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Organocatalysis in Natural Product Synthesis: A Simple One-Pot Approach to Optically Active β-Diols

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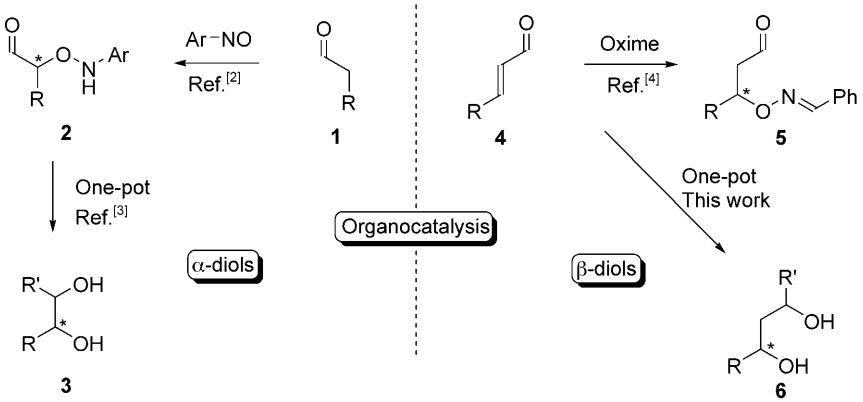
Abstract: Optically active β-diols have been prepared using an organocatalytic one-pot approach from α,β-unsaturated aldehydes using *(E)*-benzaldehyde oxime as nucleophile in an oxa-Michael reaction with subsequent *in situ* reduction or Grignard addition. With this protocol at hand, two biologically active compounds, an insect sex pheromone and a glycerol kinase substrate have been synthesized.

Keywords: asymmetric organocatalysis; diols; Grignard reaction; hydroxylation; Michael addition

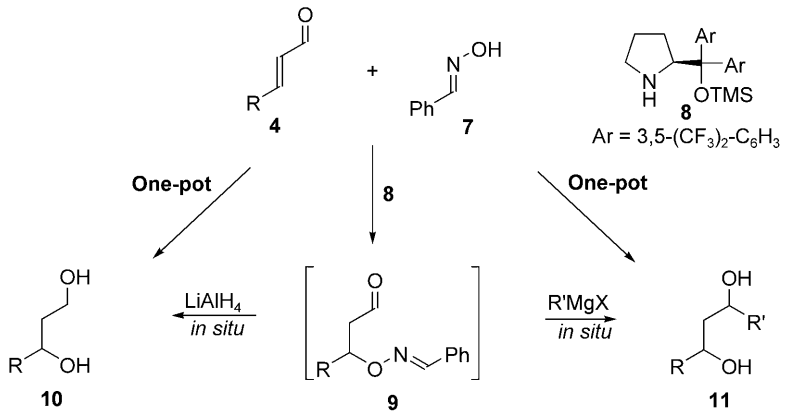
Introduction

With the successful incorporation of most non-metallic, non-halogen atoms to the β-position of α,β-unsaturated aldehydes, organocatalysis has proven its worth as a convenient method to obtain important optically active building blocks.[1] One such class of important molecules are the diols, which are easily accessible through the organocatalytic hydroxylation of aldehydes. The organocatalytic α-nitrosylation reaction was published by the groups of Hayashi, MacMillan, and Zhong in 2004.[2] Recently, this protocol was elegantly expanded by Yamamoto et al. to allow for a direct efficient access to optically active α-diols **3** by the one-pot addition of various organometallic reagents (Scheme 1).[3]

In 2007, we published the organocatalytic conjugate addition of oximes to α,β-unsaturated aldehydes **4**.[4] Oximes had previously been successfully employed as nucleophiles in the (salen)Al-catalyzed enantioselective conjugate addition to imides.[5] Following our paper, further developments in the organocatalytic conjugate addition of oximes have allowed for the hydroxylation of both ketones[6] and nitroolefins.[7] The successful use of oximes in various conjugate additions is attributed to the ability to circumvent many of the issues normally associated with oxygen nucleophiles in conjugate additions. There is a reduced tendency towards hemiacetal or acetal formation when applying oximes as nucleophiles and more importantly: the oxime adducts appear to be less prone to undergo eliminations (retro-Michael). The reversibility of the oxa-Michael additions presents a challenge not



Scheme 1. Organocatalytic approaches to optically active diols.



