Organocatalytic asymmetric aldol reaction in the presence of water

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Water was found to be a suitable solvent for the L-prolinethioamide catalysed aldol reaction of various cyclic ketones with aromatic aldehydes. Treatment of 4-nitrobenzaldehyde with as little as 1.2 equiv. of cyclohexanone in the presence of the protonated catalyst **1**–TFA, afforded aldol products in high yields (up to 97%) with high diastereo- and enantioselectivity (up to >5 : 95 dr and 98% ee). The use of a high excess of ketone was avoided by conducting the aldol addition in the presence of water. Furthermore, different 'salting-out' and 'salting-in' salts were investigated and it was proven that the rate of acceleration and the stereochemical outcome of the reaction are affected by hydrophobic aggregation. Scope and limitation studies revealed that electron deficient aldehydes afforded aldol products with high stereoselectivity in the presence of **1**–Cl_2CHCO_2H. It was shown that various cyclic ketones, under the conditions found, gave aldol products with fair yields, even if they are used in substoichiometric amounts (1.2 to 2.0 equiv.).

Introduction

Water is the most abundant solvent in Nature but organic chemists have neglected its use for a long time. In 2002, Lindström, in his review, wrote: 'this article will serve to rectify some of the misconceptions that might persist with many chemists regarding the inadequacy of water as solvent for organic reactions'.[1] However, water is a desirable solvent for chemical reactions mainly because of cost, safety, and environmental concerns.[2,3] In addition, the performance of organic reactions in aqueous conditions might lead to different results as compared with those obtained in purely organic solvents, regardless of whether the reactants are soluble or not in water.[4,5]

To develop organic reactions which are water-compatible is a great challenge since water breaks the hydrogen bonds that are crucial in many transition states.[6,7] Despite this fact, in recent years water has attracted much attention as a solvent with important advances being made.[4,8,9] However, in many cases, transition–metal complexes have been employed. Only within the last few years has the organocatalysed direct aldol reaction been rediscovered.[10–13] Although proline can catalyse direct aldol reactions in organic solvents with high enantioselectivity, it leads to racemates in water.[14–16] Therefore, given the synthetic utility of the asymmetric aldol reaction, there is a growing search for an organic catalyst that can effectively promote this reaction in water. Recently Barbas's and Hayashi's groups have independently reported highly stereoselective aldol reactions 'in water' or 'aqueous'.[17,18] Since there has been some confusion concerning the terminology or whether these reactions are 'really wet',[19] Hayashi has proposed to use the term 'a reaction in the presence of water' for reactions that proceed in a concentrated organic phase with water being present as a second phase, which influences the reaction in the organic phase.[20] Here we would like to point out that there is a huge difference between reactions in which water is used as an additive and those in which it is used as a main phase (on water). The term 'a reaction in water' has been restricted to fully homogenous conditions.

To date, aldol reactions in the presence of water have afforded aldol products with high diastereoselectivity and enantioselectivity; unfortunately, in most cases, a large excess of ketone is needed.[18,21–29] In two notable examples, the laboratories of Barbas[17] and Zhao[25] used respectively only 2 or 3 equiv. of cyclohexanone but 10 mol% of catalyst was employed. Thus, the development of efficient organocatalysts for the asymmetric aldol reaction, both in water and in the presence of water, still remains a hot area of research.

Results and discussion

New organocatalysts for the direct organocatalysed aldol reaction have been attracting much attention since the seminal discovery by List, Lerner and Barbas.[10] We have contributed to this field by showing that simple L-prolinethioamides can effectively catalyse the reaction of acetone with various aromatic aldehydes.[30–32] Later, it was proved that the TFA-assisted aldol reaction proceeded through enamine-iminium catalysis. Since Janda *et al.* wrote that the addition of TFA (or any acid) to the reaction of cyclohexanone with 4-nitrobenzaldehyde in the presence of a chiral diamine favours the formation of micelles by increasing the amphiphilic character of the catalyst,[19] we envisaged that our catalytic system of L-prolinethioamide and TFA could be used in the presence of water.

