Novel Cyclic 1,2-Diacetals Derived from (2*R*,3*R*)-(+)-Tartaric Acid: Synthesis and Application as N,O Ligands for the Enantioselective Alkylation of Benzaldehyde by Diethylzinc

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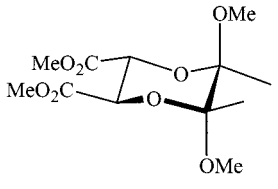
A chiral cyclic 1,2-diacetal derived from tartaric acid was used as the basic structural unit for novel ligands. Monooxazoline carbinols in which the degree of substitution of the alcohol and the nature of the stereocentre in the oxazoline ring were varied were synthesized in moderate to good yields. The influence of these structural factors on asymmetric induction was examined in the enantioselective addition of diethylzinc to benzaldehyde. Up to 60% *ee* was observed with a secondary or a tertiary alcohol as the metal-chelating group.

Introduction

1,2-Diacetals have been known for many years, but their chemistry still remains largely unexplored.[1] Cyclic 1,2-diacetals such as **1**, derived from tartaric acid, have been the subject of several studies during the last few years.[1] They have a rigid 1,4-dioxane ring in which two methoxy groups are stabilized in a *trans*-diaxial relationship by a double anomeric effect, and four chiral centres, which make them good templates for chirality transfer. They are structurally related to TADDOL **2**, which is also prepared from tartaric acid, contains a 1,3-dioxolane ring, and whose derivatives have many applications in catalysis.[2]



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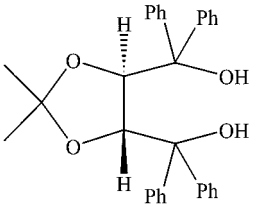

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Some derivatives of the cyclic 1,2-diacetal **1** made by other researchers have already found applications in enantioselective synthesis: as bis(oxazolines) in cyclopropanation reactions,[3] as diphosphanes in the hydrogenation of acrylate derivatives[4] and enamides,[5] as thioethers in the hydrogenation of enamides,[5] and as phosphonites in ketone hydrosilylation.[6] All the chiral ligands based on the 1,4-dioxane skeleton reported so far have C_2 symmetry. This symmetry was long believed to be the most efficient feature for ligand-induced multiplication of chirality, but recently more complex structures bearing different chelating groups and more than one element of chirality have proved to be very useful.[7] We decided to do away with C_2 symmetry, and to synthesize ligands with oxazoline and hydroxy units, i.e. with two different donor atoms, N and O, capable of chelating to metals. It is a well-known fact that in homogeneous catalysis there is an almost complete lack of useful structure−activity relationship.[8] Since most catalytic cycles consist of several consecutive discrete steps, intermediates may be quite different and hence it is difficult to predict which structural factors may be best suited to a particular reaction. We synthesized a series of ligands with different structural features which could influence the induction of chirality, such as hydroxy group substitution and the nature of the chiral substituent in the oxazoline ring, aiming to have a useful series to add to the chiral pool.

In order to assess the ability of our new catalysts to induce asymmetry in catalytic reactions we decided to study the enantioselective addition of diethylzinc to benzaldehyde to produce 1-phenylpropanol, commonly used as a chiral building block. This reaction has been widely studied since its discovery by Oguni and Omi in 1984,[9] and it has been reviewed recently.[10] Amino alcohols constitute an important part of the chiral ligands studied, and oxazoline-con-

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taining catalysts have also received some attention. Simple hydroxymethyloxazolines,[11] pyridyloxazoline alcohols,[12] ferrocene-based systems[13] and a TADDOL analog[14] have been tried with success, but a systematic investigation of the effect of altering the degree of substitution of the alcohol chelating group has not been made. The present study aimed to fill this gap as well as to explore further the chemistry of 1,2-diacetals.

Results and Discussion

A. Synthesis of TADDOL Analogs

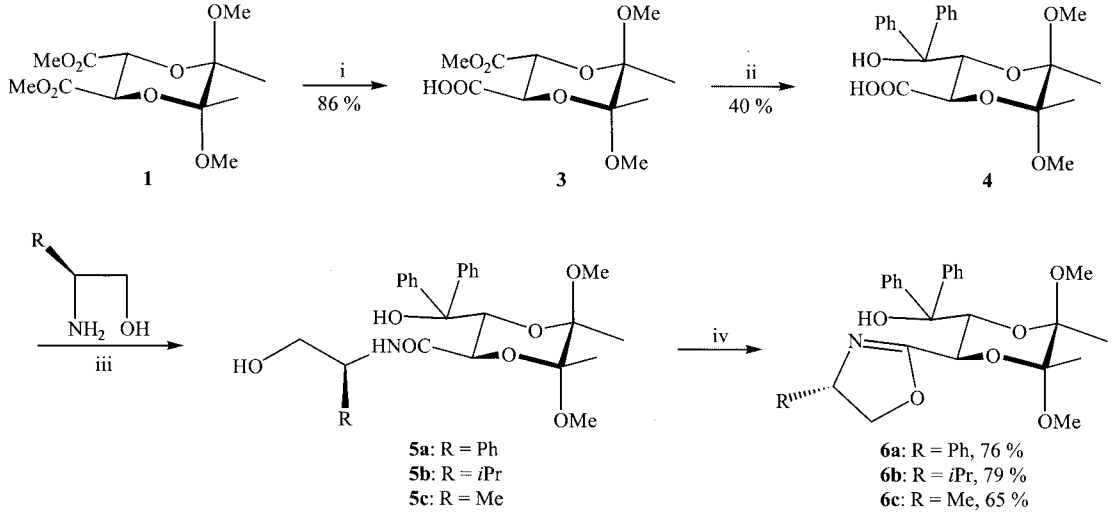
The C_2-symmetric diester **1** used as starting material for the preparation of all the catalysts was obtained from (2*R*,3*R*)-(+)-tartaric acid by an acetal exchange reaction with 2,2,3,3-tetramethoxybutane and *p*-toluenesulfonic acid as catalyst as reported previously.[15] The diester was converted into unsymmetrical derivatives via the half-ester **3**, obtained in good yield (85%) by partial hydrolysis with methanolic KOH[16] (Scheme 1). Reaction of the half-ester with an excess of Grignard reagent produced the tertiary alcohol directly, a strategy which has already been used with the TADDOL analogues.[17] Oxazolines **6a**−**c** could be readily obtained from the acid in good to high yields (65−79%) in a two-step process: amidation and dehydrative cyclization. Heating the acid in the presence of an amino alcohol to 150 °C with concomitant azeotropic removal of the water formed with a Dean−Stark trap, produced amides **5a**−**c**.

The products were pure enough to be used in the next step without prior purification. When the activation energy for this process is low enough, oxazolines may form directly in this fashion by removal of another molecule of water,[18] but in our case only one oxazoline was synthesized in this way (vide infra), and heating to higher temperatures (decalin reflux) was necessary. The amides could, however, be readily converted into oxazolines by activation of the hydroxy group as a tosylate and in situ ring closure in the presence of excess triethylamine. This method works well when there are other secondary or tertiary hydroxy groups in a molecule.[19] Novel oxazolines **6a**−**c** were synthesized in this manner. They were the only product of the reaction and were obtained in good to high yields (65−79% from the acid) after column chromatography.

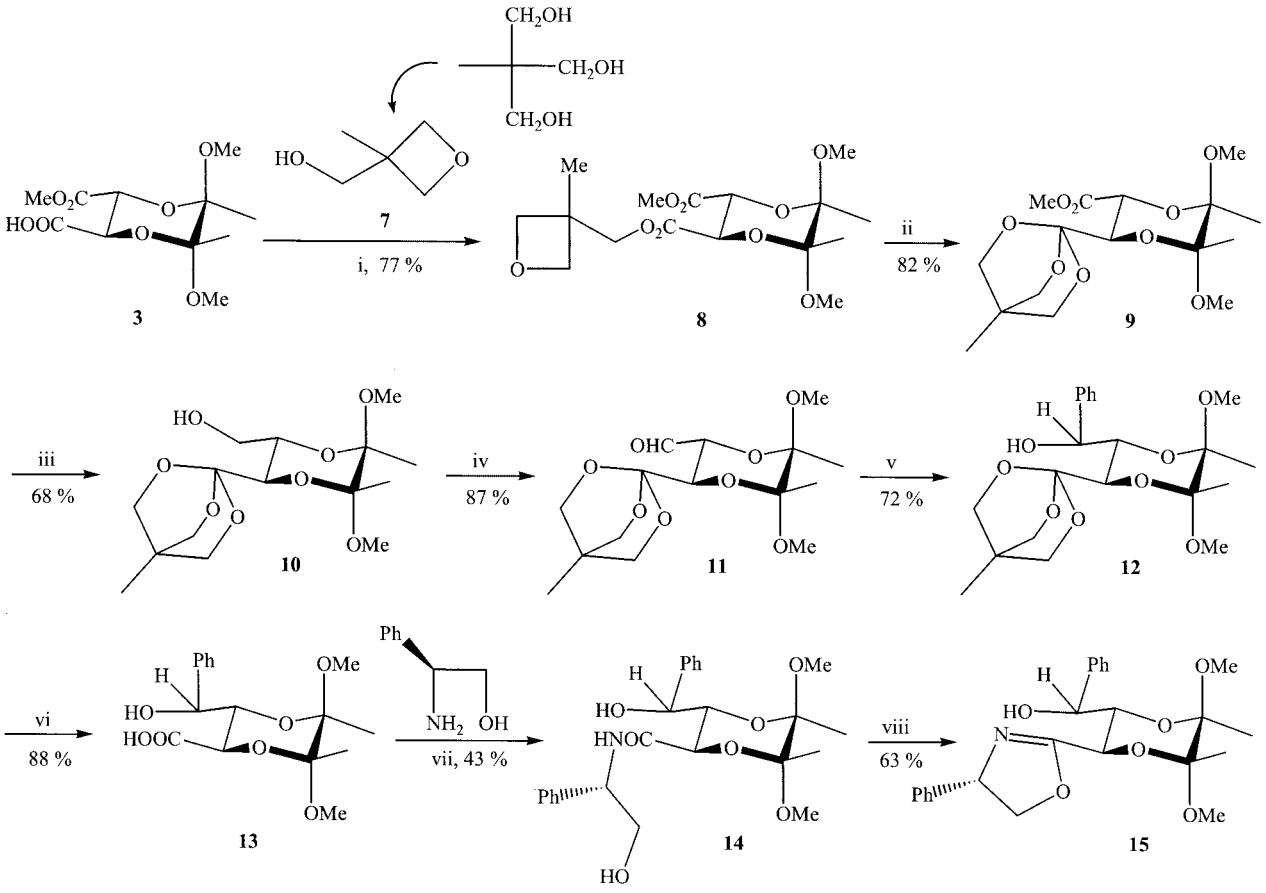
B. Synthesis of the Catalyst Containing a Secondary Hydroxy Group

