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Authors: Monserrat H Garduño-Castro and David John Procter

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Diastereoselective Hydroxyethylation of β-Hydroxyketones: a Reformatsky Cyclization-Lactone Reduction Cascade Mediated by SmI_2-H_2O

Monserrat H. Garduño-Castro,[a] and David J. Procter[a]*

[a] Department of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, UK

david.j.procter@manchester.ac.uk

Dedicated to Prof. *Philippe Renaud* on the occasion of his 60th birthday

The hydroxyethylation of β-hydroxyketones allows diastereoselective access to important 1,3,5-triols. The approach exploits a SmI_2-H_2O-mediated Reformatsky cyclization-lactone reduction cascade.

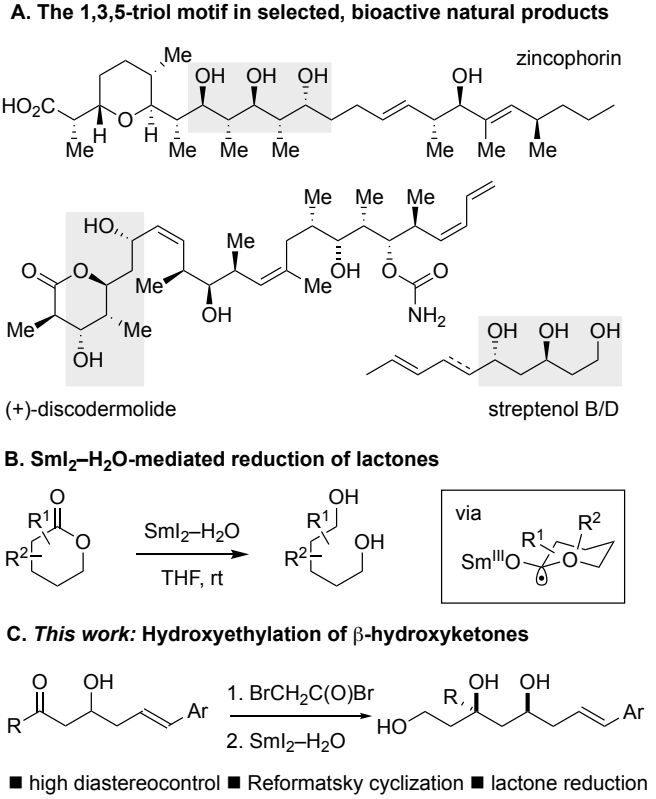
Keywords: radical • samarium diiodide • Reformatsky • lactones • cascade

Introduction

The 1,3,5-triol motif is an important motif found in a number of biologically active natural products including important polyketides (Scheme 1A).[1–5] The motif is most often constructed by diastereoselective ketone reduction.[6–12] Samarium diiodide (Kagan's reagent, SmI_2) is well-known for its ability to form carbon-carbon bonds, with high diastereoselectivity,[13–15] particularly when couplings are carried out in an intramolecular sense. Recently, our group has expanded the synthetic reach of the reagent by developing chemistry involving radicals generated from the carbonyl groups of carboxylic acid derivatives. In particular, we have developed reductions of lactones,[16,17] acyclic esters,[18] carboxylic acids,[19] nitriles,[20] and amides,[21] using SmI_2 activated by H_2O.[22] This work has culminated in the development of radical cascade reactions for the selective construction of complex architectures.[23–29] In the case of lactone reduction, we have described the ring size-selective reduction of six-membered lactones using SmI_2–H_2O that proceeds by electron-transfer to the lactone carbonyl and delivers the corresponding diol products (Scheme 1B).[16,17] Inspired by Molander's seminal work on a highly diastereoselective SmI_2-mediated intramolecular Reformatsky approach to 6-membered lactones,[30] here we describe a diastereoselective hydroxyethylation of β-hydroxyketones that delivers 1,3,5-triols and involves a SmI_2–H_2O-mediated Reformatsky cyclization-lactone reduction cascade (Scheme 1C).

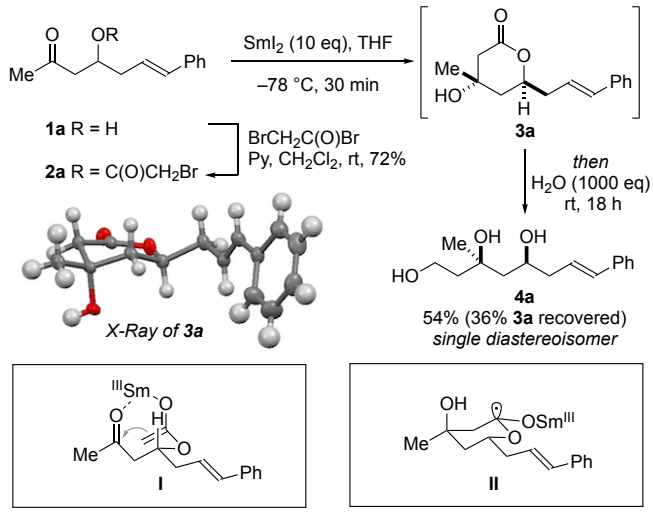
Results and Discussion

The feasibility of the hydroxyethylation process was assessed using β-hydroxyketone **1a**. After conversion to α-bromoacetate **2a** ($BrCH_2C(O)Br$, pyridine, CH_2Cl_2, 72%), treatment with SmI_2 at –78 °C for 30 min, followed by addition of H_2O to the pot, and warming to room temperature, gave the 1,3,5-triol product of hydroxyethylation **4a** in 54% yield and lactone intermediate **3a** in 36% yield, both as single diastereoisomers. The structure and relative stereochemistry of lactone intermediate **3a** was confirmed by X-Ray crystallographic analysis (See Supporting Information - CCDC Number: 1953812). The diastereoselectivity observed in the SmI_2-mediated Reformatksy cyclization of **2a** to form lactone **3a** is consistent with that observed by Molander[30] and arises from a highly organised transition structure **I** in which Sm(III) of the Sm(III)-enolate[31] coordinates to the ketone carbonyl in the substrate, with the two alkyl substituents in pseudoequatorial orientations (Scheme 2).



Scheme 1. A. Selected bioactive molecules containing the 1,3,5-triol motif. B. The selective reduction of six-membered lactones using SmI_2–H_2O. C. Diastereoselective hydroxyethylation of β-hydroxyketones.

