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Asymmetric Baylis–Hillman reaction using sugar acrylates—synthesis of optically active α-methylene-β-hydroxy alkanoates†

Palakodety Radha Krishna,* V. Kannan, A. Ilangovan and G. V. M. Sharma

Discovery Laboratory, Organic Chemistry Division III, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Abstract—A study on the asymmetric Baylis–Hillman reaction of three chiral acrylates; 1,2:5,6-di-*O*-*iso*-propylidine-α-D-glucofuranose-3-acrylate **1**, 2,3:5,6-di-*O*-*iso*-propylidine-α-D-mannofuranose-1-acrylate **2** and 1,2-*O*-*iso*-propylidine-5-*O*-*tert*-butyldimethylsilyl-α-D-xylofuranose-3-acrylate **3**, with various aldehydes was conducted, resulting in adducts with moderate diastereoselectivity (5–40% e.e.). © 2001 Elsevier Science Ltd. All rights reserved.

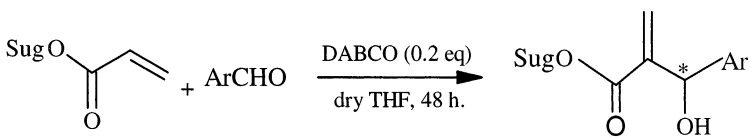
1. Introduction

Interest in the asymmetric Baylis–Hillman[1–3] protocol for the formation of homochiral α-methylene-β-hydroxy-ester (β-hydroxyacrylate) building blocks results from the utility of these compounds in the synthesis of natural products and has prompted many researchers to investigate methods for the stereoselective generation of this functionality. Successful methodological approaches for the enantioselective Baylis–Hillman reaction have been developed by Leahy[4] using Oppolzer's sultam, Chen[5] who utilised a camphor based chiral auxiliary and independently by Barrett[6] and Hatakeyama[7] who reported the use of chiral amines. Other methods, including the use of chiral tertiary amine[8] and bis-phosphine catalysts,[9] chalcogenides in the presence of $TiCl_4$[10] and C_2-symmetric 2,3-disubstituted DABCO bases,[11] gave only poor to moderate results. Hence, investigation of the asymmetric Baylis–Hillman reaction using either new auxiliaries or chiral bases remains an interesting challenge.

2. Results and discussion

Our interest in utilising monosaccharides as chirons has resulted in the synthesis of several natural products, new glyco-substances,[12–14] carrier molecules[15] and chiral auxiliaries.[16] Herein, we describe the further use of monosaccharides as chiral auxiliaries in the preparation of the sugar acrylates **1**, **2** and **3** to effect diastereocontrol during the Baylis–Hillman reaction with several aldehydes (Eq. (1)).

Accordingly, acrylates **1**, **2** and **3** (Scheme 1) were prepared from the corresponding acetonides by reaction with acryloyl chloride in the presence of Et_3N at room temperature in CH_2Cl_2. Initially, acrylate **1** was subjected to Baylis–Hillman reaction with 2-nitrobenzaldehyde **4** in the presence of a variety of bases. When DBU was used as the base,[17] hydrolysis of the acrylate was observed and no reaction was seen in THF at room temperature using either Hünig's base or n-Bu_3P.[18] However, the reaction with DABCO afforded acrylate **4a** in 91% yield.



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* Corresponding author. E-mail: prkgenius@iict.ap.nic.in

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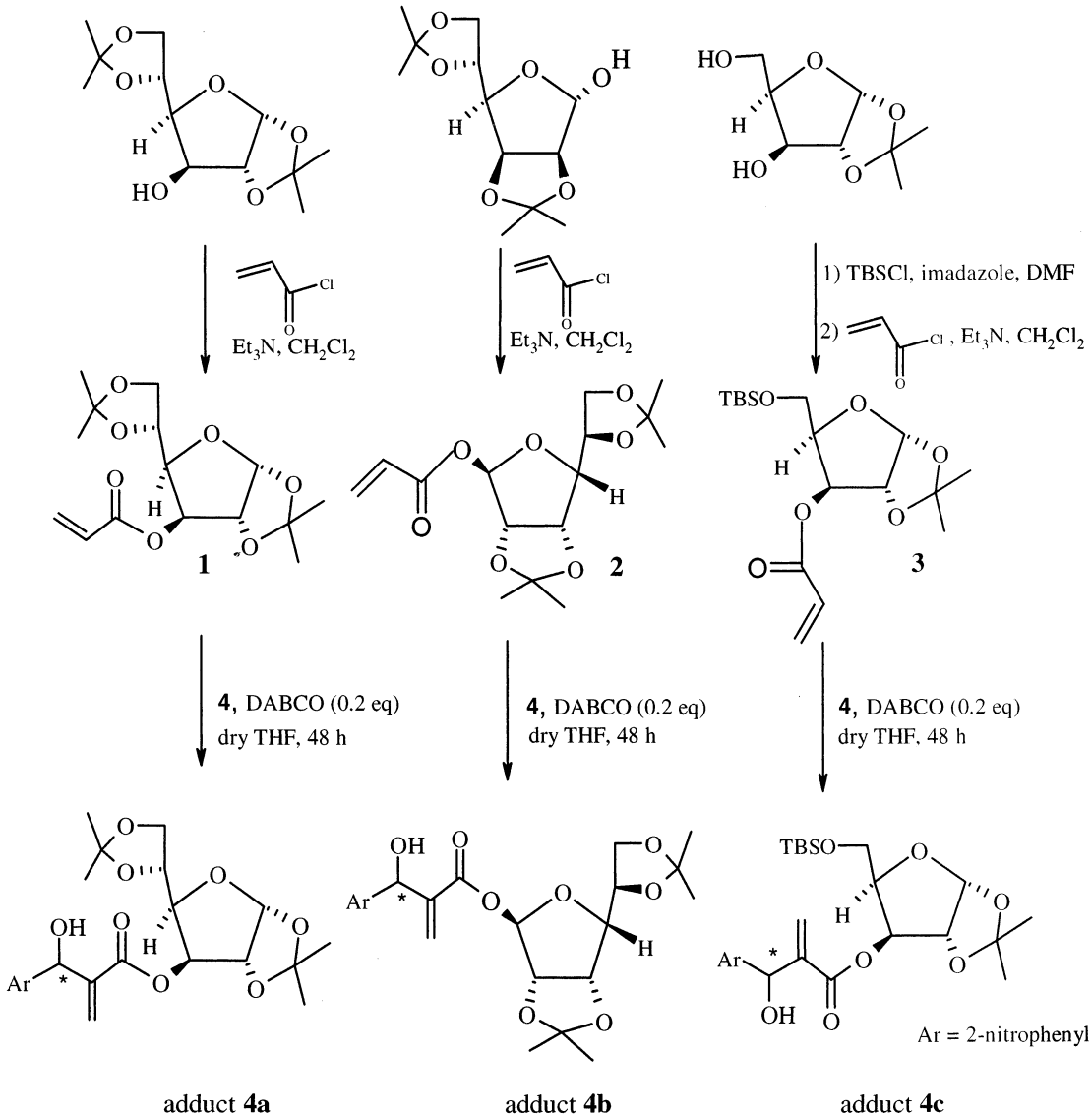
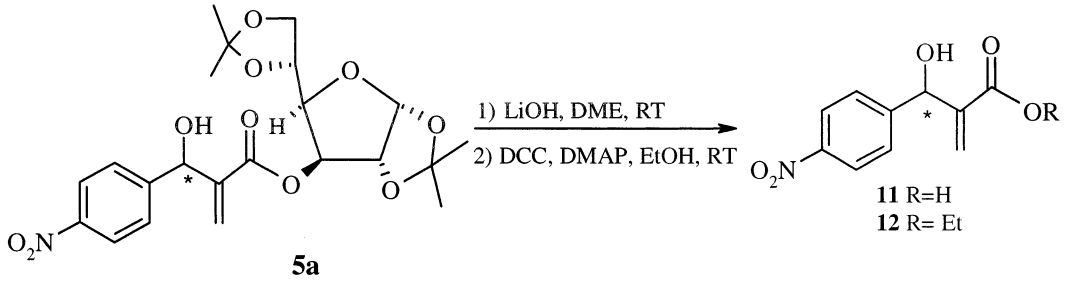


