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Novel 3-*C*-aminomethyl-hexofuranose-derived thioureas and their testing in asymmetric catalysis

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ABSTRACT

Both 1,2:5,6-di-*O*-isopropylidene- and 1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose-derived ketones provided the corresponding branched 3-*C*-nitromethyl-congeners in the Henry reaction with nitromethane anion. Reduction of the nitro moiety followed by derivatization with iso(thio)cyanates gave 3-*C*-aminomethyl-hexofuranose-derived (thio)ureas. The relative configuration of the products in each series was unambiguously established by X-ray analysis. The title products were shown to act as organocatalysts in Friedel–Crafts alkylations of indoles with β-nitrostyrenes and in Michael additions of nitromethane to *trans*-chalcones.

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1. Introduction

The structural motif of vicinal or β-amino alcohols is frequently found in natural products and synthetic biologically active substances. More importantly for the synthetic community, they are found to act as chiral catalysts, ligands for metal complexes, and privileged structural components of chiral auxiliaries.[1] Carbohydrate derived vicinal amino alcohols[2] have also been used as ligands in Reformatsky reactions[3] and in $Zn(OTf)_2$-mediated additions of alkynes to aldehydes.[4] The fine-tuning of the conformational restriction and the relative configuration of the functional groups in the monosaccharide ligand gave excellent ee's for the latter transformation.

Similarly, enantioselective additions of Et_2Zn to aldehydes have benefited from monosaccharide-based amino alcohols,[5] including *xylo*-furanose based structures.[6]

On the other hand, carbohydrate scaffolds have gained interest in the field of organocatalysis.[7] Thus, both furanose[8] and pyranose[9] derived prolinamides have shown excellent results in asymmetric aldol reactions. Simple monosaccharide-based β-amino alcohols also catalyze the latter transformation.[10] Even more examples of carbohydrate-derived catalysts can be found in the area of hydrogen-bond donor catalysis.[11] These include ureas[12] and thioureas. The thiourea derivatives arising from the corresponding glycosidic isothiocyanates and diaminocyclohexane[13] or their *N*-monosubstituted equivalents[14] among other transformations are successfully used in aza-Henry reactions, decarboxylative Mannich reactions and Michael additions to nitrostyrene. The latter reaction can be equally effectively catalyzed by carbohydrate-based thioureas containing fragments of chiral diamines of linear type.[15] The design of the aforementioned catalysts most frequently exploits the thiourea attachment via a glycosidic bond. There are only few examples in which the cores of glucosamine and 4,6-dideoxy-4,6-diamino-hexopyranose are used for thiourea synthesis.[16]

Despite the fact that β-amino alcohol derived thiourea type catalysts have shown promising results,[17] there are only a few of their counterparts in carbohydrate chemistry.[16a] It should also be noted that the comparison of a number of pyranose-based and furanose-based organocatalysts shows the predominance of the former.[18] On the other hand, furanose-like isohexides have proved to be versatile scaffolds in asymmetric catalysis.[19]

2. Results and discussion

We have recently reported a user-friendly large scale synthesis of isopropylidene-protected 3-*C*-aminomethyl-hexofuranoses via their nitro congeners.[20] Hence, we were interested in exploring the organocatalytic applications of furanose-derived ureas and thioureas **3** obtained from the branched β-amino alcohols of general type **2** (Scheme 1).

The required starting materials, isopropylidene-protected vicinal amino alcohols **5** and **6** with *allo*- and *gluco*-configuration, were

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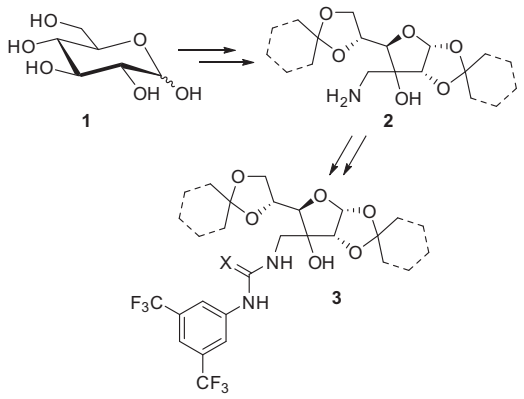
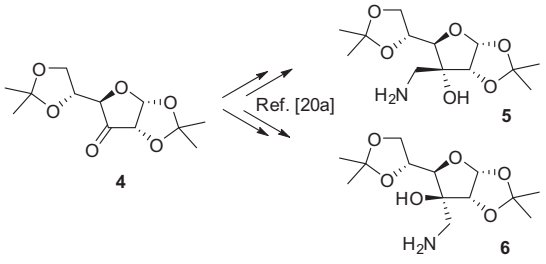


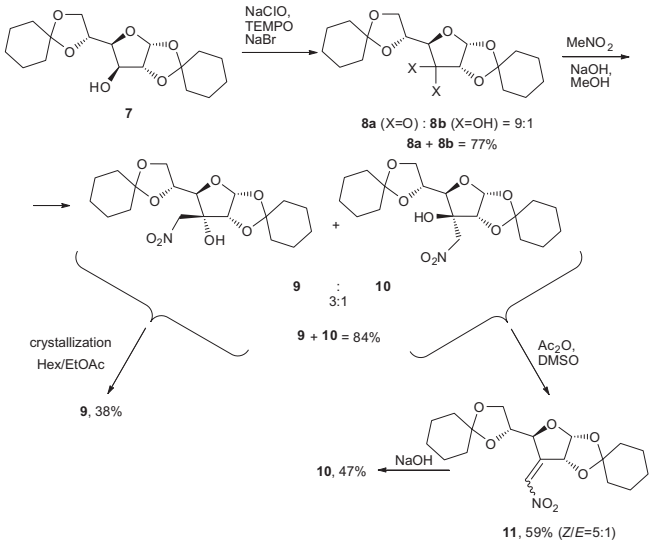
Scheme 1. General structure of furanose-based urea (X = O) and thiourea (X = S) **3** derived from 3-*C*-aminometyl-hexofuranose **2**.

prepared from the corresponding ketone **4**[21] as described earlier (Scheme 2).[20a]



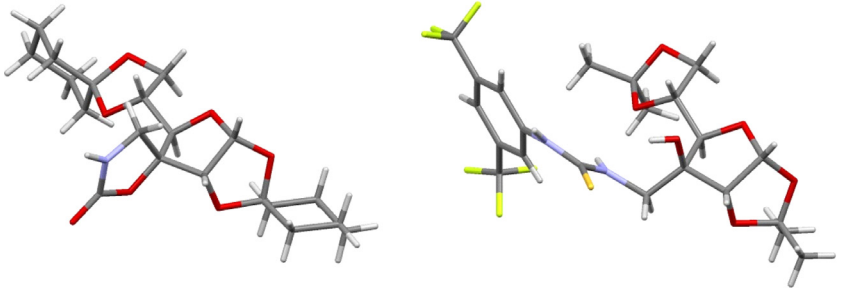
Scheme 2. General synthetic approach toward isopropylidene-protected 3-*C*-aminomethyl-allofuranose **5** and 3-*C*-aminomethyl-glucofuranose **6**.

In order to check the influence of the steric bulk of the protecting groups, a cyclohexylidene-protected version was also prepared. Its synthesis followed a similar scheme to that used for obtaining **5** and **6** (Scheme 3). The unprotected HO-group of glucose derivative **7**[22] was oxidized with bleach in the presence of TEMPO. The obtained mixture of ketone **8a** and its hydrate **8b** was submitted to a Henry reaction with nitromethane under basic conditions.[23] A mixture of nitro alcohols **9** and **10** was obtained in 84% total yield.[24] The major *allo*-isomer **9** can be obtained diastereomerically pure by direct crystallization in 38% isolated yield. The mother liquor containing **9** and **10** after evaporation was submitted to a Moffatt dehydration–rehydration sequence which provided pure *gluco*-isomer **10** via the nitromethylene intermediate **11**.[20]



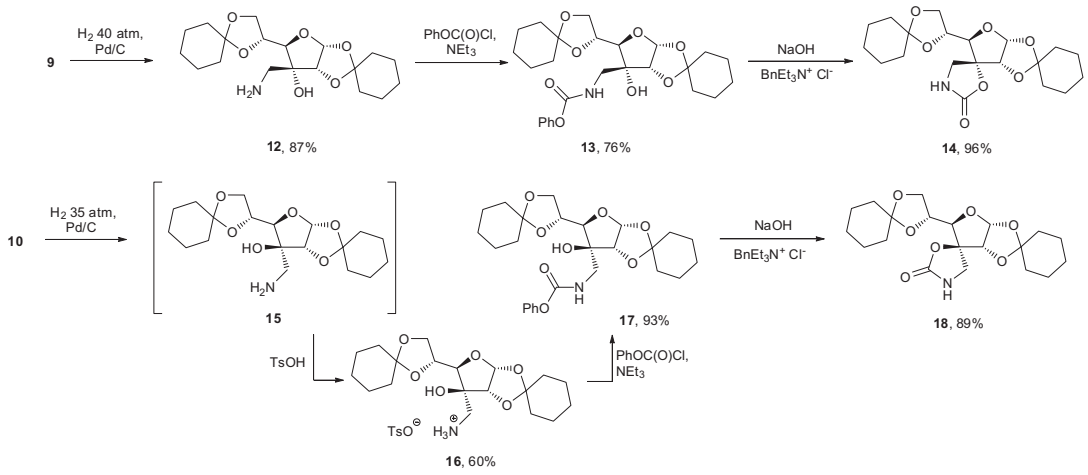
Scheme 3. Synthesis of cyclohexylidene-protected 3-*C*-nitromethyl-allofuranose **9** and 3-*C*-nitromethyl-glucofuranose **10**.

