Synthesis of Sugar-fused GABA-analogs

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Abstract: γ-Aminobutyric acid (GABA)-sugar analogs in the form of *C*-ketosides can be prepared in 4 to 7 steps starting from D- or L-Glucono- and D-Galactono-1,5-lactone. The key step in the synthesis is the trimethylsilyl-trifluoromethanesulfonate (TMS-OTf) promoted *C*-glycosylation of 2-deoxy-3-ulopyranosonates with trimethylsilyl cyanide. Hydrogenation of the resulting β-cyano esters provides GABA-analogs, which are presented on a sugar scaffold.

Key words: carbohydrates, amino acids, glycosides, GABA, *C*-ketosides

Carbohydrates find increasing application as versatile scaffolds and building blocks for combinatorial chemistry that targets non-carbohydrate recognizing proteins.[1–5] Cyclic carbohydrates are rich in stereochemistry and their relatively rigid skeletons make them ideal platforms for the presentation of pharmacophores. Additional hydroxyl derivatization of the polyol scaffold may be used to increase lipophilicity, thus making carbohydrates more drug-like, as well as to modulate the activity of pharmacophores binding to receptor subtypes. In particular, the use of sugar-derived skeletons as non-peptidomimetics of somatostatin (a cyclic tetradecapeptide) demonstrated for the first time that sugars might be privileged platforms for the presentation of pharmacophores.[1] Since then, other carbohydrate-based scaffolds designed to mimick peptides,[2] small molecules[3,4] and the morphan ring system[5] have appeared.

Here we describe the synthesis of sugar-fused γ-aminobutyric acid (GABA) analogs **2**–**7** where the GABA-pharmacophore is engineered into the carbohydrate platform in the form of a *C*-ketoside (Figure). GABA is the major inhibitory neurotransmitter in the mammalian central nervous system and interacts with two post-synaptic receptors termed $GABA_A$ and $GABA_B$. Insights into the mechanism of seizures suggest that enhancing GABA-mediated synaptic inhibition would reduce neuronal excitability and raise the seizure threshold.[6] The anticonvulsants Progabide, Vigabatrin and Gabapentin (**1**), containing a GABA substructure are marketed antiepileptic drugs which differ in their anticonvulsive mechanism.

Initially, we were interested in developing a general synthetic route to sugar-based GABA-analogs in the glucose- (compounds **2**, **3** and **5**) and galactose- (compounds **4**, **6** and **7**) series in order to explore the steric effect of the platform and it's stereochemistry. Both hydroxyl-protected (*O*-methylated) and unprotected platforms were selected. In most cases we prepared GABA-esters in order to reduce polarity (GABA's intrinsic high polarity prevents it from crossing the blood-brain barrier).[6] It was anticipated that the methyl esters would easily be hydrolyzed by lipases commonly found in the brain. An unprotected γ-aminobutyric acid-analog was also prepared (compound **7**).

