gluco-Box – a new carbohydrate-based bis(oxazoline) ligand. Synthesis and first application

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General methods

Dry solvents (DCM, MeCN), were obtained by filtration through drying columns on a M. Braun Solvent Purification System (M. Braun). Pyridine and triethylamine were used as received. All reactions with reagents sensitive to air or moisture were carried out under nitrogen atmosphere and are specially denoted. Reactions were monitored by TLC on 60 F_{254} aluminum plates (Merck) with detection by UV light and / or charring with 10% sulfuric acid in ethanol or a mixture of cerium(IV) sulfate and molybdophosphoric acid in 8% sulfuric acid. Flash chromatography was performed on Merck silica (grain size 40-63 μm). NMR spectra were recorded on an AVS 400 instrument (Bruker) at 400 MHz (^{1}H) or at 100 MHz (^{13}C) respectively. Deuterated chloroform and methanol were used as solvents and spectra were calibrated against the residual solvent peak ($CHCl_3$: 7.24 ppm, MeOH (CH_3) 3.35 ppm). Chemical shifts δ are given in ppm, coupling constants *J* are given in Hz. Electrospray mass spectra were recorded on a Micromass LCT device (Waters), injection into the HPLC instrument (Waters) was performed in loop modus. Optical rotations were recorded on a Perkin-Elmer 451 instrument under following standard conditions: Room temperature, wavelength 589.3 nm (sodium D line), cell length 1 dm, solvent and sample concentration (in 10 mg/ml) are given with individual experiment. Chiral GC experiments were carried out on a HP 5890-II device (Hewlett-Packard) with a flame ionisation detector and hydrogen as carrier gas in constant flow modus. Starting temperature was 50°C 1.1°C/min. A Hydrodex-β PM capillary column (50 m, 0.25 mm, 723370, Macherey-Nagel) was used for separation of enantiomers.

Determination of enantiomeric excesses

For all cyclopropanation products racemic samples were prepared and used as reference substances for the determination of enantiomeric excesses.

a) by gas chromatography

All compound mixtures were first analysed by a GC run on an achiral stationary phase. A racemic sample of the cyclopropanation product was analysed by GC on the chiral stationary phase. Then an enantiomerically enriched sample was injected and the enantiomeric excess was determined from the resulting chromatogram by peak integration. In one instance an equimolar amount of racemate and reaction sample were mixed and injected together showing the expected increase of the appropriate peak.

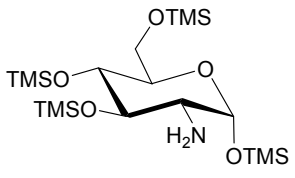
b) by ^{1}H NMR with Rh_2[*R*-(+)-MTPA]$_4$ reagent (dirhodium method)[1]

Rh_2[(+)-MTPA]$_4$, a dirhodium(II) complex with four *R*-(+)-Mosher acid ligands is a chiral complexing agent with two binding sites that can be occupied by sample molecules as ligands. A racemic sample of cyclopropanation product and of Rh_2[(+)-MTPA]$_4$ in molar ratio 1:1 were dissolved in $CDCl_3$. The NMR spectrum of this mixture shows signal splitting into two sets of equal intensity due to formation of diastereomeric adducts of the racemic sample with the dirhodium reagent. Afterwards a spectrum of an enantiomerically enriched sample was recorded under identical conditions, again showing signal splitting into sets but now with different intensities. Comparison with the racemate spectrum for peak identification and integration of a well resolved signal pair in the sample spectrum allowed determination of the enantiomeric excess.

The absolute configuration of all major products was either determined by direct comparison of product optical rotation values to literature values or else by transformation into substances with known optical rotations.