Scheme 2. Organocatalytic one-pot synthesis of optically active β-diols.

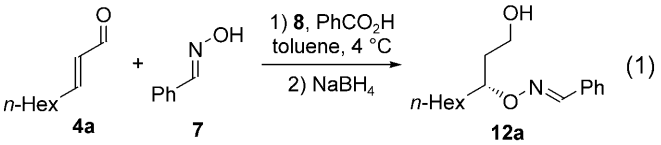
only in the purification of the adducts, but also due to a deterioration of the enantiomeric excess of the products.[8] The α-effect has been described to enhance the overall reaction rate in the organocatalytic conjugate addition of N-nucleophiles.[9] We believe that the α-effect experienced by oximes[10] leads to a decrease in the rate of the retro-Michael addition as described for methoxy amines by Bernasconi et al.[11] The obtained oxime-ethers **5** from the conjugate addition to aldehydes[4] (Scheme 1) could be isolated in good yields and stereoselectivities after reduction of the aldehyde moiety. However, the developed three-step, two-pot protocol (addition, reduction and hydrogenolysis) to obtain the optically active β-diols is hampered by the number of manual operations.

In this paper, we present results that address a number of the issues that limit the applicability of the two-pot procedure published in our preliminary study.[4] As such, we now present the first one-pot synthesis of β-diols **10** by extension of the oxime-addition protocol and finally demonstrate the versatility of the reaction with the addition of Grignard reagents to allow access to internal β-diols **11** (Scheme 2). Also of importance, the catalyst loading of the newly developed protocol is halved compared to the original procedures. We demonstrate the efficiency of the present developments with the stereoselective synthesis of biologically active β-diols, for example, nonane-1,3-diol, the main constituent of an endogenous sex pheromone from the melon fly, *Bactrocera cucurbitae*,[12] and of (*R*)-1,2,4-butanetriol, a known substrate for glycerol kinases.[13]

Results and Discussion

We initiated our work by reacting *trans*-2-nonenal **4a** with (*E*)-benzaldehyde oxime **7** in the presence of 10 mol% of (*S*)-2-{bis[3,5-bis(trifluoromethyl)phenyl]-trimethylsilanyloxymethyl}pyrrolidine **8** in toluene at 4 °C [Eq. (1), Table 1].[14]

Table 1. Screening of catalyst loading in the oxa-Michael addition.



(1)

Entry	Catalyst loading [%]	Reaction time [h]	Yield [%][a]	*ee* [%][b]
1	10	1.5	68	96
2	5	3.5	65	94
3	2	16	62	92
4	1	24	65	74

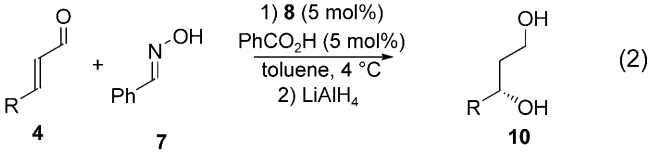
[a] Purified by FC.
[b] Determined by chiral stationary phase HPLC.

The unstable β-addition product **9a** was directly reduced to **12a** with $NaBH_4$ and **12a** was isolated in good yield and 96% *ee* (Table 1, entry 1). By lowering the catalyst loading to 5 mol% the reaction still proceeded with full conversion within 3.5 h with only a small decrease in enantioselectivity to 94% *ee* (Table 1, entry 2). Reducing the catalyst loading further, markedly increased the reaction time and caused, in the case of 1 mol% catalyst, a significant drop in enantioselectivity (Table 1, entries 3 and 4).

To simplify the process and obtain the optically active β-diols directly, we used $LiAlH_4$ as the reducing agent, which both reduces the aldehyde and cleaves the N–O bond to give the optically active β-diol efficiently in a one-pot procedure.

With these conditions at hand, the scope of the formation of the optically active β-diols in the one-pot organocatalytic procedure was examined by the reaction of a series of α,β-unsaturated aldehydes **4** with (*E*)-benzaldehyde oxime **7** in the presence of only

Table 2. Scope of formation of optically active β-diols by the one-pot organocatalytic oxa-Michael addition-reduction of α,β-unsaturated aldehydes.