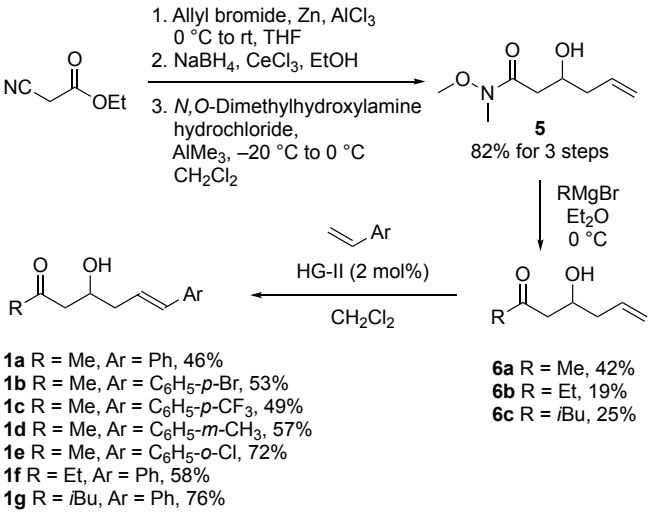
10.1002/hlca.201900227



Scheme 2. Assessing the feasibility of the diastereoselective hydroxyethylation of β-hydroxyketones. Samarium enolate intermediate **I** and samarium ketyl radical intermediate **II**. Diastereoisomeric purity was assessed by inspection of the ^{1}H NMR spectrum of the crude product mixture.

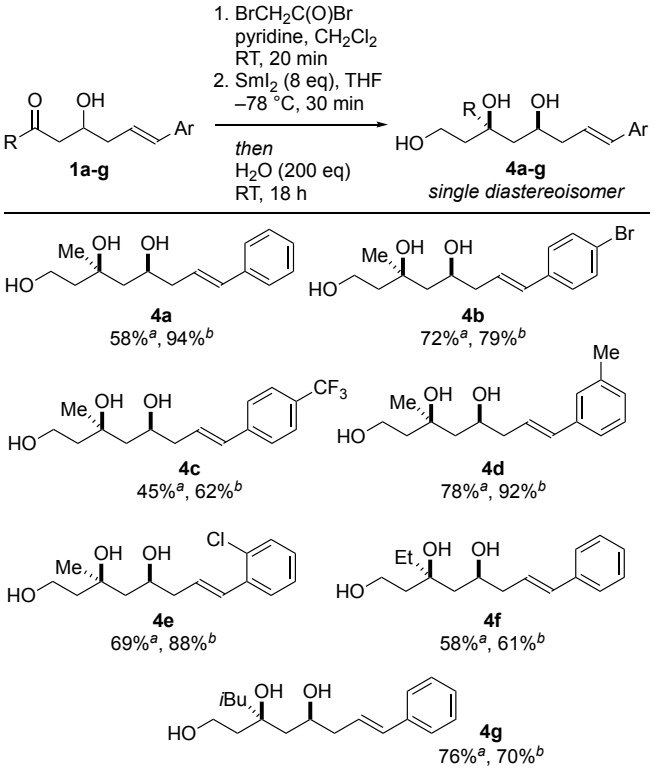
Addition of H_2O activates SmI_2[32–38] and switches on the second stage of the process by facilitating reduction of the lactone carbonyl to give unusual ketyl radical anion **II**. A sequence of further reductions and protonations delivers 1,3,5-triol **4a** as a single diastereoisomer. The conversion of **2a** to **4a** was optimized by varying the amount of SmI_2 and the amount of H_2O employed in the cascade: Using 8 equivalents of SmI_2 (a 1.3-fold excess as the cascade requires 6-electrons) and 200 equivalents of H_2O gave a 94% isolated yield of **4a**.

To explore the scope of selective 1,3,5-triol synthesis, we synthesized a range of β-hydroxyketones. Our route to substrates employed a Zn-mediated Barbier reaction involving ethyl 2-cyanoacetate and allyl bromide, with aluminium trichloride as a Lewis acid to activate the nitrile.[39] The resulting ketoester was reduced under Luche conditions and the resultant alcohol transformed to the Weinreb amide **5** using trimethyl aluminium and *N*,*O*-dimethylhydroxylamine hydrochloride. This three-step sequence could be carried out without purification and gave **5** in an overall yield of 82%. Treatment of **5** with three Grignard reagents delivered ketones **6a-c** in moderate yields. Finally, ketones **6** underwent olefin cross-metathesis, using various styrenes and the Hoveyda-Grubbs 2nd generation catalyst, to yield β-hydroxyketones **1a-g** in good yield (Scheme 3).[40,41]



Scheme 3. Synthesis of β-hydroxyketone substrates **1a-g**.

β-Hydroxyketones **1a-g** were acylated using bromoacetyl bromide prior to treatment with SmI_2 and H_2O (Scheme 4). By varying the aryl substituent on the alkene we found that the presence of potentially reduceable bromo (**4b**), chloro (**4e**), and trifluoromethyl (**4c**) functional groups was tolerated in the process. Crucially, the presence of an alkene, in a position that renders it potentially susceptible to radical cyclization, was also tolerated (**4a-g**). Finally, the alkyl group of the ketone could be varied (**4f**, **4g**). In all cases, 1,3,5-triols products were formed as single diastereoisomers (Scheme 4).



Scheme 4. Hydroxyethylation of β-hydroxyketones using a SmI_2–H_2O-mediated cascade. Diastereoisomeric purity was assessed by inspection of the ^{1}H NMR spectrum of the crude product mixture. [a]Yield for the acylation of the β-hydroxyketone. [b]Yield for the SmI_2–H_2O-mediated cascade.

Conclusions

A two-stage, hydroxyethylation of β-hydroxyketones delivers 1,3,5-triols with high diastereocontrol. After formation of the corresponding α-bromoacetate, ketone hydroxyethylation proceeds through a SmI_2–H_2O-mediated cascade reaction. The cascade process consists of a highly diastereoselective SmI_2-mediated Reformatsky cyclization, to give lactone intermediates, that are then reduced to the corresponding triols, upon addition of H_2O to the reaction pot. The process shows promising functional group compatibility and delivers important 1,3,5-triols as single diastereoisomers in good isolated yield.