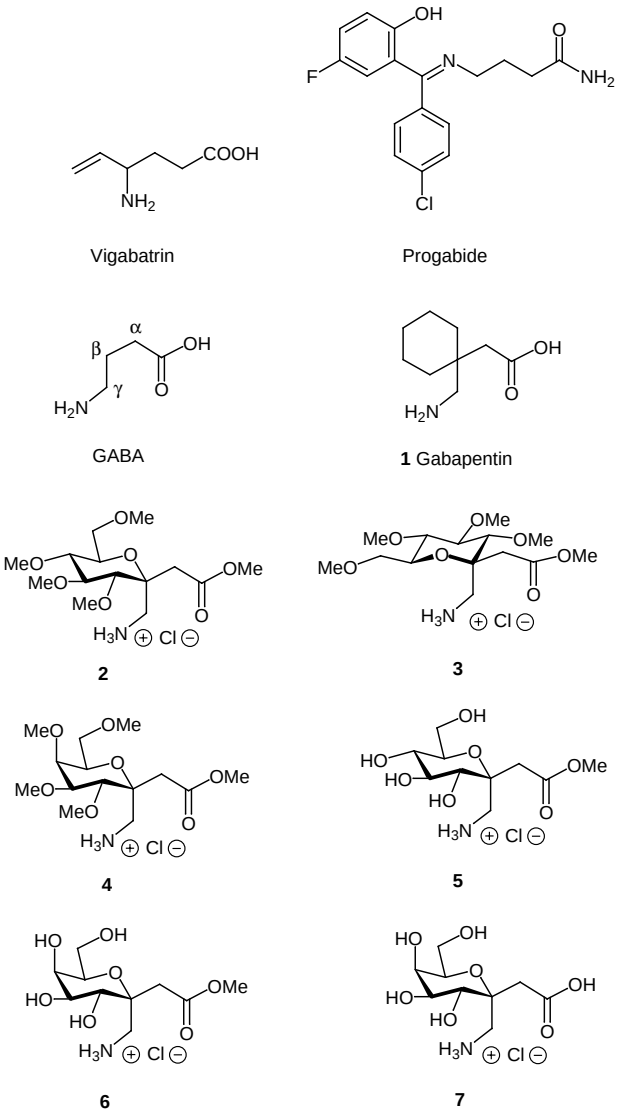

Figure Structures of GABA-sugar analogs **2**–**7**. Vigabatrin, Progabide and Gabapentin (**1**) are marketed drugs.

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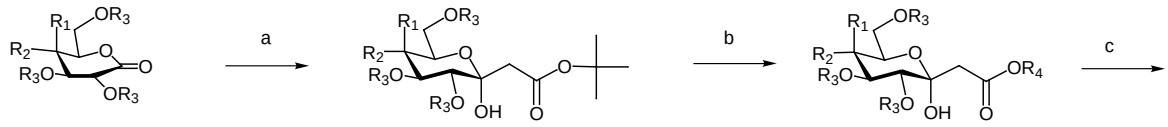
The commercially available lactones **8** and **9** as well as the known tetra-*O*-methyl sugar lactones **10**[7] and **11**[7] are readily accessible starting materials which on treatment with *tert*-butylacetate enolate at –78 °C led to the ketoses **12**–**15** in yields averaging 90% (Scheme 1). Addition of a second enolate was not observed. Compounds **12**–**15** exist entirely in the α-pyranose form as evidenced by their ^{1}H NMR spectra ($CDCl_3$), presumably as the result of a beneficial anomeric effect coupled with positioning of the larger alkyl groups in the less hindered equatorial orientation.

The *tert*-butyl group in **12** and **13** was cleaved with trifluoroacetic acid (TFA) in CH_2Cl_2 and the free acid was esterified to either the methyl or benzyl ester (Cs_2CO_3, MeI or BnBr) to afford ketoses **16**, **17** and **20** in yields averaging 70% (Scheme 1). Subjecting the *tert*-butylesters **14** and **15** to the same protocol resulted in low yields (< 15%) of the corresponding methyl esters **18** and **19**. Higher yields of **18** and **19** could however be obtained in a 4-step procedure starting from the benzyl protected ketols **16** and **17** (Scheme 2). The anomeric center was first protected as the methyl glycosides **21** and **22** by boron trifluoride diethyl etherate promoted glycosylation with methanol in acetonitrile. Subsequent debenzylation ($Pd(OH)_2/C/H_2$) and O-methylation under standard conditions (MeI, NaH, DMF) afforded the per-O-methylated sugars **23** and **24**. Deprotection of the acetal using boron trifluoride diethyl etherate in wet acetonitrile afforded the desired ketoses **18** and **19** in modest yields of 50% (over three steps, Scheme 1). The cyano-function was successfully incorporated into the acetals **16**–**20** by treatment with a mixture of TMS-CN and TMS-OTf using acetonitrile as solvent to yield the *C*-ketosides **25**–**29** in 50–55%[8,9] (Scheme 1). Analysis of the product mixture after a reaction time of 36 hours revealed in all cases the presence of unreacted starting material (approximately 20%). Increasing the reaction time, further addition of reagents (promoter and nucleophile) or changing the solvent (CH_2Cl_2) did not improve the yields. The stereochemistry of the *C*-ketosides **26, 27** and **29** was established by measuring the $^3J_{C,H}$ coupling constants between the cyano-carbon and H-4 as well as between C-2 and H-4 (Table). The observed coupling constants ($^3J_{C\text{-}2,H\text{-}4} < 4$ Hz) and ($^3J_{CN,H\text{-}4} > 7$ Hz) require the axial orientation of the cyano group.[10,11] The absence of NOEs between either H-2a or H-2b and H-7 in **25** and **28** further corroborates the axial orientation of the cyano-function. Finally, hydrogenation of the *C*-ketosides **25**–**29** using Pearlman's catalyst in acidified methanol afforded the GABA derivatives **2** and **4**–**7** in 80–90% yield.[11] In order to explore the effect of the unnatural sugar scaffold (such as metabolic stability and absolute stereochemistry of the scaffold) we also synthesized the L-gluco configured GABA analog **3** following the same protocol as described for the D-gluco compound **2**. This compound was spectroscopically identical to its enantiomer.