Catalysts containing a primary or a secondary hydroxy group required a different synthetic strategy. In these cases it was necessary to protect the carboxylic acid function before transforming the ester into an alcohol (Scheme 2). Corey's orthoester protecting group was used to protect the acid against the attack of organometallic reagents (Grignard reagents, $LiAlH_4$)[20] as its oxabicyclo[2,2,2]octyl orthoester (OBO ester **9**). This strategy could be used successfully because the base-stable cyclic orthoester is much more sensitive to acid than the cyclic 1,2-diacetal, and deprotection could be achieved under very mild conditions in which the cyclic acetal was not affected.

The OBO ester was prepared in two steps; acid **3** was initially esterified with 3-(hydroxymethyl)-3-methyloxetane and DCC/DMAP; higher yields of product **8** were obtained (77%) when an excess (two-fold) of oxetane alcohol was used. The ester was subsequently converted into the OBO ester **9** by a rearrangement reaction catalyzed by $BF_3{\cdot}Et_2O$. The reaction was complete in 1 hour at room temperature, and the OBO ester was obtained as the only product in high yield (82%). Direct reduction of protected ester **9** to the aldehyde was tried, but attempts with DIBAL-H or $LiAlH_4$/



Scheme 1. Reagents and conditions: i) 1.2 equiv. KOH, MeOH, reflux; ii) 3 equiv. PhMgBr, THF, reflux; iii) amino alcohol, xylene, reflux; iv) *p*TsCl, Et_3N, CH_2Cl_2, reflux



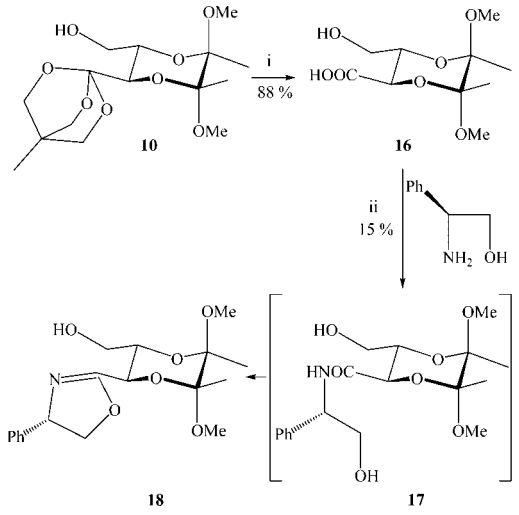
Scheme 2. Reagents and conditions: i) DCC, DMAP, CH_2Cl_2, 0 °C, 4 h; ii) $BF_3{\cdot}Et_2O$, CH_2Cl_2, room temp., 1 h; iii) $LiAlH_4$, THF, reflux; iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 °C; v) PhMgBr, THF, reflux, 1 h 30; vi) 1 M HCl, pH 1, 0 °C, 40 min, then 1 M LiOH, pH 11, reflux; vii) amino alcohol, xylene, reflux, 17 h; viii) *p*TsCl, Et_3N, CH_2Cl_2, reflux, 17 h

Et_2NH were unsuccessful. Hence the ester was first reduced with $LiAlH_4$ [21] to alcohol **10** in good yield (68%), and **10** was then converted into the aldehyde **11** (in 87% yield) by Swern oxidation under standard conditions.[22] The product was pure enough to be used in the next step without further purification. Grignard addition proceeded smoothly, and the alcohol was obtained in 72% yield after chromatography. There was no duplication of signals in spectra (^1H NMR, ^{13}C NMR), suggesting that the product formed with either full or very high stereocontrol.[23] The acid was then deprotected[24] in a sequence of two one-pot reactions. Acidifying a THF/H_2O solution of **12** at 0 °C with HCl to pH 1 and stirring for 30 min caused complete rearrangement of the OBO ester to an intermediate ester. Only one product formed in this step, as indicated by TLC. This ester may be isolated if wished. Normally it was not isolated, but the solution was treated with aqueous LiOH solution and the pH raised to 11. After a period of reflux (4:30 h), the hydrolysis was complete and acid **13** could be obtained in high yield (88%) by acidification and extraction. The amidation and subsequent oxazoline formation were carried out as described for catalysts **6a−c** to give **15** in 63% yield.

C. Synthesis of the Catalyst Containing a Primary Hydroxy Group

The approach used for the synthesis of this catalyst is shown in Scheme 3. Acid **3** was protected as the OBO ester, and the ester function was reduced to the alcohol. Deprotection was carried out as described for **12**, to give **16** in good yield (88%). The oxazoline synthesis, however, required a method different from that used for the other catalysts. After the amidation of **16**, there are two primary hydroxy groups present in the molecule which can compete in the tosylation step, and mixtures can be produced. Hence a direct approach was used. Dehydration at 135 °C in xylene produced amide **17** together with small amounts of the oxazoline; even after long periods of heating the reaction did not go to completion, and eventually other (unidentified) products formed. When the acid and the amino alcohol were heated to a higher temperature in decalin (bath temperature 210 °C) oxazoline **18** formed. The reaction goes via the amide, which is the major component of the reaction mixture after 17 h of reflux. If the amide is not isolated but the mixture is refluxed for 3−4 days, about 75%

of the starting material is converted into product. Refluxing the mixture longer (i.e. 6 days) does not increase the conversion, even though some amide is still present in the reaction mixture after this time, as indicated by ^{1}H NMR spectroscopy.



Scheme 3. Reagents and conditions: i) 1 M HCl, pH 1, 0 °C, 30 min, then 1 M LiOH, pH 11, reflux; ii) amino alcohol, decalin, reflux

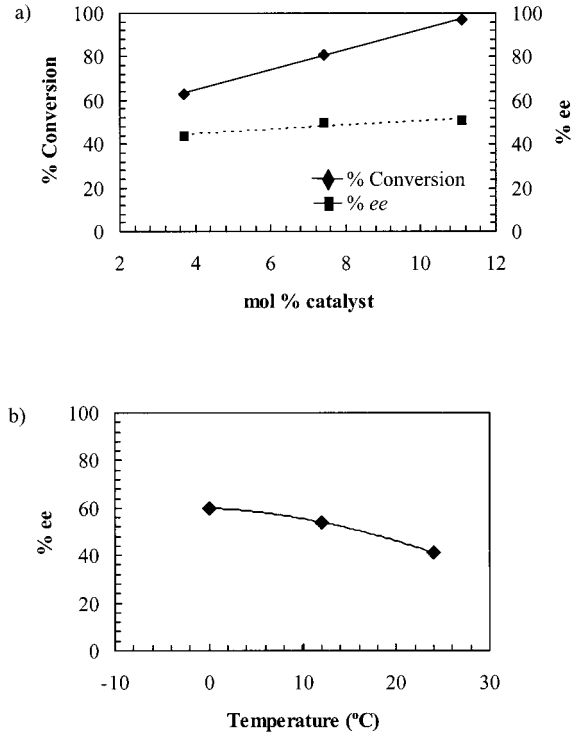
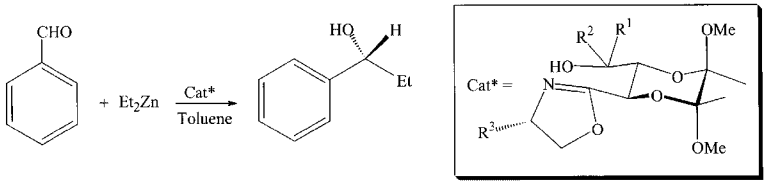


Figure 1. Variation of the *ee* as a function of the reaction conditions in the addition of diethylzinc to benzaldehyde catalyzed by **6a**: a) the effect of the catalyst concentration on *ee* and on conversion after 24 h; b) the effect of temperature observed after 24 h.[26]

