Tetrahedron: *Asymmetry* 23 (2012) 1262–1271

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

# New organocatalysts derived from tartaric and glyceric acids for direct aldol reactions

Christopher D. Maycock [a,b], M. Rita Ventura [a,*]

[a] *Instituto de Tecnologia Química e Biológica, Universidade Nova de Lisboa, Apartado 127, 2780-901 Oeiras, Portugal*
[b] *Faculdade de Ciências da Universidade de Lisboa, Departamento de Química e Bioquímica, 1749-016 Lisboa, Portugal*

ARTICLE INFO

*Article history:*
Received 2 July 2012
Accepted 14 August 2012

ABSTRACT

The synthesis of several new pyrrolidine based asymmetric organocatalysts derived from tartaric, glyceric acids and a pyrrolidine moiety is described with a study of their application in the development of an enantioselective aldol protocol. The influence of different proton donor groups, such as a primary hydroxyl or a carboxylic acid group, or their absence, on the efficiency of the organocatalyst was studied. The configuration of the tartrate derived catalysts and the presence of the rigid butane-2,3-diacetal were found to have a strong influence on the stereoselective outcome of the aldol reaction.



## 1. Introduction

The aldol reaction is one of the most important carbon–carbon bond-forming reactions in organic synthesis, and since the work of List and Barbas et al., L-proline and its structural derivatives have been extensively evaluated for their use in the organocatalysed asymmetric variant of this reaction.[1,2] The high enantioselectivity of proline mediated reactions can be attributed to their capacity to promote the formation of highly organised transition states with extensive hydrogen bonding networks. Proline is regarded as a bifunctional catalyst, since it not only acts as an enamine catalyst but also brings along its own Brønsted acid cocatalyst.[2] Moreover in some organocatalysed transformations, an acid additive is often needed.[1,10] The $pK_a$ value of proline is essential to the enamine mechanism of class I aldolase enzymes and the same has been found for proline catalysed aldol reactions.[4] In some examples, an acid is not needed,[5] but generally in these cases the catalyst is designed to induce high enantioselectivities by controlling the geometry of the enamine and through efficient face shielding.

## 2. Results and discussion

A study on the acidities of proline amide derivatives in DMSO and their influence on the stereoselectivity was recently reported.[6] An increase in amide acidity can contribute to an enhancement of enantioselectivity, this effect results from the formation of stronger hydrogen bonding and a tighter transition state. However, when the acidity of the amide varies within a relatively narrow scale, the enantioselectivity seems to depend more on structural features such as the configuration of an additional stereogenic centre or the presence of a hydroxyl or amino group at the β-position relative to the amide nitrogen, than on amide acidities.

We considered that although several simple proline derived compounds have been shown to be excellent organocatalysts,[3] the addition of extra chirality and suitably positioned participating functional groups can also create new effective organocatalysts (Fig. 1). (*S*)-Binam-L-prolinamides, in combination with benzoic acid, have recently been reported as catalysts for the aldol reactions between cycloalkyl, alkyl and α-functionalised ketones and aldehydes under solvent-free reaction conditions.[10] In these studies, 10 mol % of catalyst required 5 mol % of benzoic acid.

L-Proline amide organocatalysts derived from tartaric acid have already been described (Fig. 2).[9] The most important features recognised for the efficiency of these organocatalysts in the direct aldol reaction between 4-nitrobenzaldehyde and several ketones, with ee's ranging from 93% to >99%, were the electron-withdrawing ester groups and the presence of a free hydroxyl group in the catalyst structure. Rotational isomers are possible in this linear structure and this aspect could complicate the transition state conformations and intramolecular interactions. Tartaric and glyceric acids can be easily converted into their rigid and stereo-defined bis-acetals having, in the case of the bifunctional tartaric acid derivatives, the possibility of remote acidic (protonating) or hydrogen bonding functional groups. This rigidity combined with a pyrrolidine ring could provide a structure with catalytic activity via enamine and/or iminium intermediates. The chiral bis-acetal provides additional stereocenters, which have been shown to induce enhanced stereoselectivity in several reactions.[7,8] The selective desymmetrisation of the carboxyl groups of **8** allows the formation of difunctional molecules in enantiomerically pure form. The presence of this rigid moiety in the organocatalyst structure

* Corresponding author.
*E-mail address:* rventura@itqb.unl.pt (M. Rita Ventura).

0957-4166/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetasy.2012.08.008

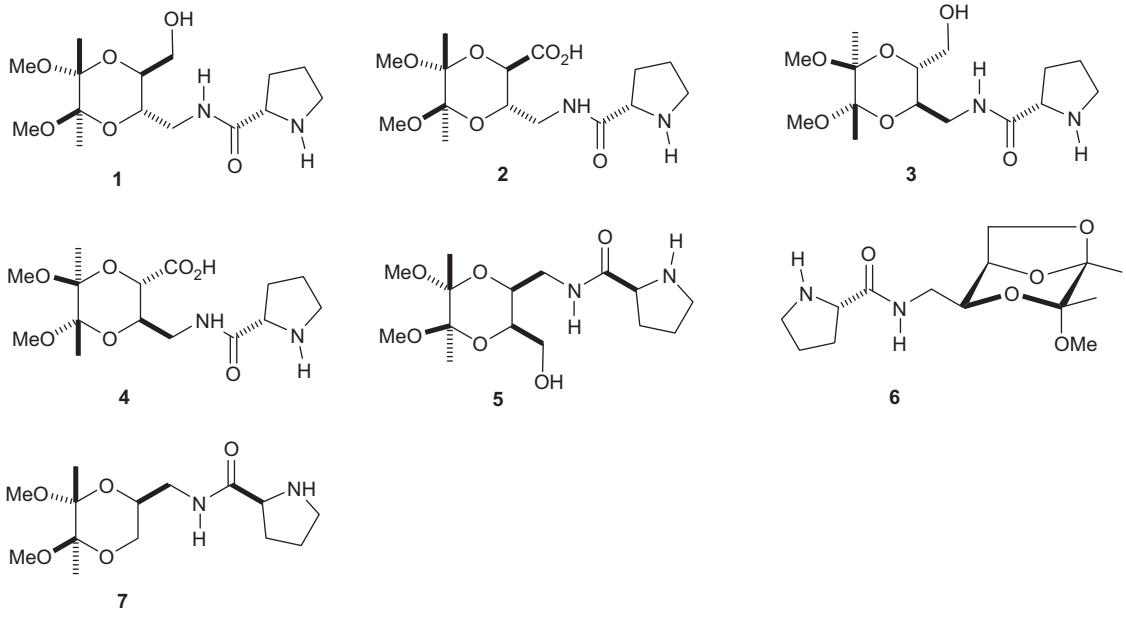



**Figure 1.** New organocatalysts from L- and D-tartaric acid and glyceric acid.

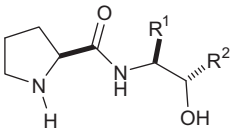



**Figure 2.** Gong's catalysts.[9]

should confer more organised and less spatially flexible transition states during the catalytic cycle, and thus favour the stereoselective outcome of the aldol reaction.

These rigid tartrate structures were coupled to a proline to form seven candidate catalysts **1**–**6** (Fig. 1), which were screened for diastereo- and enantioselectivity in aldol reactions with aromatic aldehydes. The analogous glycerate **7** was also prepared and screened. The presence of a proton donor, such as a hydroxyl or a carboxylic acid on the tartrate derivatives, and their absence, as in glycerate catalyst **7** and cyclised catalyst **6**, also provided an opportunity to determine the importance of appended acidic groups.

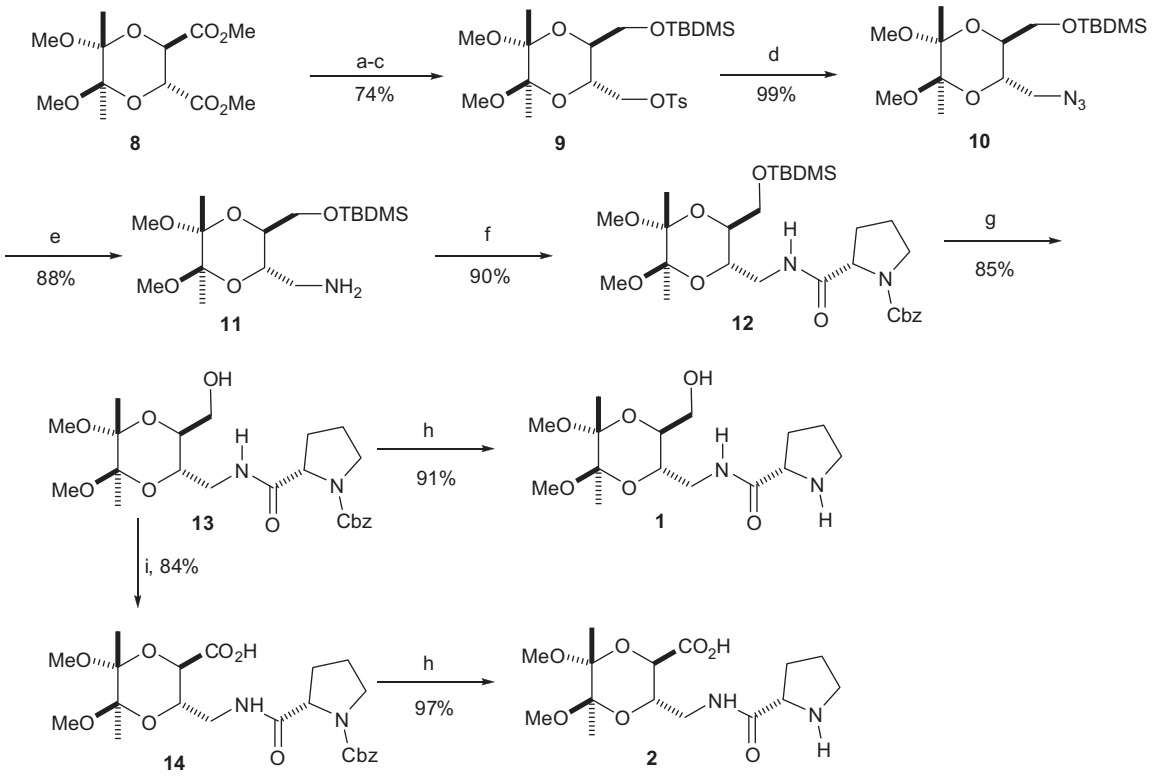
Catalysts **1** and **2** were obtained from dimethyl (2*R*,3*R*,5*R*,6*R*)-dimethoxy-2,3-dimethyl-1,4-dioxane-5,6-dicarboxylate **8**, which was easily obtained from tartaric acid.[11,12] These compounds were stable and the reactions involved in their synthesis afforded high yields.

