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A simple entry into 1,3-diols from (*R*)-2,3-cyclohexylideneglyceraldehyde: synthesis of (−)-galantinic acid

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ABSTRACT

Aldehydes **5**, **7**, and **9** derived from easily accessible (*R*)-2,3-cyclohexylideneglyceraldehyde **1** were used as novel substrates to obtain both *syn*- and *anti*-1,3-diols in several individual reactions by subjecting each of them to some practically viable metal-mediated Barbier-type allylations under moist conditions. In this regard, a detailed investigation was made regarding the compatibility and stereoselectivity associated with four such metal-mediated allylations of these aldehydes **5–7**. Good yields with moderate selectivity in several successful reactions with easy chromatographic separation of diastereoisomers of the products have been elegantly exploited to isolate two pairs of enantiomerically pure *syn*-1,3 and *anti*-1,3-diols (**6a** and **6b**; **10a** and **10b)** in substantial amounts. Finally, **10b** has been exploited to synthesize (−)-galantinic acid **A**.

1. Introduction

The 1,3-skipped polyol systems with *syn*- or *anti*-configuration are structural units of several classes of natural products including clinically valuable polyene macrolide antibiotics. This has attracted the attention of synthetic chemists to develop different strategies for the construction of functionalized *syn*-1,3- and *anti*-1,3-diols.[1]

A very common approach to obtain chiral 1,3-diols is via the stereo-differentiating allylation of β-hydroxy- or alkoxyaldehydes. This route has the advantage of producing 1,3-polyols from repeated oxidative cleavage of the olefin of the resulting homoallylic alcohol followed by allylation of the aldehyde produced. The stereo-differentiation in each allylation step can be achieved in the presence of a chiral auxiliary which exists in either the substrate or the allylating agent or both. The reaction of β-oxygenated aldehydes with chiral allylating agents is associated with a very high degree of stereoselectivity to obtain either 1,3-*syn*- or 1,3-*anti*-diol.[2] Due to the recent development of different innovative strategies for the allylation of aldehydes,[3] the stereoselective preparation of 1,3-diols employing medal-mediated allylations of chiral β-oxygenated aldehydes looked highly attractive.[1] In this regard, there is also a scope to explore the compatibility of various allylmetallations with many chiral β-oxygenated aldehydes and allow stereochemical investigations for such reactions. Presumably, due to the chelation control of all such allylation reactions, both the metal of the allylmetal and the substrate β-oxygenated aldehyde are likely to contribute significantly regarding the stereoselectivity in all individual allylations.

In our ongoing program regarding the synthesis of bioactive compounds, we have exploited an easily accessible (*R*)-2,3-cyclohexylideneglyceraldehyde **1**[4a] for the asymmetric construction of several structural units such as alkanetriols,[4,5a] ribofuranoses,[5a,b,g,h] γ-lactone,[5c] δ-lactone,[5d] isonucleosides,[5e] and 2,5-disubstituted tetrahydrofurans[5f]. Herein we report out attempts to explore the potential of **1** once again for asymmetric construction of functionalized 1,3-diols.

2. Results and discussion

The olefin unit of *anti*-homoallylic alcohol **2** derived from it[4b] was ozonolyzed and then reduced with PPh_3 to obtain hydroxyaldehyde **5** in good yield. Compound **5**, due to its unstability on standing without being purified further, was immediately subjected to Barbier-type allylations mediated with different metals under various conditions as shown in Table 1. The Zn-mediated allylation following Luche's procedure[6] did not take place (Table 1, entry A). The same disappointing results were obtained for the allylation of **5** mediated with low valent Cu or Fe prepared following bimetal redox strategy[7] (Table 1, entries B and C). The In-mediated allylation[8] of **5** took place successfully under two different aqueous conditions (Table 1, entries D and E) producing 1,3-diol **6** with varied *anti*-selectivity; the selectivity using water as solvent (Table 1, entry D) was found to be noteworthy (*syn*-**6a**:*anti*-**6b** = 20:80). The diastereomeric diols **6a**,**b** could be easily separated from each other by column chromatography and their stereochemistry was determined from ^{13}C NMR spectra of the

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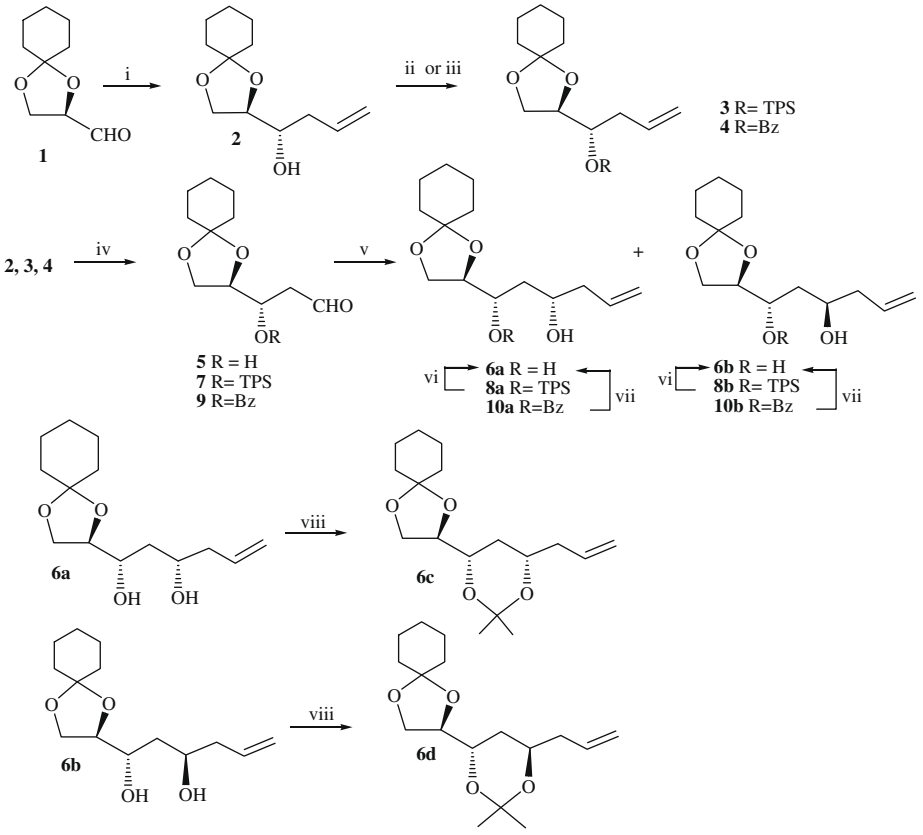
Table 1
Metal-mediated allylations of aldehydes **5**, **7**, and **9**

