Enantioselective aldol reactions with aqueous 2,2-dimethoxyacetaldehyde organocatalyzed by binam-prolinamides under solvent-free conditions
Fernando J. N. Moles, Abraham Bañón-Caballero, Gabriela Guillena,* and Carmen Nájera*
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\[
\begin{align*}
\text{C}_9\text{H}_{16}\text{O}_5 & \\
\text{(S)-3-((R)-1-Hydroxy-2,2-dimethoxyethyl)dihydro-2H-pyran-4(3H)-one} & \\
\text{Source of chirality: (S\_a)- Binam and L-Pro} & \\
\{\alpha\}_D^{20} = -18 \ (c \ 0.8, \ \text{CHCl}_3, \ 95\% \ ee \ from \ GC) & \\
\text{Absolute configuration: } (S,3R) & \\
\end{align*}
\]

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\[
\begin{align*}
\text{C}_{16}\text{H}_{22}\text{O}_4 & \\
\text{(2S,4S)-2-((R)-1-Hydroxy-2,2-dimethoxyethyl)-4-phenylcyclohexanone} & \\
\text{Source of chirality: (S\_a)-Binam and L-Pro} & \\
\{\alpha\}_D^{20} = -40 \ (c \ 1.6, \ \text{CHCl}_3, \ 97\% \ ee \ from \ HPLC) & \\
\text{Absolute configuration: } (R,2S,4S) & \\
\end{align*}
\]

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\[
\begin{align*}
\text{C}_{14}\text{H}_{26}\text{O}_4 & \\
\text{(2S,4S)-4-(tert-Butyl)-2-((R)-1-hydroxy-2,2-dimethoxyethyl)-cyclohexanone} & \\
\text{Source of chirality: (S\_a)-Binam and L-Pro} & \\
\{\alpha\}_D^{20} = -100 \ (c \ 3, \ \text{CHCl}_3, \ 95\% \ ee \ from \ GC) & \\
\text{Absolute configuration: } (R,2S,4S) & \\
\end{align*}
\]

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\[
\begin{align*}
\text{C}_7\text{H}_{14}\text{O}_4 & \\
\text{(R)-4-Hydroxy-5,5-dimethoxypentan-2-one} & \\
\text{Source of chirality: (S\_a)-Binam and L-Pro} & \\
\{\alpha\}_D^{20} = -35 \ (c \ 0.8, \ \text{CHCl}_3, \ 99\% \ ee \ from \ GC) & \\
\text{Absolute configuration: } (R) & \\
\end{align*}
\]
Enantioselective aldol reactions with aqueous 2,2-dimethoxyacetaldehyde organocatalyzed by binam-prolinamides under solvent-free conditions

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Abstract—Aqueous 2,2-dimethoxyacetaldehyde (60%wt solution) is used as acceptor in aldol reactions, with cyclic and acyclic ketones and aldehydes as donors, organocatalyzed by 10 mol% of N-tosyl-(Sa)-binam-L-prolinamide [((Sa)-binam-sulfo-L-Pro] at rt under solvent-free conditions. The corresponding monoprotected 2-hydroxy-1,4-dicarbonyl compounds are obtained in good yields and high levels of diastero- and enantioselectivity mainly as anti-aldols. In the case of 4-substituted cyclohexanones a desymetrization process takes place affording mainly the anti,anti-aldols. 2,2-Dimethyl-1,3-dioxan-5-one allows the synthesis of a useful intermediate for the preparation of carbohydrates in higher yield, de and ee than with L-Pro as organocatalyst.