The reduction of bis-acetal **8** with lithium aluminium hydride afforded the corresponding diol (98%), which was monosilylated in 89% yield.[12] Tosylation of the free hydroxyl group afforded **9** and substitution of the resulting tosyl group with sodium azide furnished azide **10** quantitatively. Amine **11** was obtained in 88% yield by catalytic hydrogenation of azide **10** with hydrogen and Pd/C, and immediately coupled with carboxybenzyl protected proline, using EDC, HOBt and triethylamine in dichloromethane, to afford proline amide **13** in excellent yield (90%). Hydrolysis of the silyl group with TBAF in THF, followed by hydrogenolysis of the Cbz amine protecting group afforded catalyst **1** in excellent yield. In order to obtain catalyst **2**, the primary hydroxyl group was efficiently oxidised into the corresponding carboxylic acid with the Tempo/BAIB reagent combination in 84% yield. Removal of the Cbz group afforded catalyst **2** (Scheme 1).

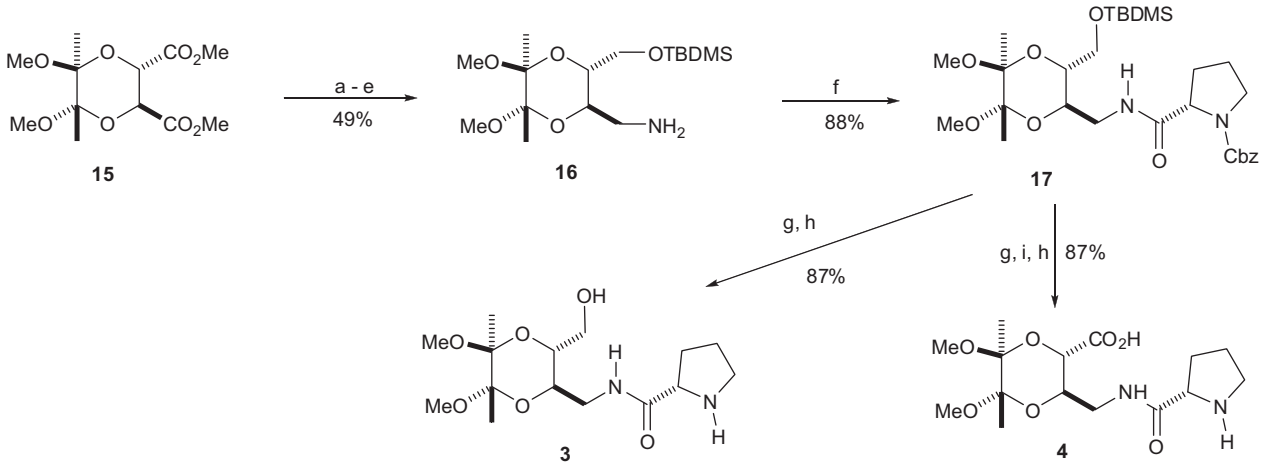
Starting from the D-tartrate derivative **15**[12,13] and following the same synthetic strategy described in Scheme 1, amine **16** was obtained in excellent overall yield (49%). Coupling with Cbz-proline produced amide **17**, a diastereoisomer of **12**, in 88% yield, which after removal of the protecting groups afforded catalyst **3**. Cleavage of the silyl group and oxidation of the free alcohol with Tempo/BAIB furnished the corresponding carboxylic acid in 96% yield. Finally, hydrogenolysis of the CBz group afforded catalyst **4** in 93% yield (Scheme 2).

The *cis*-catalyst **5**, was prepared from dithioester **18**,[12] obtained from **8**, as was described for the dimethyl tartrate **8**.[14] Oxidation of **18** by treatment with LDA in THF at −78 °C followed by the addition of 1 equiv of iodine afforded **19** in 82% yield (Scheme 3). Perhaps due to the presence of sulfur, the hydrogenation of the double bond to afford the *cis*-product was not successful. Reduction of the dithioester to afford the primary diol was attempted, however this reaction afforded a complex mixture.

Isomerisation to *cis*-dithioester **21** was performed via the formation of the enolate and reprotonation with methanol, to afford an inseparable mixture of 1.6:1 *cis*/*trans* isomers **21**:**18** (Scheme 4). Interestingly, sodium borohydride was able to selectively reduce the *trans*-isomer to the corresponding diol, and after a facile chromatographic separation, the pure *cis*-dithioester **21** was obtained. The *trans*-diol was recycled for the synthesis of organocatalysts **1** and **2** (Scheme 1). However, all attempts to reduce **21** with lithium aluminium hydride and DIBAL-H were unsuccessful, and complex mixtures were obtained. Transesterification with isopropanol and titanium tetraisopropoxide afforded the corresponding diisopropyl ester **22** in 82% yield (Scheme 5). This reaction took 10 days at 100 °C and required 2 equiv of titanium tetraisopropoxide; if less time was allowed then one of the two possible monoisopropyl esters was also recovered. Compared with the method to obtain the corresponding dimethyl *meso*-tartrate from **8**,[14] one more step is required. However this step avoids the 5d hydrogenation at very high pressure (80 bar) with high catalyst loading (20% of Rh-$Al_2O_3$). Isomerisation of **21** with DBU was studied in $CDCl_3$ and we demonstrated that enolate was formed because it was deuterated by H/D exchange from the solvent to afford the *trans*-deuterated isomer **20** (Scheme 4).




**Scheme 1.** (a) $LiAlH_4$, THF, 0 °C/rt, 98%. (b) (1) NaH, THF, rt; (2) TBDMSCl, 89%. (c) TsCl, pyr, DMAP, 0 °C/rt, 85%. (d) $NaN_3$, DMF, 70 °C. (e) $H_2$, Pd/C 10%, AcOEt/EtOH, 50 psi. (f) L-Pro-Cbz, HOBt, EDC, $Et_3N$, $CH_2Cl_2$, 0 °C/rt. (g) TBAF, THF, rt. (h) $H_2$, Pd/C 10%, MeOH, 50 psi. (i) BAIB/Tempo, $CH_2Cl_2/H_2O$.

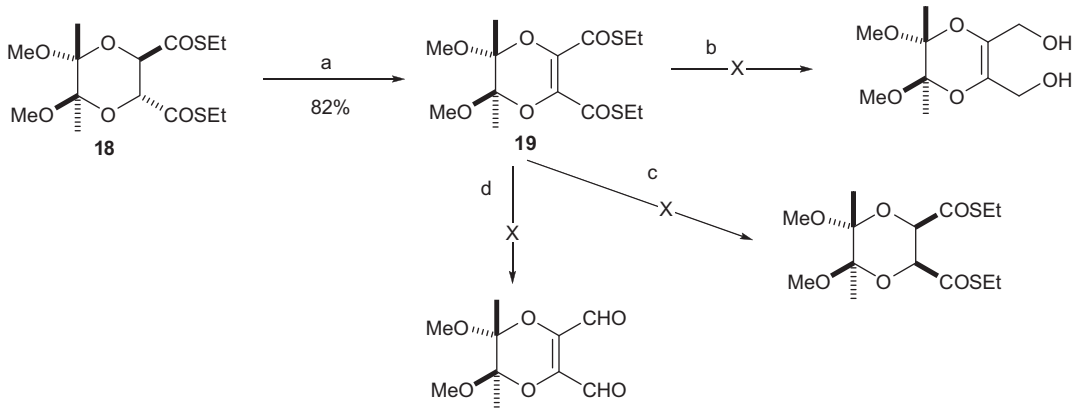



**Scheme 2.** (a) $LiAlH_4$, THF, 0 °C/rt, 81%. (b) (1) NaH, THF, rt; (2) TBDMSCl, 85%. (c) TsCl, pyr, DMAP, 0 °C/rt, 80%. (d) $NaN_3$, DMF, 70 °C, 99%. (e) $H_2$, 10%, AcOEt/EtOH, 50 psi, 90%. (f) L-Pro-Cbz, HOBt, EDC, $Et_3N$, $CH_2Cl_2$, 0 °C/rt. (g) TBAF, THF, rt, 97%. (h) $H_2$, Pd/C 10%, MeOH, 50 psi and 93%. (i) BAIB/Tempo, $CH_2Cl_2/H_2O$, rt, 96%.