To verify this hypothesis, we started from the conditions described by Barbas *et al.*[17] A reaction of 4-nitrobenzaldehyde (**3**) with cyclohexanone (**2**) catalysed by **1**–TFA in the presence of water gave product **4** in 96% yield with high diastereo- and enantioselectivity (Scheme 1; Table 1, entry 1). When the catalyst loading was lowered to 5%, the yield did not change (entry 2). However, a further decrease in the amount of catalyst or ketone used led to a decrease in the yield, but did not affect the degree of diastereo- and enantioselectivity (entries 3 and 4). On the other

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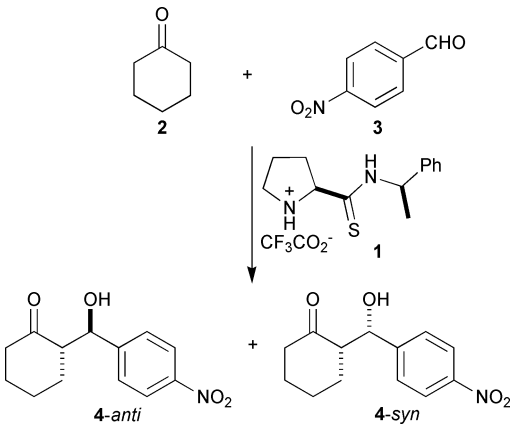
Table 1 The aldol reaction of cyclohexanone (**2**) with 4-nitrobenzaldehyde (**3**) catalysed by **1**–TFA in the presence of water[a]

Entry	Catalyst (mol%)	Ketone (mmol)	Yield (%)[b]	Ratio *syn–anti*[c]	Ee of **4**-*anti* (%)[d]
1	10	2	96	10 : 90	94
2	5	2	96	5 : 95	94
3	2.5	2	72	5 : 95	90
4	5	1.2	23	5 : 95	89
5[32]	10	Neat	82	13 : 77	86

[a] All reactions were run in the presence of **1**–TFA on 1 mmol scale in 2 ml of water at rt for 18 h. [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] Determined by chiral HPLC using an ADH-column.



Scheme 1 The model aldol reaction of 4-nitrobenzaldehyde (**2**) with cyclohexanone (**3**) catalysed by **1**–TFA in the presence of water.

hand, when cyclohexanone (**2**) was used as a solvent and as a donor, the reaction afforded aldol product **4** with lower yield and decreased diastereo- and enantioselectivity (entry 5). Thus, the role of water in the studied reaction is not only as the reaction medium, but it also influences the reaction rate and stereoselectivity. A similar phenomenon was observed by Sharpless *et al.* and these types of reactions are called 'on water'.[5] However, it is still not clear whether reactions 'on water' are influenced by hydrophobic aggregation or by other effects.[33,34]

To clarify whether the hydrophobic effect plays a crucial role in the L-prolinethioamide catalysed aldol reaction, experiments with 'salting-out' and 'salting-in' salts were conducted.[35] 'Salting-out' salts increase the hydrophobic effect, by electrostriction of water, which decreases the solubility of hydrocarbons and thus promotes their association. Conversely, 'salting-in' decreases the association of hydrocarbon residues in water. Takabe and Barbas *et al.*, who used brine as the aqueous medium in a direct Michael reaction, for the first time added NaCl to an organocatalysed reaction in the presence of water.[36] The beneficial influence of brine over water was explained only on the basis of ionic complexation and the 'salting-out' effect was not taken into consideration.

In our case, the use of brine as the reaction medium for the aldol reaction of cyclohexanone (**2**) with **3** catalysed by **1**–TFA, allowed us to decrease the amount of the ketone **2** to as little as 1.2 equiv. per 1 mmol of **3** (Table 2, entry 1). Reactions in the presence of less saturated NaCl aqueous solutions gave the same stereochemical results, but lower yields (entries 3–5). Furthermore, other 'salting-out' salts were tested and the results are presented in Table 2 (entries 6–12). The reaction in the presence of an aqueous solution of NH_4Cl afforded only 45% of aldol product **4**, presumably

Table 2 'Salting-out' and 'salting-in' salts as additives for the aldol reaction in the presence of water[a]