D. Catalysis

The potential of the novel chiral oxazoline carbinols to catalyze the asymmetric addition of Et_2Zn to benzaldehyde was investigated. Preliminary experiments showed that 2 mol equivalents of Et_2Zn were necessary, otherwise the reaction would not go further than half-way, irrespective of the length of time used. The addition was tried with **6a** as catalyst, at different temperatures and different catalyst concentrations, to establish the best reaction conditions. Figure 1 (see a and b) illustrate some of the results. The reaction was slow; after 24 h at 12 °C there was more than 80% conversion, but small amounts of aldehyde remained unchanged. This also happened at room temperature, with 9% unchanged aldehyde remaining even after 47 h, as determined by ^{1}H NMR spectroscopy. It seems that the alkoxide formed inhibits the reaction, as reported to occur in some

Table 1. Enantioselective addition of diethylzinc to benzaldehyde catalyzed by various oxazoline carbinols



Entry[a]	Catalyst	R^1	R^2	R^3	Substrate[b] [%]	BzOH[b] [%]	Conversion[c] [%]	*ee*[d] [%]
1	**6a**	Ph	Ph	Ph	16	< 9	67	54
2	**6b**	Ph	Ph	*i*Pr	11	< 5	nd[e]	46
3	**6c**	Ph	Ph	Me	20	< 5	66	20
4	**16**	Ph	H	Ph	nf[f]	< 5	79	49
5	**18**	H	H	Ph	2	< 10	58	11

[a] Reactions were carried out under argon, and a molar ratio of Et_2Zn/benzaldehyde/catalyst = 2.1:1:0.1. Additions took place at 0 °C and the mixtures were afterwards stirred for 24 h at 12−15 °C. [b] Determined from the ^{1}H NMR spectrum. [c] Determined by HPLC analysis, using 1-phenylethanol as internal standard. [d] Determined by HPLC analysis, on a Chiralcel OB-H column from Daicel. [e] Not determined. [f] Not found.

cases by other researchers. The highest enantiomeric excess was obtained when the reaction was carried out at 0 °C (61%), but at this temperature the reaction was even slower; a benzaldehyde to alcohol ratio of 1:3.7 was obtained after 42 h, and propiophenone also formed in large amounts (20%) as a by-product. Propiophenone results from a slow disproportionation reaction between the ethylation product ethylzinc 1-phenyl-1-propoxide and benzaldehyde.[25]

At higher temperatures, i.e. 12−15 °C, no propiophenone formed, as determined by ^{1}H NMR spectroscopy, and the enantiomeric excess was 54%. Raising the temperature speeded up the reaction more, but the *ee* dropped slightly (41% was obtained after 24 h). Varying the catalyst concentration had a small effect on the enantioselectivity of the reaction, but a large effect on the rate. Hence changing the catalyst concentration from 3.7 to 11.0 mmol equivalents increased the *ee* from 44 to 55%, whereas the conversion changed from 63 to 97% in 24 h. When the final reaction conditions were selected, a compromise between these factors was made, so that a good conversion could be reached at a low catalyst concentration. All the catalysts prepared were then assessed under identical conditions, and the results are presented in Table 1.

Benzyl alcohol, which forms by β-hydride reduction, is sometimes obtained as a major by-product of the reaction between benzaldehyde and diethylzinc. In our reactions under optimized conditions it was present as less than 10% of the crude reaction mixtures. The (*R*)-isomer was the predominant product in all cases. The highest enantiomeric excess was obtained with catalyst **6a**, the catalyst containing a tertiary alcohol group (54%), and the lowest (11%) with **18**, containing a primary hydroxy group. Catalyst **4** (containing a secondary hydroxy group, and hence another chiral centre near the active reaction centre) provided nearly the same induction as **6a** (49%), but it also gave the largest enhancement in rate (all the substrate had reacted after 24 h). A separate experiment showed that after 16 h only < 2% of the starting material remained unchanged. These results suggest that steric effects play an important role in reducing the number of conformations possible in the transition state, and hence the catalyst containing a tertiary alcohol group gave the best induction.

Conclusion

In the course of this work methods for the synthesis of novel chiral oxazoline carbinols were developed. They were obtained in good to moderate yields from a cyclic 1,2-diacetal derived from tartaric acid. Structural features such as the degree of substitution of the alcohol as well as the nature of the chiral substituent in the oxazoline ring were varied. The effect of these modifications on the ability of these ligands to induce chirality was investigated in a model reaction, the enantioselective addition of diethylzinc to benzaldehyde. Steric effects near the hydroxy group seemed to be more important than the presence of an extra stereogenic centre near the coordination sphere of the metal. Thus, a change from the diphenylhydroxymethyl to the phenylhydroxymethyl group had little influence on induction despite an increase in the reaction rate, but a change from the diphenylhydroxymethyl to the hydroxymethyl group had a large influence on induction. In the oxazoline unit, the nature of the chiral substituent as well as steric effects had a strong influence on induction, which decreased in the order Ph > *i*Pr > Me.

Experimental Section

General Remarks: All reactions were carried out under argon. Solvents were purified by standard procedures and distilled before use. 2,2,3,3-Tetramethoxybutane,[27] dioxane dimethyl ester **1**,[1] and the hydroxymethyloxetane **7**,[20a] were prepared according to literature procedures. Column chromatography was carried out on Macherey−Nagel silica gel (230−400 mesh). Melting points were measured with an Electrothermal Melting Point apparatus or with a Reichert Thermovar apparatus, and are uncorrected. Elemental analyses (C, H, N) were performed by the Laboratory for External Services of CQFB-Lab Associado/REQUIMTE, of the Department of Chemistry, FCT, UNL, Monte de Caparica. NMR spectra were obtained with a Bruker AR X400 NMR spectrometer. Chemical shifts are reported relative to TMS. Signals in ^{13}C NMR spectra were assigned with the aid of DEPT spectra. Two-dimensional spectra (COSY 45, HMQC, SECSY) were recorded whenever necessary for structure elucidation. IR spectra were obtained with a Mattson Instruments Satellite FTIR spectrometer. Optical rotations (0.5-dm cell, 1-mL capacity) were measured with an AA−1000 Polarimeter from Optical Activity Ltd. HPLC analyses were carried out with a Merck Hitachi instrument equipped with a Chiralcel OB-H column, with hexane/*i*PrOH as eluent (flow 0.9 mL/min), and a Merck−Hitachi L-4250 UV−VIS detector.

(2*R*,3*R*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-dicarboxylic Acid Monomethyl Ester (3): The diester (5.33 g, 0.018 mol) was suspended in dry MeOH (12 mL). Potassium hydroxide (1.25 g, 0. 022 mol) in MeOH (10 mL) was added dropwise, at room temperature, over a period of 1 h. The solution was afterwards refluxed for 2 h 30. The solvent was then evaporated off, and the mixture was distributed between $CHCl_3$ and water. The aqueous layer was extracted twice more with $CHCl_3$. The combined chloroform fractions were dried with anhydrous magnesium sulfate and the solvent evaporated off. The residue was checked for the presence of unchanged diester. The diester obtained (0.349 g) was later recycled. The remaining aqueous phase was acidified with HCl solution (2 M) to pH 1 and extracted with diethyl ether. The pH was adjusted with HCl before each extraction. After drying, the solvent was evaporated off to give the product as a viscous colourless liquid (4.34 g, 86%). $[\alpha]_D^{21} = -132$ (c = 2.03, $CHCl_3$). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.36 (s, 3 H, CH_3), 1.37 (s, 3 H, 2 × CH_3), 3.32 (s, 3 H, OCH_3), 3.33 (s, 3 H, OCH_3), 3.78 (s, 3 H, $COOCH_3$), 4.49 (d, J = 5 Hz, 1 H, dioxane CH), 4.60 (d, J = 5 Hz, 1 H, dioxane CH), 9.00−9.25 (br. s, COOH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.3 (2 × CH_3), 48.6 (2 × OCH_3), 52.6 (CH_3), 68.3 (CH), 68.7 (CH), 99.2 (acetal C), 99.6 (acetal C), 168.2 (CO), 171.7 (CO) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3668, 3483, 3028, 3001, 2954, 2908, 2839, 2613, 2556, 1744, 1440, 1380, 1354, 1292, 1231, 1202, 1178, 1143, 1114, 1040, 898, 889, 855, 772, 664, 579, 428 cm^{-1}. $C_{11}H_{18}O_8$ (278.26): calcd. C 47.48, H 6.52; found C 47.57, H 6.87.