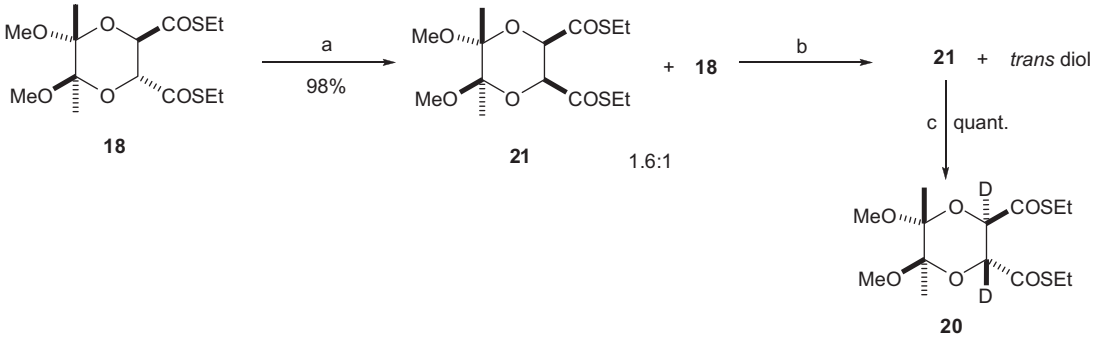
Reduction of **22** with lithium aluminium hydride afforded the *cis*-diol in excellent yield (96%, Scheme 5). Treatment of the *cis*-diol with TBDMSCl and NaH, in THF and pentane[15,16] afforded the axial silyl ether with high selectivity (60% yield). Without the use of pentane as the co-solvent, a lower selectivity of 5:1 was obtained, although the yield was higher. Attempts to silylate the equatorial hydroxyl group with TBDMSCl and imidazole in THF were unsuccessful,[15,17] and the silylated product of alcohol **28** was obtained as the major product.

The synthesis of **5** used the same sequence of steps as for the synthesis of **1**; however the treatment of the corresponding tosylated *cis*-analogue of **9** with sodium azide did not afford azide **23**, even after heating the reaction mixture for several days. Fortunately, the Mitsunobu reaction with hydrazoic acid on the mono alcohol rapidly afforded the desired azide **23** in very good yield (84%). The final steps afforded the expected products in excellent yields and the new compound **5** was obtained (Scheme 5). In order to prepare the corresponding carboxylic acid, the oxidation of the primary hydroxyl group of CBz protected **5** with TEMPO/BAIB was attempted; however a complex mixture was obtained. Organocatalyst **7** was readily prepared from glyceric acid methyl ester[8] as described in Scheme 6.

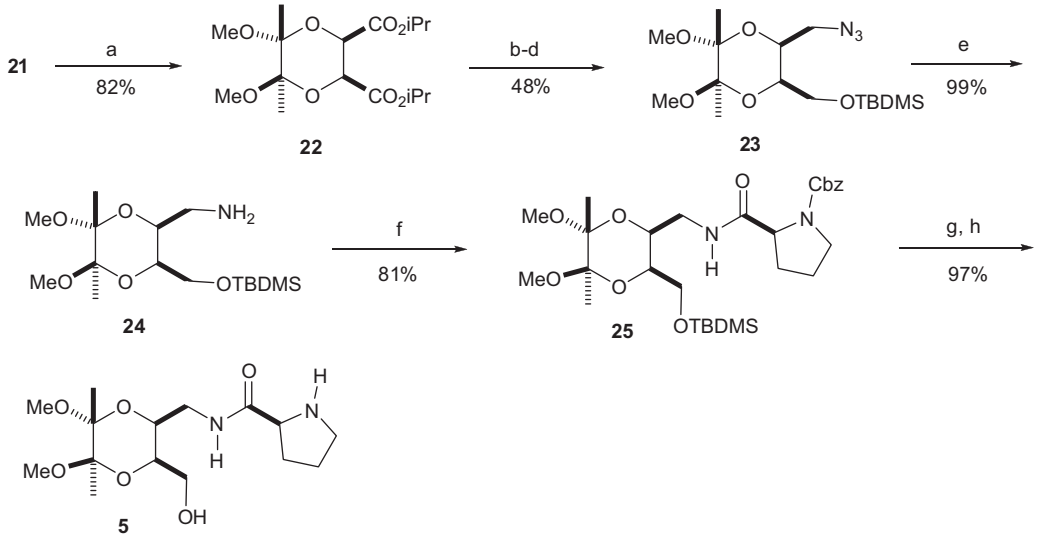
Finally, organocatalyst **6** was prepared from the bicyclic product[15] **28** with all of the steps being straightforward (Scheme 7).




**Scheme 3.** (a) (1) LDA, −78 °C; (2) $I_2$. (b) $LiAlH_4$, THF, rt/$NaBH_4$, MeOH, rt. (c) Rh/C 5%, MeOH, $H_2$ 80 atm. (d) DIBAL-H, THF, −78 °C.



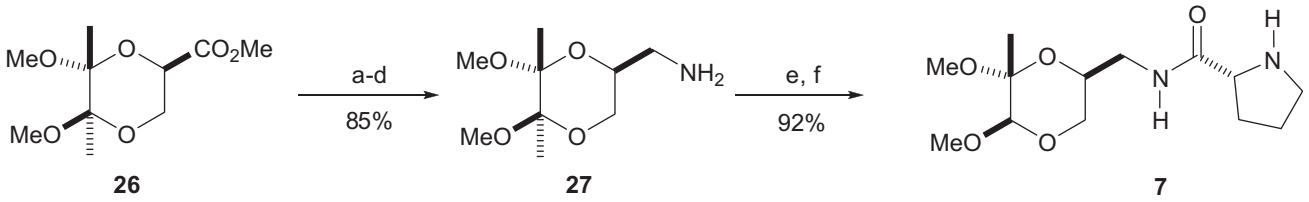

**Scheme 4.** (a) (1) LDA, THF, −78 °C; (2) MeOH. (b) $NaBH_4$, MeOH, 0 °C/rt. (c) DBU, $CDCl_3$, rt, 48 h.



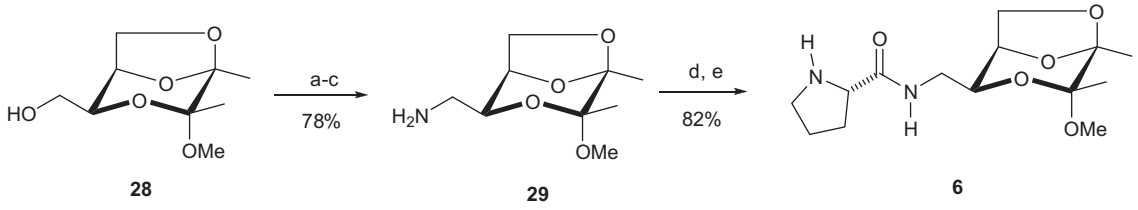

**Scheme 5.** (a) Ti(O*i*Pr)$_4$ (2 eq), *i*PrOH, 10 °C, 10 days, 82%. (b) $LiAlH_4$, THF, 70 °C, 96%. (c) (1) NaH, THF, pentane, rt; (2) TBDPSCl, rt, 60%. (d) $HN_3$, $PPh_3$, DIAD, THF, 0 °C, 84%. (e) $H_2$, Pd/C 10%, AcOEt/EtOH, 50 psi. (f) L-Pro-Cbz, HOBt, EDC, $Et_3N$, $CH_2Cl_2$, 0 °C/rt. (g) TBAF, THF, rt, 98%. (h) $H_2$, Pd/C 10%, MeOH, 50 psi, 99%.

The scope and limitations of catalysts **1**–**7** were then examined in the aldol reaction of several substituted aromatic aldehydes with acetone, cyclopentanone and cyclohexanone (Tables 1–3).

Analysis of Tables 1–3, allowed us to conclude that the best results were obtained with cyclic ketones, with ee's of up to 91% (Table 2, entry 5, Table 3, entry 8) and dr of up to 3:97 (Table 2, entry 11). We believe that the amide NH participated in the transition state, establishing a hydrogen bond with the aldehyde,[9] and that the reaction proceeded through an enamine intermediate. In Figure 3, a proposed transition state for the aldol reaction between cyclohexanone and 2-nitrobenzaldehyde catalysed by **3** is shown. In general, 2-nitrobenzaldehyde afforded higher enantioselectivities than 4-nitrobenzaldehyde, and this may be explained by the formation of a hydrogen bond between the alcohol (or carboxylic acid) group of the catalyst and the nitro group at the *ortho*-position. With 4-nitrobenzaldehyde, the formation of the

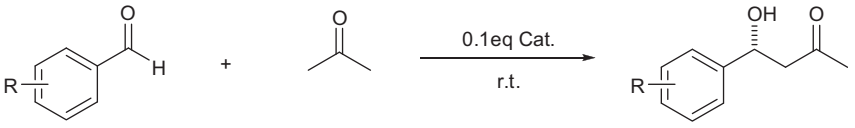



**Scheme 6.** (a) $LiAlH_4$, THF, 97%. (b) TsCl, Pyr, DMAP, 95%. (c) $NaN_3$, DMF, 70 °C, 93%. (d) $H_2$, Pd/C 10%, AcOEt/EtOH, 50 psi, 99%. (e) L-Pro-CBz, HOBt, EDC, $Et_3N$, $CH_2Cl_2$, 93%. (f) $H_2$, Pd/C 10%, MeOH, 50 psi, 99%.




**Scheme 7.** (a) TsCl, pyr, DMAP, 0 °C/rt, 87%. (b) $NaN_3$, DMF, 70 °C, 90%. (c) $H_2$, Pd/C 10%, AcOEt/EtOH, 50 psi, 99%. (d) L-Pro-CBz, HOBt, EDC, $Et_3N$, $CH_2Cl_2$, 0 °C/rt, 83%. (e) $H_2$, Pd/C 10%, MeOH, 50 psi, 99%.