Ligand synthesis

2-Amino-2-deoxy-1,3,4,6-tetra-*O*-trimethylsilyl-α-D-glucopyranose (2)



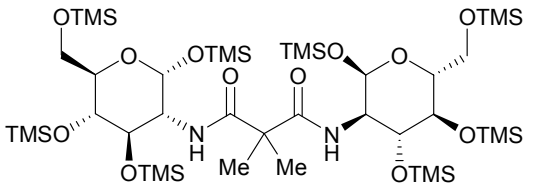
To a suspension of glucosamine hydrochloride (**1**) (10.00 g, 43.36 mmol, 1eq) in pyridine HMDS (54 cm^3, 463.74 mmol, 10 eq) was added followed by TMSCl (60 cm^3, 463.74 mmol, 10 eq). The resulting mixture was stirred at rt and the reaction monitored via TLC (petroleum ether / ethyl acetate 5:1). During the reaction a lot of salt byproduct precipitated. After completion of the reaction (approx. 4 h), the mixture was evaporated *in*

[1] (a) H. Duddeck, *Chem. Rec.*, 2005, **5**, 396-409; (b) E. Díaz Gómez, J. Jios, C. O. DellaVédova, H. D. March, H. E. Di Loreto, G. Tóth, A. Simon, D. Albert, S. Moeller, R. Wartchow, H. Duddeck, *Tetrahedron Asymm.,* 2005, **16**, 2285-2293.

vacuo with a cooling trap between rotary evaporator and pump stand. The residue was twice co-evaporated with toluene to remove residual pyridine. The raw material was then submitted to short column filtration over silica gel (petroleum ether / ethyl acetate 5:1) to remove the pyridinium salts. The acid sensitive title compound **2** was obtained as a colourless crystalline solid after refrigerating over night (19.53 g, 41.72 mmol, 90%). The product can be stored in the refrigerator over several months.

$[\alpha]_D^{25}$ +87 (*c* 3.4 in chloroform); δ_H (400 MHz; $CDCl_3$) 0.08, 0.17, 0.15, 0.20, (each 9H, each s, OSi(C*H*$_3$)$_3$), 1.38 (2H, bs, N*H*$_2$), 2.52 (1H, dd, $J_{1,2}$ 3.3, $J_{2,3}$ 9.7, H-2), 3.44 (1H, dd ≈ t, $J_{3,4}$ 8.7, $J_{4,5}$ 9.4, H-4), 3.52 (1H dd ≈ t, $J_{2,3}$ 9.7, $J_{3,4}$ 8.7, H-3), 3.61 (1H, ddd, $J_{4,5}$ 9.4, $J_{5,6}$ 4.3, $J_{5,6'}$ 2.5, H-5), 3.64-3.75 (2H, m, H-6, H-6'), 5.12 (1H, d, $J_{1,2}$ 3.3, H-1); δ_C (100 MHz, $CDCl_3$) 0.2, 0.4, 0.9, 1.4, (each 3 x t, OSi(<u>C</u>H$_3$)$_3$), 57.7 (t, C-2), 62.0 (s, C-6), 78.2, 72.9, 72.0, (3 x t, C-3, C-4, C-5), 95.8 (t, C-1); HRMS (ESI) $C_{18}H_{46}O_5NSi_4$ $[M+H]^+$ calcd. 468.2453, found 468.2456.

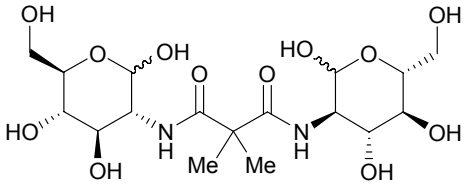
Bis-(2-amino-2-deoxy-1,3,4,6-tetra-*O*-trimethylsilyl-α-D-glucopyranosido)-dimethyl malonamide (3)



Under nitrogen atmosphere, *O*-TMS protected amino sugar **2** (18.52 g, 39.58 mmol, 1 eq) was dissolved in dry dichloromethane (250 cm^3) and the resulting solution was cooled to 0°C. Then triethylamine (11 cm^3, 8.02 g, 79.17 mmol, 2eq) followed by dimethyl malonyl dichloride (2.6 cm^3, 3.35 g, 19.79 mmol, 0.5 eq) was added. Progress of the reaction was monitored by TLC (petroleum ether / ethyl acetate 2:1). After approximately 2 h the solvent was evaporated *in vacuo* and the raw product subjected to short column filtration over silica gel (petroleum ether / ethyl acetate 3:1). The bis(amide) **3** was isolated as a colourless foam (19.60 g, 19.00 mmol, 96%). The title compound can be stored in the refrigerator over several months.