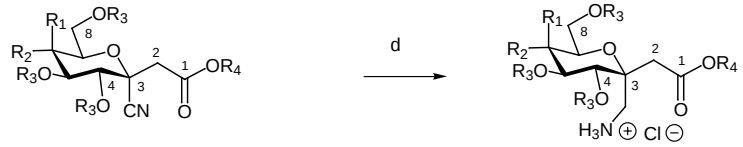
The procedure described here allows the synthesis of novel GABA-analogs presented on a sugar scaffold. Additional derivatization of the polyol-moiety may be used to increase hydrophobicity or modulate the receptor specificity once the biological activity of compounds **2**–**7** have been determined.



8 R_1 = H; R_2 = OBn; R_3 = Bn
9 R_1 = OBn; R_2 = H; R_3 = Bn
10 R_1 = H; R_2 = OMe; R_3 = OMe
11 R_1 = OMe; R_2 = H; R_3 = OMe

12 R_1 = H; R_2 = OBn; R_3 = Bn
13 R_1 = OBn; R_2 = H; R_3 = Bn
14 R_1 = H; R_2 = OMe; R_3 = OMe
15 R_1 = OMe; R_2 = H; R_3 = OMe

16 R_1 = H; R_2 = OBn; R_3 = Bn; R_4 = Me
17 R_1 = OBn; R_2 = H; R_3 = Bn; R_4 = Me
18 R_1 = H; R_2 = OMe; R_3 = OMe; R_4 = Me
19 R_1 = OMe; R_2 = H; R_3 = OMe; R_4 = Me
20 R_1 = OBn; R_2 = H; R_3 = Bn; R_4 = Bn



25 R_1 = H; R_2 = OBn; R_3 = Bn; R_4 = Me
26 R_1 = OBn; R_2 = H; R_3 = Bn; R_4 = Me
27 R_1 = H; R_2 = OMe; R_3 = OMe; R_4 = Me
28 R_1 = OMe; R_2 = H; R_3 = OMe; R_4 = Me
29 R_1 = OBn; R_2 = H; R_3 = Bn; R_4 = Bn

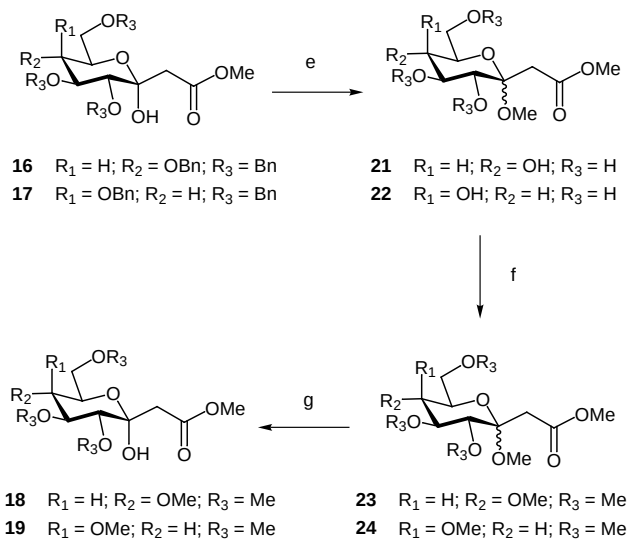
5 R_1 = H; R_2 = OH; R_3 = H; R_4 = Me
6 R_1 = OH; R_2 = H; R_3 = H; R_4 = Me
2 R_1 = H; R_2 = OMe; R_3 = OMe; R_4 = Me
4 R_1 = OMe; R_2 = H; R_3 = OMe; R_4 = Me
7 R_1 = OH; R_2 = H; R_3 = H; R_4 = OH

