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Metal-dependent modulation of diastereoselectivity in the Barbier-type crotylation of (*R*)-cyclohexylideneglyceraldehyde

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ABSTRACT

The diastereoselectivity of the Barbier-type crotylation of (*R*)-cyclohexylideneglyceraldehyde could be tuned by changing the metal atom and solvent. The Ga-mediated reaction in [bmim][Br] produced the best diastereoselectivity, furnishing the all-*anti* product in good yield.

1. Introduction

The development of simple and efficient strategies is a highly desirable goal in organic synthesis. Despite impressive progress,[1a] this remains a very dynamic and challenging area in asymmetric synthesis.[1b,c] The most practical method is aimed at producing the target compounds via a reliable route utilizing inexpensive and readily available materials. Over the past several years, we have found cyclohexylideneglyceraldehyde **1** as an extremely versatile, easily available and inexpensive chiral template for various enantioselective transformations. Many of these have also been used for the synthesis of a diverse array of bioactive compounds. The cyclohexylidene moiety of the aldehyde **1** provides considerable steric bias in the addition of organometallics to its aldehyde function, and also ensures easy separation of the resultant epimeric carbinols by normal column chromatography.

Asymmetric allylation/crotylation of aldehydes[2a] is one of the most extensively studied processes for carbon–carbon bond formation, driven in part by the versatility of the homoallylic alcohols as synthetic intermediates.[2b,c] The crotylation reaction is valued more as it generates two new stereogenic centres. Different approaches involving various metals, crotylating agents and solvents have been explored to address issues such as regio-, diastereo- and enantioselectivities.[3a–e] The asymmetric version of crotylation is accomplished by incorporating a chiral auxiliary in the substrate and/or the reagent. While the design and synthesis of the required chiral auxiliary provide adequate challenge, the efforts are often very taxing, and at times frustrating. Furthermore, syntheses of the sterically robust chiral auxiliaries may require several steps, and involve expensive reagents. It was envisaged that a method based on using a natural chiral pool-derived template might provide a suitable alternative for the designated transformation.

Based on our own experience, aldehyde **1** appeared well-suited as a versatile chiral template for this purpose. We were particularly interested in expanding the substrate-controlled strategy, since the alcohol stereomers, obtained by crotylation of **1** are functionally sufficiently enriched for elaboration to various target compounds.[4] Hence, for the present work, we attempted the reaction using various metals, and solvents under varying reaction conditions leading to the development of an efficient asymmetric crotylation strategy of **1** with Ga in [bmim][Br] (Scheme 1). The studies also revealed that the diastereoselectivity of Barbier-type crotylation of **1** can be efficiently tuned by judicious choice of metal and solvent.

2. Results and discussion

The initial motivation for the present work stems from our previous observation that the stereochemistry of crotylation of **1** can be tuned by changing the metals, and perhaps using different media. For example, while the Zn-mediated crotylation of **1** in wet THF proceeded with modest *anti*-selectivity to furnish the diastereomeric alcohols **2a–c** in a 2.4:33.1:64.5 ratio,[5a] when the reaction was carried out with In/H_2O, compounds **2b** and **2c** were obtained in a ~1:1 ratio.[5b] Admittedly, the diastereoselectivity of both the protocols was unimpressive. This prompted us to study the diastereoselectivity of the reaction by changing the metals (Mg, In, Ga and Sb) and solvents (organic, aqueous and a room temperature ionic liquid, [bmim][Br]). The results are summarized in Table 1. With Mg in ethereal solvents, practically no selectivity was obtained, and the compounds **2a–c** were produced almost in equal amounts (Table 1, entries 1 and 2). The use of Sb in aqueous THF or H_2O gave a similar diastereoselectivity, but poor yields, and required an additional metal activator (KF) (Table 1, entries 3 and 4). The In-mediated reaction proceeded well in H_2O, but not in THF (Table 1, entries 5–8), resulting in the preferential formation of **2b** and **2c** in a ~1:1 ratio, as the major products. On the other hand, the Ga-mediated reaction in THF produced the products in poor

