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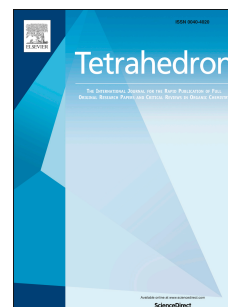
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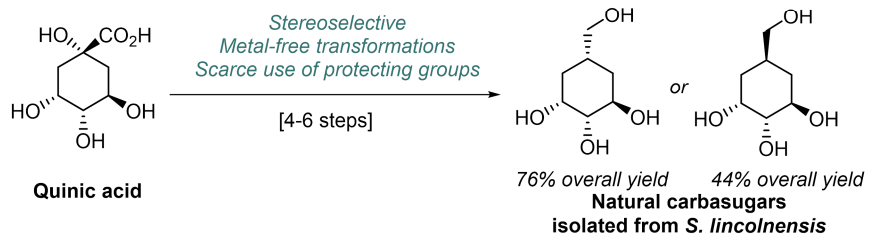
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A Concise synthesis of carbasugars isolated from *Streptomyces lincolnensis*

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ABSTRACT

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(-)-Quinic acid was used as a starting material in the hemisynthesis of two epimeric carbasugars isolated from *Streptomyces lincolnensis*. Previous 10–12 steps syntheses for the carbasugars have been herein shortened to 4–6 steps by using quinic acid as a chiron, based on a regioselective reduction step, with stereoinversion of a tertiary center. Both C-5 epimers of (1*R*, 2*R*, 3*R*)-5-(hydroxymethyl)cyclohexane-1,2,3-triol were obtained in up to 76% overall yield.

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1. Introduction

Natural product-driven drug discovery combined with hemisynthesis brings together nature's maximum potential to create new biologically active molecules and the development of their structural analogs. Carbasugars are a group of organic small molecules that are abundant in nature and have wide biological potency due to the ability to mimic carbohydrates in biological processes.^{1,2} It is noteworthy that the first synthesis of a natural carbasugar by McCasland³ preceded its isolation in 7 years,⁴ followed by extensive studies and raising the interest of many research groups. Simpler cyclitols often are side chains and subunits of larger natural products owning versatile biological activity (e.g. massonioside B⁵, nicotiflorin⁶, and verbasoside⁷ are carba-L-rhamnose derivatives).

In 2004 Sedmera *et al.* isolated two structurally new carbasugars **1** and **2** from *Streptomyces lincolnensis*, which is known to produce many antibiotics such as antibacterial lincomycin as well as C7 cyclitols like valienol and gabosine I.⁸ The first total synthesis of these carbasugars has been reported by Nanda *et al.* three years after their isolation from natural sources.⁹ Such de novo synthesis relied on the kinetic enzymatic resolution and the use of (hydroxymethyl)cycloalkenone scaffold as a key intermediate. Subsequent oxidations into several epimers provided natural and unnatural carbasugars. Overall, final carbasugars **1** and **2** were obtained in 10–12 steps, through formation of the above-mentioned key intermediate in 8 steps. In 1986, before the isolation and the first total synthesis of carbasugars **1** and **2**, a protected analog of **1** has been prepared and used as a synthetic intermediate by Trost *et al.* in the stereoselective synthesis of isoquinulidines from quinic acid.¹⁰

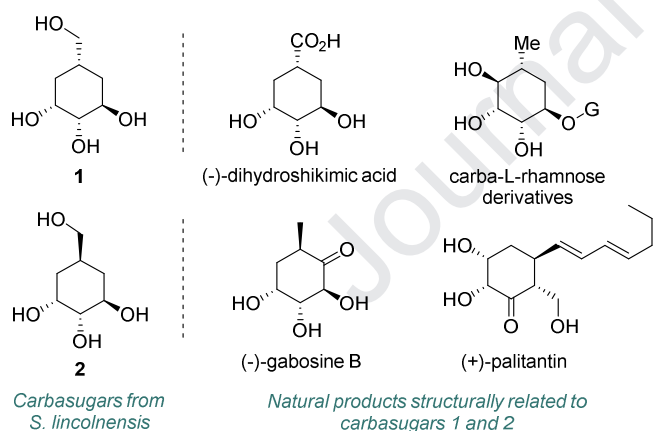


Figure 1. Selected natural products structurally related to carbasugars **1** and **2**.