Entry	R_1CHO	RBr	Reagents	Time (h)	Products	Yield (%)	Products Ratio(*syn*/*anti*)
A	**5**	Allyl	Zn, NH_4Cl(aq), THF	24	—		No reaction
B	**5**	Allyl	$FeCl_3$, Zn, THF	24	—	—	No reaction
C	**5**	Allyl	$CuCl_2{\cdot}2H_2O$, Zn, THF	24	—	—	No reaction
D	**5**	Allyl	In, H_2O	24	**6a** and **6b**	77.0	20:80[a]
E	**5**	Allyl	In, H_2O:THF	24	**6a** and **6b**	74.3	38:62[a]
F	**7**	Allyl	Zn, NH_4Cl(aq), THF	6	**8a** and **8b**	81.7	48:52[b]
G	**7**	Allyl	$FeCl_3$, Zn, THF	4	**8a** and **8b**	84.8	35:65[b]
H	**7**	Allyl	$CuCl_2{\cdot}2H_2O$, THF	20	**8a** and **8b**	82.4	45:55[b]
I	**7**	Allyl	In, H_2O	24	—	—	No reaction
J	**7**	Allyl	In, H_2O:THF	24	**8a** and **8b**	15[c]	40: 60[b]
K	**9**	Allyl	Zn, NH_4Cl(aq), THF	6	**10a** and **10b**	80.8	40:60[a]
L	**9**	Allyl	$FeCl_3$, Zn, THF	24	—	—	No reaction
M	**9**	Allyl	$CuCl_2{\cdot}2H_2O$, THF	24	—	—	No reaction
N	**9**	Allyl	In, H_2O	24	—	—	No reaction
O	**9**	Allyl	In, H_2O:THF	24	—	—	No reaction

[a] The ratio was determined after separation of diastereomers by column chromatography.
[b] The ratio was determined after desilylation of the crude mixture followed by separation of diastereomer diols **6a** and **6b** by column chromatography.
[c] The majority of the substrate remained unreacted.

corresponding acetonides **6c**,**d**[9] (Scheme 1). The signals of *syn*-diol acetonide **6c** were observed at δ 98.4 for a quaternary carbon and at 19.8 and 33.6 for the methyl carbons, respectively, whereas for *anti*-diol acetonide **6d** the same signals appeared at δ 100.2 for a quaternary carbon and at 24.7 and 25.1, respectively.

Our next attempt was to investigate the efficacy and stereoselectivity of similar allylations of the O-silylated **7** and O-benzoylated **9** hydroxyaldehydes, which were prepared, respectively, from the corresponding protected homoallylic alcohols **3** and **4** derived from **2** following similar reaction protocols viz. ozonolysis followed by reduction with PPh_3. Since both the aldehydes **7** and **9** are unstable on long standing they were immediately used for the next reaction. Very interestingly, the later allylations afforded results at some variance with the earlier ones and are worth reporting (Table 1). For silyl derivative **7**, Luche's allylation took place but with poor selectivity producing **8a** and **8b** in nearly equal proportions (*syn*-**8a**:*anti*-**8b** = 48:52). (Table 1, entry F) Low valent Cu- and Fe-mediated reactions took place with excellent yields but with little improved *anti*-selectivity in both the cases [for Cu *syn*-**8a**:*anti*-**8b** = 45:55; for Fe *syn*-**8a**:*anti*-**8b** = 35:65] compared to that obtained using Luche's procedure (Table 1, entries G and H). The In-mediated reaction in water gave poor results (Table 1, entry I).



Scheme 1. (i) Ref. 4; (ii) TBDPSCl/imidazole/CH_2Cl_2; (iii) BzCN, TEA/CH_2Cl_2; (iv) O_3/CH_2Cl_2/PPh_3; (v) allylBr/In, H_2O/THF or Zn/aq NH_4Cl/THF or $FeCl_3$/Zn/THF or $CuCl_2$, $2H_2O$/Zn/THF; (vi) TBAF, THF; (vii) K_2CO_3, MeOH; (viii) 2,2-dimethoxypropane/PTSA.

Using water/THF as a solvent, the In-mediated reaction showed little progress as the majority of aldehyde remained unreacted. (Table 1, entry J). In this case the diastereoisomers **8a/b** were inseparable from each other by column chromatography. Hence they were identified and quantified on desilylation of the mixture with TBAF and chromatographic separation of the corresponding diols **6a/b**. Luche's allylation of benzoylated derivative **9** (Table 1, entry K), proceeded well to produce **10** with reasonable *anti*-selectivity (*syn*-**10a**:*anti*-**10b** = 40:60) which could be separated by column chromatography to obtain both monoprotected 1,3-diols (**10a** and **10b**) in homochiral form. Both **10a**/**b** could be identified after converting them to the corresponding diols **6a/b** by alkaline hydrolysis (Scheme 2). However, no reaction took place for allylations mediated with low valent Cu or Fe (Table 1, entries L and M) or In under both conditions (Table 1, entries N and O).