Scheme 1.

Table 1. Asymmetric Baylis–Hillman reaction of aldehydes with sugar acrylates

S. No.	Aldehyde[a]	Chiral acrylate	Time	Yield[b] (%)	d.e.[d] (%)
1	2-Nitro-benzaldehyde **4**	1	2 days	**4a**, 91	40 (*R*)
		2	2 days	**4b**, 88	40 (*R*)
		3	6 days	**4c**, 85	40 (*R*)
2	4-Nitro-benzaldehyde **5**	1	2 days	**5a**, 87	40 (*R*)
		2	2 days	**5b**, 86	40 (*R*)
3	Isobutyraldehyde **6**	1	20 h	**6a**[c], 67	0
		2	20 h	**6b**[c], 76	0
4	Benzaldehyde **7**	1	6 days	**7a**, 90	5 (*R*)[e]
5	2,3-Dichlorobenzaldehyde **8**	1	2 days	**8a**, 97	0
6	2-Nitro-5-*n*-propoxybenzaldehyde **9**	1	4 days	**9a**, 95	15 (*R*)
7	2-Nitro-5-methoxybenzaldehyde **10**	1	4 days	**10a**, 92	24 (*R*)

[a] DABCO (0.2 equiv.), THF, rt.
[b] Isolated yields of the respective auxiliary bound adducts.
[c] Acrylate cleavage was also observed.
[d] As determined by ^{1}H NMR and HPLC analysis (column Chiralcel OD; 1 cm ID and 25 cm length, *n*-hexane/propan-2-ol = 5.66:1, flow rate = 1.6 mL/min, UV = 225 nm).
[e] Based on the literature[21] $[\alpha]_D$ values for the acid **17**.



Scheme 2.

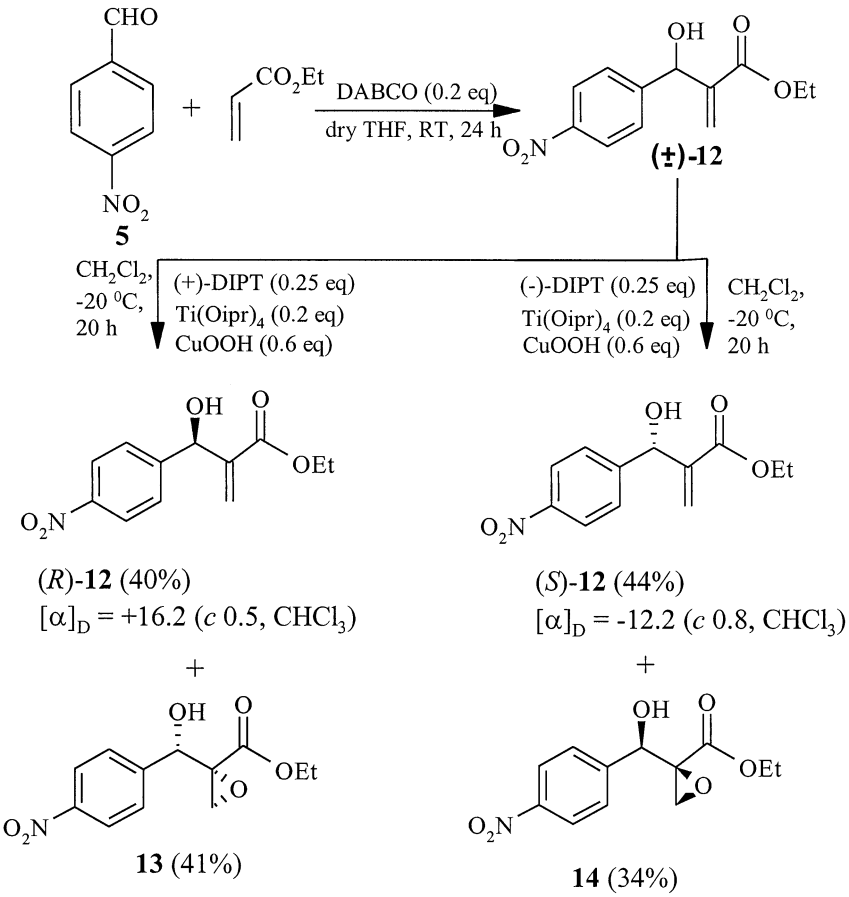
The reaction of **4** was carried out independently with **2** and **3** in the presence of DABCO (0.2 equivalents) at room temperature to afford the adducts **4b** (reaction time: 2 days) and **4c** (reaction time: 6 days) in 88 and 85% yields, respectively (Table 1). Since the Baylis–Hillman reaction of **4** with **1**, **2** and **3** occurred with similar selectivity it was decided to continue further studies with **1** and **2**.

On changing the solvent from THF to DMSO,[5] a marked increase in the rate of the reaction (which reached completion in 24 h) was seen. When the temperature of the reaction between **1** with **4** carried out in THF was lowered to 0°C, the reaction was unworkably slow and no improvement in the stereoselectivity was seen.

The structure of the adducts and the diastereoselectivity of the reactions were unambiguously determined from the ^{1}H NMR spectrum, where the relative integration of the separate proton resonances for each enantiomer allowed the ratio of isomeric adducts to be found. For example, in the ^{1}H NMR spectrum of **4a**, the H-1 doublet resonated at δ 5.7 for the minor isomer and at δ 5.85 for the major isomer and the H-2 doublet was observed at δ 4.48 for the major isomer, while the H-2 doublet for the minor isomer resonated at δ 4.4. The integral ratio for **4a** was found to be 7:3 (d.e. = 40%).

The study of acrylates **1** and **2** was then extended to the aldehyde **5** to give the adducts **5a** and **5b** (Table 1), respectively, in good yields and moderate enantiomeric purity. However, aldehyde **6** on reaction with **1** and **2** gave adducts **6a** and **6b**, respectively, in good chemical yields albeit with no stereochemical induction.