4 7 10 (2)

Entry	Substrate	R	Product	Yield [%][a]	*ee* [%][b]
1	**4a**	*n*-Hexyl	**10a**	54	94
2	**4b**	*n*-Butyl	**10b**	67	92
3	**4c**	*n*-Propyl	**10c**	58	92
4	**dd**	Ethyl	**10d**	56	95
5	**4e**	Hex-3-enyl	**10e**	52	91
6[c]	**4f**	Bn-O-CH_2	**10f**	80	−95

[a] Purified by FC.
[b] Determined by chiral stationary phase HPLC.
[c] Catalyst *ent*-**8** was used instead of **8**.

5 mol% (*S*)-2-{bis[3,5-bis(trifluoromethyl)phenyl]trimethylsilanyloxymethyl}pyrrolidine **8** as catalyst [Eq. (2), Table 2].

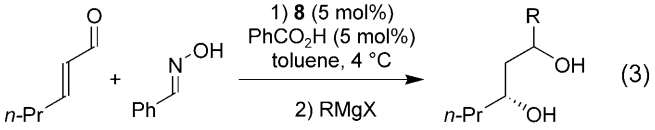
The results summarized in Table 2 show that the one-pot formation of the optically active β-diols proceeds smoothly and with good yields and high enantioselectivities for all the α,β-unsaturated aldehydes applied. For aldehydes having linear alkyl chains **4a–d**, the optically active β-diols **10a–d** were obtained in 54–67% yield and 92–95% *ee* (Table 2, entries 1–4). The product, nonane-1,3-diol **10a** is the main constituent of an endogenous sex pheromone from the melon fly, *Bactrocera cucurbitae*.[12] The present approach provides a very simple access to this natural product in 54% yield and 94% *ee*.

In terms of yield and stereoselectivity, similar results were obtained for the polyunsaturated *trans*-2,*cis*-6-nonadienal **4e**, which gave **10e** in 52% yield and 91% *ee* (Table 2, entry 5). Gratifyingly, the α,β-unsaturated aldehyde (*E*)-4-(benzyloxy)but-2-enal **4f**, carrying an additional benzylated alcohol proved to be highly reactive under these conditions and gave the optically active β-diol **10f** in 80% yield and 95% *ee* (Table 2, entry 6).

The organocatalytic reaction leading to the results obtained in Table 2, entry 6 was performed with (*R*)-2-{bis[3,5-bis(trifluoromethylphenyl]trimethylsilanyloxymethyl}pyrrolidine, *ent*-**8** as the catalyst, since the product obtained (**10f**) is highly interesting as it could easily be converted to the glycerol kinase substrate (*R*)-1,2,4-butanetriol **13** in 97% yield by standard hydrogenolysis as presented in Scheme 3. In previous reports, enantiomerically enriched 1,2,4-butanetriol **13** was obtained either by kinetic or thermodynamic resolution,[15] or from optically active starting materials.[16] Thus, the present procedure offers a very simple alternative synthesis of this important molecule.

The optically active oxime-ether **9** can also be submitted to other one-pot reaction conditions to further underline the applicability of this common intermediate. In order to expand the scope of the oxa-Michael reaction, a direct addition of Grignard reagents was examined. The organometallic reagents both add to the carbonyl and cleave the N−O bond. Using three different Grignard reagents we directly obtained the diols **11a–c** in a multi-component one-pot reaction from the commercially available *trans*-2-hexenal in good yields and consistently high enantiomeric excess [Eq. (3), Table 3].

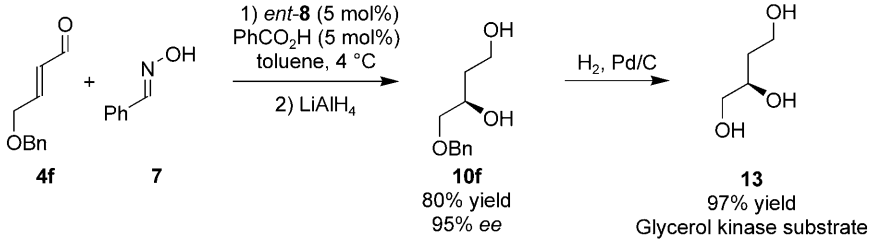
Table 3. Screening of different Grignard reagents for the synthesis of β-diols **11a–c**.