(2*R*,3*R*,5*R*,6*R*)-3-(Hydroxydiphenylmethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carboxylic Acid (4): A flame-dried two-necked flask was charged with a phenylmagnesium bromide solution (21.5 mL of a 1 M solution in THF, 21.5 mmol). Half-ester **3** (1.99 g, 0.716 mmol) in dry THF (2.9 mL) was added dropwise at room temperature over 1 h while the solution was stirred under argon. Afterwards the mixture was refluxed for 17 h. The reaction mixture was then cooled in an ice bath, and ice (3 g) was added. The pH was lowered to 1 with 1 M HCl and the product was extracted with diethyl ether. The combined extracts were washed with a saturated salt solution, filtered through anhydrous sodium sulfate and the solvent was removed using a rotary evaporator. The sample was dried. The product was purified by column chromatography on silica gel treated with 1% Et_3N in hexane (EtOAc/MeOH, 8:2). Some product eluted as a salt, which was converted into the free acid after dissolution in water, acidification to pH ≈ 1 with 2 M HCl and extraction with diethyl ether. The product was obtained as a white solid. Total yield: 1.16 g, 40%. M.p. 163−164 °C. $[\alpha]_D^{27}$ = −26.6 (*c* = 2.00, $CHCl_3$). ^1H NMR (400.1 MHz, $CDCl_3$): δ = 1.18 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 3.13 (s, 3 H, OCH_3), 3.29 (s, 3 H, OCH_3), 4.46 (d, *J* = 9.0 Hz, 1 H, CH), 4.84 (d, *J* = 9.0 Hz, 1 H, CH), 7.10 (t, *J* = 7.3 Hz, 1 H, Ph), 7.18 (t, *J* = 7.8 Hz, 2 × H, Ph-H), 7.25 (t, *J* = 7.3 Hz, 1 H, Ph-H), 7.35 (t, *J* = 7.8 Hz, 2 × H, Ph-H), 7.42 (d, *J* = 7.5 Hz, 2 × H, Ph-H), 7.72 (d, *J* = 7.5 Hz, 2 × H, Ph-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.3 (CH_3), 17.4 (CH_3), 48.5 (OCH_3), 48.9 (OCH_3), 68.8 (CH), 72.7 (CH), 78.1 (COH), 98.6 (acetal C), 99.1 (acetal C), 126.6 (4 × CH, Ph), 126.9 (4 × CH, Ph), 127.0 (2 × CH, Ph), 127.4 (CH, Ph), 127.6 (4 × CH, Ph), 127.9 (4 × CH, Ph), 142.1 (CH, Ph), 144.5 (2 × CH, Ph), 173.2 (CO) ppm. IR ($CHCl_3$): ṽ = 3671, 3550, 3415, 3062, 3027, 3010, 2950, 2837, 1727, 1600, 1493, 1450, 1377, 1144, 1128, 1119, 1038, 977, 912, 891, 876, 703, 664 cm^{-1}. $C_{22}H_{26}O_7$·MeOH (434.49): calcd. C 63.58, H 6.96; found C 63.80, H 6.90.

General Procedure for Amidation: A reaction flask topped with a Dean−Stark apparatus and a condenser was charged with acid **4** (1.00 mmol), the amino alcohol (1.00 mmol) and xylene (4.60 mL). The mixture was refluxed for 17 h under argon. The solvent was then removed in vacuo, and the product was dried. Amides **5a−c** were prepared in this way and were obtained as solids which were used in the next step without further purification.

(2*R*,3*R*,5*R*,6*R*)-*N*-[(*S*)-2-Hydroxyl-1-phenylethyl]-3-(hydroxydiphenylmethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carboxamide (5a): Prepared from (*S*)-(+)-2-amino-2-phenylethanol (0.200 g, 1.41 mmol) and acid **4** (0.569 g, 1.41 mmol) as described under the general procedure for amidation. It may be purified by chromatography on silica gel (EtOAc/hexane, 7.4:2.6) and recrystallized from EtOAc/hexane to give white crystals. M.p. 166 °C. $[\alpha]_D^{21}$ = +63.9 (*c* = 0.26, $CHCl_3$). ^1H NMR (400.1 MHz, $CHCl_3$): δ = 1.06 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 2.60 (s, 3 H, OCH_3), 3.12 (s, 3 H, OCH_3), 3.80 (dd, J_{vic} = 5.6, J_{gem} = 11.2 Hz, CH_aCH_b), 3.86 (dd, J_{vic} = 4.0, J_{gem} = 11.2 Hz, 1 H, CH_aCH_b), 4.10 (d, *J* = 9.6 Hz, 1 H, dioxane CH), 4.51 (d, *J* 10 Hz, 1 H, dioxane CH), 4.98 (m, 1 H, CHN), 7.06−7.32 (m, 14 H, Ph-H), 7.64 (d, *J* 8 Hz, 1 H, CONH), 7.92 (d, *J* = 7.2 Hz, 2 H, Ph-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$; DEPT): δ = 17.3 (2 × CH_3), 48.0 (OCH_3), 48.3 (OCH_3), 55.2 (CH or NHCH), 65.8 (CH_2), 69.9 (CH or NHCH), 76.1 (CH or NHCH), 78.3 (Ph_2COH), 98.9 (acetal C), 99.1 (acetal C), 126.5 (CH, Ph), 126.6 (CH, Ph), 127.1 (CH, Ph), 127.5 (CH, Ph), 127.8 (CH, Ph), 128.9 (CH, Ph), 138.4 (C_{quat}, Ph), 143.4 (C_{quat}, Ph), 145.1 (C_{quat}, Ph), 171.8 (CONH) ppm. IR ($CHCl_3$): ṽ = 3666, 3597, 3408, 3301, 3065, 3010, 2950, 2837, 1650, 1529, 1495, 1450, 1378, 1201, 1143, 1132, 1121, 1039, 911, 701 cm^{-1}. $C_{30}H_{35}NO_7$ (521.61): calcd. C 69.08, H 6.76, N 2.69; found C 69.25, H 6.75, N 2.68.

(2*R*,3*R*,5*R*,6*R*)-*N*-[(*S*)-1-Hydroxymethylisopropyl]-3-(hydroxydiphenylmethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carboxamide (5b): Prepared from (*S*)-(+)-2-amino-3-methyl-1-butanol (0.103 g, 0.989 mmol) and acid **4** (0.398 g, 0.989 mmol), as described under the general procedure for amidation. It may be purified by chromatography on silica gel (EtOAc/hexane, 6:4). M.p. 149−150 °C. $[\alpha]_D^{22}$ = +28.9 (*c* = 0.52, $CHCl_3$). The assignments of the NMR signals were made by HMBC. ^1H NMR (400.1 MHz, $CDCl_3$): δ = 0.89 [d, *J* = 6.8 Hz, 3 H, $CH(CH_3)_2$], 0.93 [d, *J* = 6.4 Hz, 3 H, $CH(CH_3)_2$], 1.13 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 1.88−1.97 [m, 1 H, $CH(CH_3)_2$], 2.19 (t, *J* = 5.6 Hz, 1 H, CH_2OH), 2.64 (s, 3 H, OCH_3), 3.20 (s, 3 H, OCH_3), 3.65−3.78 (m, 3 H, CHN + CH_2), 4.10 (d, *J* = 9.2 Hz, 1 H, dioxane CH), 4.58 (d, *J* = 9.2 Hz, 1 H, dioxane CH), 6.01 (s, 1 H, OH), 7.14 (t, *J* = 7.2 Hz, 2 H, Ph-H), 7.21 (t, *J* = 7.2 Hz, 2 H, Ph-H), 7.29 (t, *J* = 7.2 Hz, 2 H, Ph-H), 7.36−7.40 (m, 3 H, 2 H of Ph + NH), 8.00 (d, *J* = 7.6 Hz, 2 H, Ph-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = 17.3 (2 × CH_3), 18.6 [CH_3, $CH(CH_3)_2$], 19.5 [CH_3, $CH(CH_3)_2$], 28.7 [CH, $CH(CH_3)_2$], 48.0 (CH_3 of OCH_3), 48.2 (CH_3 of OCH_3), 57.1 (CHN), 63.3 (CH_2), 70.0 (dioxane CH), 76.4 (dioxane CH), 126.6 (CH, Ph), 127.1 (4 × CH, Ph), 127.6 (CH, Ph), 127.8 (4 × CH, Ph), 143.6 (C_{quat}, Ph), 146.0 (C_{quat}, Ph), 166.7 (CONH), 172.3 (CONH) ppm. IR ($CHCl_3$): ṽ = 3409, 3062, 2995, 2965, 2898, 2836, 1648, 1531, 1493, 1449, 1377, 1265, 1205, 1143, 1131, 1122, 1044, 925, 908, 745, 722, 702 cm^{-1}. $C_{27}H_{37}NO_7$ (487.59): calcd. C 66.51, H 7.65, N 2.87; found C 66.38, H 7.67, N 2.95.

(2*R*,3*R*,5*R*,6*R*)-*N*-[(*S*)-2-Hydroxy-1-methylethyl]-3-(hydroxydiphenylmethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carboxamide (5c): Prepared from (*S*)-(+)-2-amino-1-propanol (0.053 g, 0.692 mmol) and acid **4** (0.281 g, 0.699 mmol), as described in the general procedure for amidation. ^1H NMR (400.1 MHz, $CHCl_3$): δ = 1.12 (s, 3 H, CH_3), 1.17 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 2.66 (s, 3 H, OCH_3), 3.20 (s, 3 H, OCH_3), 3.58 (dd, *J* = 4.8, 10.8 Hz, 1 H, CH_aH_bOH), 3.69 (dd, *J* = 4.0, 11.2 Hz, 1 H, CH_aH_bOH), 4.02 (m, 1 H, CHN), 4.10 (d, *J* = 9.2 Hz. Hz, 1 H, CH), 4.53 (d, *J* = 9.6 Hz, 1 H, CH), 6.20 (br. s, 1 H, OH), 7.16 (t, 2 H, Ph), 7.21 (t, 2 H, Ph), 7.29 (t, 1 H, Ph), 7.39 (t, 3 H, Ph), 8.00 (d, *J* = 7.6 Hz, 2 H, Ph) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = 16.8 (CH_3), 17.3 (2 × CH_3), 47.5 ($CHCH_3$), 48.0 (OCH_3), 48.4 (OCH_3), 65.9 (CH_2OH), 69.8 (CH), 76.2 (CH), 78.3 ($C_{quat}OH$), 98.8 (acetal C), 99.1 (acetal C), 126.6 (CH, Ph), 127.1 (CH, Ph), 127.6 (CH, Ph), 127.8 (CH, Ph), 128.9 (CH, Ph), 143.5 (C_{quat}, Ph), 145.2 (C_{quat}, Ph), 171.7 (CONH) ppm. IR ($CHCl_3$): ṽ = 3690, 3409, 3061, 3010, 2950, 2837, 1647, 1602, 1534, 1493, 1450, 1378, 1214, 1143, 1131, 1043, 913, 774, 744, 702, 665 cm^{-1}.

