃) ₃ (5)	(<i>S</i>)-Josiphos (5) + PhCOOH (20)	Toluene	48	74	57 - 40:60	46 (25:75)
5	[Cp*IrCl ₂] ₂ (5)	NaHCO ₃ (40)	Toluene	24	57	41 - 80:20	nd
6	(<i>S,S</i>)-Ir1 (5)	-	Toluene	24	68	60 - 75:25	nd
7	(<i>S,S</i>)-Ir1 (5)	(PhO) ₂ P(O)OH (5)	Toluene	24	80	78 - 85:15	nd
8	(<i>S,S</i>)-Ir1 (5)	(PhO) ₂ P(O)OH (5)	Toluene ^b	24	99	97 - 85:15	nd
9	(<i>R,R</i>)-Ir1 (5)	(PhO) ₂ P(O)OH (5)	Toluene ^b	24	96	94 - 90:10	66^c (>99:1)
10	Ir2 (5)	(PhO) ₂ P(O)OH (5)	Toluene ^b	24	100	99 - 95:05	70^c (>99:1)
11	Ir2 (5)	PhCOOH (5)	Toluene ^b	24	100	59 - 76:24	nd
12	Ir2 (5)	-	Toluene	24	46	44 - 90:10	nd
13	Ir2 (5)	(PhO) ₂ P(O)OH (5)	^t Amyl alcohol ^b	24	100	97 - 90:10	nd
14	Ir2 (5)	(PhO) ₂ P(O)OH (5)	CPME ^b	24	100	94 - 92:08	nd
15	Ir2 (5)	(PhO) ₂ P(O)OH (5)	CPME ^b	2	100	99 - 91:09	74^c (>99:1)

observed by-product

4aa

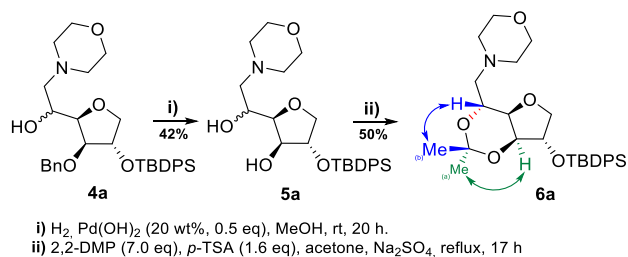
catalysts

(*R,R*)-Ir1 (*S,S*)-Ir1 Ir2

Reaction conditions: **1** (1 eq.), morpholine (1.1 eq.), metal catalyst, additive, solvent [0.6M], 120°C. a) Conversion rate, dr and NMR yield were determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. b) 3 Å MS was added. c) Minor stereoisomer was not isolated.

Disappointed by the results obtained with ruthenium catalysts, we switched to iridium catalysts that proved to be efficient for the diastereoselective amination of isohexides.¹⁷ The use of the dimer $[\text{Cp}^*\text{IrCl}_2]_2$ and NaHCO_3 led to the formation of **4a** with a moderate yield of 41% but with a better dr of 80:20 (entry 5). A similar dr was obtained using the chiral $[S,S]\text{-Ir1}$ catalyst but the yield increased to 60% (entry 6). As observed for the amination of alcohols,^{17,23} the addition of a Brønsted acid as well as molecular sieves significantly increased the conversion and the yield (up to 97%) of the reaction (entries 7-8). Noticeably, the chirality of the iridium complex has no influence on the diastereoselectivity of the reduction step as similar results were obtained independently with $(S,S)\text{-Ir1}$ or $(R,R)\text{-Ir1}$ (entries 8-9). A simple achiral neutral chloride iridium complex Ir2 in cooperation with phosphoric acid and molecular sieves in toluene at 120 °C led to the formation of the amine **4a** within quantitative yield and 95:5 dr (entry 10). After purification, the major diastereoisomer (dr > 99:1) was isolated within 70% yield. Once again, the use of a diphenylphosphoric acid as Brønsted acid was pivotal. The use of benzoic acid led to a decrease of both the yield (56%) and the dr (76:24 - entry 11). The blank reaction run without acid confirmed its importance as only 46% of conversion was quantified (entry 12). With these first set of experimental conditions, an evaluation of greener solvents (4-*t*-amyl alcohol, cyclopentyl methyl ether CPME) pointed out the better results with CPME (99% NMR yield and dr = 92:8 - entry 14). Reactions were initially performed over 24 h, but we noticed that within 2 h the reaction was over and **4a** was isolated within 74% yield (entry 15). Pleasingly the reaction could also be scaled up to 2 g of 1,2-diol **1** affording **4a** within quantitative isolated yield and similar 91:9 dr after increasing time to 24 hours.

