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trans-3,4-Disubstituted pyrrolidines by 1,3-dipolar cycloaddition: enantioselective approaches and their limitations

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Abstract

In the presence of a chiral Lewis acid as co-catalyst, the acid-catalysed 1,3-dipolar cycloaddition reaction yielding *trans*-3,4-disubstituted pyrrolidines from an azomethine ylide and achiral α,β-unsaturated dipolarophiles proceeded with low enantioselectivity. Therefore a number of α,β-unsaturated dipolarophiles linked to chiral auxiliaries were examined as substrates. Camphorsultam was the best auxiliary and gave good diastereoselectivity (dr=74:26). When combining chiral Lewis acids with a dipolarophile linked to a chiral auxiliary, the enantioselectivity could be slightly increased. As judged by ^{13}C NMR, the small effect of the chiral Lewis acids on selectivity was probably due to breakdown of the initially formed complex with the dipolarophile caused by the dipole precursor.

1. Introduction

Substituted, stereoisomerically pure pyrrolidines are important building blocks for the synthesis of many natural products and pharmaceuticals.[1–3] Compounds containing a pyrrolidine ring can be prepared in a simple manner using a one-step 1,3-dipolar cycloaddition reaction between a dipolarophile and nitrogen-containing 1,3-dipoles.[4,5]

Chiral copper(II)-containing Lewis acids have been successfully used in some enantioselective electrocyclic reactions e.g. of the Diels–Alder type, in which the catalyst forms a complex with the dienophile.[6–8]

The use of chiral auxiliaries attached to a dipolarophile in 1,3-dipolar cycloaddition reactions with azomethine ylides has been briefly described previously.[9,10] The present study describes our efforts to develop enantio- and diastereoselective methods for the preparation of *trans*-3,4-disubstituted pyrroli-

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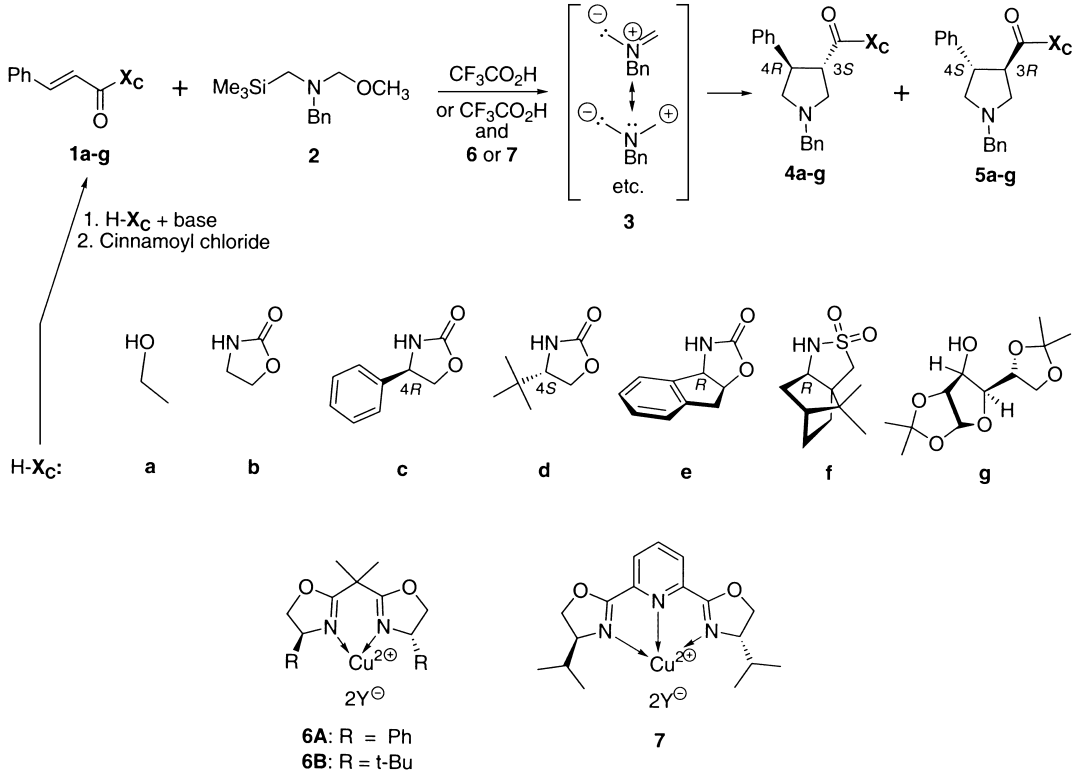
dines in 1,3-dipolar cycloadditions using either enantiopure Lewis acid catalysts or chiral auxiliaries or a combination of both.

2. Results and discussion

It is known that acid-catalysed transformation of *N*-benzyl-*N*-methoxymethyl-*N*-trimethylsilylmethylamine **2** (Scheme 1) generates a 1,3-dipole, the azomethine ylide **3**, which reacts in situ with a number of substituted alkenes.[4,5,11–14]



Scheme 1. 1,3-Dipolar cycloadditions between dipole **3** and chiral/achiral dipolarophiles **1a**–**g** in the presence or absence of chiral Lewis acid **6** or **7**

The cycloaddition reaction of prochiral dipolarophile *trans*-**1a** with **2** in the presence of Cu(II)-(*S*,*S*)-bis(isopropyloxazolin-2′-yl)pyridine [(*S*,*S*)-ip-pybox][15] **7** furnished (3*S*,4*R*)-**4a** with 8% ee and in quantitative yield (entry 10, Table 1). Reaction with the oxazolidinone-derived prochiral dipolarophile *trans*-**1b** in the presence of Cu(II)-(*S*)-isopropylidenebis(4-phenyloxazoline) **6A** gave (3*S*,4*R*)-**4b** in 2% ee (entry 12). This established that when using only a chiral Lewis acid catalyst in this type of reaction, it was possible to obtain a certain but low enantioselectivity. Therefore, this approach did not encourage further investigation.