In a further study, aldehydes **7**, **8**, **9** and **10** were reacted with acrylate **1** under the same conditions to give adducts **7a** (90%), **8a** (97%), **9a** (95%) and **10a** (92%), respectively,



Scheme 3.

with moderate stereochemical induction, as seen in Table 1. The ratios of the diastereomers in these adducts were determined from the relative integrations in the ^{1}H NMR spectra. To ascertain the absolute configuration of the major isomer formed, the adduct **5a** was subjected to hydrolysis (Scheme 2) with LiOH in DME at room temperature to give the acid **11** in 95% yield, which on reaction with ethanol in the presence of DCC[19]-DMAP was converted into its ethyl ester **12** in good yield.

To establish the absolute configuration of adduct **12**, Katsuki–Sharpless asymmetric epoxidation conditions[20] were employed to synthesise reference samples of (*R*)-**12** and (*S*)-**12** by kinetic resolution of the racemate with (+)-DIPT and (−)-DIPT, respectively. Accordingly, the requisite (±)-**12** was prepared in 97% yield from reaction of **5** and ethyl acrylate in the presence of DABCO (Scheme 3). Kinetic resolution of (±)-**12** with (+)-DIPT afforded (*R*)-**12** and epoxide **13**. Similarly, reaction of (−)-DIPT with (±)-**12** gave (*S*)-**12** and the epoxide **14**. The specific rotation value of **12** was similar to (*R*)-**12**, hence (*R*) absolute configuration of the product was assigned. Further, chiral HPLC (Chiralcel OD) was consistent with the major isomers of Baylis–Hillman adducts **4a**, **4b**, **4c**, **5a**, **5b**, **7a**, **9a** and **10a** obtained with acrylates **1**–**3** being of (*R*) absolute configuration.

Based on the literature evidence,[22,23] the following isoxazoline intermediate (Fig. 1) was envisaged as the possible enolate of sugar acrylate **1** to give the (*R*)-stereoisomer as the major product. Selectivity results

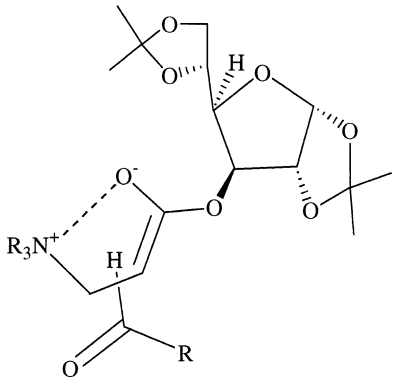


Figure 1.

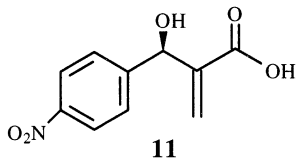
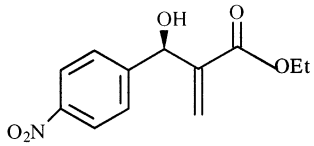
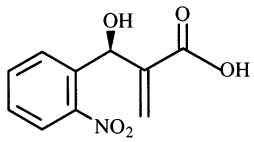
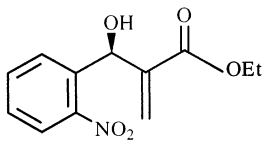
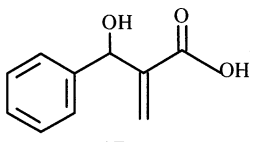
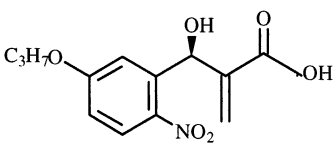
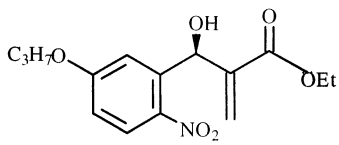
from approach of the incoming aldehyde to the enolate in such a fashion as to minimise steric interactions with the bulky alkyl group.

Similarly the other adducts **4a**, **7a** and **9a** were subjected to the same set of reactions to give acids **15**, **17**, and **18**, respectively, **15** and **18** were converted into esters **16** and **19**, respectively, in good yield (Table 2).

3. Conclusion

The present study demonstrates the use of monosaccharide acrylates for the stereoselective Baylis–Hillman reac-

Table 2. Hydrolysis and esterification of sugar linked Baylis–Hillman adducts

S. No.	Adduct	Acid	Ester
1.	**5a**	 **11**	 **12**
2.	**4a**	 **15**	 **16**
3.	**7a**	 **17**	
4.	**9a**	 **18**	 **19**

tion resulting in the formation of adducts with yields of 67–97% and d.e. ratios ranging from 7:3 to 3:2, as determined using ^{1}H NMR and chiral HPLC analysis. The selectivities were moderate (5–40% d.e.) and are comparable with the earlier reported protocols. Further work on designing new sugar derived acrylates for the asymmetric Baylis–Hillman reaction and the utility of Baylis–Hillman adducts is currently under investigation.

4. Experimental

Solvents were dried over standard drying agents and freshly distilled prior to use. ^{1}H NMR (200 and 400 MHz) and ^{13}C NMR (50 MHz) spectra were measured with a Varian Gemini spectrometer, with tetramethylsilane as internal standard for solutions in deuteriochloroform. *J* values are given in Hz. Optical rotations were measured with a JASCO DIP-370 instrument and $[\alpha]_D$ values are in units of 10^{-1} deg cm^2 g^{-1}. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40°C in vacuo. HPLC was performed with Chiralcel OD column (1 cm ID×25 cm length) using *n*-hexane/*iso*-propanol: 5.66:1, flow rate 16 mL/min, UV 225 nm (unless otherwise stated). Nomenclature used in the experimental section was assisted by the software ACD/Name Version 1.0, developed by M/s Advanced Chemistry Development Inc., Toronto, Canada.

4.1. 1,2:5,6-Di-*O*-*iso*-propylidine-α-D-glucofuranose-3-acrylate 1

To a stirred solution of 1,2:5,6-di-*O*-*iso*-propylidine-α-D-glucofuranoside (2.0 g, 7.69 mmol) and triethylamine (1.6 mL, 11.53 mmol) in CH_2Cl_2 (10 mL) acryloyl chloride (0.68 mL, 8.46 mmol) was added dropwise at 0°C and stirred at room temperature for 10 h. The reaction mixture was treated with water (25 mL) and extracted into CH_2Cl_2 (3×50 mL). The combined organic layers were washed with water (2×100 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane–EtOAc, 8.5:1.5) to afford the auxiliary **1** (2.06 g, 85%) as a white solid. Mp 67–69°C. $[\alpha]_D = -37.9$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 6.53 (s, 1H, olefinic), 6.43 (s, 1H, olefinic), 6.18 (s, 1H, olefinic), 5.97 (d, 1H, $J = 2.04$ Hz, H-1), 5.32 (br.s, 1H, H-3), 4.52 (d, 1H, $J = 3.67$ Hz, H-2), 4.22 (m, 2H, H-4, 5), 4.1–4.0 (m, 2H, H-6, 6′), 1.55 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.3 (br. s, 6H, $2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.6, 131.7, 127.8, 112.3, 109.3, 105.1, 83.4, 79.8, 76.3, 72.5, 67.1, 26.7, 26.5, 26.2, 25.2. Anal. calcd for $C_{15}H_{22}O_7$: C, 57.32; H, 7.05. Found: C, 57.20; H, 7.15%.