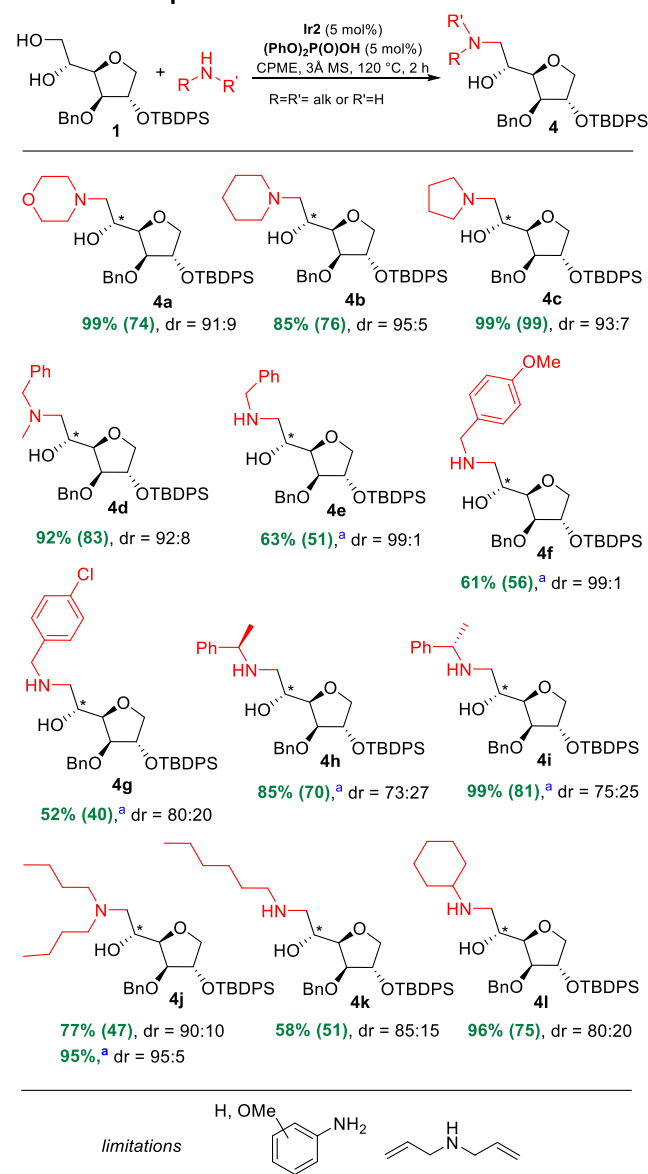
Scheme 3 Synthesis of acetone 6a and observed Noesy correlations



According to reported mechanisms for the regioselective amination of 1,2-diol^{21b} as well as our observations,²⁴ a racemization of the unreacted alcohol could occur during the reaction. In order to determine the accuracy of the stereochemistry of major stereoisomer, the corresponding acetone **6a** was prepared from **4a**. Hydrogenation of the benzyl group followed by reaction of 1,3-diol **5a** under standard conditions afforded the corresponding acetone **6a** as reported on Scheme . According to Rychnovsky rules,²⁵ the ^{13}C NMR of compound **6a** displayed chemical shifts of 23.9 ppm for Me(a) and 24.6 ppm for Me(b), confirming that the *anti* configuration. This observation was further supported by

a Noesy experiment, thus confirming retrospectively the stereochemistry of **4a** (see supporting information). With the optimized conditions in hands, the scope of the reaction was investigated with various amines (Scheme).

Scheme 4. Scope of the amination of 1^a



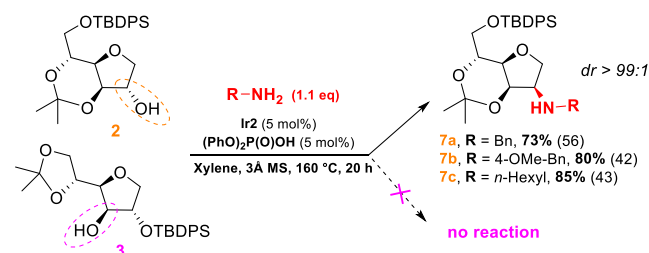
^a **Reaction conditions**: **1** (1 eq.), amine (1.1 eq.), Ir2 (5 mol%), $(\text{PhO})_2\text{P}(\text{O})\text{OH}$ (5 mol%), 3Å MS, CPME [0.6M], 120°C, 2h. NMR yields and dr were determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard on the crude mixture. Isolated yield under brackets. **a**) reaction performed over 6 h