Experimental Section

*General procedure A for the preparation of α-bromoacetates **2a-g**.* β-Hydroxyketone **1** (1 equivalent) was dissolved in CH_2Cl_2. Pyridine (2 equivalents) was added followed by the dropwise addition of bromoacetyl bromide (1.5 equivalent) at 0 °C. The reaction was stirred at that temperature for 30 min and quenched with aqueous 1 M HCl. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (10 ml), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography, eluting with EtOAc/hexane (30:70), gave α-bromoacetates **2** as yellow oils.

*General procedure B for the preparation of 1,3,5-triols **4a-g**.* To a solution of SmI_2 (8 equivalents, 0.1 M in THF), under N_2, at –78 °C, was added α-bromoacetate **2** (1 equivalent) in THF (0.5 mL), dropwise and the resulting mixture stirred for 30 min. The reaction was then allowed to slowly warm to room temperature and degassed H_2O (200 equivalents) was added. The reaction was stirred at room temperature for 18 h before being quenched by opening to air, followed by the addition of saturated aqueous Rochelle's salt. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography, eluting with EtOAc/hexane (50:50), gave the 1,3,5-triols as single diastereoisomers and as colourless oils.

(*E*)-6-Oxo-1-phenylhept-1-en-4-yl 2-bromoacetate 2a

Prepared according to general procedure A using (*E*)-4-hydroxy-7-phenylhept-6-en-2-one **1a** (356 mg, 1.74 mmol), pyridine (0.280 mL, 3.48 mmol) and bromoacetyl bromide (0.230 mL, 2.61 mmol) to give the title compound as a yellow oil (406 mg, 1.00 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3 H, C*H*$_3$), 2.57 (dtd, *J* = 7.5, 6.0, 1.4 Hz, 2 H, C*H*$_2$CH=CHAr), 2.68 – 2.88 (m, 2 H, C*H*$_2$C(O)), 3.78 (s, 2 H, C*H*$_2$Br), 5.44 (dq, *J* = 7.3, 5.8 Hz, 1 H, C*H*), 6.12 (dt, *J* = 15.6, 7.3 Hz, 1 H, C*H*=CHAr), 6.46 (dt, *J* = 15.8, 1.4 Hz, 1 H, CH=C*H*Ar), 7.20 – 7.25 (m, 1 H, ArC*H*), 7.28 – 7.37 (m, 4 H, ArC*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.9 (*C*H$_2$Br), 30.7 (*C*H$_3$), 37.4 (*C*H$_2$CH=CHAr), 46.6 (*C*H$_2$C(O)), 71.6 (*C*H), 123.9 (*C*H=CHAr), 126.3 (Ar*C*H), 127.7 (Ar*C*H), 128.7 (Ar*C*H), 134.1 (CH=*C*HAr), 137.0 (Ar*C*), 166.6 (*C*(O)CH$_2$Br), 205.1 (*C*(O)) ppm. IR ν_{max} (neat/cm^{-1}): 3025, 1732, 1715, 1495, 1421, 1378, 1357, 1276, 1159, 1106, 1042, 967, 795, 745, 693. HRMS calcd for $C_{15}H_{18}O_3Br$ [M + H]$^+$: 325.0434, found 325.0427.

(*E*)-1-(4-Bromophenyl)-6-oxohept-1-en-4-yl 2-bromoacetate 2b

Prepared according to general procedure A using (*E*)-7-(4-bromophenyl)-4-hydroxyhept-6-en-2-one **1b** (165 mg, 0.580 mmol), pyridine (0.090 mL, 1.16 mmol) and bromoacetyl bromide (0.080 mL, 0.88 mmol) to give the title compound as a yellow oil (169 mg, 0.420 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3 H, C*H*$_3$), 2.47 – 2.63 (m, 2 H, C*H*$_2$CH=CHAr), 2.67 – 2.87 (m, 2 H, C*H*$_2$C(O)), 3.77 (s, 2 H, C*H*$_2$Br), 5.42 (dq, *J* = 7.2, 5.7 Hz, 1 H, C*H*), 6.11 (dt, *J* = 15.8, 7.3 Hz, 1 H, C*H*=CHAr), 6.35 – 6.42 (m, 1 H, CH=C*H*Ar), 7.17 – 7.23 (m, 2 H, ArC*H*), 7.38 – 7.45 (m, 2 H, ArC*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.9 (*C*H$_2$Br), 30.7 (*C*H$_3$), 37.4 (*C*H$_2$CH=CHAr), 46.7 (*C*H$_2$C(O), 71.4 (*C*H), 121.4 (Ar*C*), 124.8 (*C*H=CHAr), 127.9 (Ar*C*H), 131.8 (Ar*C*H), 132.9 (CH=*C*HAr), 136.0 (Ar*C*), 166.6 (*C*(O)CH$_2$Br), 204.9 (*C*(O)) ppm. IR ν_{max} (neat/cm^{-1}): 2923, 1732, 1716, 1587, 1486, 1401, 1357, 1301, 1151, 1105, 1043, 1071, 1008, 968, 796, 731. HRMS calcd for $C_{15}H_{16}O_3Br_2Na$ [M + Na]$^+$: 424.9358, found 424.9345.