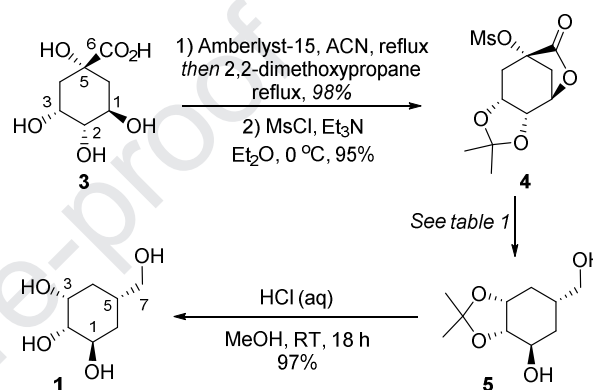
In the present work, we redesigned the hemisynthesis strategy aiming at a more concise and simple synthesis for these natural carbasugars from a common synthetic intermediate. Quinic acid, a secondary metabolite of the shikimate pathway¹¹, has been explored in many natural product syntheses as chiral pool elements^{12,13} and the quest for new compounds with biological activity.^{14–16} The three-dimensional arrangement of the secondary hydroxy groups and methylene unit serves as a great overlap of the functional groups to be adapted for the chiron strategy in total synthesis.^{17–19} Indeed this plain strategy is a powerful tool to synthesize natural products with similar scaffolds such as the ones shown in Figure 1. Structurally, carbasugar **1** corresponds to (-)-dihydroshikimic acid with only one oxidation state difference and is an analog to many carba-L-rhamnose side chains derivatives. Additionally, carbasugar **2** is a structural analog to (-

)-gabosine B²⁰ and (+)-palitantin²¹. We herein present an efficient total synthesis of natural carbasugars **1** and further modification to its epimer **2**, both isolated from *S. lincolnensis*.

2. Results and discussion

2.1. Synthesis of (1*R*,2*R*,3*R*,5*S*)-5-(hydroxymethyl)cyclohexane-1,2,3-triol (**1**)

The synthesis of **1** started with the simultaneous protection of quinic acid's (**3**) carboxylic acid and secondary hydroxy functionalities yielding acetal protected lactone **4** as previously described (Scheme 1).²² We envisioned that preparation of diol **5** (or its C-5 epimer), previously prepared by Trost¹⁰, could be shortened by *in situ* formation of an epoxide during the reduction of the lactone, followed by its regioselective reduction.^{23–25} While not certain about the stereo- and regioselectivity of the epoxide opening, the reduction of mesylated **4** was carefully optimized with common hydride sources (Table 1).



Scheme 1. Synthesis of carbasugar **1** from (-)-quinic acid.

Table 1. Optimization of reduction conditions.

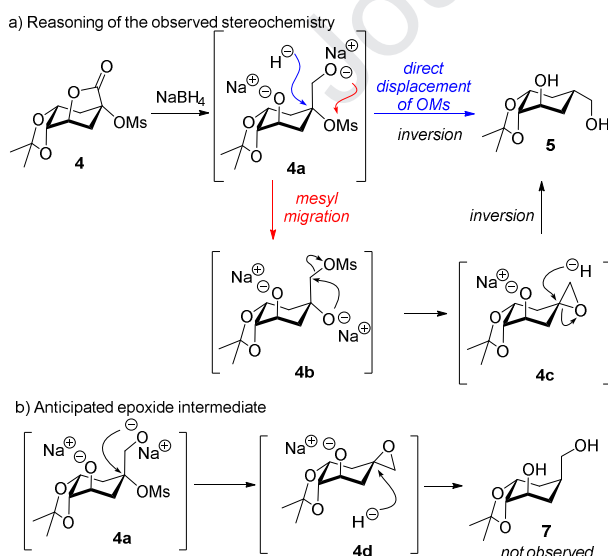
Entry ^a	Hydride (equiv.)	Conditions	5 Yield %
1	LiAlH ₄ (2)	THF, 0 °C	traces ^c
2	DIBAL-H (2)	THF, 0 °C to reflux	n.d. ^c
3	NaBH ₄ (2)	DMSO, 0 °C to 80 °C	3
4	NaBH ₄ (2)	EtOH, 0 °C to RT	39
5	NaBH ₄ (10)	MeOH, 0 °C to RT	42
6 ^b	NaBH ₄ (10)	THF/MeOH 9:1, 0 °C	55
7 ^b	NaBH ₄ (3)	THF/MeOH 9:1, -5 °C	84

^aLactone **4** was dissolved in the specified solvent and the mixture cooled to 0 °C or maintained at room temperature. The reducing agent was added, and the mixture allowed to stir 3–18 h. The starting temperature was raised if no reaction was observed. ^bLactone **4** in THF was added to a stirred suspension of NaBH₄ in THF/MeOH. ^cComplex mixture of multiple products, no product isolation.