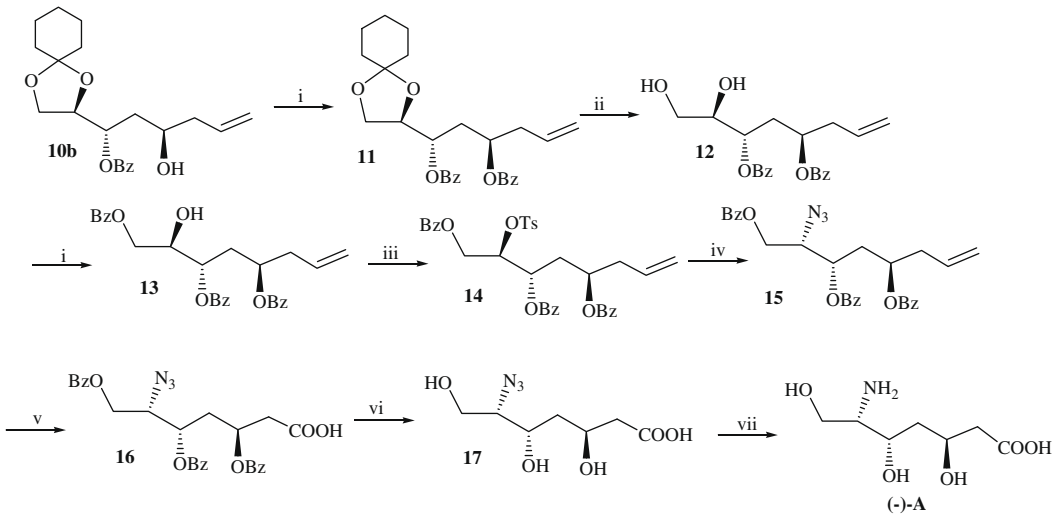
Thus, a detailed investigation on the compatibility of four different metal-mediated Barbier-type allylations[6–8] in wet media of three β-oxygenated aldehydes (**5**, **7**, and **9**) derived from **1** was carried out. As shown in Table 1, the aldehydes were found to be inconsistently reactive toward all four allylations we attempted. However, each aldehyde was found to be compatible with at least one of the allylations (Table 1, entries D, E, F, G, H, and K). Due to their moderate stereoselectivity, some successful allylations afforded both *syn*-1,3-**6a** and *anti*-1,3-**6b** diols either directly (Table 1, entries D and E) or through desilylation (Table 1, entries E, F, G, H, and J) while some provided both diastereoisomers of monoprotected diols **10a** and **10b** (Table 1, entry K) in homochiral form. It is worth mentioning that all the diastereoisomeric alcohols **6a** and **6b**, and **10a** and **10b** due to their possession of different types of functionalities on both ends of the diol moiety are amenable for versatile chemical manipulations. In conclusion, the good compatibility of **5**, **7,** and **9** with moderate stereoselectivity under several allylation reactions and the easy chromatographic separation of the diastereoisomers of **6** and **10** enabled us to directly obtain substantial amounts of both *syn*- and *anti*-1,3 diols **6a** and **6b** or **10a** and **10b** from each of them (Table 1, entries E, F, G, H, and K), instead of performing the stereoselective allylation separately using chiral allylating agents[2] with the same aldehydes. Furthermore, the isolation of homochiral monoprotected *syn*- and *anti*-1,3-diols **10a**,**b** (Table 1, entry K) is worth mentioning as both their hydroxyls and other functionalities are individually amenable for a variety of chemical elaborations, that will impart more versatility regarding their synthetic potential.

Having achieved the preparation of homochiral 1,3-diols in good yields following this approach we next turned our attention to exploit the major isomer **10b** to prepare (−)-galantinic acid **A**. This is a non-protenogenic natural amino acid and a constituent of the peptide antibiotic Galantanin 1. It was first isolated from the culture broth of *Bacillus pulvifaciens*[10] as a degradation product. Its acyclic structure has been correctly assigned by Ohfume et al. in 1990[11] after correcting the wrong structure, which had been proposed earlier. In support of their proposal regarding the structure and absolute configuration of A, Ohfume et al. reported its first synthesis.[11] Later, due to its interesting biological properties, other syntheses of **A** were reported employing several asymmetric strategies.[12]

Benzoylation of **10b** yielded **11**, which on deketalization on treatment with aqueous acid afforded diol **12**. This was subjected to monobenzoylation at its primary hydroxyl to afford tribenzoate **13** in good yield. Its remaining hydroxyl at C-2 was subjected to S_N2 invertive azidation in two steps comprising tosylation and treatment of the corresponding tosylate **14** with NaN_3 in good overall yield. Next, the olefin of **15** was subjected to oxidative cleavage on treatment with $NaIO_4$/ $RuCl_3$ to afford **16**. This was transformed into (−)-galantinic acid **A** in two simple steps (Scheme 2) involving exhaustive debenzoylation under alkaline conditions followed by hydrogenation of the resulting triol **17**. The physical and spectroscopic data of our synthesized **A** are in accordance with those reported in the literature (Scheme 2).[11a]