1. Introduction

Organocatalyzed direct aldol reactions has become a fundamental reaction in asymmetric synthesis.1 Since the pioneering work of List2 using L-proline as catalysts for intermolecular aldol reactions a plethora of organocatalysts under several reaction conditions have been developed.7 The scope of ketones and aldehydes as donors and electrophiles has been extensively studied. Of special interest is the use of glyoxal dimethyl acetal as acceptor for the direct access to monoprotected 2-hydroxy-1,4-dicarbonyl compounds. This synthetic equivalent to protected glyoxal is available as 60%wt solution in water and has been used directly in biomimetic organocatalyzed asymmetric synthesis of carbohydrates by means of aldol reactions.8 However, few examples using this aldehyde as acceptor has been described. For the aldehyde-ketone aldol reaction,4a-d L-Pro in DMF4a,b or in DMSO,4c,d O-tert-Bu-L-threonine (1)4e in NMP and its derivative 2,4f primary amines such as the trans-cyclohexane-1,2-diamine derived catalyst 3 with TfOH4g and 4 with H3PW12O404h have been used as catalysts (Figure 1). Hayashi et al. used L-Pro under solvent free conditions8 with moderate to high diastere and enantioselectivity. On the other hand, for the aldehyde-aldehyde aldol reaction using glyoxal dimethyl acetal as acceptor,4j-m different organocatalysts such as 4-hydroxy-L-proline derivative 5 in water,4j the diarylpropionol 64k in DMF and L-histidine in water4l,m have been employed (Figure 1). In addition, L-Pro under solvent-free conditions has been also used for the aldol reaction of phenylpropanal.4i

Figure 1. Organocatalysts used in aldol reactions with 2,2-dimethoxyacetaldehyde.

Our research group and also others have found that (Sa)-binam-derived prolinamides 7-10 and their enantiomers5,6 have shown good catalytic activity in inter and intramolecular aldol reactions in organic solvents, in aqueous media and specially under solvent-free7 conditions (Figure 2). Prolinamides 7 and 8 have been used as recoverable catalysts in intermolecular aldol reactions by simple extractive acid-base work-up.5 On the other hand, N-tosyl-(Sa)-binam-L-prolinamides [(Sa)-binam-sulfo-L-Pro] 9a and 10a have shown their

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efficiency as general organocatalysts for inter- and intramolecular aldol reactions in water and under solvent-free conditions. However, in order to recover and to reuse them, they have covalently supported to polymers and also in silica gel (Figure 2). We report in this paper the application of binam-prolinamides as catalysts for the direct asymmetric aldol reaction of 2,2-dimethoxyacetalddehyde with different carbonyl compounds for the enantioselective and general synthesis of 2-hydroxy-1,4-dicarbonyl compounds.

2. Results and discussion

Initial attempts were carried out using commercially available aqueous 60% wt solution of 2,2-dimethoxyacetalddehyde with 10 equiv of cyclohexanone as a model reaction (11c) and 20 mol% of the organocatalyst at rt under conventional magnetic stirring (Scheme 1 and Table 1). By using (S)-binam-L-Pro 7, the anti-aldol 12c was obtained quantitatively with 91% de and 88% ee after 1 d reaction time (Table 1, entry 1). The absolute configuration of 12c was assigned according to the data of the same compound prepared by using L-Pro as catalyst. Diasteromeric catalyst (S)-binam-D-Pro 8 afforded ent-12c in poorer results, 88% de and 72% ee, than 7 (Table 1, entry 2).

Scheme 1. Aldol reaction between cyclohexanone and 2,2-dimethoxyacetalddehyde

Table 1

<table>
<thead>
<tr>
<th>Ent. Cat. (mol%)</th>
<th>11c (eq.)</th>
<th>Additive</th>
<th>T (ºC)</th>
<th>t (d)</th>
<th>Conv (%)</th>
<th>Yld (%)</th>
<th>de (%)</th>
<th>ee (%)</th>
</tr>
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<td>-</td>
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</tr>
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<td>3</td>
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<td>75</td>
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<tr>
<td>9</td>
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<td>-</td>
<td>25</td>
<td>7</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>10</td>
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<td>-</td>
<td>25</td>
<td>7</td>
<td>-</td>
<td>-</td>
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<tr>
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<td>60</td>
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<td>100</td>
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<td>-</td>
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<td>69</td>
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<td>1</td>
<td>71</td>
<td>-</td>
<td>95</td>
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</table>

a) Determined by 1H NMR (300 MHz).

