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Tetrahedron
Tetrahedron 63 (2007) 3102–3107

Organocatalytic direct aldol and nitroaldol reactions between azetidine-2,3-diones and ketones or nitromethane

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Received 19 December 2006; revised 30 January 2007; accepted 7 February 2007
Available online 13 February 2007

Abstract—The reactions of enantiopure azetidine-2,3-diones with unmodified ketones or nitromethane were catalyzed by proline and *N*-methylephedrine, respectively, to give the corresponding 3-functionalized 3-hydroxy-β-lactams with good yields and total diastereoselectivities. It was observed that the use of both enantiomers of proline or of *N*-methylephedrine does result in identical levels of stereocontrol in the aldol and nitroaldol reactions.
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1. Introduction

Organocatalysis has received much interest in organic chemistry because of the obvious advantages over its metal-mediated counterpart.[1] An organocatalytic molecule that has been studied extensively is proline, which promotes a range of transformations such as the asymmetric direct aldol reaction between carbonyls and unmodified ketones.[2,3] A major limitation of this process has been the rather narrow substrate scope, involving the majority of examples reported to date simple achiral carbonyls. Thus, matching and mismatching effects remain almost unexplored in the proline-catalyzed aldol reaction.[4] On the other hand, 3-substituted 3-hydroxy-β-lactams are important substrates both for studies of biological activity[5] as well as convenient precursors for β-amino-α-hydroxy acids (isoserines),[6] therefore, being the development of practical methods for their stereocontrolled preparation of interest. Continuing with our work on the asymmetric synthesis of nitrogenated compounds of biological interest,[7] in this contribution we report the organocatalytic direct aldol and nitroaldol reactions of enantiopure azetidine-2,3-diones, which resulted in 3-functionalized 3-hydroxy-β-lactams.

2. Results and discussion

Starting materials, enantiopure azetidine-2,3-diones **1a–c**, were efficiently prepared from aromatic or aliphatic (*R*)-2,3-*O*-isopropylideneglyceraldehyde-derived imines, via Staudinger reaction with acetoxyacetyl chloride in the presence of Et_3N, followed by sequential transesterification and Swern oxidation, as we previously reported.[8] Ketones **1** are α-amino carbonyl compounds, most of which have been well-known to be both chemically and configurationally labile because of the rather acidic proton positioned α to the carbonyl group.[9] In contrast to organocatalytic direct aldolizations with aldehydes as acceptors, however, those related with ketones as acceptors have been rarely reported and thus are even more challenging.[10]

The choice of the catalyst is critical for stability of the amino carbonyl moiety because of their sensitivity to racemization. Because proline has emerged as a particularly mild and efficient catalyst of the aldol reaction mimicking the type I aldolase mechanism,[3] we decided to explore the proline-catalyzed direct aldol reaction between azetidine-2,3-diones **1** and ketones. Given chiral starting materials, we investigated whether the chiral amino acid catalyst could control the diastereoselectivity in the addition, either by enhancing or overcoming the intrinsic substrate-controlled preference. For our first example we chose azetidine-2,3-dione (+)-**1a** as a model system for the aldol reaction with acetone and optimized the reaction conditions in terms of yield and diastereomeric ratio (Scheme 1, Table 1). Taken into account the facial preference of ketones **1** when reacting with stabilized organometallics,[8] D-proline was initially selected because presumably azetidine-2,3-diones **1** and D-proline are a matched pair for diastereoselectivity induction. Indeed, the desired adduct (+)-**2a** with a quaternary stereogenic center was formed as single isomer when the reaction was catalyzed (10 mol %) by D-proline, and was conducted in

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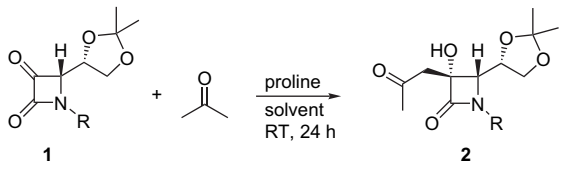
doi:10.1016/j.tet.2007.02.024

DMSO (yield 65%, Table 1, entry 1), DMF (yield 60%, Table 1, entry 2), or acetone (yield 79%, Table 1, entry 3). Acetone was elected as the solvent for all further reactions since a higher yield was obtained for aldol (+)-**2a**. The effect of the amount of the organocatalyst on the conversion rate as well as on the product ratio was studied. Slightly lower yields and prolonged reaction times were observed when the amount of catalyst was decreased (5 mol %, Table 1, entry 4). It was found that the efficiency of the process did not increase on increasing the amount of catalyst (20 mol %, Table 1, entry 5).