**Table 1**
Aldol reaction of various 2- and 4-substituted benzaldehydes with acetone catalysed by pyrrolidines **1–7**




| Entry | Catalyst | R | Time (h) | Yield (%) | ee[a] (%) |
|---|---|---|---|---|---|
| 1 | **1** | 4-$NO_2$ | 48 | 10 | 48 |
| 2 | **2** | 4-$NO_2$ | 48 | 76 | 25 |
| 3 | **3** | 4-$NO_2$ | 106 | 8 | — |
| 4 | **4** | 4-$NO_2$ | 24 | 43 | 69 |
| 5 | **5** | 4-$NO_2$ | 48 | 55 | 30 |
| 6 | **6** | 4-$NO_2$ | 26 | 55 | 21 |
| 7 | **7** | 4-$NO_2$ | 48 | 66[b] | — |
| 8 | **1** | 2-$NO_2$ | 48 | 19 | 61 |
| 9 | **2** | 2-$NO_2$ | 48 | 70 | 40 |
| 10 | **3** | 2-$NO_2$ | 106 | 19 | 42 |
| 11 | **4** | 2-$NO_2$ | 48 | 80 | 74 |
| 12 | **5** | 2-$NO_2$ | 48 | 64 | 39 |
| 13 | **6** | 2-$NO_2$ | 26 | 53 | 21 |
| 14 | **7** | 2-$NO_2$ | 48 | 42 | 43 |

[a] Determined by HPLC on a chiralpak AD-H column. Entries 1–7: flow 0.8 mL/min, $\lambda$ = 254 nm, *i*PrOH/hexane = 1:9, $t_R$ (major) = 20.5 min (*R*), $t_R$ (minor) = 21.7 min (*S*).[18] Entries 8–14: flow 0.8 mL/min, $\lambda$ = 254 nm, *i*PrOH/hexane = 0.5:9.5, $t_R$ (major) = 33.0 min (*R*), $t_R$ (minor) = 34.7 min (*S*).[19]

[b] The elimination product was obtained.

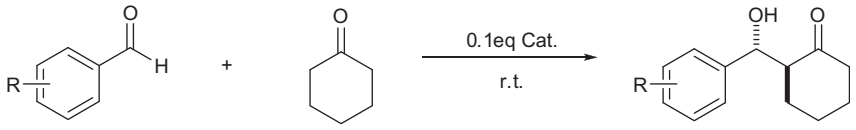
corresponding hydrogen bond is very unlikely. The rigid acetal structure constrains the positions of the substituents at the tartrate carbons 2 and 3 since no rotation around the bond between these two carbons is allowed, and the conformation of the six membered ring of the acetal also imposes strong limitations on the position of the hydroxymethyl and the prolinamidemethyl groups.

Catalyst **1** afforded very good enantioselectivities in the aldol reactions of cyclohexanone with 2-nitrobenzaldehyde (ee 89%, Table 2, entry 8), and of cyclopentanone with the same aldehyde (ee 91% for the *anti*-isomer, Table 3, entry 8). Catalyst **5**, with a *cis*-orientation of the hydroxyl group and the amide bond of proline, was not generally a better catalyst than the *trans* one, however it was a very efficient catalyst for the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde, affording 81% of a mixture of *syn*- and *anti*-diastereoisomers with an ee of 91% for the *anti*-isomer (Table 2, entry 5).

In general, catalysts **1**, **3** and **6** were the best ones for the aldol reactions with cyclopentanone with each aldehyde tested (Table 3). Catalysts **6** and **7** did not possess an extra proton donor group nor an additional stereogenic centre, however compound **7** was a very good catalyst for the reaction between 4-nitrobenzaldehyde and cyclopentanone (82% yield, ee 81% for the *syn*-isomer, Table 3, entry 7), and also for the same reaction employing 2-nitrobenzaldehyde (Table 3, entry 14). This same catalyst afforded exclusively the elimination product in the aldol reaction between acetone and 4-nitrobenzaldehyde (66% yield, Table 1, entry 7).

Some aldehydes were better substrates than others, 2-nitrobenzaldehyde afforded the best results, followed by 4-nitrobenzaldehyde. The addition of additives had different effects, acetic acid improved the yields of most of the reactions catalysed by **1** and **3**. The addition of TFA did not cause any significant improvements, while the use of DMSO as a co-solvent, which improves the yield of

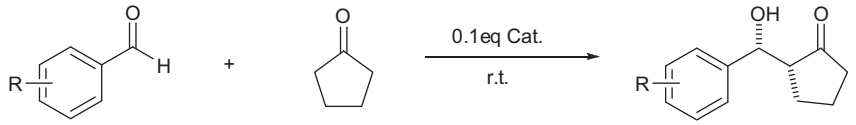
**Table 2**
Aldol reaction of various 2- and 4-substituted benzaldehydes with cyclohexanone catalysed by pyrrolidines **1–7**




| Entry | Catalyst | R | Time (h) | Yield (%) | dr[a] (*syn*:*anti* %) | ee[b] (%) |
|---|---|---|---|---|---|---|
| 1 | **1** | 4-$NO_2$ | 48 | 49 | 37:63 | 22/54 |
| 2 | **2** | 4-$NO_2$ | 43 | 51 | 14:86 | 10/46 |
| 3 | **3** | 4-$NO_2$ | 90 | 49 | 23:77 | 5/84 |
| 4 | **4** | 4-$NO_2$ | 20 | 25 | 29:71 | 29/65 |
| 5 | **5** | 4-$NO_2$ | 48 | 81 | 31:67 | 11/91 |
| 6 | **6** | 4-$NO_2$ | 22 | 42 | 42:58 | 11/58 |
| 7 | **7** | 4-$NO_2$ | 48 | 44 | 43:57 | 28/34 |
| 8 | **1** | 2-$NO_2$ | 44 | 51 | 18:82 | —/89 |
| 9 | **2** | 2-$NO_2$ | 43 | 43 | 13:87 | 77/27 |
| 10 | **3** | 2-$NO_2$ | 90 | 40 | 10:90 | —/87 |
| 11 | **4** | 2-$NO_2$ | 48 | 76 | 3:97 | —/79 |
| 12 | **5** | 2-$NO_2$ | 48 | 54 | 37:63 | 10/37 |
| 13 | **6** | 2-$NO_2$ | 72 | 38 | 36:54 | 84/26 |
| 14 | **7** | 2-$NO_2$ | 48 | 53 | 28:72 | 72/85 |

[a] Determined from the crude $^1$H NMR spectrum.
[b] Determined by HPLC on a chiralpak AD-H column. Entries 1–7: flow 0.8 mL/min, $\lambda$ = 254 nm, *i*PrOH/hexane = 1:9, *syn* isomers: $t_R$ = 23.8 min, $t_R$ = 26.7 min, *anti* isomers: $t_R$ (minor) = 29.3 min (2*S*,1′*R*) $t_R$ (major) = 39.7 min (2*R*,1′*S*).[18,20] Entries 8–14: flow 1 mL/min, $\lambda$ = 254 nm, *i*PrOH/hexane = 0.5:9.5, *syn* isomers: $t_R$ (major) = 29.7 min, $t_R$ (minor) = 30.9 min, *anti* isomers: $t_R$ (major) = 51.2 min (2*S*,1′*R*), $t_R$ (minor) = 55.6 min (2*R*,1′*S*).[18,20]

**Table 3**
Aldol reaction of various 2- and 4-substituted benzaldehydes with cyclopentanone catalysed by pyrrolidines **1–7**




| Entry | Catalyst | R | Time (h) | Yield (%) | dr[a] (*syn*:*anti* %) | ee[b] (%) |
|---|---|---|---|---|---|---|
| 1 | **1** | 4-$NO_2$ | 46 | 58 | 61:39 | 54/61 |
| 2 | **2** | 4-$NO_2$ | 46 | 36 | 70:30 | 10/41 |
| 3 | **3** | 4-$NO_2$ | 46 | 47 | 66:34 | 43/80 |
| 4 | **4** | 4-$NO_2$ | 46 | 36 | 70:30 | 14/28 |
| 5 | **5** | 4-$NO_2$ | 48 | 41 | 52:48 | 34/13 |
| 6 | **6** | 4-$NO_2$ | 46 | 21 | 63:37 | 1/0.3 |
| 7 | **7** | 4-$NO_2$ | 46 | 82 | 61:39 | 49/81 |
| 8 | **1** | 2-$NO_2$ | 47 | 19 | 75:25 | 70/91 |
| 9 | **2** | 2-$NO_2$ | 46 | 40 | 76:24 | 26/46 |
| 10 | **3** | 2-$NO_2$ | 47 | 10 | 74:26 | 61/85 |
| 11 | **4** | 2-$NO_2$ | 47 | 10 | 55:45 | 9/16 |
| 12 | **5** | 2-$NO_2$ | 48 | 37 | 77:23 | 10/37 |
| 13 | **6** | 2-$NO_2$ | 48 | 17 | 78:22 | 2/18 |
| 14 | **7** | 2-$NO_2$ | 46 | 48 | 67:33 | 63/85 |

[a] Determined from the crude $^1$H NMR spectrum.
[b] Determined by HPLC on a chiralpak AD-H column. Entries 1–7: flow 0.8 mL/min, $\lambda$ = 254 nm, *i*PrOH/hexane = 1:9, *syn* isomers: $t_R$ (major) = 18.2 min, $t_R$ (minor) = 23.5 min, *anti* isomers: $t_R$ (minor) = 30.3 min (2*S*,1′*R*), $t_R$ (major) = 31.7 min (2*R*,1′*S*).[20] Entries 8–14: flow 1 mL/min, $\lambda$ = 254 nm, *i*PrOH/hexane = 0.5:9.5, *syn* isomers: $t_R$ (major) = 11.7 min, $t_R$ (minor) = 20.1 min, *anti* isomers: $t_R$ (major) = 26.6 min, $t_R$ (minor) = 29.2 min.[21–23]

L-proline catalysed aldol reactions,[24] also did not have any effect with our organocatalysts. Performing the reactions at lower temperatures, that is, −20 °C, with catalyst **2**, reduced the yield and ee of the aldol reaction between acetone and 2- and 4-nitrobenzaldehyde.