In order to unambiguously prove the relative configuration of the obtained nitro alcohols **9** and **10** by X-ray analysis, we derivatized them into the corresponding spiro-oxazolidinones. Thus, nitro alcohols **9** and **10** were catalytically hydrogenated in the presence of palladium catalyst (Scheme 4). Product **12** with an *allo*-configuration was obtained as a white solid in 87% yield. It was further transformed into phenylcarbamate **13** and then cyclized into spirooxazolidinone **14**. The latter provided crystals suitable for single crystal X-ray analysis, which unambiguously established its relative configuration (Fig. 1).[25] In this way, the relative configuration of all cyclohexylidene-protected product sequence **9** → **12** → **13** → **14** and thus the diastereoselectivity of Henry reaction **8a**,**b** → **9**+**10** was proved. The minor nitro alcohol isomer **10** was transformed by hydrogenation and the addition of TsOH into the amine tosylate salt **16** which provided an additional option for purification via crystallization. The same approach as described above gave a rise to spirooxazolidinone **18** in excellent yield. It should be noted, that chiral oxazolidinones are well-established chiral auxiliaries in asymmetric synthesis.[26] Several types of diastereoselective transformations have profited from oxazolidinones which were derived from conformationally defined carbohydrate scaffolds.[27] Carbohydrate–nitrogen heterocycle conjugates with non-glycosidic spiranic junction are interesting in terms of their biological activity.[20a]



Compound **14** Compound **23**

Figure 1. X-ray structures of spiro-oxazolidinone **14** and thiourea **23**.



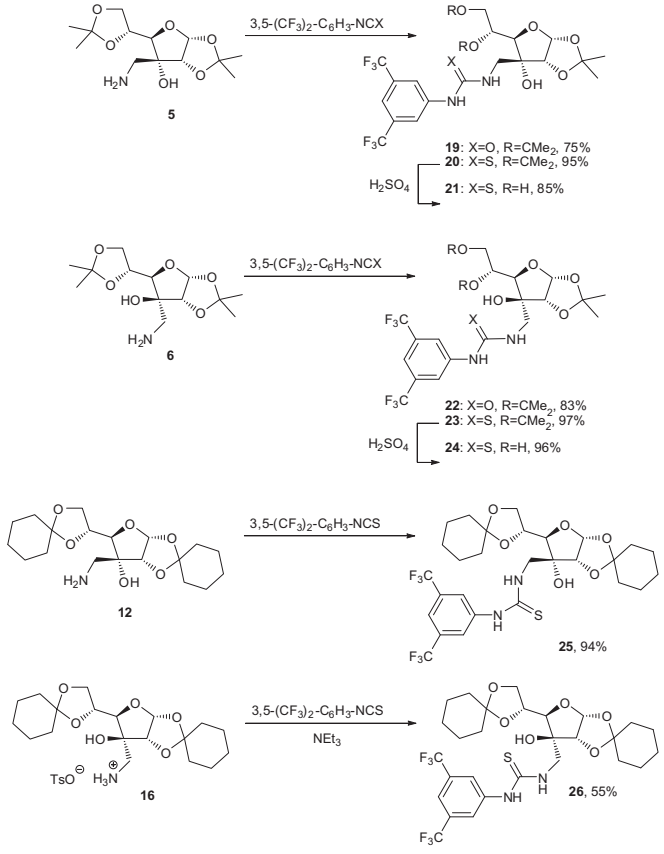
Scheme 4. Synthesis of cyclohexylidene-protected 3-*C*-aminomethyl-hexofuranoses **12** and **15** and their transformations into spiro-oxazolidinones **14** and **18** via carbamate approach.

Next, all four available 3-*C*-aminomethyl-hexofuranoses **5**, **6**, **12,** and the tosylate salt **16** were transformed into the planned urea and thiourea derivatives **19**–**26** (Scheme 5). The 5,6-*O*-isopropylidene protecting groups in compounds **20** and **23** were selectively cleaved to obtain compounds with additional hydrogen bond donating structural motifs. The molecular structure of furanose-derived thiourea catalyst **23** was unambiguously established by X-ray analysis (Fig. 1).[28]

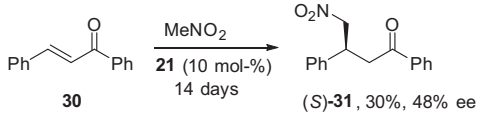
With two urea and six thiourea catalysts in hand, we evaluated their activity in several organocatalytic transformations. We started with the Friedel–Crafts alkylation of indole **27**[17a] with β-nitrostyrene **28** (Table 1).[29] All of the prepared furanose-based urea and thiourea derivatives were catalytically active and provided the expected product **29** in good to excellent yields, but required relatively long reaction times and gave poor enantiomeric excess. The best ee for compound **29** (20%) was obtained with cyclohexylidene-protected *allo*-furanose derivative **25** at ambient temperature. Chiral carboxylic and sulfonic acid additives decreased the reaction time, but did not increase the ee. For example, either stereoisomer of 10-camphorsulfonic acid as a sole substance catalyzed the reaction equally fast, but gave a racemate (Table 1, entry 14).

The best combination of catalyst and additive was **25** and (1*R*,3*S*)-(+)-camphoric acid which provided product **29** in 81% yield and 20% ee (Table 1, entry 14). It is interesting to note that in all cases, even in those with almost racemic product **29**, a distinct selectivity was observed: *allo*-furanose derived catalysts **19**, **20**, **21,** and **25** gave predominantly (*S*)-**29**, but *gluco*-furanose derived catalysts **22**, **23**, **24,** and **26** gave predominantly (*R*)-**29**.

On the other hand, the aforementioned urea and thiourea compounds did not catalyze the classic Michael additions of acetone and diethylmalonate into β-nitrostyrene, most probably due to the absence of the additional basic functionality (e.g., amine) in the structure of the catalysts. However, we found that nitromethane adds to *trans*-chalcone **30** in the presence of 1,2-*O*-isopropylidene protected *allo*-furanose derived thiourea **21** (Scheme 6). The reaction took place over 14 days and gave product (*S*)-**31** in 30% yield and 48% ee. For substrate **30**, which does not contain additional complexation sites[17b] and for a standard thiourea catalyst without enhanced N–H acidity,[17e,17d] this is a reasonable achievement.



Scheme 5. Synthesis of 3-*C*-aminomethyl-hexofuranose-based urea and thiourea organocatalysts.



Scheme 6. Organocatalyzed Michael addition of nitromethane to *trans*-chalcone **30**.

3. Conclusion

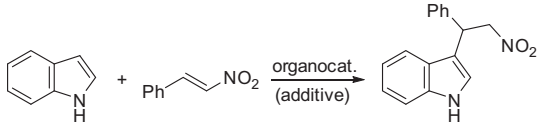
In conclusion, we have developed a straightforward synthesis of novel 3-*C*-aminomethyl-hexofuranose-based ureas and thioureas. En route to this we have validated the nitromethane addition chemistry on cyclohexylidene-protected glucofuranose. The spirooxazolidinones derived from the latter might be useful as chiral auxiliaries in the future. The selected model reactions of indole alkylation and Michael addition of nitromethane have, in principle, proved the potential of the title compounds as organocatalysts. Further elaboration of the described molecular scaffolds might produce easy to access furanose-based organocatalysts.

4. Experimental

4.1. General

All non-aqueous reactions were carried out under an inert atmosphere of argon in oven-dried glassware unless otherwise noted. Commercial reagents were used without purification. Solvents were distilled prior to use and, if required, dried over standard drying agents (THF from metallic sodium, DMSO, DMF, and Et_3N form CaH_2). Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel $60F_{254}$. Preparative flash chromatography was performed on silica gel (60 Å, 40–63 μm, ROCC). Melting points were recorded with a *Fisher Digital Melting Point Analyzer Model 355* apparatus and are uncorrected. IR spectra were recorded as thin films on KBr plates or in KBr with *FT-IR Perkin Elmer Spectrum BX*. Optical rotations were measured at 25 °C on a *Anton Paar MCP 500* polarimeter using a sodium lamp as the light source (589 nm). ^1H and ^{13}C NMR spectra were recorded on a *Bruker* 300 MHz and *Varian* 400 MHz spectrometers in $CDCl_3$ or DMSO-d_6. The proton signals for residual non-deuterated solvents (δ 7.26 for $CDCl_3$ and δ 2.50 for DMSO-d_6) and carbon signals (δ 77.1 for $CDCl_3$ and δ 39.5 for DMSO-d_6) were used as internal references for ^1H NMR and ^{13}C NMR spectra, respectively. Chemical shift (δ) values are reported in ppm and coupling constants *J* in

Table 1
Organocatalyzed alkylation of indole **27** + **28** → **29**[a]