Instead we turned our attention to the use of chiral auxiliaries attached to the dipolarophile. Thus, we prepared the *trans*-cinnamoyl esters or amides **1c**–**g** from the reaction of cinnamoyl chloride with either the conjugate bases of the oxazolidines **c**–**e** or the sultam **f** or with the sugar-derived alcohol **g** (Scheme 1). When a cinnamoyl derivative **1c**–**g** and compound **2** were treated with trifluoracetic acid the ylide **3** was

Table 1
Diastereomeric ratio in 1,3-dipolar cycloaddition reaction in CH_2Cl_2 between **1a**, **1b** or **1c** and **2** in the presence of a chiral Lewis acid[a]

Entry	Xc	Lewis acid	Y⁻	Temp (° C)	Yield (%)[a]	dr **4:5**[b]
1	**c**	**6A**	OTf^{-}[c]	40	73	60:40
2	**c**	**6A**	OTf^{-}[c]	-20	41	58:42
3	**c**	**6A**	SbF_6^{-}[d]	40	95	58:42
4	**c**	**6A**	SbF_6^{-}[d]	-20	53	61:39
5	**c**	**6B**	OTf^{-}[c]	40	74	58:42
6[e]	**c**	**6B**	OTf^{-}[c]	20	8	66:34
7	**c**	**6B**	OTf^{-}[c]	-20	20	60:40
8	**c**	**6B**	SbF_6^{-}[d]	40	95	59:41
9	**c**	**6B**	SbF_6^{-}[d]	-20	53	58:42
10[f]	**a**	**7**	OTf^{-}[c]	0	98	54:46
11[g]	**c**	-	-	0	99	57:43
12	**b**	**6A**	OTf^{-}[c]	20	70[h]	51:49[i]

[a] Reaction yields were estimated by GC analysis
[b] Diastereomeric ratio was determined by ^{1}H NMR
[c] The reactions were performed according to method **B** (see experimental section)
[d] Method **C** in experimental section
[e] A mixture of **2** and CF_3COOH was added slowly to a reaction flask containing the dipolarophile **1c** and the chiral Lewis acid **6B** (5 eq.)
[f] The dr was calculated by ^{1}H NMR after in situ hydrolysis of the ester function and generation of the acyl chloride followed by synthesis of the amide derivative **4c** and **5c** according to the general method for amide synthesis (see experimental section)
[g] Control reaction (absence of chiral Lewis acid).
[h] Isolated yield
[i] Enantiomeric ratio (er) determined by optical rotation measurement after transformation to the corresponding ethyl esters (**4a** and **5a**), see experimental section.

produced in situ and reacted with the cinnamoyl derivative furnishing a mixture of *trans*-3,4-disubstituted pyrrolidines **4** and **5** in good yields and with low to good diastereoselectivities (see Table 2).

Since the dipole precursor **2** showed a tendency to dimerise under certain reaction conditions, a large excess of this was sometimes required. The diastereomeric mixtures of (3*S*,4*R*)-**4c–f** and (3*R*,4*S*)-**5c–f** were easily separated by column chromatography, whereas that of the diastereomeric esters **4g** and **5g** was not. In some cases low temperatures gave low conversions (entries 3 and 5, Table 2). For some substrates a slight improvement in the diastereomeric ratio (dr), was observed going from lower to higher temperatures (entries 4–7). The camphorsultam auxiliary **f** gave the best diastereoselectivity (entries 6 and 7).

Table 2
Diastereomeric ratio in 1,3-dipolar cycloaddition reaction between **1c–g** and **2**[a,b]

Entry	Xc	Temp (° C)	dr **4:5**[c]
1	**c**	0	57:43
2	**c**	-20	58:42
3[d]	**c**	-78	58:42
4	**d**	20	64:36
5[e]	**d**	-20	59:41
6	**f**	40	74:26
7	**f**	-20	69:31
8	**g**	40	42:58
9	**g**	-20	48:52
10	**e**	40	55:45
11	**e**	-20	54:46

[a] The syntheses were performed following method A in CH_2Cl_2 (see experimental section).
[b] The reactions occurred with quantitative yields according to ^{1}H NMR.
[c] Diastereomeric ratio was determined by ^{1}H NMR.
[d] 10% calculated yield;
[e] 55% calculated yield.

An X-ray crystallographic structure determination performed on the major diastereomer obtained from dipolarophile **1d** established that this diastereomer was **4d** having the absolute configuration (3*S*,4*R*) in the pyrrolidine ring (see Fig. 1). Ethanolysis of **4d** with $Ti(OiPr)_4$[16,17] in the presence of a large excess of ethanol gave a (−)-ester which was (3*S*,4*R*)-**4a**. The products **4b**,**c**,**e**–**g** or **5b**,**c**,**e**–**g** gave the enantiomerically pure ester **4a** or **5a** or alternatively a mixture of enantiomers in the case of ethanolysis of **4b** and **5b**. The specific rotations of the esters obtained were used for the assignments of the configurations of the major product in each reaction. Surprisingly the (*R*)-oxazolidinone auxiliaries **c** and **e** both gave the same chiral induction as the (*S*)-oxazolidinone auxiliary **d** [(3*S*,4*R*)-configuration in the pyrrolidine ring as the major diastereomer]. The reason for this reversal of diastereoselectivity is unclear. A possible explanation might be that the cycloaddition reaction can take place via two conformers of the dipolarophile, either the **U**- or the ***Z***-conformer (see Fig. 2). The **U**-conformer of **1c** would lead to (3*S*,4*R*)-**4c** as would the ***Z***-conformer of **1d**. Molecular modelling (CS Chem3D Pro™ 4.0) indicated that the energy differences between the high energy **U**- and the low energy ***Z***-conformer of dipolarophiles **1c** and **1d** were 3.5 and 5.5 kcal/mol, respectively. Therefore it is possible that the dipolarophile **1c** reacts mainly via **U**-**1c**, whereas the higher energy difference for **1d** forces it to react directly from the low energy conformation ***Z***-**1d** (see Fig. 2).

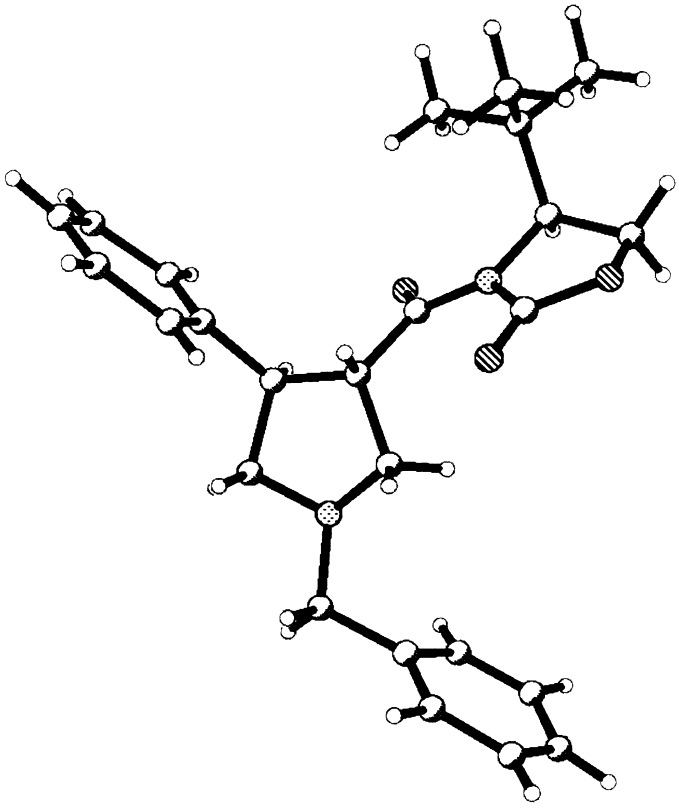


Figure 1. Structure and solid state conformation of (−)-(3*S*,4*R*)-1-benzyl-4-phenyl-3-[(4′-(*S*)-*tert*-butyl-2′-oxazolidinone-3′-yl)-carbonyl]-pyrrolidine (**4d**)