4.2. 2,3:5,6-Di-*O*-*iso*-propylidine-α-D-mannofuranose-1-acrylate 2

Reaction of 2,3:5,6-di-*O*-*iso*-propylidine-α-D-mannofuranoside (2.0 g, 7.69 mmol) and acryloyl chloride (0.68 mL, 8.46 mmol) in the presence of triethylamine (1.6 mL, 11.53 mmol) for 10 h, as reported for **1**, gave **2** (1.96 g, 81%) as a syrup. $[\alpha]_D = +48.6$ (*c* 1.25, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.4 (s, 1H, olefinic), 6.16 (s, 1H, olefinic), 6.08 (s, 1H, olefinic), 5.9 (d, 1H, $J = 0.97$ Hz, H-1), 4.82 (m, 1H, H-3), 4.7 (d, 1H, $J = 5.85$ Hz, H-2), 4.35 (m, 1H, H-4), 4.1–3.92 (m, 3H, H-5, 6, 6′), 1.5 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.38 (br.s, 6H, $2CH_3$). Anal. calcd for $C_{15}H_{22}O_7$: C, 57.32; H, 7.05. Found: C, 57.27; H, 7.10%.

4.3. 1,2-*O*-*iso*-Propylidine-5-*O*-*tert*-butyldimethylsilyl-α-D-xylofuranoside-3-acrylate 3

To a solution of 1,2-*O*-*iso*-propylidene-α-D-xylofuranoside (0.20 g, 1.05 mmol) and imidazole (0.21 g, 3.15 mmol) in dry DMF (2 mL) was added TBDMSCl (0.16 g, 1.05 mmol) and stirred for 8 h. The reaction mixture was diluted with ether (10 mL) and washed sequentially with water (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4), evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, hexane–EtOAc, 3:1) to afford 1,2-*O*-*iso*-propylidine-5-*O*-*tert*-butyldimethyl-α-D-xylofuranoside (0.32 g, 90%) as a syrup. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.89 (d, 1H, $J = 3.4$ Hz, H-1), 4.43 (d, 1H, $J = 4.3$ Hz, H-3), 4.24 (s, 1H, H-2), 4.18–4.10 (m, 3H, H-4, 5, 5′), 1.47 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 0.89 (s, 9H, Me_3C), 0.11 (s, 6H, $2CH_3$).

1,2-*O*-*iso*-Propylidine-5-*O*-*tert*-butyldimethylsilyl-α-D-xylofuranoside (0.30 g, 0.98 mmol) was treated with acryloyl chloride (0.09 mL, 1.08 mmol) and triethylamine (0.20 mL, 1.47 mmol) as reported for **1** to afford the acrylate **3** (0.40 g, 89%) as a syrup. $[\alpha]_D = -29.4$ (*c* 0.53, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.33 (s, 1H, olefinic), 6.06 (s, 1H, olefinic), 5.85–5.8 (m, 2H, olefinic, H-1), 5.38 (d, 1H, $J = 3.72$ Hz, H-3), 4.5 (d, 1H, $J = 4.18$ Hz, H-2), 4.22 (m, 1H, H-4), 3.9–3.75 (m, 2H, H-5, 5′), 1.5 (s, 3H, CH_3), 1.3 (s, 3H, CH_3), 1.12–0.98 (br. s, 9H, Me_3C), 0.11 (s, 6H, $2CH_3$). Anal. calcd for $C_{17}H_{30}O_6Si$: C, 56.96; H, 8.43. Found: C, 56.87; H, 8.09%.

The Baylis–Hillman reaction of sugar acrylates with aldehydes (general procedure)

To a solution of acrylate (1 mmol) in dry THF (2 mL) was added DABCO (0.20 mmol), aldehyde (1.2 mmol) and the mixture was stirred at room temperature for 2–6 days. The solvent was removed from the mixture under reduced pressure and the residue purified by column chromatography (silica gel, hexane–EtOAc) to afford product in yields of 67–95%.

4.4. 5-[2,2-Dimethyl-(4*R*)-1,3-dioxolan-4-yl]-2,2-dimethyl-(3a*R*,6*S*,6a*R*)-perhydrofuro [2,3-*d*][1,3]-dioxol-6-yl 2-hydroxy(2-nitrophenyl)methylacrylate 4a

To a solution of **1** (0.20 g, 0.64 mmol) in THF (2 mL), **4** (0.12 g, 0.76 mmol) and DABCO (0.014 g, 0.13 mmol) were added and the mixture was allowed to stir at room temperature for 2 days. Solvent was removed to give the residue, which on purification by column

chromatography (silica gel, hexane:EtOAc, 8:2) afforded **4a** (0.27 g, 91%) as a syrup. $[\alpha]_D = -20.9$ (*c* 1.65, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.05–7.95 (m, 1H, Ar-H), 7.85–7.65 (m, 2H, Ar-H), 7.56–7.45 (m, 1H, Ar-H), 6.38 (s, 1H, olefinic), 6.25–6.13 (m, 1H, olefinic), 5.85 (d, 0.7H, $J = 3.81$ Hz, H-1), 5.7 (d, 0.3H, $J = 3.81$ Hz, H-1), 5.55 (s, 1H, benzylic), 5.3 (d, 0.7H, $J = 3.33$ Hz, H-3), 5.22 (d, 0.3H, $J = 3.33$ Hz, H-3), 4.48 (d, 0.7H, $J = 3.81$ Hz, H-2), 4.4 (d, 0.3H, $J = 3.81$ Hz, H-2), 4.2–3.95 (m, 4H, H-4, 5, 6, 6′), 3.4–3.25 (bs, 1H, -OH), 1.56–1.2 (br.s, 12H, $4CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.3, 141.2, 140.8, 136.2, 133.3, 128.7, 128.5, 127.0, 124.5, 112.1, 109.3, 104.9, 83.1, 79.7, 76.8, 72.5, 67.5, 67.1, 26.5 (2C), 26.0, 24.8; EIMS (M^+-15): 450; HRMS calcd for $C_{22}H_{27}NO_{10}$ (M^+-15): 450.140021. Found: 450.142441.