Reaction was very efficient with secondary amines such as piperidine, pyrrolidine and *N*-methyl benzylamine affording the desired amino alcohols **4b-d** within 76 to 99% isolated yields and excellent diastereoselectivity (dr from 92:8 to 95:5). In the course of regioselective amination of 1,2-diols, only secondary amines were reported. The use of primary amines was more challenging due to the possible formation of diaminated compounds as recently reported by Zhao.²⁶ We thus investigated the reaction using primary amines such as benzylamines. Pleasingly, using either benzylamine or 4-methoxybenzylamine, a complete regioselective amination of the primary alcohol was observed affording the corresponding

amino alcohols **4e-f** within respectively 51 and 56% yield and excellent dr > 99:1. Noticeably, reaction time had to be extended to 6 h in order to have a full conversion of the sorbitan derivative and although with a large excess of amines (up to 3 eq.), no diaminated products were observed. Chlorinated amine **4g** was obtained with a lower yield of 40% (52% NMR yield) and a moderate dr of 80:20. Chiral amines were also investigated and with both the (*R*) and the (*S*)- α -methylbenzylamine, desired amino alcohols **4h** and **4i** were obtained with good yields (70 to 81%) and similar dr close to 75:25. As reported by Feringa and Barta,²⁷ no racemization of the α -methylbenzylamine was observed in the final products. Aliphatic amines were also investigated. Amination of **1** with *n*-dibutylamine, an acyclic secondary amine, afforded the desired amine **4j** within good yield and diastereoselectivity after 6 hours. Using primary amines such as *n*-hexylamine and cyclohexylamine, complete conversion was observed after 2 h and the amines **4k** and **4l** were obtained within 51 to 75% yield and moderate dr of 85:15 to 80:20. Noticeably, no reaction took place with anilines and diallylamine.

In order to further investigate the reactivity of the two other secondary alcohols, sorbitan derivatives **2** and **3** were synthesized and submitted to our optimized conditions. At 120 °C to 140 °C, no conversion was observed. As previously reported on isosorbide, both by calculations²⁸ and experimental observations,^{22a,17} oxidation of the *exo* hydroxyl group remains more difficult. Beller *et al.* showed that under high temperature (170 °C), the *exo* hydroxyl group of isosorbide could undergo amination with ammonia. Pleasingly, the reaction of **2** (bearing a OH closely related to the *exo* hydroxyl of isosorbide) with benzylamine using iridacycle **Ir2**, phosphoric acid in xylene and 3 Å MS at 160 °C for 20 h led to the formation of the aminated sorbitan derivative **7a** as a single diastereoisomer within 73% NMR yield and 56% isolated yield (Scheme 5). Few primary amines (benzylic and aliphatic ones) were also investigated leading to the formation of the corresponding amines **7b-c** within 80 and 85% NMR yields respectively and excellent dr. Extending the scope to cyclic amine such as morpholine led to decreased reactivity with poor conversion of 30%. Running the reaction at higher temperature with cyclic amines led to complete degradation. As observed with isohexide derivatives, amination with iridium complex led to the formation of the *endo* amine.²⁹

Scheme 5 Amination reactions of compounds **2** and **3**^a



^aNMR yield and dr were determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. Isolated yield under brackets.

Unfortunately, even under high temperature (160 °C), amination of **3** could not be achieved and the starting material was recovered. No epimerization was observed showing that under those conditions, the free *endo* hydroxyl group in position C₃ could not be oxidized.

In summary, a new BH methodology has been developed providing access to novel chiral biobased amines. Indeed, sorbitan derivative **1**, with a 1,2-diol moiety, could undergo regio- and diastereoselective amination using various primary and secondary amines. Moreover, we highlighted the different reactivity of the sorbitan hydroxyl groups in BH amination. Preliminary experiments suggested the possibility of functionalizing the C₄ position, keeping unreactive the C₃ position. Further considerations are under progress to bring better understanding to such a difference of reactivity between these hydroxyl groups. In particular, those observations should allow us now to consider the direct regioselective amination of the unprotected sorbitan, which is currently being explored.

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Acknowledgment

The authors are grateful for the access to the MS analysis at the CCSM and NMR facilities at CCRMN at the Université Lyon 1. INSA Lyon (Projet BQR 2018, ICBMS) is acknowledged for M.P.'s master grant.

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