4c 7 11 (3)

Entry	R	Product	Yield [%][a]	*dr*[b]	*ee* [%][c]
1	Phenyl	**11a**	59	1:1	94
2	*i*-Propyl	**11b**	53	1:1	94
3	*n*-Pentyl	**11c**	51	1:1	92

[a] Purified by FC.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by chiral stationary phase HPLC.



4f 7 **10f** 80% yield 95% *ee* **13** 97% yield Glycerol kinase substrate

Scheme 3. Organocatalytic procedure for the synthesis of the optically active glycerol kinase substrate (*R*)-1,2,4-butanetriol **13**.

The enantioselectivity of the oxa-Michael reaction remains unaffected under these conditions and good yields and enantioselectivities in the range of 92–94% *ee* were obtained for the optically active β-diols **11a–c** having two secondary alcohol stereocenters [Eq. (3), Table 3]. However, the β-stereocenter showed to have no effect on the diastereoselectivity in the following addition to the carbonyl functionality. The addition of different transition metal complexes to coordinate to the two oxygen atoms in the intermediate, in order to facilitate a diastereoselective reaction, gave similar results. Both diastereoisomers were obtained in a 1:1 ratio.

Conclusions

In conclusion, we have presented the first one-pot, organocatalytic synthesis of highly enantioenriched β-diols from α,β-unsaturated aldehydes. The potential of the methodology was demonstrated by the synthesis of a number of optically active β-diols. The optically active nonane-1,3-diol, which is the main constituent of an endogenous sex pheromone from the melon fly, *Bactrocera cucurbitae* and the glycerol kinase substrate (*R*)-1,2,4-butanetriol were successfully synthesized using this simple, novel procedure.

Experimental Section

General

The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm relative to $CDCl_3$ ($\delta = 7.26$) or MeOD-d_3 ($\delta = 3.30$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) or MeOD-d_3 resonance ($\delta = 49.0$) for ^{13}C NMR. Purification of reaction products was carried out by flash chromatography (FC) using silica gel 60 (230–400 mesh from Merck). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Chiralcel OD, OJ, AD or AS column. Optical rotation was measured on a Perkin–Elmer 241 polarimeter. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES^+) ionization techniques.

Materials

Commercially available starting materials and solvents were used without further purification.

Oxa-Michael Addition of (*E*)-Benzaldehyde Oxime to *trans*-2-Nonenal (General Procedure A)

In a representative reaction, (*E*)-benzaldehyde oxime (1.50 mmol) was added at 4 °C to a stirred solution of catalyst (1–10 mol%), $PhCO_2H$ (1–10 mol%) and *trans*-2-nonenal (0.5 mmol) in toluene (250 μL). After complete consumption of the aldehyde (as monitored by ^{1}H NMR spectroscopy), MeOH (1 mL) and instantaneously $NaBH_4$ (0.75 mmol) were added and the mixture was stirred for 30 min at room temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 × 2 mL). Evaporation and FC afforded the pure product.

Oxa-Michael Addition Followed by $LiAlH_4$ Reduction (General Procedure B)

In a standard reaction, (*E*)-benzaldehyde oxime (1.50 mmol) was added at 4 °C to a stirred solution of catalyst (0.025 mmol), $PhCO_2H$ (0.025 mmol) and aldehyde (0.5 mmol) in toluene (125 μL). After complete consumption of the aldehyde (as monitored by ^{1}H NMR spectroscopy), the reaction mixture was cooled to 0 °C and flushed with N_2, before addition of a 1 M solution of $LiAlH_4$ in THF (2 mL). The reaction mixture was stirred overnight at room temperature under N_2. The reaction was quenched by careful addition of H_2O (0.1 mL), 10% aqueous NaOH (0.2 mL) and H_2O (0.3 mL). Filtering through Celite with CH_2Cl_2, evaporation and FC afforded the pure product.