In an effort to influence the diastereoselectivity in the 1,3-dipolar cycloaddition between dipole **3** and dipolarophile **1c**, the chiral enantiopure Cu(II)-containing Lewis acids (**6A** and **6B**)[6,8] were tried as catalysts. In these cases one enantiomer of the dipolarophile would be expected to enhance enantioselectivity (matched case), whereas the other would have the opposite effect (mismatched case). When combining **6A** and the enantiomer of **1c** we observed a decrease in diastereomeric ratio. Therefore,

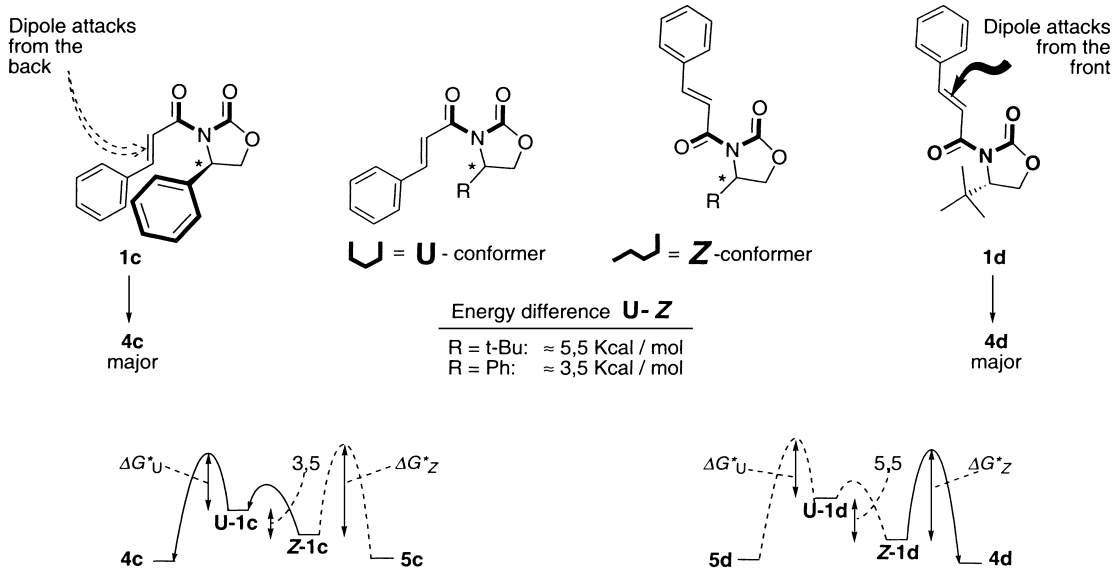


Figure 2. Proposed reaction path via two low energy conformers of **1c** and **1d**. It is assumed that ΔG^*_U and ΔG^*_Z are approximately equal for both reactions of dipole **3** with **1c** and **1d** and that $\Delta G^*_U < \Delta G^*_Z$ for the individual reactions

the combination of **6A** with **1c** represented the matched case. It was found that reactions performed in the presence of either the chiral Lewis acids **6A** or **6B** generally gave a slight improvement in diastereoselectivity (see Table 1). Substituting the counterion TfO^- with the less nucleophilic SbF_6^- did not lead to any improvement in the dr.[8]

The formation of a complex between the dipolarophile **1a** and the chiral Lewis acid **7** was established by ^{13}C NMR. Thus, different chemical shifts of the carbonyl carbon of the dipolarophile **1a** were observed in the absence (167 ppm) and in the presence (171 ppm) of the Lewis acid. However, the chemical shift of the uncomplexed starting material (167 ppm) was restored upon addition of the dipole precursor **2** and this clearly indicated a competition between the dipolarophile and **2** for the chiral Lewis acid. In an effort to minimise such a competition, compound **2** and CF_3COOH were slowly added to a mixture of the dipolarophile **1c** and an excess of the chiral Lewis acid **6B**, resulting in a 16% improvement of the dr at the expense of yield (entry 6, Table 1).

The results obtained in the reactions performed in the presence of the chiral catalysts **6A**, **6B** or **7** indicated that the diastereoselectivity in this cycloaddition was mainly controlled by the substrate rather than by the chiral Lewis acid.

We also examined the effects of the solvent. Thus reactions performed with oxazolidinones **1c** and **1e** in toluene both led to an improvement of the dr compared with that obtained with dichloromethane. In contrast, when using the camphorsultam **1f**, dichloromethane seemed to be the solvent of choice (Table 3).

3. Conclusion

In conclusion some *trans*-3,4-disubstituted pyrrolidines have been prepared in relatively high diastereomeric ratios using an approach where a chiral substrate is reacted with the dipole **3**. The camphorsultam auxiliary **f** was found to be the most effective. In general, the diastereoselectivities increased slightly with increasing temperature. By changing the solvent, a relatively large effect on the dr was observed. The use of chiral Lewis acids as catalysts in these reactions did not significantly improve

Table 3
Diastereomeric ratio in 1,3-dipolar cycloaddition reaction between **1c**, **1e**, or **1f** and **2** either in the absence or the presence of chiral Lewis acid **6B** (Y=TfO^-) in different solvents at room temperature[a,b]

Entry	1 (Xc)	Solvent	Lewis acid	dr **4**:**5**[c]
1	**c**	Dichloromethane	yes	58:42
2	**c**	Toluene	yes	68:32
3	**c**	Toluene	no[d]	70:30
4	**c**	1,4-Dioxane	yes	66:34
5	**c**	1,4-Dioxane	no[d]	63:37
6	**c**	*N,N*-Dimethylformamide	yes	55:45
7	**c**	Methylisobutylketone	yes	59:41
8	**c**	Acetonitrile	yes	62:38
9[e]	**c**	Heptane	yes	60:40
10	**c**	*N*-Methylformamide	no[d]	62:38
11	**e**	Toluene	no[d]	63:37 (55:45)[f]
12	**f**	Toluene	no[d]	66:34 (74:26)[f]

[a] The reactions were performed following method **B** (see experimental section).
[b] The reactions occurred with quantitative yields according to GC analysis.
[c] Diastereomeric ratio (dr) was determined by ^{1}H NMR.
[d] The syntheses were performed following method A (see experimental section).
[e] The reaction occurred in 65% yield.
[f] dr obtained from reactions in CH_2Cl_2 under the same conditions.

the diastereomeric ratios. This was probably due to the ability of the dipole precursor **2** to displace the dipolarophile initially complexed with the Lewis acid.