Entry	Salt	Catalyst (mol%)	Yield of **4** (%)[b]	Ratio *syn–anti*[c]	Ee of **4**-*anti*[d]
1	NaCl (sat)	5	90	> 5 : 95	92
2	NaCl (sat)	2.5	56	> 5 : 95	87
3	NaCl (350 mg)	5	90	> 5 : 95	90
4	NaCl (350 mg)[e]	5	33	> 5 : 95	95
5	NaCl (175 mg)	5	66	> 5 : 95	91
6	LiCl (sat)	5	24	15 : 85	85
7	KCl (sat)	5	86	> 5 : 95	94
8	$CaCl_2$ (sat)	5	24	> 5 : 95	93
9	NH_4Cl (sat))	5	45	> 5 : 95	93
10	Na_2SO_4 (sat	5	93	> 5 : 95	91
11	$MgSO_4$ (sat)	5	90	> 5 : 95	93
12	$LiClO_4$ (sat)	5	Traces	nd	nd
13	Guanidine chloride (sat)	5	Traces	nd	nd
14	Urea (sat)	5	Traces	nd	nd
15	Phosphate buffer	10	Traces	nd	nd
16	Phosphate buffer[f]	20	100	10 : 90	85%
17	Phosphate buffer[g]	20	51	10 : 90	rac

[a] Reactions were carried out using 1.2 mmol of **2** for 1 mmol of aldehyde **3** in the presence of **1**–TFA (indicated in the Table) in 2 ml of water at rt for 18 h. [b] Isolated yields. [c] Determined by ^{1}H NMR analyses of the crude product. [d] Determined by chiral-phase HPLC analyses. [e] The reaction was run at 4 °C. [f] The reaction was run in phosphate buffer (pH = 7.2) for 2 days. [g] Free base catalyst was used.

because of different water–salt interactions as shown by Symons[37] (entry 9). To support our hypothesis concerning the hydrophobic effect, 'salting-in' materials such as guanidinium chloride and urea were tested in the model aldol reaction. Reactions in such aqueous solutions led only to the recovery of the starting material **3** (entries 13 and 14).

On the other hand, the rate acceleration may be attributed to hydrogen bonding interactions. Symons has pointed out the changes in water properties that occur when different types of anions are added.[37] Small coordinating anions bind to water protons and thus decrease the ability of water to hydrogen bond other substrates. Following Breslow and Rizzo's studies,[35] we also considered the hydrogen bonding explanation for the rate acceleration, reactions in the presence of LiCl and $LiClO_4$ were conducted. If hydrogen bonds influence the reaction, $LiClO_4$ should speed up the reaction more than LiCl does; the salting-in explanation would predict the opposite effect. We found that the direct aldol reaction catalysed by **1**–TFA in the presence of a saturated aqueous solution of $LiClO_4$ was indeed slower as compared with the one conducted in the presence of a LiCl solution (compare entries 6 and 12). These data confirm the idea that hydrophobic packing effects contribute to the L-prolinethioamide catalysed aldol reaction in the presence of water. Finally, since no small molecule catalysts have provided relevant enantioselectivity in aqueous buffered solutions,[38,39] we have checked our **1**–TFA system using those conditions. Using 20 mol% of the catalyst (**1**–TFA), the model aldol reaction in phosphate buffer (pH = 7.2) afforded exclusively 3-hydroxy ketone **4** with high diastereoselectivity and 85% ee (entry 16). The reaction without TFA led to a decrease in the enantiomeric enrichment, the addition of an acid favours the formation of micelles increasing the amphiphilic character of the catalyst (entry 17).

Following our recent publication on the influence of an acid on the aldol reaction, we thought it worthy to study whether the nature of the acid is also an important factor for this transformation conducted in the presence of water.[32]

Surprisingly, the reaction of cyclohexanone (**2**) with 4-nitrobenzaldehyde (**3**) by **1**–HCl in the presence of brine gave aldol product **4**, contrary to the reaction of acetone with **3** (Table 3, entry 1). However, the best results were obtained with the use of **1**–Cl_2CHCO_2H; the catalyst loading could be lowered to as little as 2.5% mol (entry 5). A further decrease in the amount of the catalyst led to a decrease in the reaction rate which subsequently lowered the enantiomeric purity of the *anti*-aldol **4** (entry 6) (the longer the reaction time, the lower the enantiomeric purity of **4**-*anti*).

A range of aromatic aldehydes, **5–16**, was explored and the results are summarised in Table 4.

Regardless of the aldehyde used, high diastereo- and enantioselectivity was observed, though the rate of the aldol reaction strongly depended on the electrodeficiency of the substrate. In most cases, 1.5 equiv., instead of 1.2 equiv., of cyclohexanone (**2**) had to be used and/or longer reaction times were required at the slight cost of diastereo- and enantioselectivity. Under the present reaction conditions, less reactive aldehydes did not afford aldol products with acceptable yields, although the stereoselectivity remained at the same level, for example, see entry 16. Though Nájera *et al.* found that for BINAM-prolineamides, an excess of acid had beneficial effects on the yield and enantioselectivity,[22] in our case, the use of higher amounts of acid did not improve the catalytic activity of our system, and resulted in a decrease of the stereoselectivity (entry 17).