General Procedure for Oxazoline Synthesis: The oxazolines **6a−c** were prepared from the corresponding amides **5a−c** as follows: the amide (1.00 mmol) was dissolved in CH_2Cl_2 (3.0 mL). Dry triethylamine (4.99 mmol) and *p*-toluenesulfonyl chloride (1.06 mmol) were added, and the mixture was refluxed under argon for 17 h. After cooling to room temp. water (1.00 mmol) was added, and the mixture was refluxed for 40 min. It was then cooled and extracted four times with water. The organic layer was dried through anhydrous sodium sulfate, and the product was obtained as a solid after evaporation of the solvent.

{(2*R*,3*R*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-3-[(*S*)-4-phenyl-4,5-dihydrooxazol-2-yl]-1,4-dioxan-2-yl}diphenylmethanol (6a): White solid (76% based on the amide); purification by chromatography

on silica gel (CH_2Cl_2/EtOAc, 8:2). M.p. 79−80 °C (sublimes). $[\alpha]_D^{32} = -99.0$ (c = 2.00, $CHCl_3$). The assignments of the NMR signals were made by HMBC. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.07 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 3.00 (s, 3 H, OCH_3), 3.22 (s, 3 H, OCH_3), 3.85 (t, J = 8.3 Hz, 1 H, OCH_aH_b), 4.27 (t, J = 10.3 Hz, 1 H, OCH_aH_b), 4.60 (t, J 9 Hz, 1 H, CHN), 4.80 (AB system, $J \approx 0$ Hz, 2 H, 2 × dioxane CH), 6.95 (d, J = 7.0 Hz, 2 H, Ph-H), 7.07 (t, J = 7.2 Hz, 1 H, Ph-H), 7.17 (m, 6 H, Ph-H), 7.22 (t, J = 7.4 Hz, 2 H, Ph-H), 7.46 (d, J = 7.7 Hz, 2 H Hz, Ph-H), 7.70 (d, J = 7.7 Hz, 2 H, Ph-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = 17.2 (CH_3), 17.4 (CH_3), 48.3 (OCH_3), 48.8 (OCH_3), 65.6 (CH), 68.3 (N*C*HPh), 73.3 (CH), 74.4 (CH_2), 78.0 (*C*Ph_2OH), 98.7 (acetal C), 99.3 (acetal C), 126.5 (CH, Ph), 126.7 (CH, Ph), 126.8 (2 × CH, Ph), 127.1 (CH, Ph), 127.3 (CH, Ph), 127.5 (CH, Ph), 127.7 (CH, Ph), 128.5 (CH, Ph), 141.0 (C_{quat}, Ph), 143.3 (C_{quat}, Ph), 144.6 (C_{quat}, Ph), 165.4 (OCN) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3676, 3559, 3089, 3066, 3034, 3026, 3010, 2964, 2951, 2907, 2837, 1753, 1673, 1600, 1494, 1471, 1450, 1377, 1262, 1217, 1176, 1165, 1217, 1176, 1165, 1143, 1129, 1118, 1035, 987, 786, 767, 749, 737, 701, 670, 664 cm^{-1}. $C_{30}H_{33}NO_6$ (503.60): calcd. C 71.55, H 6.61, N 2.78; found C 71.27, H 6.64, N 2.73.

{(3*R*,3*R*,5*R*,6*R*)-3-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl}diphenylmethanol (6b): White solid (79% based on acid **4**); purification by chromatography on silica gel (CH_2Cl_2/EtOAc, 8.5:1.5). M.p. 58−59 °C. $[\alpha]_D^{25} = -84.7$ (c = 2.02, $CHCl_3$). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.77 (d, J = 6.8 Hz, 3 H, CH_3 of *i*Pr), 0.84 (d, J = 7.2 Hz, 3 H, CH_3 of *i*Pr), 1.10 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.58 [m, 1 H, *CH*(CH_3)$_2$], 2.96 (s, 3 H, OCH_3), 3.25 (s, 3 H, OCH_3), 3.61 (m, 1 H, CHN), 3.83 (t, J = 8.0 Hz, 1 H, CH_aH_bO), 4.07 (dd, J = 8.4 Hz, 1 H, CH_aH_bO), 4.67 (AB system, $J \approx 0$ Hz, 2 H, 2 × dioxane CH), 7.13 (t, J = 7.2 Hz, 1 H, Ph-H), 7.23 (m, 3 H, Ph-H), 7.34 (t, J = 7.2 Hz, 2 H, Ph-H), 7.48 (d, J = 8.4 Hz, 2 H, Ph-H), 7.86 (d, J = 7.2 Hz, 2 H, Ph-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = 17.1 (CH_3), 17.3 (CH_3), 18.0 (CH_3 of *i*Pr), 18.4 (CH_3 of *i*Pr), 32.1 (CH of *i*Pr), 48.2 (OCH_3), 48.6 (OCH_3), 65.7 (dioxane CH), 70.3 (CH_2), 70.8 (CHN), 74.1 (dioxane CH), 77.9 (CPh_2OH), 98.7 (acetal C), 99.2 (acetal C), 126.6 (CH, Ph), 126.8 (CH, Ph), 127.2 (CH, Ph), 127.4 (CH, Ph), 127.6 (CH, Ph), 144.1 (C_{quat}, Ph), 164.7 (OCN) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3558, 3090, 3062, 3009, 2964, 2908, 2875, 2837, 1676, 1600, 1492, 1464, 1449, 1375, 1212, 1202, 1142, 1129, 1120, 1035, 987, 946, 911, 892, 881 cm^{-1}. $C_{27}H_{35}NO_6$ (469.56): calcd. C 69.06, H 7.51, N 2.98; found C 69.12, H 7.51, N 2.95.

{(2*R*,3*R*,5*R*,6*R*)-5,6-Dimethoxy-3-[(*S*)-4-methyl-4,5-dihydrooxazol-2-yl]-5,6-dimethyl-1,4-dioxan-2-yl}diphenylmethanol (6c): White solid (65% based on acid **4**); purification by chromatography on silica gel (EtOAc/CH_2Cl_2, 1:1). M.p. 124 °C (sublimes). $[\alpha]_D^{27} = -88.9$ (c = 2.01, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.08 (d, J = 6.6 Hz, 3 H, oxazoline CH_3), 1.13 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 3.08 (s, 3 H, OCH_3), 3.26 (s, 3 H, OCH_3), 3.59 (t, J = 7.9 Hz, 1 H, CH_aH_b), 3.69 (m, 1 H, *CH*CH_3), 4.06 (t, J = 8.7 Hz, 1 H, CH_aH_b), 4.67 (d, J = 9.7 Hz, 1 H, dioxane CH), 4.82 (d, J = 9.7 Hz, 1 H, dioxane CH), 5.69 (br. s, 1 H, OH), 7.12 (t, J = 7.2 Hz, 1 H, Ph-H), 7.23 (q, J = 7.7 Hz, 1 H, CH, Ph-H), 7.33 (t, J = 7.4 Hz, 2 H, Ph-H), 7.51 (d, J = 7.7 Hz, 2 H, Ph-H), 7.77 (d, J = 7.7 Hz, 2 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$, DEPT): δ = 17.2 (CH_3), 17.4 (CH_3), 20.7 (oxazoline CH_3), 48.2 (OCH_3), 48.8 (OCH_3), 60.5 (CHN), 65.5 (dioxane CH), 73.3 (dioxane CH), 73.6 (CH_2), 78.0 (C_{quat}-OH), 98.6 (acetal C), 99.2 (acetal C), 126.7 (CH, Ph), 126.8 (CH, Ph), 127.1 (CH, Ph), 127.3 (CH, Ph), 127.6 (CH, Ph), 143.4 (C_{quat}, Ph), 144.7 (C_{quat}, Ph), 163.8 (O−C=N) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3556, 3061, 3009, 2970, 2953, 2905, 2837, 1676, 1600, 1492, 1473, 1450, 1377, 1143, 1129, 1036, 986, 946. $C_{25}H_{31}NO_6$ (441.52): calcd. C 68.01, H 7.08, N 3.17; found C 68.06, H 7.18, N 3.16.