3. Conclusion

Thus, (*R*)-2,3-cyclohexylideneglyceraldehyde **1** could be efficiently utilized to obtain a number of *syn*- and *anti*-1,3-diols **6** and **10** in homochiral form by employing several metal-mediated Barbier-type allylations of aldehydes **5**, **7,** and **9** derived from it in wet media. The novelty of this approach stems from its exhaustive application of environmentally benign green chemistry by preparing many compounds associated with it, viz. **1**,[4a] **2**[4b] and 1,3-diols **6**, **8**, and **10** (Table 1). It is worth mentioning, that the hydrophobicity of the cyclohexylidene moiety in the aldehydes **5**, **7**, and **9** did not inhibit their reactivity in a wet medium as each of them could be successfully allylated under at least one of the four conditions carried out herein. Conversely by protecting the 1,2-diol in **6a**,**b** and **10a**,**b**, the cyclohexylidene moiety is likely to facilitate a wide range of chemical manipulations of all their



Scheme 2. (i) BzCN/TEA/DCM; (ii) TFA:H_2O/DCM; (iii) *p*-TsCl Py; (iv) NaN_3, DMF, 90 °C; (v) $RuCl_3$, $NaIO_4$, H_2O; (vi) K_2CO_3, MeOH; (vii) 10% Pd/C, H_2 MeOH.

functionalities, thereby enhancing their synthetic utility. Finally, as a representative application of the 1,3-diols constructed here, the stereo-selective synthesis of galantinic acid **A**[10] has been developed from a major *anti*-1,3-diol **10b**. Our investigation on the efficacy and stereoselectivity of several metal-mediated allylations with a few more aldehydes derived from **1** is currently in progress.

4. Experimental

Chemicals used as starting materials are commercially available and were employed without further purification. All solvents used for extraction and chromatography were distilled twice at atmospheric pressure prior to use. The ^{1}H NMR and ^{13}C NMR spectra were scanned with a Brucker Ac-200 (200 MHz) instrument in $CDCl_3$. The organic extracts were desiccated over dry Na_2SO_4.

4.1. (2*R*,3*S*)-1,2-*O*-Cyclohexylidene-3-(*tert*)-butyldiphenylsilyloxy-5-hexene 3

To a stirred solution of **2** (2.5 g, 11.79 mmol) and imidazole (0.962 g, 14.15 mmol) in CH_2Cl_2 (50 mL) was added TBDPSCl (3.87 g, 14.15 mmol) in CH_2Cl_2 (15 mL) and the reaction mixture was stirred overnight. It was then poured in water, and the organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic extracts were washed with water, brine, and dried. Solvent removal under reduced pressure followed by column chromatography of the residue (Silica gel, 0–10% EtOAc/hexane) afforded **3** (4.75 g, 89.6%); $[\alpha]_D^{25} = +15.3$ (*c* 2.8, $CHCl_3$); ^{1}H NMR: δ 1.0 (s, 9H), 1.12–1.57 (m, 10H), 2.03–2.17 (m, 2H), 3.70–3.77 (m,1H), 3.89–3.95 (m, 2H), 4.02–4.08 (m, 1H), 4.86–4.98 (m, 2H), 5.63–5.84 (m, 1H), 7.24–7.39 (m, 6H), 7.67–7.73 (m, 4H). ^{13}C NMR: 19.3, 23.8, 23.9, 25.1, 26.9, 34.7, 36.0, 38.6, 65.8, 73.0, 77.5, 109.2, 117.3, 127.37, 127.44, 129.5, 129.6, 133.5, 133.8, 133.9, 135.8, 135.9. Anal. Calcd for $C_{28}H_{38}O_3Si$: C, 74.63; H, 8.49. Found: C, 74.88; H, 8.70.

4.2. (2*R*,3*S*)-1,2-*O*-Cyclohexylidene-3-benzoyloxy-5-hexene 4

To a stirred and cooled (0 °C) solution of **2** (3.0 g, 14.15 mmol) and TEA (2.88 g, 28.30 mmol) in CH_2Cl_2 (50 mL) was added benzoyl cyanide (2.1 g, 16 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at 0 °C for 5 h till the disappearance of starting material (TLC). Mixture was then treated with H_2O. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic extracts were washed successively with 5% aqueous HCl, water, brine, and then dried. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0–15% EtOAc/hexane) afforded pure **4**. Yield: 4.38 g (98%); ^{1}H NMR: 1.2–1.60 (m, 10H), 2.38–2.52 (m, 2H), 3.85–3.93 (m,1H), 4.00–4.07 (m, 1H), 4.19–4.28 (m, 1H), 5.00–5.13 (m, 2H), 5.21–5.30 (m,1H), 5.71–5.91 (m, 1H), 7.35–7.51 (m, 3H), 8.01 (d, J = 7 Hz, 2H). ^{13}C NMR: 23.7, 23.8, 25.0, 34.7, 35.5, 36.0, 65.7, 73.3, 75.8, 110.0, 118.1, 128.2, 129.5, 130.0, 132.9, 165.6. Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.64. Found: C, 71.88; H, 7.84.

4.3. General method for ozonolysis

To a stirred and cooled (−78 °C) solution of **2** (1.06 g, 5 mmol) or **3** (2.25 g, 5 mmol) or **4** (1.58 g, 5 mmol) in CH_2Cl_2 (50 mL) was bubbled ozone gas until a blue color persisted. Excess ozone was removed by flushing with argon. Next, PPh_3 (2.0 g, 8 mmol) was added to the mixture causing immediate disappearance of the blue color. The solution was brought to room temperature and stirred for an additional 5 h and concentrated under reduced pressure. The residue was chromatographed through silica gel eluting with different solvent systems (0–3% MeOH in $CHCl_3$ for **5**, 0–10% EtOAc in hexane for **7** and 0–15% EtOAc in hexane for **9**) to afford aldehyde **5**, **7**, or **9**, all of which tended to decompose on long standing and hence were used immediately for the subsequent allylation reactions.