4. Experimental

All chemicals were used as received unless otherwise stated. THF was distilled from Na/benzophenone and freshly used. The other solvents were dried and stored over molecular sieves (4 Å). ^{1}H NMR and ^{13}C NMR spectra were recorded with a Jeol EX 270 or a Bruker DRX 500 spectrometer operating at 270/67.5 or 500/125 MHz using Me_4Si as internal standard. TLC was performed on silica gel plates (60 F_{254}, Merck) and flash column chromatography on silica gel 60 (230–400 mesh). GC analyses were carried out using a capillary column cross-linked 5% phenylmethylsilicone, 10 m, 0.53 mm i.d., d_f=0.26 μm, carrier gas N_2 (6 psi). The elemental analyses (C, H and N) were performed by Mikro Kemi AB, SE-752 28 Uppsala, Sweden. Melting points are uncorrected and determined in open glass capillaries on an electrothermal melting point apparatus. Optical rotations were measured with a Perkin–Elmer 241 MC polarimeter in a 1 dm cell. The reaction yields were estimated by either quantitative GC analysis or by ^{1}H NMR. The determination of yield percentages of **4** and **5** by GC analysis were based on peak-area measurements corrected with response factors calculated from a standard solution of each component to be examined using (±)-**4b** as internal standard. The ^{1}H NMR determination of yield percentages were based on peak-area measurements of products **4**, **5** and unreacted **1**.

4.1. General method for amidation[18]

A solution of CH_3MgCl in THF (2.2 M, 2.4 mL, 5.3 mmol) was added dropwise to a stirred solution of the chiral or achiral auxiliaries **b**–**f** (5.2 mmol), respectively, in THF (40 mL) at 0°C. The mixture was stirred at 0°C for 10 min followed by slow addition of cinnamoyl chloride (6 mmol) in THF (10 mL). The mixture was stirred at 0°C for 10 min and for an additional hour at room temperature. The reaction was quenched with NH_4Cl (10 ml, saturated aqueous solution). The volatiles were evaporated and the residue was treated with CH_2Cl_2 (100 mL). The organic phase was washed with $NaHCO_3$ (40 ml, saturated aqueous solution) and with NH_4Cl (40 ml, saturated aqueous solution). The organic layer was

separated, dried ($MgSO_4$) and concentrated to give **1b–f** in purity >95% (GC). No further purification was performed unless otherwise stated.

*4.2. 3-[(*E*)-3-Phenyl-2-propenoyl]-2-oxazolidinone **1b***

Compound **1b** (1.2 g, 96%) was obtained as a colourless solid from cinnamoyl chloride (0.5 g, 3 mmol) and 2-oxazolidinone (0.34 g, 2.6 mmol) according to the general method for amidation. Purity >99% (GC), m.p. 148–150°C (lit.[19] 151.0–152.5°C). Anal. calcd for $C_{12}H_{11}NO_3$: C, 66.4; H, 5.1; N, 6.4. Found: C, 66.0; H, 5.0; N, 6.4.

*4.3. 3-[(*E*)-3-Phenylpropenoyl]-4-(*R*)-phenyl-2-oxazolidinone **1c***

Compound **1c** (1.5 g, 98%) was obtained as a colourless solid from cinnamoyl chloride (1.0 g, 6 mmol) and (*R*)-4-phenyl-2-oxazolidinone (0.85 g, 5.2 mmol) according to the general method for amidation. Purity 98% (GC), m.p. 158–160°C. $[\alpha]_D^{25}=-10.8$ (c=1.0, CH_2Cl_2). ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.32 (dd, 1H, *J*=4.0, 8.9 Hz); 4.74 (t, 1H, *J*=8.9 Hz); 5.56 (dd, 1H, *J*=4.0, 8.9 Hz); 7.3–7.6 (m, 10H, arom); 7.78 (d, 1H, *J*=15.8 Hz); 7.94 (d, 1H, *J*=15.8 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 57.8, 70.0, 116.8, 126.0, 128.6 (2Cs), 128.7 (2Cs), 128.8 (2Cs), 129.2 (2Cs), 130.7, 134.4, 139.0, 146.7, 153.8, 164.7. Anal. calcd for $C_{18}H_{15}NO_3$: C, 73.7; H, 5.2; N, 4.8. Found: C, 73.8; H, 5.2; N, 4.7.

*4.4. 3-[(*E*)-3-Phenylpropenoyl]-4-(*S*)-*tert*-butyl-2-oxazolidinone **1d***

Compound **1d** (0.56 g, 86%) was obtained as a colourless solid from cinnamoyl chloride (0.47 g, 2.8 mmol) and (*S*)-4-*tert*-butyl-2-oxazolidinone (0.35 g, 2.4 mmol) according to the general method for amidation. The crude product was further recrystallized from *c*-hexane. Purity ≥99% (GC), m.p. 99–100°C, $[\alpha]_D^{25}=+115.4$ (c=0.5, CH_2Cl_2); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.98 (s, 9H); 4.29 (dd, 1H, *J*=7.5, 9.2 Hz); 4.33 (dd, 1H, *J*=1.8, 9.2 Hz); 4.60 (dd, 1H, *J*=1.8, 7.5 Hz); 7.37–7.41 (m, 3H); 7.60–7.63 (m, 2H); 7.85 (d, 1H, *J*=15.7 Hz); 7.95 (d, 1H, *J*=15.7 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 25.7 (3Cs), 36.0, 61.0, 65.3, 117.2, 128.6 (2Cs), 128.9 (2Cs), 130.6, 134.6, 146.4, 154.8, 165.6. Anal. calcd for $C_{16}H_{19}NO_3$: C, 70.3; H, 7.0; N, 5.1. Found: C, 70.3; H, 7.0; N, 4.9.

*4.5. 3-[(*E*)-3-Phenylpropenoyl]-3a-(*R*)*-cis*-*3,3a,8,8a-tetrahydro-2*H*-indeno[1,2*-d*]-2-oxazolidinone **1e***

Compound **1e** (0.99 g, 95%) was obtained as a colourless solid from cinnamoyl chloride (0.67 g, 4.0 mmol) and 3a-(*R*)-*cis*-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one (0.60 g, 3.4 mmol) according to the general method for amidation. Purity >99% (GC), m.p. 185–188°C. $[\alpha]_D^{25}=-280$ (c=1.0, CH_2Cl_2). ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.41–3.42 (m, 2H); 5.33–5.35 (m, 1H); 6.07 (d, 1H, *J*=6.9 Hz); 7.28–7.41 (m, 6H); 7.60–7.63 (m, 2H); 7.73 (d, 1H, *J*=7.6 Hz); 7.92 (d, 1H, *J*=15.7 Hz); 7.95 (d, 1H, *J*=15.8 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 38.0, 63.3, 78.1, 117.0, 125.2, 127.5, 128.2, 128.6 (2Cs), 128.9 (2Cs), 129.9, 130.7, 134.6, 139.2, 139.5, 146.5, 153.1, 165.6. Anal. calcd for $C_{19}H_{15}NO_3 \cdot 0.1H_2O$: C, 74.3; H, 5.0; N, 4.6. Found: C, 74.1; H, 5.0; N, 4.5.