3-Methyl (2-Methyloxetan-2-yl)methyl (2*R*,3*R*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-dicarboxylate (8): Half-ester **3** (0.664 g, 2.39 mmol), 3-hydroxymethyl-3-methyloxetane (0.526 g, 5.15 mmol) and 4-dimethylaminopyridine (0.032 g, 0.262 mmol) were dissolved in CH_2Cl_2 (4.6 mL), and the solution was cooled to 0 °C. 1,3-Dicyclohexylcarbodiimide (0.592 g, 2.87 mmol) dissolved in CH_2Cl_2 (2.3 mL) was added dropwise. The urea started to precipitate within a few minutes. The solution was then stirred at 0 °C under argon for 4 h. The precipitated urea was filtered off with the aid of CH_2Cl_2. The solvent was removed using a rotary evaporator, the solid residue was redissolved in CH_2Cl_2 and filtered. The solution was then washed successively with water, HCl (0.2 M) and saturated sodium hydrogencarbonate solution. The solvent was removed using a rotary evaporator. The crude product was purified by flash chromatography on silica gel pre-treated with 1% Et_3N in hexane (hexane/EtOAc, 1:1) to give a viscous liquid (0.593 g, 77%). $[\alpha]_D^{27} = -111.1$ (c = 2.01, $CHCl_3$). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.34 (s, 3 H, CH_3), 1.35 (s, 6 H, 2 × CH_3), 3.33 (s, 6 H, 2 × OCH_3), 3.77 (s, 3 H, CO_2CH_3), 4.25 (virtual q, J = 8 Hz, 2 H, CH_2OCO), 4.37 (d, J = 6 Hz, 2 H, CH_2O), 4.52 (d, J = 6 Hz, 2 H, CH_2O), 4.55 (s, 1 H, CH), 4.56 (s, 1 H, CH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = 17.1 (CH_3, 2 × CH_3), 20.9 (CH_3), 38.9 (C_{quat}, *C*−CH_3), 48.1 (CH_3, 2 × OMe), 52.3 (CH_3, 2 × CO_2Me), 68.1 (CH), 68.2 (CH), 69.2 (CH_2, CH_2OCO), 79.0 (CH_2, 2 × CH_2O), 98.9 (C_{quat}, 2 × acetal C), 167.6 (C_{quat}, CO_2), 168.0 (C_{quat}, CO_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3010, 2956, 2879, 2838, 1749, 1460, 1440, 1380, 1289, 1230, 1178, 1144, 1113, 1039, 984, 890, 755, 664. $C_{16}H_{26}O_9$ (362.38): calcd. C 53.03, H 7.23; found C 53.28, H 7.17.

Methyl (2*R*,3*R*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-3-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-1,4-dioxane-2-carboxylate (9): A suspension of the oxetanyl ester **8** (3.50 g, 9.61 mmol) in dry CH_2Cl_2 (12.4 mL) was stirred at room temp. under argon. Boron trifluoride−etherate (0.307 mL, 2.48 mmol) was added dropwise. The resulting solution changed from colourless to yellow brown in less than 10 min. One hour later Et_3N (1.4 mL) was added, the solution was stirred for 5−10 min and diethyl ether was added to precipitate the boron trifluoride−triethylamine complex. After stirring for about 10 min, the precipitate was filtered off and the solvent was removed using a rotary evaporator. The product was purified by column chromatography on silica gel pre-treated with 1% Et_3N in hexane[28] (EtOAc) to give a white solid (2.87 g, 82%). M.p. 78 °C. $[\alpha]_D^{31} = -131.9$ (c = 0.81, $CHCl_3$). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.79 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 3.29 (s, 3 H, OCH_3), 3.31 (s, 3 H, OCH_3), 3.73 (s, 3 H, CO_2CH_3), 3.89 (s, 6 H, 3 × CH_2), 4.06 (d, J = 10 Hz, 1 H, CH), 4.44 (d, J = 10 Hz, 1 H, CH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.3 (CH_3), 17.3 (CH_3), 17.5 (CH_3), 30.5 (C_{quat}-CH_3), 48.1 (2 × OCH_3), 53.2 (CO_2CH_3), 69.5 (CH), 69.9 (CH), 72.4 (3 × CH_2O), 98.5 (acetal C), 99.1 (acetal C), 106.5 (orthoester C), 169.0 (CO_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3009, 2952, 2885, 2837, 1746, 1471, 1460, 1439, 1404, 1379, 1353, 1289, 1199, 1141, 1119, 1076, 1043, 993, 892, 854, 821, 767, 739, 664, 562, 540, 440 cm^{-1}. $C_{16}H_{26}O_9$ (362.19): calcd. C 53.06, H 7.18; found C 52.84, H 7.24.

[(2*R*,3*R*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-3-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-1,4-dioxan-2-yl]methanol (10): A two-necked round-bottom flask was flame dried and charged with $LiAlH_4$ (51.0 mg, 1.34 mmol) and dry THF (0.48 mL). Protected half-ester **9** (0.396 g, 1.09 mmol) dissolved in dry THF (2.6 mL)

was added dropwise at room temperature. The resulting suspension was refluxed for 3 h or until a TLC plate showed that the starting material had all been consumed. The mixture was then warmed to room temperature and an aqueous solution of KOH (10%) was added dropwise. The flask was stirred vigorously after each addition until the mixture turned white. Refluxing was continued for another hour. The solution was filtered and the product extracted a few times with boiling THF. The pooled extracts were dried with anhydrous sodium sulfate, and the solvent removed using a rotary evaporator. The solid obtained was purified by column chromatography on silica gel pre-treated with 1% Et_3N in hexane[28] (EtOAc/hexane, 8:2) to give the product as a white hygroscopic solid (0.250 g, 68%). $[\alpha]_D^{22} = -112.2$ ($c = 2.00$, $CHCl_3$). ^1H NMR (400.1 MHz, $CDCl_3$): δ = 0.82 (s, 3 H, CH_3 of OBO ester), 1.30 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 2.27 (br. s, OH), 3.25 (s, 3 H, OCH_3), 3.28 (s, 3 H, OCH_3), 3.76 (m, 3 H, 1 CH + CH_2OH), 3.92 (br. s, 7 H, 3 × orthoester CH_2 + CH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$; DEPT): δ = 12.9 (CH_3), 17.4 (2 × CH_3), 30.4 (C_{quat}, C_{quat}-CH_3), 47.8 (OCH_3), 48.0 (OCH_3), 62.7 (CH_2, CH_2OH), 69.0 (CH), 69.8 (CH), 72.4 (CH_2, 3 × CH_2O of OBO ester), 98.6 (C_{quat}, acetal C), 99.1 (C_{quat}, acetal C), 107.1 (orthoester C) ppm. IR (KBr): $\tilde{\nu}$ = 3574, 3487, 2983, 2939, 2833, 1617, 1474, 1459, 1404, 1316, 1299, 1285, 1256, 1198, 1123, 1038, 979, 940, 912, 888, 863, 752, 745, 736, 643, 660, 607 cm^{-1}. $C_{15}H_{25}O_8$ (333.36): calcd. C 54.05, H 7.56; found C 53.81, H 7.66.

(2*R*,3*R*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-3-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-1,4-dioxane-2-carbaldehyde (11): A reaction vessel was purged with argon, flame-dried and charged with dry CH_2Cl_2 (3.2 mL) and $(COCl)_2$ (0.152 mL, 1.75 mmol). The solution was cooled to −60 °C. Dry DMSO (0.264 mL, 3.72 mol) dissolved in dry CH_2Cl_2 (0.77 mL) was added dropwise at a good rate. The temperature was kept between −50 and −60 °C. Five minutes later alcohol **10** (0.513 g, 1.53 mmol) dissolved in dry CH_2Cl_2 (2.2 mL) was added over 10 min. The mixture was stirred for 40 min at −50 to −60 °C, then Et_3N (1.1 mL) was added dropwise. The mixture was stirred for 5 min at this temperature, then it was placed in an ice−NaCl bath and stirred for 30 min at 0 °C. CH_2Cl_2 was added to the cold solution, and the mixture was washed successively with ice-cold NH_4Cl (5% solution) and a saturated NaCl solution. It was filtered through anhydrous magnesium sulfate and the solvent was evaporated to give a solid (0.374 g, 87%), which was used in the next reaction without purification. For analytical determinations the product was purified by column chromatography on silica gel treated with 1% Et_3N in hexane (EtOAc/hexane, 8:2). M.p. 73−74 °C. $[\alpha]_D^{30} = -117.0$ ($c = 2.04$, $CHCl_3$). ^1H NMR (400.1 MHz, $CDCl_3$): δ = 0.81 (s, 3 H, CH_3 of OBO ester), 1.33 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 3.26 (s, 3 H, OCH_3), 3.30 (s, 3 H, OCH_3), 3.91 (s, 6 H, 3 × orthoester CH_2), 4.01 (d, $J = 10$ Hz, 1 H, CH), 4.32 (dd, $J = 3.2$, 9.6 Hz, 1 H, CH), 9.53 (d, $J = 3.2$ Hz, 1 H, CHO) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.3 (orthoester CH_3), 17.3 (CH_3), 17.4 (CH_3), 30.6 (orthoester *C*-CH_3), 48.1 (2 × OCH_3), 69.1 (CH), 72.4 (3 × orthoester CH_2), 72.9 (*C*H-CHO), 98.6 (acetal C), 99.2 (acetal C), 106.4 (orthoester C), 195.2 (CHO) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3010, 2960, 2949, 2885, 2837, 1735, 1472, 1459, 1403, 1460, 1403, 1378, 1353, 1241, 1139, 1122, 1072, 1049, 1024, 999, 932, 889, 875, 756, 741, 593, 563 cm^{-1}. $C_{15}H_{24}O_8$ (332.35): calcd. C 54.21, H 7.28; found C 54.17, H 7.45.