(*E*)-6-Oxo-1-(4-(trifluoromethyl)phenyl)hept-1-en-4-yl 2-bromoacetate 2c

Prepared according to general procedure A using (*E*)-4-hydroxy-7-(4-(trifluoromethyl)phenyl)hept-6-en-2-one **1c** (118 mg, 0.430 mmol), pyridine (0.070 mL, 0.86 mmol) and bromoacetyl bromide (0.060 mL, 0.65 mmol) to give the title compound as a yellow oil (76.3 mg, 0.190 mmol, 45%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (d, *J* = 1.9 Hz, 3 H, C*H*$_3$), 2.58 – 2.63 (m, 2 H, C*H*$_2$CH=CHAr), 2.78 – 2.85 (m, 2 H, C*H*$_2$C(O)), 3.77 (d, *J* = 1.9 Hz, 2 H, C*H*$_2$Br), 5.45 (p, *J* = 6.1 Hz, 1 H, C*H*), 6.19 – 6.28 (m, 1 H, C*H*=CHAr), 6.48 (d, *J* = 15.8 Hz, 1 H, CH=C*H*Ar), 7.42 (d, *J* = 8.1 Hz, 2 H, ArC*H*), 7.55 (d, *J* = 8.0 Hz, 2 H, ArC*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.8 (*C*H$_2$Br), 30.7 (*C*H$_3$), 37.4 (*C*H$_2$CH=CHAr), 46.7 (*C*H$_2$C(O)), 71.2 (*C*H), 123.2 (Ar*C*), 125.6 (Ar*C*H), 126.5 (Ar*C*H), 126.9 (C*H*=CHAr), 132.7 (CH=*C*HAr), 140.4 (Ar*C*), 166.6 (*C*(O)CH$_2$Br), 197.4 (*C*(O)) ppm (CF_3 not observed). IR ν_{max} (neat/cm^{-1}): 2953, 1735, 1718, 1615, 1414, 1323, 1278, 1161, 1110, 1066, 1045, 971, 908, 857, 730, 649. HRMS calcd for $C_{16}H_{16}O_3BrF_3Na$ [M + Na]$^+$: 415.0127, found 415.0112.

(*E*)-6-Oxo-1-(*m*-tolyl)hept-1-en-4-yl 2-bromoacetate 2d

Prepared according to general procedure A using (*E*)-4-hydroxy-7-(m-tolyl)hept-6-en-2-one **1d** (146 mg, 0.670 mmol), pyridine (0.110 mL, 1.34 mmol) and bromoacetyl bromide (0.09 mL, 1 mmol) to give the title compound as a yellow oil (178 mg, 0.520 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3 H, C*H*$_3$), 2.34 (s, 3 H, ArC*H*$_3$), 2.48 – 2.62 (m, 2 H, C*H*$_2$CH=CHAr), 2.67 – 2.87 (m, 2 H, C*H*$_2$C(O)), 3.79 (s, 2 H, C*H*$_2$Br), 5.43 (dq, *J* = 7.5, 5.8 Hz, 1 H, C*H*), 6.10 (dt, *J* = 15.8, 7.3 Hz, 1 H, C*H*=CHAr), 6.42 (dd, *J* = 15.8, 1.5 Hz, 1 H, CH=C*H*Ar), 7.03 – 7.07 (m, 1 H, ArC*H*), 7.12 – 7.23 (m, 3 H, ArC*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.5 (ArC*H*$_3$), 25.9 (*C*H$_2$Br), 30.7 (*C*H$_3$), 37.4 (*C*H$_2$CH=CHAr), 46.6 (*C*H$_2$C(O)), 71.6 (*C*H), 123.5 (Ar*C*H), 123.6 (*C*H=CHAr), 127.0 (Ar*C*H), 128.5 (Ar*C*H), 128.6 (Ar*C*H), 134.2 (CH=*C*HAr), 137.0 (Ar*C*), 138.3 (Ar*C*), 166.6 (*C*(O)CH$_2$Br), 205.0 (*C*(O)) ppm. IR ν_{max}

(neat/cm^{-1}): 2922, 1735, 1716, 1602, 1485, 1421, 1378, 1357, 1276, 1159, 1106, 1042, 967, 774, 732, 694. HRMS calcd for $C_{16}H_{19}O_3BrNa$ [M + Na]$^+$: 361.0410, found 361.0392.

(*E*)-1-(2-Chlorophenyl)-6-oxohept-1-en-4-yl 2-bromoacetate 2e

Prepared according to general procedure A using (*E*)-7-(2-chlorophenyl)-4-hydroxyhept-6-en-2-one **1e** (176 mg, 0.740 mmol), pyridine (0.120 mL, 1.47 mmol) and bromoacetyl bromide (0.10 mL, 1.1 mmol) to give the title compound as a yellow oil (183 mg, 0.510 mmol, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3 H, CH_3), 2.52 – 2.67 (m, 2 H, CH_2CH=CHAr), 2.70 – 2.90 (m, 2 H, CH_2C(O)), 3.79 (s, 2 H, CH_2Br), 5.41 – 5.50 (m, 1 H, C*H*), 6.10 (ddd, *J* = 15.7, 7.9, 7.0 Hz, 1 H, C*H*=CHAr), 6.75 – 6.85 (m, 1 H, CH=C*H*Ar), 7.14 – 7.25 (m, 2 H, ArC*H*), 7.33 (dd, *J* = 7.8, 1.5 Hz, 1 H, ArC*H*), 7.47 (dd, *J* = 7.6, 1.9 Hz, 1 H, ArC*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.9 (*C*H_2Br), 30.7 (*C*H_3), 37.6 (*C*H_2CH=CHAr), 46.7 (*C*H_2C(O)), 71.3 (*C*H), 127.0 (2 × Ar*C*H, C*H*=CHAr), 128.7 (Ar*C*H), 129.7 (Ar*C*H), 130.3 (CH=*C*HAr), 132.8 (Ar*C*), 135.2 (Ar*C*), 166.6 (*C*(O)CH_2Br), 204.9 (*C*(O)) ppm. IR ν_{max} (neat/cm^{-1}): 2962, 1733, 1716, 1591, 1470, 1423, 1357, 1275, 1150, 1105, 1034, 967, 751, 694. HRMS calcd for $C_{15}H_{16}O_3BrClNa$ [M + Na]$^+$: 380.9864, found 380.9850.