1 **2**

Scheme 1. Aldol reaction of azetidine-2,3-diones **1** with acetone.

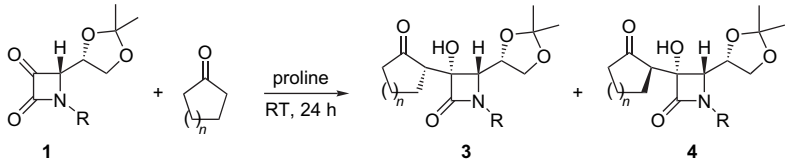
Table 1. Reaction of azetidine-2,3-diones **1** with acetone under modified proline-catalyzed aldol reaction conditions[a]

Entry	Ketone	R	Solvent	Catalyst	Product	Yield[b] (%)
1	(+)-**1a**	PMP	DMSO	D-Proline	(+)-**2a**	65
2	(+)-**1a**	PMP	DMF	D-Proline	(+)-**2a**	60
3	(+)-**1a**	PMP	Acetone	D-Proline	(+)-**2a**	79
4	(+)-**1a**	PMP	Acetone	D-Proline[c]	(+)-**2a**	70
5	(+)-**1a**	PMP	Acetone	D-Proline[d]	(+)-**2a**	79
6	(+)-**1a**	PMP	Acetone	L-Proline	(+)-**2a**	75
7	(+)-**1a**	PMP	Acetone	D,L-Proline	(+)-**2a**	76
8	(−)-**1b**	Allyl	Acetone	D-Proline	(−)-**2b**	44
9	(−)-**1b**	Allyl	Acetone	L-Proline	(−)-**2b**	48
10	(−)-**1c**	Benzyl	Acetone	D-Proline	(−)-**2c**	66
11	(−)-**1c**	Benzyl	Acetone	L-Proline	(−)-**2c**	62

[a] Proline of 10 mol % was used except otherwise stated. PMP=4-$MeOC_6H_4$.
[b] Yield of pure, isolated product with correct analytical and spectral data.
[c] Proline of 5 mol % was used. It was necessary to run the experiment for 48 h for complete disappearance of the starting α-oxo-β-lactam.
[d] Proline of 20 mol % was used.

To afford a direct comparison of the stereoselectivity of the aldol process by variation of the chirality of proline, the same reaction was also evaluated under the same conditions but using L-proline. The addition promoted by L-proline proceeded to complete conversion, giving the aldol (+)-**2a** as sole product (Table 1, entry 6). These proline-catalyzed aldol reactions are proceeding with total asymmetric induction by the substrate, with the chirality of the catalyst having no effect on the overall stereoselectivity. Thereupon, racemic proline was also examined. Aldol reaction of azetidine-2,3-dione (+)-**1a** using D,L-proline also provides adduct (+)-**2a** as single isomer (Table 1, entry 7). Similar results were obtained in the proline (L- or D-) promoted aldol reaction between acetone and different azetidine-2,3-diones **1** (Table 1, entries 8–11). The use of the achiral catalyst *N*-benzylglycine in the aldol reaction of azetidine-2,3-diones was not effective because ketones **1** were almost unaffected.[11] Slower reactions and decreased chemical yields of the aldol adducts were noted by using glycine as the catalyst.[12] Aldol reactions of ketones **1** catalyzed by simple achiral bases such as triethylamine and Hünig's base were too sluggish and did not go to completion, observing instead the epimerization of the starting azetidine-2,3-dione.[13] The use of the system pyrrolidine/acetic acid (1:1) was able to catalyze the aldol reaction of azetidine-2,3-diones **1** with acetone but not as efficiently as proline.[14] The generality of this protocol with L- or D-proline was next established through the stereoselective addition of cyclic ketones. We were also able to show that the aldol reaction of ketone acceptors **1** with cyclobutanone or cyclopentanone proceeds with reasonable *anti*/*syn* ratios under substrate chirality control to afford adducts **3** and **4** (Scheme 2, Table 2).