Scheme 1 Synthesis of GABA-sugars **2** and **4**–**7**; a) $LiCH_2COOtBu$ (4 equiv), THF, –78 °C to r.t., 1 h, 85–95%; b) 50% TFA in CH_2Cl_2 then Cs_2CO_3 (1.3 equiv), MeI or BnBr (3 equiv), DMF, r.t., 1 h, 70% (for **16**, **17** and **18**) and < 15% (for **19** and **20**); c) TMSOTf (3 equiv), TMSCN (5 equiv) CH_3CN, 0 °C to r.t., 36 h, 50–55%; d) $C/Pd(OH)_2$, H_2, MeOH, HCl (48–72 h), 80–90%.

Table Characteristic ^{1}H NMR (600 MHz, $CDCl_3$, 27.0 °C), ^{13}C NMR data (75.5 MHz, $CDCl_3$) and MS (ES) data for compounds **25**–**29**; $^3J_{CH}$ coupling constants are based on HMBC experiments with an error margin of about 10%

Compound	HMBC $^3J_{C\text{-}2;H\text{-}4}$	HMBC $^3J_{CN;H\text{-}4}$	^{13}C NMR (CN)	^{13}C NMR (C-2)	^{1}H NMR (H-4)/($^3J_{H\text{-}4;H\text{-}5}$)	MS (ES) $[M + H]^+$
25	[a,b]	[a,b]	116.2	40.5	3.77/(9.2 Hz)	622.2
26	3.6 Hz	7.3 Hz	116.5	41.2	4.01/(9.7 Hz)	622.2
27	2.0 Hz	8.0 Hz	116.8	40.8	3.22/(9.4 Hz)	318.1
28	[a,b]	[a,b]	116.4	41.2	3.50/(9.8 Hz)	318.1
29	3.8 Hz	8.5 Hz	116.3	41.3	4.03/(9.9 Hz)	698.3

[a] Coupling constants could not be determined due to spectral overlap and/or higher order effects.
[b] No NOE was observed between H-2a/H-2b and H-7.



16 R_1 = H; R_2 = OBn; R_3 = Bn
17 R_1 = OBn; R_2 = H; R_3 = Bn
21 R_1 = H; R_2 = OH; R_3 = H
22 R_1 = OH; R_2 = H; R_3 = H
18 R_1 = H; R_2 = OMe; R_3 = Me
19 R_1 = OMe; R_2 = H; R_3 = Me
23 R_1 = H; R_2 = OMe; R_3 = Me
24 R_1 = OMe; R_2 = H; R_3 = Me

Scheme 2 Improved synthesis of **18** and **19**; e) $BF_3{\cdot}O(Et)_2$, MeOH (10 equiv), CH_3CN, 1 h, then $C/Pd(OH)_2$, H_2, MeOH, 3 h, 95%; f) NaH, MeI, DMF, 55–60%; g) $BF_3{\cdot}O(Et)_2$, wet CH_3CN, quant.

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(8) The preference for the axial orientation of the cyano function in compounds **25**–**29** may be the result of greater thermodynamic stability coupled with kinetically preferred axial attack due to stereoelectronic effects. In all cases small amounts of another material (~5%) having the same molecular ion peaks as compounds **25**–**29** could be isolated. Preliminary NMR-data suggest that this material is identical with the C-3 epimer of compounds **25**–**29**.

(9) Typical procedure for the synthesis of the cyano-compounds **25**–**29**: ketol **16**–**20** (0.1 mmol) was dissolved in acetonitrile (5 mL) and trimethylsilyl-cyanide (0.5 mmol) was added. The mixture was stirred for 5 min before TMS-OTf (0.3 mmol) was added at 0 °C. After 90 min, the ice-bath was removed and the mixture was stirred for an additional 36 h. Aq work up with sodium bicarbonate followed by chromatographic purification afforded the *C*-ketosides **25**–**29** in 50–55% yield.