In the case of (S)-binam-sulfo-L-Pro 9a and D-Pro 10a anti-12c was obtained after 1 d in 80 and 63% isolated yield, respectively, giving 9a the best stereochemical results for 12c, 96% de and 97% ee (Table 1, entries 3 and 4, respectively). Whereas, ent-12a was obtained in lower 92% de and 91% ee using organocatalyst 10a (Table 1, entry 4).
For the screening of the stoichiometry of the reaction 9a was used as organocatalyst showing that the amount of cyclohexanone (11e) could be reduced to 2 equiv giving full conversion and similar stereochemical results (Table 1, compare entries 3 and 6). When the catalyst loading was reduced to 10 and 5 mol% lower conversions were observed but with similar stereochemical results than with 20 mol% (Table 1, entries 7 and 8). Unfortunately, using supported catalysts 9b and 9d (10 mol%) and 2 equiv of 11a for 7 d, the reaction failed (Table 1, entries 9 and 10). Under the same reaction conditions L-Pro afforded lower for 7 d, the reaction failed (Table 1, entries 9 and 10). Under the same reaction conditions L-Pro afforded lower conversions than with 9a (Table 1, compare entries 7 and 11). In the case of Hayashi’s conditions, anti–12c was obtained, after 92 h reaction time and using 5 equiv of 11c and 30 mol% of L-Pro, in 80% yield as a 10:1 diastereomer ratio and 93% ee. The influence of the reaction temperature was then determined. Thus, when the temperature was lowered down to 0 °C the enantioselection for anti–12c remained essentially the same than when working at 25 °C, but the reaction time increased form 1 to 2 d (Table 1, entry 12). The effect of acids as additives was studied with 5 mol% of catalyst 9a and 5 mol% loading of benzoic, 4-nitrobenzoic, acetic and dichloroacetic acids (Table 1, entries 13-16). In general similar results were obtained than without additive (Table 1, compare entry 8 with entries 13-16).

The scope of the aldol reaction with different cyclic ketones (2 equiv) were performed with 9a (10 mol%) at rt (Scheme 2 and Table 2). Cyclobutanone (11a) showed a lower diastereoselectivity than cyclohexanone affording anti–12a in 34% de and modest 50% yield, although in 97% ee (Table 2, entry 1). On the other hand, cyclopentanone (11b) afforded as usual mainly syn–12b in 62% de, higher than the 0% de obtained under L-Pro catalysis. The syn-aldol 12b was obtained in similar 95% ee than with L-Pro (93%) in high yields, de and ee (Table 2, entries 9-11).

Table 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>No.</th>
<th>t (h)</th>
<th>Yield (%)</th>
<th>dr</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12a</td>
<td>48</td>
<td>50</td>
<td>67:33</td>
<td>97</td>
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<tr>
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<td>12b</td>
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<td>74</td>
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<tr>
<td>3</td>
<td>12c</td>
<td>32</td>
<td>87</td>
<td>98:2</td>
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</tr>
<tr>
<td>4</td>
<td>12d</td>
<td>50</td>
<td>82</td>
<td>97:3</td>
<td>95</td>
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</tr>
<tr>
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<td>12e</td>
<td>50</td>
<td>73</td>
<td>91:9</td>
<td>92</td>
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</tr>
<tr>
<td>6</td>
<td>12f</td>
<td>48</td>
<td>66</td>
<td>99:1</td>
<td>92</td>
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<tr>
<td>7</td>
<td>12g</td>
<td>48</td>
<td>81</td>
<td>26:74</td>
<td>96</td>
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</tr>
<tr>
<td>8</td>
<td>12h</td>
<td>48</td>
<td>68</td>
<td>98:2</td>
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</tr>
<tr>
<td>9</td>
<td>12i</td>
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<td>80</td>
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<td>10</td>
<td>12j</td>
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<tr>
<td>11</td>
<td>12k</td>
<td>48</td>
<td>93</td>
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<td>95</td>
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</tbody>
</table>