Despite the complete consumption of lactone **4**, reduction attempts with lithium aluminum hydride provided only traces of the desired product **5**, while no product was observed with less reactive DIBAL-H (Table 1, entries 1 and 2). When changing the reducing agent to NaBH₄ in DMSO, **5** was isolated in 3% yield (Table 1, entry 3) from a complex mixture of non-characterized products (as judged by TLC). Motivated by the previous use of this reductant in the cleavage of primary, secondary, and tertiary alkyl halides and tosylates,²⁶ we set to increase the selectivity towards formation of **5**. As sodium borohydride reductions are known to be solvent dependent,^{27,28} we decided to test different solvents. Replacing DMSO by protic ethanol resulted in the formation of **5** in a moderate 39% yield (Table 1, entry 4). The complete consumption of starting material was achieved by

increasing the amount of hydride to 10 equivalents in methanol (Table 1, entry 5). Ketal **5** was obtained in similar 42% yield as when using 2 equivalents of hydride source (entry 4), together with plenty of uncharacterized side products. The addition of methanol to THF has been demonstrated to improve selectivity in the reduction of esters and lactones with NaBH_4 .²⁹ Upon testing similar conditions and inverting the addition order, we were glad to obtain **5** in improved 55% yield (Table 1, entry 6). Generally, the portion-wise addition of the dissolved lactone to a suspension of NaBH_4 provided better yields than the standard portion-wise addition of powder reducing agent to the solution of the lactone. We believe this can be due to the high reactivity of the product towards the reducing agent. Ultimately, the best conditions obtained for the reduction of the lactone and removal of the tertiary hydroxy group derivative relied on using low temperatures to slow down the reactivity during the exothermic addition of the lactone to an excess of NaBH_4 (3 equivalents). The desired synthetic intermediate **5** was obtained in 84% yield (Table 1, entry 7).

Regioselectivities on epoxide opening have been reported to depend on the electrophilicity of hydride reagents.³⁰ Namely, BH_3 allows the opening of epoxides from the most substituted carbon.³¹ With this in mind, different possibilities to justify the unexpected stereochemistry of the product obtained have been considered (Scheme 2a). After the reduction of the lactone moiety and putative formation of unidentified borane hydride species, the reactive primary alkoxide **4a** can undergo two different paths. The direct displacement of the methanesulfonate group by the hydride may provide the observed compound **5** if, a somewhat concerted hydride delivery on the stereochemically hindered tertiary carbon occurs. Alternatively, **4a** may undergo *O*, *O*-methanesulfonyl migration to form primary mesylate **4b**.³² ³⁴ The obtained stereocenter inversion may occur upon hydride delivery on the more substituted carbon of the epoxide intermediate **4c**, formed by the attack of tertiary alkoxide. Notably, the more immediate formation of epoxide **4d** (Scheme 2b), upon the attack of the primary alkoxide to the tertiary vicinal carbon in **4a**, could lead to epimer **7**, which we have not been able to identify in our mixtures.



Scheme 2. Proposed reaction mechanism for the formation of **5**. After deoxygenation, the acetal deprotection with HCl/MeOH yielded natural carbasugar **1** (Scheme 1) with a 76% overall yield from (–)-quinic acid. The spectral comparison with the original reports on the isolation of this natural product⁸ confirmed the removal of the tertiary hydroxy group and the stereo-inversion of the C-5 carbon.

The unexpected stereoinversion at C-5 upon hydride delivery in **4**→**5** was further confirmed by a careful comparison of the reported⁸ chemical shifts and *J*-couplings of natural product **1**. The two hydroxymethyl protons show very similar chemical shifts (3.301 and 3.265 ppm) in the form of a multiplet that deconvolves to two sets of doublet of doublets with 11.3 and 6.6 Hz coupling constants (*vs* 11.0 and 6.3 Hz).⁸ The hydrogen at C-5 has a chemical shift of 1.715 ppm appearing as a multiplet due to the multiple couplings with the vicinal protons (at C-4, C-6 and C-7), also matching closely with the original report (1.714 ppm). Notably, all ¹³C NMR chemical shifts of the final product differ from the paper on isolation of **1** in less than 0.06 ppm. Secondary C-7 and tertiary C-5 resonate at 66.55 and 32.71 ppm, respectively, in close agreement with Sedmera's report (66.55 and 32.71 ppm).⁸