Oxa-Michael Addition Followed by Grignard Addition (General Procedure C)

In a standard reaction, (*E*)-benzaldehyde oxime (1.50 mmol) was added at 4 °C to a stirred solution of catalyst (0.025 mmol), $PhCO_2H$ (0.025 mmol) and aldehyde (0.5 mmol) in toluene (125 μL). After complete consumption of the aldehyde (as monitored by ^{1}H NMR spectroscopy), the reaction mixture was cooled to 0 °C and flushed with N_2, before addition of a 2 M solution of a Grignard reagent in Et_2O or THF (2 mL). The reaction mixture was stirred overnight at room temperature under N_2. The reduction was quenched by careful addition of 1 M aqueous HCl (4 mL). The organic layer was collected and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered, evaporated under reduced pressure, and the product was purified by FC.

Derivatization of 1,3-Diols with 4-Chlorobenzoyl Chloride (General Procedure D)

In a standard reaction, the 1,3-diol (0.1 mmol) was reacted with 1.2 equiv. of Et_3N and 1.2 equiv. of 4-chlorobenzoyl chloride in Et_2O (125 μL). The reaction mixture was stirred 2 h at room temperature for primary alcohols **10a–f** and overnight for secondary alcohols **11a–c**. FC afforded the pure mono-4-chlorobenzoylated products.

Analytical and Spectroscopic Data

(*E*)-Benzaldehyde-*O*-1-hydroxynonan-3-yl oxime (12): The product was obtained following the general procedure A. The enantiomeric excess was determined by HPLC using a Daicel Chiralpak OD column [hexane/*i*-PrOH (95/5)]: flow rate 1.0 mL min^{-1}: $\tau_{minor} = 9.8$ min, $\tau_{major} = 7.4$ min (74–96% *ee*); ^{1}H NMR: $\delta = 8.08$ (s, 1H), 7.56 (m, 2H), 7.38–7.36 (m, 3H), 4.41–4.35 (m, 1H), 3.86–3.73 (m, 2H), 2.37 (t, 1H, $J = 6.0$ Hz), 1.96–1.24 (m, 12H), 0.88 (t, 3H, $J = 6.6$ Hz); ^{13}C NMR: $\delta = 148.1$, 132.1, 129.6, 128.6 (2C), 126.8 (2C), 81.3, 59.6, 36.9, 34.2, 31.7, 29.2, 25.3, 22.5, 14.0; MS (TOF

ES$^+$): m/z = 286.1787, calcd. for $C_{16}H_{25}NO_2$ $[M+Na]^+$: 286.1783; $[\alpha]_D^{20}$: +7.9 (c 1.00, CH_2Cl_2).

Nonane-1,3-diol (10a): The product was obtained following the general procedure B. The enantiomeric excess was determined by HPLC using a Daicel Chiralpak OJ column on the corresponding mono-4-chlorobenzoylated 1,3-diol according to general procedure D [hexane/*i*-PrOH (95/5)]: flow rate 1.0 mL min^{-1}: τ_{minor} = 5.0 min, τ_{major} = 5.5 min (94% *ee*); ^{1}H NMR: δ = 3.90–3.79 (m, 3H), 2.36 (s, 1H), 2.29 (s, 1H), 1.74–1.17 (m, 12H), 0.87 (t, 3H, J = 6.7 Hz); ^{13}C NMR: δ = 71.8, 61.3, 38.1, 37.7, 31.7, 29.3, 25.5, 22.5, 14.0; MS (TOF ES$^+$): m/z = 183.1358, calcd. for $C_9H_{20}O_2$ $[M+Na]^+$: 183.1361; $[\alpha]_D^{20}$: −5.9 (c 1.07, CH_2Cl_2) {lit: $[\alpha]_D^{20}$: −5.2 (c 0.10, MeOH)}.[17]

Heptane-1,3-diol (10b): The product was obtained following the general procedure B. The enantiomeric excess was determined by HPLC using a Daicel Chiralpak OJ column on the corresponding mono-4-chlorobenzoylated 1,3-diol according to general procedure D [hexane/*i*-PrOH (97/3)]: flow rate 1.0 mL min^{-1}: τ_{major} = 17.0 min, τ_{minor} = 15.2 min (92% *ee*); ^{1}H NMR; δ = 3,91–3,80 (m, 3H), 2.34 (br s, 1H), 2.20 (br s, 1H), 1.75–1.23 (m, 8H), 0.91 (t, J = 6.8 Hz, 3H); ^{13}C NMR: δ = 72.7, 62.2, 38.4, 37.7, 27.8, 22.8, 14.2; MS (TOF ES$^+$): m/z = 155.1046, calcd. for $C_7H_{16}O_2$ $[M+Na]^+$: 155.1048; $[\alpha]_D^{20}$: −1.7 (c 0.18, CH_2Cl_2) {lit: $[\alpha]_D^{20}$: −1.94 (c 1.64, $CHCl_3$)}.[18]