Despite the great variety of aldol acceptors that have been used in direct aldol reactions under water conditions, the range of donors has remained narrow. Recently, Xiao *et al.* have reported the highly diastereo- and enantioselective aldol reactions of heterocyclic ketones with aldehydes in organic solvent.[40] It was shown that heterocyclic ketones such as 4-thianone, 4-Boc piperidinone and tetrahydro-4*H*-pyran-4-one afforded aldol products with excellent yields and stereoselectivities, though an excess of ketone was necessary. Given the fact that these donors are not the cheapest ones and that they must be separated from the aldol product (that is not an easy task), it would be beneficial if the amount of ketone could be stoichiometric or at least substoichiometric. In a very elegant report, Pihko *et al.* described conditions for the stoichiometric aldol reaction of tetrahydro-4*H*-thiopyran-4-one with benzaldehyde, however the reaction was sluggish.[41]

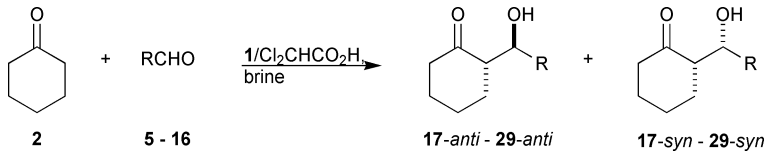
We studied the use of various cyclic **30–32** and heterocyclic **33–35** ketones for the aldol reaction in the presence of water and the results are summarized in Table 5. 4-Methylcyclohexanone (**30**) and monoprotected cyclohexane-dione **31** afforded almost exclusively optically pure *anti*-adducts **36** and **37** respectively (entries 1 and 2). The reaction of cyclopentanone (**32**) with **3** gave a mixture of *syn* and *anti* product **38** with moderate enantioselectivity, which could be attributed to the higher miscibility of **32** with water (entry 3). For heterocyclic ketones **33–35**, new reaction conditions were defined. Tetrahydro-4*H*-thiopyran-4-one (**33**) and 1-Boc-4-piperidone (**34**) smoothly reacted with 4-nitrobenzaldehyde (**3**) leading to *anti*-aldol products **39** and **40** respectively with fair diastereo- and enantioselectivity (entries 7 and 9). Since both

Table 3 The influence of an acid additive on the model aldol reaction[a]

Entry	Acid	Catalyst (mol%)	Reaction time/h	Yield (%)[b]	Ratio *syn–anti*[c]	Ee of **4**-*anti*[d]
1	HCl	5	16	50	10 : 90	85
2	4-Methylbenzoic acid	5	16	92	19 : 81	78
3	Cl_2CHCO_2H	5	16	97	7 : 93	92
4	Cl_2CHCO_2H	5	6	64	5 : 95	94
5	Cl_2CHCO_2H	2.5	28	97	7 : 93	93
6	Cl_2CHCO_2H	1.25	60	72	7 : 93	79

[a] Reactions were carried out using 1.2 mmol of **2** for 1 mmol of aldehyde **3** in the presence of **1**–acid (indicated in the Table) in 2 ml of brine at rt. [b] Isolated yields. [c] Determined by ^{1}H NMR analyses of the crude product. [d] Determined by chiral-phase HPLC analyses.

Table 4 Scope and limitation studies[a]