## 3. Conclusion

We can conclude that the configuration of the tartrate has a relevant influence on the stereochemistry of the aldol reaction and the presence of the proton donor group was also important for the stereocontrol. None of the catalysts were generally applicable

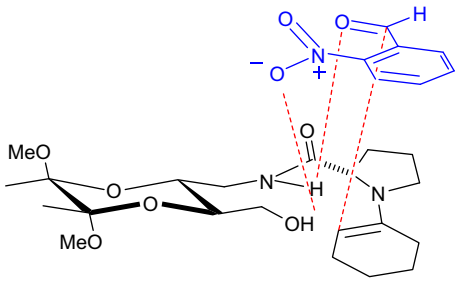



**Figure 3.** Proposed transition state for the aldol reaction of 2-nitrobenzaldehyde with cyclohexanone catalysed by **3**.

but they were very good catalysts for particular aldol reactions although highly dependent on the substrate structure, both the aldehyde and the ketone. We think that this is a consequence of the conformational rigidity conferred by the chiral dioxane acetal. This could be an important feature for the development of new selective organocatalysts requiring precise tuning of the configuration of the substituents on tartrate, the choice of the proton donor group and the configuration of the proline, the latter of which was not studied herein. Future work involving detailed theoretical studies of the possible transition states for the reactions presented, and the application of these new organocatalysts in other reactions is currently in progress.

## 4. Experimental

### 4.1. General

$^1$H NMR spectra were obtained at 400 MHz in $CDCl_3$, DMSO-$d_6$ or $D_2O$ with chemical shift values ($\delta$) in ppm downfield from tetramethylsilane in the case of $CDCl_3$, and $^{13}$C NMR spectra were obtained at 100.61 MHz in $CDCl_3$, DMSO-$d_6$ or $D_2O$. Assignments are supported by 2D correlation NMR studies. Medium pressure preparative column chromatography: silica gel Merck 60 H. Analytical TLC: Aluminium-backed silica gel Merck 60 $F_{254}$. Specific rotations ($[\alpha]_D^{20}$) were measured using an automatic polarimeter. Reagents and solvents were purified and dried according to the literature.[25] All reactions were carried out under an inert atmosphere (argon), except when the solvents were undried. The enantiomeric excesses were determined by HPLC on a Waters 600E/U6K instrument using a Daicel Chiralpack AD-H column.

### 4.2. (2*R*,3*R*,5*R*,6*R*)-3-*tert*-Butyldimethylsilyloxymethyl-2-*p*-toluenesulfonyloxymethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane 9

To a solution of (2*R*,3*R*,5*R*,6*R*)-3-*tert*-butyldimethylsilyloxymethyl-2-hydroxymethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane (2.38 g, 6.8 mol) in pyridine (10 mL) at 0 °C, was added *p*-toluenesulfonyl chloride (1.94 g, 10.2 mmol) and a catalytic quantity of DMAP and the mixture was stirred for 20 h at rt. The mixture was then washed with a solution $NaHCO_3$ (sat) and extracted with ethyl ether (3 × 10 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated to afford a light yellow oil. The crude product was subjected to flash column chromatography on silica gel (2/8 AcOEt/hexane) to afford the pure product **9** (2.8 g, 85%) as colourless oil. $[\alpha]_D^{20} = -80.2$ (*c* 0.56, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ 7.78 (2H, d, *J* = 8.3 Hz), 7.31 (2H, d, *J* = 8.0 Hz), 4.39 (1H, dd, *J* = 10.8 Hz, *J* = 2.4 Hz), 4.01 (1H, dd, *J* = 10.8 Hz, *J* = 7.6 Hz), 3.91–3.86 (1H, m), 3.60 (2H, d, *J* = 5.2 Hz), 3.54–3.49 (1H, m), 3.21 (3H, s), 3.18 (3H, s), 2.44 (3H, s), 1.23 (3H, s), 1.20 (3H, s), 0.85 (9H, s), 0.039 (3H, s), 0.027 (3H, s). $^{13}$C NMR ($CDCl_3$): $\delta$ 144.6, 133.2, 129.7, 128.0, 98.7, 98.5, 69.5, 69.4, 68.9, 63.3, 47.9, 47.8, 25.7, 21.6, 18.1, 17.4, 17.3, −5.52, −5.55. FT-IR (film): 2954, 2930, 1265 cm$^{-1}$. Anal. Calcd for $C_{23}H_{40}O_8SSi$: C 54.73, H 7.99, S 6.35. Found: C 54.40, H 7.69, S 6.30.

### 4.3. (2*R*,3*R*,5*R*,6*R*)-3-*tert*-Butyldimethylsilyloxymethyl-2-azidomethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane 10

To a solution of **9** (2.5 g, 4.9 mmol) in DMF (10 mL) was added sodium azide (0.348 g, 5.4 mmol) at room temperature. The mixture was stirred during 18 h at 70 °C, after which the mixture was washed with water and extracted with ethyl acetate (3 × 10 mL). The organic phase was dried over anhydrous magnesium sulfate and the solvents were evaporated under reduced pressure to give compound **10** as a light yellow oil, (1.8 g, 99%). $[\alpha]_D^{20} = -45.5$ (*c* 1.4, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ 3.86–3.79 (1H, m), 3.66–3.60 (3H, m), 3.40–3.39 (2H, m), 3.54–3.49 (1H, m), 3.30 (3H, s), 3.26 (3H, s), 1.32 (3H, s), 1.27 (3H, s), 0.88 (9H, s), 0.06 (3H, s), 0.05 (3H, s). $^{13}$C NMR ($CDCl_3$): $\delta$ 98.7, 71.4, 69.7, 63.7, 50.9, 47.9, 25.8, 18.2, 17.5, 17.4, −5.45, 5.47. FT-IR (film): 2098 cm$^{-1}$. Anal. Calcd for $C_{16}H_{33}N_3O_5Si$: C 51.17, H 8.86, N 11.19. Found: C 50.90, H 8.56, N 10.99.

### 4.4. (2*R*,3*R*,5*R*,6*R*)-3-*tert*-Butyldimethylsilyloxymethyl-2-aminomethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane 11

Azide **10** (1.2 g, 3.18 mmol) in AcOEt/EtOH (10 mL/10 mL) was hydrogenated at 50 psi in the presence of a catalytic amount of Pd/C 10% (0.25 equiv). After 3 h, the reaction mixture was filtered, the solvent was evaporated and the residue dried under vacuum to afford amine **11** as a viscous colourless oil (1.0 g, 88%). This material was sufficiently pure to proceed with the next step. $[\alpha]_D^{20} = -98.1$ (*c* 0.80, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ 3.70–3.59 (3H, m), 3.20 (6H, s), 2.88–2.72 (2H, m), 1.32 (3H, s), 1.30 (3H, s), 0.88 (9H, s), 0.06 (6H, s). $^{13}$C NMR ($CDCl_3$): $\delta$ 98.6, 98.4, 72.3, 70.6, 63.7, 47.8, 47.7, 42.7, 25.8, 18.2, 17.6, 17.5, −5.44, −5.47. FT-IR (film): 3690, 1265 cm$^{-1}$. HR-MS: Calcd for $C_{16}H_{36}O_5NSi$ [M$^+$+H]: 350.2357. Found: 350.2365.

### 4.5. (2*S*)-*N*-Benzyloxycarbonylprolinyl-[(2*R*,3*R*,5*R*,6*R*)-3-*tert*-butyldimethylsilyloxymethyl-2-aminomethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane]-amide 12

To a solution of *N*-benzyloxycarbonyl-L-proline (0.688 g, 2.76 mmol) in dichloromethane (8 mL) was added **11**, EDC (0.635 g, 3.32 mmol), HOBt (0.448 g, 3.32 mmol) and $Et_3N$ (0.46 mL, 3.32 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h, after which water was added and the aqueous layer was extracted with ethyl acetate (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated. The residue was purified through flash column chromatography on silica gel with hexane-ethyl acetate (5:5) to afford **12** as a colourless viscous oil (1.44 g, 90%). $[\alpha]_D^{20} = -109.8$ (*c* 0.51, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ 7.57–7.44 (5H, m), 5.18 (1H, dd, *J* = 12.2 Hz, *J* = 2.0 Hz), 5.02 (1H, dd, *J* = 18.9 Hz, *J* = 12.2 Hz), 3.90–3.88 (1H, m), 3.74–3.38 (6H, m), 3.30 (3H, s), 3.27 (3H, s), 3.09–3.01 (1H, m), 2.34–2.31 (1H, m), 1.98–1.88 (3H, m), 1.32 (3H, s), 1.30 (3H, s), 0.88 (9H, s), 0.06 (3H, s), 0.05 (3H, s). $^{13}$C NMR ($CDCl_3$): $\delta$ 171.5, 156.0, 136.0, 128.7, 128.1, 127.9, 98.6, 98.5, 71.0, 69.1, 67.4, 63.4, 60.8, 48.2, 47.1, 39.6, 28.7, 25.9, 24.4, 18.4, 17.6, 17.5, −5.2, −5.3. FT-IR (film): 1706, 1687 cm$^{-1}$. HR-MS: Calcd for $C_{29}H_{48}O_8N_2SiNa$ [M$^+$+Na]: 603.3072. Found: 603.3069.

### 4.6. (2*S*)-*N*-Benzyloxycarbonylprolinyl-[(2*R*,3*R*,5*R*,6*R*)-3-hydroxymethyl-2-aminomethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane]-amide 13

To a solution of compound **12** (0.914 g, 1.6 mmol) in THF (5 mL) was added tetrabutylammonium fluoride 1 M in THF (0.49 mL, 1.9 mmol). The reaction mixture was stirred at room temperature for 1 h, after which 5 mL of water was added. The mixture was then extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried over anhydrous magnesium sulfate. After removal of solvent, the residue was purified by flash column chromatography on silica gel (1/9 AcOEt/hexane) to afford the pure product **13** (0.63 g, 86%) as a viscous colourless oil. $[\alpha]_D^{20} = -85.4$ (*c* 0.32, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ 7.35–7.10 (5H, m), 5.20–5.07 (1H, m), 4.38–4.35 (1H, m), 3.78–3.43 (8H, m), 3.23 (3H, s), 3.20 (3H, s),

2.32–2.27 (1H, m), 2.04–1.91 (3H, m), 1.29 (6H, broad s). $^{13}$C NMR ($CDCl_3$): $\delta$ 169.1, 156.0, 136.3, 128.6, 128.2, 127.9, 98.7, 69.9, 67.8, 67.3, 62.3, 60.7, 47.9, 47.8, 47.0, 39.7, 28.7, 24.4, 17.5, 17.4. FT-IR (film): 3440, 3264, 1701, 1681 cm$^{-1}$. MS (ESI): *m*/*z* 405 [M$^+$−2xOMe]. HR-MS: Calcd for $C_{23}H_{34}O_8N_2Na$ [M$^+$+Na]: 489.2207. Found: 489.2217.