(*E*)-6-Oxo-1-phenyloct-1-en-4-yl 2-bromoacetate 2f

Prepared according to general procedure A using (*E*)-5-hydroxy-8-phenyloct-7-en-3-one **1f** (62.0 mg, 0.280 mmol), pyridine (0.050 mL, 0.57 mmol) and bromoacetyl bromide (0.040 mL, 0.43 mmol) to give the title compound as a yellow oil (55.5 mg, 0.160 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.3 Hz, 3 H, CH_3), 2.36 (qd, *J* = 7.3, 1.9 Hz, 2 H, CH_3CH_2), 2.50 (dtd, *J* = 7.5, 5.8, 1.4 Hz, 2 H, CH_2CH=CHAr), 2.58 – 2.78 (m, 2 H, CH_2C(O)), 3.71 (s, 2H, CH_2Br), 5.39 (ddt, *J* = 13.4, 7.7, 5.9 Hz, 1 H, C*H*), 6.05 (dtd, *J* = 15.8, 7.3, 4.8 Hz, 1 H, C*H*=CHAr), 6.38 (dd, *J* = 15.8, 1.6 Hz, 1 H, CH=C*H*Ar), 7.12 – 7.19 (m, 1 H, ArC*H*), 7.21 – 7.31 (m, 4 H, ArC*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.6 (*C*H_3), 25.9 (*C*H_2Br), 36.7 (CH_3*C*H_2), 37.4 (*C*H_2CH=CHAr), 45.4 (*C*H_2C(O)), 71.7 (*C*H), 123.9 (*C*H=CHAr), 126.3 (Ar*C*H), 127.6 (Ar*C*H), 128.7 (Ar*C*H), 134.0 (CH=*C*HAr), 137.0 (Ar*C*), 166.6 (*C*(O)CH_2Br), 207.7 (*C*(O)) ppm. IR ν_{max} (neat/cm^{-1}): 2975, 1732, 1714, 1449, 1410, 1378, 1277, 1165, 1109, 966, 910, 751, 701. HRMS calcd for $C_{16}H_{19}O_3BrNa$ [M + Na]$^+$: 361.0410, found 361.0394.

(*E*)-8-Methyl-6-oxo-1-phenylnon-1-en-4-yl 2-bromoacetate 2g

Prepared according to general procedure A using (*E*)-6-hydroxy-2-methyl-9-phenylnon-8-en-4-one **1g** (33.1 mg, 0.13 mmol), pyridine (0.02 mL, 0.27 mmol) and bromoacetyl bromide (0.02 mL, 0.20 mmol) to give the title compound as a yellow oil (37.4 mg, 0.10 mmol, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.1 Hz, 3 H, CH_3), 0.91 (d, *J* = 6.1 Hz, 3 H, CH_3), 2.06 – 2.17 (m, 1 H, $(CH_3)_2$C*H*), 2.29 (dd, *J* = 7.0, 2.4 Hz, 2 H, $(CH_3)_2$CHCH_2), 2.51 – 2.62 (m, 2 H, CH_2CH=CHAr), 2.63 – 2.83 (m, 2 H, CH_2C(O)), 3.78 (s, 2 H, CH_2Br), 5.45 (dq, *J* = 7.4, 5.8 Hz, 1 H, C*H*), 6.14 (tt, *J* = 15.3, 7.3 Hz, 1 H, C*H*=CHAr), 6.45 (d, *J* = 15.8 Hz, 1 H, CH=C*H*Ar), 7.21 – 7.25 (m, 1 H, ArC*H*), 7.28 – 7.35 (m, 4 H, ArC*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.6 (2 × CH_3), 24.6 ($(CH_3)_2$CH), 25.9 (*C*H_2Br)), 37.4 (*C*H_2CH=CH_2), 46.2 (*C*H_2C(O)), 52.5 ($(CH_3)_2$CH*C*H_2), 71.6 (*C*H), 124.0 (*C*H=CHAr), 126.3 (Ar*C*H), 127.7 (Ar*C*H), 128.7 (Ar*C*H), 134.0 (CH=*C*HAr), 137.1 (Ar*C*), 166.6 (*C*(O)CH_2Br), 207.1 (*C*(O)) ppm. IR ν_{max} (neat/cm^{-1}): 2958, 2254, 1737, 1405, 1367, 1277, 1166, 1107, 967, 907, 694, 649. HRMS calcd for $C_{18}H_{23}O_3BrNa$ [M + Na]$^+$: 389.0723, found 389.0706.

***rac*-(3*R*,5*S*,*E*)-3-Methyl-8-phenyloct-7-ene-1,3,5-triol 4a**

Prepared according to general procedure B using SmI_2 (2.46 mL, 0.25 mmol, 0.1 M in THF), ethyl (*E*)-6-oxo-1-phenylhept-1-en-4-yl 2-bromoacetate **2a** (0.01 mg, 0.03 mmol) and H_2O (0.11 mL, 6.14 mmol) to give the title compound as a colourless oil (7.20 mg, 0.03 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 3 H, CH_3), 1.51 – 1.63 (m, 1 H, $C_{quat}CH_aH_bCH$), 1.75 (tt, *J* = 5.2, 2.3 Hz, 2 H, $C_{quat}CH_2CH_2OH$), 1.87 – 1.92 (m, 1 H, $C_{quat}CH_aH_bCH$), 2.41 (ddd, *J* = 7.4, 6.1, 1.4 Hz, 2 H, CH_2CH=CH), 3.03 (s, 1 H, O*H*), 3.29 (s, 1 H, O*H*), 3.92 (t, *J* = 5.5 Hz, 2 H, CH_2OH), 4.20 (ddt, *J* = 7.9, 6.0, 3.0 Hz, 1 H, C*H*), 4.27 (s, 1 H, OH), 6.16 – 6.28 (m, 1 H, C*H*=CHAr), 6.49 (dd, *J* = 15.8, 3.3 Hz, 1 H, CH=C*H*Ar), 7.20 – 7.25 (m, 1 H, ArC*H*), 7.31 (dd, *J* = 7.6, 7.6 Hz, 2 H, ArC*H*), 7.37 (dt, *J* = 5.8, 1.4 Hz, 2 H, ArC*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 26.4 (*C*H_3), 42.2 (*C*H_2CH=CH), 43.8 ($C_{quat}CH_2CH_2OH$), 45.8 ($C_{quat}CH_2CH$), 59.8 (*C*H_2OH), 69.0 (*C*H), 74.5 (C_{quat}), 125.7 (*C*H=CHAr), 126.3 (Ar*C*H), 127.5 (Ar*C*H), 128.7 (Ar*C*H), 133.6 (CH=*C*HAr), 137.2 (Ar*C*) ppm. IR ν_{max} (neat/cm^{-1}): 3341, 2934, 2042, 1665, 1426, 1259, 1117, 1053, 967, 744. HRMS calcd for $C_{15}H_{21}O_3$ [M - H]$^-$: 249.1496, found 249.1498.