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(11) Compounds **5** and **6** tend to lactamize slowly in methanolic solution (< 10% over a time periode of 48 h). Compound **7** was hydrogenated in methanol:water (1:1) to prevent acid catalyzed esterfication. Characteristic ^{1}H NMR (600 MHz, 27.0°C and high resolution MS (ES)-data and (HRMS) data for compounds **2** and **4**–**7**. **2**: ^{1}H NMR (600 MHz, 27.0 °C, CD_3OD): δ = 2.70 (d, ^3J = 15.0 Hz, 1 H), 2.73 (d, ^3J = 15.0 Hz, 1 H), 3.10 (dd, ^3J = 9.1 Hz, ^3J = 10.0 Hz, 1 H), 3.34 (d, ^3J~14 Hz, 1 H), 3.37–3.40 (m, 5 H), 3.47 (d, ^3J = 9.1 Hz, 1 H), 3.48–3.50 (m, 4 H), 3.53–3.55 (m, 4 H), 3.57–3.60 (m, 3 H), 3.70 (s, 3 H). HRMS (ES, $[M + H]^+$): *m/z* calcd for 322.18657, found 322.18634. ^{13}C NMR (75 MHz, 25.0 °C, $CDCl_3$): 170.1, 85.1, 83.7, 79.2, 75.6, 73.3, 70.8, 61.2, 60.5, 60.2, 59.4, 51.9, 41.2, 38.7.
4: ^{1}H NMR (600 MHz, 27.0 °C, CD_3OD): δ = 2.67 (d, ^3J = 15.4 Hz, 1 H), 2.71 (d, 1 H, ^3J = 15.4 Hz), 3.67 (d, ^3J = 10.0 Hz, 1 H). ^{13}C NMR (75 MHz, 25.0 °C, $CDCl_3$): δ = 170.8, 82.2, 81.5, 75.8, 74.9, 71.5, 70.7, 61.7, 61.3, 59.4, 57.7, 52.2, 42.5, 38.8, HRMS (ES, $[M + H]^+$): *m/z* calcd for 322.18657, found 322.18629.
5: ^{1}H NMR (600 MHz, 27.0 °C, CD_3OD): δ = 2.56

(d, ^3J = 14.8 Hz, 1 H), 2.63 (d, ^3J = 14.8 Hz, 1 H), 3.06 (dd, ^3J = 2 × 9.3 Hz, 1 H), 3.72 (dd, ^3J = 10.2 Hz, ^3J = 1.5 Hz). ^{13}C NMR (75 MHz, 25.0 °C, CD_3OD): δ = 171.9, 77.1, 76.4 (2 x), 76.1, 71.4, 63.2, 52.5, 42.0, 39.1. HRMS (ES, $[M + H]^+$): *m/z* calcd for 266.12398, found 266.12344.

6: ^{1}H NMR (600 MHz, 27.0 °C, D_2O): δ = 2.78 (d, ^3J = 14.6 Hz, 1 H), 2.84 (d, ^3J = 14.6 Hz, 1 H), 3.50 (s, 2 H). ^{13}C NMR (75 MHz, 25.0 °C, D_2O, ext. acetone): δ = 172.9, 77.0, 74.0, 72.4, 70.6, 69.7, 62.2, 53.5, 42.0, 38.1. HRMS (ES, $[M + H]^+$): *m/z* calcd for 266.12398, found 266.12359.

7: ^{1}H NMR (600 MHz, 27.0 °C, D_2O): δ = 2.66 (d, ^3J = 14.8 Hz, 1 H), 2.92 (d, ^3J = 14.8 Hz, 1 H), 3.44 (d, ^3J = 14.1 Hz, 1 H), 3.47 (d, ^3J = 14.1 Hz, 1 H), 3.78 (dd, ^3J = 10.2 Hz, ^3J = 3.1 Hz, 1 H), 3.83 (d, ^3J = 10.2 Hz, 1 H), 3.96 (d, ^3J = 3.1 Hz, 1 H). HRMS (ES, $[M + H]^+$): *m/z* calcd for 252.10833, found 252.10857.