2 **5 - 16** **17**-*anti* - **29**-*anti* **17**-*syn* - **29**-*syn*

Entry	Aldehyde		Catalyst (mol%)	Amount of **2** (equiv.)	Reaction time/h	Yield (%)[b]		Ration *syn–anti*[c]	Ee of *anti*[d]
1	2-$NO_2C_6H_4$	(**5**)	5	1.2	48	91	(**17**)	12 : 88	97
2	2-$NO_2C_6H_4$	(**5**)	5	1.5	16	90	(**17**)	7 : 93	97
3	3-$NO_2C_6H_4$	(**6**)	5	1.2	48	72	(**18**)	9 : 91	94
4	3-$NO_2C_6H_4$	(**6**)	5	1.5	16	80	(**18**)	4 : 96	96
5	4-CNC_6H_4	(**7**)	5	1.2	16	87	(**19**)	> 5 : 95	93
6	4-CNC_6H_4	(**7**)	5	1.5	16	96	(**19**)	9 : 91	93
7	2-ClC_6H_4	(**8**)	5	1.5	16	80	(**20**)	9 : 91	96
8	3-ClC_6H_4	(**9**)	5	1.5	48	82	(**21**)	> 5 : 95	93
9	4-ClC_6H_4	(**10**)	5	1.5	48	48	(**22**)	> 5 : 95	92
10	4-ClC_6H_4	(**10**)	5	3.0	48	58	(**22**)	> 5 : 95	96
11	4-FC_6H_4	(**11**)	5	3.0	18	25	(**23**)	> 5 : 95	91
12	4-BrC_6H_4	(**12**)	5	1.5	48	57	(**24**)	> 5 : 95	93
13	F_5C_6	(**13**)	5	1.5	16	86	(**25**)	> 5 : 95	97
14	4-$CF_3C_6H_4$	(**14**)	2.5	1.2	16	82	(**26**)	> 5 : 95	98
15	4-$CO_2MeC_6H_4$	(**15**)	5	1.5	48	86	(**27**)	> 5 : 95	98
16	2-Naphthyl	(**16**)	5	1.5	48	23	(**28**)	> 5 : 95	83
17	2-Naphthyl	(**16**)	10[e]	1.5	48	23	(**29**)	> 5 : 95	68

[a] Reactions were run on 1 mmol scale in 2 ml of water at rt. [b] Isolated yields. [c] Determined by ^{1}H NMR analyses of the crude product. [d] Determined by chiral-phase HPLC analyses. [e] Additional 10% of Cl_2CHCO_2H was used.

the ketones **33**, **34** and the aldehyde **3** are water-insoluble solids, contrary to **1**–Cl_2CHCO_2H, the reactions were slower and 2 equiv. of ketone had to be used. Thus, the reactions may be regarded as biphasic.

Surprisingly, with liquid tetrahydro-4*H*-pyran-4-one (**35**), the aldol reaction afforded product **41** with a moderate yield. From this, one could conclude that the miscibility is not the most important factor influencing the studied reaction (entry 11).

Though the stereochemical results for the aldol reaction of heterocyclic ketones with aldehydes reported by Xiao are superior to those presented in the current paper, our reaction conditions offer several advantages. From a preparative point of view, the ability to conduct the reactions 'on water' in substoichiometric conditions holds significant advantages. Further studies focusing on the improvement of the catalyst structure are currently under investigation.

Conclusions

In conclusion, we have shown that water is a suitable solvent for the direct asymmetric aldol reaction of various cyclic ketones with aromatic aldehydes in the presence of L-prolinethioamide **1** and an acid. The use of water effectively enhanced the activity of the catalyst, allowing it to be used in only 1.3 mol%. At the same time, 1.2 equiv. of ketone per 1 mmol of aldehyde was enough to obtain a high yield within a reasonable period of time.

Furthermore, our studies with 'salting-out' and 'salting-in' materials showed that the hydrophobic effect plays a crucial role in the aldol reaction conducted in the presence of water. Experiments with the addition of $LiClO_4$ and LiCl confirm the idea that hydrophobic packing effects contribute to the L-prolinethioamide catalysed aldol reaction in the presence of water, one could even state that the reactions were run at hydrophobic control.

Experimental

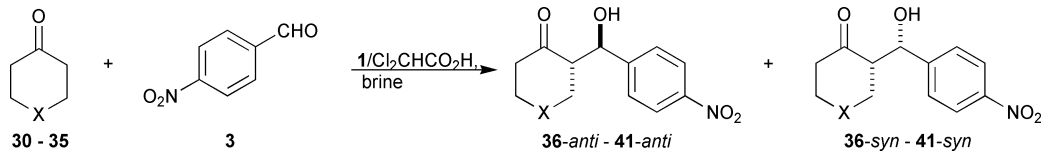
General

All chemicals were used as received unless otherwise noted. Reagent grade solvents (CH_2Cl_2, hexanes) were distilled prior to use. All reported ^{1}H NMR spectra were collected on a Bruker spectrometer at 500 (^{1}H NMR) and 125 (^{13}C NMR) MHz. Chemical shifts are reported as δ values relative to TMS signal defined at $\delta = 0.00$ (^{1}H NMR) or $\delta = 0.0$ (^{13}C NMR). IR spectra were obtained on a Perkin-Elmer 1640 FTIR unit. Mass spectra were obtained on a Mariner PerSeptive Biosystem instrument using the ESI technique. Chromatography was performed on silica gel (Kieselgel 60, 70–230 mesh). Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. The ee values were determined by HPLC using a Daicel OD–H, AS–H or AD–H column and the configuration was assigned as *R* by comparison of the retention time with the reported data.