*4.6. 3-[(*E*)-3-Phenylpropenoyl]-1(*S*),5(*R*)-camphorsultam **1f***

Compound **1f** (1.25 g, 97%) was obtained as a colourless solid from cinnamoyl chloride (1.1 g, 6.4 mmol) and (−)-(1*S*)-2,10-camphorsultam according to the general method for amidation. Purity 97%

(GC), m.p. 183–186°C. $[\alpha]_D^{25}$=−94.0 (c=1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (s, 3H); 1.21 (s, 3H); 1.35–1.50 (m, 2H); 1.88–1.98 (m, 3H); 2.12–2.23 (m, 2H); 3.48 (d, 1H, *J*=13.7 Hz); 3.55 (d, 1H, *J*=13.7 Hz); 4.00 (dd, 1H, *J*=5.3, 7.3 Hz); 7.17 (d, 1H, *J*=15.5 Hz); 7.37–7.39 (m, 3H); 7.57–7.61 (m, 2H); 7.79 (d, 1H, *J*=15.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.9, 20.9, 26.6, 32.9, 38.6, 44.8, 47.9, 48.6, 53.2, 65.3, 117.5, 128.6 (2Cs), 128.8 (2Cs), 130.6, 134.4, 145.6, 164.3. Anal. calcd for $C_{19}H_{23}NO_3S$: C, 66.1; H, 6.7; N, 4.0. Found: C, 65.8; H, 6.7; N, 4.1.

*4.7. 3-[(*E*)-3-Phenylpropenoyl]-1,2,5,6-di-*O*-isopropylidene-*D*-glycofuranosyl-ester* ***1g***

A solution of cinnamoyl chloride (430 mg, 2.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of 1,2,5,6-di-*O*-isopropylidene-D-glycofuranose (473 mg, 1.8 mmol) in CH_2Cl_2 (30 mL) and pyridine (8 mL) at room temperature under an N_2 atmosphere. The mixture was refluxed overnight, the volatiles evaporated and the residue was purified by column chromatography [SiO_2, ethyl acetate (20%) in *n*-hexane as eluent] to give **1g** (0.7 g, 100%) as an oil with purity >99% (GC). $[\alpha]_D^{25}$=−39.7 (c=1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (s, 3H); 1.32 (s, 3H); 1.42 (s, 3H); 1.54 (s, 3H); 4.11–4.14 (m, 2H); 4.27–4.33 (m, 2H); 4.58 (d, 1H, *J*=3.7 Hz); 5.40 (d, 1H, *J*=2.5 Hz); 5.93 (d, 1H, *J*=3.7 Hz); 6.43 (d, 1H, *J*=16.0 Hz); 7.37–7.41 (m, 3H); 7.51–7.55 (m, 2H); 7.72 (d, 1H, *J*=16.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.3, 26.2, 26.7, 26.8; 67.1, 72.5, 76.2, 79.9, 83.4, 105.1, 109.3, 112.3, 117.1, 128.2 (2Cs), 129.0 (2Cs), 130.6, 134.1, 146.0, 165.5. Anal. calcd for $C_{21}H_{26}O_7$: C, 64.6; H, 6.7. Found: C, 65.0; H, 6.6.

4.8. N-*Benzyl*-N-*(methoxymethyl)-trimethylsilylmethylamine* ***2***

Compound **2** was prepared following the same procedure as reported by Hosomi et al.[4] ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.04 (s, 9H); 2.22 (s, 2H); 3.27 (s, 3H); 3.79 (s, 2H); 4.03 (s, 2H); 7.28–7.35 (m, 5H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −1.5 (3Cs), 42.8, 55.3, 59.5, 88.4, 126.8, 128.1 (2Cs), 128.7 (2Cs), 139.7.

4.9. General method for the 1,3-dipolar cycloaddition[5]

4.9.1. Method A

TFA (0.2 mL, 1 M solution in CH_2Cl_2) was added dropwise at 0°C to a solution of *N*-benzyl-*N*-(methoxymethyl)-trimethylsilylmethylamine **2** (332 mg, 1.4 mmol) and chiral or achiral dipolarophiles **1b**–**g** (0.7 mmol) in dry CH_2Cl_2 (3 mL). The reaction was stirred at 0°C for 3 h, then quenched with $NaHCO_3$ (5 mL, saturated aqueous solution) followed by the addition of CH_2Cl_2 (20 mL). The organic phase was separated and washed with NH_4Cl (saturated aqueous solution). The organic layer was collected, dried (Na_2SO_4) and concentrated to give a residue consisting of two diastereoisomers or racemates in quantitative yield. The residue was further purified by flash column chromatography (SiO_2) to give the two diastereoisomers **4c**–**g** and **5c**–**g** separated from each other, or (±)-**4b** which was obtained as a racemate and used as internal standard.

4.9.2. Method B[8]

Dipolarophile **1** (**a**,**b** or **c**) (0.068 mmol) was added to a stirred solution of chiral Lewis acid prepared from $Cu(OTf)_2$ (0.068 mmol) and **6A** or **6B** or **7** (0.068 mmol) in different solvents (0.5 mL) at room temperature. The mixture was stirred overnight followed by addition of trifluoroacetic acid (0.2 mL,

0.5 M) and **2** (0.34 mmol). The reaction was stirred for 3 h followed by the work-up procedure used in method A for isolation or directly analysed after extraction with $NaHCO_3$ (aq. sat.) and drying (Na_2SO_4).

4.9.3. *Method C*[8]

Dipolarophile (**1a** or **1c**, 0.068 mmol) was added to a stirred solution of chiral Lewis acid prepared from $AgSbF_6$ (0.136 mmol), $CuCl_2$ (0.068 mmol) and **6A** or **6B** or **7** (0.068 mmol) in CH_2Cl_2 (0.5 mL). The mixture was stirred overnight followed by addition of trifluoroacetic acid (0.2 mL, 0.5 M) and **2** (0.34 mmol). The reaction was stirred for 3 h followed by the work-up procedure used in method A or B.

4.10. *(−)-(3*S*,4*R*)- and (+)-(3*R*,4*S*)-Ethyl-1-benzyl-4-phenylpyrrolidine-3-carboxylate (−)-**4a** and (+)-**5a***[20]

$Ti(OiPr)_4$ (10 equiv.) was added to a solution of one of the compounds **4c**–**g** or **5c**–**g** (1 equiv.) in EtOH. The reaction was heated at reflux temperature overnight. The volatiles were evaporated and the residue was purified by column chromatography [SiO_2, ethyl acetate (30%) in *n*-hexane as eluent] to give (−)-**4a** or (+)-**5a** (80%).

(−)-(3*S*,4*R*)-**4a** and (+)-(3*R*,4*S*)-**5a**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.20 (t, 3H, *J*=7.1 Hz); 2.74–3.09 (m, 5H); 3.67–3.74 (m, 3H); 4.12 (dq, 2H, *J*=7.1 Hz); 7.20–7.38 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.2, 46.9, 51.8, 57.4, 59.9, 60.7, 61.8, 126.5, 127.0, 127.4 (2Cs), 128.3 (2Cs), 128.5 (2Cs), 128.6 (2Cs), 138.8, 144.2, 174.2.