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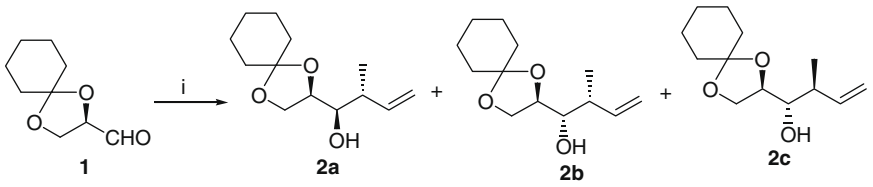


Scheme 1. Reagents: (i) Crotyl bromide/metal/additive/solvent.

Table 1
Steric course of the crotylation of **1** with different metals and solvents[a]

Entry	Crotyl bromide (equiv)	Metal (equiv)	Solvent	Additive	Time (h)	Yield[b] (%)	**2a**:**2b**:**2c**[c]
1	3.0	Mg (5.0)	Et_2O	—	8	74	38.1:33.2:28.7
2	3.0	Mg (5.0)	THF	—	8	35	29.0:26.1:44.9
3	2.5	Sb (5.0)	H_2O–THF (1:1)	KF (2 M)	12	37	30.6:40.8:28.6
4	2.5	Sb (5.0)	H_2O	KF (2 M)	14	48	40:47.7:12.2
5	3.0	In (5.0)	H_2O	—	14	75	4.0:52.2:43.8
6	1.2	In (2.0)	H_2O	LiCl + KI[d]	14	72	3.7:52.3:44.0
7	3.0	In (5.0)	H_2O	LiCl + KI[d]	14	72	3.7:52.3:44.0
8	3.0	In (5.0)	THF	—	12	0	—
9	4	Ga (2.5)	H_2O	—	—	0	—
10	3.5	Ga (2.5)	THF	KI + LiCl[d]	10	55	5:35:60
11	1.2	In (2.0)	[bmim][Br]	—	4	81	9.3:13.4:77.3
12	1.2	Ga (1.0)	[bmim][Br]	—	5	82	3:5:92

[a] The reactions were carried out on a 2 mmol scale.
[b] Total yield of the diastereomeric mixtures.
[c] Based on the yields of isolated individual diastereomers.
[d] The reaction was carried out in the presence of 1.0 equiv of each of the additives.

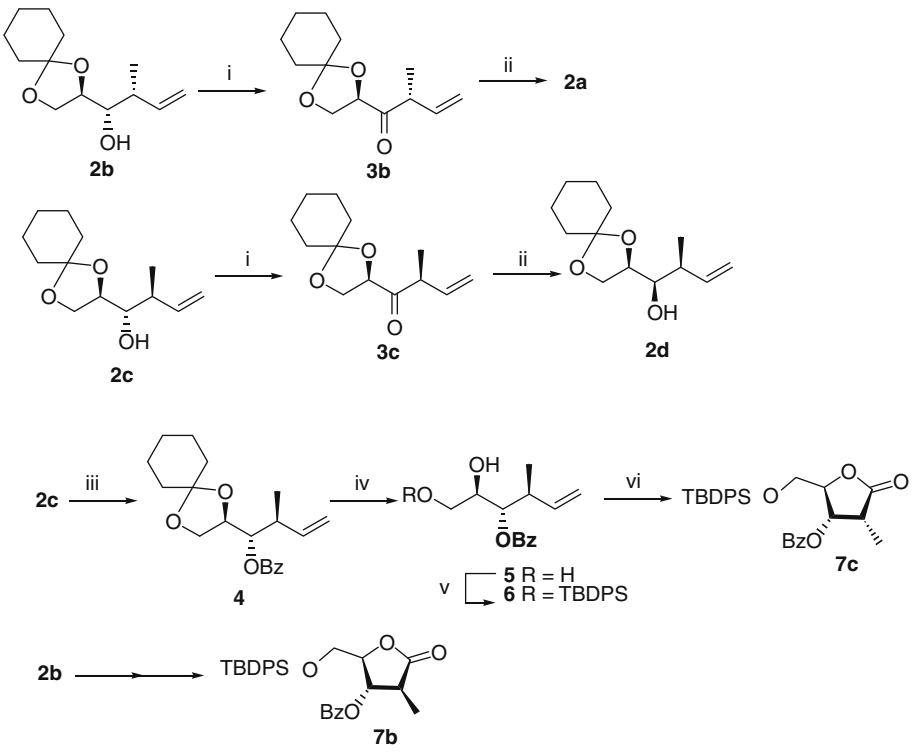
yields even under metal activation and resulted in a modest **2c**/**2b** selectivity (Table 1, entry 10), as observed with Zn. The inability of Ga to carry out the reaction in H_2O (Table 1, entry 9) is consistent with the fact that Ga requires thermal or ultrasonic activation,[6] while we carried out the reactions at room temperature.