Acyclic ketones 11l-p were allowed to react with 2,2-dimethoxyacetalddehyde under the same reaction time, 12h in 47% yield, 90% de and 83% ee under the same solvent-free conditions. Whereas, L-Pro (30 mol%) in DMF at 2 °C gave 12h in 69% yield, 88% de and 90% ee. Under similar reaction conditions using L-Pro (20 mol%) but at 4 °C, 12h was obtained in 60% yield, 18:1 dr and 98% ee. Similar results, 60% yield, 84% de and 96% ee have been obtained using dry DMSO at 5 °C in the presence of LiCl. When 4-substituted cyclohexanones 11l-k were used as donors a concomitant desymmetrization took place giving mainly anti,anti-aldols 12i-k in high yields, de and ee (Table 2, entries 9-11).
conditions to give aldols 12l-p (Scheme 3, Table 3). Acetone (11i) gave aldol 12l in high 99% ee and moderate 55% yield (Table 3, entry 1). In the case of butan-2-one (11m), a 1:9 mixture of regioisomers 12m were obtained (Table 3, entry 2). The major iso-isomer was isolated in 48% yield and in 95% ee. When α-alkoxyacetones 11n and 11o were allowed to react with 2,2-dimethoxyacetaldelyde, anti- and iso-aldols 12n and 12o were obtained as 2:1 and 1:1 regiosomeric mixtures, respectively (Table 3, entries 3 and 4). The anti-aldols 12n and 12o were isolated in 82 and 90% de, respectively, and in 90 and 94% ee. A higher regioselectivity was observed in the case of α-chloroacetone (11p) affording aldol 12p as a 9:1 mixture of anti:iso regioisomers (Table 3, entry 5). The major anti-isomer 12p was isolated in 80% de and in 97% ee.

![Scheme 3](image)

Scheme 3. Aldol reaction between acyclic ketones and 2,2-dimethoxyacetaldelyde.

<table>
<thead>
<tr>
<th>Ent.</th>
<th>Product</th>
<th>No.</th>
<th>t (d)</th>
<th>Yield (°)</th>
<th>anti/syn</th>
<th>de (b)</th>
<th>ee (c)</th>
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<td>55</td>
<td></td>
<td>-</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>12m</td>
<td>4</td>
<td>48</td>
<td>10:90</td>
<td>-</td>
<td>95</td>
</tr>
<tr>
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<td>53</td>
<td>90:10</td>
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<td>97</td>
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</tbody>
</table>

a) Reaction conditions: 60%wt aqueous 2,2-dimethoxyacetaldelyde (0.25 mmol), alkanone (0.5 mmol) and 9a (10 mol%) at rt.
b) Determined by GC with a chiral column CP CHIRALSIL DEX CB.
c) Determined by HPLC with a chiral column Chiralpak IA.

d) Determined by HPLC with a chiral column Chiralpak AD-H, and automatic injector Agilent Technologies 1100, using mixtures of n-hexane/isopropl alcohol (IPA) as mobile phase, at 25 °C. Analytical TLC was performed on silica gel plates and the spots were visualized using KMnO4 solution. For flash chromatography we employed silica gel 60 (0.040–0.063 mm). The absolute configuration of aldols 12b,c,h and diol 14 was assigned according to the literature data and the rest of aldols by analogy with the [α]D26 values.

d) Determined by HPLC with a chiral column Chiralpak IA.

d) Determined by GC with a chiral column CP CHIRALSIL DEX CB.

d) Determined by GC with a chiral column Chiralpak IA.

d) Determined by HPLC with a chiral column Chiralpak AD-H, and automatic injector Agilent Technologies 1100, using mixtures of n-hexane/isopropl alcohol (IPA) as mobile phase, at 25 °C. Analytical TLC was performed on silica gel plates and the spots were visualized using KMnO4 solution. For flash chromatography we employed silica gel 60 (0.040–0.063 mm). The absolute configuration of aldols 12b,c,h and diol 14 was assigned according to the literature data and the rest of aldols by analogy with the [α]D26 values.