Hexane-1,3-diol (10c): The product was obtained following the general procedure B. The enantiomeric excess was determined by HPLC using a Daicel Chiralpak OJ column on the corresponding mono-4-chlorobenzoylated 1,3-diol according to general procedure D [hexane/*i*-PrOH (95/5)]: flow rate 1.0 mL min^{-1}: τ_{minor} = 8.5 min, τ_{major} = 9.7 min (92% *ee*); ^{1}H NMR: δ = 3.90–3.78 (m, 3H), 2.60 (s, 2H), 1.74–1.60 (m, 2H), 1.53–1.33 (m, 4H), 0.92 (t, 3H, J = 7.1 Hz); ^{13}C NMR: δ = 72.0, 61.8, 39.9, 38.2, 18.7, 14.0; MS (TOF ES$^+$): m/z = 141.0891, calcd. for $C_6H_{14}O_2$ $[M+Na]^+$: 141.0891; $[\alpha]_D^{20}$: −1.9 (c 1.11, CH_2Cl_2) {lit: $[\alpha]_D^{20}$: M > - > 0.75 (c 0.67, $CHCl_3$)}.[19]

3-Hydroxypentyl 4-chlorobenzoate (10′d): (*E*)-Benzaldehyde oxime (181 mg, 1.50 mmol) was added at 4 °C to a stirred solution of the catalyst (15 mg, 0.025 mmol), $PhCO_2H$ (3 mg, 0.025 mmol) and aldehyde (49 μL, 0.5 mmol) in toluene (250 μL). After complete consumption of the aldehyde (as monitored by ^{1}H NMR spectroscopy), the reaction mixture was cooled to 0 °C and flushed with N_2, before addition of a 1 M solution of $LiAlH_4$ in THF (2 mL). The reaction mixture was stirred overnight at room temperature under N_2. The reaction was quenched by careful addition of H_2O (4 mL). The organic layer was collected and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated at low pressure. The crude product was dissolved in CH_2Cl_2 (2 mL) and added 4-chlorobenzoyl chloride (0.64 mL, 5.0 mmol) and Et_3N (0.70 mL, 5.0 mmol). The reaction mixture was stirred over night, and evaporated to dryness under vacuum. FC (EtOAc/pentane 1:4) gave the pure product. The enantiomeric excess was determined by HPLC using a Daicel Chiralpak OJ column on the corresponding mono-4-chlorobenzoylated 1,3-diol according to general procedure D [hexane/*i*-PrOH (98/2)]: flow rate 1.0 mL min^{-1}: τ_{major} = 11.8 min, τ_{minor} = 13.3 min (95% *ee*); ^{1}H NMR: δ = 7.96 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 4.62–4.56 (m, 1H), 4.43–4.38 (m, 1H), 3.72–3.64 (m, 1H), 2.05 (d, J = 4.6 Hz, 1H), 2.00–1.92 (m, 1H), 1.83–1.75 (m, 1H), 1.60–1.48 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR: δ = 166.1, 139.4, 131.0 (2C), 128.7 (2C), 128.5, 69.9, 62.5, 36.0, 30.3, 9.9; MS (TOF ES$^+$): m/z = 265.0612, calcd. for $C_{12}H_{15}O_3Cl$ $[M+Na]^+$: 265.0607; $[\alpha]_D^{20}$: −15.5 (c 1.02, CH_2Cl_2).