27 **28** **29**

Entry	Catalyst	Additive	React. time (h)	Yield of **29** (%)	ee (%), config.[b]
1	**19** 5 mol-%	—	375	67	7 (*S*)
2	**22**[c] 40 mol-%	—	84	3	11 (*R*)
3	**20**	—	160	94	12 (*S*)
4	**21**[d]		624	48	7 (*S*)
5	**23**[e] 100 mol-%	—	240	41	5 (*R*)
6	**24**	—	720	70	9 (*R*)
7	**25**	—	312	28	20 (*S*)
8	**25**[f]	—	144	78	10 (*S*)
9	**26**	—	288	48	*rac*
10	**25**	(+)-Di-*O*-benzoyl-D-tartaric acid 15 mol-%	144	92	7 (*S*)
11	**25**	(−)-Di-*O*-benzoyl-L-tartaric acid 15 mol-%	144	81	15 (*S*)
12	**25**	(1*R*)-(-)-10- Camphorsulfonic acid 15 mol-%[g]	168	50	*rac*
13	**25**[e] 12 mol-%	(1*R*)-(-)-10- Camphorsulfonic acid 15 mol-%	72	19	*rac*
14	—	(1*R*)-(−)-10-Camphorsulfonic acid 15 mol-%[g]	168	81	*rac*
15	**25**	(1*R*,3*S*)-(+)-Camphoric acid 15 mol-%	168	81	20 (*S*)
16	**25**	(*S*)-(+)-α-Methoxyphenylacetic acid 15 mol-%[g]	144	99	9 (*S*)
17	**25**	Acetic acid 15 mol-%	144	81	15 (*S*)
18	**25**	Benzoic acid 15 mol-%	144	89	15 (*S*)

[a] Reaction conditions: 20 mol-% catalyst in CH_2Cl_2 (1 M in substrates, 0.2 M in catalyst) at ambient temperature if not stated otherwise.
[b] Enantiomeric ratio was determined by HPLC analysis of **29** using Chiralpak IA column (0.46 × 25 cm). Isocratic method: 5% ^{i}PrOH/Hex; 40 min; injection 5 μl (0.70 mg/mL Hex + 30% ^{i}PrOH); flow rate 1 mL/min; detector wavelength 254 nm. The absolute configuration of the product was determined by comparing the specific rotation of **29** with that of literature data.
[c] CH_2Cl_2:toluene = 1:1, +4 °C.
[d] $CHCl_3$.
[e] +5 °C.
[f] +35 °C.
[g] The enantiomer gave nearly equal result in terms of yield and ee.

Hz. HRMS spectra (ESI+) were performed using a *Q-TOF Micromass* and elemental analyses on a *Carlo-Erba EA1108* analyzer. Yields refer to chromatographically and spectroscopically homogeneous materials.

4.1.1. A 9:1 mixture of 1,2:5,6-di-*O*-cyclohexylidene-α-D-ribo-3-hexofuranose-3-ulose 8a and its hydrate 8b

In an open-mouth beaker equipped with mechanical stirrer, a solution of NaBr (1.36 g, 13.0 mmol, 0.15 equiv) in water (6 mL) was added to a solution of 1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose-3-ulose **7** (30.0 g, 88.0 mmol, 1.0 equiv) in CH_2Cl_2 (200 mL), followed by TEMPO (0.220 g, 1.41 mmol, 0.016 equiv). The resulting mixture was cooled to −10 °C (internal temperature) and vigorously stirred, and an aqueous solution of NaClO (~1.6 mol/L, pH 9.5 (pH-meter control; adjusted by $NaHCO_3$), 330 mL, 0.528 mol, 6 equiv) was added dropwise in 45 min while keeping the internal temperature in the range of −10 to 0 °C. After addition of the bleach solution, the resulting reaction mixture was stirred for 5 min. The organic layer was separated and washed successively with a solution of KI (0.730 g, 4.40 mmol, 5.5 mol-%) in 0.5 M aqueous sulfuric acid (80 mL), a 10% aqueous solution of $Na_2S_2O_3$ (80 mL), a saturated aqueous solution of $NaHCO_3$ (200 mL), and brine (200 mL). After drying (Na_2SO_4), filtration and evaporation under reduced pressure, the crude product (23.0 g, 77%) contained a mixture of ketone **8a** and ketone hydrate **8b** in a ~9:1 ratio. The NMR data and other characteristics of products **8a** fully corresponded to those reported earlier.[22] Data for compound **8a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.15 (d, 1H, ^3J = 4.5 Hz, H-C(1)), 4.41–4.31 (m, 3H, H-C(2), H-C(4), H_a-C(6)), 4.04–4.01 (m, 2H, H-C(5), H_b-C(6)), 1.71–1.30 (m, 20H, $(Chx)_2$-C(1,2:5,6)).

4.1.2. A 3:1 mixture of (3*R*)-3-*C*-nitromethyl-1,2:5,6-di-*O*-cyclohexylidene-α-D-allofuranose 9 and (3*S*)-3-*C*-nitromethyl-1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose 10

Nitromethane (23.0 mL, 0.410 mol, 6 equiv) was added to a solution of NaOH (5.40 g, 0.135 mol, 2 equiv) in MeOH (100 mL) at 0 °C and stirred for 10 min. The resulting mixture was added to a solution of a 3:1 mixture of ketone **8a** and ketone hydrate **8b** (23.0 g, 0.068 mol, 1 equiv) in MeOH (60 mL) at 0–10 °C and vigorously stirred for 30 min. The reaction mixture was stirred at ambient temperature for 2.5 h and then poured into a saturated aqueous solution of $(NH_4)_2SO_4$ (150 mL) at 0 °C. The organic layer was separated and, after evaporation under reduced pressure, the residual mixture was dissolved in ethyl acetate (200 mL). The water layer was extracted by EtOAc (60 mL). The combined organic layer was washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure to afford a mixture of compounds **9** and **10** in a ~3:1 ratio (30.0 g). The purification of the crude product by column chromatography on silica gel (300 g) (Hex/EtOAc 8–15%) and crystallization yielded **9** (10.3 g, 38%, de >95%) as a white solid. The filtrate was evaporated under reduced pressure to afford brown oil (12.3 g, 46%) which consists of epimers **9** (50%) and **10** (50%). The total yield of the major isomer **9** was 6.15 g, 61% and minor isomer **10** 6.15 g, 23%. This mixture of **9** and **10** was used in the next step without additional purification. NMR data and other physicochemical data of the product **9** were consistent with those reported earlier.[23] Data for compound **9**: $[\alpha]_D^{23}$ = 48 (*c* 0.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.86 (d, 1H, ^3J = 4.0 Hz, H-C(1)), 4.99 (d, AB syst., 1H, ^2J = 12.1 Hz, H_a-C(3′)), 4.87 (d, 1H, ^3J = 4.0 Hz, H-C(2)), 4.49 (d, AB syst., 1H, ^2J = 12.1 Hz, H_b-C(3′)), 4.13 (dd, AB syst., 1H, ^2J = 8.1 Hz, ^3J = 5.5 Hz, H_a-C(6)), 4.00 (ddd, 1H, ^3J = 8.5, 5.5, 4.7 Hz, H-C(5)), 3.93 (dd, AB syst., 1H, ^2J = 8.1 Hz, ^3J = 4.7 Hz, H_b-C(6)), 3.86 (d, 1H, ^3J = 8.5 Hz, H-C(4)), 3.28 (br s, 1H, HO-C(3)), 1.73–1.32 (m, 20H, $(Chx)_2$-C(1,2:5,6)); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 114.1, 111.1, 103.3, 81.9, 79.4, 78.5, 77.1, 72.7, 67.8, 36.3, 36.1, 35.9, 34.6, 25.0, 24.8, 24.0, 23.9, 23.8, 23.5.

4.1.3. 3-Deoxy-3-*C*-nitromethylene-1,2:5,6-di-*O*-cyclohexylidene-α-D-*ribo*-hexofuranose 11