Although great efforts have been devoted to implement the direct catalytic asymmetric aldol reaction, no significant progress has been achieved until recently for the analogous reaction involving nitroalkane donors (Henry reaction),[15] despite it may provide efficient access to valuable functionalized structural motifs such as α-hydroxy carboxylic acids



1 **3** **4**

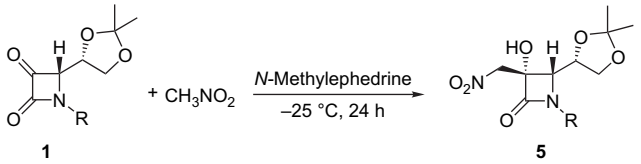
Scheme 2. Aldol reaction of azetidine-2,3-diones **1** with cyclic ketones.

Table 2. Reaction of azetidine-2,3-diones **1** with cyclic ketones under proline catalysis[a]

Entry	Ketone	R	*n*	Proline	Products	dr[b]	Yield[c] (%)
1	(+)-**1a**	PMP	0	D	(+)-**3a**/(+)-**4a**	80:20	50/12
2	(+)-**1a**	PMP	0	L	(+)-**3a**/(+)-**4a**	85:15	56/10
3	(−)-**1b**	Allyl	0	D	(−)-**3b**/(+)-**4b**	75:25	37/12
4	(−)-**1b**	Allyl	0	L	(−)-**3b**/(+)-**4b**	80:20	40/10
5	(+)-**1a**	PMP	1	D	(+)-**3c**/(+)-**4c**	80:20	49/12
6	(+)-**1a**	PMP	1	L	(+)-**3c**/(+)-**4c**	85:15	55/10
7	(−)-**1c**	Benzyl	1	D	(−)-**3d/4d**	95:5	52/0
8	(−)-**1c**	Benzyl	1	L	(−)-**3d/4d**	95:5	56/0

[a] Proline of 10 mol %was used. PMP=4-$MeOC_6H_4$.
[b] The ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures before purification.
[c] Yield of isolated product with correct analytical and spectral data.

and 1,2-amino alcohols.[16] With the absence of match or mismatch effect observed in the proline-catalyzed direct aldol reaction of α-oxo-β-lactams **1** with ketone donors,[17] we went on to check the inherent facial selectivity of carbonyls **1** with nitromethane under organocatalysis (Scheme 3, Table 3). Unfortunately, proline was unable to promote this Henry reaction (Table 3, entry 1). However, we identified *N*-methylephedrine as an effective organocatalyst for the addition of nitromethane to azetidine-2,3-diones **1**. Under the optimal reaction conditions, (+)-*N*-methylephedrine [(+)-NME] and (−)-*N*-methylephedrine [(−)-NME] were found to be suitable catalysts for nitroaldol reaction giving the corresponding Henry adducts **5** in good yields.[18] As expected, full stereocontrol was observed in all cases, and chirality control of the substrate versus catalyst was again observed.



Scheme 3. Nitroaldol reaction of azetidine-2,3-diones **1** with nitromethane.

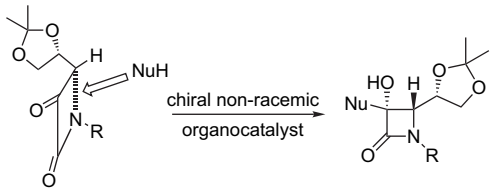
Table 3. Organocatalytic Henry reaction of azetidine-2,3-diones **1** with nitromethane[a]

Entry	Ketone	R	Catalyst	Product	Yield[b] (%)
1	(+)-**1a**	PMP	L-Proline	(+)-**5a**	[c]
2	(+)-**1a**	PMP	(+)-NME	(+)-**5a**	68
3	(+)-**1a**	PMP	(−)-NME	(+)-**5a**	70
4	(+)-**1a**	PMP	(±)-NME	(+)-**5a**	70
5	(−)-**1b**	Allyl	(+)-NME	(−)-**5b**	47
6	(−)-**1b**	Allyl	(−)-NME	(−)-**5b**	50
7	(−)-**1c**	Benzyl	(+)-NME	(+)-**5c**	62
8	(−)-**1c**	Benzyl	(−)-NME	(+)-**5c**	65

[a] *N*-Methylephedrine of 35 mol % was used except otherwise stated. PMP=4-MeOC$_6$H$_4$.
[b] Yield of pure, isolated product with correct analytical and spectral data.
[c] Unreacted starting material together with its C4 epimer was recovered after 2 days of reaction at rt.