2.2. Synthesis of (1*R*,2*R*,3*R*,5*R*)-5-(hydroxymethyl)cyclohexane-1,2,3-triol (**2**)

Considering the synthesis of the epimer **2**, we envisioned that this second natural product could be achieved by epimerization of the α -carbonyl position of the corresponding aldehyde (Scheme 3). The putative establishment of an intramolecular hydrogen bond between the hydroxy group and the carbonyl groups on the same face of the six-membered ring should drive the epimerization towards the desired product. Bearing this in mind, conditions to target the selective oxidation of the primary alcohol were investigated and the results are presented in Table 2. The reaction suffered a lack of regioselectivity and the yields were poor for the exclusive oxidation of primary alcohol despite the use of parsimonious oxidizing agents (Table 2, entries 1 and 2). Better regioselectivity was observed when oxidizing with catalytic TEMPO in combination with (diacetoxyiodo)benzene, although the isolated yield remained poor (Table 2, entry 3). Changing the oxidizing agent from iodobenzene based oxidizing agents to *N*-chlorosuccinimide, resulted in an increased formation of **6** in 77% yield after 45 min (Table 2, entry 4). Precise control of the reaction time was required, as extended reaction times resulted in increased amounts of side products whilst shorter reaction times were not sufficient for complete consumption of the starting material.

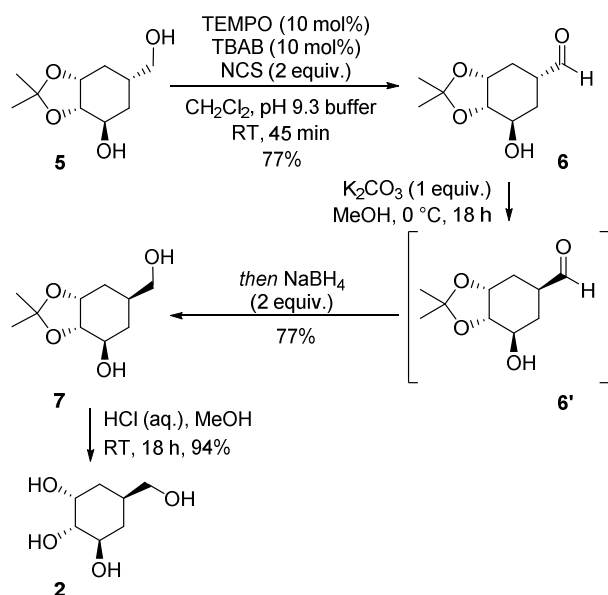
Table 2. Optimization of oxidation conditions.

Entry	Oxidation conditions	Yield %
1 ^a	DMP (1 equiv.), CH_2Cl_2 , RT, 1 h	15
2 ^a	PCC (1.2 equiv.), CH_2Cl_2 , RT, 20 h	13
3 ^a	TEMPO (20 mol%), $\text{PhI}(\text{OAc})_2$, (2 equiv.), CH_2Cl_2 , RT, 4 h	34
4 ^b	TEMPO (10 mol%), TBAB (10 mol%), NCS (2 equiv.), $\text{CH}_2\text{Cl}_2/\text{buffer}$, RT, 45 min	77

^aAlcohol **5** was dissolved in CH_2Cl_2 (0.1 M) and the specified oxidizing agent was added at RT. Mixture was stirred at for specified time, quenched and purified using flash column chromatography. ^bProcedure described in experimental section.

The α -carbonyl position of the aldehyde **6** was epimerized using 1 equivalent of K_2CO_3 as base (Scheme 3) in methanol. While testing epimerization conditions, the TLC analysis from reaction mixtures showed the aldehyde **6** being a minor product and the equilibrium largely favoring epimer **6'**. The simple evaporation of the reaction solvent or quenching by adjusting to pH 7 (using aqueous HCl) followed by column chromatography purification resulted in equilibration to starting material **6**. The difficult isolation of **6'** was circumvented by *in situ* reduction to alcohol **7** with sodium borohydride, thus allowing the isolation of the diol in 77% yield. Finally, the acetal deprotection gave the natural carbasugar **2**, also with NMR spectral characterization in

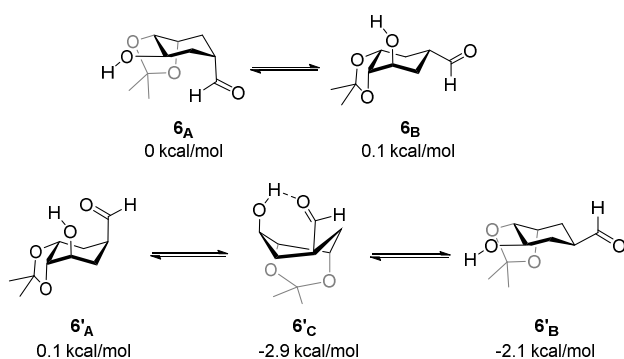
close agreement with the values reported by Sedmera.⁸ Comparison of chemical shifts of **1** and **2** show little changes in positions 1, 3 and 7, contrarily to the remaining cyclohexyl positions. A significant change in the chemical shift of C-2 between **1** (71.71 ppm) and **2** (76.30 ppm) could be explained by the establishment of an intramolecular hydrogen bond with C-1 in **1**.