Acetic anhydride (161 mL, 1.70 mol, 50 equiv) was added to a stirred solution of a diastereomeric mixture of nitro sugars **9** and **10** (13.6 g, 34.0 mmol, 1 equiv) in dry DMSO (48.0 mL, 68.3 mmol, 20 equiv) at room temperature. The resulting reaction mixture was stirred at ambient temperature for 48 h and the Ac_2O was evaporated (~120 mL, 50 °C, 8 mbar). The residual mixture was cooled to 0 °C and poured with vigorous stirring into a cold acetate buffer solution (32.0 g AcONa in 130 mL H_2O adjusted to pH 6 with AcOH) at −10 °C. The resulting mixture was further neutralized with solid $NaHCO_3$ (~30 g) to pH 6 followed by extraction with EtOAc (3 × 30 mL). The combined organic layer was washed with brine (6 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated. The purification of the crude product by column chromatography on silica gel (150 g) (Hex/EtOAc (4%) provided product **11** (7.59 g, 59%) which consisted of isomers *Z*-**11**:*E*-**11** in a 5:1 ratio and unreacted starting material compound **10** (Hex/EtOAc 3%) (4.30 g, 32% from starting material loading). The purification of product **11** was carried out repeatedly by column chromatography on silica gel (Hex/EtOAc 3%) to yield isomers (*Z*)-**11**:(*E*)-**11** in a 25:1 ratio. Data for compound (*Z*)-**11**: R_f = 0.55 (EtOAc/Hex 1:6); $[\alpha]_D^{23}$ = +138 (*c* 0.48, $CHCl_3$) (*Z*-**11**:*E*-**11** = 25:1); IR (KBr): 2934, 2857, 1531, 1366, 1348, 1280, 1162, 1117, 1090, 1027. (*Z*-**11**:*E*-**11** = 25:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.47 (t, 1H, ^4J = 1.7 Hz, H-C(3′)), 5.90 (d, 1H, ^3J = 4.1 Hz, H-C(1)), 5.80 (dt, 1H, ^3J = 4.1, ^4J = 1.7 Hz, H-C(2)), 4.73 (dt, 1H, ^3J = 8.2, ^4J = 1.9, Hz, H-C(4)), 4.13 (dd, 1H, ^2J = 8.7 Hz, ^3J = 5.8 Hz, H_a-C(6)), 4.04 (dd, 1H, ^2J = 8.7 Hz, ^3J = 4.3 Hz, H_b-C(6)), 4.00 (ddd, 1H, ^3J = 8.2, 5.8, 4.3 Hz, H-C(5)), 1.70–1.32 (m, 20H, $(Chx)_2$-C(1,2:5,6)); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 149.7, 135.7, 114.2, 111.3, 104.6, 79.3, 78.0, 75.9, 67.2, 36.9, 36.6 (2C), 34.6, 25.0, 24.7, 24.1, 23.9, 23.8, 23.6. HRMS: calcd $[C_{19}H_{27}NO_7+H^+]$ 382.1860, found 382.1861.

4.1.4. (3*S*)-3-*C*-Nitromethyl-1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose 10

An aqueous (30 mL) solution of NaOH (0.770 g, 19.0 mmol, 1.2 equiv) was added to a solution of nitro-ene derivative **11** (*Z*-**11**:*E*-**11** = 5:1) (6.14 g, 16.60 mmol, 1 equiv) in THF (20 mL) at 30 °C. The resulting mixture was stirred for 3 h at 30 °C and was monitored by TLC. The reaction mixture was neutralized by saturated aqueous (40 mL) solution of $(NH_4)_2SO_4$ and stirred for 30 min until pH 6–7. After evaporation of THF, the residue was dissolved in EtOAc (200 mL). The phases were separated and the organic layer was washed with brine (5 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The purification of the crude product by column chromatography on silica gel (60 g) (Hex/EtOAc 5%) provided product **10** (2.99 g, 47%). NMR and other physicochemical data of the product **10** were consistent with those reported earlier. $[\alpha]_D^{25}$ = +28.1 (*c* 0.77, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.94 (d, 1H, ^3J = 3.7 Hz, H-C(1)), 4.95 (d, AB syst., 1H, ^2J = 14.8 Hz, H_a-C(3′)), 4.76 (d, AB syst., 1H, ^2J = 14.8 Hz, H_b-C(3′)), 4.59 (d, 1H, ^3J = 3.7 Hz, H-C(2)), 4.39 (ddd, 1H, ^3J = 8.9, 6.3, 4.8 Hz, H-C(5)), 4.15 (dd, AB syst., 1H, ^2J = 8.9 Hz, ^3J = 6.3 Hz, H_a-C(6)), 3.99 (dd, AB syst., 1H, ^2J = 8.9 Hz, ^3J = 4.8 Hz, H_b-C(6)), 3.69 (d, 1H, ^3J = 8.9 Hz, H-C(4)), 3.48 (br s, 1H, HO-C(3)), 1.81–1.32 (m, 20H, $(Chx)_2$-C(1,2:5,6)); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 113.8, 110.5, 104.5, 85.0, 81.5, 79.8, 76.0, 71.5, 67.3, 36.6, 36.45, 35.8, 34.4, 25.0, 24.8, 24.1, 23.9, 23.7, 23.5.

4.1.5. (3*R*)-3-*C*-Aminomethyl-1,2:5,6-di-*O*-cyclohexylidene-α-D-allofuranose 12

A solution of nitro alcohol **9** (10.7 g, 27.0 mmol, 1 equiv) in EtOH (400 mL) was hydrogenated at 40 atm and 40 °C in the presence of 10% Pd/C (1.00 g) for 14 h. The resulting mixture was filtered through Celite and washed by EtOH (200 mL). The filtrate was evaporated to dryness under reduced pressure. The crude product **12** (10.4 g) was purified by column chromatography (EtOAc/EtOH (5%)) and recrystallized (Hex/EtOAc). Product **12** was obtained as a white solid (8.56 g, 87%). R_f = 0.79 (CH_2Cl_2/EtOH 1:1, 1% NH_3); $[\alpha]_D^{25}$ = +24 (*c* 0.38, $CHCl_3$); mp = 92–94 °C; IR (KBr): 3543, 2936, 2862, 1615, 1449, 1369, 1284, 1165, 1118, 1014; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.75 (d, 1H, ^3J = 4.0 Hz, H-C(1)), 4.61 (d, 1H, ^3J = 4.0 Hz, H-C(2)), 4.12–4.04 (m, 2H, H-C(5), H_a-C(6)), 3.93–3.85 (m, 1H, H_b-C(6)), 3.80 (d, 1H, ^3J = 8.3 Hz, H-C(4)), 3.21 (d, AB syst., 1H, ^2J = 13.0 Hz, H_a-C(3′)), 2.67 (d, AB syst., 1H, ^2J = 13.0 Hz, H_b-C(3′)), 2.54 (br s, 3H, H_2N-C(3′), HO-C(3)), 1.82–1.32 (m, 20H, $(Chx)_2$-C(1,2:5,6)); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 113.2, 110.4, 103.2, 81.9, 80.1, 79.3, 72.8, 67.8, 42.6, 36.2 (2C), 36.0, 34.8, 25.1, 24.9, 24.1, 23.9 (2C), 23.5; HRMS: calcd [$C_{19}H_{31}NO_6$+H^+] 370.0222; found 370.0222.

4.1.6. 3-*C*-(*N*-Phenyloxycarbonyl)aminomethyl-1,2:5,6-di-*O*-cyclohexylidene-α-D-allofuranose 13

Triethylamine (2.56 mL, 18.4 mmol, 1.7 equiv) was added to a stirred solution of **12** (4.00 g, 11.0 mmol, 1 equiv) in dry THF (70 mL) under an argon atmosphere cooled to 0 °C. After 10 min, phenyl chloroformate (2.15 mL, 16.5 mmol, 1.5 equiv) was added dropwise at 0 °C. The resulting reaction mixture was stirred at ambient temperature for 1.5 h, then it was evaporated to dryness under reduced pressure, and redissolved in ethyl acetate (50 mL). The organic layer was washed with a saturated aqueous solution of $CuSO_4$ (2 × 15 mL) and a saturated aqueous solution of $NaHCO_3$ (4 × 20 mL), dried over Na_2SO_4, and evaporated under reduced pressure. Recrystallization of the crude product from hexane/ethylacetate afforded the title compound **13** (4.02 g, 76%). R_f = 0.43 (EtOAc/Hex 3:7); $[\alpha]_D^{23}$ = +48 (*c* 0.65, $CHCl_3$); mp = 129–131 °C; IR (KBr): 3387, 2942, 2889, 2854, 1727, 1526, 1451, 1481, 1457, 1446, 1400; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.36 (t, 2H, ^3J = 7.8 Hz, H-C(Ar)), 7.20 (t, 1H, ^3J = 7.0 Hz, H-C(Ar)), 7.14 (d, 2H, ^3J = 7.8 Hz, H-C(Ar)), 5.80 (d, 1H, ^3J = 4.0 Hz, H-C(1)), 5.71 (t, 1H, ^3J = 5.8 Hz, H-N-C(3′)), 4.39 (d, 1H, ^3J = 4.0 Hz, H-C(2)), 4.18–4.08 (m, 2H, H-C(5), H_a-C(6)), 3.95–3.85 (m, 1H, H_b-C(6)), 3.78 (d, 1H, ^3J = 7.9 Hz, H-C(4)), 3.60 (d, AB syst., 1H, ^2J = 11.6 Hz, H_a-C(3′)), 3.54 (d, AB syst., 1H, ^2J = 11.6 Hz, H_b-C(3′)), 3.00 (s, 1H, HO-C(3)), 1.83–1.32 (m, 20H, $(Chx)_2$-C(1,2:5,6)); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 155.3, 150.9, 129.4, 125.5, 121.5, 113.5, 110.7, 103.3, 81.6, 80.1, 79.4, 72.8, 68.0, 42.4, 36.3, 36.1 (2C), 34.7, 25.1, 24.8, 24.1, 23.9, 23.8, 23.5; HRMS: calcd [$C_{26}H_{35}NO_8$+Na^+] 512.2255; found 512.2239.