4.4. General method for Luche's allylation of aldehydes 5, 7, and 9

To a well-stirred mixture of the crude aldehyde **5** or **7** or **9** [obtained from ozonolysis of their respective olefin precursor (5 mmol)], allyl bromide (10 mmol), and Zn dust (1 g, 15 mmol) in THF (50 mL), was added saturated aqueous NH_4Cl solution (7 mL) in portions over a period of 20 min. For aldehyde **5**, no reaction took place (TLC) even after stirring the mixture for an additional 24 h. For aldehydes **7** and **9**, the reaction mixture was stirred for another 1.5 h until the complete disappearance of the starting material (TLC). The mixture was filtered and washed thoroughly with EtOAc. The combined organic layer was washed with 5% HCl to dissolve the suspended turbid material and then with water and brine and dried. Solvent removal under reduced pressure and column chromatography (silica gel, 0–20% EtOAc/hexane) of the residue afforded an inseparable diastereomeric mixture (2.02 g of **8a**/**8b**, 81.7%) and separable diastereomers (582 mg of **10a** and 873 mg of **10b**) in their respective cases.

4.5. Desilylation of 8a/8b

A solution of tetrabutylammonium fluoride in THF (8 mL, 1 M solution) was added to a solution of **8a**/**8b** (2.02 g) obtained above in THF (30 mL). The resulting solution was stirred overnight at room temperature. The reaction was quenched by the addition of saturated aqueous solution of NH_4Cl (10 mL). The mixture was diluted with EtOAc, and phases were separated. The aqueous phase was thoroughly extracted with EtOAc. The combined organic layer was washed successively with water and brine and dried. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0–5% MeOH/$CHCl_3$) afforded pure diols **6a** (502 mg 39.2%) and **6b** (544 mg, 42.5%).

4.6. General procedure for allylation of aldehydes 5, 7, and 9 employing bimetal redox strategy

To a cooled (10 °C) solution of crude aldehyde **5** or **7** or **9** [obtained from ozonolysis of their respective olefin precursor (5 mmol)], in THF (50 mL), $CuCl_2{\cdot}2H_2O$ (15 mmol) or anhydrous $FeCl_3$ (10 mmol) was added. The mixture was stirred well for 2 min. To this stirred suspension allyl bromide (15 mmol) was added. Then Zn dust (30 mmol) was added to it in portions over a period of 20 min. For aldehydes **5** and **9** no reaction took place (TLC) even after stirring the mixture for an additional 24 h. For aldehyde **7**, the mixture was stirred further at the same temperature for an additional period of 10 h for $CuCl_2{\cdot}2H_2O$ and 1 h for $FeCl_3$ until the total disappearance of the starting material (TLC). The reaction mixture was gradually brought to room temperature and stirred for another 2 h. It was then treated successively with water (25 mL) and EtOAc (50 mL). The mixture was stirred for 10 min and then filtered. The filtrate was treated with 2% aqueous HCl to dissolve the small amount of suspended particles. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extract was washed with water and brine and then dried. Solvent removal under reduced pressure afforded residue which on column chromatography (silica gel, 0–20% EtOAc/hexane) gave an inseparable mixture of diastereomers (**8a** and **8b**) [2.1 g for $FeCl_3$/Zn; 2.04 g(82.4%) for $CuCl_2{\cdot}2H_2O$/Zn] of the resulting homoallylic alcohol in pure form. Desilylation of the mixture of **8a**/**8b** following a similar procedure as carried out

above afforded individual diols [**6a** (380 mg (29.7%) and **6b** (706 mg (55.1%) for $FeCl_3$/Zn; **6a** (475 mg (37.1%) and **6b** (580 mg (45.3%) for $CuCl_2{\cdot}2H_2O$ /Zn].

4.7. General method for Indium-mediated allylation of aldehydes 5, 7, and 9 in H_2O

To a magnetically stirred solution of crude aldehyde **5** or **7** or **9** [obtained from ozonolysis of their respective olefin precursor (5 mmol)], and allyl bromide (10 mmol) in water (8 mL) was added indium metal (99.99% pure ingot, Alfa Aesar make, 632 mg, 5.5 mmol). The reaction mixture was stirred for 24 h. For aldehydes **7** and **9** no reaction took place (TLC). For aldehyde **5**, the mixture was treated with EtOAc (20 mL) and stirred for an additional 1 h. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with water and brine and then dried. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0–5% MeOH/$CHCl_3$) afforded pure diols **6a** (191 mg, 15.3%) and **6b** (788 mg, 61.7%).

4.8. General method for indium-mediated allylation in H_2O/THF

To a magnetically stirred solution of crude aldehyde **5** or **7** or **9** [obtained from ozonolysis of their respective olefin precursor (5 mmol)], and allyl bromide (10 mmol) in a 1:1 solvent mixture of water and THF (8 mL) was added indium (99.99% pure ingot, Alfa Aesar, 632 mg, 5.5 mmol). The reaction mixture was stirred for 24 h. For aldehyde **9** no reaction took place. For aldehyde **5**, the mixture was treated with EtOAc (20 mL) and stirred for an additional 1 h. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extract was washed with water and brine and then dried. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0–20% EtOAc/hexane) afforded pure diols **6a** (361 mg, 28.2%) and **6b** (590 mg, 46.1%). For aldehyde **7**, the reaction took place to a slight extent after stirring the mixture for an additional 10 h (TLC). The mixture was treated with EtOAc and worked up in similar manner as carried out above for the In-mediated reaction in water. Solvent removal under reduced pressure, column chromatography (silica gel, 0–20% EtOAc/hexane) of the residue to obtain a mixture of **8a** and **8b**, its desilylation with TBAF as carried out earlier and column chromatography (silica gel, 0–5% MeOH/$CHCl_3$) of the product after the usual work-up afforded diols **6a** (78 mg, 6.0%) and **6b** (115 mg, 9.0%) in pure form.