![Scheme 4](image)

Scheme 4. Aldol reaction between 3-phenylpropanal (13) and 2,2-dimethoxyacetaldelyde.

3. Conclusions

It can be concluded that binam-prolinamides can be used as chiral catalysts to perform the aldol reaction of 2,2-dimethoxyacetaldelyde as acceptor with cyclic and acyclic ketones as well as aldehydes under solvent-free conditions, just in the presence of 3.8 equiv of water from the aqueous 60%wt 2,2-dimethoxyacetaldelyde. From the assayed unsupported and supported binam-derived organocatalysts, (S)-binam-sulfo-L-prolinamide has shown the highest efficiency for this type of aldol reaction better than the previous described reactions with L-Pro under the same solvent-free conditions.

4. Experimental

4.1. General

Catalysts 7-10 were prepared according to literature. All the reagents were commercially available and used without further purification. 1H NMR (300 MHz) and 13C NMR (75 MHz) spectra were obtained at 25 °C using CDCl3 as solvent and chemical shifts are reported as δ values relative to TMS as internal standard. IR spectra were obtained with Jasco 4100 LE (Pike Piracle ATR). High resolution mass spectra (HRMS-ESI) were obtained on a Waters LCT Premier XE apfortus equipped with a time of flight (TOF) analyzer and the samples were ionized by ESI techniques and introduced through an ultra-high pressure liquid chromatography (UPLC) model Waters ACQUITY H CLASS. Optical rotations were measured on a Jasco P-1030 polarimeter with a 5 cm cell (c given in g/100 mL). GC analyses were performed on an Agilent Technologies 7820 GC System. HPLC analyses were performed on equipped with a chiral columns Chiralpak IA and Chiralpak AD-H, and automatic injector Agilent 1100, using mixtures of n-hexane/isopropl alcohol (IPA) as mobile phase, at 25 °C. Analytical TLC was performed on silica gel plates and the spots were visualized using KMnO4 solution. For flash chromatography we employed silica gel 60 (0.040–0.063 mm). The absolute configuration of aldols 12b,c,h and diol 14 was assigned according to the literature data and the rest of aldols by analogy with the [α]D26 values.

4.2. General procedure for the aldol reaction

To a mixture of the 2,2-dimethoxyacetaldelyde 60%wt aqueous solution (0.038 mL, 0.25 mmol) and organocatalyst 9a (10 mol%) at rt was added the
corresponding carbonyl compound (0.5 mmol). The reaction was stirred until the 2,2-dimethoxyacetalddehyde was consumed (monitored by TLC). The resulting residue was purified by column chromatography on silica gel (hexanes/EtOAc) to yield the pure aldo product.

4.2.1. (S)-2-((R)-1-Hydroxy-2,2-dimethoxyethyl)cyclobutanone 12a

Colorless oil (21 mg, 50%); [α]D = –5 (c 0.5, CHCl3, anti/syn: 67/33, ee = 97% from GC); Rf = 0.32 (Hex/EtOAc: 1/1). IR: ν 3642 (OH), 1579 (C=O). 1H NMR (300 MHz, CDCl3): δ 4.55 (d, J = 7.1 Hz, 1H), 3.74 (dd, J = 7.0, 4.1 Hz, 1H), 3.68–3.53 (m, 1H), 3.48 (s, 3H), 3.48 (s, 3H), 3.06–2.95 (m, 2H), 2.24–2.05 (m, 3H). 13C NMR (75 MHz, CDCl3, diastereomer mixture (60:40): δ 210.3, 207.4, 105.1, 104.6, 77.2, 76.6, 70.5, 68.4, 61.4, 60.8, 56.1, 55.0, 45.9, 45.6, 13.3, 11.6. HRMS calculated for C9H16O4: 217.0862; found: 217.0863 (M+ + Na).