4.1.7. (3*R*)-1,2:5,6-Di-*O*-cyclohexylidene-spiro(3-deoxy-α-D-allofuranose-3,5′-oxazolidin)-2′-one 14

A solution of NaOH (0.810 g, 20.0 mmol, 2.1 equiv) in water (23.0 mL) and benzyltrimethylammonium chloride (0.110 g, 48.0 mmol, 5-mol %) was added to a stirred solution of **13** (4.73 g, 9.66 mmol, 1 equiv) in CH_2Cl_2 (30 mL) at 0 °C. The resulting biphasic reaction mixture was stirred at 0 °C for 10 min followed by 3.5 h at ambient temperature. The phases were separated and the aqueous residue was extracted with CH_2Cl_2 (4 × 25 mL). The combined CH_2Cl_2 layer was extracted with aq 2 M NaOH solution (2 × 20 mL) and with brine (5 × 10 mL). The resulting solution was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to afford the title compound **14** (3.67 g, 96%). R_f = 0.18 (EtOAc/Tol 2:3); mp = 180–181 °C; $[\alpha]_D^{23}$ = +63 (*c* 0.37, $CHCl_3$); IR (KBr): 3374, 2944, 2896, 2862, 1760, 1451, 1443, 1367, 1281, 1235, 1169, 1133; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.71 (d, 1H, ^3J = 3.4 Hz, H-C(1)), 5.62 (br s, 1H, H-N-C(3′)), 4.46 (d, 1H, ^3J = 3.4 Hz, H-C(2)), 4.17–4.06 (m, 3H, H-C(4), H-C(5), H_a-C(6)), 3.97 (dd, AB syst., 1H, ^2J = 8.3 Hz, ^3J = 3.6 Hz, H_b-C(6)), 3.89 (d, AB syst., 1H, ^2J = 8.7 Hz, H_a-C(4′)), 3.26 (d, AB syst., 1H, ^2J = 8.7 Hz, H_b-C(4′)), 1.88–1.30 (m, 20H, $(Chx)_2$-C(1,2:5,6)); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 158.3, 115.2, 110.9, 102.7, 85.6, 83.6, 77.5, 73.5, 68.0, 44.3, 36.3 (2C), 36.0, 34.8, 25.1, 24.8, 23.9, 23.8 (2C), 23.6; HRMS: calcd [$C_{20}H_{29}NO_7$+H^+] 396.2017; found 396.2014.

4.1.8. (1,2:5,6-Di-*O*-cyclohexylidene-α-D-glucofuranos-3-*C*-yl)methylamonium tosylate 16

A solution of nitro alcohol **10** (7.08 g, 17.7 mmol, 1 equiv) in ethanol (300 mL) was hydrogenated at 40 atm and 40 °C in the presence of 10% Pd/C (0.700 g) for 24 h. The resulting mixture was filtered through Celite and washed by EtOH (100 mL). The filtrate was evaporated to dryness under reduced pressure. A solution of *p*-TsOH (2.32 g, 1.31 mmol, 1 equiv) in EtOAc (50 mL) was added to a solution of crude product **15** (6.40 g) in EtOAc (100 mL) at −10 °C. The resulting reaction mixture was stirred at temperature −10 °C for 30 min and filtered. Product **16** was obtained as a white solid (5.76 g, 60%). R_f = 0.7 (EtOAc/EtOH 4:1); $[\alpha]_D^{23}$ = +1.7 (*c* 0.4, $CHCl_3$); mp = 184–189 °C (decomp.); IR (KBr): 3251, 3086, 2934, 2862, 2671, 1614, 1603, 1504, 1462, 1449, 1368, 1336, 1276; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 7.80 (br s, 3H, H_3N-C(3′)), 7.47 (d, 2H, ^3J = 7.8 Hz, H-C(Ar)), 7.11 (d, ^3J = 7.8 Hz, H-C(Ar)), 6.11 (br s, 1H, HO-C(3′)), 5.87 (d, 1H, ^3J = 3.6 Hz, H-C(1)), 4.43 (d, 1H, ^3J = 3.6 Hz, H-C(2)), 4.20 (ddd, 1H, ^3J = 8.3, 6.4, 5.4 Hz, H-C(5)), 4.04 (dd, AB syst., 1H, ^2J = 8.4 Hz, ^3J = 6.4 Hz, H_a-C(6)), 3.81 (dd, AB syst., 1H, ^2J = 8.4 Hz, ^3J = 5.4 Hz, H_b-C(6)), 3.64 (d, 1H, ^3J = 8.3 Hz, H-C(4)), 3.14 (d, AB syst., ^2J = 12.8 Hz, 1H, H_a-C(3′)), 3.04 (d, AB syst., ^2J = 12.8 Hz, 1H, H_b-C(3′)), 2.28 (s, 3H, H_3C-C(Ar)), 1.66–1.30 (m, 20H, $(Chx)_2$-C(1,2:5,6)); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 146.1, 138.1, 128.5, 126.0, 112.9, 109.8, 104.2, 83.8, 81.7, 79.3, 71.8, 66.9, 40.2, 36.6, 36.3, 35.9, 34.9, 25.0, 24.8, 24.1 (2C), 23.9, 23.6, 21.2; HRMS: calcd [$C_{26}H_{39}NO_9S$+H^+] 370.2224; found 370.2223.

4.1.9. 3-*C*-(*N*-Phenyloxycarbonyl)aminomethyl-1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose 17

Triethylamine (1.94 mL, 14.0 mmol, 2.7 equiv) was added to a stirred solution of **16** (2.80 g, 5.17 mmol, 1 equiv) in dry THF (55 mL) under an argon atmosphere and the resulting mixture was cooled to 0 °C. After 10 min, phenyl chloroformate (1.00 mL, 7.75 mmol, 1.5 equiv) was added dropwise at 0 °C. The resulting reaction mixture was stirred at 0 °C for 10 min followed by 2.5 h at ambient temperature, then it was evaporated to dryness under reduced pressure, and redissolved in ethyl acetate (40 mL). The ethyl acetate layer was washed with a saturated aqueous solution of $CuSO_4$ (2 × 15 mL), a saturated aqueous solution of $NaHCO_3$ (2 × 20 mL), brine (3 × 30 mL) and dried over Na_2SO_4, and evaporated under reduced pressure. Recrystallization of the crude product from hexane/ethylacetate afforded the title compound **17** as a white solid (2.34 g, 93%). R_f = 0.60 (EtOAc/Hex 2:3); $[\alpha]_D^{23}$ = +73 (*c* 0.17, $CHCl_3$); IR (KBr): 3402, 3351, 2934, 2863, 1740, 1494, 1370, 1270, 1211, 1164, 1121; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.39 (t, 2H, ^3J = 7.7 Hz, H-C(Ar)), 7.24 (t, 1H, ^3J = 7.4 Hz, H-C(Ar)), 7.17 (d, 2H, ^3J = 7.5 Hz, H-C(Ar)), 5.93 (t, 1H, ^3J = 6.1 Hz, H-N-C(3′)), 5.92 (d, 1H, ^3J = 3.8 Hz, H-C(1)), 4.46 (d, 1H, ^3J = 3.8 Hz, H-C(2)), 4.33 (ddd, 1H, ^3J = 8.5, 6.2, 5.5 Hz, H-C(5)), 4.18 (dd, 1H, ^2J = 8.7 Hz, ^3J = 6.2 Hz, H_a-C(6)), 4.00 (dd, 1H, ^2J = 8.7 Hz, ^3J = 5.5 Hz, H_b-C(6)), 3.84 (dd, AB syst., 1H, ^2J = 14.7 Hz, ^3J = 5.8 Hz, H_a-C(3′)), 3.81 (d, 1H, ^3J = 8.5 Hz, H-C(4)), 3.65 (d, AB syst., 1H, ^2J = 14.7 Hz, ^3J = 7.0 Hz, H_b-C(3′)), 3.34–3.14 (br s, 1H, HO-C(3)), 1.79–1.36 (m, 20H, $(Chx)_2$-C(1,2:5,6)); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 156.7, 151.0, 129.4, 125.6, 121.5, 113.4, 110.5, 104.3, 86.0, 83.0, 82.2, 71.8, 67.6, 44.3,

36.7, 36.5, 36.0, 34.6, 25.1, 24.9, 24.1, 24.0, 23.7, 23.6; HRMS: calcd [$C_{26}H_{35}NO_8$+Na^+] 512.2255; found 512.2239.

4.1.10. (3*S*)-1,2:5,6-Di-*O*-cyclohexylidene-spiro(3-deoxy-α-D-glucofuranose-3,5′-oxazolidin)-2′-one 18

A solution of NaOH (0.383 g, 9.58 mmol, 2.1 equiv) in water (10 mL) and benzyltrimethylammonium chloride (0.052 g, 0.228 mmol, 5-mol %) was added to a stirred solution of **17** (2.23 g, 4.56 mmol, 1 equiv) in CH_2Cl_2 (15 mL) at 0 °C. The resulting biphasic reaction mixture was stirred at 0 °C for 10 min followed by 2 h at ambient temperature. The phases were separated and the aqueous residue was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layer was extracted with a solution of 2 M NaOH (2 × 15 mL), with a saturated aqueous solution of NaCl (5 × 25 mL) and dried over Na_2SO_4. The resulting solution was filtered and evaporated under reduced pressure to afford the title compound **18** (1.60 g, 89%). R_f = 0.45 (EtOAc/Tol 3:7); $[\alpha]_D^{23}$ = +21.6 (*c* 0.52, $CHCl_3$); IR (KBr): 3302, 2938, 2862, 1768, 1433, 1368, 1279, 1218, 1164, 1101, 1076, 1016; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.92 (d, 1H, ^3J = 3.6 Hz, H-C(1)), 5.26 (s, 1H, H-N-C(3′)), 4.54 (d, 1H, ^3J = 3.6 Hz, H-C(2)), 4.36 (ddd, 1H, ^3J = 8.5, 6.2, 5.3 Hz, H-C(5)), 4.15 (dd, AB syst. 1H, ^2J = 8.7 Hz, ^3J = 6.2 Hz, H_a-C(6)), 3.98 (dd, AB syst., 1H, ^2J = 8.7 Hz, ^3J = 5.3 Hz, H_b-C(6)), 3.87 (d, 1H, AB syst., ^2J = 8.9 Hz, H_a-C(4′)), 3.79 (d, 1H, ^3J = 8.5 Hz, H-C(4)), 3.81 (d, 1H, AB syst., ^2J = 8.9 Hz, H_b-C(4′)), 1.73-1.34 (m, 20H, $(Chx)_2$-C(1,2:5,6)); ^{13}C NMR ($CDCl_3$), 75.5 MHz) δ: 159.9, 113.7, 110.4, 104.5, 88.1, 83.6, 81.6, 72.2, 67.5, 42.1, 36.6 (2C), 36.0, 34.4, 25.1, 24.8, 24.2, 23.9, 23.7, 23.6; HRMS: calcd [$C_{20}H_{29}NO_7$+H^+] 396.2017; found 396.2014.