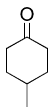
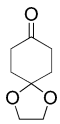
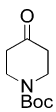
General procedure for the 1–acid catalysed aldol reaction in the presence of water

To a solution of **1**–Cl_2CHCO_2H in water (2 mL), cyclohexanone (**2**) was added, followed by 4-nitrobenzaldehyde (**3**) (151 mg, 1 mmol). The reaction mixture was vigorously stirred for the indicated period of time. Amounts of **1**–acid and of **2** and reaction times are specified in Tables 4 and 5. After the removal of water, the resulting solid was dissolved in CH_2Cl_2 and the solution was

Table 5 Investigation of the ketone scope[a]



30 - 35 **3** **36**-*anti* - **41**-*anti* **36**-*syn* - **41**-*syn*

Entry	Ketone		Amount of ketone (equiv.)	Catalyst (mol%)	Time/h	Yield (%)[b]		Ratio *syn*–*anti*[c]	Ee of *anti*[d]
1		(**30**)[e]	1.5	5	16	87	(**36**)	> 5 : 95	97
2			1.5	5	36	97		> 5 : 95	92
3		(**31**)	1.5	10	36	96	(**37**)	> 5 : 95	95
4		(**32**)	1.5	5	16	72	(**38**)	45 : 55	87
5		(**33**)	1.2	10	16	32	(**39**)	> 5 : 95	97
6			2.0	10	36	69		> 5 : 95	95
7			2.0	20	36	85		> 5 : 95	94
8		(**34**)	1.5	10	36	65	(**40**)	11 : 89	81
9			2.0	10	36	96		40 : 60	91
10		(**35**)	2.0	10	36	43	(**41**)	40 : 60	86
11			2.0	20	36	54		38 : 62	88

[a] Reactions were run on 1 mmol scale in 2 ml of brine at rt. [b] Isolated yields. [c] Determined by ^{1}H NMR analyses of the crude product. [d] Determined by chiral-phase HPLC analyses. [e] Dr with respect to the methyl group was > 5 : 95.

dried over Na_2SO_4. Diastereoselectivity was determined by ^{1}H NMR of the crude reaction mixture. Purification using column chromatography (hexanes–AcOEt, gradually) gave aldol product **4**. The enantiomeric excess of **4** was determined by chiral-phase HPLC analysis.

(*S*)-2-[(*R*)-Hydroxy(4-carboxymethylphenyl)methyl]cyclohexanone 27-*anti*. Purification using flash column chromatography (hexanes–AcOEt, gradually) gave title compound **27**-*anti* (224 mg, 86%) as a white solid (found: C, 68.61; H, 7.08. $C_{15}H_{18}O_4$ requires C, 68.89; H, 6.92%); mp 62–64 °C; $[a]_D^{20} = +23.8$ ($c = 1.0$, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3517, 2943, 1716, 1697, 1442, 1017, 885 and 706; δ_H(500 MHz, $CDCl_3$; Me_4Si) 8.01 (2 H, m), 7.39 (2 H, m), 4.84 (1 H, d, *J* 8.5 Hz), 4.02 (1 H, s), 3.91 (3 H, s), 2.61 (1 H, m), 2.44–2.50 (1 H, m), 2.31–2.40 (1 H, m), 2.05–2.12 (1 H, m), 1.75–1.85 (1 H, m), 1.66 (1 H, m), 1.50–1.60 (2 H, m) and 1.33 (1 H, m); δ_C(125 MHz, $CDCl_3$; Me_4Si) 215.0, 166.8, 146.1, 129.7, 129.6, 127.0, 74.3, 57.2, 52.0, 42.6, 30.7, 27.7 and 24.6; *m*/*z* (ESI) 285.1111. $C_{15}H_{18}O_4Na$ requires 285.1097. HPLC: Daicel Chiralpak ADH column. Hexane–iPrOH, 9 : 1, 1 mL min^{-1}, 232 nm: *t*R (major) = 23.28 min, *t*R (minor) = 24.17.

Acknowledgements

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