### 4.7. (2*S*)-Prolinyl-[(2*R*,3*R*,5*R*,6*R*)-3-hydroxymethyl-2-aminomethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane]-amide 1

Alcohol **13** (0.63 g, 1.35 mmol) in MeOH (7 mL) was hydrogenated at 50 psi in the presence of a catalytic amount of Pd/C 10% (0.25 equiv). After 3 h, the reaction mixture was filtered, the solvent was evaporated and the residue dried under vacuum to afford **1** as a viscous colourless oil (0.430 g, 96%). $[\alpha]_D^{20} = -157.3$ (*c* 1.0, $CH_2Cl_2$). $^1$H NMR (DMSO-$d_6$): $\delta$ 8.55 (1H, broad s), 4.12–5.07 (1H, m), 3.55–3.48 (2H, m), 3.38–3.31 (3H, m), 3.10 (2H, broad s), 3.08 (3H, s), 3.07 (3H, s), 2.98–2.93 (1H, m), 2.23–2.18 (1H, m), 1.80–1.70 (3H, m), 1.12 (3H, s), 1.10 (3H, s). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 168.5, 98.0, 97.9, 70.5, 68.3, 60.9, 58.7, 47.2, 47.1, 45.4, 39.0, 29.8, 23.7, 17.4, 17.39. FT-IR (film): 3388, 1677 cm$^{-1}$. HR-MS: Calcd for $C_9H_{17}O_4N_2Na$ [M$^+$−$C_6H_{11}$+Na]: 240.1086. Found: 240.1588.

### 4.8. (2*S*)-*N*-Benzyloxycarbonylprolinyl-[(2*R*,3*R*,5*R*,6*R*)-3-hydroxycarbonyl-2-aminomethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane]-amide 14

To compound **13** (0.63 g, 1.35 mmol) in dichloromethane (5 mL) and water (2.5 mL) were added BAIB (1.08 g, 3.37 mmol) and Tempo (0.044 g, 0.83 mmol). The mixture was vigorously stirred at room temperature for 3 h and then a 20% solution of $Na_2SO_3$ (5 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 5 mL). The organic phase was then washed with sat. aqueous $NaHCO_3$ solution. The aqueous phase was washed with ethyl ether and then acidified with HCl 10% to pH 3, and finally extracted with AcOEt (3 × 10 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give the corresponding product **14** (0.560 g, 84%). $[\alpha]_D^{20} = -84.2$ (*c* 0.26, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ 7.35 (5H, broad s), 5.22–5.09 (1H, m), 4.43–4.41 (1H, m), 4.17–4.10 (1H, m), 3.91 (1H, broad s), 3.54–3.41 (4H, m), 3.23 (6H, s), 2.28–2.20 (1H, m), 2.03–1.92 (3H, m), 1.35 (6H, broad s). $^{13}$C NMR ($CDCl_3$): $\delta$ 176.4, 170.1, 156.1, 136.1, 128.6, 128.2, 127.9, 99.1, 98.7, 69.7, 67.5, 67.2, 60.6, 48.3, 48.1, 47.1, 40.1, 28.8, 24.4, 17.3, 17.2. FT-IR (film): 3343, 1704, 1689 cm$^{-1}$. MS (ESI): *m*/*z* 479 [M$^+$−H]. HR-MS: Calcd for $C_{23}H_{32}O_9N_2Na$ [M$^+$+Na]: 503.2000. Found: 503.2008.

### 4.9. (2*S*)-Prolinyl-[(2*R*,3*R*,5*R*,6*R*)-3-hydroxycarbonyl-2-aminomethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane]-amide 2

Compound **14** (0.430 g, 0.89 mmol) in MeOH (6 mL) was hydrogenated at 50 psi in the presence of a catalytic amount of Pd/C 10% (0.25 equiv). After 3 h, the reaction mixture was filtered, the solvent was evaporated and the residue dried under vacuum to afford **2** as a viscous colourless oil (0.310 g, 97%). $[\alpha]_D^{20} = -131.1$ (*c* 0.37, $CH_2Cl_2$). $^1$H NMR ($D_2O$): $\delta$ 4.30–4.27 (1H, m), 3.88 (1H, d, *J* = 10.3 Hz), 3.77 (1H, ddd, *J* = 10.9 Hz, *J* = 7.6 Hz, *J* = 3.3 Hz), 3.36–3.24 (2H, m), 3.21 (4H, broad s), 3.18 (3H, s), 2.37–2.34 (1H, m), 2.00–1.92 (3H, m), 1.23 (3H, s), 1.25 (3H, s). $^{13}$C NMR ($D_2O$): $\delta$ 174.7, 169.5, 99.1, 72.5, 68.2, 59.7, 47.8, 47.7, 46.4, 40.2, 29.7, 23.7, 16.8, 16.6. FT-IR (film): 3413, 1679, 1611 cm$^{-1}$. HR-MS: Calcd for $C_{11}H_{16}O_6N$ [M$^+$−$C_4H_{10}NO$]: 258.0978. Found: 258.1285.

### 4.10. (2*S*)-*N*-Benzyloxycarbonylprolinyl-[(2*S*,3*S*,5*S*,6*S*)-3-*tert*-butyldimethylsilyloxymethyl-2-aminomethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane]-amide 17

Starting from amine **16** (0.556 g, 2.23 mmol) the same procedure for obtaining **12** was followed and afforded 1.23 g (88%) of **17** as a viscous oil. $[\alpha]_D^{20} = +30.4$ (*c* 0.85, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ 7.34 (5H, broad s), 5.18–5.09 (1H, m), 4.38–4.34 (1H, m), 3.74–3.42 (7H, m), 3.25 (3H, s), 3.17 (3H, s), 3.15–3.10 (1H, m), 2.33–2.31 (1H, m), 1.98–1.89 (3H, m), 1.28 (3H, s), 1.27 (3H, s), 0.89 (9H, s), 0.08 (3H, s), 0.07 (3H, s). $^{13}$C NMR ($CDCl_3$): $\delta$ 172.1, 136.3, 128.6, 128.2, 127.8, 98.6, 98.5, 70.9, 68.9, 67.2, 63.4, 60.7, 47.9, 47.6, 46.9, 39.9, 28.6, 25.8, 24.1, 18.2, 17.5, 17.4, −5.4, −5.3. FT-IR (film): 1709, 1689 cm$^{-1}$. HR-MS: Calcd for $C_{29}H_{48}O_8N_2SiNa$ [M$^+$+Na]: 603.3072. Found: 603.3051.

### 4.11. (2*S*)-Prolinyl-[(2*S*,3*S*,5*S*,6*S*)-3-hydroxymethyl-2-aminomethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane]-amide 3

Compound **17** (0.321 g, 0.561 mmol) after the removal of the protecting groups following the same procedure for obtaining **1** afforded 0.160 g (87%, 2 steps) of **3** as a viscous oil. $[\alpha]_D^{20} = +109.0$ (*c* 0.3, $CH_2Cl_2$). $^1$H NMR (DMSO-$d_6$): $\delta$ 8.53 (1H, broad s), 4.12–4.09 (1H, m), 3.66–3.62 (1H, m), 3.48–3.17 (7H, m), 3.14 (6H, s), 2.26–2.23 (1H, m), 1.87–1.78 (3H, m), 1.19 (3H, s), 1.18 (3H, s). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 168.9, 98.0, 97.9, 70.5, 68.1, 60.9, 58.9, 47.3, 47.2, 45.6, 39.0, 29.9, 23.8, 17.4, 17.3. FT-IR (film): 3353, 1658 cm$^{-1}$. MS (ESI): *m*/*z* 331 [M$^+$−H]. HR-MS: Calcd for $C_9H_{17}O_4N_2Na$ [M$^+$−$C_6H_{11}$+Na]: 240.1086. Found: 240.1321.

### 4.12. (2*S*)-*N*-Prolinyl-[(2*S*,3*S*,5*S*,6*S*)-3-hydroxycarbonyl-2-aminomethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane]-amide 4

Compound **17** (0.349 g, 0.61 mmol), following the same three sequencing steps employed for obtaining catalyst **2**, afforded 0.149 g (87%, 3 steps) of **4** as a viscous oil. $[\alpha]_D^{20} = +112.3$ (*c* 0.26, $CH_2Cl_2$). $^1$H NMR ($D_2O$): $\delta$ 4.28–4.24 (1H, m), 3.87 (1H, d, *J* = 10.3 Hz), 3.79–3.74 (1H, m), 3.45–3.43 (2H, m), 3.41–3.21 (2H, m), 3.21 (3H, s), 3.18 (3H, s), 2.37–2.34 (1H, m), 2.00–1.94 (3H, m), 1.25 (3H, s), 1.22 (3H, s). $^{13}$C NMR ($D_2O$): $\delta$ 174.6, 169.8, 99.1, 72.7, 68.2, 59.8, 47.9, 47.8, 46.4, 40.2, 29.8, 23.8, 16.8, 16.7. FT-IR (film): 3434, 3246, 1674, 1607 cm$^{-1}$. MS (ESI): *m*/*z* 347 [M$^+$+H]. HR-MS: Calcd for $C_{11}H_{16}O_6N$ [M$^+$−$C_4H_{10}NO$]: 258.0978. Found: 258.1337.