Scheme 3. Synthesis of carbasugar **2** from protected carbasugar **5**.

2.3. Computational Study

In order to verify our assumption on the stabilization of epimer **6'** due to the establishment of an intramolecular hydrogen bond, we have performed the conformational analysis of both C-5 epimers using DFT³⁵ (Scheme 4). The conformational analysis of **6** resulted in the identification of the two chair conformers **6_A** and **6_B** as the most stable conformations. A somewhat distorted chair conformation can be detected in the case of **6_A**, due to an intramolecular hydrogen bond between the secondary hydroxy group and the vicinal oxygen from the acetonide. Notwithstanding a similar effect observed for the most stable chair conformation of epimer **6'**, i.e. **6'_A**, the placement of the carbonyl group in the more favorable equatorial position has a clear stabilizing effect (-2.1 kcal/mol) when compared with epimer **6**. As envisioned, a more stable conformation for epimer **6'** could be found, namely twist-boat conformation **6'_C** (-2.9 kcal/mol) where an intramolecular hydrogen bond is established between the aldehyde oxygen and the hydroxy group (2.027 Å).



Scheme 4. Simplified conformational analysis of epimers **6** and **6'**. Energy values relate to **6_A** as the zero value and are given as electronic energies, optimized at PBE1PBE/6-31G** level of theory.

3. Conclusion

In summary, we herein report the shortest and the highest yielding synthesis of the two natural 3,4,5-trihydroxycyclohexyl cyclitols isolated from *Streptomyces lincolnensis*. Both C-5 epimers of (1*R*, 2*R*, 3*R*)-5-(hydroxymethyl)cyclohexane-1,2,3-triol were obtained in 4–6 steps in 76% or 44% overall yields from (-)-quinic acid. The regioselective reduction of a quinic acid-derived lactone was used as a key step in the installation of the hydroxymethyl substituent, upon stereoselective hydride delivery to a tertiary carbon. The unprecedented conversion of the less stable epimer of the corresponding aldehyde into the more stable C-5 epimer allowed the preparation of both natural carbasugars by the insertion of an oxidation-epimerization-reduction sequence.

4. Experimental Section

4.1. General Remarks

All syntheses were carried out in oven-dried glassware under inert atmosphere. Anhydrous diethyl ether and triethylamine were obtained using PureSolv Micro multi-unit purification system. Acetonitrile was left standing over 3 Å molecular sieves and used without further purification. All other reagents were purchased from Sigma Aldrich or TCI and used without purification. Reactions were monitored through thin-layer chromatography (TLC) with commercial silica gel plates (Merck silica gel, 60 F254). Plates were visualized by staining upon heating with vanillin stain. Flash column chromatography was performed on silica gel 60 (40–63 μm) as stationary phase. The ¹H and ¹³C spectra were recorded at 500 MHz and 125 MHz respectively in a JEOL ECZR 500 instrument. CDCl₃ or D₂O (in D₂O samples 4 μl of acetone was used as internal reference) were used as solvents for NMR analysis. Chemical shifts (δ) are reported in ppm and are referenced to the residual chloroform signal (δ ¹H 7.26 ppm, δ ¹³C 77.16 ppm) or to the internal acetone (δ ¹H 2.03 ppm, δ ¹³C 30.50 ppm). The following abbreviations were used to describe peak splitting patterns: s = singlet, d = doublet, t = triplet, m = multiplet. Coupling constants *J* were reported in Hertz (Hz). High-resolution mass spectra were recorded on a Waters ESI-TOF MS spectrometer.