(*trans*)-Non-6-ene-1,3-diol (10e): The product was obtained following the general procedure B. The enantiomeric excess was determined by HPLC using a Daicel Chiralpak OJ column on the corresponding mono-4-chlorobenzoylated 1,3-diol according to general procedure D [hexane/*i*-PrOH (95/5)]: flow rate 1.0 mL min^{-1}: τ_{minor} = 8.0 min, τ_{major} = 9.1 min (91% *ee*); ^{1}H NMR: δ = 5.44–5.32 (m, 2H), 3.92–3.80 (m, 3H), 2.40 (s, 2H), 2.22–1.98 (m, 4H), 1.76–1.49 (m, 4H), 0.96 (t, 3H, J = 7.5 Hz); ^{13}C NMR: δ = 132.4, 128.3, 72.0, 61.7, 38.2, 37.5, 23.3, 20.5, 14.3; MS (TOF ES$^+$): m/z = 181.1204, calcd. for $C_9H_{18}O_2$ $[M+Na]^+$: 181.1204; $[\alpha]_D^{20}$: +1.7 (c 1.06, CH_2Cl_2).

4-(Benzyloxy)butane-1,3-diol (10f): The product was obtained following the general procedure B. The enantiomeric excess was determined by HPLC using a Daicel Chiralpak AS column on the corresponding mono-4-chlorobenzoylated 1,3-diol according to general procedure D [hexane/*i*-PrOH (90/10)]: flow rate 1.0 mL min^{-1}: τ_{minor} = 15.1 min, τ_{major} = 10.9 min (95% *ee*); ^{1}H NMR: δ = 7.38–7.28 (m, 5H), 4.56 (s, 2H), 4.09–4.03 (m, 1H), 3.82 (t, 2H, J = 5.4 Hz), 3.50 (dd, 1H, J = 3.6 Hz, 9.5 Hz), 3.40 (dd, 1H, J = 7.5 Hz, 9.5 Hz), 2.58 (s, 2H), 1.76–1.65 (m, 2H); ^{13}C NMR: δ = 137.8, 128.5 (2C), 127.8, 127.7 (2C), 74.3, 73.4, 70.2, 60.9, 34.8; MS (TOF ES$^+$): m/z = 219.0997, calcd. for $C_{11}H_{16}O_3$ $[M+Na]^+$: 219.0997; $[\alpha]_D^{20}$: +9.0 (c 1.01, CH_2Cl_2) {lit: $[\alpha]_D^{20}$: +8.98 (c 0.88, MeOH)}.[20]

1-Phenylhexane-1,3-diol (11a): The product was obtained following the general procedure C in a 1:1 diastereomeric mixture. The enantiomeric excess was determined by HPLC using a Daicel Chiralpak AD column on the corresponding mono-4-chlorobenzoylated 1,3-diol according to general procedure D [hexane/*i*-PrOH (95/5)]: flow rate 1.0 mL min^{-1}: τ_{minor} = 13.3 min, τ_{major} = 14.6 min (94% *ee*); ^{1}H NMR: δ = 7.34–7.23 (m, 10H), 5.02 (dd, 1H, J = 3.3 Hz, 8.1 Hz), 4.89 (dd, 1H, J = 3.8 Hz, 9.3 Hz), 3.95–3.81 (m, 2H), 3.52 (s, 2H), 2.84 (s, 2H), 1.91–1.72 (m, 4H), 1.54–1.29 (m, 8H), 0.90 (dt, 6H, J = 6.0 Hz, 12.1 Hz); ^{13}C NMR: δ = 144.6, 144.5, 128.4 (2C), 128.3 (2C), 127.5, 127.2, 125.6 (2C), 125.5 (2C), 75.3, 72.5, 71.5, 68.9, 45.2, 44.5, 40.1, 39.5, 18.8, 18.4, 14.0 (2C); MS (TOF ES$^+$): m/z = 217.1195, calcd. for $C_{12}H_{18}O_2$ $[M+Na]^+$: 217.1204.