### 4.13. (2*S*,5*R*,6*R*)-2-Aminomethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane 27

Compound **26** (2.07 g, 8.83 mmol), following the same procedure to obtain compound **11**, afforded 1.45 g of **27** (80% overall yield for 4 steps) as a colourless oil. $[\alpha]_D^{20} = -180.4$ (*c* 0.36, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ 3.91–3.85 (1H, m), 3.59 (1H, t, *J* = 11.2 Hz), 3.45 (1H, dd, *J* = 11.2 Hz, *J* = 3.2 Hz), 3.30 (3H, s), 3.27 (3H, s), 2.76 (1H, dd, *J* = 13.0 Hz, *J* = 7.8 Hz), 2.68 (1H, dd, *J* = 13.0 Hz, *J* = 4.0 Hz), 1.31 (3H, s), 1.30 (3H, s). $^{13}$C NMR ($CDCl_3$): $\delta$ 98.9, 98.1, 69.0, 61.5, 48.0, 47.9, 42.9, 17.8, 17.5. FT-IR (film): 3384 cm$^{-1}$. HR-MS: Calcd for $C_9H_{20}O_4N$ [M$^+$+H]: 206.1387. Found: 206.1381.

### 4.14. (2*S*)-Prolinyl-[(2*S*,5*R*,6*R*)-2-aminomethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane]-amide 7

Amine **27** (0.507 g, 2.5 mmol), following the same reaction procedures to obtain **12** and **1**, afforded **7** (0.656 g, 92% 2 steps) as a colourless viscous oil. $[\alpha]_D^{20} = -150.8$ (*c* 0.80, $CH_2Cl_2$). $^1$H NMR

($CDCl_3$): $\delta$ 7.97 (1H, broad s), 5.20–5.09 (2H, m), 3.97–3.92 (1H, m), 3.74 (1H, dd, $J$ = 9.0 Hz, $J$ = 5.0 Hz), 3.56 (1H, t, $J$ = 11.2 Hz), 3.48–3.37 (2H, m), 3.26 (3H, s), 3.24 (3H, s), 3.22–3.16 (1H, m), 3.03–2.99 (1H, m), 2.93–2.89 (1H, m), 2.15–2.09 (1H, m), 1.95–1.89 (1H, m), 1.75–1.69 (2H, m), 1.30 (3H, s), 1.28 (3H, s). $^{13}$C NMR ($CDCl_3$): $\delta$ 175.1, 99.1, 97.9, 66.5, 61.0, 60.6, 48.1, 48.0, 47.2, 39.2, 30.9, 26.1, 17.7, 17.5. FT-IR (film): 1733, 1686 cm$^{-1}$. MS (ESI): $m/z$ 302 [M$^+$]. HR-MS: Calcd for $C_{14}H_{26}O_5N_2K$ [M$^+$+K]: 341.1489. Found: 341.2066.

### 4.15. (2*S*)-Prolinyl-[(1*R*,2*S*,4*R*,5*R*)-2-aminomethyl-4-methoxy-4,5-dimethyl-3,6,8-trioxabicyclo[3.2.1]octane]-amide 6

From alcohol **28** (0.187 g, 0.922 mmol) catalyst **6** was obtained as a colourless viscous oil (0.174 g, 64%, 5 steps) using the same reaction sequence to obtain **1** and **7**. $[\alpha]_D^{20} = -103.7$ ($c$ 0.43, acetone). $^1$H NMR ($D_2O$): $\delta$ 4.45 (1H, d, $J$ = 5.3 Hz), 4.34–4.30 (1H, m), 4.12 (1H, d, $J$ = 7.9 Hz), 4.09–4.06 (1H, m), 3.78 (1H, d, $J$ = 7.7 Hz, $J$ = 5.2 Hz), 3.44–3.31 (3H, m), 3.21 (3H, s), 2.11 (1H, dd, $J$ = 14.2 Hz, $J$ = 8.2 Hz), 2.41–2.39 (1H, m), 2.02–1.92 (3H, m), 1.34 (3H, s), 1.24 (3H, s). $^{13}$C NMR ($D_2O$): $\delta$ 169.7, 106.6, 100.2, 75.5, 70.8, 64.1, 59.7, 48.1, 46.4, 39.2, 29.8, 23.7, 17.4, 17.3. FT-IR (film): 1679 cm$^{-1}$. HR-MS: Calcd for $C_{13}H_{21}O_4N_2$ [M−OMe]$^+$: 269.1501. Found: 269.1522.

### 4.16. (2*R*,3*S*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-[1,4]-dioxane-2,3-dicarbothioic acid di-S-ethyl ester 21

To a solution of diisopropylamine (1.05 mL, 6.8 mmol) in THF (5.3 mL) at 0 °C was slowly added BuLi (1.6 M in hexanes, 3.9 mL, 6.2 mmol). After 15 min, a solution of **18**[8] (1 g, 2.8 mmol) in THF (5 mL) was added at −78 °C. After 30 min at −78 °C, MeOH (2.8 mL) was added. After 15 min, saturated aqueous $NH_4Cl$ solution (10 mL) was added and the aqueous layer extracted with $CH_2Cl_2$ (3 × 8 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated to afford a mixture of isomers **21** and **18** (1.6:1, 1 g, 99% yield) as a yellow oil. To a solution of this mixture (1 g) in MeOH (8 mL) at 0 °C was added $NaBH_4$ (0.171 g, 4.5 mmol) and the mixture was stirred at rt for 1 h. A saturated aqueous $NH_4Cl$ solution (10 mL) was added and the aqueous layer extracted with AcOEt (3 × 10 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated. Purification by medium pressure chromatography (3/7 AcOEt/hexane) afforded **21** (0.549 g) as a colourless oil and *trans*-diol[6] (0.338 g) as white crystals. **21**: $[\alpha]_D^{20} = -82.4$ ($c$ 1.20, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ 4.72 (1H, d, $J$ = 4.2 Hz), 4.64 (1H, d, $J$ = 4.2 Hz), 3.33 (3H, s), 3.24 (3H, s), 2.95–2.85 (4H, m), 1.42 (3H, s), 1.36 (3H, s), 1.27 (6H, q, $J$ = 7.4 Hz). $^{13}$C NMR ($CDCl_3$): $\delta$ 198.3, 197.3, 101.4, 100.2, 75.6, 74.5, 50.0, 48.6, 22.8, 22.2, 18.2, 18.1, 14.45, 14.43. FT-IR (film): 1679 cm$^{-1}$. Anal. Calcd for $C_{14}H_{24}O_6S_2$: C 47.71, H 6.86, N 11.19. Found: C 47.40, H 6.68.

### 4.17. (2*R*,3*S*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-[1,4]-dioxane-2,3-dicarboxylic acid diisopropyl ester 22

To a solution of dithioester **21** (0.654 g, 1.8 mmol) in isopropanol (30 mL) in a sealed tube was added $Ti(OiPr)_4$ (1.1 mL, 3.6 mmol). The reaction mixture was stirred at 100 °C for 10 days. After cooling, water (20 mL) was added and the aqueous layer was extracted with AcOEt (3 × 8 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated. Purification by medium pressure chromatography (1/9–2/8 AcOEt/hexane) afforded **22** (0.531 g, 82%) as a colourless oil. $[\alpha]_D^{20} = -90.1$ ($c$ 0.43, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ 5.10–5.01 (2H, m), 4.59 (1H, d, $J$ = 4.0 Hz), 4.40 (1H, d, $J$ = 4.0 Hz), 3.29 (3H, s), 3.21 (3H, s), 1.38 (3H, s), 1.33 (3H, s), 1.28 (3H, d, $J$ = 6.6 Hz), 1.27 (3H, d, $J$ = 2.9 Hz), 1.25 (3H, d, $J$ = 2.8 Hz), 1.21 (3H, $J$ = 6.3 Hz). $^{13}$C NMR ($CDCl_3$): $\delta$ 168.5, 167.4, 100.6, 99.2, 69.2, 69.1, 68.5, 66.2, 50.3, 48.4, 21.8, 17.9, 17.6. FT-IR (film): 1739 cm$^{-1}$. Anal. Calcd for $C_{16}H_{28}O_8$: C 55.16, H 8.10. Found: C 54.79, H 8.23.

### 4.18. (2*R*,3*S*,5*R*,6*R*)-3-*tert*-Butyldimethylsilyloxymethyl-2-azidomethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane 23

To a solution of monoalcohol, derived from **22** after reduction to the diol and monosylilation,[15,16] (0.264 g, 0.75 mmol) in THF (6 mL) at 0 °C were added triphenylphosphine (0.299 g, 1.1 mmol), hydrazoic acid (1.6 M in benzene, 0.712 mL, 1.1 mmol) and DIAD (0.220 mL, 1.1 mmol). The reaction mixture was then stirred at rt. When all of the starting material had been consumed (TLC), the solvent was evaporated and the residue was purified by medium pressure column chromatography (2/8 AcOEt/hexane) to afford azide **23** (0.237 g, 84%) as a colourless oil. $[\alpha]_D^{20} = -26.1$ ($c$ 0.92, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ 4.34–4.30 (1H, m), 4.27 (1H, t, $H$ = 10.5 Hz), 3.60–3.54 (2H, m), 3.46 (1H, dd, $J$ = 13.4 Hz, $J$ = 10.0 Hz), 3.34 (3H, s), 3.24 (3H, s), 3.19 (1H, dd, $J$ = 13.4 Hz, $J$ = 2.5 Hz), 1.31 (3H, s), 1.27 (3H, s), 0.88 (9H, s), 0.06 (3H, s), 0.05 (3H, s). $^{13}$C NMR ($CDCl_3$): $\delta$ 99.7, 98.1, 73.0, 69.0, 61.8, 51.3, 49.3, 47.9, 25.8, 18.1, 18.0, 17.8, −5.4, −5.5. FT-IR (film): 2096 cm$^{-1}$. HR-MS: Calcd for $C_{15}H_{29}O_4N_3SiNa$ [M−OMe−H+Na]$^+$: 366.1825. Found: 366.1881.