4.5. 6-[2,2-Dimethyl-(4*R*)-1,3-dioxolan-4-yl]-2,2-dimethyl-(3a*S*,4*R*,6*R*,6a*S*)-perhydrofuro [3,4-*d*][1,3]-dioxol-4-yl 2-hydroxy(2-nitrophenyl)methylacrylate 4b

To a solution of **2** (0.20 g, 0.64 mmol) in THF (2 mL), **4** (0.12 g, 0.76 mmol) and DABCO (0.014 g, 0.13 mmol) were added and the reaction was performed as reported for **4a**, to give **4b** (0.26 g, 88%) as a syrup. $[\alpha]_D = +15.1$ (*c* 2.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.98–7.9 (m, 1-H, Ar-H), 7.65 (d, 2H, $J = 4.18$ Hz, Ar-H), 7.5–7.4 (m, 1H, Ar-H), 6.42 (br.s, 1H, olefinic), 6.08 (s, 1H, H-1), 6.1 (s, 1H, olefinic), 5.91 (br.s, 1H, benzylic), 4.81–4.72 (m, 1H, H-3), 4.61 (br.d, 0.7H, $J = 5.12$ Hz, H-2), 4.42 (br.d, 0.3H, $J = 5.12$ Hz, H-2), 4.12–3.9 (m, 2H, H-4, 5), 3.7 (d, 1H, $J = 4.65$ Hz, H-6), 3.42 (d, 1H, $J = 3.72$ Hz, H-6′), 1.45 (s, 6H, $2CH_3$), 1.31 (s, 6H); EIMS (M^+-15): 450; HRMS calcd for $C_{22}H_{27}NO_{10}$ (M^+-15): 450.140021. Found: 450.137848.

4.6. 5-*tert*-Butyldimethylsilyloxymethyl-2,2-dimethyl-(3a*R*,6*S*,6a*R*)-perhydrofuro [2,3-*d*][1,3]-dioxol-6-yl 2-hydroxy(2-nitrophenyl)methylacrylate 4c

To a solution of **3** (0.31 g, 0.86 mmol) in THF (3 mL), **4** (0.16 g, 1.04 mmol) and DABCO (0.02 g, 0.17 mmol) were added and the contents were stirred for 6 days at room temperature. Work-up and purification as described for **4a** gave **4c** (0.38 g, 85%) as a syrup. $[\alpha]_D = -2.5$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.6 (m, 2H, Ar-H), 7.4 (br.s, 2H, Ar-H), 6.32 (s, 1H, olefinic), 6.2 (s, 1H, olefinic), 5.82 (d, 0.3H, $J = 4.38$ Hz, H-1), 5.75 (s, 1H, benzylic), 5.6 (d, 0.7H, $J = 4.38$ Hz, H-1), 5.38 (d, 0.3H, $J = 3.41$ Hz, H-3), 5.28 (d, 0.7H, $J = 3.41$ Hz, H-3), 4.44 (d, 0.3H, $J = 3.89$ Hz, H-2), 4.23 (d, 0.7H, $J = 3.89$ Hz, H-2), 3.82 (m, 1H, H-4), 3.74–3.62 (m, 2H, H-5, 5′), 3.3–3.18 (br.s, 1H, -OH), 1.5 (br. s, 3H, $-CH_3$), 1.3 (br. s, 3H, $-CH_3$), 1.01 (s, 9H, $-C(CH_3)_3$), 0.12 (s, 6H, $2CH_3$); anal. calcd for $C_{24}H_{35}NO_9Si$: C, 56.56; H, 6.92. Found: C, 56.23; H, 6.16%.

4.7. 5-[2,2-Dimethyl-(4*R*)-1,3-dioxolan-4-yl]-2,2-dimethyl-(3a*R*,6*S*,6a*R*)-perhydrofuro [2,3-*d*][1,3]-dioxol-6-yl 2-hydroxy(4-nitrophenyl)methylacrylate 5a

Method A: To a solution of **1** (0.92 g, 2.92 mmol) in THF (6 mL) **5** (0.53 g, 3.51 mmol) and DABCO (0.07 g, 0.58 mmol) were added and the contents were stirred at room temperature for 2 days. Work-up and purification as reported for **4a** gave **5a** (1.18 g, 87%) as a syrup. $[\alpha]_D = -2.4$ (*c* 1.2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.25 (d, 2H, $J = 7.5$ Hz, Ar-H), 7.65 (d, 2H, $J = 7.5$ Hz, Ar-H), 6.3 (d, 1H, $J = 5.5$ Hz, olefinic), 5.95 (s, 1H, olefinic), 5.85 (d, 0.3H, $J = 3.75$ Hz, H-1), 5.8 (d, 0.7H, $J = 3.75$ Hz, H-1), 5.7 (d, 1H, $J = 3.75$ Hz, benzylic), 5.3 (s, 1H, H-3), 4.5 (d, 0.3H, $J = 3.75$ Hz, H-2), 4.4 (d, 0.7H, $J = 3.75$ Hz, H-2), 4.2–3.98 (m, 4H, H-4, 5, 6, 6′), 3.45 (br.d, 0.3H, $J = 5.5$ Hz, -OH), 3.13 (br.d, -OH, $J = 5.5$ Hz, 0.7H), 1.6–1.25 (br.s, 12H, $4CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.5, 148.75, 141.0, 127.42, 127.28, 123.35 (2C), 112.19, 109.32, 106.2, 104.82, 83.62, 79.65, 76.34, 74.76, 69.63, 67.13, 64.74, 26.9, 26.46, 26.25, 25.97. HREIMS calcd for $C_{22}H_{27}NO_{10}$ (M^+-15): 450.140021. Found: 450.1386.

Method B: A mixture of **1** (0.20 g, 0.64 mmol), **5** (0.12 g, 0.76 mmol) and DABCO (0.014 g, 0.13 mmol) in DMSO (1 mL) were stirred for 24 h at room temperature. The reaction mixture was treated with water (20 mL), brine (25 mL) and extracted into ether (3×25 mL), the combined organic layers were washed with water (2×25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography to afford **5a** (0.28 g, 95%) as a syrup, which was identical spectroscopically to **5a** prepared by method A.

4.8. 6-[2,2-Dimethyl-(4*R*)-1,3-dioxolan-4-yl]-2,2-dimethyl-(3a*S*,4*R*,6*R*,6a*S*)-perhydrofuro [3,4-*d*][1,3]-dioxol-4-yl 2-hydroxy(4-nitrophenyl)methylacrylate 5b

To a solution of **2** (0.20 g, 0.64 mmol) in THF (2 mL) **5** (0.12 g, 0.76 mmol) and DABCO (0.014 g, 0.13 mmol) were added and the contents stirred for 2 days at room temperature. Work-up and purification as for **4a** gave **5b** (0.29 g, 86%) as a syrup. $[\alpha]_D = +20.8$ (*c* 1.83, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.24 (d, 2H, $J = 9.52$ Hz, Ar-H), 7.6 (d, 2H, $J = 7.61$ Hz, Ar-H), 6.38 (d, 1H, $J = 3.81$ Hz, olefinic), 6.16 (s, 1H, olefinic), 6.0 (s, 0.7H, H-1), 5.9 (s, 0.3H, H-1), 5.64 (s, 1H, benzylic), 4.8 (m, 1H, H-3), 4.62 (d, 1H, $J = 5.71$ Hz, H-2), 4.38 (m, 1H, H-4), 4.1–3.85 (m, 3H, H-5, 6, 6′), 3.2 (br. s, 0.3H, -OH), 3.1 (br. s, 0.7H, -OH), 1.45–1.3 (br. s, 12H, $4CH_3$). EIMS (M^+-15): 450; HREIMS calcd for $C_{22}H_{27}NO_{10}$ (M^+-15): 450.140021. Found: 450.137848.