4.2. (3*aR*,4*R*,7*S*,8*aR*)-2,2-dimethyl-6-oxotetrahydro-4,7-methano[1,3]dioxolo[4,5-*c*]oxepin-7(6*H*)-yl methanesulfonate (**4**)

i) Quinic acid **3** (3.0 g, 15.6 mmol) was weighed into round bottomed flask equipped with stirring bar. Acetonitrile (200 mL) was added, followed by addition of Amberlyst 15 (3.5 g), and the mixture was refluxed for 2 days. The mixture was cooled to room temperature and 2,2-dimethoxypropane (3.8 mL, 3.25 g, 31.2 mmol, 2 equiv.) was added and refluxed for 3 hours. The reaction mixture was filtrated through Celite plug and the solvent was evaporated to give pure (3*aR*,4*R*,7*S*,8*aR*)-7-hydroxy-2,2-dimethyltetrahydro-4,7-methano[1,3]dioxolo[4,5-*c*]oxepin-6(4*H*)-one as a beige solid (3.28 g, 98%). ¹H NMR (500 MHz, CDCl₃): δ 4.71 (dd, *J* = 6.1, 2.5 Hz, 1H-1), 4.51–4.47 (m, 1H-3), 4.29 (ddd, *J* = 6.7, 2.4, 1.5 Hz, 1H-2), 3.16 (s, 1H-OH), 2.63 (d, *J* = 11.7 Hz, 1H-6), 2.36 (ddd, *J* = 14.7, 7.6, 2.3 Hz, 1H-4), 2.33 – 2.27 (m, 1H-6), 2.17 (dd, *J* = 14.6, 2.9 Hz, 1H-4), 1.51 (s, 3H-CH₃), 1.31 (s, 3H-CH₃); ¹³C NMR (125 MHz, CDCl₃): δ 179.08 (C=O), 109.90 (C_{isop.}), 75.97 (C1), 72.19 (C5), 71.66 (C2), 71.60 (C3), 38.23 (C4), 34.37 (C6), 27.08 (CH₃), 24.41 (CH₃); HRMS calculated for [M]⁺ 214.0841, found 214.0913. The spectral data of the compound is consistent with the literature data.¹⁰

ii) Lactone ((3*aR*,4*R*,7*S*,8*aR*)-7-hydroxy-2,2-dimethyltetrahydro-4,7-methano[1,3]dioxolo[4,5-*c*]oxepin-6(4*H*)-one) synthesized in section 4.2 *i*) (3.28 g, 15.3 mmol) was dissolved in Et₂O (100 mL) at 0 °C. Et₃N (4.3 mL, 3.1 g, 30.6 mmol, 2 equiv.) was added followed by slow addition of MsCl (1.8 mL, 2.6 g, 23 mmol, 1 equiv.). The ice bath was removed after 5 min and the mixture was left stirring for 2 hours at room temperature forming a thick solution. The mixture was diluted with EtOAc (100 mL) and quenched with H₂O (100 mL). Layers were separated and the aqueous phase was extracted with CH₂Cl₂ (3 x 50 mL). The organic phases were combined, dried with anhydrous MgSO₄, filtered through silica pad (3 cm) and the solvents were evaporated to give pure **4** as a beige solid (4.24 g, 95%). ¹H NMR (500 MHz, CDCl₃): δ 4.80 (dd, *J* = 6.4, 2.5 Hz, 1H-1), 4.57–4.45 (m, 1H-3), 4.31 (ddd, *J* = 6.2, 2.1, 0.9 Hz, 1H-2), 3.28 (s, 3H -OMs-CH₃), 3.12–3.05 (m, 1H-6), 2.83 (d, *J* = 11.8 Hz, 1H-4), 2.54 (ddd, *J* = 14.4, 7.7, 2.4 Hz, 1H-6), 2.39 (dd, *J* = 14.5, 3.0 Hz, 1H-4), 1.52 (s, 3H-CH₃), 1.32 (s, 3H-CH₃). ¹³C NMR (125 MHz, CDCl₃): δ 172.91 (C=O), 110.41 (C_{isop.}), 82.27 (C5), 75.82 (C1), 72.01 (C2), 71.17 (C3), 41.34 (OMs-CH₃), 36.60 (C4), 33.24 (C6), 27.06 (CH₃), 24.45 (CH₃); HRMS calculated for [M+Na]⁺ 315.0515, found 315.0479. The spectral data of the compound is consistent with the literature data.³⁶

4.3. (3*aS*,4*R*,6*R*,7*aR*)-6-(hydroxymethyl)-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxol-4-ol (**5**)