Consequently, we explored the In- and Ga-mediated reactions in [bmim][Br] as the RTIL. So far, the hydrophobic RTILs are generally used in Barbier-type reactions,[7] while the simplest of them, [bmim][Br] is unexplored. We used [bmim][Br], since it possesses high hydrophilicity and water-mimicking properties that are ideal for the Barbier-type allylation. The In-mediated crotylation in [bmim][Br] proceeded with an improved diastereoselectivity namely,. **2a**:**2b**:**2c** ~9:13.5:77.5 (Table 1, entry 11). The selectivity of **2a**:**2b**:**2c** could be improved to 3:5:92 by carrying out the reaction with Ga-metal (Table 1, entry 12). Additionally, the yields were also very good in both these cases, and the reaction could be accomplished much faster with almost stoichiometric amounts of the reagents. In other solvents, the results were significantly inferior, even with a large excess of the reagents and prolonged reaction time. Surprisingly, the Zn-mediated crotylation of **1** did not take place in [bmim][Br]. Compounds **2a**–**2c** could be separated by column chromatography and characterized by their NMR spectra.[5a,b]

Initially the stereochemistry of each of the diastereomers was identified by comparing the pattern of the signals in the region of δ 3.3–4.2 of their ^{1}H NMR spectra with those reported[8a,b] for the corresponding isopropylidene derivatives. For further confirmation, compounds **2b** and **2c** were oxidized separately with pyridinium chlorochromate (PCC) to give the respective ketones **3b** and **3c**. Following our own method,[9] ketone **3b** was reduced with K-Selectride to furnish the corresponding alcohol, which showed identical NMR spectra to that of **2a**. This confirmed that compounds **2a** and **2b** were C-3 epimers. The K-Selectride reduction of the ketone **3c**, however, furnished the other diastereomeric alcohol **2d**, as revealed by its ^{1}H NMR spectrum.[4d] Since the K-Selectride reduction of the glyceraldehyde-derived ketones such as **3b/c** is known[9] to produce the 2,3-*syn* carbinols almost exclusively, the configuration of alcohol **2d** would be (2*R*,3*R*), and hence, the 2,3-stereochemistry of its progenitor **2c** would be (2*R*,3*S*).

To establish the C-4 configuration of **2c**, it was converted into the corresponding benzoate derivative **4** by treatment with BzCN in the presence of Et_3N. Deacetalization of **4** with aqueous trifluoroacetic acid (TFA) in CH_2Cl_2 afforded diol **5**. Treatment of **5** with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in the presence of Et_3N in CH_2Cl_2 furnished the mono silylated compound **6**. Its ozonolysis under alkaline condition[10] directly produced the γ-lactone **7c** (Scheme 2). The ^{1}H NMR resonance of the –CH(OBz) proton appeared at δ 5.96 (dd, J = 13.6, 2.2 Hz). The coupling constant values established the *syn*- and *anti*-relationships of H-4 (containing the OBz group) with its two neighbouring protons, H-3 and H-5.[11] This revealed the absolute stereochemistry of **7c** as (3*R*,4*S*,5*R*), and hence that of **2c** as (2*R*,3*S*,4*S*). For determining the configuration of **2b**, it was converted to the lactone **7b** in a similar manner. The ^{1}H NMR coupling constant values of its CH(OBz) proton revealed it to have a (3*S*,4*S*,5*R*)-configuration, confirming the stereochemistry of its precursor, **2b** as (2*R*,3*S*,4*R*). Hence, compound **2a** must possess a (2*R*,3*R*,4*R*)-configuration as it is the C-3 epimer of **2b**.