(−)-(3*S*,4*R*)-**4a**: $[\alpha]_D^{25}$=−43.5 (c=1.0, CH_2Cl_2); (−)-**4a**·HCl. Anal. calcd for $C_{20}H_{23}NO_2 \cdot HCl \cdot 0.5H_2O$: C, 67.7; H, 7.1; N, 4.0. Found: C, 68.1; H, 7.3; N, 4.0.

(+)-(3*R*,4*S*)-**5a**: $[\alpha]_D^{25}$=+39.5 (c=1.0, CH_2Cl_2); (+)-**5a**·HCl. Anal. calcd for $C_{20}H_{23}NO_2 \cdot HCl \cdot 0.5H_2O$: C, 67.7; H, 7.1; N, 4.0. Found: C, 67.7; H, 7.0; N, 4.0.

4.11. *(±)*-trans-*1-Benzyl-4-phenyl-3-(2′-oxazolidinone-3′-yl)-carbonyl-pyrrolidine (±)-**4b***

Compound (±)-**4b** was prepared and isolated, according to the general method for 1,3-dipolar cycloaddition (method A), from **1b** (0.54 g, 2.5 mmol) and **2** (1.2 g, 5.0 mmol). The crude mixture was purified by column chromatography [SiO_2, ethyl acetate (30%) in *n*-hexane as eluent] to give (±)-**4b** (0.7 g, 2 mmol) as an oil in >99% purity (GC). The free base was transformed into the hydrochloride salt (±)-**4b**·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.68 (t, 1H, *J*=8.6 Hz); 2.81 (dd, 1H, *J*=5.6, 9.6 Hz); 3.17 (t, 1H, *J*=7.6 Hz); 3.23 (t, 1H, *J*=9.4 Hz); 3.61 (d, 1H, *J*=12.9 Hz); 3.73 (d, 1H, *J*=12.9 Hz); 3.93 (t, 2H, *J*=7.9 Hz); 4.05 (q, 1H, *J*=7.4 Hz); 4.12–4.25 (m, 1H); 4.28–4.32 (m, 2H); 7.16–7.36 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.8, 45.5, 50.8, 58.2, 59.9, 61.9, 62.0, 126.6, 127.0, 127.8 (2Cs), 128.2 (2Cs), 128.5 (2Cs), 128.7 (2Cs), 138.8, 143.0, 153.1, 173.6. HCl-salt: Anal. calcd for $C_{21}H_{22}N_2O_3 \cdot HCl \cdot 0.5H_2O$: C, 63.7; H, 6.1; N, 7.1. Found: C, 64.0; H, 6.2; N, 7.1.

4.12. *(−)-(3*S*,4*R*)- and (−)-(3*R*,4*S*)-1-Benzyl-4-phenyl-3-[(4′-(*R*)-phenyl-2′-oxazolidinon-3′-yl)-carbonyl]-pyrrolidine **4c** and **5c***

Compounds **4c** and **5c** were prepared and isolated, according to the general method for the 1,3-dipolar cycloaddition (method A) from **1c** (0.2 g, 0.68 mmol) and **2** (0.3 g, 1.36 mmol). The mixture of **4c** and **5c** was separated by column chromatography [SiO_2, ethyl acetate (gradient 20–40%) in *n*-hexane as eluent] to give **4c** (143 mg, 0.34 mmol) and **5c** (112 mg, 0.26 mmol) as colourless solids in purity >99% (GC).

(3*S*,4*R*)-**4c**: $[\alpha]_D^{25}$=−147.0 (c=0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.66 (t, 1H, *J*=8.6 Hz); 2.74 (dd, 1H, *J*=5.6, 9.6 Hz); 3.09 (t, 1H, *J*=8.4 Hz); 3.28 (t, 1H, *J*=9.6 Hz); 3.54 (d, 1H, *J*=12.9 Hz); 3.72 (d, 1H, *J*=13.2 Hz); 4.00 (q, 1H, *J*=7.8 Hz); 4.13–4.22 (m, 2H); 4.60 (t, 1H, *J*=8.9 Hz); 5.37 (dd, 1H, *J*=4.1, 8.8 Hz); 7.20–7.40 (m, 15H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.9, 51.6, 57.8, 58.0, 59.7, 61.9, 70.0, 125.7 (2Cs), 126.6, 126.9, 127.8 (2Cs), 128.2 (2Cs), 128.5 (4Cs), 128.6, 129.3 (2Cs), 138.9, 139.0, 143.2, 153.3, 172.8. M.p. for $C_{27}H_{26}N_2O_3 \cdot HCl \cdot 0.25H_2O$: 130–134°C. HCl-salt: Anal. calcd for $C_{27}H_{26}N_2O_3 \cdot HCl \cdot 0.25H_2O$: C, 69.4; H, 5.9; N, 6.0. Found: C, 69.2; H, 5.9; N, 6.0.

(3*R*,4*S*)-**5c**: $[\alpha]_D^{25}$=−10.0 (c=0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.69 (t, 1H, *J*=8.4 Hz); 2.85 (dd, 1H, *J*=5.9, 9.6 Hz); 3.09 (t, 1H, *J*=8.4 Hz); 3.22 (t, 1H, *J*=9.4 Hz); 3.63 (d, 1H, *J*=13.2 Hz); 3.73 (d, 1H, *J*=13.2 Hz); 3.79 (q, 1H, *J*=7.6 Hz); 4.15 (dd, 1H, *J*=4.3, 8.9 Hz); 4.30–4.38 (m, 1H); 4.61 (t, 1H, *J*=8.9 Hz); 5.40 (dd, 1H, *J*=4.3, 8.8 Hz); 7.10–7.36 (m, 15H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.9, 50.7, 57.9, 58.0, 59.9, 61.5, 69.7, 125.8 (2Cs), 126.5, 126.9, 127.5 (2Cs), 128.2 (2Cs), 128.4 (2Cs), 128.6 (3Cs), 129.1 (2Cs), 138.7, 138.9, 142.7, 153.3, 173.8. M.p. for $C_{27}H_{26}N_2O_3 \cdot HCl \cdot 0.5H_2O$: 188–190°C. Anal. calcd for $C_{27}H_{26}N_2O_3 \cdot HCl \cdot 0.5H_2O$: C, 68.7; H, 6.0; N, 5.9. Found: C, 69.0; H, 6.2; N, 5.8.

*4.13. (−)-(3*S*,4*R*)- and (+)-(3*R*,4*S*)-1-Benzyl-4-phenyl-3-[(4′-(*S*)-*tert*-butyl-2′-oxazolidinone-3′-yl)-carbonyl]-pyrrolidine **4d** and **5d***

Compounds **4d** and **5d** were prepared and isolated, according to the general method for the 1,3-dipolar cycloaddition (method A), from **1d** (0.42 g, 1.5 mmol) and **2** (0.71 g, 3.0 mmol). The mixture of **4d** and **5d** was separated by column chromatography [SiO_2, ethyl acetate (gradient 10% and 20%) in *n*-hexane as eluent] and further purified from by-products by recrystallisation from *n*-hexane to give **4d** (0.28 g, 0.7 mmol) and **5d** (0.12 g, 0.3 mmol) as colourless solids in >99% purity (GC).