2-Methyloctane-3,5-diol (11b): The product was obtained following the general procedure C in a 1:1 diastereomeric mixture. The enantiomeric excess was determined by HPLC using a Daicel Chiralpak AD column on the corresponding mono-4-chlorobenzoylated 1,3-diol according to general procedure D [hexane/*i*-PrOH (95/5)}: flow rate 1.0 mL min^{-1}: τ_{minor} = 9.3 min, τ_{minor} = 11.8 min (94% *ee*); ^{1}H NMR: δ = 3.99–1.91 (m, 1H), 3.89–3.82 (m, 1H), 3.71–3.62 (m, 2H), 2.93 (s, 2H), 2.78 (s, 2H), 2.20–2.13 (m, 2H), 1.73–1.32 (m, 12H), 0.96–0.90 (m, 18H); ^{13}C NMR: δ = 78.0, 73.8, 73.0, 69.9, 40.4, 39.5, 39.3, 39.2, 34.2, 33.7, 19.0, 18.6, 18.5, 18.2, 18.0, 17.4, 14.0, 14.0; MS (TOF ES$^+$): m/z = 183.1359, calcd. for $C_9H_{20}O_2$ $[M+Na]^+$: 183.1361.

Undecane-4,6-diol (11c): The product was obtained following the general procedure C in a 1:1 diastereomeric mixture. The enantiomeric excess was determined by HPLC using a Daicel Chiralpak AD column on the corresponding mono-4-chlorobenzoylated 1,3-diol according to general procedure D [hexane/*i*-PrOH (95/5)]: flow rate 1.0 mL min^{-1}: τ_{minor} = 8.6 min, τ_{major} = 9.5 min (92% *ee*).; ^{1}H NMR: δ = 3.90–3.82 (m, 4H), 2.82 (s, 4H), 1.63–1.26 (m, 28H), 0.91 (dt, 12H, J = 6.9 Hz, 16.2 Hz); ^{13}C NMR: δ = 73.2, 72.9, 69.3, 69.0, 42.7, 42.3, 40.3, 39.6, 38.2, 37.4, 31.8 (2C), 25.4, 25.0, 22.6 (2C), 18.9, 18.5, 14.0 (2C), 14.0 (2C); MS (TOF ES$^+$): m/z = 211.1674, calcd. for $C_{11}H_{24}O_2$ $[M+Na]^+$: 211.1674.

3-Hydroxyhexyl 4-chlorobenzoate (10′c): The product was obtained following the general procedure D. The enantiomeric excess was determined by HPLC using a Daicel Chiralpak OJ column [hexane/*i*-PrOH (95/5)]: flow rate 1.0 mL min^{-1}: τ_{minor} = 8.5 min, τ_{major} = 9.7 min (92% *ee*); ^{1}H NMR: δ = 7.97 (d, 2H, J = 8.5 Hz), 7.41 (d, 2H, J = 8.5 Hz), 4.63–4.57 (m, 1H), 4.43–4.37 (m, 1H), 3.80–3.73 (m, 1H), 2.00–1.91 (m, 2H), 1.83–1.75 (m, 1H), 1.54–1.38 (m, 4H), 0.93 (t, 3H, J = 6.8 Hz); ^{13}C NMR: δ = 166.1, 139.5, 131.0 (2C), 128.7 (2C), 128.6, 68.4, 62.5, 39.7, 36.4, 18.8, 14.0; MS (TOF ES$^+$): m/z = 279.0757, calcd. for $C_{13}H_{17}ClO_3$ $[M+Na]^+$: 279.0764.

1,2,4-Butanetriol (13): Pd/C (10%, 7 mg, 7 μmol) was added at room temperature to a solution of 4-(benzyloxy)-butane-1,3-diol (**10f**, 28 mg, 0.14 mmol) in MeOH (2.0 mL) under an H_2 atmosphere (1 bar), and after 24 h additional Pd/C (10%, 21 mg, 20 μmol) was added. After completion of the reaction (as monitored by TLC), the reaction mixture was filtered through a layer of Celite and evaporated under reduced pressure to obtain the product **13**; yield: 14.7 mg (97%). ^{1}H NMR (MeOD-d_3): δ = 3.78–3.68 (m, 3H), 3.51–3.42 (m, 2H), 1.77–1.69 (m, 1H), 1.64–1.55 (m, 1H); ^{13}C NMR (MeOD-d_3): δ = 70.8, 67.5, 60.0, 37.1; MS (TOF ES$^+$): m/z = 129.0530, calcd. for $C_4H_{10}O_3$ $[M+Na]^+$: 129.0528; $[\alpha]_D^{20}$: +25.1 (*c* 0.31, MeOH) {lit: $[\alpha]_D^{20}$: +24.6 (*c* 2.6, MeOH)}.[21]

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