Methanol (0.2 mL) was added to a -5 °C suspension of NaBH₄ (78 mg, 2.1 mmol, 3 equiv.) in THF (1 mL) and the mixture was stirred until little bubbling was visible. A solution of lactone **4** (200 mg, 0.68 mmol) in THF (2.2 mL) was added dropwise and the reaction mixture was allowed to warm up to room temperature and was left stirring overnight. The reaction was quenched with H₂O (3 mL) and after 30 min stirring, solvents were evaporated under reduced pressure. The residue was purified by flash column chromatography (dry loading) using EtOAc as eluent to yield product **5** as a clear oil (116 mg, 84%). ¹H NMR (500 MHz, CDCl₃): δ 4.35 (dd, *J* = 11.5, 6.1 Hz, 1H-1), 4.09 (td, *J* = 7.5, 3.8 Hz, 1H-3), 3.96 (t, *J* = 5.6 Hz, 1H-2), 3.64–3.55 (m, 2H-7), 2.07–1.98 (m, 2H-5 and 6), 1.91 (t, *J* = 5.3 Hz, 1H-OH), 1.79 (d, *J* = 4.6 Hz, 1H-OH), 1.76 (dd, *J* = 7.5, 3.9 Hz, 1H-4), 1.65–1.58 (m, 2H-6 and 4), 1.50 (s, 3H-CH₃), 1.36 (s, 3H-CH₃); ¹³C NMR (125 MHz, CDCl₃): δ 108.77 (C_{isop.}), 78.71 (C2), 73.37 (C1), 68.64 (C3), 67.06 (C7), 31.87 (C5), 30.26 (C4), 29.25 (C6), 27.99 (CH₃), 25.80 (CH₃); HRMS calculated for [M+H]⁺ 203.1283, found 203.1296. The spectral data of the compound is consistent with the literature data.¹⁰

4.4. (1*R*,2*S*,3*R*,5*S*)-5-(hydroxymethyl)cyclohexane-1,2,3-triol (**1**)

Protected alcohol **5** (115 mg, 0.57 mmol) was dissolved in MeOH (4 mL) and aqueous 4M HCl (0.4 mL) was added. The mixture was stirred for 18 h at room temperature and then diluted with MeOH and neutralized with NaOH (4 M aq. soln.). Solvents were evaporated and crude compound was purified using flash column chromatography (EtOAc/MeOH 9:1) to yield product **1** as white solid (89 mg, 97%). ¹H NMR (500 MHz, D₂O): δ 3.86 (q, *J* = 3.3 Hz, 1H-3), 3.75 (ddd, *J* = 11.7, 4.4, 3.1 Hz, 1H-1), 3.63 (t, *J* = 3.4 Hz, 1H-2), 3.30 (dd, *J* = 11.3, 6.6 Hz, 1H-7), 3.26 (dd, *J* = 11.3, 6.6 Hz, 1H-7), 1.76–1.66 (m, 1H-5), 1.54 (dt, *J* = 12.2, 3.9 Hz, 1H-6), 1.43 (d, *J* = 14.4 Hz, 1H-4), 1.27–1.19 (m, 1H-4), 1.12 (q, *J* = 11.9 Hz, 1H-6); ¹³C NMR (125 MHz, D₂O): δ 71.71 (C2), 70.04 (C3), 67.85 (C1), 66.55 (C7), 32.71 (C5), 30.36 (C6), 29.18 (C4). HRMS calculated for [M+Cl]⁻ 197.0581, found 197.0591. The spectral data of the compound is consistent with the literature data.⁸

4.5. (3*aR*,5*R*,7*R*,7*aS*)-7-hydroxy-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxole-5-carbaldehyde (**6**)

Alcohol **5** (430 mg, 2.1 mmol) was dissolved in CH₂Cl₂ (20 mL) followed by addition of TEMPO (33 mg, 0.2 mmol, 0.1 equiv.) and TBAB (68 mg, 0.2 mmol, 0.1 equiv.). Then 20 mL of aqueous buffer solution (0.5M NaHCO₃, 0.05M K₂CO₃) was added followed by addition of *N*-chlorosuccinimide (560 mg, 4.3 mmol, 2 equiv.) and the mixture was allowed to stir at room temperature for 45 min after which layers were separated, aqueous phase was saturated with NaCl and extracted with CH₂Cl₂ (5 x 10 mL). Combined organic phases were dried with anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified using flash column chromatography (CH₂Cl₂/EtOAc, 1:1) to yield product **6** as a pale yellow oil (330 mg, 77%). ¹H NMR (500 MHz, CDCl₃): δ 9.68 (s, 1H-7), 4.39–4.33 (m, 1H-1), 4.02–3.96 (m, 1H-3), 3.93 (t, *J* = 5.5 Hz, 1H-2), 2.61–2.54 (m, 1H-5), 2.25 (ddd, *J* = 10.3, 8.2, 4.4 Hz, 2H-4,6), 2.15 (ddd, *J* = 14.9, 6.7, 4.4 Hz, 1H-6), 1.62 (ddd, *J* = 14.1, 8.5, 5.7 Hz, 1H-4), 1.41 (s, 3H-CH₃), 1.34 (s, 3H-CH₃); ¹³C NMR (125 MHz, CDCl₃): δ 203.19 (C7), 109.24 (C_{isop.}), 79.00 (C2), 72.92 (C1), 68.08 (C3), 42.45 (C5), 27.69 (C4), 27.27 (CH₃), 25.98 (C6), 25.93 (CH₃); HRMS calculated for [M+Na]⁺ 223.0946, found 223.0918.