The stereochemistry at the *C*3-heterosubstituted quaternary center for compounds **2**–**5** was assigned by qualitative homonuclear NOE difference spectra. On azetidine-2,3-diones **1**, the full stereocontrol was achieved due to the presence of a bulky chiral group at C4, which was able to control the stereochemistry of the new *C*3-substituted *C*3-hydroxy quaternary center. One face of the carbonyl group is blocked preferentially, thus the nucleophilic species being delivered to the less hindered face, and as a consequence the diastereoselectivity was complete in all cases (Scheme 4). These organocatalytic aldol and nitroaldol reactions are proceeding with total asymmetric induction by ketones **1**,[19] with the chirality of the catalyst (proline or *N*-methylephedrine) having no effect on the overall stereoselectivity.

In conclusion, using organocatalytic systems we have successfully accomplished the direct aldol and nitroaldol reactions between enantiopure azetidine-2,3-diones and ketones or nitromethane. These proline- or *N*-methylephedrine-catalyzed aldol or Henry reactions are proceeding with total asymmetric induction by the substrate, with the chirality of the catalyst having no effect on the overall stereoselectivity.



Scheme 4. Model to explain the observed substrate-controlled stereochemistry by delivery of the nucleophile to the less hindered face of the ketone. NuH=acetone, cyclopentanone, and nitromethane. Organocatalyst=D-proline, L-proline, (+)-NME, (−)-NME.

3. Experimental

3.1. General methods

Melting points were taken using a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 781 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-300, Varian VRX-300S, or Bruker AC-200. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in parts per million relative to TMS (^{1}H, 0.0 ppm) or $CDCl_3$ (^{13}C, 76.9 ppm). Mass spectra were recorded on a Hewlett–Packard 5989A spectrometer. Microanalyses were performed in the UCM Microanalysis Service (Facultad de Farmacia, UCM, Madrid). Optical rotations were measured using a Perkin–Elmer 241 polarimeter. Specific rotation $[\alpha]_D$ is given in degree per decimeter at 25 °C, and the concentration (*c*) is expressed in gram per 100 mL. All commercially available compounds were used without further purification. THF was distilled from Na–benzophenone. Benzene, dichloromethane, and triethylamine were distilled from CaH_2. Flame-dried glassware and standard Schlenk techniques were used for moisture sensitive reactions. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). Identification of products was made by TLC (Kieselgel 60F$_{254}$). UV light (λ=254 nm), and a vanillin solution in sulfuric acid and 95% EtOH (1 g vanillin, 5 mL H_2SO_4, 150 mL EtOH) were used to develop the plates.

3.2. General procedure for the synthesis of aldols 2–4. Proline-catalyzed reaction between unmodified ketones and azetidine-2,3-diones 1

L-Proline or D-proline (10.4 mg, 0.09 mmol) was added to a well stirred solution of the appropriate ketone acceptor **1** (0.90 mmol) in the corresponding ketone donor (9 mL) at room temperature. After disappearance of the starting material (TLC), saturated aqueous sodium hydrogen carbonate (5 mL) was added before being extracted with ethyl acetate (3×10 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure aldols **2**–**4**.

3.2.1. Aldol (+)-2a. From 35 mg (0.12 mmol) of azetidine-2,3-dione (+)-**1a** and after chromatography of the residue

using hexanes/ethyl acetate (1:1) as eluant gave compound (+)-**2a** (33 mg, 79%) as a colorless solid. Mp: 103–104 °C (hexanes/ethyl acetate). $[\alpha]_D$ +97.5 (*c* 1.0, CH_2Cl_2). ^1H NMR: δ 7.50 and 6.86 (d, *J*=9.0 Hz, each 2H), 4.50 (m, 1H), 4.23 and 3.87 (dd, *J*=8.8, 6.6 Hz, each 1H), 4.19 (d, *J*=5.9 Hz, 1H), 3.79 (s, 3H), 3.18 and 2.79 (d, *J*=16.8 Hz, each 1H), 2.28 (s, 3H), 1.41 and 1.34 (s, each 3H). ^{13}C NMR: δ 207.5, 166.8, 156.7, 130.7, 120.0, 114.1, 109.8, 82.3, 76.1, 66.4, 65.8, 55.4, 46.4, 31.7, 26.3, 25.1. IR (KBr, cm^{-1}): ν 3375, 1751, 1718. MS (ES), *m/z*: 350 (M^++1, 100), 349 (M^+, 11). Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 62.02; H, 6.59; N, 4.04.