### 4.19. (2*S*)-*N*-Benzyloxycarbonylprolinyl-[(2*R*,3*S*,5*R*,6*R*)-3-*tert*-butyldimethylsilyloxymethyl-2-aminomethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane]-amide 25

Azide **23** (0.213 g, 0.60 mmol) was converted into compound **25** (0.265 g, 80%, 2 steps, colourless viscous oil) following the same procedure for obtaining compound **12** from azide **10**. $[\alpha]_D^{20} = -77.1$ ($c$ 2.39, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): $\delta$ 7.33 (5H, broad s), 5.15–5.07 (2H, m), 4.28–4.18 (2H, m), 3.62–3.32 (7H, m), 1.22 (6H, broad s), 2.12 (1H, broad s), 1.92–1.86 (3H, m), 1.25 (3H, s), 1.23 (3H, s), 0.89 (9H, s), 0.06 (3H, s), 0.05 (3H, s). $^{13}$C NMR ($CDCl_3$): $\delta$ 171.5, 155.9, 136.3, 128.5, 128.0, 127.9, 127.8, 99.5, 98.1, 73.03, 67.2, 66.7, 62.2, 60.8, 49.3, 47.0, 39.4, 28.8, 25.9, 24.5, 18.3, 17.8, −5.39, −5.4. FT-IR (film): 1711, 1689 cm$^{-1}$. HR-MS: Calcd for $C_{29}H_{48}O_8N_2SiNa$ [M$^+$+Na]: 603.3072. Found: 603.3056.

### 4.20. (2*S*)-Prolinyl-[(2*R*,3*S*,5*R*,6*R*)-3-hydroxymethyl-2-aminomethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane]-amide 5

Compound **25** (0.217 g, 0.37 mmol) was converted into catalyst **5** (0.123 g, 99%, colourless viscous oil) using the same procedure to obtain **1**. $[\alpha]_D^{20} = -122.7$ ($c$ 0.30, $CH_2Cl_2$). $^1$H NMR ($D_2O$): $\delta$ 4.15–4.12 (1H, m), 3.86–3.83 (1H, m), 3.78–4.65 (3H, m), 3.47 (14.2 Hz, $J$ = 3.5 Hz), 3.26 (3H, s), 3.18 (3H, s), 3.16–3.13 (1H, m), 2.90–2.85 (2H, m), 2.11–2.08 (1H, m), 1.73–1.65 (3H, m), 1.27 (3H, s), 1.23 (3H, s). $^{13}$C NMR ($D_2O$): $\delta$ 176.9, 100.0, 98.9, 72.6, 67.2, 60.4, 60.1, 49.4, 47.7, 39.0, 30.5, 25.2, 17.3, 17.0. FT-IR (film): 3342, 1668 cm$^{-1}$. HR-MS: Calcd for $C_9H_{17}O_4N_2Na^+$ [M$^+$−$C_6H_{11}$+Na]: 240.1086. Found: 240.1532.

### 4.21. (5*R*,6*R*)-(*S*,*S*)-Diethyl 5,6-dimethoxy-5,6-dimethyl-5,6-dihydro-1,4-dioxine-2,3-bis(carbothioate) 19

To a solution of diisopropylamine (1.14 mL, 8.2 mmol) in THF (6.0 mL) at 0 °C was slowly added BuLi (1.6 M in hexanes, 4.26 mL, 6.8 mmol). After 15 min, a solution of **18** (1.2 g, 3.4 mmol) in THF (5 mL) was added at −78 °C. After 30 min at −78 °C, $I_2$

(0.860 g, 3.4 mmol) was added. After 5 min, a saturated aqueous $NH_4Cl$ solution (10 mL) and a 20% aqueous $Na_2S_2O_3$ solution were added and the aqueous layer extracted with $E_2O$ (3 × 10 mL). The organic phase was dried with anhydrous $MgSO_4$ and concentrated to afford a residue which was purified by medium pressure column chromatography (1/9 AcOEt/hexane) and afforded **19** (0.984 g, 82%) as white crystals. $[\alpha]_D^{20} = -158.1$ (*c* 1.0, $CH_2Cl_2$). $^1H$ NMR ($CDCl_3$): $\delta$ 3.39 (6H, s), 3.03–2.91 (4H, m), 1.55 (6H, s), 1.29 (6H, t, *J* = 7.4 Hz). $^{13}C$ NMR ($CDCl_3$): $\delta$ 186.7, 133.1, 99.2, 49.7, 23.2, 16.8, 14.2. HR-MS: Calcd for $C_{14}H_{22}O_6S_2Na$ [$M^+$+Na]: 373.0750. Found: 373.0751.

### 4.22. (5*R*,6*R*)-(*S*,*S*)-Diethyl 5,6-dimethoxy-5,6-dimethyl-2,3-dideuterium-1,4-dioxane-2,3-bis(carbothioate) 20

To a solution of **21** (0.020 g, 0.06 mmol) in $CDCl_3$ (1.0 mL) in an NMR tube was added one drop of DBU. After 48 h, $^1H$ NMR analysis showed complete deuterium exchange and isomerisation. Saturated $NH_4Cl$ solution was added and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 5 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated to afford a residue which was purified by preparative TLC (3/7 AcOEt/hexane) and afforded **20** (0.021 g, 99%) as a colourless oil. $[\alpha]_D^{20} = -35.8$ (*c* 0.9, $CH_2Cl_2$). $^1H$ NMR ($CDCl_3$): $\delta$ 3.32 (6H, s), 2.91 (4H, q, *J* = 7.4 Hz), 1.36 (6H, s), 1.27 (6H, t, *J* = 7.4 Hz). $^{13}C$ NMR ($CDCl_3$): $\delta$ 195.9, 99.6, 73.9 (t, $J_{CD}$ = 22.2 Hz), 48.5, 22.9, 17.3, 14.2. *m*/*z* 354.5 ($M^+$), 322.9 ($M^+$−OMe). HR-MS: Calcd for $C_{14}H_{22}D_2O_6S_2Na$ [M+Na]$^+$: 377.1032. Found: 377.1031.

## Acknowledgements

We thank Rita Lopes for her contribution to this work and Paula Chicau for helping with HPLC analyses.

The NMR spectrometers are part of the National NMR Network and were purchased in the framework of the National Programme for Scientific Re-equipment, contract REDE/1517/RMN/2005, with funds from POCI 2010 (FEDER) and Fundação para a Ciência e a Tecnologia (FCT). This work was supported by the FCT grant PEst-OE/EQB/LA0004/2011.

## References

1. Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175.
2. Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.
3. (a) Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498; (b) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2004**, 1808–1809; (c) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558–560; (d) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983–1986; (e) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962–5963; (f) Davies, S. G.; Sheppard, R. L.; Smith, A. D.; Thomson, J. E. *Chem. Commun.* **2005**, 3802–3804; (g) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biol. Chem.* **2005**, *3*, 84–96; (h) Limbach, M. *Tetrahedron Lett.* **2006**, *47*, 3843–3847; (i) Davies, S. G.; Russell, A. J.; Sheppard, R. L.; Smith, A. D.; Thomson, J. E. *Org. Biol. Chem.* **2007**, *5*, 3190–3200.
4. Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267.
5. Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304.
6. Huang, X.-Y.; Wang, H.-J.; Shi, J. *J. Phys. Chem. A* **2010**, *114*, 1068–1081.
7. Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Org. Lett.* **2003**, *5*, 4097–4099.
8. Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Org. Lett.* **2002**, *4*, 2035–2038.
9. Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285–9289.
10. Guilena, G.; Hita, M.; del, C.; Nájera, C.; Viózquez, S. F. *J. Org. Chem.* **2008**, *73*, 5933–5943.
11. Barros, M. T.; Burke, A. J.; Maycock, C. D. *Tetrahedron Lett.* **1999**, *40*, 1538–1586.
12. Barlow, J. S.; Dixon, D. J.; Foster, A. C.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1627–1629.
13. Burke, A. J.; Maycock, C. D.; Ventura, M. R. *Org. Biomol. Chem.* **2006**, *4*, 2361–2363.
14. Dixon, D. J.; Foster, A. C.; Ley, S. V.; Reynolds, D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1631–1633.
15. Dixon, D. J.; Foster, A. C.; Ley, S. V.; Reynolds, D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1635–1637.
16. Dixon, D. J.; Ley, S. V.; Reynolds, D. *J Chem. Eur. J.* **2002**, *8*, 1621–1635.
17. Dixon, D. J.; Foster, A. C.; Ley, S. V. *Can. J. Chem.* **2001**, *79*, 1668–1680.
18. Paradowska, J.; Pasternak, M.; Gut, B.; Gryzlo, B.; Mlynarski, J. *J. Org. Chem.* **2012**, *77*, 173–187.
19. Tong, S.-T. A.; Harris, P. W. R.; Barker, D.; Brimble, M. A. *Eur. J. Org. Chem.* **2008**, 164–170.
20. Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 734–735.
21. Wu, C.; Fu, X.; Ma, X.; Li, S. *Tetrahedron: Asymmetry* **2010**, *21*, 2465–2470.
22. Giacalone, F.; Gruttadauria, M.; Meo, P. L.; Riela, S.; Noto, R. *Adv. Synth. Catal.* **2008**, *350*, 2747–2760.
23. Fu, Y.-Q.; Li, Z.-C.; Ding, L.-N.; Tao, J.-C.; Zhang, S.-H.; Tang, M.-S. *Tetrahedron: Asymmetry* **2006**, *17*, 3351–3357.
24. List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
25. Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 5th ed.; Elsevier, 2003.