***rac*-(3*R*,5*S*,*E*)-8-(4-Bromophenyl)-3-methyloct-7-ene-1,3,5-triol 4b**

Prepared according to general procedure B using SmI_2 (6.00 mL, 0.60 mmol, 0.1 M in THF), (*E*)-1-(4-bromophenyl)-6-oxohept-1-en-4-yl 2-bromoacetate **2b** (30.3 mg, 0.075 mmol) and H_2O (0.27 mL, 15 mmol) to give the title compound as a colourless oil (19.6 mg, 0.059 mmol, 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, 3 H, CH_3), 1.48 – 1.54 (m, 1 H, $C_{quat}CH_aH_bCH$), 1.65 – 1.78 (m, 2 H, $C_{quat}CH_2CH_2OH$), 1.85 – 1.92 (m, 1 H, $C_{quat}CH_aH_bCH$), 2.38 (dd, *J* = 7.3, 7.3 Hz, 2 H, CH_2CH=CH), 3.08 (s, 1 H, O*H*), 3.59 (s, 1 H, O*H*), 3.92 (t, *J* = 5.7 Hz, 2 H, CH_2OH), 4.19 (dq, *J* = 16.0, 9.6, 8.0 Hz, 1 H, C*H*), 4.33 (s, 1 H, O*H*), 6.17 – 6.29 (m, 1 H, C*H*=CHAr), 6.41 (d, *J* = 15.8 Hz, 1 H, CH=C*H*Ar), 7.15 – 7.24 (m, 2 H, ArC*H*), 7.42 (dd, *J* = 8.5, 1.9 Hz, 2 H, ArC*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.3 (*C*H_3), 42.1 (*C*H_2CH=CH), 43.7 ($C_{quat}CH_2CH_2OH$), 45.7 ($C_{quat}CH_2CH$), 59.8 (*C*H_2OH), 68.8 (*C*H), 74.6 (C_{quat}), 121.1 (Ar*C*H), 126.9 (*C*H=CHAr), 127.8 (Ar*C*H), 131.7 (CH=*C*HAr), 132.2 (Ar*C*), 136.2 (Ar*C*) ppm. IR ν_{max} (neat/cm^{-1}): 3347, 2930 1651, 1486, 1401, 1378, 1117, 1071, 1008, 968, 908, 798, 733, 648. HRMS calcd for $C_{15}H_{21}O_3BrNa$ [M + Na]$^+$: 351.0566, found 351.0554.

***rac*-(3*R*,5*S*,*E*)-3-Methyl-8-(4-(trifluoromethyl)phenyl)oct-7-ene-1,3,5-triol 4c**

Prepared according to general procedure B using SmI_2 (4.00 mL, 0.40 mmol, 0.1 M in THF), (*E*)-6-oxo-1-(4-(trifluoromethyl)phenyl)hept-1-en-4-yl 2-bromoacetate **2c** (19.6 mg, 0.05 mmol) and H_2O (0.18 mL, 0.01 mmol) to give the title compound as a colourless oil (9.86 mg, 0.031 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 3 H, CH_3), 1.45 – 1.52 (m, 1 H,

$C_{quat}CH_aH_bCH$), 1.69 – 1.78 (m, 2 H, $C_{quat}CH_2CH_2OH$), 1.79 – 1.91 (m, 1 H, $C_{quat}CH_aH_bCH$), 2.43 (ddd, *J* = 7.4, 4.8, 3.1 Hz, 2 H, $CH_2CH=CH$), 2.87 (s, 1 H, O*H*), 3.62 (s, 1 H, O*H*), 3.93-4.05 (m, 3 H, CH_2OH, O*H*), 4.18 – 4.29 (m, 1 H, C*H*), 6.35 (dt, *J* = 15.9, 7.2 Hz, 1 H, C*H*=CHAr), 6.51 (d, *J* = 15.9 Hz, 1 H, CH=C*H*Ar), 7.45 (d, *J* = 8.1 Hz, 2 H, ArC*H*), 7.53 (d, *J* = 8.8 Hz, 2 H, ArC*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 26.3 (CH_3), 42.1 ($CH_2CH=CH$), 43.7 ($C_{quat}CH_2CH_2OH$), 45.9 ($C_{quat}CH_2CH$), 59.8 (CH_2OH), 68.8 (*C*H), 74.6 (C_{quat}), 125.4 (Ar*C*H), 126.4 (Ar*C*H), 128.6 (*C*H=CHAr), 129.0 (Ar*C*), 132.0 (CH=*C*HAr), 140.8 (Ar*C*) ppm (CF_3 not observed). IR ν_{max} (neat/cm^{-1}): 3322, 2936, 1615, 1415, 1352, 1163, 1120, 1067, 1017, 908, 856, 732, 649. HRMS calcd for $C_{16}H_{22}O_3F_3$ [M + H]$^+$: 319.1516, found 319.1512.

rac-(3*R*,5*S*,*E*)-3-Methyl-8-(*m*-tolyl)oct-7-ene-1,3,5-triol 4d

Prepared according to general procedure B using SmI_2 (6.00 mL, 0.60 mmol, 0.1 M in THF), (*E*)-6-oxo-1-(*m*-tolyl)hept-1-en-4-yl 2-bromoacetate **2d** (25.4 mg, 0.075 mmol) and H_2O (0.27 mL, 15 mmol) to give the title compound as a colourless oil (18.2 mg, 0.068 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3 H, CH_3), 1.50 – 1.56 (m, 1 H, $C_{quat}CH_aH_bCH$), 1.73 (tq, *J* = 5.7, 3.6, 3.0 Hz, 2 H, $C_{quat}CH_2CH_2OH$), 1.86 – 1.92 (m, 1 H, $C_{quat}CH_aH_bCH$), 2.34 (s, 3 H, ArCH_3), 2.40 (td, *J* = 7.2, 1.4 Hz, 2 H, $CH_2CH=CH$), 3.21 (s, 1 H, O*H*), 3.42 (s, 1 H, O*H*), 3.91 (t, *J* = 5.6 Hz, 2 H, CH_2OH), 4.20 (dtd, *J* = 11.1, 6.2, 2.0 Hz, 1 H, C*H*), 4.36 (s, 1 H, O*H*), 6.20 (dt, *J* = 15.9, 7.3 Hz, 1 H, C*H*=CHAr), 6.45 (dt, *J* = 15.9, 1.4 Hz, 1 H, CH=C*H*Ar), 7.01 – 7.06 (m, 1 H, ArC*H*), 7.14 – 7.23 (m, 3 H, ArC*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.5 (ArCH_3), 26.4 (CH_3), 42.2 ($CH_2CH=CH$), 43.7 ($C_{quat}CH_2CH_2OH$), 45.7 ($C_{quat}CH_2CH$), 59.7 (CH_2OH), 69.0 (*C*H), 74.5 (C_{quat}), 123.4 (Ar*C*H), 125.5 (*C*H=CHAr), 127.0 (Ar*C*H), 128.3 (Ar*C*H), 128.6 (Ar*C*H), 133.6 (CH=*C*HAr), 137.2 (Ar*C*), 138.2 (Ar*C*) ppm. IR ν_{max} (neat/cm^{-1}): 3343, 2924, 2245, 1603, 1429, 1377, 1117, 1053, 966, 908, 857, 774, 732, 693, 648. HRMS calcd for $C_{16}H_{24}O_3Na$ [M + Na]$^+$: 287.1618, found 287.1605.