[(2*R*,3*R*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-3-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-1,4-dioxan-2-yl]phenylmethanol (12): Phenylmagnesium bromide (0.78 mL, 0.78 mmol of a 1 M solution in hexanes) was added to a round-bottom two-necked flask, cooled in an ice bath, and stirred under argon. Aldehyde **11** (0.214 g, 0.521 mmol) dissolved in dry THF (1.75 mL), was added dropwise over a period of 40 min. The solution was then placed in a oil bath and heated to reflux. After 1 h 20 it was cooled to room temperature, ammonium chloride solution (5%) was added, and the product extracted three times with diethyl ether. The combined extracts were dried with anhydrous sodium sulfate, and the solvent removed using a rotary evaporator. The product was purified by column chromatography on silica gel pre-treated with 1% Et_3N in hexane EtOAc/hexane, 1:1) to give a white solid (0.153 g, 72%). M.p. 161−162 °C. $[\alpha]_D^{27} = -141.0$ ($c = 0.58$, $CHCl_3$). The assignments of the NMR signals were made by COSY. ^1H NMR (400.1 MHz, $CDCl_3$): δ = 0.85 (s, 3 H, orthoester CH_3), 1.14 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 2.60 (s, 3 H, OCH_3), 2.94 (d, $J = 8$ Hz, 1 H, CH−C, orthoester), 3.28 (s, 3 H, OCH_3), 3.99 (s, 6 H, 3 × orthoester CH_2), 4.06 (m, 1 H, C*H*OH), 5.22 (d, $J = 8.4$ Hz, 1 H, dioxane C*H*CPh), 7.21 (t, $J = 7.2$ Hz, 1 H, Ph), 7.30 (t, $J = 7.4$ Hz, 2 H, Ph-H), 7.39 (d, $J = 7.5$ Hz, 2 H, Ph-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = 14.4 (orthoester Me), 17.3 (CH_3), 17.4 (CH_3), 30.6 (orthoester C_{quat}), 47.3 (OCH_3), 47.9 (OCH_3), 69.5 (CH), 71.4 (CH), 72.1 (CH), 72.5 (3 × CH_2), 98.9 (acetal C), 99.2 (acetal C), 107.4 (orthoester C_{quat}), 126.0 (CH, Ph), 126.6 (CH, Ph), 127.6 (CH, Ph), 141.8 (C_{quat}, Ph) ppm. IR (KBr): $\tilde{\nu}$ = 3557.1, 3436.0, 3083, 3057, 3031, 2991.3, 2947.5, 2882.9, 2832.7, 1495.7, 1469.0, 1453.1, 1403.7, 1377.3, 1282.8, 1197.2, 1133.2, 1071.7, 1052.0, 1022.5, 993.0, 903.9, 887.1, 853.2, 828.3, 753.8, 738.6, 753.8, 738.8, 701.4, 571.2 cm^{-1}. $C_{21}H_{30}O_8$ (410.46): calcd. C 61.45, H 7.37; found C 61.23, H 7.40.

(2*R*,3*R*,5*R*,6*R*)-3-(Hydroxyphenylmethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carboxylic Acid (13): Monoalcohol **12** (0.491 g, 1.20 mmol) was dissolved in THF/H_2O (40:1, 6.16 mL). The solution was cooled to 0 °C and the pH was adjusted to 1 with HCl (2 M). The mixture was then stirred at this temperature for 40 min, by which time the OBO ester had been fully converted into the ester as indicated by a TLC plate. The pH was then raised to 11 with LiOH solution (1 M) and the mixture was heated and refluxed for 4 h 40, or until the ester could no longer be detected by TLC. During this time the pH was checked two or three times, and adjusted again with LiOH to pH 11 if the solution was found to have become neutral. After cooling, the pH of the solution was adjusted to 1 and the product was extracted four times with diethyl ether. The combined diethyl ether extracts were filtered through anhydrous sodium sulfate and the solvent was removed using a rotary evaporator to give a white crystalline product (0.343 g, 88%), which was used as it was in the next step. The product may be recrystallized from diethyl ether/hexane to give white crystals. M.p. 142−143 °C. $[\alpha]_D^{22} = -148.0$ ($c = 2.01$, $CHCl_3$). ^1H NMR (400.1 MHz, $CDCl_3$): δ = 1.23 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 2.78 (s, 3 H, OCH_3), 3.32 (s, 3 H, OCH_3), 3.98 (dd, $J = 1.6$, 10.0 Hz, CH), 4.66 (d, ABX system, $J = 10.0$ Hz, 1 H, C*H*OH), 5.20 (AB system, 1 H, C*H*COO), 7.26 (d, $J = 7.2$ Hz, 1 H, Ph-H), 7.33 (t, $J = 6.4$ Hz, 2 H, Ph-H), 7.40 (d, $J = 7.2$ Hz, 2 H, Ph-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = 17.3 (2 × CH_3), 47.8 (OCH_3), 48.6 (OCH_3), 68.4 (CHOH or dioxane CH), 71.6 (CHOH or dioxane CH), 71.8 (CHOH or dioxane CH), 98.9 (acetal C), 99.4 (acetal C), 126.1 (CH, Ph), 127.4 (CH, Ph), 128.0 (CH, Ph), 140.8 (C_{quat}, Ph), 171.2 (COOH) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3674, 3556, 3426, 3026, 3012, 2951, 2837, 1772, 1739, 1604, 1453, 1378, 1230, 1198, 1143, 1130, 1037, 907, 890, 855, 826, 781, 778, 770, 766, 760, 755, 750, 746, 742, 734, 701, 666, 634 cm^{-1}. $C_{16}H_{22}O_7$ (326.35): calcd. C 58.89, H 6.80; found C 58.99, H 6.88.

(2*R*,3*R*,5*R*,6*R*)-*N*-[(*S*)-2-Hydroxy-1-phenylethyl]-3-(hydroxyphenylmethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carb-

oxamide (14): (*S*)-(+)-2-Amino-2-phenylethanol (0.064 g, 0.457 mmol), acid **13** (0.149 g, 0.457 mmol) and xylene (2.1 mL) were heated to reflux and treated as described for amides **5a−c**. The product obtained was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 3:2) to give a white solid (0.087 g, 43%). M.p. 153 °C. $[\alpha]_D^{21} = -67.2$ (c = 1.75, $CHCl_3$). The assignments of the NMR signals were made by HMBC. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.23 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 1.67 (br. s, OH), 2.49 (br. s, OH), 2.82 (s, 3 H, OCH_3), 3.21 (s, 3 H, OCH_3), 3.90 (dd, J = 1.6 Hz, 1 H, 10 Hz, 1 H, dioxane CH), 3.94 (m, 2 H, 2 × H of CH_2), 4.50 (d, J = 10 Hz, dioxane CH), 5.13 (m, 1 H, CHN), 5.26 (br. s, C*H*OH), 7.23 (t, J = 7.2 Hz, 2 H, Ph-H), 7.31 (m, 5 H, Ph-H), 7.38 (d, J = 7.2 Hz, 1 H, CONH), 7.43 (m, 3 H, Ph-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = 17.3 (CH_3), 17.4 (CH_3), 47.9 (OCH_3), 48.4 (OCH_3), 55.5 (CH, CHPh), 66.5 (CH_2), 69.3 (CH, dioxane CHCON), 72.0 (CH, *C*HPh(OH), 73.0 (CH, dioxane CH), 98.9 (acetal C), 99.3 (acetal C), 126.4 (2 × CH, Ph), 126.6 (2 × CH, Ph), 127.0 (CH), 127.8 (2 × CH, Ph), 128.1 (CH), 129.0 (2 × CH, Ph), 138.5 (C_{quat}, Ph), 141.1 (C_{quat}, Ph), 170.0 (CONH) ppm. IR ($CHCl_3$): ṽ = 3676, 3412, 3066, 3012, 2951, 2837, 1668, 1522, 1496, 1454, 1378, 1233, 1197, 1143, 1132, 1037, 948, 908, 891, 827, 782, 778, 774, 768, 764, 755, 750, 744, 738, 702 cm^{-1}. $C_{24}H_{31}NO_7$ (445.51): calcd. C 64.70, H 7.01, N 3.14; found C 64.47, H 6.73, N 3.04.