4.2.2. (R)-2-((R)-1-Hydroxy-2,2-dimethoxyethyl)cyclopentanone 12b

Yellow oil (35 mg, 74%); [α]D = –50 (c 3, CHCl3, anti/syn: 14/86, ee = 95% from GC); Rf = 0.34 (Hex/EtOAc: 1/1). IR: ν 3555 (OH), 1623 (C=O). 1H NMR (300 MHz, CDCl3): δ 4.30 (d, J = 6.8 Hz, 1H), 4.19 (dd, J = 6.6, 3.5 Hz, 1H), 3.48 (d, J = 3.0 Hz, 1H), 3.46 (s, 3H), 3.42 (s, 3H), 2.44–2.26 (m, 2H), 2.19–2.03 (m, 4H).

4.2.3. (S)-2-((R)-1-Hydroxy-2,2-dimethoxyethyl)cyclohexanone 12c

Colorless oil (44 mg, 87%); [α]D = –12 (c 0.5, CHCl3, anti/syn: 98/2, ee = 97% from GC); Rf = 0.37 (Hex/EtOAc: 1/1). IR: ν 3473 (OH), 1699 (C=O). 1H NMR (300 MHz, CDCl3): δ 4.51 (d, J = 5.7 Hz, 1H), 3.63 (dd, J = 11.3, 5.6 Hz, 1H), 3.47 (s, 3H), 3.42 (s, 3H), 3.24 (d, J = 7.4 Hz, 1H), 2.71 (dd, J = 9.9, 7.2, 4.4 Hz, 1H), 1.45–2.31 (m, 2H), 2.19–2.05 (m, 2H), 1.98–1.87 (m, 1H), 1.87–1.67 (m, 3H). 13C NMR (75 MHz, CDCl3): δ 215.0, 105.4, 73.0, 55.7, 54.4, 51.4, 43.0 (CH2), 31.6 (CH2), 27.9 (CH2), 24.9 (CH3). MS (EI) m/z (%) for C9H16O4: M+ = 188 (3), 157 (10), 125 (10), 75 (100).

4.2.4. (S)-3-((R)-1-Hydroxy-2,2-dimethoxyethyl)dihydro-2H-pyran-4(3H)-one 12d

Colorless oil (42 mg, 82%); [α]D = –18 (c 0.8, CHCl3, anti/syn: 97/3, ee = 95% from GC); Rf = 0.22 (Hex/EtOAc: 1/1). IR: ν 3458 (OH), 1710 (C=O). 1H NMR (300 MHz, CDCl3): δ 4.49 (d, J = 5.7 Hz, 1H), 4.18–4.07 (m, 2H), 3.86–3.78 (m, 2H), 3.75 (dd, J = 9.9, 4.9 Hz, 1H), 3.43 (s, 3H), 3.42 (s, 3H), 3.06 (d, J = 5.2 Hz, 1H), 2.91–2.81 (m, 1H), 2.64–2.43 (m, 2H).

4.2.5. (S)-3-((R)-1-Hydroxy-2,2-dimethoxyethyl)-2-thiopyran-4(3H)-one 12e

Yellow oil (40 mg, 73%); [α]D = –47 (c 3.8, CHCl3, anti/syn: 91/9, ee = 97% from GC); Rf = 0.29 (Hex/EtOAc: 1/1). IR: ν 3460 (OH), 1704 (C=O). 1H NMR (300 MHz, CDCl3): δ 4.49 (d, J = 5.5 Hz, 1H), 3.90 (dd, J = 10.2, 6.8 Hz, 1H), 3.47 (s, 3H), 3.45 (s, 3H), 3.09–3.04 (m, 2H), 3.05–2.96 (m, 2H), 2.95 (d, J = 6.8 Hz, 1H), 2.83–2.72 (m, 4H). 13C NMR (75 MHz, CDCl3): δ 211.3, 105.6, 72.1, 55.8, 54.7, 53.9, 44.6, 33.4, 30.6. HRMS calculated for C9H16O5S: 220.0769; found: 220.0767 (M+ + Na, recalculated 220.0767).