rac-(3*R*,5*S*,*E*)-8-(2-Chlorophenyl)-3-methyloct-7-ene-1,3,5-triol 4e

Prepared according to general procedure B using SmI_2 (6.00 mL, 0.60 mmol, 0.1 M in THF), (*E*)-1-(2-chlorophenyl)-6-oxohept-1-en-4-yl 2-bromoacetate **2e** (26.9 mg, 0.075 mmol) and H_2O (0.27 mL, 15 mmol) to give the title compound as a colourless oil (18.9 mg, 0.066 mmol, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (d, *J* = 2.0 Hz, 3 H, CH_3), 1.51 – 1.56 (m, 1 H, $C_{quat}CH_aH_bCH$), 1.70 – 1.80 (m, 2 H, $C_{quat}CH_2CH_2OH$), 1.84 – 1.91 (m, 1 H, $C_{quat}CH_aH_bCH$), 2.39 – 2.50 (m, 2 H, $CH_2CH=CH$), 3.18 (s, 1 H, O*H*), 3.64 (s, 1 H, O*H*), 3.92 (t, *J* = 5.9 Hz, 2 H, CH_2OH), 4.23 (dt, *J* = 11.9, 6.3 Hz, 1 H, C*H*), 4.38 (s, 1 H, O*H*), 6.15 – 6.26 (m, 1 H, C*H*=CHAr), 6.85 (d, *J* = 15.8 Hz, 1 H, CH=C*H*Ar), 7.16 (t, *J* = 7.7 Hz, 1 H, ArC*H*), 7.21 (t, *J* = 7.5 Hz, 1 H, ArC*H*), 7.33 (d, *J* = 7.9 Hz, 1 H, ArC*H*), 7.52 (d, *J* = 7.7 Hz, 1 H, ArC*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.4 (CH_3), 42.2 ($CH_2CH=CH$), 43.7 ($C_{quat}CH_2CH_2OH$), 45.7 ($C_{quat}CH_2CH$), 59.7 (CH_2OH), 68.9 (*C*H), 74.6 (C_{quat}), 126.9 (Ar*C*H), 126.9 (ArCH), 128.5 (Ar*C*H), 129.0 (*C*H=CHAr), 129.5 (Ar*C*H), 129.8 (CH=*C*HAr), 132.8 (Ar*C*), 135.4 (Ar*C*) ppm. IR ν_{max} (neat/cm^{-1}): 3345, 2928, 1648, 1469, 1439, 1377, 1115, 1055, 1033, 967, 908, 857, 750, 695. HRMS calcd for $C_{15}H_{21}O_3ClNa$ [M + Na]$^+$: 307.1071, found 307.1058.

rac-(3*R*,5*S*,*E*)-3-Ethyl-8-phenyloct-7-ene-1,3,5-triol 4f

Prepared according to general procedure B using SmI_2 (6.50 mL, 0.65 mmol, 0.1 M in THF), (*E*)-6-oxo-1-phenyloct-1-en-4-yl 2-bromoacetate **2f** (27.7 mg, 0.08 mmol) and H_2O (0.29 mL, 16.3 mmol) to give the title compound as a colourless oil (13.3 mg, 0.05 mmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7.6 Hz, 3 H, CH_3), 1.55 – 1.67 (m, 2 H, 1 H from $C_{quat}CH_2CH$, 1 H from $C_{quat}CH_2CH_2OH$), 1.69 – 1.85 (m, 4 H, 2 H from CH_3CH_2, 1 H from $C_{quat}CH_2CH$, 1 H from $C_{quat}CH_2CH_2OH$), 2.40 (tt, *J* = 6.9, 1.6 Hz, 2 H, $CH_2CH=CH$), 3.21 (s, 1 H, O*H*), 3.45 (s, 1 H, O*H*), 3.79 – 3.97 (m, 2 H, CH_2OH), 4.06 – 4.18 (m, 1 H, C*H*), 4.34 (s, 1 H, O*H*), 6.21 (dt, *J* = 15.4, 7.3 Hz, 1 H, C*H*=CHAr), 6.48 (d, *J* = 15.8 Hz, 1 H, CH=C*H*Ar), 7.19 – 7.25 (m, 1 H, ArC*H*), 7.30 (dd, *J* = 7.6, 7.6 Hz, 2 H, ArC*H*), 7.36 (d, *J* = 7.2 Hz, 2 H, ArC*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 9.1 (CH_3), 31.5 (CH_3CH_2), 39.6 ($C_{quat}CH_2CH_2OH$), 42.2 ($CH_2CH=CH$, $C_{quat}CH_2CH$), 59.6 (CH_2OH), 68.7 (*C*H), 77.0 (C_{quat}), 125.7 (*C*H=CHAr), 126.3 (Ar*C*H), 127.5 (Ar*C*H), 128.7 (Ar*C*H), 133.5 (CH=*C*HAr), 137.3 (Ar*C*) ppm. IR ν_{max} (neat/cm^{-1}): 3344, 3026, 2940, 1598, 1495, 1432, 1329, 1108, 1051, 966, 908, 852, 692, 648. HRMS calcd for $C_{16}H_{24}O_3Na$ [M + Na]$^+$: 287.1618, found 287.1604.