3.2.2. Aldol (−)-2b. From 34 mg (0.15 mmol) of azetidine-2,3-dione (−)-**1b** and after chromatography of the residue using hexanes/ethyl acetate (1:2) as eluant gave compound (−)-**2b** (20 mg, 48%) as a colorless oil. $[\alpha]_D$ −25.5 (*c* 0.7, tetrahydrofuran). ^1H NMR: δ 5.75 (m, 1H), 5.24 (m, 2H), 4.44 (m, 1H), 4.24 (ddt, *J*=15.4, 4.9, 1.6 Hz, 1H), 4.18 (dd, *J*=9.0, 7.0 Hz, 1H), 3.85 (dd, *J*=9.0, 5.0 Hz, 1H), 3.67 (m, 1H), 3.13 and 2.68 (d, *J*=16.7 Hz, each 1H), 2.26 (s, 3H), 1.44 and 1.35 (s, each 3H). ^{13}C NMR: δ 207.4, 169.0, 131.4, 119.1, 109.9, 82.9, 75.2, 66.4, 64.8, 46.4, 43.4, 31.6, 26.4, 24.8. IR ($CHCl_3$, cm^{-1}): ν 3370, 1750, 1720. MS (ES), *m/z*: 284 (M^++1, 100), 283 (M^+, 9). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.47; H, 7.42; N, 4.91.

3.2.3. Aldol (−)-2c. From 31 mg (0.11 mmol) of azetidine-2,3-dione (−)-**1c** and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluant gave compound (−)-**2c** (24 mg, 66%) as a colorless solid. Mp: 121–122 °C (hexanes/ethyl acetate). $[\alpha]_D$ −13.7 (*c* 1.8, CH_2Cl_2). ^1H NMR: δ 7.29 (m, 5H), 4.88 and 4.13 (d, *J*=14.7 Hz, each 1H), 4.43 (m, 1H), 4.15 (ddt, *J*=9.0, 6.9 Hz, 1H), 3.76 (dd, *J*=9.0, 5.2 Hz, 1H), 3.43 (d, *J*=5.9 Hz, 1H), 3.10 and 2.56 (d, *J*=16.7 Hz, each 1H), 2.22 (s, 3H), 1.41 and 1.34 (s, each 3H). ^{13}C NMR: δ 207.4, 169.2, 135.4, 128.8, 128.7, 128.4, 109.8, 82.9, 75.5, 66.4, 64.7, 46.0, 44.7, 31.6, 26.4, 24.9. IR ($CHCl_3$, cm^{-1}): ν 3356, 1753, 1736. MS (ES), *m/z*: 234 (M^++1, 100), 233 (M^+, 10). Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.72; H, 6.90; N, 4.16.

3.2.4. Preparation of aldols (+)-3a and (+)-4a. From 35 mg (0.12 mmol) of azetidine-2,3-dione (+)-**1a** and after column chromatography eluting with hexanes/ethyl acetate (1:1), 24 mg (56%) of the less polar compound (+)-**3a** and 5 mg (10%) of the more polar compound (+)-**4a** were obtained.