$[\alpha]_D^{25}$ +83 (*c* 1.6 in chloroform); δ_H (400 MHz; $CDCl_3$) 0.10, 0.17, 0.19, 0.21, (each 18H, each s, OSi(C*H*$_3$)$_3$), 1.48 (6H, s, (C*H*$_3$)$_2$C(CO)$_2$), 3.61 (2H, dd ≈ t, $J_{3,4}$ $J_{4,5}$ 8.4, H-4), 3.65-3.81 (8H, m, H-3, H-5, H-6, H-6'), 3.99 (2H, ddd ≈ td, $J_{1,2}$ 3.1, $J_{2,3}$ $J_{2,NH}$ 9.2, H-2), 5.06 (2H, d, $J_{1,2}$ 3.1, H-1), 7.08 (2H, d, $J_{2,NH}$ 9.2,NH), δ_C (100 MHz, $CDCl_3$) -0.43, -0.27, 0.60, 0.98, (each 8 x t, OSi(<u>C</u>H$_3$)$_3$), 24.4 (2 x t, (<u>C</u>H$_3$)$_2$C(CO)$_2$), 49.1 (q, (CH$_3$)$_2$<u>C</u>(CO)$_2$), 54.8 (2 x t, C-2), 61.5 (2 x s, C-6), 73.6, 73.1, 71.5, (6 x t, C-3, C-4, C-5), 91.7 (2 x t, C-1), 173.6 (2 x q, (CH$_3$)$_2$C(<u>C</u>O)$_2$); HRMS (ESI) $C_{41}H_{95}N_2O_{12}Si_8$ $[M+H]^+$ calcd. 1031.5039, found 1031.5077, $C_{41}H_{94}N_2O_{12}Si_8Na$ $[M+Na]^+$ calcd. 1053.4858, found 1053.4911.

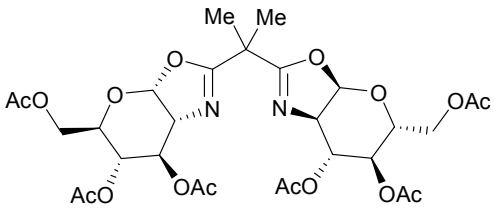
Bis-(2-amino-2-deoxy-D-glucopyranosido)-dimethyl malonamide (4)



TMS protected bis(amide) **3** (9.96 g, 9.66 mmol) was treated with methanol / TFA (9:1) (150 cm^3) at room temperature. TLC (MeOH / DCM 1:9) indicated the complete consumption of all staring material after 2 h. The solvent was removed *in vacuo* and the residue was co-evaporated with toluene until it solidified to a colourless mass. The powdery raw product was stirred with ethyl acetate (100 cm^3), filtered by suction and washed with some more ethyl acetate to remove residual organosilicon by-products of the deprotection reaction. The colourless product **4** was isolated in near quantitative yield and used for the next step without further purification. As each of the two carbohydrate moieties of bis(amide) **4** can individually occur in both anomeric forms, a total of three bis(amides) different anomeric configurations is obtained. The (α,α), (α,β) and (β,β) configured compounds have all slightly different chemical shifts in the ^1H and ^{13}C NMR spectra, complicating interpretation. Therefore full NMR characterisation of **4** was not attempted.

$[\alpha]_D^{25}$ +40.8 (*c* 1.02 in methanol); HRMS (ESI) $C_{17}H_{30}O_{12}N_2Na$ $[M+Na]^+$ calcd. 477.1696, found 477.1700.

2'',2''-Bis-{4',5'-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyranosido-[2',1'-d]-oxazolin-2'-yl}-propan (*gluco*-Box) (6)



a) Bis(amide) **4** (1.00 g, 2.20 mmol, 1 eq) was taken up in acetyl chloride (10 cm^3) (note: the acetyl chloride should not be distilled prior to use, as a catalytic amount of hydrogen chloride is necessary for the reaction!) and stirred for 16 h. Reaction progress was monitored by TLC (DCM / acetone 5:1). The acetyl chloride was then removed on the rotary evaporator and the raw chloride **5** was twice co-evaporated with toluene to remove residual acetyl chloride and then directly used for the next step.