4.9. (2*R*,3*S*,5*S*)-1,2-*O*-Cyclohexylidene-1,2,3,5-tetrahydroxy-oct-7-ene 6a

$[\alpha]_D^{26} = +10.4$ (*c* 2.0, $CHCl_3$) ^{1}H NMR: 1.3–1.8 (m, 12H), 2.2–2.3 (m, 2H), 3.2 (br s, 1H), 3.5 (br s, 1H), 3.84–3.98 (m, 5H), 5.0–5.1 (m, 2H), 5.6–5.9, (m, 1H); ^{13}C NMR: 23.4, 23.6, 24.7, 34.4, 35.9, 38.1, 42.0, 65.0, 71.2, 72.3, 77.7, 109.4, 117.9, 133.8. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44. Found: C, 65.78; H, 9.66.

4.10. (2*R*,3*S*,5*R*)-1,2-*O*-Cyclohexylidene-1,2,3,5-tetrahydroxy-oct-7-ene 6b

$[\alpha]_D^{26} = +0.5$ (*c* 1.2, $CHCl_3$); ^{1}H NMR: δ 1.2–1.9 (m, 12H), 2.2–2.5 (m, 2H), 2.5 (br s, 1H), 2.9 (br s, 1H), 3.84–4.0 (m, 5H), 5.0–5.15 (m, 2H), 5.5–5.9, (m, 1H); ^{13}C NMR: 23.4, 23.6, 24.8, 34.4, 35.9, 38.0, 41.7, 65.0, 67.7, 68.8, 77.6, 109.4, 118.0, 134.0. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44. Found: C, 65.38; H, 9.26.

4.11. (2*R*,3*S*,5*S*)-1,2-*O*-Cyclohexylidene-3-*O*-benzoyl-1,2,3,5-tetrahydroxy-oct-7-ene 10a

$[\alpha]_D^{26} = +10.8$ (*c* 1.04, $CHCl_3$); ^{1}H NMR: δ 1.2–1.6 (m, 10H), 1.70–1.84 (m, 2H), 2.22–2.28 (m, 2H), 2.55 (br s, 1H), 3.55–3.65 (m, 1H), 3.86–3.93 (m, 1H), 4.06–4.13 (m, 1H), 4.23–4.32 (m, 1H), 5.04–5.12 (m, 2H), 5.30–5.40 (m, 1H), 5.71–5.88 (m, 1H), 7.40–7.48 (m, 2H), 7.54–7.62 (m, 3H), 8.04 (dd, *J* = 7.2 Hz, 2H); ^{13}C NMR: 23.7, 23.8, 25.0, 34.6, 35.9, 38.7, 41.8, 65.6, 66.5, 72.2, 77.8, 110.3, 117.5, 128.4, 129.5, 129.8, 133.3, 134.6, 166.8. Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 70.20; H, 7.64.

4.12. (2*R*,3*S*,5*R*)-1,2-*O*-Cyclohexylidene-3-*O*-benzoyl-1,2,3,5-tetrahydroxy-oct-7-ene 10b

$[\alpha]_D^{25} = +12.7$ (*c* 1.76, $CHCl_3$); ^{1}H NMR: δ 1.24–1.57 (m, 10H), 1.91–1.99 (m, 2H), 2.13–2.35 (m, 2H, overlapped with a br s, 1H), 3.83–3.92 (m, 2H), 4.05–4.12 (m, 1H), 4.26–4.35 (m, 1H), 5.07–5.15 (m, 2H), 5.26–5.35 (m, 1H), 5.70–5.87 (m, 1H), 7.39–7.60 (m, 3H), 7.99–8.04 (m, 2H); ^{13}C NMR: 23.7, 24.9, 34.6, 36.0, 37.9, 41.6, 65.5, 67.8, 72.0, 76.5, 110.1, 117.7, 128.2, 129.5, 129.9, 132.8, 134.3, 165.8. Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 70.19; H, 8.04.

4.13. (2*R*,3*S*,5*S*)-1,2-*O*-Cyclohexylidene-3,5-*O*-isopropylidene-1,2,3,5-tetrahydroxy-oct-7-ene 6c

A solution of **6a** (100 mg, 0.39 mmol) in 2,2-dimethoxypropane (5 mL) and containing *para*-toluenesulfonic acid (PTS) (50 mg) was stirred for 1 h. After the completion of the reaction (cf. TLC), it was diluted with ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed water and brine and dried. Removal of solvent under reduced pressure and column chromatography (silica gel, 0–15 EtOAc/hexane) of the residue afforded pure **6c** 208 mg (90%); δ ^{13}C NMR: δ 19.8, 23.7, 24.0, 25.0, 29.9, 33.6, 34.6, 36.4, 40.7, 65.8, 68.3, 70.7, 77.9, 98.4, 109.7, 117.1, 133.9.