3.2.4.1. Aldol (+)-3a. Colorless solid. Mp: 136–137 °C (hexanes/ethyl acetate). $[\alpha]_D$ +76.8 (*c* 0.7, tetrahydrofuran). ^1H NMR: δ 7.45 and 6.85 (d, *J*=9.0 Hz, each 2H), 4.45 (m, 1H), 4.28 (d, *J*=5.1 Hz, 1H), 4.20 and 3.94 (dd, *J*=9.0, 6.6 Hz, each 1H), 3.79 (s, 3H), 3.68 (dd, *J*=9.8, 6.9 Hz, 1H), 3.12 (t, *J*=8.7 Hz, 2H), 2.30 (m, 2H), 1.40 and 1.35 (s, each 3H). ^{13}C NMR: δ 209.4, 161.2, 156.8, 130.5, 120.0, 114.2, 109.9, 83.3, 75.7, 66.8, 64.8, 63.5, 55.4, 46.9, 26.2, 25.3, 12.5. IR ($CHCl_3$, cm^{-1}): ν 3369, 1734, 1718. MS (ES), *m/z*: 362 (M^++1, 100), 361 (M^+, 22). Anal. Calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41; N, 3.88. Found: C, 63.28; H, 6.37; N, 3.85.

3.2.4.2. Aldol (+)-4a. Colorless oil. $[\alpha]_D$ +55.6 (*c* 0.5, tetrahydrofuran). ^1H NMR: δ 7.47 and 6.84 (d, *J*=9.0 Hz, each 2H), 4.45 (m, 1H), 4.27 (d, *J*=5.6 Hz, 1H), 4.23 (dd, *J*=9.0, 6.6 Hz, 1H), 3.80 (m, 1H), 3.78 (s, 3H), 3.07 (m, 2H), 2.26 (m, 2H), 1.42 and 1.35 (s, each 3H). IR ($CHCl_3$, cm^{-1}): ν 3365, 1737, 1719. MS (ES), *m/z*: 362 (M^++1, 100), 361 (M^+, 17). Anal. Calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41; N, 3.88. Found: C, 63.26; H, 6.45; N, 3.85.

3.2.5. Preparation of aldols (−)-3b and (+)-4b. From 39 mg (0.17 mmol) of azetidine-2,3-dione (−)-**1b** and after column chromatography eluting with hexanes/ethyl acetate (1:1), 19 mg (40%) of the less polar compound (−)-**3b** and 5 mg (10%) of the more polar compound (+)-**4b** were obtained.

3.2.5.1. Aldol (−)-3b. Colorless solid. Mp: 87–88 °C (hexanes/ethyl acetate). $[\alpha]_D$ –49.4 (*c* 0.8, CH_2Cl_2). ^1H NMR: δ 5.72 (m, 1H), 5.24 (m, 2H), 4.98 (s, 1H), 4.35 (m, 1H), 4.20 (ddt, *J*=15.2, 4.8, 1.4 Hz, 1H), 4.14 (dd, *J*=9.0, 6.9 Hz, 1H), 3.94 (dd, *J*=9.0, 5.0 Hz, 1H), 3.68 (d, *J*=6.0 Hz, 1H), 3.66 (m, 1H), 3.55 (dd, *J*=9.0, 6.9 Hz, 1H), 3.08 (m, 2H), 2.40 and 2.24 (m, each 1H), 1.44 and 1.34 (s, each 3H). ^{13}C NMR: δ 208.4, 169.8, 131.1, 119.3, 114.2, 109.9, 83.3, 75.4, 66.2, 64.6, 63.6, 46.9, 43.5, 26.4, 24.9, 12.4. IR ($CHCl_3$, cm^{-1}): ν 3350, 1734, 1710. MS (ES), *m/z*: 296 (M^++1, 100), 295 (M^+, 7). Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.14; H, 7.12; N, 4.71.

3.2.5.2. Aldol (+)-4b. Colorless oil. $[\alpha]_D$ +33.1 (*c* 0.6, tetrahydrofuran). ^1H NMR: δ 5.78 (m, 1H), 5.26 (m, 2H), 4.29 (m, 3H), 3.81 (dd, *J*=9.0, 5.0 Hz, 1H), 3.71 (m, 3H), 3.07 (m, 2H), 2.24 (m, 2H), 1.63 (s, 1H), 1.45 and 1.35 (s, each 3H). IR ($CHCl_3$, cm^{-1}): ν 3356, 1735, 1714. MS (ES), *m/z*: 296 (M^++1, 100), 295 (M^+, 9). Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.16; H, 7.21; N, 4.70.

3.2.6. Preparation of aldols (+)-3c and (+)-4c. From 40 mg (0.14 mmol) of azetidine-2,3-dione (+)-**1a** and after column chromatography eluting with hexanes/ethyl acetate (1:1), 27 mg (55%) of the less polar compound (+)-**3c** and 5 mg (10%) of the more polar compound (+)-**4c** were obtained.