b) Raw chloride **5** was dissolved in dry acetonitrile (10 cm^3). Tetraethylammonium chloride (0.86 g, 5.20 mmol 2.4 eq) and sodium hydrogen carbonate (0.86 g, 10.48 mmol, 4.7 eq) were added and the resulting mixture was stirred at rt fr 16 h. Reaction progress can be monitored via TLC (DCM / acetone 3:1). The solvent was removed *in vacuo*, the residue taken up in DCM (20 cm^3) washed with water (20 cm^3). The organic phase was dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica

gel (petroleum ether / ethyl acetate 1:1) yielded the bis(oxazoline) **6** as a yellow foam (1.40 g, 2.12 mmol, 94%).

$[\alpha]_D^{25}$ +53 (*c* 1.9 in chloroform); δ_H (400 MHz; $CDCl_3$) 1.58 (6H, s, $(CH_3)_2C$), 1.98, 2.16, 2.05 (each 6H, each s, CH_3CO), 3.86 (2H, ddd, $J_{4,5}$ 9.2, $J_{5,6}$ 4.8, H-5), 4.13 (2H, dd, $J_{5,6'}$ 2.7, $J_{6,6'}$ 12.3, H-6'), 4.18 (2H, ddd, $J_{1,2}$ 7.5, $J_{2,3}$ 2.4, $J_{2,4}$ 1.3, H-2), 4.22 (2H, dd, $J_{5,6}$ 4.8, $J_{6,6'}$ 12.3, H-6), 4.94 (2H, ddd, $J_{3,4}$ 2.4, $J_{2,4}$ 1.3, $J_{4,5}$ 9.2, H-4), 5.31 (2H, dd ≈ t, $J_{2,3}$ $J_{3,4}$ 2.4, H-3), 6.05 (2H, d, $J_{1,2}$ 7.5, H-1); δ_C (100 MHz, $CDCl_3$) 20.7, 20.8, 20.9 (each 2 x t, $\underline{C}H_3CO$), 23.8 (2 x t, $(\underline{C}H_3)_2C$), 39.2 (q, $(CH_3)_2\underline{C}$), 62.8 (2 x s, C-6), 64.8 (2 x t, C-2), 67.8 (2 x t, C-5), 68.3, (2 x t, C-4), 70.1, (2 x t, C-3), 100.0 (2 x t, C-1), 170.6, 170.2, 169.5, 169.2 (each 2 x q, $CH_3\underline{C}O$, $\underline{C}N$); HRMS (ESI) $C_{29}H_{39}O_{16}N_2$ $[M+H]^+$ calcd. 671.2300, found 671.2298, $C_{29}H_{38}O_{16}N_2Na$ $[M+Na]^+$ calcd. 693.2119, found 693.2036.

Cyclopropanes

Absolute configurations were assigned by optical rotation of the respective compound and comparison with literature data.

Ethyl (1*S*,2*S*)-2-phenylcyclopropylcarboxylat (9a *trans*)

δ_H (200 MHz; $CDCl_3$) 1.24-1.38 (4H, m, cyclopropyl H, OCH_2CH_3), 1.61 (1H, ddd, *J* 4.5, 5.3, 9.2, cyclopropyl H); 1.92 (1H, ddd, *J* 4.1, 5.3, 8.3, cyclopropyl H); 2.53 (1H, ddd, *J* 4.2, 6.5, 9.2, cyclopropyl H), 4.19 (2H, q, *J* 7.1, OCH_2CH_3), 7.07–7.30 (5H, m, arom. H).

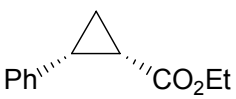
$[\alpha]_D^{25}$ +223 (*c* 1.00 in chloroform) Lit.[2] $[\alpha]_D$ +296

retention times (GC):

racemic mixture: t_R= 85.59 min, t_R = 85.99 min

title compound: t_R= 85.74 min (minor), t_R= 86.09 min (major)

Ethyl (1*S*,2*R*)-2-phenylcyclopropylcarboxylat (9a *cis*)



The compound could not be separated from diethyl fumarate formed as a by-product of the reaction. Only the values of the title compound are given.