It is worth mentioning that earlier, better stereocontrol in crotylation was accomplished with reagents such as crotyltrifluorosilane,[3c,d] and crotyltrifluoroborates[3e] which need to be synthesized separately. In that light, the present approach, using inexpensive and commercially available reagents such as crotyl bromide, [bmim][Br] and Ga and the widely used chiral template, **1** provides a simple and convenient strategy for asymmetric crotylation. Incidentally, this is the first application of a hydrophilic RTIL in the Barbier-type allylation. Amongst the imidazole-based RTILs, [bmim][Br] is least expensive and possesses negligible vapour pressure, providing additional advantages for the process. The homoallylic alcohols **2a**–**c** have many desirable attributes of being versatile synthons in view of their small-carbon frameworks with high functional density that can be selectively manoeuvred for various target compounds. Especially the structural moiety possessing



Scheme 2. Reagents and conditions: (i) PCC/NaOAc/CH_2Cl_2; (ii) K-Selectride/THF/−78 °C; (iii) BzCN/Et_3N/CH_2Cl_2; (iv) aqueous TFA/CH_2Cl_2; (v) TBDPSCl/imidazole/CH_2Cl_2; (vi) O_3/NaOH/MeOH–CH_2Cl_2/−15 °C.

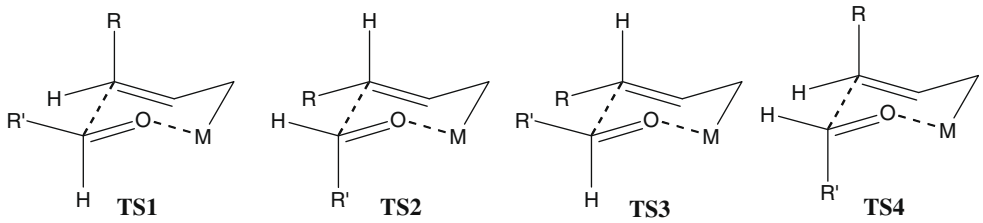
the adjacent asymmetric centres, bearing a hydroxyl group and methyl branching is a common structural element of many polyketide metabolites such as octalactins A and B, tylosin and leucomycins.[12a,b]

Although an α- or a β-oxygenation in carbonyl compounds is reported to be the most effective for chelation to metals,[13] aldehyde **1** predominantly gave 4,5-*anti*-diols with both In and Ga. The observed diastereoselectivity in the coupling indicated that due to the bulky cyclohexanedioxy group, chelation control was not operational. The results are consistent with our previous results with Zn and can be rationalized by the Felkin–Anh model.[14]

The 3,4-diastereoselectivity of the reaction involving γ-substituted (Me) allylic metal reagents and aldehydes may, in principle, involve a series of cyclic transition states, wherein the allylmetal reagent coordinates intramolecularly to the oxygen atom of the carbonyl group (Scheme 3). The formation of **TS1** and/or **TS2** leads to the *syn*-adduct, while the *anti*-product is obtained from **TS3** and/or **TS4**. Given that no other intramolecular chelation operates for this reaction, the transition state **TS3** leading to the 3,4-*anti*-adduct is most favourable from the steric point of view, because both Me and R (cyclohexylidene) groups adopt equatorial positions, and the allylic-metal exists as the *E*-form, irrespective of the geometry of the starting bromide.[15] The stereoselectivity is considered to be the outcome of the orientation of the R group. This explains the preferential formation of **2c** in the crotylation of **1**. However, the effect of the metal and solvent on the diastereoselectivity of the reactivity is unclear. A large number of other factors such as the nature of the metal,[16a–c] nature of the counter ion and aggregation state of the nucleophiles[17a–c] may be involved in dictating this diastereoselectivity and any more detailed rationalization would, at best, be speculative.