4.1.11. (3*R*)-3-*C*-[(3,5-Bis(trifluoromethyl)phenylureidomethyl]-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose hemihydrate 19

Bis(3,5-trifluoromethyl)phenyl isocyanate (0.041 mL, 0.159 mmol, 1.15 equiv) was added to a solution of amino alcohol **5** (40.0 mg, 0.138 mmol, 1 equiv) in CH_2Cl_2 (1.5 mL). After stirring at reflux at 40 °C for 4 h, the solvent was removed under reduced pressure. Purification by column chromatography (EtOAc/Hex 25%) yielded **19** (76.0 mg, 75%). R_f = 0.39 (EtOAc/Hex 2:3); $[\alpha]_D^{25}$ = +26 (*c* 1.2, $CHCl_3$); mp = 95–99 °C (Hex/EtOAc); IR (KBr): 3370, 2993, 2141, 1664, 1571, 1389, 1280, 1182, 1132; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.84 (s, 2H, H-C(Ar)), 7.59–7.39 (br s, 2H, H-C(Ar), H-N-C(Ar)), 5.84 (d, 1H, ^3J = 3.6 Hz, H-C(1)), 5.67 (dd, 1H, ^3J = 5.6, 5.0, Hz, H-N-C(3′)), 4.39 (d, 1H, ^3J = 3.6 Hz, H-C(2)), 4.20–4.12 (m, 2H, H-C(5)), H_a-C(6)), 3.99–3.92 (m, 1H, H_b-C(6)), 3.80 (d, 1H, ^3J = 8.2 Hz, H-C(4)), 3.68–3.53 (m, 2H, H-C(3′)), 3.24–3.15 (br s, 1H, HO-C(3)), 1.75 (1H, 0.5H_2O), 1.57, 1.45, (2s, 6H, $(H_3C)_2$C-O-C(1)), 1.34 (1s, 6H, $(H_3C)_2$C-O-C(5)); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 155.5, 140.5, 132.3 (q, $^2J_{C-F}$ = 34 Hz), 123.2 (q, $^1J_{C-F}$ = 273 Hz), 118.7 (q, $^3J_{C-F}$ = 3.3 Hz), 116.1 (sept, $^3J_{C-F}$ = 3.8 Hz), 113.0, 110.1, 103.7, 81.3, 80.4, 79.9, 73.0, 68.1, 41.2, 26.8, 26.2 (2C), 25.2; Elemental analysis: calcd $C_{22}H_{26}F_6N_2O_7$·0.5H_2O (553.17): C, 47.74; H, 4.92; N, 5.06; found C, 47.98; H, 4.80; N, 4.81.

4.1.12. (3*R*)-3-*C*-[(3,5-Bis(trifluoromethyl) phenylthioureidomethyl]-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose 20

Bis(3,5-trifluoromethyl)phenyl isothiocyanate (1.45 mL, 8.00 mmol, 1.15 equiv) was added to a solution of amino alcohol **5** (2.00 g, 7.00 mmol, 1 equiv) in CH_2Cl_2 (30 mL). After stirring at reflux at 40 °C for 4 h, the solvent was removed under reduced pressure. Purification by column chromatography (EtOAc/Hex 25%) yielded **20** (3.62 g, 94%). R_f = 0.48 (EtOAc/Hex 2:3); $[\alpha]_D^{25}$ = +8 (*c* 1.0, $CHCl_3$); mp = 100–102 °C (Hex/EtOAc); IR (KBr): 3374, 3306, 2990, 2943, 2888, 1521, 1382, 1281, 1181, 1136, 1080; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 10.53–10.40 (br s, 1H, H-N-C(Ar)), 8.33 (s, 2H, H-C(Ar)), 8.07 (t, 1H, ^3J = 4.7 Hz, H-N-C(3′)), 7.75 (s, 1H, H-C(Ar)), 5.75 (d, 1H, ^3J = 3.7 Hz, H-C(1)), 5.49 (s, 1H, HO-C(3)), 4.32 (d, 1H, ^3J = 3.7 Hz, H-C(2)), 4.16 (q, 1H, ^3J = 6.4 Hz H-C(5)), 3.98 (dd, AB syst., 1H, ^2J = 7.9 Hz, ^3J = 6.4 Hz, H_a-C(6)), 3.90 (d, 1H, ^3J = 6.4 Hz, H-C(4)), 3.80–3.72 (m, 1H, H_a-C(3′)), 3.71 (dd, AB syst., 1H, ^2J = 7.9 Hz, ^3J = 6.4 Hz, H_b-C(6)), 3.58 (dd, AB syst., 1H, ^2J = 13.8 Hz, ^3J = 4.7 Hz, H_b-C(3′)), 1.50, 1.33, 1.26, 1.23 (4s, 12H, $(H_3C)_2$C-O-C(1,5)); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ: 181.2, 142.3, 130.7 (q, $^2J_{C-F}$ = 33 Hz), 123.7 (q, $^1J_{C-F}$ = 274 Hz), 122.0 (m), 116.7 (m), 112.1, 108.8, 103.5, 81.4, 80.7, 79.6, 73.3, 66.5, 46.1, 27.1, 26.8 (2C), 25.5; HRMS: calcd [$C_{22}H_{26}F_6N_2O_6S$+H^+] 560.1489; found 560.1483.

4.1.13. (3*R*)-3-*C*-[(3,5-Bis(trifluoromethyl)phenylthioureidomethyl]-1,2-*O*-isopropylidene-α-D-allofuranose 21

At first, 1 M H_2SO_4 (1.38 mL, 1.38 mmol, 0.2 equiv) was added to a solution of thiourea **20** (3.87 g, 6.91 mmol, 1 equiv) in MeOH (25 mL) and CH_2Cl_2 (50 mL), and stirred at 60 °C for 4 h. Next, anhydrous $NaHCO_3$ (0.29 g, 3.45 mmol, 0.5 equiv) was added to the resulting reaction mixture at 0 °C followed by stirring 30 min at ambient temperature. The reaction mixture was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by column chromatography (EtOAc/Hex 70%) yielded **21** (3.07 g, 85%). R_f = 0.39 (EtOAc); $[\alpha]_D^{20}$ = +54.3 (*c* 0.74, $CHCl_3$); IR (KBr): 3337, 3102, 2993, 2941, 2888, 1542, 1474, 1385, 1278, 1177, 1133; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 10.47–10.35 (br s, 1H, H-N-C(Ar)), 8.35 (s, 2H, H-C(Ar)), 8.22–8.04 (br s, 1H, H-N-C(3′)), 7.74 (s, 1H, H-C(Ar)), 5.69 (d, 1H, ^3J = 3.7 Hz, H-C(1)), 5.08–4.98 (br s, 1H, HO-C(3)), 4.82 (d, 1H, ^3J = 4.9 Hz, HO-C(5)), 4.59 (t, 1H, ^3J = 5.8 Hz, HO-C(6)), 4.32 (d, 1H, ^3J = 3.7 Hz, H-C(2)), 3.94 (dd, AB syst., 1H, ^2J = 14.1 Hz, ^3J = 5.7 Hz, H_a-C(3′)), 3.83 (d, 1H, ^3J = 7.4 Hz, H-C(4)), 3.72 (dd, AB syst., 1H, ^2J = 14.1 Hz, ^3J = 2.6 Hz, H_b-C(3′)), 3.67–3.53 (m, 2H, H_a-C(6), H-C(5)), 3.38 (dd, AB syst., 1H, ^2J = 11.1 Hz, ^3J = 5.8 Hz, H_b-C(6)), 1.47, 1.25 (2s, 6H, $(H_3C)_2$C-O-C(1)); ^{13}C NMR (CD_3OD, 75.5 MHz) δ: 180.6, 140.3, 129.8 (q, $^2J_{C-F}$ = 34 Hz), 121.8 (q, $^1J_{C-F}$ = 272 Hz), 120.8 (q, $^3J_{C-F}$ = 3 Hz), 115.1 (m), 111.78, 102.0, 79.6, 78.6, 77.5, 68.8, 62.3, 43.9, 23.9, 23.7; HRMS: calcd [$C_{19}H_{22}F_6N_2O_6S$+H^+] 521.1176; found 521.1172.