rac-(3*R*,5*S*,*E*)-3-Isobutyl-8-phenyloct-7-ene-1,3,5-triol 4g

Prepared according to general procedure B using SmI_2 (5.50 mL, 0.55 mmol, 0.1 M in THF), (*E*)-8-methyl-6-oxo-1-phenylnon-1-en-4-yl 2-bromoacetate **2g** (25.3 mg, 0.07 mmol) and H_2O (0.25 mL, 13.8 mmol) to give the title compound as a colourless oil (14.3 mg, 0.05 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, *J* = 6.4 Hz, 3 H, CH_3), 0.98 (d, *J* = 6.4 Hz, 3 H, CH_3) 1.52 – 1.64 (m, 3 H, $(CH_3)_2CH$, 1 H from $C_{quat}CH_2CH_2OH$, 1 H from $C_{quat}CH_2CH$), 1.65 – 1.73 (m, 2 H, $(CH_3)_2CHCH_2$), 1.80 – 1.99 (m, 2 H, 1 H from $C_{quat}CH_2CH_2OH$, 1 H from $C_{quat}CH_2CH$), 2.40 (ddt, *J* = 7.2, 5.8, 1.4 Hz, 2 H, $CH_2CH=CH$), 3.27 (d, *J* = 9.9 Hz, 1 H, O*H*), 3.44 (s, 1 H, O*H*), 3.80 – 4.01 (m, 2 H, CH_2OH), 4.18 (dt, *J* = 11.9, 6.4 Hz, 1 H, C*H*), 4.32 (s, 1 H, O*H*), 6.21 (dt, *J* = 15.9, 7.4 Hz, 1 H, C*H*=CHAr), 6.48 (d, *J* = 15.8 Hz, 1 H, CH=C*H*Ar), 7.19 – 7.25 (m, 1 H, ArC*H*), 7.30 (dd, *J* = 8.4, 6.7 Hz, 2 H, ArC*H*), 7.34 – 7.38 (m, 2 H, ArC*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.5 (CH_3), 24.6 (CH_3), 25.1 ($(CH_3)_2CHCH_2$), 40.7 ($C_{quat}CH_2CH_2OH$), 42.3 ($CH_2CH=CH$), 43.9 ($C_{quat}CH_2CH$), 47.9 ($(CH_3)_2CH$), 59.7 (CH_2OH), 68.8 (*C*H), 77.0 (C_{quat}), 125.7 (*C*H=CHAr), 126.3 (Ar*C*H), 127.5 (Ar*C*H), 128.7 (Ar*C*H), 133.6 (CH=*C*HAr), 137.2 (Ar*C*). IR ν_{max} (neat/cm^{-1}): 3335, 2953, 2247, 1431, 1081, 966, 907, 727, 693, 647. HRMS calcd for $C_{18}H_{28}O_3Na$ [M + Na]$^+$: 315.1931, found 315.1915.

rac-(4*R*,6*S*)-6-Cinnamyl-4-hydroxy-4-methyltetrahydro-2H-pyran-2-one 3a

To a solution of SmI_2 (0.95 mL, 0.095 mmol, 0.1 M in THF), under N_2, at -78 °C, (*E*)-6-oxo-1-phenylhept-1-en-4-yl 2-bromoacetate bromoacetate **2a** (12.4 mg, 0.038 mmol) in THF (0.5 mL) was added dropwise and the mixture stirred for 30 min. After that time, the reaction was allowed to slowly warm to room temperature before being quenched with air, followed by a saturated aqueous solution of Rochelle's salt (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined

organic layers were washed with brine (10 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography eluting with EtOAc/hexane (50:50), to give title compound as a colourless oil (9.32 mg, 0.038 mmol, quantitative). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (s, 3 H, *C*H$_3$), 1.49 (s, 1 H, O*H*), 1.63 – 1.96 (m, 2 H, C*H*$_2$CHCH$_2$CH=CHAr), 2.44 – 2.69 (m, 4 H, C*H*$_2$C(O), C*H*$_2$CH=CHAr), 4.82 (dtd, *J* = 11.9, 6.0, 3.0 Hz, 1 H, C*H*), 6.23 (dt, *J* = 15.8, 7.3 Hz, 1 H, C*H*=CHAr), 6.50 (d, *J* = 15.8 Hz, 1 H, CH=C*H*Ar), 7.21 – 7.25 (m, 1 H, ArC*H*), 7.31 (dd, *J* = 8.5, 6.8 Hz, 2 H, ArC*H*), 7.36 (d, *J* = 7.4 Hz, 2 H, ArC*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 30.5 (*C*H$_3$), 38.9 (*C*H$_2$CH=CHAr), 41.1 (*C*H$_2$CHCH$_2$CH=CHAr), 44.3 (*C*H$_2$C(O)), 68.6 (C_{quat}), 76.5 (*C*H), 124.0 (*C*H=CHAr), 126.3 (Ar*C*H), 127.6 (Ar*C*H), 128.7 (Ar*C*H), 133.9 (CH=*C*HAr), 137.1 (Ar*C*), 170.4 (*C*(O))ppm. IR ν_{max} (neat/cm^{-1}): 3431, 2925, 2854, 1741, 1449, 1379, 1256, 1130, 1029, 969, 934, 817, 747, 695. HRMS calcd for $C_{15}H_{17}O_3$ $[M - H]^-$: 245.1183, found 245.1185.

Supplementary Material

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/MS-number.

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Author Contribution Statement

M.H.G.-C. and D.J.P. conceived the study and co-wrote the manuscript. M.H.G-C. designed and performed experiments.

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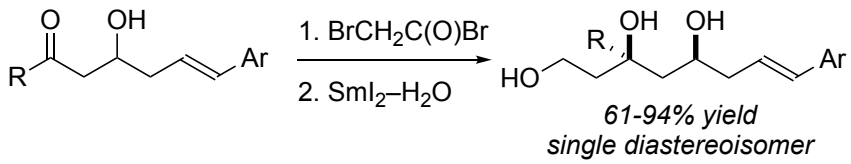
Entry for the Table of Contents



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Procter's diastereoselective hydroxyethylation of beta-hydroxyketones, mediated by SmI_2–H_2O, for the construction of 1,3,5-triols.