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[2] D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc.*, 1991, **113**, 726-728.

δ_H (200 MHz; $CDCl_3$) 0.97 (3H, t, *J* 7.2, OCH_2CH_3), 1.24-1.39 (1H, m, cyclopropyl H), 1.71 (1H, ddd, *J* 5.2, 5.5, 7.3, cyclopropyl H), 2.08 (1H, ddd, *J* 5.6, 7.8, 9.3, cyclopropyl H), 2.52-2.64 (1H, m, cyclopropyl H), 3.87 (2H, q, *J* 7.2, OCH_2CH_3), 7.26–7.28 (5H, m, arom. H).

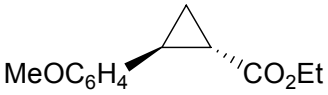
$[\alpha]_D^{25}$ +26° (c 1.02 in chloroform) Lit.[2] $[\alpha]_D$ +19°

retention times (GC):

racemic mixture t_R= 82.17 min, t_R = 83.07 min

title compound t_R= 82.19 min (major), t_R= 83.16 min (minor)

Ethyl (1*S*,2*S*)-2-(*p*-methoxyphenyl)-cyclopropylcarboxylat (9b *trans*)

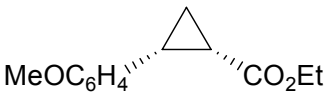


δ_H (400 MHz; $CDCl_3$) 1.24-1.34 (4H, m, OCH_2CH_3,, cyclopropyl H) 1.58 (1H, ddd, *J* 4.4, 5.1, 9.3, cyclopropyl H), 1.85 (1H, ddd, *J* 4.2, 5.3, 8.4, cyclopropyl H), 2.51 (1H, ddd, *J* 4.1, 6.5, 9.2, cyclopropyl H), 3.81 (3H, s, OCH_3), 4.19 (2H, q, *J* 7.2, OCH_2CH_3), 6.81-6.88 (2H, m, arom. H), 7.03-7.08 (2H, m, arom. H).

$[\alpha]_D^{25}$ +223 (*c* 1.01 in chloroform) Lit.[3] $[\alpha]_D$+245

Enantiomeric excess determined by NMR

Ethyl (1*S*,2*R*)-2-(*p*-methoxyphenyl)-cyclopropylcarboxylat (9b *cis*)



δ_H (400 MHz; $CDCl_3$) 1.04 (3H, t, *J* 7.2, OCH_2CH_3), 1.32 (1H, ddd, *J* 5.0, 7.8, 8.7, cyclopropyl H), 1.68 (1H, ddd ≈ dt, *J* 5.3, 7.4, cyclopropyl H), 2.05 (1H, ddd, *J* 5.6, 7.8, 9.1, cyclopropyl H), 2.54 (1H, m, cyclopropyl H), 3.80 (3H, s, OCH_3), 3.92 (2H, q, *J* 7.1, OCH_2CH_3), 6.81-6.67 (2H, m, arom. H), 7.15-7.25 (2H, m, arom. H).

$[\alpha]_D^{25}$ - 6° (*c* 1.01 in chloroform) Lit.[3] $[\alpha]_D$ -5

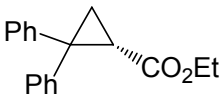
retention times (GC)

racemic mixture 108.42 min, t_R = 109.16 min

title compound t_R = 108.40 min (major), t_R = 109.09 min (minor)

[3] A. Nakamura, A. Konishi, R. Tsujitani, M. Kudo, S. Otsuka, *J. Am. Chem. Soc*,. 1978, **100**, 3449-3461.