(3*S*,4*R*)-**4d**: $[\alpha]_D^{25}$=−20.8 (c=0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.72 (s, 9H); 2.68 (t, 1H, *J*=8.6 Hz); 2.75 (dd, 1H, *J*=6.3, 9.4 Hz); 3.09–3.12 (m, 2H); 3.60 (d, 1H, *J*=13.1 Hz); 3.69 (d, 1H, *J*=13.1 Hz); 3.88 (q, 1H, *J*=7.8 Hz); 4.08 (dd, 1H, *J*=7.7, 9.2 Hz); 4.13 (dd, 1H, *J*=1.6, 9.2 Hz); 4.36–4.41 (m, 2H); 7.11–7.30 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.4 (3Cs), 35.6, 47.9, 50.2, 57.8, 59.9, 61.0, 61.7, 64.9, 126.6, 126.9, 127.6 (2Cs), 128.2 (2Cs), 128.4 (2Cs), 128.6 (2Cs), 138.9, 142.4, 154.1, 174.3. M.p. 97–99°C. Anal. calcd for $C_{25}H_{30}N_2O_3$: C, 73.9; H, 7.4; N, 6.9. Found: C, 73.8; H, 7.6; N, 7.0.

(3*R*,4*S*)-**5d**: $[\alpha]_D^{25}$=+81.8 (c=0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (s, 9H); 2.57 (t, 1H, *J*=8.7 Hz); 2.88 (dd, 1H, *J*=4.8, 9.7 Hz); 3.15–3.22 (m, 2H); 3.50 (d, 1H, *J*=13 Hz); 3.74 (d, 1H, *J*=13 Hz); 4.00–4.10 (m, 3H); 4.15 (dd, 1H, *J*=1.5, 7.7 Hz); 4.35 (dd, 1H, *J*=1.5, 7.6 Hz); 7.11–7.29 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6 (3Cs), 35.8, 44.5, 51.9, 59.0, 59.7, 60.9, 62.1, 65.3, 126.5, 126.9, 127.8 (2Cs), 128.2 (2Cs), 128.5 (2Cs), 128.6 (2Cs), 138.8, 143.3, 154.1, 173.4. M.p. 119–121°C. Anal. calcd for $C_{25}H_{30}N_2O_3$: C, 73.9; H, 7.4; N, 6.9. Found: C, 74.0; H, 7.4; N, 7.0.

*4.14. (−)-(3*S*,4*R*)- and (−)-(3*R*,4*S*)-1-Benzyl-4-phenyl-3-[(3′a-(*R*)-cis-3′,3′a,8′,8′a-tetrahydro-2*H*-indeno-(1,2-d)-oxazol-2′-one-3′-yl)-carbonyl]-pyrrolidine **4e** and **5e***

Compounds **4e** and **5e** were prepared and isolated, according to the general method for the 1,3-dipolar cycloaddition (method A), from **1e** (0.50 g, 1.6 mmol) and **2** (0.76 g, 3.2 mmol). The mixture of **4e** and **5e** was separated by column chromatography [SiO_2, ethyl acetate (gradient 15 and 30%) in *n*-hexane as eluent] to give **4e** (0.31 g, 0.72 mmol) and **5e** (0.26 g, 0.58 mmol) as colourless solids in purity >99% (GC).

(3*S*,4*R*)-**4e**: $[\alpha]_D^{25}$=−185 (c=1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.68–2.74 (m, 2H); 3.17–3.24 (m, 2H); 3.29–3.37 (m, 2H); 3.59 (d, 1H, *J*=13.2 Hz); 3.73 (d, 1H, *J*=13.2 Hz); 4.13–4.21

(m, 2H); 5.16–5.19 (m, 1H); 5.89 (d, 1H, *J*=6.9 Hz); 7.17–7.62 (m, 13H); 7.61 (d, 1H, *J*=7.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.9, 45.3, 51.1, 58.3, 59.7, 62.1, 63.2, 78.2, 125.2, 126.6, 126.8, 126.9, 127.8 (2Cs), 128.2 (2Cs), 128.3, 128.5 (4Cs), 129.8, 138.8, 139.2, 139.4, 143.1, 152.6, 173.9. M.p. 63–66°C. Anal. calcd for $C_{28}H_{26}N_2O_3 \cdot 0.1H_2O$: C, 76.4; H, 6.0; N, 6.4. Found: C, 76.2; H, 6.0; N, 6.4.

(3*R*,4*S*)-**5e**: $[\alpha]_D^{25}$=−67.0 (c=1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.71 (t, 1H, *J*=8.5 Hz); 2.87 (dd, 1H, *J*=5.7, 9.6 Hz); 3.19–3.23 (m, 2H); 3.28–3.38 (m, 2H); 3.66 (d, 1H, *J*=13.0 Hz); 3.75 (d, 1H, *J*=13.0 Hz); 4.09 (q, 1H, *J*=7.6 Hz); 4.21–4.25 (m, 1H); 5.21–5.24 (m, 1H); 5.93 (d, 1H, *J*=7.0 Hz); 7.12–7.38 (m, 13H); 7.56 (d, 1H, *J*=7.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.0, 45.8, 50.7, 58.0, 59.9, 61.5, 63.4, 77.8, 125.1, 126.5, 127.0, 127.2, 127.6 (2Cs), 128.1, 128.3 (2Cs), 128.4 (2Cs), 128.7 (2Cs), 129.8, 138.8, 139.0, 139.4, 142.8, 152.5, 174.2. M.p. 114–116°C. Anal. calcd for $C_{28}H_{26}N_2O_3 \cdot 0.1H_2O$: C, 76.4; H, 6.0; N, 6.4. Found: C, 76.2; H, 6.0; N, 6.4.

*4.15. (−)-(3*S*,4*R*)- and (−)-(3*R*,4*S*)-1-Benzyl-4-phenyl-3-[(1′*S*,5′*R*)-camphorsultam-3′-yl)-carbonyl]-pyrrolidine **4f** and **5f***

Compounds **4f** and **5f** were prepared and isolated, according to the general method for the 1,3-dipolar cycloaddition (method A), from **1f** (278 mg, 0.8 mmol) and **2** (0.38 g, 1.6 mmol). The mixture of **4f** and **5f** was separated by column chromatography [SiO_2, ethyl acetate (15%) in *n*-hexane as eluent] to give **4f** (230 mg, 0.49 mmol) and **5f** (78 mg, 0.16 mmol) as colourless solids in >99% purity (GC).