4.2.6. (S)-tert-Butyl-3-((R)-1-hydroxy-2,2-dimethoxyethyl)-4-oxopiperidin-1-carboxylate 12f

Colorless oil (55 mg, 66%); [α]D = –20 (c 1.2, CHCl3, anti/syn: 99/1, ee = 92% from GC); Rf = 0.2 (Hex/EtOAc: 1/1). IR: ν 3435 (OH), 1689 (C=O). 1H NMR (300 MHz, CDCl3): δ 4.52 (d, J = 5.6 Hz, 1H), 4.05 (dd, J = 13.5, 5.7 Hz, 1H), 3.79–3.65 (m, 2H), 3.47–3.39 (m, 8H), 3.00–2.84 (m, 1H), 2.80–2.68 (m, 1H), 2.57–2.37 (m, 2H), 1.47 (s, 9H). 13C NMR (75 MHz, CDCl3): δ 210.0, 154.6, 80.5, 70.8, 55.9, 54.7, 54.4, 51.1, 43.1, 41.4, 41.1, 28.3. HRMS calculated for C12H14NO5: 303.1682; found: 326.1581 (M+ + Na, recalculated 326.1580). HPLC: Chiralpak IA column (98% hexane, 2% PrOH, 25°C, 1 mL/min, 230 nm), Rr = 30.0 min (major anti), Rr = 33.6 min (syn), Rr = 40.3 min (major anti).

4.2.7. (R)-2-((R)-1-Hydroxy-2,2-dimethoxyethyl)cyclohexane-1,4-dione 12g

Brown oil (43 mg, 81%); [α]D = –18 (c 1.2, CHCl3, anti/syn: 26/74, ee = 96% from GC); Rf = 0.35 (Hex/EtOAc: 1/1). IR: ν 3429 (OH), 1707 (C=O). 1H NMR (300 MHz, CDCl3): δ 4.57 (d, J = 6.8 Hz, 1H), 4.28 (dd, J = 15.7, 6.8 Hz, 1H), 3.76 (dt, J = 6.6, 3.2 Hz, 1H), 3.47–3.42 (m, 6H), 3.00–2.59 (m, 7H). 13C NMR (75 MHz, CDCl3, diastereomer mixture 1:1): δ 209.7, 208.6, 104.9, 104.1, 73.2, 69.6, 56.0, 55.0, 54.8, 54.7, 47.1, 47.0.
4.2.8. (S)-4-((R)-1-Hydroxy-2,2-dimethoxyethyl)-2,2-dimethyl-1,3-dioxan-5-one 12h

Colorless oil (39 mg, 68%); [α]D26 = −12 (c 0.6, CHCl3, anti/syn: 98/2, ee 92% from GC); Rf = 018 (Hex/EtOAc: 1/1). IR: ν 3449 (OH), 1748 (C=O). 1H NMR (300 MHz, CDCl3): δ 6.46 (d, J = 6.8 Hz, 1H), 4.49 (dd, J = 13.9, 1.3 Hz, 1H), 4.36–3.92 (m, 4H), 3.50–3.44 (m, 6H), 1.50 (s, 6H). 13C NMR (75 MHz, CDCl3): δ 206.5, 103.2, 76.0, 71.1, 67.0, 55.3, 54.3, 25.3, 24.9, 22.9. MS (EI) m/z: 239.0837. GC: CP CHIRALSIL DEX CB column (150 °C, 13.4 Psi), Rt = 24.7 min (minor syn), Rf = 25.3 min (major anti).