4.9. 5-[2,2-Dimethyl-(4*R*)-1,3-dioxolan-4-yl]-2,2-dimethyl-(3a*R*,6*S*,6a*R*)-perhydrofuro [2,3-*d*][1,3]-dioxol-6-yl 2-(1-hydroxy-3-methylbutyl)acrylate 6a

To a solution of **1** (0.20 g, 64 mmol) in THF (2 mL) **6** (0.05 mL, 0.76 mmol) and DABCO (0.014 g, 0.13 mmol) were added and the contents were stirred for 20 h at room temperature. Work-up and purification as reported for **4a** afforded **6a** (0.17 g, 67%) as a syrup. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.22 (s, 1H, olefinic), 5.82 (d, 1H, $J = 3.63$ Hz, H-1), 5.78 (s, 1H, olefinic), 5.28 (br.s, 1H, allylic), 4.48 (d, 1H, $J = 3.63$ Hz, H-2), 4.18–3.92 (m, 5H, H-3, 4, 5, 6, 6′), 2.28 (br.s, 1H, -OH), 1.95–1.85 (m, 1H, Me_2CH-), 1.5 (s, 3H, CH_3), 1.4 (s, 3H, CH_3), 1.29 (br.s, 6H, $2CH_3$), 0.95–0.85 (2d, 6H, $J = 5.45$, 5.9 Hz); EIMS

(M^+–15): 371; HREIMS calcd for $C_{19}H_{30}O_8$ (M^+–15): 371.170593. Found: 371.171901.

4.10. 6-[2,2-Dimethyl-(4*R*)-1,3-dioxolan-4-yl]-2,2-dimethyl-(3a*S*,4*R*,6*R*,6a*S*)-perhydrofuro [3,4-*d*][1,3]-dioxol-4-yl 2-(1-hydroxy-3-methylbutyl)acrylate 6b

To a solution of **2** (0.15 g, 0.48 mmol) in THF (2 mL) **6** (0.05 ml, 0.57 mmol) and DABCO (0.011 g, 0.095 mmol) were added and the contents were stirred at room temperature for 20 h. Work-up and purification as reported for **4a** afforded **6b** (0.14 g, 76%) as a syrup. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.41 (d, 1H, J=1.0 Hz, olefinic), 6.14 (s, 1H, olefinic), 5.91 (s, 1H, H-1), 5.32 (s, 1H, allylic), 4.8–4.7 (m, 1H, H-3), 4.55 (d, 1H, J=5.0 Hz, H-2), 4.35–4.28 (m, 1H, H-4), 4.15–3.95 (m, 3H, H-5, 6, 6′), 2.3 (br.s, 1H, -OH), 1.92–1.80 (m, 1H, Me_2CH-), 1.5–1.22 (br.s, 12H, 4CH_3), 0.98–082 (2d, 6H, J=5.5, 6.0 Hz, Me_2CH-); EIMS (M^+–15): 371; HREIMS calcd for $C_{19}H_{30}O_8$ (M^+–15): 371.170593. Found: 371.171056.

4.11. 5-[2,2-Dimethyl-(4*R*)-1,3-dioxolan-4-yl]-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)-perhydrofuro [2,3-*d*][1,3]-dioxol-6-yl 2-hydroxy(phenyl)methylacrylate 7a

To a solution of **1** (0.50 g, 1.59 mmol) in THF (5 mL) **7** (0.20 g, 1.90 mmol) and DABCO (0.035 g, 0.32 mmol) were added and the contents were stirred at room temperature for 6 days. Work-up and purification as reported for **4a** gave **7a** (0.60 g, 90%) as a syrup. $[\alpha]_D$=−27.5 (c 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.3–7.21 (m, 5-H, Ar-H), 6.44 (s, 1H, olefinic), 5.92 (s, 1H, olefinic), 5.88 (d, 1H, J= 4.0 Hz, H-1), 5.6 (s, 1H, benzylic), 4.78 (s, 1H, H-3), 4.59 (d, 1H, J=4.5 Hz, H-2), 4.35 (m, 1H, H-4), 4–3.84 (m, 3H, H-5, 6, 6′), 3.12 (br.s, 1H, -OH), 1.42–1.31 (br.s 12H, 4 CH_3); MSEI (M^+–15): 405; anal. calcd for $C_{22}H_{28}O_8$: C, 62.85; H, 6.7. Found: C, 62.61; H, 6.3%.

4.12. 5-[2,2-Dimethyl-(4*R*)-1,3-dioxolan-4-yl]-2,2-dimethyl-(3a*R*,6*S*,6a*R*)-perhydrofuro [2,3-*d*][1,3]-dioxol-6-yl 2-[2,3-dichlorophenyl(hydroxy)methyl]acrylate 8a

To a solution of **1** (0.20 g, 0.64 mmol) in THF (2 mL) **8** (0.13 g, 0.76 mmol) and DABCO (0.014 g, 0.13 mmol) were added and the contents were stirred at room temperature for 2 days. Work-up and purification as reported for **4a** gave **8a** (0.30 g, 97%) as a thick syrup. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.57.4 (m, 2H, Ar-H), 7.25 (s, 1H, Ar-H), 6.32 (d, 1H, J= 5.36 Hz, olefinic), 5.95 (s, 1H, olefinic), 5.88 (d, 0.5H, J=2.92 Hz, H-1), 5.79 (d, 0.5H, J=2.92 Hz, H-1), 5.61 (s, 0.5H, H-3), 5.4 (s, 0.5H, H-3), 5.33 (s, 0.5H, benzylic), 5.27 (s, 0.5H, benzylic), 4.5 (d, 1H, J=3.41 Hz, H-2), 4.22–3.9 (m, 4H, H-4, 5, 6, 6′), 1.5 (s, 3H, -CH_3), 1.45–1.2 (br.s, 9H, 3CH_3); (M^+–15) 473; HREIMS calcd for $C_{22}H_{26}Cl_2O_8$ (M^+–15): 473.076111. Found: 473.076998.

4.13. 5-[2,2-Dimethyl-(4*R*)-1,3-dioxolan-4-yl]-2,2-dimethyl-(3a*R*,6*S*,6a*R*)-perhydrofuro [2,3-*d*][1,3]-dioxol-6-yl 2-hydroxy(2-nitro-5-*n*-propoxyphenyl)-methylacrylate 9a

To a solution of **1** (0.10 g, 0.32 mmol) in THF (2 mL) **9** (0.73 g, 0.35 mmol) and DABCO (0.007 g, 0.06 mmol) were added and the contents were stirred at room temperature for 4 days. Work-up and purification as reported for **4a** afforded **9a** (0.16 g, 95%) as a thick syrup. $[\alpha]_D$=−33.5 (c 1.15, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.1 (d, 1H, J=3.72 Hz, Ar-H), 7.3 (m, 1H, Ar-H), 6.89 (br.d, 1H, Ar-H), 6.3 (br.d, 2H, J=8.83 Hz, olefinic), 5.85 (d, 0.57H, J=3.72 Hz, H-1), 5.78 (d, 0.43H, J=3.72 Hz, H-1), 5.62 (s, 0.57H, benzylic), 5.42 (s, 0.43H, benzylic), 5.32 (d, 1H, J=3.72 Hz, H-3), 4.5 (d, 1H, J=4.18 Hz, H-2), 4.2 (br.s, 1H, H-4), 4.2–3.9 (m, 5H, H-5, 6, 6, -CH_2-), 3.4 (br.s, 1H, -OH), 1.85 (m, 2H, -CH_2-), 1.5 (s, 3H, CH_3), 1.45–1.25 (br.s, 9H, 3CH_3), 1.09 (t, 3H, J=8.5 Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.6, 141.6, 141.1, 139.0 (2C), 127.7, 126.7, 114.1, 113.6, 112.2, 109.3, 105.0, 83.2, 79.9, 76.7, 72.2, 70.2, 67.6, 67.5, 26.7 (2C), 26.1, 25.1, 22.2, 10.3; FABMS (M^+); 523. Anal. calcd for $C_{25}H_{33}NO_{11}$: C, 57.36; H, 6.35. Found. C, 56.97; H, 6.62%.