3. Conclusion

In conclusion, we have disclosed that by careful choice of metal and solvent, the stereochemical profile of the Barbier-type crotylation of the aldehyde **1** can be tuned. Of particular interest is the combination of Ga/[bmim][Br], which ensured a very fast reaction with stoichiometric amounts of the reagents, without any additional metal activation (chemical, thermal or ultrasonic). The reaction provides functionalized chiral homoallylic alcohols with high yield and diastereoselectivity. To the best of our knowledge, this is the first report of the Barbier-type allylation in a hydrophilic RTIL.



Scheme 3.

4. Experimental

4.1. General experimental details

All the chemicals (Fluka and Lancanster) were used as received. Other reagents were of AR grade. Unless otherwise mentioned, the organic extracts were dried over anhydrous Na_2SO_4. The IR spectra as thin films were scanned with a Jasco model A-202 FT-IR spectrophotometer. The ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded with a Bruker Ac-200 spectrometer using $CDCl_3$ as the solvent. The optical rotations were recorded with a Jasco DIP 360 digital polarimeter.

4.2. General method for crotylation of 1 via Grignard route

To a stirred solution of **1** (1.70 g, 0.01 mol) in THF (25 mL) was slowly injected the Grignard reagent [prepared from crotyl bromide (4.10 g, 0.03 mol) and Mg-turnings (1.20 g, 0.05 mol)] in Et_2O or THF (40 mL). After stirring for 12 h, the reaction was quenched with aqueous saturated NH_4Cl (2 mL). The organic layer was separated and the aqueous portion was extracted with Et_2O (2×15 mL). The combined organic extracts were washed with brine (1×5 mL), and dried. Solvent removal in vacuo and column chromatography of the residue afforded the pure alcohols **2a**–**c**.

4.3. General procedure for Barbier-type crotylation of 1 in H_2O or THF

Finely divided metal powder (In or Sb or Ga) was added to a mixture of **1** (5.0 g, 0.029 mol) and crotyl bromide (equivalents specified in Table 1) in H_2O (30 mL) or THF (30 mL) and the mixture was magnetically stirred for the time specified in Table 1. The mixture was filtered and worked-up to isolate pure **2a**–**c** as mentioned above. For the reaction with Sb, an aqueous solution of KF (5–6 mL, 2 M) was also added into the reaction mixture. The In-mediated reaction was also carried out in the presence of LiCl and KI (1.0 equiv each).

4.4. Typical procedure for the metal-mediated crotylation reactions in [bmim][Br]

A mixture of the metal (In or Ga) and crotyl bromide (quantities specified in Table 1) in [bmim][Br] (3 mL/mmol) was stirred at room temperature for 0.5 h, followed by the addition of aldehyde **1**. The reaction mixture was stirred at room temperature for 4–5 h. After completion of the reaction (cf. TLC), the mixture was extracted with Et_2O (3×10 mL), the ether extract was evaporated in vacuo and the residue was purified by column chromatography (silica gel, 0–15% EtOAc/hexane) to give **2a**–**c**.

4.5. (2*R*,3*R*,4*R*)-1,2-Cyclohexylidenedioxy-4-methylhex-5-en-3-ol 2a

Colourless thick oil; $[\alpha]_D^{24} = +45.9$ (c 1.81, $CHCl_3$), {lit.[5a] $[\alpha]_D^{23} = +47.1$ (c 1.4, $CHCl_3$)}; IR: 3408, 1648, 990 cm^{-1}; ^1H NMR: δ 1.09 (d, J = 6.8 Hz, 3H), 1.33–1.58 (m, 10H), 2.22–2.30 (m, 1H), 2.68 (br s, 1H), 3.31–3.39 (m, 1H), 3.71–3.76 (m, 1H), 3.93–4.15 (m, 2H), 4.98–5.08 (m, 2H), 5.68–5.84 (m, 1H); ^{13}C NMR: δ 12.4, 16.9, 23.9, 25.1, 35.0, 36.2, 41.3, 65.7, 74.6, 75.4, 109.6, 112.8, 139.6. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.81; H, 9.95.