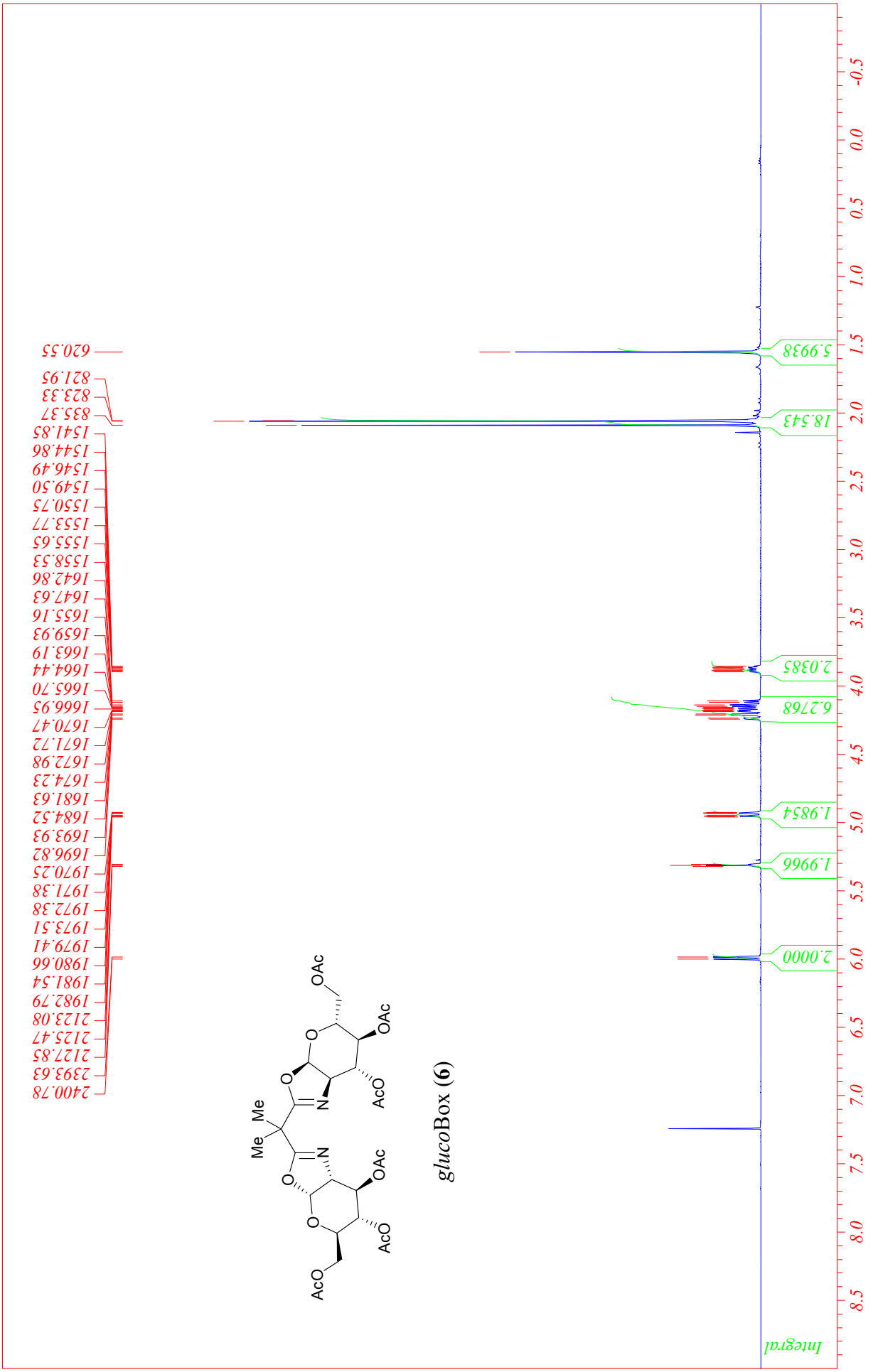
Ethyl (1*S*)-2,2-diphenylcycloprpoylcarboxylat (9c)



δ_H (400 MHz; $CDCl_3$) 1.03 (3H, t, *J* 7.1, OCH_2CH_3), 1.61 (1H, dd, *J* 4.8, 8.2, cyclopropyl H), 2.20 (1H, dd, *J* 4.9, 6.0, cyclopropyl H), 2.56 (1H, dd, *J* 5.9, 8.2, cyclopropyl H), 3.88-4.02 (2H, m, OCH_2CH_3), 7.20-7.45 (10H, m, arom. H).