3.2.6.1. Aldol (+)-3c. Pale yellow oil. $[\alpha]_D$ +7.8 (*c* 0.5, tetrahydrofuran). ^1H NMR: δ 7.49 and 6.86 (d, *J*=9.0 Hz, each 2H), 4.83 (br s, 1H), 4.50 (m, 1H), 4.33 (d, *J*=5.4 Hz, 1H), 4.24 and 3.89 (dd, *J*=9.0, 6.6 Hz, each 1H), 3.79 (s, 3H), 2.16 (m, 7H), 1.41 and 1.34 (s, each 3H). ^{13}C NMR: δ 219.9, 167.1, 156.7, 130.7, 120.0, 114.2, 109.9, 85.1, 76.0, 66.5, 64.8, 55.5, 51.6, 39.1, 26.4, 25.2, 24.6, 20.7. IR ($CHCl_3$, cm^{-1}): ν 3365, 1735, 1715. MS (ES), *m/z*: 376 (M^++1, 100), 375 (M^+, 14). Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.99; H, 6.71; N, 3.73. Found: C, 64.12; H, 6.67; N, 3.70.

3.2.6.2. Aldol (+)-4c. Pale yellow oil. $[\alpha]_D$ +66.7 (*c* 0.5, tetrahydrofuran). ^1H NMR: δ 7.56 and 6.86 (d, *J*=9.0 Hz, each 2H), 4.49 (m, 1H), 4.23 (m, 1H), 4.12 (d, *J*=7.0 Hz, 1H), 3.79 (s, 3H), 3.65 (dd, *J*=8.8, 6.8 Hz, 1H), 2.75 (m, 1H), 2.11 (m, 6H), 1.45 and 1.33 (s, each 3H). IR ($CHCl_3$,

cm^{-1}): ν 3366, 1737, 1718. MS (ES), *m/z*: 376 (M$^+$+1, 100), 375 (M$^+$, 12). Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.99; H, 6.71; N, 3.73. Found: C, 64.14; H, 6.66; N, 3.77.

3.2.7. Aldol (−)-3d. From 36 mg (0.13 mmol) of azetidine-2,3-dione (−)-**1c** and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluant gave compound (−)-**3d** (26 mg, 56%) as a colorless oil. $[\alpha]_D$ −59.6 (*c* 1.2, CH_2Cl_2). ^{1}H NMR: δ 7.29 (m, 5H), 4.90 and 4.11 (d, *J*=14.7 Hz, each 1H), 4.71 (br s, 1H), 4.42 (m, 1H), 4.14 (dd, *J*=9.0, 7.0 Hz, 1H), 3.80 (dd, *J*=9.0, 4.9 Hz, 1H), 3.61 (d, *J*=5.4 Hz, 1H), 1.99 (m, 7H), 1.45 and 1.35 (s, each 3H). ^{13}C NMR: δ 220.0, 164.9, 135.4, 128.7, 128.5, 127.8, 109.9, 85.5, 75.2, 66.4, 63.8, 51.3, 44.6, 39.0, 26.4, 24.8, 24.5, 20.7. IR ($CHCl_3$, cm^{-1}): ν 3360, 1738, 1718. MS (ES), *m/z*: 360 (M$^+$+1, 100), 359 (M$^+$, 12). Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.90. Found: C, 66.96; H, 7.06; N, 3.87.

3.3. General procedure for the synthesis of nitroaldols 5

N-Methylephedrine (8.4 mg, 0.046 mmol) was added to a well stirred solution of the appropriate ketone acceptor **1** (0.10 mmol) in nitromethane (9 mL) cooled at −25 °C. After disappearance of the starting material (TLC), saturated aqueous sodium hydrogen carbonate (2 mL) was added and the mixture was allowed to warm to room temperature, before being extracted with ethyl acetate (3×10 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds **5**. Spectroscopic and analytical data for some representative forms of **5** are as follows.