4.6. (2*R*,3*S*,4*R*)-1,2-Cyclohexylidenedioxy-4-methylhex-5-en-3-ol 2b

Colourless thick oil; $[\alpha]_D^{24} = +29.8$ (c 1.40, $CHCl_3$), {lit.[5a] $[\alpha]_D^{23} = +29.65$ (c 1.45, $CHCl_3$)}; IR: 3400, 1651, 995 cm^{-1}; ^1H NMR: δ 1.09 (d, J = 6.8 Hz, 3H), 1.38–1.62 (m, 10H), 2.14 (br s, 1H), 2.21–2.28 (m, 1H), 3.62–3.71 (m, 1H), 3.78–3.84 (m, 2H), 4.02–4.14 (m, 1H), 4.93–5.12 (m, 2H), 5.68–5.84 (m, 1H); ^{13}C NMR: δ 12.5, 17.4, 24.1, 25.4, 35.3, 35.8, 41.2, 65.4, 74.7, 75.6, 109.2, 114.1, 138.8. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.12; H, 9.91.

4.7. (2*R*,3*S*,4*S*)-1,2-Cyclohexylidenedioxy-4-methylhex-5-en-3-ol 2c

Colourless thick oil; $[\alpha]_D^{24} = +2.4$ (c 1.17, $CHCl_3$), {lit.[5a] $[\alpha]_D^{23} = +2.6$ (c 2.05, $CHCl_3$)}; IR: 3408, 1657, 997 cm^{-1}; ^1H NMR: δ 1.07 (d, J = 6.6 Hz, 3H), 1.40–1.59 (m, 10H), 2.07 (br s, 1H), 2.20–2.43 (m, 1H), 3.53–3.58 (m, 1H), 3.82–4.06 (m, 3H), 5.0–5.12 (m, 2H), 5.71–5.91 (m, 1H); ^{13}C NMR: δ 12.7, 16.4, 23.9, 25.1, 34.8, 36.2, 40.7, 65.1, 71.7, 74.8, 109.1, 115.9, 139.8. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.12; H, 9.91.

4.8. (2*R*,4*R*)- and (2*R*,4*S*)-1,2-Cyclohexylidenedioxy-4-methyl-5-hexen-3-one 3b and 3c

To a cooled (0 °C) and stirred solution of PCC (1.6 g, 5.0 mmol) and NaOAc (0.3 g) in CH_2Cl_2 (10 mL) were added **2b** and **2c** (1.0 g, 4.42 mmol) in CH_2Cl_2 (10 mL). After stirring the reaction mixture for 3 h, it was diluted with dry Et_2O (80 mL), and the supernatant was filtered through a pad of silica gel. The eluate was concentrated in vacuo and the residue was subjected to column chromatography (silica gel, 0–15% EtOAc/hexane) to give **3b** and **3c**. Compound **3b**: Yield 0.74 g (75%); colourless thick oil; $[\alpha]_D^{24} = +10.2$ (c 1.56, $CHCl_3$); IR: 1741 cm^{-1}; ^1H NMR: δ 1.04 (d, J = 7.6 Hz, 3H), 1.41–1.63 (m, 10H), 3.62–3.75 (m, 1H), 3.85–4.05 (m, 2H), 4.43 (dd, J = 5.8 and 7.4 Hz, 1H), 4.82–5.07 (m, 2H), 5.64–5.84 (m, 1H); ^{13}C NMR: δ 14.7, 23.4, 23.6, 24.7, 34.2, 35.3, 46.0, 65.5, 78.4, 110.9, 116.8, 136.2, 209.7. Compound **3c**: Yield 0.78 g (79%); colourless thick oil; $[\alpha]_D^{24} = +5.9$ (c 1.08, $CHCl_3$), (lit.[4d] $[\alpha]_D^{22} = +5.7$ (c 1.12, $CHCl_3$)); IR: 1740 cm^{-1}; ^1H NMR: δ 1.01 (d, J = 7.0 Hz, 3H), 1.32–1.54 (m, 10H), 3.41–3.62 (m, 1H), 3.78–3.91 (m, 1H), 3.97–4.21 (m, 1H), 4.35–4.48 (m, 1H), 4.85–5.05 (m, 2H), 5.72–5.96 (m, 1H); ^{13}C NMR: δ 13.9, 22.8, 23.1, 25.0, 34.6, 35.8, 46.2, 63.3, 76.5, 110.7, 116.9, 135.8, 205.4.