$[\alpha]_D^{25}$ +171 (*c* 1.05 in chloroform) Lit.[2] $[\alpha]_D$ +212

Enantiomeric excess determined by NMR.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1979.41
1980.66
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2393.63
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Integral
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8.0
7.5
7.0
6.5
6.0
5.5
5.0
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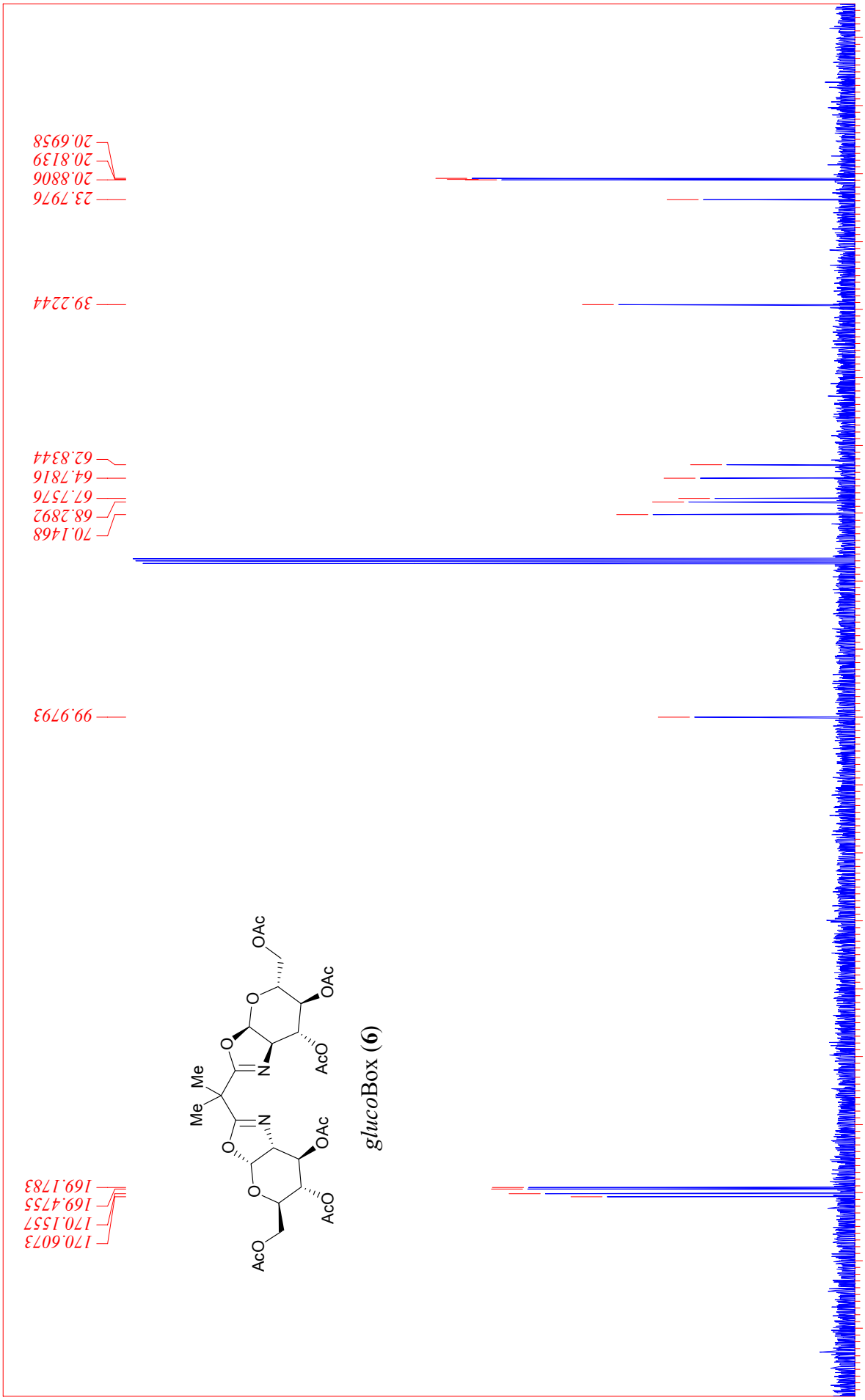
(ppm)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170
180
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OAc
AcO
Me
Me
N
N
O
O
O
O
OAc
OAc
AcO
AcO

*gluco*Box (**6**)