4.1.14. (3*S*)-3-*C*-[(3,5-Bis(trifluoromethyl)phenylureidomethyl]-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose hydrate 22

Bis(3,5-trifluoromethyl)phenyl isocyanate (0.101 mL, 0.398 mmol, 1.15 equiv) was added to a solution of amino alcohol **6** (0.100 g, 0.346 mmol, 1 equiv) in CH_2Cl_2 (3 mL). After stirring at reflux at 40 °C for 4 h, the solvent was removed under reduced pressure. Purification by column chromatography (EtOAc/Hex 25%) yielded **22** (0.162 g, 83%). R_f = 0.48 (EtOAc/Hex 2:3); $[\alpha]_D^{25}$ = +31 (*c* 0.5, $CHCl_3$); mp = 93–98 °C (Hex/EtOAc); IR (KBr): 3359, 3123, 2992, 2941, 1673, 1573, 1475, 1388, 1280, 1181, 1133, 1074; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.84 (s, 2H, H-C(Ar)), 7.51 (s, 1H, H-C(Ar)), 7.20–7.06 (br s, 1H, H-N-C(Ar)), 5.90 (d, 1H, ^3J = 3.6 Hz, H-C(1)), 5.66 (dd, 1H, ^3J = 6.6, 6.0, Hz, H-N-C(3′)), 4.58–5.45 (br s, 1H, HO-C(3)), 4.42 (d, 1H, ^3J = 3.6 Hz, H-C(2)), 4.39 (ddd, 1H, ^3J = 8.2, 6.4, 4.9 Hz, H-C(5)), 4.15 (dd, AB syst., 1H, ^2J = 8.9 Hz, ^3J = 6.4 Hz, H_a-C(6)), 4.04 (dd, AB syst., 1H, ^2J = 8.9 Hz, ^3J = 4.9 Hz, H_b-C(6)), 3.90 (dd, AB syst., 1H, ^2J = 14.9 Hz, ^3J = 6.0 Hz, H_a-C(3′)), 3.80 (d, 1H, ^3J = 8.2 Hz, H-C(4)), 3.47 (dd, AB syst., 1H, ^2J = 14.9 Hz, ^3J = 6.6 Hz, H_b-C(3′)), 1.81 (br s, 2H, H_2O), 1.53, 1.43, 1.35, 1.31 (4s, 12H, $(H_3C)_2$C-O-C(1,5)); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 155.7, 0.2, 132.4 (q, $^2J_{C-F}$ = 34 Hz), 124.7 (q, $^1J_{C-F}$ = 274 Hz), 118.9 (q, $^3J_{C-F}$ = 4 Hz), 116.5 (sept, $^3J_{C-F}$ = 4 Hz), 113.0, 109.7, 104.7, 86.0, 82.9, 82.3, 72.6, 67.6, 43.6, 27.2, 26.9, 26.5, 25.2; Elemental analysis: calcd $C_{22}H_{26}F_6N_2O_7$·H_2O (562.18): C, 46.98; H, 5.02; N, 4.98; found C, 46.62; H, 4.90; N, 5.00.

4.1.15. (3*S*)-3-*C*-[(3,5-Bis(trifluoromethyl)phenylthioureidomethyl]-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose 23

Bis(3,5-trifluoromethyl)phenyl isothiocyanate (0.036 mL, 0.199 mmol, 1.15 equiv) was added to a solution of amino alcohol

6 (50.0 mg, 0.173 mmol, 1 equiv) in CH_2Cl_2 (2 mL). After stirring at reflux at 40 °C for 4 h, the solvent was removed under reduced pressure. Purification by column chromatography (EtOAc/Hex 20%) yielded **23** (94.0 mg, 97%). R_f = 0.58 (EtOAc/Hex 2:3); $[\alpha]_D^{25}$ = −13.2 (*c* 1.0, $CHCl_3$); mp = 85–90 °C (Hex/EtOAc); IR (KBr): 3304, 2991, 2940, 2894, 1623, 1542, 1472, 1378, 1280, 1180, 1138, 1071; ^{1}H NMR (DMSO-d_6, 80 °C, 300 MHz) δ: 10.43–10.34 (br s, 1H, H-N-C(Ar)), 8.29 (s, 2H, H-C(Ar)), 7.97 (t, 1H, ^3J = 4.8 Hz, H-N-C(3′)), 7.74 (s, 1H, H-C(Ar)), 5.86 (d, 1H, ^3J = 3.6 Hz, H-C(1)), 5.75 (s, 1H, HO-C(3)), 4.38 (d, 1H, ^3J = 3.6 Hz, H-C(2)), 4.27 (q, 1H, ^3J = 6.3 Hz, H-C(5)), 4.01 (dd, AB syst., 1H, ^2J = 8.3 Hz, ^3J = 6.3 Hz, H_a-C(6)), 3.95–3.82 (m, 3H, H_b-C(6), H_a-C(3′), H-C(4)), 3.77 (dd, AB syst., 1H, ^2J = 13.9 Hz, ^3J = 4.8 Hz, H_b-C(3′)), 1.47, 1.33, 1.30, 1.24 (4s, 12H, $(H_3C)_2$C-O-C(1,5)); ^{13}C NMR (DMSO-d_6), 75.5 MHz) δ: 181.4, 142.8, 131.2 (q, $^2J_{C-F}$ = 33 Hz), 124.1 (q, $^1J_{C-F}$ = 274 Hz), 122.3 (m), 116.8 (sept, $^3J_{C-F}$ = 4 Hz), 112.6, 109.1, 105.0, 86.3, 83.0, 80.6, 73.2, 67.1, 47.2, 27.8, 27.4, 27.3, 26.1; Elemental analysis: calcd $C_{22}H_{26}F_6N_2O_6S$ (560.14): C, 47.14; H, 4.68; N, 5.00; found C, 47.07; H, 4.62; N, 4.84.

4.1.16. (3*S*)-3-*C*-[(3,5-Bis(trifluoromethyl)phenylthioureidomethyl]-1,2-*O*-isopropylidene-α-D-glucofuranose 24

At first, 1 M H_2SO_4 (1.38 mL, 1.38 mmol, 0.2 equiv) was added to a solution of thiourea **23** (3.87 g, 6.91 mol, 1 equiv) in MeOH (25 mL) and CH_2Cl_2 (70 mL) and stirred at 60 °C for 2.5 h. Next, anhydrous $NaHCO_3$ (0.29 g, 3.45 mmol, 0.5 equiv) was added to the resulting reaction mixture at 0 °C followed by stirring 30 min at ambient temperature. The reaction mixture was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by column chromatography (EtOAc/Hex 50%) yielded **24** (3.45 g, 96%). R_f = 0.56 (EtOAc/Hex 3:2, 0.5% MeOH); $[\alpha]_D^{23}$ = +18 (*c* 0.35, $CHCl_3$); IR (KBr): 3327, 2993, 2942, 2888, 1542, 1474, 1380, 1279, 1176, 1136, 1069; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 10.40–10.29 (br s, 1H, H-N-C(Ar)), 8.32 (s, 2H, H-C(Ar)), 8.18–8.12 (br s, 1H, H-N-C(3′)), 7.72 (s, 1H, H-C(Ar)), 5.82 (d, 1H, ^3J = 3.6 Hz, H-C(1)), 5.55–5.48 (br s, 1H, HO-C(3)), 4.89–4.78 (br s, 1H, HO-C(5)), 4.52 (t, 1H, ^3J = 5.6 Hz, HO-C(6)), 4.32 (d, 1H, ^3J = 3.6 Hz, H-C(2)), 3.82–3.66 (m, 4H, H-C(3′), H-C(4), H-C(5)), 3.57 (ddd, AB syst., 1H, ^2J = 11.2 Hz, ^3J = 5.3 Hz, ^3J = 2.5 Hz, H_a-C(6)), 3.39 (dd, AB syst., 1H, ^2J = 11.2 Hz, ^3J = 5.6 Hz, H_b-C(6)), 1.42, 1.26 (2s, 6H, $(H_3C)_2$C-O-C(1)); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ: 180.8, 142.4, 130.7 (q, $^2J_{C-F}$ = 34 Hz), 123.7 (q, $^1J_{C-F}$ = 273 Hz), 121.6 (m), 116.3 (m), 111.9, 104.1, 85.7, 81.4, 80.6, 69.1, 64.0, 47.3, 27.4, 27.0; HRMS: calcd $[C_{19}H_{22}F_6N_2O_6S+H^+]$ 520.1176; found 521.1175.