4.6. (3*aS*,4*R*,6*S*,7*aR*)-6-(hydroxymethyl)-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxol-4-ol (**7**)

Aldehyde **6** (70 mg, 0.34 mmol) was dissolved in MeOH (4 mL), K₂CO₃ (48 mg, 0.34 mmol, 1.0 equiv.) was added and the mixture was stirred 18 hours at room temperature. The mixture was cooled down to 0 °C, stirred at 0 °C for 2 hours, NaBH₄ (26 mg, 0.7 mmol, 2 equiv.) was added, and the reaction mixture was allowed to warm up to room temperature over 2 h while stirring. Reaction mixture was diluted with EtOAc and quenched with H₂O (0.2 mL). The solvents were evaporated and the residue was purified using flash column chromatography (dry loading) using EtOAc as eluent to yield product **7** as a clear oil (54 mg, 77%). ¹H NMR (500 MHz, CDCl₃): δ 4.37 (bs, 1H-1), 3.81 (t, *J* = 5.8 Hz, 1H-2), 3.77–3.67 (m, 1H-3), 3.6–3.46 (m, 2H-7), 2.79 (s, 1H-OH), 2.13 (d, *J* = 14.9 Hz, 1H-6), 2.07–1.85 (m, 3H-4, 5, OH), 1.49 (s, 4H, overlapped peaks 6, CH₃), 1.36 (s, 3H-CH₃), 1.16–1.03 (m, 1H-4); ¹³C NMR (125 MHz, CDCl₃): δ 108.81 (C_{isop.}), 81.27 (C2), 74.20 (C1), 72.25 (C3), 66.95 (C7), 33.17 (C5), 33.15 (C4), 29.21 (C6), 28.42 (CH₃), 26.23 (CH₃); HRMS calculated for [M+H]⁺ 203.1283, found 203.1290.

4.7. (1*R*,2*R*,3*R*,5*R*)-5-(hydroxymethyl)cyclohexane-1,2,3-triol (**2**)

Protected alcohol **7** (20 mg, 0.1 mmol) was dissolved in MeOH (1 mL) and aqueous 4M HCl (0.1 mL) was added. The mixture was stirred for 18 h at room temperature after which MeOH was added and the mixture neutralized with NaOH (4 M aq. soln.). Solvents were evaporated and the mixture was purified using flash column chromatography (EtOAc/MeOH 9:1) to yield product **2** as a white solid (15 mg, 94%). ¹H NMR (500 MHz, D₂O): δ 3.93 (bs, 1H-3), 3.59 (td, *J* = 10.1, 4.2 Hz, 1H-1), 3.32–3.25 (m, 2H-7), 3.19 (dd, *J* = 9.6, 2.9 Hz, 1H-2), 1.82–1.79 (m, 1H-5), 1.76–1.74 (m, 1H-4), 1.64 (d, *J* = 14.2 Hz, 1H-4), 1.10 (t, *J* = 13.4 Hz, 1H-4), 0.87 (q, *J* = 11.8 Hz, 1H-6); ¹³C NMR (125 MHz, D₂O): δ 76.30 (C2), 70.04 (C3), 69.45 (C1), 66.25 (C7), 35.49 (C6), 33.50 (C4), 32.43 (C5); HRMS calculated for [M+Cl]⁻ 197.0581, found 197.0612. The spectral data of the compound is consistent with the literature data.⁸

4.8. Computational details

All calculations were performed using the Gaussian 09 software package,³⁷ without symmetry constraints. The optimized

geometries were obtained employing the PBE1PBE functional with a standard 6-31G(d,p)³⁸⁻⁴² basis set. That functional uses a hybrid generalized gradient approximation (GGA), including 25% mixture of Hartree-Fock⁴³ exchange with DFT³⁵ exchange-correlation, given by Perdew, Burke and Ernzerhof functional (PBE).^{44,45} Frequency calculations were performed to confirm the nature of the stationary points, yielding no imaginary frequency for the minima

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Supplementary Material

Spectral characterization of the compounds prepared and coordinates of the computational optimized are available as supplementary material.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: