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Asymmetric Baylis–Hillman reactions using (*R*)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl) benzoic acid acrylate derivatives in solution and on solid support

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Abstract—The influence of several variables on the course of the Baylis–Hillman reaction between the (*R*)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl) benzoic acid acrylate derivatives (*R*)-**2** and (*R*)-**3** and aromatic aldehydes has been investigated both in solution and on solid support: these resulted in comparable results with the formation of adducts in high yield and moderate selectivity.

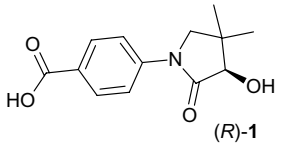
1. Introduction

The Baylis–Hillman reaction allows the direct preparation of β-hydroxy-α-methylene carbonyl compounds by the base-catalyzed reaction of α,β-unsaturated carbonyl compounds with aldehydes.[1] These functionalized Baylis–Hillman products are versatile starting materials for the synthesis of a variety of natural and nonnatural target molecules.[2]

The asymmetric version of the Baylis–Hillman reaction has attracted much attention in recent years.[3] Among these methods, the reaction of chiral acrylate with an achiral aldehyde is a conventional strategy. However, only a few examples result in significant amounts of enantiopure β-hydroxy-α-methylene carbonyl compounds. Indeed, moderate diastereoselectivity was obtained using bornyl or sugar acrylate esters[4] while the use of pure menthyl acrylate, in some cases, resulted in acceptable diastereoisomeric excesses.[5] Alternatively, by using Oppolzer's sultame as the chiral auxiliary and various aldehydes both Leahy et al.[6] and subsequently Chen et al.[7] using a novel camphor derivative, obtained the corresponding compounds with high stereoselectivity.

2. Results and discussion

We have recently reported the preparation of a new enantiopure chiral auxiliary, the (*R*)- or (*S*)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl) benzoic acid **1** and found that the acrylate derivative was an efficient dienophile under Diels–Alder reaction conditions both in solution and on solid support.[8] Compound **1** has a carboxylic acid function that can be protected in solution or can be used for attachment to an amine-functionalized insoluble polymer.



(*R*)-**1**

As part of our programme directed towards the development of asymmetric reactions[9] using auxiliary **1**, we planned to examine the asymmetric Baylis–Hillman reaction with the corresponding acrylates **2** and **3** as chiral-activated alkenes, respectively, in solution or in solid phase synthesis conditions.

To date and to the best of our knowledge, there are no examples of asymmetric Baylis–Hillman reaction using a polymer supported chiral acrylate. Some recent examples describe the synthesis of racemic compounds on

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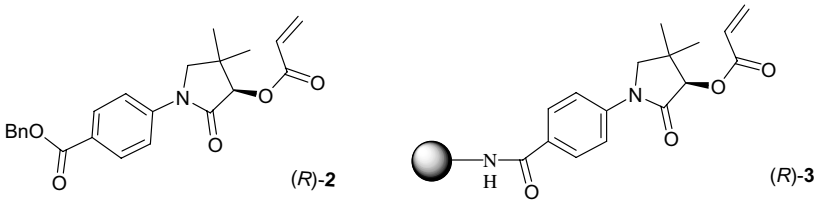


solid support.[10] The use of a supported chiral auxiliary is an attractive approach since it allows easy elimination of by-products and excess reagents, facile separation and recovery of the chiral material and simple isolation of the desired compound.

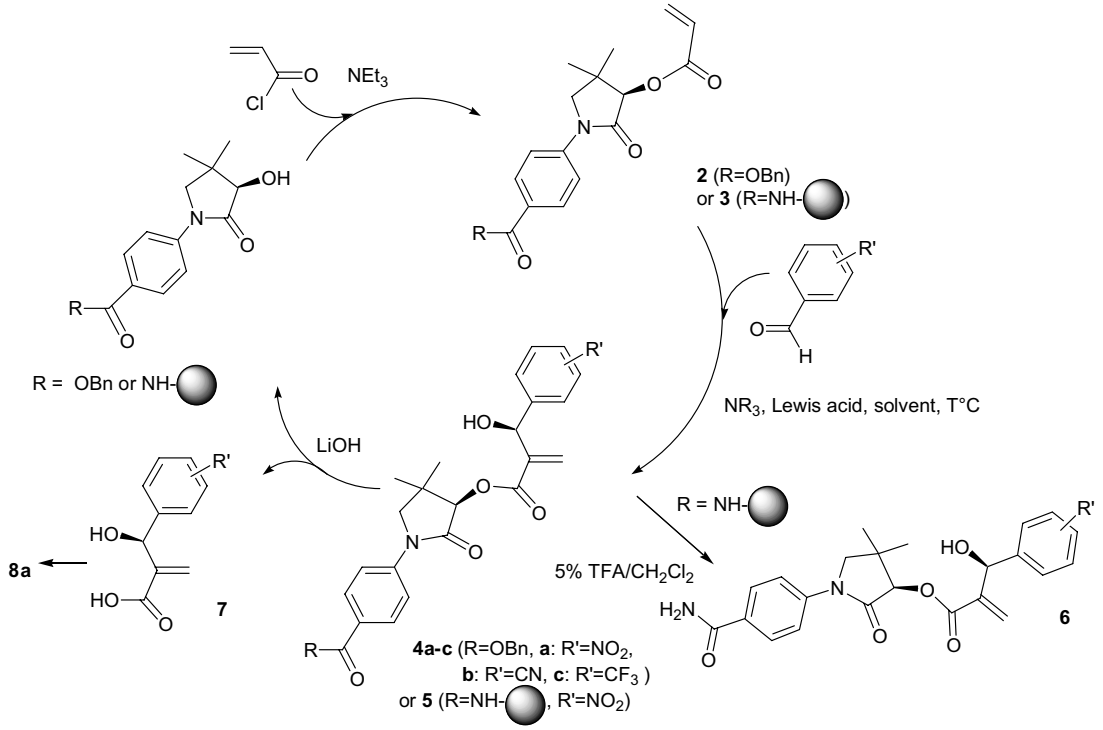
The enantiomerically pure (*R*)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl) benzoic acid (*R*)-**1**, the corresponding acrylate benzyl ester (*R*)-**2** and the supported acrylic ester (*R*)-**3** were prepared as previously described.[8b] We used a Rink amide resin[11] because the benzhydrylamine bond created between the alcohol and the polymer remained stable under the reaction conditions and during the final base hydrolysis of the ester bond (LiOH, H_2O/THF) (Scheme 1). Furthermore, removal of compound **6** from resin **5** could be performed in an acidic medium (5% TFA in CH_2Cl_2) (Scheme 1). This strategy was of great help for the control of the different solid phase synthetic steps.

Application of the Baylis–Hillman reaction is often limited by slow rates and moderate substrate-dependent yields. Generally, the reaction rate was significantly increased using nucleophilic nonhindered bases, such as 1,4-diazabicyclo[2.2.2]octane (DABCO), the most common employed catalyst, or 3-hydroxyquinuclidine (3-HQD).[1,3] When using activated alkenes and/or electrophiles, excess of catalyst, high pressure or microwave irradiation, further improvements in yields were observed.[1]

The influence of several variables on the course of the reaction (Scheme 1) between compounds (*R*)-**2** and *p*-nitrobenzaldehyde used as a representative aldehyde was investigated. The nature and the amount of catalyst, the nature of the solvent and the absence or presence of Lewis acids were studied. The results of these experiments are summarized in Table 1.

The reaction of *p*-nitrobenzaldehyde with acrylate (*R*)-**2** in the presence of 0.2 equiv of 3-HQD in DMF (Table 1, entry 2) was faster than when using DABCO (Table 1, entry 1). This effect, already observed in the presence of hydrogen donors such as 3-HQD, has been explained by a stabilization of the enolate intermediate or by activation of the aldehyde resulting from the formation of hydrogen bonds.[1c,3]

When changing DMF with DMSO, we observed both a significant increase in the rate and in the stereoselectivity (Table 1, entries 1, 2, 5 and 6). When the temperature was lowered, the reaction became slower and a moderate



Scheme 1. Baylis–Hillman reaction between the acrylate derivatives (*R*)-**2** and (*R*)-**3** and aldehydes in solution or on solid support.

Table 1. Baylis–Hillman reaction of aldehydes[a] with the acrylate (*R*)-**2**

Entry	R′	NR_3 (equiv)	Lewis acid (equiv)	Solvent (temperature)	Yield[b] % (reaction time h)	**4** (% de)[13]
1	NO_2	DABCO (0.2)	/	DMF (rt)	100 (36)	23
2	NO_2	3-HQD (0.2)	/	DMF (rt)	100 (18)	20
3	NO_2	3-HQD (0.2)	/	DMF (0 °C)	80 (18)	30
4	NO_2	3-HQD (0.2)	/	DMF (−40 °C)	39 (36)	40
5	NO_2	DABCO (0.2)	/	DMSO (rt)	100 (18)	36
6	NO_2	3-HQD (0.2; 1)	/	DMSO (rt)	100 (4; 1)	36
7	NO_2	3-HQD (0.2; 1)	/	ACN (rt)	100 (18; 5)	26
8	NO_2	3-HQD (0.2)	/	CH_2Cl_2 (rt)	100 (18)	5
9	NO_2	3-HQD (0.2)	/	THF/H_2O (rt)	100 (18)	28
10	NO_2	3-HQD (0.2)	/	IPA/DMSO	100 (18)	30
11	NO_2	3-HQD (0.2)	$La(OTf)_3$ (0.2)	DMSO (rt)	43 (4); 64 (18); 90 (140)	40; 38; 34
12	NO_2	DABCO (0.2)	$La(OTf)_3$ (0.2)	DMSO (rt)	82 (18)	37
13	NO_2	3-HQD (0.2)	$La(OTf)_3$ (1)	DMSO (rt)	41 (40); 48 (88)	42; 36
14	NO_2	DABCO (0.2)	$La(OTf)_3$ (1)	DMSO (rt)	32 (1); 35 (5); 45 (140)	48; 44; 40
15	**NO_2**	**DABCO (0.4)**	**$La(OTf)_3$ (1)**	**DMSO (rt)**	**71 (1); 93 (4)**	**40; 38**
16	**CN**	**DABCO (0.4)**	**$La(OTf)_3$ (1)**	**DMSO (rt)**	**80 (24); 94 (120)**	**36**
17	**CF_3**	**DABCO (0.4)**	**$La(OTf)_3$ (1)**	**DMSO (rt)**	**58 (5); 74 (18); 82 (120)**	**34**

[a] 10 equiv.
[b] Determined by HPLC analysis.

yield that remained unchanged after 36 h at −40 °C was obtained in the presence of 3-HQD. However an improvement in stereoselectivity from 20% to 40% was observed by decreasing the reaction temperature (Table 1, entries 2–4). Changing the solvent had little or no effect on the reaction rate or on the stereoselectivity except when CH_2Cl_2 was used (entry 8). In this case there was no stereoselectivity (Table 1, entries 7–10).

In an attempt to increase the stereoselectivity of the reaction, we investigated the effects of lanthanide triflate used as a co-catalyst.[12] When 0.2 equiv of $La(OTf)_3$ was used, no effect was observed with DABCO (Table 1, entries 5 and 12), whereas a decrease in the yield was observed with 3-HQD (43% instead of 100% after 4 h) (Table 1, entries 6 and 11). Furthermore, with 1 equiv of $La(OTf)_3$, an increase of the de value parallel to a decrease in the yield was observed. This was even more marked with DABCO (Table 1, entries 5, 6 and 13, 14). However, when longer reaction times were applied, chemical yields were higher but stereoselectivity became lower (Table 1, entries 13 and 14). Finally, the best result was observed when using 0.4 equiv of DABCO with 1 equiv of $La(Otf)_3$, leading to high yield and moderate de (Table 1, entry 15).

The β-hydroxy-α-methylene carbonyl derivatives **4a** (R′ = NO_2) were isolated pure after column chromatography on silica gel using hexane/ethyl acetate (1/1) as eluent (37% yield, (3′*R*,2*S*)/(3′*R*,2*R*)-**4a**: 67/33). Under these conditions, diastereoisomer (3′*S*,2*R*)-**4a** (12% yield, 92% de) was also isolated. The structure of ester **4a** (R′ = NO_2) was characterized by ^1H and ^{13}C NMR and MS analysis. The diastereoisomeric ratio was determined from crude or purified products by chiral HPLC or ^1H NMR analysis.[13]

To ascertain the absolute configuration of the major ester when using the chiral auxiliary (*R*)-**2**, adduct **4a** was subjected to saponification with LiOH at room temperature to yield the corresponding β-hydroxy-α-methylene carboxylic acid derivative **7a** (R′ = NO_2), which on reaction with trimethylsilyldiazomethane ($TMSCHN_2$) was converted into its methyl ester **8a**. Comparison with the literature data on chiral HPLC separation of the racemic mixture of **8a**, showed the major isomer to have an (*S*)-configuration.[14]

Two other aromatic aldehydes were subjected to the same reactions to yield esters **4b** (R′ = CN) and **4c** (R′ = CF_3) (Table 1, entries 16 and 17). Esters **4b** [145 mg, 42% yield, (3′*R*,2*S*)/(3′*R*,2*R*)-**4b**: 65/35] and **4c** [126 mg, 33.6% yield, (3′*R*,2*S*)/(3′*R*,2*R*)-**4c**: 65/35] were obtained pure after column chromatography on silica gel using hexane/ethyl acetate (1/1) as eluent. These results showed that a decrease in electronegativity of the benzene ring substituent led to a decrease of the reaction rate. The enantiomerically enriched compounds (3′*R*,2*S*)-**4b** (9% yield, 95% de) and (3′*R*,2*S*)-**4c** (6% yield, 94% de) were obtained during this purification step. The absolute configuration (3′*R*,2*S*) of the major ester was assigned by analogy with **4a** after chiral HPLC, ^1H and ^{13}C NMR analysis.

We investigated this methodology on solid support using a Rink amide resin, as to the best of our knowledge, this is the first solid phase asymmetric version of the Baylis–Hillman reaction using a chiral auxiliary. Polymer bound chiral acrylic ester (*R*)-**3** was reacted with an excess of *p*-nitrobenzaldehyde varying the solvent and the amount of base in the presence or absence of a Lewis acid. The results of these experiments are summarized in Table 2.

Using a large excess of DABCO, the same stereoselectivity was observed both in DMSO or DMF with the concentration only affecting the reaction rate (Table 2, entries 1–6). As previously reported, when reactions were carried out in solution, a significant increase of the reaction rate was observed using DMSO or 3-HQD although the stereoselectivity became slightly lower in the presence of 3-HQD (Table 2, entries 3 and 4).

Table 2. Baylis–Hillman reaction of *p*-nitrobenzaldehydes[a] with the polymer bound acrylate (*R*)-**3**[b]

Entry	NR_3 (equiv)	Lewis acid (equiv)	Solvent[c]	Yield[d]% (reaction time h)	**6** (% de)[13]
1	DABCO (10)	/	4 mL DMF	36 (48); 95 (120)	28
2	DABCO (10)	/	4 mL DMSO	97 (5); 100 (18)	28
3	3-HQD (10)	/	4 mL DMF	70 (5); 100 (18)	24
4	3-HQD (10)	/	4 mL DMSO	100 (5)	24
5	DABCO (10)	/	15 mL DMSO	80 (18); 100 (42)	28
6	DABCO (10)	/	15 mL DMF	20 (5); 90 (144)	28
7	**DABCO (1)**	**/**	**4 mL DMF**	**90 (48); 95 (72)**	**34**
8	DABCO (1)	/	10 mL DMF	17 (24); 61 (144)	44; 33
9	3-HQD (1)	/	10 mL DMF	41 (48); 65 (192)	30; 26
10	3-HQD (1)	/	10 mL DMSO	64 (24); 100 (96)	30; 28
11	DABCO (0.4)	/	4 mL DMF	74 (192)	24
12	DABCO (0.4)	$La(OTf)_3$ (0.2)	10 mL DMF	22 (144)	20
13	DABCO (0.4)	$La(OTf)_3$ (0.2)	10 mL DMSO	30 (96); 35 (168)	34; 32

[a] 16 equiv.
[b] 200 mg of the polymer bound acrylate (0.143 mmol).
[c] Room temperature.
[d] Determined by HPLC analysis of the crude product isolated after acid cleavage of the benzhydrylamine bond.

In contrast to that observed in solution conditions, on solid support, long reaction times as well as lower selectivity were observed using a small amount of catalyst (Table 2, entry 11) while no improvement was obtained in the presence of lanthanide triflate as a co-catalyst (Table 2, entries 12 and 13). The best result was obtained when using 1 equiv of DABCO in DMF leading to high yield but moderate de (Table 2, entry 7).

3. Conclusion

In conclusion, we have reported the use of (*R*)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl) benzoic acid acrylate derivatives for the stereoselective Baylis–Hillman reaction in solution and on solid support. Solution synthesis has been successfully transferred to the solid phase. The formation of adducts in high yield and moderate selectivity (24–44% de) was similar in solution to solid support. Although the reaction was not totally diastereoselective the main diastereoisomeric product can be partially isolated in high de, but in low yield which limits application of this methodology.

4. Experimental

4.1. General

All reagents were used as purchased from commercial suppliers without further purification. Solvents were dried and purified by conventional methods prior to use. Melting points were determined with a Kofler Heizbank apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 341 polarimeter. ^1H or ^{13}C NMR spectra ($^1H/^{13}C$ 2D-correlations) were recorded with a Bruker A DRX 400 spectrometer using the solvent as the internal reference. Data are reported as follows: chemical shifts (δ) in parts per million, coupling constants (J) in hertz. The ESI mass spectra were recorded with a platform II quadrupole mass spectrometer (Micromass, Manchester, UK) fitted with an electrospray source. HPLC analyses were performed with a Waters model 510 instrument with a variable detector at 214 nm using: column A: reversed phase Nucleosil C_{18}, 5 μm (250 × 10 mm), flow: 1 mL/min, H_2O/CH_3CN/0.1% TFA gradient 0→100% (15 min) and 100% (4 min); column B: Chiralcel OD-R, 5 μm, (250 × 10 mm), flow: 1 mL/min, eluent I: H_2O (0.1% TFA)/CH_3CN (0.1% TFA) 40/60; eluent II: H_2O (0.1% TFA)/CH_3CN (0.1% TFA) 50/50; eluent III: H_2O (0.1% TFA)/CH_3CN (0.1% TFA) 70/30 column C: Chiralcel OD, flow: 0.5 mL/min, 2-propanol–hexane 2:98–4:96 for 40 min, 4:96 for 20 min, 4:96–10:90 for 30 min. The enantiomerically pure chiral auxiliary (*R*)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl) benzoic acid (*R*)-**1**, the corresponding acrylate benzyl ester (*R*)-**2** and the Rink amide supported acrylic ester (*R*)-**3** were prepared as previously described.[8b]

4.2. General procedure for Baylis–Hillman reaction of the acrylate ester (*R*)-2 with aldehydes

To a solution of acrylate (*R*)-**2** (235 mg, 0.6 mmol) in dry DMSO or DMF (3.5 mL) were added DABCO or 3-HQD and the aldehyde (10 equiv, 6 mmol) at room temperature under an argon atmosphere. The mixture was stirred at room temperature and the reaction monitored by HPLC (column A). The residue diluted with AcOEt (15 mL) was washed with 0.1 M HCl solution (10 mL) and water (10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo.

4.3. 4-(3-[2-(4-Nitrophenyl)hydroxymethylacryloyloxy]-4,4-dimethyl-2-oxopyrrolidin-1-yl) benzoic acid benzyl ester 4a

Following the general procedure using DABCO (26.4 mg, 0.24 mmol, 0.4 equiv), $La(OTf)_3$ (345.6 mg, 1 equiv, 0.6 mmol) and DMSO from (*R*)-**2** and *p*-nitrobenzaldehyde, a pure mixture of ester **4a** (121 mg, 37% yield, (3′*R*,2*S*)/(3′*R*,2*R*)-**4a**: 67/33) together with diastereoisomer (3′*R*,2*S*)-**4a** (40 mg, 12% yield, 92% de) were

isolated after column chromatography on silica gel [eluting with ethyl acetate/hexane (1/1)] of the crude product (>100% yield, (3′*R*,2*S*)/(3′*R*,*R*)-**4a**: 69/31).

4.3.1. Compound (3′*R*,2*S*)-4a. Colourless oil, 92% de; $[\alpha]_D^{20} = -22$ (*c* 0.3, CH_2Cl_2); MS (ESI) *m/z*: 545.1 [(M+H)$^+$]; t_R (HPLC column A) 14.1 min; t_R (HPLC column B, eluent I) 17.7 min; ^{1}H NMR ($CDCl_3$): δ 0.76 (s, 3H, C*H*$_3$), 1.13 (s, 3H, C*H*$_3$), 3.44 (d, *J* = 9.7, 1H, HC*H*-5), 3.55 (d, *J* = 9.7, 1H, HC*H*-5), 5.29 (s, 2H, OC*H*$_2$C$_6$H$_5$), 5.32 (s, 1H, C*H*-3), 5.60 (br d, 1H, C*H*OH), 5.97 (s, 1H, HC*H*=), 6.51 (s, 1H, HC*H*=), 7.32 (m, 5H, H-arom), 7.54 (m, 2H, H-arom), 7.63 (m, 2H, H-arom), 7.98 (m, 2H, H-arom), 8.14 (m, 2H, H-arom); ^{13}C NMR ($CDCl_3$): δ 20.83, 24.56 (*C*H$_3$), 37.52 (*C*-4), 57.48 (*C*-5), 66.77 (O*C*H$_2$C$_6$H$_5$), 73.19 (C*H*OH), 78.99 (*C*-3), 118.44 (*C*H-arom), 123.62 (*C*H-arom), 126.36 (C=), 127.01, 127.74, 128.20, 128.63, 129.28 (*C*H-arom), 130.85 (H$_2$*C*=), 135.99, 140.51, 142.65, 147.36, 149.09 (*C*-arom), 164.66, 165.74, 169.22 (*C*O); HRMS (FAB) Calcd for $C_{30}H_{29}N_2O_8$ (MH$^+$) 545.1924. Found 545.1945.

4.3.2. Compound (3′*R*,2*R*)-4a.[15] t_R (HPLC column A) 14.1 min; t_R (HPLC column B, eluent I) 16.3 min; ^{1}H NMR ($CDCl_3$): δ 1.00 (s, 3H, C*H*$_3$), 1.18 (s, 3H, C*H*$_3$), 3.48 (d, *J* = 9.7, 1H, HC*H*-5), 3.58 (d, *J* = 9.7, 1H, HC*H*-5), 5.29 (s, 2H, OC*H*$_2$C$_6$H$_5$), 5.38 (s, 1H, C*H*-3), 5.69 (br d, 1H, C*H*OH), 5.70 (s, 1H, HC*H*=), 6.44 (s, 1H, HC*H*=), 7.32 (m, 5H, H-arom), 7.54 (m, 2H, H-arom), 7.63 (m, 2H, H-arom), 7.98 (m, 2H, H-arom), 8.14 (m, 2H, H-arom); ^{13}C NMR ($CDCl_3$): δ 21.15, 24.68 (*C*H$_3$), 37.52 (*C*-4), 57.42 (*C*-5), 66.77 (O*C*H$_2$C$_6$H$_5$), 72.03 (C*H*OH), 78.99 (*C*-3), 118.44 (*C*H-arom), 123.68 (*C*H-arom), 126.36 (C=), 127.01, 127.74, 128.20, 128.31, 128.59, 129.28 (*C*H-arom), 128.63 (H$_2$*C*=), 135.99, 141.15, 142.65, 147.94, 149.09 (*C*-arom), 165.16, 165.74, 169.22 (*C*O).

4.4. 4-(3-[2-(4-Cyanophenyl)hydroxymethylacryloyloxy]-4,4-dimethyl-2-oxo-pyrrolidin-1-yl) benzoic acid benzyl ester 4b

Following the general procedure using DABCO (26.4 mg, 0.24 mmol, 0.4 equiv), La(OTf)$_3$ (345.6 mg, 1 equiv, 0.6 mmol) and DMSO from (*R*)-**2** and 4-cyanobenzaldehyde, a pure mixture of the ester **4b** (145 mg, 42% yield, (3′*R*,2*S*)/(3′*R*,2*R*)-**4b**: 65/35) together with diastereoisomer (3′*R*,2*S*)-**4b** (13.1 mg, 9% yield, 95% de) were isolated after column chromatography on silica gel (eluting with ethyl acetate/hexane (1/1)) of the crude product [>100% yield, (3′*R*,2*S*)/(3′*R*,2*R*)-**4b**: 68/32].

4.4.1. Compound (3′*R*,2*S*)-4b. Colourless oil, 95% de; $[\alpha]_D^{20} = -41$ (*c* 0.3, CH_2Cl_2); MS (ESI) *m/z*: 524.8 [(M+H)$^+$]; t_R (HPLC column A) 13.7 min; t_R (HPLC column B, eluent II) 40.5 min; ^{1}H NMR ($CDCl_3$): δ 0.75 (s, 3H, C*H*$_3$), 1.15 (s, 3H, C*H*$_3$), 3.42 (d, *J* = 9.7, 1H, HC*H*-5), 3.52 (d, *J* = 9.7, 1H, HC*H*-5), 3.71 (br d, 1H, OH), 5.27 (s, 2H, OC*H*$_2$C$_6$H$_5$), 5.30 (s, 1H, C*H*-3), 5.54 (br d, 1H, C*H*OH), 5.95 (s, 1H, HC*H*=), 6.47 (s, 1H, HC*H*=), 7.32 (m, 5H, *H*-arom), 7.50 (m, 4H, *H*-arom), 7.57 (m, 2H, *H*-arom), 8.00 (m, 2H, *H*-arom); ^{13}C NMR ($CDCl_3$): δ 20.82, 24.54 (*C*H$_3$), 37.46 (*C*-4), 57.43 (*C*-5), 66.76 (O*C*H$_2$C$_6$H$_5$), 73.13 (C*H*OH), 78.91 (*C*-3), 111.33 (CN), 118.45 (*C*H-arom), 118.77 (*C*-arom), 126.43 (C=), 126.94, 127.66, 128.20, 128.64 (*C*H-arom), 129.01 (H$_2$*C*=), 130.83, 132.29 (*C*H-arom), 135.99, 141.16, 142.76, 147.21 (*C*-arom), 164.69, 165.75, 169.25 (*C*O); HRMS (FAB) Calcd for $C_{31}H_{29}N_2O_6$ (MH$^+$) 525.5811. Found 525.2200.

4.4.2. Compound (3′*R*,2*R*)-4b.[15] t_R (HPLC column A) 13.7 min; t_R (HPLC column B, eluent II) 37.4 min; ^{1}H NMR ($CDCl_3$): δ 0.95 (s, 3H, C*H*$_3$), 1.19 (s, 3H, C*H*$_3$), 3.46 (d, *J* = 9.7, 1H, HC*H*-5), 3.56 (d, *J* = 9.7, 1H, HC*H*-5), 3.58 (br d, 1H, OH), 5.27 (s, 2H, OC*H*$_2$C$_6$H$_5$), 5.35 (s, 1H, C*H*-3), 5.62 (br s, 1H, C*H*OH), 5.73 (s, 1H, HC*H*=), 6.43 (s, 1H, HC*H*=), 7.31 (m, 5H, *H*-arom), 7.49 (m, 4H, *H*-arom), 7.60 (m, 2H, *H*-arom), 8.00 (m, 2H, *H*-arom); ^{13}C NMR ($CDCl_3$): δ 21.10, 24.65 (*C*H$_3$), 37.46 (*C*-4), 57.43 (*C*-5), 66.76 (O*C*H$_2$C$_6$H$_5$), 72.09 (C*H*OH), 78.91 (*C*-3), 111.70 (CN), 118.45 (*C*H-arom), 118.77 (*C*-arom), 126.43 (C=), 126.94, 127.66, 128.20, 128.31 (*C*H-arom), 128.44 (H$_2$*C*=), 128.64 (*C*H-arom), 130.83, 132.22 (*C*H-arom), 135.99, 141.16, 142.70, 146.17 (*C*-arom), 165.14, 165.75, 169.33 (*C*O).

4.5. 4-(3-[2-(4-Trifluoromethylphenyl)hydroxymethyl-acryloyloxy]-4,4-dimethyl-2-oxopyrrolidin-1-yl) benzoic acid benzyl ester 4c

Following the general procedure using DABCO (26.4 mg, 0.24 mmol, 0.4 equiv), La(OTf)$_3$ (345,6 mg, 1 equiv, 0.6 mmol) and DMSO from (*R*)-**2** and 4-trifluoromethylbenzaldehyde, a pure mixture of ester **4c** (126 mg, 34% yield, (3′*R*,2*S*)/(3′*R*,2*R*)-**4c**: 65/35) together with diastereoisomer (3′*R*,2*S*)-**4c** (22.5 mg, 6% yield, 94% de) were isolated after column chromatography on silica gel [eluting with ethyl acetate/hexane (1/1)] of the crude product [>100% yield, (3′*R*,2*S*)/(3′*R*,2*R*)-**4c**: 67/33].

4.5.1. Compound (3′*R*,2*S*)-4c. Colourless oil; 94% de; $[\alpha]_D^{20} = -21$ (*c* 0.56, CH_2Cl_2); MS (ESI) *m/z*: 545.1 [(M+H)$^+$]; t_R (HPLC column A) 14.8 min; t_R (HPLC column B, eluent I) 20.0 min; ^{1}H NMR ($CDCl_3$): δ 0.73 (s, 3H, C*H*$_3$), 1.14 (s, 3H, C*H*$_3$), 3.40 (d, *J* = 9.7, 1H, HC*H*-5), 3.54 (d, *J* = 9.7, 1H, HC*H*-5), 5.27 (s, 2H, OC*H*$_2$C$_6$H$_5$), 5.30 (s, 1H, C*H*-3), 5.56 (br s, 1H, C*H*OH), 5.92 (s, 1H, HC*H*=), 6.46 (s, 1H, HC*H*=), 7.31 (m, 5H, *H*-arom), 7.49 (m, 4H, *H*-arom), 7.60 (m, 2H, *H*-arom), 8.00 (m, 2H, *H*-arom); ^{13}C NMR ($CDCl_3$): δ 20.29, 24.52 (*C*H$_3$), 37.46 (*C*-4), 57.44 (*C*-5), 66.76 (O*C*H$_2$C$_6$H$_5$), 73.21 (C*H*OH), 78.83 (*C*-3), 118.44 (*C*H-arom), 125.37 (m, CF$_3$), 126.30 (C=), 126.83, 127.30, 128.20, 128.31, 128.63 (*C*H-arom), 128.79 (H$_2$*C*=), 130.82 (*C*H-arom), 136.00, 140.93, 141.41, 142.74, 144.79 (*C*-arom), 165.31, 169.31, 169.37 (*C*O); HRMS (FAB) Calcd for $C_{31}H_{29}NO_6F_3$ (MH$^+$) 568.1947. Found 568.1938.

4.5.2. Compound (3′*R*,2*R*)-4b.[15] t_R (HPLC column A) 14.8 min; t_R (HPLC column B, eluent I) 18.6 min; ^{1}H NMR ($CDCl_3$): δ 0.94 (s, 3H, C*H*$_3$), 1.18 (s, 3H, C*H*$_3$),

3.44 (d, $J = 9.7$, 1H, HC*H*-5), 3.51 (d, $J = 9.7$, 1H, HC*H*-5), 5.27 (s, 2H, OCH_2C$_6$H$_5$), 5.36 (s, 1H, C*H*-3), 5.64 (br s, 1H, C*H*OH), 5.73 (s, 1H, HC*H*=), 6.43 (s, 1H, HC*H*=), 7.31 (m, 5H, *H*-arom), 7.49 (m, 4H, *H*-arom), 7.60 (m, 2H, *H*-arom), 8.00 (m, 2H, *H*-arom); ^{13}C NMR ($CDCl_3$): δ 21.02, 24.61 (*C*H$_3$), 37.46 (*C*-4), 57.44 (*C*-5), 66.76 (O*C*H$_2$C$_6$H$_5$), 72.19 (C*H*OH), 78.83 (*C*-3), 118.44 (*C*H-arom), 125.37 (m, *C*F$_3$), 126.28 (*C*=), 126.83, 127.30, 128.20, 128.31, 128.63 (*C*H-arom), 128.33 (H$_2$*C*=), 130.82 (*C*H-arom), 136.00, 140.93, 141.41, 142.74, 142.80 (*C*-arom), 165.79, 169.31, 169.37 (*C*O).

4.6. General procedure for the Baylis–Hillman reaction of the supported acrylate ester (*R*)-3 with *p*-nitrobenzaldehyde

To a suspension of the supported acrylate (*R*)-**3** (1.2 g, 0.9 mmol) in dry DMSO or DMF (24 mL) was added DABCO or 3-HQD and the *p*-nitrobenzaldehyde (14.4 mmol, 16 equiv). The suspension was stirred at room temperature. The reaction was monitored by HPLC (column A) after removal of the reaction product from an aliquot of the resin by acidic cleavage of the benzhydrylamine bond. The solvent was then removed from the resin by filtration and resin **5** washed with DMF (3×30 mL), CH_2Cl_2 (3×30 mL), CH_2Cl_2/CH_3OH (8/2) (3×30 mL), CH_2Cl_2 (3×30 mL).

4.7. General procedure for the benzhydrylamine bond hydrolysis: formation of the [1-(4-carbamoylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl] 2-[(4-nitrophenyl)hydroxymethyl] acrylic acid ester 6

To resin **5** was added 30 mL of a solution of 5% TFA in dry CH_2Cl_2 and the suspension stirred for 40 min. The solution was removed from the resin by filtration and the resin washed with CH_2Cl_2 (3×30 mL). A second cleavage was realized under the same conditions. Evaporation of the combined filtrates in vacuo afforded the expected ester **6**.

A pure mixture of ester **6** (167 mg, 41% yield, (3′*R*,2*S*)/(3′*R*,2*R*)-**6**: 60/40) together with the enriched diastereoisomer (3′*R*,2*S*)-**6** (35 mg, 8.5% yield, 64% de) were isolated after column chromatography on silica gel (eluting with ethyl acetate) of the crude product (382 mg, 94% yield, (3′*R*,2*S*)/(3′*R*,2*R*)-**6**: 67/33).