4.2.9. (2S,4S)-2-((R)-1-Hydroxy-2,2-dimethoxyethyl)-4-phenylcyclohexanone 12i

Colorless oil (59 mg, 80%); [α]D26 = −40 (c 1.6, CHCl3, dr: 95/3/2/1, ee 97% from HPLC); Rf = 0.36 (Hex/EtOAc: 1/1). IR: ν 3439 (OH), 1704 (C=O). 1H NMR (300 MHz, CDCl3): δ 7.45–7.17 (m, 5H), 4.34 (d, J = 6.0 Hz, 1H), 3.89 (dd, J = 5.2, 4.7 Hz, 1H), 3.50 (s, 3H), 3.49 (s, 3H), 3.44–3.35 (m, 1H), 2.83–2.76 (m, 1H), 2.72 (d, J = 4.1 Hz, 1H), 2.69–2.62 (m, 1H), 2.56–2.47 (m, 1H), 2.28–2.02 (m, 4H). 13C NMR (75 MHz, CDCl3): δ 213.1, 144.6, 128.6, 126.8, 126.4, 105.7, 73.4, 56.1, 55.2, 49.7, 41.0, 38.0, 37.0, 32.0. HRMS calculated for C16H22O4: 278.3435; found: 279.1592 (M+ + H, recalculated 279.1596). HPLC: Chiralpak IA column (98% hexane, 2% PrOH, 25°C, 1 mL/min, 210 nm), Rt = 24.7 min (minor anti), Rf = 26.4 min (major anti).

4.2.10. (2S,4S)-2-((R)-1-Hydroxy-2,2-dimethoxyethyl)-4-methylcyclohexanone 12j

Colorless oil (49 mg, 92%); [α]D26 = −80 (c 2.5, CHCl3, dr: 94/4/1, ee 96% from GC); Rf = 0.4 (Hex/EtOAc: 1/1). IR: ν 3489 (OH), 1738 (C=O). 1H NMR (300 MHz, CDCl3): δ 4.36 (d, J = 5.9 Hz, 1H), 3.68 (dd, J = 10.8, 5.6 Hz, 1H), 3.44 (s, 3H), 3.43 (s, 3H), 2.87 (d, J = 5.7 Hz, 1H), 2.72 (dd, J = 12.5, 6.1 Hz, 1H), 2.48–2.33 (m, 2H), 2.24–2.11 (m, 1H), 2.08–1.88 (m, 2H), 1.74–1.51 (m, 2H), 1.08 (d, J = 6.8 Hz, 3H). 13C NMR (75 MHz, CDCl3): δ 214.4, 105.4, 73.1, 57.7, 54.8, 48.3, 39.7, 37.7, 33.8, 27.1, 19.7. HRMS calculated for C17H24O2: 216.1362; found: 239.1248 (M+ + Na, recalculated 239.1259). GC: CP CHIRALSIL DEX CB column (120 °C, 13.4 Psi), Rt = 50.7 min (minor), Rf = 51.9 min (major).
4.2.15. (3S,4R)-3-(Benzoylxy)-4-hydroxy-5,5-dimethoxypentan-2-one 12o

Brown oil (33 mg, 49%); [α]D 26 = -28 (c 1.0, CHCl3, anti/syn: 95/5, ee 94% from HPLC); Rf = 0.15 (Hex/EtOAc; 1:1). IR: ν 3463, 1530, 1458, 1377, 1254, 1130, 1067, 840, 569 cm⁻¹. 1H NMR (300 MHz, CDCl3): δ 7.30-7.20 (m, 5H), 4.44 (d, J = 6.8 Hz, 1H), 3.84 (dd, J = 8.6, 5.7 Hz, 1H), 3.69 (m, 1H), 3.63 (m, 1H), 3.44 (s, 3H), 3.32 (s, 3H), 2.87 (s, 1H), 2.85 (s, 1H), 2.73 (br s, 1H), 2.60 (br s, 1H), 2.12-2.00 (m, 1H). 13C NMR (101 MHz, CDCl3) δ 140.1, 129.2, 128.4, 126.1, 105.1, 73.2, 62.4, 55.1, 54.4, 42.1, 35.1. HPLC (anti-product): Chiralpak AD-H column (97% hexane, 3% PrOH, 25°C, 1 mL/min, 210 nm), Rf = 27.6 min (minor), Rr = 31.3 min (major).

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