4.1.17. (3*R*)-3-*C*-[(3,5-Bis(trifluoromethyl)phenylthioureidomethyl]-1,2:5,6-di-*O*-cyclohexylidene-α-D-allofuranose 25

Bis(3,5-trifluoromethyl)phenyl isothiocyanate (0.227 mL, 1.25 mmol, 1.15 equiv) was added to a solution of amino alcohol **12** (0.400 g, 1.08 mmol, 1 equiv) in CH_2Cl_2 (5 mL). After stirring at reflux at 40 °C for 3 h, the solvent was removed under reduced pressure. Purification by column chromatography (EtOAc/Hex 8%) yielded **25** (0.653 g, 94%). R_f = 0.65 (EtOAc/Hex 7:12); $[\alpha]_D^{23}$ = +6.4 (*c* 0.43, $CHCl_3$); IR (KBr): 3523, 3356, 2940, 2864, 1624, 1541, 1473, 1451, 1384, 1280, 1145, 1015; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 10.45 (s, 1H, H-N-C(Ar)), 8.33 (s, 2H, H-C(Ar)), 8.19–8.05 (br s, 1H, H-N-C(3′)), 7.76 (s, 1H, H-C(Ar)), 5.75 (d, 1H, ^3J = 3.6 Hz, H-C(1)), 5.53–5.43 (br s, 1H, HO-C(3)), 4.30 (d, 1H, ^3J = 3.6 Hz, H-C(2)), 4.16 (m, 1H, H-C(5)), 3.98 (m, 1H, H_a-C(6)), 3.88 (d, 1H, ^3J = 6.1 Hz, H-C(4)), 3.81–3.57 (m, 3H, H-C(3′), H_b-C(6)), 1.78–1.17 (m, 20H, $(Chx)_2$-C(1,2:5,6)); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ: 181.1, 142.3, 130.7 (q, $^2J_{C-F}$ = 33 Hz), 123.7 (q, $^1J_{C-F}$ = 273 Hz), 122.0 (m), 116.7 (m), 112.6, 109.3, 103.1, 80.9, 80.7, 79.6, 72.9, 66.4, 46.0, 36.4, 36.0 (2C), 34.7, 25.1, 24.9, 24.0 (2C), 23.8 (2C); HRMS: calcd $[C_{28}H_{34}F_6N_2O_6S+Na^+]$ 663.1934; found 663.1925.

4.1.18. (3*S*)-3-*C*-[(3,5-Bis(trifluoromethyl)phenylthioureidomethyl]-1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose 26

At first, Et_3N (0.103 mL, 0.738 mmol, 1 equiv) was added to a solution of ammonium tosylate **16** (0.400 g, 0.738 mmol, 1 equiv) in CH_2Cl_2 (5 mL). The resulting mixture was stirred for 10 min and bis(3,5-trifluoromethyl)phenyl isothiocyanate (0.103 mL, 0.738 mmol, 1 equiv) was added. After stirring at reflux at 35 °C for 6 h, the solvent was removed under reduced pressure. The residue mixture was dissolved in ethyl acetate (30 mL), washed with brine (5 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by column chromatography (EtOAc/Hex 8%) yielded **26** (0.260 g, 55%). R_f = 0.36 (EtOAc/Hex 1:3); $[\alpha]_D^{20}$ = 4.0 (*c* 0.55, $CHCl_3$); IR (KBr): 3294, 2941, 2864, 1542, 1466, 1377, 1279, 1181, 1137; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 10.36 (s, 1H, H-N-C(Ar)), 8.31 (s, 2H, H-C(Ar)), 7.98–7.92 (br s, 1H, H-N-C(3′)), 7.74 (s, 1H, H-C(Ar)), 5.86 (d, 1H, ^3J = 3.4 Hz, H-C(1)), 5.72 (s, 1H, HO-C(3)), 4.34 (d, 1H, ^3J = 3.4 Hz, H-C(2)), 4.26–4.14 (m, 1H, H-C(5)), 4.07–3.96 (m, 2H, H_a-C(3′), H_a-C(6)), 3.87–3.76 (m, 3H, H_b-C(3′), H-C(4), H_b-C(6)), 1.69–1.21 (m, 20H, $(Chx)_2$-C(1,2:5,6)); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ: 181.0, 142.4, 130.8 (q, $^2J_{C-F}$ = 32 Hz), 123.8 (q, $^1J_{C-F}$ = 273 Hz), 121.8 (m), 116.5 (m), 112.7, 109.3, 104.2, 85.5, 82.7, 80.3, 72.3, 66.6, 46.9, 36.8, 36.4, 36.1, 35.0, 25.1, 24.8, 24.1, 24.0, 23.8, 23.7; HRMS: calcd $[C_{28}H_{34}F_6N_2O_6S+Na^+]$ 641.2115; found 641.2096.

4.1.19. Catalytic enantioselective Friedel–Crafts alkylation of indoles with *trans*-β-nitrostyrene

General procedure (reaction conditions and results are summarize in Table 1): A mixture of indole **27**, *trans*-β-nitrostyrene **28**, selected catalyst organocatalyst and additives were dissolved in a selected solvent. The resulting reaction mixture was held at the given temperature and controlled by GC–MS [a sample (10 μl) was taken from the reaction mixture, diluted with CH_2Cl_2 (2 mL) and analyzed by GC–MS]. Solvents were removed under reduced pressure. Purification by column chromatography (EtOAc/Hex 3%) yielded the product. The NMR data and other characteristics of product **29** fully corresponded to those reported earlier.[17c] The absolute configuration of the product was determined by comparing the specific optical rotation with that of the literature data: $[\alpha]_D^{20}$ = −6.1 (*c* 1.0, $CHCl_3$), 74% ee (*R*); $[\alpha]_D^{rt}$ = −8 (*c* 0.65, $CHCl_3$), 85% ee (*R*).[30] The enantiomeric excess was determined by HPLC analysis of **29** using Chiralpak IA column (0.46 × 25 cm) (isocratic method: 5% ^{i}PrOH/Hex; 40 min; Injection 5 μl (0.70 mg/mL Hex + 30% ^{i}PrOH); Flow rate 1 mL/min; Detector wavelength 254 nm.): t_R = 27.9 (*S*); t_R = 25.0 (*R*).

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.10 (br s, 1H, H-N(1)), 7.46 (d, 1H, ^3J = 8.1 Hz, H-C(c)), 7.37–7.25 (m, 6H, H-C(e), H-C(g), H-C(4), H-C(5), H-C(6), H-C(7)), 7.21 (td, 1H, ^3J = 8.3 Hz, ^4J = 0.9 Hz, H-C(d)), 7.09 (td, 1H, ^3J = 8.1 Hz, ^4J = 0.9 Hz, H-C(f)), 7.03 (d, 1H, ^3J = 2.5 Hz, H-C(2)), 5.20 (dd, 1H, ^3J = 7.7 Hz, ^3J = 8.1 Hz, H-C(a)), 5.08 (dd, AB syst., 1H, ^2J = 12.4 Hz, ^3J = 7.5 Hz, H_a-C(b)), 4.95 (dd, AB syst., 1H, ^2J = 12.4 Hz, ^3J = 8.3 Hz, H_a-C(b)); ^{13}C NMR ($CDCl_3$), 75 MHz) δ: 139.2, 136.6, 129.0, 127.8, 127.6, 122.8, 121.7, 120.1, 119.0, 114.5, 111.4, 79.6, 41.6.

4.1.20. Catalytic Michael 1,4-addition of nitromethane to *trans*-chalcone: synthesis of (*S*)-3-nitro methyl-1,3-diphenyl-2-propen-1-one (*S*)-31

Nitromethane (46.0 μL, 0.85 mmol, 3.0 equiv) was added to a solution of 1,3-diphenyl-2-propen-1-one **30** (60 mg, 0.289 mmol, 1.0 equiv) and organocatalyst **21** (15 mg, 0.029 mmol, 0.1 equiv) in toluene (0.2 mL). The reaction was controlled by GC–MS [a

sample (10 μl) was taken from the reaction mixture, diluted with CH_2Cl_2 (2 mL) and analyzed by GC–MS]. After 14 days at 18 °C, the solvent was removed under reduced pressure. Purification by column chromatography (2% EtOAc/Hex) yielded product **31** (23 mg, 30%). The NMR data and other characteristics of product **31** corresponded fully to those reported earlier.[31] The absolute configuration of the product was determined by comparing the specific rotation of **31** with that of the literature data: $[\alpha]_D^{22} = -5.6$ (*c* 0.43, $CHCl_3$); Lit.: $[\alpha]_D^{22} = -7.3$ (*c* 1.05, $CHCl_3$), 90% ee, (*S*). The enantiomeric excess (48% ee) was determined by HPLC analysis of **31** using Chiralpak IA column (0.46 × 25 cm) (Isocratic method: 5% ^{i}PrOH/Hex; 40 min; Injection 30 μl (1.00 mg/mL Hex + 30% ^{i}PrOH); Flow rate 1 mL/min; Detector wavelength 254 nm.): $t_R = 15.0$ (*S*); $t_R = 19.3$ (*R*). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.92 (d, 3H, $^3J = 7.3$ Hz, H-C(2″), H-C(6″)), 7.58 (t, 1H, $^3J = 7.3$ Hz, H-C(4″)), 7.46 (t, 2H, $^3J = 7.5$ Hz, H-C(3″), H-C(5″)), 7.38–7.24 (m, 5H, H-C(Ar)), 4.84 (dd, AB syst., 1H, $^2J = 12.4$ Hz, $^3J = 6.8$ Hz, H_a-C(3′)), 4.69 (dd, AB syst., 1H, $^2J = 12.4$ Hz, $^3J = 7.9$ Hz, H_b-C(3′)), 4.23 (quintet, 1H, $^3J = 7.2$ Hz, H-C(3)), 3.53–3.37 (m, 2H, H-C(2)).

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