4.9. (3*S*,4*S*,5*R*)-4-Benzoyloxy-5,6-cyclohexylidenedioxy-3-methyl-1-hexene 4

To a well stirred and cooled (0 °C) solution of **2c** (1.1 g, 4.86 mmol) and Et_3N (0.74 g, 7.3 mmol) in CH_2Cl_2 (25 mL) was added a solution BzCN (0.76 g, 5.83 mmol) in CH_2Cl_2 (10 mL) over 40 min. After the completion of the reaction (cf. TLC, 2 h) the reaction mixture was poured into water, the organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2×15 mL). The combined organic extracts were washed with water (2×10 mL) and brine (1×5 mL), and dried. Solvent removal in vacuo followed by column chromatography (silica gel, 5–15% EtOAc/hexane) of the residue gave **4**. Yield 1.52 g (95%); colourless oil; $[\alpha]_D^{24} = +14.2$ (c 1.47, $CHCl_3$); IR: 1722, 995, 920 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.07 (d, J = 7.0 Hz, 3H), 1.31–1.43 (m, 8H), 1.58–1.67 (m, 2H), 2.65–2.75 (m, 1H) 3.83–3.90 (m, 1H), 3.95–4.03 (m, 1H), 4.20–4.26 (m, 1H), 5.06–5.18 (m, 2H), 5.26 (dd, J = 4.0 and 6.6 Hz, 1H), 5.77–5.87 (m, 1H), 7.38–7.54 (m, 3H), 7.99–8.04 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 16.9, 23.8, 25.0, 34.9, 36.1, 39.8, 65.9, 74.9, 76.7, 109.6, 116.3, 128.3, 129.6, 129.9, 132.9, 138.4, 165.8. Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.72; H, 8.12.

4.10. (2*R*,3*S*,4*S*)-3-Benzoyloxy-4-methyl-5-hexene-1,2-diol 5

To a stirred and cooled (0 °C) solution of **4** (1.4 g, 4.24 mmol) in CH_2Cl_2 (25 mL) was added aqueous TFA (10 mL) in portions. After

stirring the mixture for 2.5 h, when the reaction was complete (cf. TLC), $NaHCO_3$ was added to decompose the excess TFA, followed by water, and the mixture was extracted with $CHCl_3$ (2 × 10 mL). The combined organic extracts were washed with water (2 × 10 mL) and brine (1 × 5 mL), and dried. Removal of the solvent in vacuo followed by column chromatography (silica gel, 5% $CHCl_3$/MeOH) of the residue afforded **5**. Yield 0.92 g (86%); colourless thick oil; $[\alpha]_D^{24} = +7.5$ (*c* 1.04, $CHCl_3$); IR: 3411, 1724, 995, 920 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.98 (d, *J* = 7.0 Hz, 3H), 2.86–2.96 (m, 3H), 3.56–3.71 (m, 2H), 3.76–3.84 (m, 1H), 5.01 (dd, *J* = 2.8 and 8.6 Hz, 1H), 5.13–5.25 (m, 2H), 5.77–5.88 (m, 1H), 7.40–7.58 (m, 3H), 7.99–8.04 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 17.4, 38.5, 62.6, 70.7, 76.7, 116.8, 128.5, 129.3, 129.8, 133.5, 138.1, 167.2. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.32; H, 7.09.