4.14. 5-[2,2-Dimethyl-(4*R*)-1,3-dioxolan-4-yl]-2,2-dimethyl-(3a*R*,6*S*,6a*R*)-perhydrofuro [2,3-*d*][1,3]-dioxol-6-yl 2-hydroxy(5-methoxy-2-nitrophenyl)methylacrylate 10a

To a solution of **1** (0.10 g, 0.32 mmol) in THF (2 mL) **10** (0.07 g, 0.38 mmol) and DABCO (0.007 g, 0.06 mmol) were added and the contents were stirred at room temperature for 4 days. Work-up and purification as for **4a** afforded **10a** (0.14 g, 92%) as a thick syrup. $[\alpha]_D$=−9.8 (c 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (m, 1H, Ar-H), 7.3 (m, 1H, Ar-H), 6.85 (s, 1H, Ar-H), 6.25 (s, 2H, olefinic), 5.8 (d, 0.62H, J=1.97 Hz, H-1), 5.78 (d, 0.38H, J=1.97 Hz, H-1), 5.58 (s, 1H, benzylic), 5.3 (s, 0.62H, H-3), 5.22 (s, 0.38H, H-3), 4.5 (d, 1H, J=1.97 Hz, H-2), 4.18 (s, 1H, H-4), 4.1 (m, 1H, H-5), 3.96 (m, 2H, H-6, 6′), 3.9 (s, 3H, -OMe), 1.5 (s, 3H, CH_3), 1.4–1.2 (br.s, 9H, 3CH_3); FABMS (M^+): 495. Anal. calcd for $C_{23}H_{29}NO_{11}$: C, 55.75; H, 5.90. Found: C, 55.35; H, 5.85%.

4.15. Ethyl-2-hydroxy(4-nitrophenyl)methylacrylate 12

Method A: To a stirred solution of **5a** (0.20 g, 0.43 mmol) in DME (2 mL) was added aq. LiOH (1N, 0.05 g, 2.14 mmol) and stirred for 2 h. The reaction mixture was taken in EtOAc (10 mL), washed with dil. HCl (5 mL) and water (10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane:EtOAc, 3:1) to afford (4-nitrophenyl) 2-hydroxy methylacrylic acid **11** (0.082 g, 86%) as a syrup. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.2 (d, 2H, J=8.78 Hz, Ar-H), 7.58 (d, 2H, J=9.26 Hz, Ar-H), 6.49 (s, 1H), 5.93 (s, 1H), 5.6 (s, 1H).

To a stirred solution of **11** (0.10 g, 0.44 mmol) in CH_2Cl_2 (2 mL) containing DMAP (5 mg), absolute ethanol (1 mL) and DCC (0.09 g, 0.45 mmol) were added at 0°C and stirred for 2 h at 20°C. The reaction mixture was filtered off and washed with CH_2Cl_2 (5 mL). The filtrate was evaporated under reduced pressure, the residue taken in CH_2Cl_2 (5 mL) and washed with 0.5N HCl (5 mL) and saturated $NaHCO_3$ (5 mL). The organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane:EtOAc, 8.5:1.5) to afford **12** (0.11 g, 95%) as a syrup. HPLC: rt, 30.2 (68.8%), 31.6 (30.5%). $[\alpha]_D=+6.4$ (*c* 0.3, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 8.2 (d, 2H, $J=8.3$ Hz, Ar-H), 7.56 (d, 2H, $J=8.83$ Hz, Ar-H), 6.35 (s, 1H), 5.8 (s, 1H), 5.55 (s, 1H), 4.25–4.1 (q, 2H, -CH_2), 3.25 (br.s, 1H, -OH), 1.3–1.2 (s, 3H, -CH_3); EIMS (M^+): 251; HREIMS calcd for $C_{12}H_{13}NO_5$ (M^+): 251.079373. Found: 251.080030.

Method B: To a stirred solution of **5b** (0.25 g, 0.54 mmol) in DME (2 mL) was added 1N aq. LiOH (0.06 g, 2.68 mmol) and the mixture was stirred for 2 h. The reaction mixture was taken in EtOAc (10 mL), washed with dil. HCl (5 mL) and water (10 mL). Work-up and purification as reported in the previous experiment gave **11** (0.11 g, 91%), which was esterified with DMAP (5 mg), absolute ethanol (1 mL) and DCC (0.09 g, 0.45 mmol) at 0°C. Work-up and purification as reported in the previous experiment resulted in **12** (0.11 g, 94%), whose spectral data were comparable in all respects with the sample prepared earlier including rotation and HPLC.

4.16. Synthesis of (±)-ethyl-2-hydroxy(4-nitrophenyl)-methylacrylate 12

To a stirred solution of 4-nitro benzaldehyde **5** (1.0 g, 6.62 mmol) in dry THF (6 mL) were added DABCO (0.15 g, 1.32 mmol), ethyl acrylate (0.8 mL, 7.28 mmol) and the mixture was stirred for 24 h. Solvent was removed and the residue was purified by column chromatography (silica gel, hexane:EtOAc, 8.5:1.5) to afford the adduct (±)-**12** (1.62 g, 97%) as a syrup, whose spectral data were identical with **12** prepared earlier.