(3*S*,4*R*)-**4f**: $[\alpha]_D^{25}$=−119.8 (c=0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (s, 3H); 1.04 (s, 3H); 1.26–1.38 (m, 2H); 1.85–1.89 (m, 3H); 2.06–2.07 (m, 2H); 2.67 (t, 1H, *J*=8.4 Hz); 2.82 (dd, 1H, *J*=5.9, 9.6 Hz); 3.14 (t, 1H, *J*=8.4 Hz); 3.23 (t, 1H, *J*=9.5 Hz); 3.36 (d, 1H, *J*=13.7 Hz); 3.42 (d, 1H, *J*=13.7 Hz); 3.61 (d, 1H, *J*=13.1 Hz); 3.73–3.77 (m, 2H); 3.86 (t, 1H, *J*=6.3 Hz); 4.04 (q, 1H, *J*=7.3 Hz); 7.15–7.34 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.8, 20.8, 26.4, 32.8, 38.4, 44.6, 45.1, 47.7, 48.3, 51.9, 53.0, 59.2, 59.7, 61.5, 65.3, 126.4, 126.9, 127.6 (2Cs), 128.2 (2Cs), 128.4 (2Cs), 128.6 (2Cs), 138.9, 142.8, 172.7. M.p. for $C_{28}H_{34}N_2O_3S \cdot HCl \cdot 0.5H_2O$: 123–129°C. HCl-salt: Anal. calcd for $C_{28}H_{34}N_2O_3S \cdot HCl \cdot 0.5H_2O$: C, 64.2; H, 6.9; N, 5.3. Found: C, 64.6; H, 6.8; N, 5.4.

(3*R*,4*S*)-**5f**: $[\alpha]_D^{25}$=−2.0 (c=0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (s, 3H); 0.88 (s, 3H); 1.26–1.33 (m, 2H); 1.77–1.92 (m, 4H); 2.02 (dd, 1H, *J*=7.8, 13.8 Hz); 2.81 (dd, 1H, *J*=7.8, 9.2 Hz); 2.97 (dd, 1H, *J*=7.3, 9.5 Hz); 3.12 (dd, 1H, *J*=7.8, 9.2 Hz); 3.18 (t, 1H, *J*=8.9 Hz); 3.33 (d, 1H, *J*=13.8 Hz); 3.38 (d, 1H, *J*=13.8 Hz); 3.67 (d, 1H, *J*=13.1 Hz); 3.74 (q, 1H, *J*=7.8 Hz); 3.78–3.82 (m, 3H); 7.15–7.37 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.8, 20.5, 26.4); 32.8, 38.5, 44.7, 47.6, 48.1, 50.3, 51.5, 53.1, 57.8, 60.1, 61.2, 65.2, 126.7, 126.9, 127.5 (2Cs), 128.2 (2Cs), 128.4 (2Cs), 128.6 (2Cs), 139.1, 141.6, 173.8. M.p. for $C_{28}H_{34}N_2O_3S \cdot HCl \cdot 1.5H_2O$: 124–127°C. HCl-salt: Anal. calcd for $C_{28}H_{34}N_2O_3S \cdot HCl \cdot 1.5H_2O$: C, 62.0; H, 7.1; N, 5.2. Found: C, 62.4; H, 6.9; N, 5.4.

*4.16. (−)-(3*S*,4*R*)- and (+)-(3*R*,4*S*)-1-Benzyl-4-phenyl-3-[(1′,2′,5′,6′-di-*O*-isopropyliden-*D*-glycofuranosyl)-carbonyl]-pyrrolidine **4g** and **5g***

Compounds **4g** and **5g** were prepared and isolated, according to the general method for the 1,3-dipolar cycloaddition (method A), from **1g** (300 mg, 0.77 mmol) and **2** (365 mg, 1.54 mmol) with the exception for the work-up procedure where the organic phase was washed only with $NaHCO_3$. The mixture of **4g** and **5g** was separated by several flash column chromatographies [SiO_2, diethylether (10%) in CH_2Cl_2 as eluent]. Pure fractions were collected to give **4g** and **5g** as colourless oils in a total yield of 95%.

(3*S*,4*R*)-**4g**: $[\alpha]_D^{25}$=−32.8 (c=0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (s, 3H); 1.29 (s, 3H); 1.38 (s, 3H); 1.50 (s, 3H); 2.72 (dd, 1H, *J*=6.5, 9.3 Hz); 2.93 (dd, 1H, *J*=6.5, 9.4 Hz); 2.99 (t, 1H, *J*=8.8

Hz); 3.06 (t, 1H, *J*=8.7 Hz); 3.11 (q, 1H, *J*=7.1 Hz); 3.63 (d, 1H, *J*=12.9 Hz); 3.66–3.69 (m, 1H); 3.73 (d, 1H, *J*=13.3 Hz); 3.92–3.94 (m, 2H); 3.98–4.02 (m, 1H); 4.15 (dd, 1H, *J*=3.0, 8.2 Hz); 4.40 (d, 1H, *J*=3.6 Hz); 5.25 (d, 1H, *J*=3.1 Hz); 5.76 (d, 1H, *J*=3.7 Hz); 7.19–7.37 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.2, 26.2, 26.7, 26.9, 47.2, 51.5, 57.1, 59.8, 62.0, 67.5, 72.4, 76.3, 79.8, 83.4, 105.0, 109.3, 112.3, 126.7, 127.1, 127.4 (2Cs), 128.3 (2Cs), 128.5 (2Cs), 128.6 (2Cs), 138.8, 143.8, 172.9. Anal. calcd for $C_{30}H_{37}NO_7$: C, 68.8; H, 7.1; N, 2.7. Found: C, 68.4; H, 7.0; N, 2.6.

(3*R*,4*S*)-**5g**: $[\alpha]_D^{25}$=+2.0 (c=0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (s, 3H); 1.28 (s, 3H); 1.36 (s, 3H); 1.49 (s, 3H); 2.77 (dd, 1H, *J*=6.7, 9.3 Hz); 2.92 (dd, 1H, *J*=7.1, 9.1 Hz); 2.99–3.07 (m, 2H); 3.10–3.15 (m, 1H); 3.64–3.71 (m, 3H); 3.88 (dd, 1H, *J*=4.0, 7.3 Hz); 3.96–4.01 (m, 2H); 4.13 (dd, 1H, *J*=3.0, 8.0 Hz); 4.38 (d, 1H, *J*=3.6 Hz); 5.24 (d, 1H, *J*=3.1 Hz); 5.72 (d, 1H, *J*=3.7 Hz); 7.16–7.35 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.1, 26.2, 26.7 (2Cs), 47.2, 51.8, 57.0, 59.9, 61.8, 67.5, 72.3, 76.3, 80.1, 83.4, 105.1, 109.3, 112.3, 126.7, 127.1, 127.5 (2Cs), 128.2 (2Cs), 128.6 (4Cs), 138.7, 143.6, 172.6. Anal. calcd for $C_{30}H_{37}NO_7$: C, 68.8; H, 7.1; N, 2.7. Found: C, 69.2; H, 7.4; N, 2.6.

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