3.3.1. Nitroaldol (+)-5a. From 30 mg (0.10 mmol) of azetidine-2,3-dione (+)-**1a** and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluant gave compound (+)-**5a** (25 mg, 70%) as a colorless oil. $[\alpha]_D$ +113.3 (*c* 1.4, CH_2Cl_2). ^{1}H NMR: δ 7.46 and 6.87 (d, *J*=9.0 Hz, each 2H), 5.18 (br s, 1H), 4.86 and 4.66 (d, *J*=13.0 Hz, each 1H), 4.68 (d, *J*=4.6 Hz, 1H), 4.49 (m, 1H), 4.20 and 3.89 (dd, *J*=9.0, 6.7 Hz, each 1H), 3.79 (s, 3H), 1.40 and 1.35 (s, each 3H). ^{13}C NMR: δ 164.0, 157.2, 129.7, 120.4, 114.2, 110.2, 82.2, 77.7, 75.3, 66.1, 64.3, 55.4, 26.1, 25.3. IR (KBr, cm^{-1}): ν 3352, 1757, 1560. MS (ES), *m/z*: 353 (M$^+$+1, 100), 352 (M$^+$, 9). Anal. Calcd for $C_{16}H_{20}N_2O_7$: C, 54.54; H, 5.72; N, 7.95. Found: C, 54.42; H, 5.76; N, 7.81.

3.3.2. Nitroaldol (−)-5b. From 43 mg (0.19 mmol) of azetidine-2,3-dione (−)-**1b** and after chromatography of the residue using hexanes/ethyl acetate (1:2) as eluant gave compound (−)-**5b** (28 mg, 50%) as a colorless oil. $[\alpha]_D$ −0.4 (*c* 1.0, CH_2Cl_2). ^{1}H NMR: δ 5.75 (m, 1H), 5.29 (m, 2H), 4.83 and 4.54 (d, *J*=13.3 Hz, each 1H), 4.62 (br s, 1H), 4.47 (m, 1H), 4.33 (dd, *J*=15.3, 4.7 Hz, 1H), 4.21 (dd, *J*=9.2, 7.2 Hz, 1H), 4.12 (d, *J*=4.0 Hz, 1H), 3.94 (dd, *J*=9.2, 4.4 Hz, 1H), 3.69 (dd, *J*=15.3, 8.1 Hz, 1H), 1.48 and 1.37 (s, each 3H). ^{13}C NMR: δ 166.5, 130.8, 120.1, 110.6, 83.1, 77.5, 73.8, 66.0, 63.6, 43.6, 26.2, 24.7. IR ($CHCl_3$, cm^{-1}): ν 3354, 1752, 1564. MS (ES), *m/z*: 287 (M$^+$+1, 100), 286 (M$^+$, 5). Anal. Calcd for $C_{12}H_{18}N_2O_6$: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.47; H, 6.29; N, 9.72.

3.3.3. Nitroaldol (+)-5c. From 30 mg (0.11 mmol) of azetidine-2,3-dione (−)-**1c** and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluant gave compound (+)-**5c** (24 mg, 65%) as a colorless oil. $[\alpha]_D$ +3.8 (*c* 0.9, CH_2Cl_2). ^{1}H NMR: δ 7.38 (m, 3H), 7.28 (m, 2H), 4.96 and 4.15 (d, *J*=14.7 Hz, each 1H), 4.82 and 4.43 (d, *J*=13.4 Hz, each 1H), 4.79 (br s, 1H), 4.44 (m, 1H), 4.16 (dd, *J*=9.3, 7.1 Hz, 1H), 3.88 (d, *J*=4.1 Hz, 1H), 3.84 (dd, *J*=9.3, 4.5 Hz, 1H), 1.50 and 1.38 (s, each 3H). ^{13}C NMR: δ 166.6, 134.5, 129.1, 128.3, 110.6, 83.0, 77.2, 74.1, 66.1, 63.4, 44.9, 26.2, 24.7. IR ($CHCl_3$, cm^{-1}): ν 3352, 1750, 1562. MS (ES), *m/z*: 337 (M$^+$+1, 100), 336 (M$^+$, 5). Anal. Calcd for $C_{16}H_{20}N_2O_6$: C, 57.14; H, 5.99; N, 8.33. Found: C, 57.12; H, 5.95; N, 8.27.

Acknowledgements

We would like to thank the DGI-MEC (Projects BQU2003-07793-C02-01 and CTQ2006-10292) and CAM-UCM (Grant GR45/05) for financial support.

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