4.17. Kinetic resolution of (±)-ethyl 2-hydroxy(4-nitrophenyl)methylacrylate 12 with (+)-DIPT

To a stirred suspension of activated 4 Å MS (0.30 g) in CH_2Cl_2 (5 mL) was added $Ti(OPr^i)_4$ (0.045 g, 0.15 mmol) at room temperature, the mixture was cooled to −20°C and treated with (+)-DIPT (0.046 g, 0.20 mmol) in CH_2Cl_2 (1 mL). After 30 min a solution of (±)-**12** (0.20 g, 0.79 mmol) in CH_2Cl_2 (4 mL) was added dropwise and stirred for 1 h. Cumenehydroperoxide (0.07 mL, 0.47 mmol) was added slowly and stirred for 20 h at −20°C. The reaction mixture was quenched with Me_2S (0.07 mL, 1.03 mmol) and the mixture was stirred for 30 min at the same temperature. To this mixture were sequentially added 10% aq. tartaric acid (1 mL), NaF (3 g) and the mixture was vigorously stirred for 3 h at room temperature. The precipitate was filtered through a pad of Celite and washed with ether (25 mL). The ether layer was washed with saturated $NaHCO_3$ (10 mL), brine (10 mL), dried (Na_2SO_4), evaporated and the resulting residue was purified by column chromatography (silica gel, hexane: EtOAc, 8.5:1.5). First eluted was (*R*)-**12** (0.08 g, 40%) as a syrup, $[\alpha]_D=+16.2$ (*c* 0.5, $CHCl_3$), HPLC: rt, 27.2 (97%). Second eluted was epoxy alcohol **13** (0.09 g, 41%) as a syrup. $[\alpha]_D=-15.1$ (*c* 0.6, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 8.2 (d, 2H, $J=9.0$ Hz, Ar-H), 7.64 (d, 2H, $J=10.0$ Hz, Ar-H), 5.3 (d, 1H, $J=6.0$ Hz, benzylic), 4.15 (q, 2H, -CH_2-), 3.15 (d, 2H, $J=7.0$ Hz, epoxy), 2.92 (d, 1H, $J=7.5$ Hz, -OH), 1.24 (t, 3H, $J=7.5$ Hz, -CH_3). Anal. calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.9. Found: C, 53.61; H, 4.22%.

4.18. Kinetic resolution of (±)-12 with (−)-DIPT

Sharpless kinetic resolution of (±)-**12** (0.30 g, 1.1 mmol) as in the previous experiment with (−)-DIPT (0.07 g, 0.30 mmol), TIP (0.07 mL, 0.24 mmol) and cumenehydroperoxide (0.13 mL, 0.72 mmol) after column chromatography, first afforded (*S*)-**12** (0.15 g, 44%) as a syrup, $[\alpha]_D=-12.2$ (*c* 0.8, $CHCl_3$); HPLC: rt, 31 (75%). Second eluted was epoxy alcohol **14** (0.11 g, 34%) as a syrup. $[\alpha]_D=+19.1$ (*c* 0.7, $CHCl_3$). Anal. calcd for $C_{12}H_{13}NO_6$. Found: C, 53.58; H, 4.57%.

4.19. Ethyl-2-hydroxy(2-nitrophenyl)methylacrylate 16

To a solution of **4a** (0.10 g, 0.22 mmol) in DME (2 mL) was added LiOH (0.024 g, 1.07 mmol) and the mixture was stirred for 2 h. Work-up and purification as described for **11** gave 2-hydroxy(2-nitrophenyl)methylacrylic acid (**15**; 0.05 g, 96%) as a syrup. ^1H NMR (200 MHz, $CDCl_3$): δ 7.9 (br.d, 1H, $J=7.0$ Hz, Ar-H), 7.78 (t, 1H, Ar-H), 7.69 (t, 1H, Ar-H), 7.53–7.44 (m, 1H, Ar-H), 6.52 (s, 1H, olefinic), 6.18 (s, 1H, olefinic), 5.85 (s, 1H, benzylic).

To a solution of **15** (0.10 g, 0.44 mmol) in CH_2Cl_2 (2 mL) were added DCC (0.09 g, 0.45 mmol), DMAP (5 mg) and EtOH (2 mL) and the mixture was stirred for 2 h at 20°C. Work-up and purification as described for **12** gave **16** (0.11 g, 96%) as a syrup. $[\alpha]_D=+3.7$ (*c* 0.5, $CHCl_3$); ^1H NMR (200 MHz $CDCl_3$): δ 7.98 (d, 1H, $J=8.09$ Hz, Ar-H), 7.78 (d, 1H, $J=7.62$ Hz, Ar-H), 7.68 (t, 1H, Ar-H), 7.51 (t, 1H, Ar-H), 6.38 (s, 1H, olefinic), 6.19 (s, 1H, olefinic), 5.75 (s, 1H, benzylic), 4.19 (q, 2H, -CH_2-), 3.48 (br.s, 1H, -OH), 1.28 (t, 3H, $J=8.57$ Hz, -CH_3). Anal. calcd for $C_{12}H_{13}NO_5$: C, 57.37, H, 5.22. Found: C, 57.30; H, 5.18%.

4.20. 2-Hydroxy(phenyl)methylacrylic acid 17

To a solution of **7a** (0.20 g, 0.48 mmol) in DME (3 mL) was added LiOH (0.06 g, 2.38 mmol) and stirred for 2 h, work-up and purification as described for **11** gave **17** (0.08 g, 94%) as a syrup. $[\alpha]_D=-1.2$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.35 (m, 5H, Ar-H), 6.32 (s, 1H, olefinic), 5.78 (s, 1H, olefinic), 5.5 (s, 1H, benzylic), 2.96 (br.s, 1H, -OH).

4.21. Ethyl 2-[2-nitro-5-propoxyphenyl(hydroxy)methyl]-acrylate 19

To a solution of **9a** (0.15 g, 0.29 mmol) in DME (2 mL) was added LiOH (0.04 g, 1.47 mmol) and the mixture was stirred at room temperature for 2 h, work-up and purification as described for **11** gave 2-[2-nitro-5-propoxyphenyl(hydroxy)methyl]acrylic acid (**18**; 0.07 g, 94%) as a syrup. ^{1}H NMR ($CDCl_3$): δ 8.1 (br.d, 1H, $J=10$ Hz, Ar-H), 7.28 (d, 1H, $J=4.5$ Hz, Ar-H), 6.91 (d, 1H, $J=1.5$ Hz, Ar-H), 6.41 (s, 1H, olefinic), 5.62 (s, 1H, olefinic), 5.33 (s, 1H, benzylic), 4.06 (t, 2H, $J=7.5$ Hz, -CH_2-O-), 3.5 (br.s, 1H, -OH), 1.87–1.78 (m, 2H, -CH_2), 1.13 (t, 3H, $J=8.0$ Hz, -CH_3).

To a solution of **18** (0.10 g, 0.37 mmol) in CH_2Cl_2 (2 mL) were added DCC (0.08 g, 0.37 mmol), DMAP (5 mg) and EtOH (2 mL) and the mixture was stirred for 2 h at 20°C. Work-up and purification as described for **12** gave **19** (0.11 g, 95%) as a syrup. $[\alpha]_D=-3.31$ (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.1 (br.d, 1H, $J=10.0$ Hz, Ar-H), 7.28 (d, 1H, $J=4.50$ Hz, Ar-H), 6.92 (d, 1H, $J=1.5$ Hz, Ar-H), 6.4 (s, 1H, olefinic), 5.6 (s, 1H, olefinic), 5.32 (s, 1H, benzylic), 4.28 (q, 2H), 4.05 (t, 2H, $J=7.5$ Hz, -CH_2-O-), 3.5 (br.s, 1H, -OH), 1.86 (m, 2H, -CH_2-), 1.32 (t, 3H, $J=4.0$ Hz, -CH_3), 1.11 (t, 3H, $J=8.0$ Hz, -CH_3). Anal. calcd for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19. Found: C, 58.11; H, 6.06%.

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