4.14. (2*R*,3*S*,5*R*)-1,2-*O*-Cyclohexylidene-3,5-*O*-isopropylidene-1,2,3,5-tetrahydroxy-oct-7-ene 6d

Compound **6d** was prepared from **6b** (100 mg, 0.39 mmol) following a similar procedure as described above for the preparation of **6c**. Yield 212 mg; ^{13}C NMR: δ 23.7, 23.9, 24.7, 24.9, 25.1, 34.4, 34.7, 36.3, 40.0, 65.7, 66.0, 66.9, 68.1, 100.2, 109.8, 116.9, 134.2.

4.15. (2*R*,3*S*,5*RS*)-1,2-*O*-Cyclohexylidene-3-*O*-*tert*-butyldiphenylsilyl-1,2,3,5-tetrahydroxy-oct-7-enes 8a,b

^{1}H NMR: δ 1.06 (s, 9H), 1.28–1.61 (m, 10H), 1.67–1.71 (m, 2H), 2.0–2.2 (m, 2H), 2.70 (br s, 1H), 3.59–3.66 (m, 1H), 3.79–4.25 (m, 4H), 4.92–5.03 (m, 2H), 5.6–5.8 (m, 1H), 7.32–7.43 (m, 6H), 7.64–7.73 (m, 4H); ^{13}C NMR: 19.3, 23.7, 25.0, 26.9, 29.6, 34.7, 35.9, 41.5, 41.9, 42.1, 42.2, 66.9, 67.4, 67.5, 68.0, 72.3, 74.1, 76.4, 78.1, 78.5, 110.0, 117.2, 117.3, 127.6, 129.8, 133.1, 133.3, 133.4, 133.6, 134.7, 134.8, 135.5, 135.9.

4.16. (2*R*,3*S*,5*R*)-1,2-*O*-Cyclohexylidene-3,5-O-di-benzoyl-1,2,3,5-tetrahydroxy-oct-7-ene 11

To a cooled (0 °C) solution of **10b** (2.5 g, 7 mmol) in CH_2Cl_2 (75 mL) containing triethylamine (3.5 mL) was added benzoyl cyanide (982 mg, 7.5 mmol). The mixture was stirred for 5 h at 0 °C until the completion of the reaction (cf. TLC), after which it was treated with water and extracted with $CHCl_3$. The combined organic extract was washed with 5% HCl, then with water until acid free

and brine and dried. Solvent removal under reduced pressure and column chromatography (silica gel, 0–10% EtOAc/hexane) of the residue afforded pure **11** (3.06 g, 95%); ^{1}H NMR: δ 1.56–1.66 (m, 10H), 2.13–2.19 (m, 2H), 2.48–2.55 (m, 2H), 3.82–3.89 (m, 1H), 4.03–4.06 (m, 1H), 4.30–4.42 (m, 1H), 5.07–5.10 (m, 2H), 5.31–5.35 (m, 2H), 5.70–5.87 (m, 1H), 7.25–7.54 (m, 10H).; ^{13}C NMR: 23.7, 23.9, 25.1, 34.3, 34.7, 36.1, 38.9, 60.8, 65.9, 76.2, 110.3, 118.4, 128.1, 128.2, 128.2, 129.5, 129.6, 129.8, 130.2, 130.4, 132.7, 132.9, 165.6, 165.8.

4.17. (2*R*,3*S*,5*R*)-3,5-*O*-Di-benzoyl-1,2,3,5-tetrahydroxy-oct-7-ene 12

To a cooled (0 °C) solution of **11** (2.5 g, 5.38 mmol) in CH_2Cl_2 (50 mL) was added 80% aqueous trifluoroacetic acid (8 mL). The mixture was stirred for 2.5 h until the completion of the reaction (TLC), after which it was treated with water (50 mL) and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$. The combined organic extract was washed successively with water and brine and dried. Removal of the solvent under reduced pressure and column chromatography (silica gel, 5% MeOH/$CHCl_3$) of the crude afforded pure **12** (1.62 g, 78.2%); $[\alpha]_D^{24} = -13.2$ (*c* 4.78, $CHCl_3$); ^{1}H NMR: δ 2.15–2.36 (m, 2H), 2.42–2.53 (m, 2H), 3.1 (br s, 2H), 3.54–3.78 (m, 3H), 5.05–5.15 (m, 3H), 5.31–5.35 (m, 1H), 5.74–5.82 (m, 1H), 7.28–7.50 (m, 6H), 7.50–7.93 (m, 4H).; ^{13}C NMR: 34.4, 49.0, 62.6, 70.4, 71.1, 72.9, 118.5, 128.2, 128.3, 129.4, 129.5, 129.7, 130.0, 132.8, 132.9, 133.0, 133.2, 166.1, 166.7. Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. Found: C, 68.51; H, 6.52.

4.18. (2*R*,3*S*,5*R*)-1,3,5-*O*-Tri-benzoyl-1,2,3,5-tetrahydroxy- oct-7-ene-2-ol 13

Following a similar procedure as done for the preparation of **11**, compound **12** (1.5 g, 3.9 mmol) was benzoylated with benzoyl cyanide (524 mg, 4 mmol) in the presence of triethyl amine (2 mL) in CH_2Cl_2 (75 mL) at 0 °C to obtain **13** (1.73 g, 91%); $[\alpha]_D^{24} = -19.1$ (*c* 1.57, $CHCl_3$); ^{1}H NMR: δ 2.26–2.32 (m, overlapped with br s, 3H), 2.49–2.55 (m, 2H), 4.28–4.55 (m, 3H), 5.06–5.16 (m, 2H), 5.36–5.39 (m, 2H), 5.74–5.83 (m, 1H), 7.29–7.57 (m, 10H), 7.89–8.09 (m, 5H).; ^{13}C NMR: 33.7, 38.9, 65.5, 70.0, 70.2, 71.1, 71.8, 118.5, 128.0, 128.2, 128.2, 129.4, 129.6, 130.0, 132.7, 133.1, 165.9, 166.0, 166.7. Anal. Calcd for $C_{29}H_{28}O_7$: C, 71.29; H, 5.77. Found: C, 71.48; H, 5.98.