[(2*R*,3*R*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-3-[(*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)-1,4-dioxan-2-yl]phenylmethanol (15): Amide **14** (0.263 mmol) was dissolved in CH_2Cl_2 (0.80 mL) and *p*-toluenesulfonyl chloride (0.051 g, 0.269 mmol) and dry triethylamine (0.18 mL, 5.00 mmol) were added. The mixture was refluxed for 17 h and treated as described for oxazolines **6a−c**. The product was purified by chromatography on silica gel (EtOAc/hexane, 7:3) to give a white solid (0.071 g, 63%). M.p. 47−48 °C. $[\alpha]_D^{22} = -129.0$ (c = 0.77, $CHCl_3$). The assignments of the NMR signals were made by COSY and HMBC. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.32 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 3.07 (s, 3 H, OCH_3), 3.31 (s, 3 H, OCH_3), 4.05 (d, J = 8 Hz, 1 H, OH, exchanges with D_2O), 4.07 (t, J = 8.8 Hz, 1 H, CH_aH$_b$), 4.30 (dd, J = 3.2, 9.6 Hz, 1 H, CHCOH), 4.44 (dd, J = 8.4 Hz, 10 Hz, 1 H, CH$_a$$H_b$), 4.61 (d, J = 10 Hz, 1 H, CH), 4.92 (dd, J = 2.8, 7.6 Hz, 1 H, *CH*PhOH), 5.03 (app. t, J = 10 Hz, 1 H, NCHPh), 7.20 (d, J = 6.8 Hz, 2 H, Ph-H), 7.33 (m, 6 H, Ph-H), 7.42 (d, J = 7.2 Hz, 2 H, Ph-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.3 (CH_3), 17.5 (CH_3), 48.01 (OCH_3), 48.3 (OCH_3), 65.3 (dioxane CH), 69.2 (*C*HPhN), 72.5 (*C*HCPh), 72.6 (*C*HPhOH), 74.6 (CH_2), 99.08 (acetal C), 99.09 (acetal C), 126.7 (2 × CH, Ph), 127.4 (CH, Ph), 127.8 (CH, Ph), 127.9 (CH, Ph), 128.7 (CH, Ph), 140.8 (C_{quat}, Ph), 141.4 (C_{quat}, Ph), 164.6 (O−C=N) ppm. IR (KBr): ṽ = 3542, 3431, 3087, 3062, 3029, 2993, 2950, 2834, 1668, 1495, 1454, 1377, 1199, 1183, 1142, 1128, 1037, 922, 857, 759, 746, 701 cm^{-1}. $C_{24}H_{29}NO_6$ (427.50): calcd. C 67.43, H 6.84, N 3.28; found C 67.16, H 6.86, N 3.24.

(2*R*,3*R*,5*R*,6*R*)-3-(Hydroxymethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carboxylic Acid (16): Monoalcohol **10** (1.519 g, 4.54 mmol) was dissolved in THF/H_2O (40:1, 23.6 mL). The solution was cooled to 0 °C and the pH was adjusted to 1 with HCl (2 M). The mixture was then stirred at this temperature for 30 min, by which time the OBO ester had been fully converted into the acid as indicated by a TLC plate. The pH was then raised to 11 with a solution of LiOH (1 M) and the mixture was heated and refluxed for 2 h, or until the ester could no longer be detected by TLC. After cooling, the pH of the solution was adjusted to 1 and the product was extracted four times with diethyl ether. The sample was dried with anhydrous sodium sulfate and the solvent was removed using a rotary evaporator to give a white crystalline product (1.01 g, 88%), used in the next reaction without further purification. It may be recrystallized from diethyl ether/hexane mixtures. M.p. 132 °C. $[\alpha]_D^{28} = -148.7$ (c = 1.95, MeOH). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.32 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 3.27 (s, 3 H, OCH_3), 3.30 (s, 3 H, OCH_3), 3.81−3.93 (m, 3 H, 2 × H of CH_2 + CH), 4.44 (d, J = 9.9 Hz, 6 Hz, 1 H, CH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.3 (CH_3), 17.4 (CH_3), 48.2 (OCH_3), 48.6 (OCH_3), 62.2 (CH_2OH), 68.5 (CH), 68.9 (CH), 98.8 (acetal C), 99.5 (acetal C), 170.6 (COOH) ppm. IR (KBr): ṽ = 3401, 2996, 2959, 2841, 2685, 1755, 1458, 1405, 1382, 1354, 1336, 1312, 1210, 1130, 1069, 1046, 966, 946, 890, 866, 773, 739, 670, 650 cm^{-1}. $C_{10}H_{18}O_7$ (250.25): calcd. C 48.00, H 7.25; found C 48.20, H 7.41.

(2*R*,3*R*,5*R*,6*R*)-*N*-[(*S*)-2-Hydroxy-1-phenylethyl]-3-(hydroxymethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carboxamide (17): A two-necked round-bottom flask was charged with acid **16** (0.253 g, 1.00 mmol), (*S*)-(+)-2-amino-2-phenylethanol (0.134 g, 0.098 mmol) and xylene (0.32 mL). The resulting suspension was stirred and refluxed under argon for 17 h. The solvent was removed under reduced pressure and the product was dried to give the crude amide. The assignments of the NMR signals were made by decoupling. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.31 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 2.62 (br. s, OH), 3.25 (s, 3 H, OCH_3), 3.28 (s, 3 H, OCH_3), 3.71 (s, 1 H, OH), 3.71−3.81 (m, 3 H, dioxane CH + CH_2), 3.89−3.93 (m, 2 H, PhCHCH_2), 4.30 (d, J = 9.2 Hz, 1 H, CHCO), 5.07−5.11 (m, 1 H, CHN), 7.21−7.33 (m, 5 H, Ph-H), 7.54 (d, J = 7.2 Hz, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = 17.40 (2 × CH_3), 48.1 (OCH_3), 48.3 (OCH_3), 55.1 (CH), 63.0 (CH_2), 65.5 (CH_2), 70.1 (CH), 70.9 (CH), 98.7 (C_{quat}, acetal C), 99.3 (C_{quat}, acetal C), 126.5 (2 × CH, Ph), 127.7 (CH, Ph), 128.7 (2 × CH, Ph), 138.8 (C_{quat}, Ph), 169.8 (CONH) ppm.

[(2*R*,3*R*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-3-[(*S*)-4-phenyl-4,5-dihydrooxazol-2-yl]-1,4-dioxan-2-yl]methanol (18): Acid **16** (0.253 g, 1.00 mmol) and (*S*)-(+)-2-amino-2-phenylethanol (0.144 g, 1.02 mmol) were mixed in decalin (2.98 mL) and refluxed for 94 h with a Dean−Stark trap, under argon, using a sand bath kept at 210 °C. After this time the solvent was removed under reduced pressure to give a crude mixture consisting of oxazoline, starting material and one unidentified product, with the oxazoline being the major component. Refluxing the mixture longer did not improve the outcome. The solid was stirred in EtOH with charcoal and filtered through Celite. After column chromatography on silica gel ($CHCl_3$/EtOAc, 1:5) the product was obtained as a pale-yellow solid (0.046 g, 15%). $[\alpha]_D^{19} = -107.4$ (c = 0.51, $CHCl_3$). The assignments of the NMR signals were made by HMBC. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.33 (s, 3 H, Me), 1.39 (s, 3 H, Me), 3.30 (s, 3 H, OMe), 3.35 (s, 3 H, OMe), 3.75 (dd, J = 4.4, 12.4 Hz, 1 H, CH_aH$_b$OH), 3.82 (dd, J = 4.8, 12.4 Hz, 1 H, CH$_a$$H_b$OH), 4.16 (m, oxazoline H of CH_2 + dioxane CH), 4.59 (d, J = 10 Hz, dioxane CH), 4.70 (dd, J = 8.8 Hz, 10 Hz, 1 H, oxazoline H of CH_2), 5.24 (t, J = 10 Hz, 1 H, oxazoline NCH), 7.21 (d, J = 6.8 Hz, 1 H, Ar-H), 7.37−7.27 (m, Ar-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = 17.4 (CH_3), 17.5 (CH_3), 48.1 (CH_3), 48.4 (CH_3), 62.9 (CH_2OH), 66.0 (CHN), 69.3 (dioxane CH), 69.8 (dioxane CH), 74.8 (oxazoline CH_2), 98.9 (acetal C), 99.1 (acetal C), 126.5 (2 × CH, Ph), 127.8 (CH, Ph), 128.8 (2 × CH, Ph), 141.3 (C_{quat}, Ph), 165.1 (O−C=N) ppm. IR ($CHCl_3$): ṽ = 3671, 3587, 3406, 3010, 2964, 2949, 2837, 1667, 1604, 1495, 1455, 1378, 1232, 1142, 1132, 1120, 1036, 924, 890, 869, 700, 664 cm^{-1}. $C_{18}H_{25}NO_6$ (351.40): calcd. C 61.52, H 7.17, N 3.99; found C 61.51, H 6.97, N 4.18.

General Procedure for the Catalyzed Enantioselective Addition of Diethylzinc to Benzaldehyde: A Schlenk flask was flame-dried in

vacuo and filled with argon when cool. The catalyst was added (10 mol %) and then dry distilled toluene (0.96 mL). The solution was degassed three times by freeze−pump−thaw, it was returned to an argon line and the flask was refilled with argon. The solution was cooled to 0 °C and a solution of diethylzinc in hexane (2.16 mL, 1.0 M, 2.2 equiv.) was added dropwise. The mixture was stirred for 10 min and freshly distilled benzaldehyde (0.100 mL, 0.984 mmol) was added dropwise. The flask was then closed, placed in a covered bath at the temperature required, and stirred for the period indicated in each experiment. Afterwards 1 M HCl solution was added dropwise, the product was extracted with CH_2Cl_2, dried with anhydrous $MgSO_4$ and the solvent removed using a rotary evaporator.

Determination of Enantiomeric Excesses: HPLC analysis on a chiral column was used under the following conditions: column, Daicel Co. CHIRALCEL OB-H; eluent, hexane/2-propanol 85.5:1.5; flow-rate, 0.9 mL/min; detection, 254 nm. Under these conditions racemic 1-phenyl-1-propanol exhibited baseline separation of peaks: (*S*) isomer t_R 13 min, (*R*) isomer t_R 16 min.[29] Peaks were assigned on the basis of the known order of elution of the enantiomers on this column. For quantitative determinations, racemic 1-phenylethanol was used as internal standard.

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