4.11. (3*S*,4*S*,5*R*)-4-Benzoyloxy-6-(*tert*)-butyldiphenylsilyloxy-3-methyl-1-hexene 6

A cooled (0 °C) solution of **5** (0.8 g, 3.2 mmol), TBDPSCl (0.89 g, 3.2 mmol) and imidazole (0.26 g, 3.84 mmol) in CH_2Cl_2 (20 mL) was stirred for 4 h. Water (15 mL) was added to the mixture, which was extracted with $CHCl_3$ (2 × 10 mL). The combined organic extracts were washed with water (2 × 10 mL) and brine (1 × 5 mL), dried and concentrated in vacuo. The residue was subjected to column chromatography (silica gel, 5–15% EtOAc/hexane) to afford **6**. Yield 1.25 g (80%); colourless oil; $[\alpha]_D^{24} = +7.9$ (*c* 0.971, $CHCl_3$); IR: 3450, 1726, 997, 924 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.01 (d, *J* = 6.8 Hz, 3H), 1.09 (s, 9H), 1.12 (br s, 1H), 2.66–2.70 (m, 1H), 3.00–3.35 (m, 2H), 3.81–4.12 (m, 1H), 5.03 (dd, *J* = 2.4 and 7.8 Hz, 1H), 5.21–5.29 (m, 2H), 5.82–5.98 (m, 1H), 7.25–7.38 (m, 4H), 7.46–7.84 (m, 9H), 7.98–8.02 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 17.4, 19.1, 37.7, 63.5, 72.1, 75.9, 116.6, 127.2, 127.5, 128.5, 129.3, 130.4, 133.5, 138.3, 171.2. Anal. Calcd for $C_{30}H_{36}O_4Si$: C, 73.73; H, 7.43. Found: C, 73.61; H, 7.59.

4.12. (3*R*,4*S*,5*R*)-(4-Benzoyloxy-3-methyl-5-(*tert*)-butyldiphenylsilyloxymethyl) dihydro-2(3*H*)-furanone 7c

Ozone was bubbled for 20 min through a solution of **6** (1 g, 2.03 mmol) and methanolic NaOH (1.5 mL, 2.5 M) in CH_2Cl_2 (20 mL) at −78 °C. After stirring the mixture for 3 h at the same temperature, it was diluted with $CHCl_3$ and water, and brought to room temperature. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic extracts were washed with water and brine, and dried. Removal of solvent in vacuo followed by chromatographic purification (silica gel, 5–15% $CHCl_3$/MeOH) afforded **7c**. Yield 0.72 g (72%); colourless oil; $[\alpha]_D^{24} = +16.3$ (*c* 0.884, $CHCl_3$); IR: 1742, 1695 cm^{-1}; ^1H NMR: δ 0.91 (d, *J* = 6.8 Hz, 3H), 1.14 (s, 9H), 3.40–3.50 (m, 1H), 3.90–4.20 (m, 2H), 4.63–4.70 (m, 1H), 5.96 (dd, *J* = 13.6 and 2.2 Hz, 1H), 7.27–7.37 (m, 4H), 7.44–7.81 (m, 9H), 7.97–8.01 (m, 2H). Anal. Calcd for $C_{19}H_{28}O_5Si$: C, 62.61; H, 7.74. Found: C, 62.77; H, 7.91.

4.13. (3*S*,4*S*,5*R*)-(4-Benzoyloxy-3-methyl-5-(*tert*)-butyldiphenylsilyloxymethyl) dihydro-2(3*H*)-furanone 7b

Colourless oil; $[\alpha]_D^{24} = +21.1$ (*c* 0.721, $CHCl_3$); IR: 1739, 1692 cm^{-1}; ^1H NMR: δ 0.93 (d, *J* = 6.4 Hz, 3H), 1.17 (s, 9H), 2.92–2.98 (m, 1H), 3.78–3.88 (m, 2H), 4.61–4.67 (m, 1H), 5.84 (dd, *J* = 12.2 and 9.7 Hz, 1H), 7.29–7.37 (m, 4H), 7.48–7.75 (m, 9H), 7.95–8.02 (m, 2H). Anal. Calcd for $C_{19}H_{28}O_5Si$: C, 62.61; H, 7.74. Found: C, 62.75; H, 7.62.

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