4.19. (2*S*,3*S*,5*R*)-2-Azido-1,3,5-tri-benzoyloxy-oct-7-ene 15

To an ice-cooled (0 °C) solution of **13** (1.5 g, 3.07 mmol) in pyridine (20 mL) containing 4-(dimethylamino)pyridine (50 mg) was added *p*-TsCl (700 mg, 3.67 mmol). The mixture was stirred at the same temperature for 4.0 h. After completion of reaction (TLC), it was treated with water and extracted with ethyl acetate. The organic layer was separated and the aqueous layer was washed with ethyl acetate. The combined organic extracts were washed with 5% HCl, water, and brine and dried. Removal of the solvent under reduced pressure yielded a crude residue containing tosylate **14**. This was taken in dimethylformamide (DMF) (25 mL), after which sodium azide (NaN_3) (280 mg, 4.3 mmol) was added to it. The reaction mixture was heated at 90 °C for 4 h. After completion of the reaction (TLC), it was brought to room temperature, treated with water and extracted with EtOAc. The combined organic extract was washed successively with water and brine and dried. Solvent removal under reduced pressure and column chromatography (0–15% EtOAc/hexane) of the residue afforded **15** (1.1 g, 70%); $[\alpha]_D^{22} = -13.7$ (*c* 4.78, $CHCl_3$); ^{1}H NMR: δ 2.21–2.30 (m, 2H), 2.52 (t, *J* = 6.3 Hz, 2H), 3.96–4.02 (m, 1H), 4.40–4.49 (m, 1H), 4.57–4.65 (m, 1H), 5.08–5.17 (m, 2H), 5.23–5.25 (m, 1H), 5.55–5.59 (m, 1H), 5.74–5.82 (m, 1H), 7.31–7.58 (m, 9H), 7.93–8.00 (m, 6H); ^{13}C NMR: 34.7, 38.7, 62.3, 63.9, 69.4, 69.9, 118.7, 128.2, 128.3, 129.0, 129.4, 129.6, 129.7, 129.9, 132.5, 132.8, 133.2, 165.3, 165.7, 165.9. Anal. Calcd for $C_{29}H_{27}O_6N_3$: C, 67.82; H, 5.29; N, 8.18. Found: C, 68.07; H, 5.11; N, 8.36.

4.20. (2*S*,3*S*,5*S*)-2-Azido-1,3,5-tribenzoyloxy-heptanoic acid 16

Compound **15** (800 mg, 1.56 mmol) was taken in a solvent mixture of carbon tetrachloride (2 mL), acetonitrile (2 mL), and water (3 mL). The biphasic mixture was stirred, treated with sodium metaperiodate (1.34 g, 6.26 mmol), followed by the addition of ruthenium trichloride hydrate (10 mg). The entire mixture was stirred vigorously for 2 h at room temperature. After completion of the reaction (TLC), CH_2Cl_2 (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extract was washed with water and brine and dried. Solvent removal under reduced pressure and column chromatography (0–7% MeOH/$CHCl_3$) of the residue afforded **16** (0.588 g, 71%); ^{1}H NMR: δ 2.39–2.49 (m, 2H), 2.73–2.97 (m, 2H), 4.03–4.25 (m, 1H), 4.41–4.65 (m, 2H), 5.56 (m, 2H), 7.27–7.54 (m, 9H), 7.89–7.99 (m, 6H), 8.36 (br s, 1H); ^{13}C NMR: 35.04, 38.6, 62.2, 63.9, 70.9, 72.5, 128.2, 128.4, 128.7, 128.9, 129.0, 129.5, 129.6, 129.8, 133.0, 133.3, 134.1, 147.0, 157.9, 165.5, 165.6, 165.9, 174.9.

4.21. Galantinic acid A

To a well-stirred and cooled (0 °C) solution of **16** (0.300 g, 0.584 mmol) in MeOH (25 mL) was added powdered K_2CO_3 (0.322 g, 2.34 mmol). This mixture was allowed to stir for 2.5 h. After completion of reaction (TLC), MeOH was removed in vacuo to afford a crude residue which was dissolved in $CHCl_3$. The solution was washed with water and brine and dried. Solvent removal under reduced pressure afforded the residue containing **17**. This was taken in methanol (25 mL). To this methanolic solution, 10% Pd/C (100 mg) was added. The mixture was subjected to hydrogenation for 2 h with stirring. After completion of reaction (TLC) the reaction mixture was passed through a small silica pad. The silica pad was washed with methanol (70 mL). Solvent removal under reduced pressure and column chromatography (0–20% MeOH/$CHCl_3$) of the residue afforded **A** as colorless crystals (0.050 g (71%). Melting point: 122–126 °C; lit[11a] Melting point: 125–130 °C; $[\alpha]_D^{22} = -25.0$ (*c* 2.9, D_2O); lit[11a] $[\alpha]_D^{25} = -29.0$ (*c* 3.5, D_2O), ^{1}H NMR (D_2O): δ 1.51–1.65 (m, 2H), 2.27–2.29 (m, 2H), 3.05–3.07 (m, 1H), 3.52–3.61 (m, 1H), 3.68–3.76 (m, 1H), 3.81–3.91 (m, 1H), 4.05–4.11 (m, 1H). ^{13}C NMR (D_2O): 39.6, 45.4, 57.3, 59.6, 65.3, 180.0.

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