4.7.1. Compound (3′*R*,2*S*)-6. 64% de; MS (ESI) *m*/*z*: 454.2 [(M+H)$^+$]; t_R (HPLC column A) 10.2 min; t_R (HPLC column B, eluent III) 23.8 min; ^{1}H NMR (CD_3COCD_3): δ 0.90 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 3.52 (d, $J = 9.7$, 1H, HC*H*-5), 3.66 (d, $J = 9.7$, 1H, HC*H*-5), 5.13 (d, $J = 5.2$, 1H, O*H*), 5.39 (s, 1H, C*H*-3), 5.68 (d, $J = 4.7$, 1H, C*H*OH), 6.12 (t, $J = J' = 1.3$, 1H, HC*H*=), 6.37 (s, 1H, HC*H*=), 6.53 (br s, 1H, HN*H*), 7.34 (br s, 1H, HN*H*), 7.63 (m, 4H, *H*-arom), 7.83 (m, 2H, *H*-arom), 8.07 (m, 2H, *H*-arom); ^{13}C NMR (CD_3COCD_3): δ 20.42, 23.57 (*C*H$_3$), 37.00 (*C*-4), 56.76 (*C*-5), 71.07 (C*H*OH), 78.47 (*C*-3), 118.28, 123.28 (*C*H-arom), 126.16 (H$_2$*C*=), 127.96, 128.29 (*C*H-arom), 129.98, 142.11, 142.69, 147.28, 150.50 (*C*-arom and *C*=), 164.48, 167.42, 168.88 (*C*O); HRMS (FAB) Calcd for $C_{23}H_{24}N_3O_7$ (MH$^+$) 454.1614. Found 454.1617.

4.7.2. Compound (3′*R*,2*R*)-6.[15] t_R (HPLC column A) 10.2 min; t_R (HPLC column B, eluent III) 21.0 min; ^{1}H NMR (CD_3COCD_3): δ 0.87 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 3.50 (d, $J = 9.6$, 1H, HC*H*-5), 3.65 (d, $J = 9.6$, 1H, HC*H*-5), 5.16 (d, $J = 5.2$, 1H, O*H*), 5.38 (s, 1H, C*H*-3), 5.68 (d, $J = 4.7$, 1H, C*H*OH), 6.10 (t, $J = J' = 1.3$, 1H, HC*H*=), 6.41 (s, 1H, HC*H*=), 6.53 (br s, 1H, HN*H*), 7.34 (br s, 1H, HN*H*), 7.63 (m, 4H, *H*-arom), 7.83 (m, 2H, *H*-arom), 8.07 (m, 2H, *H*-arom); ^{13}C NMR (CD_3COCD_3): δ 20.42, 23.64 (*C*H$_3$), 37.04 (*C*-4), 56.72 (*C*-5), 70.86 (C*H*OH), 78.50 (*C*-3), 118.25, 123.23 (*C*H-arom), 126.38 (H$_2$*C*=), 127.92, 128.24 (*C*H-arom), 129.95, 142.21, 142.57, 147.30, 150.30 (*C*-arom and *C*=), 164.50, 167.42, 168.92 (*C*O).

4.8. Methyl-2-hydroxy(4-nitrophenyl)methylacrylate 8a

To a solution of compound **4a** (0.1 mmol) in THF (1 mL) was added dropwise a solution of LiOH, H_2O (0.11 mmol, 1.1 equiv) in water (2 mL) and the mixture stirred at room temperature for 18 h. The organic solvent was then removed in vacuo and saturated aqueous $NaHCO_3$ (2 mL) was added. The mixture was washed with CH_2Cl_2 (2×5 mL). The aqueous phase was acidified (pH = 1) and then extracted with CH_2Cl_2 (2×10 mL). The combined organic phases were dried with anhydrous Na_2SO_4 and concentrated in vacuo to yield acid **7a** as a colourless oil (17 mg, 76% yield); t_R (HPLC column A) 8.6 min; ^{1}H NMR ($CDCl_3$): δ 5.60 (s, 1H, C*H*OH), 5.97 (s, 1H, HC*H*=), 6.51 (s, 1H, HC*H*=), 7.53 (d, $J = 8.7$, 2H, H-arom), 8.17 (d, $J = 8.7$, 2H, H-arom).

To a stirred solution of compound **7a** (0.05 mmol) in dry methanol (0.5 mL) was added dropwise a 2.0 M solution of trimethylsilyldiazomethane ($TMSCHN_2$) (0.10 mmol, 2 equiv) in hexane at 0 °C. The mixture was stirred at room temperature for 5 h and the organic solvent then removed in vacuo to afford the expected ester **8a** as a colourless oil. t_R (HPLC column A) 9.9 min, t_R (HPLC column C) 66.6 min (*R*) and 73.4 min (*S*); ^{1}H NMR ($CDCl_3$): δ 3.69 (s, 3H, OCH_3), 5.58 (s, 1H, C*H*OH), 5.82 (s, 1H, HC*H*=), 6.35 (s, 1H, HC*H*=), 7.52 (d, $J = 8.6$, 2H, *H*-arom), 8.15 (d, $J = 8.6$, 2H, *H*-arom).

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