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AN ADVANTAGEOUS SYNTHESIS OF 5,6,7,8-TETRAHYDROTETRAZOLO[1,5-a]PYRIDINES

by Stefan Vonhoff and Andrea Vasella*

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Abstract: The one-step synthesis of various *O*-benzyl-protected glyconotetrazoles from the corresponding glyconolactams is reported. The method is superior to the previously employed cycloaddition of azidonitriles as it uses readily available starting materials and leads to higher yields.

Introduction. — We and others have shown that the *gluco*-tetrazole **1** [1], its *manno*-, *galacto*- and *rhamno*-analogues **2** [2,3], **4** [4], and **5** [3], and the *N*-acetyl-D-glucosamine-derived tetrazole **3** [4] are inhibitors of retaining β-glycosidases with K_I-values between 0.2 and 200 μM (*Figure 1*). These tetrazoles have been designed as neutral transition-state analogues possessing a half-chair conformation.[2] Unlike the corresponding D-glycono-1,5-lactones the tetrazoles are stable towards hydrolysis over a wide range of pH values.

Key step of previous syntheses of the glyconotetrazoles is an efficient intramolecular 1,3-dipolar cycloaddition of a 5-azido-aldononitrile. However, the syntheses are rather long with overall yields ranging between 17 and 42%. Considering the potential application of glycono-tetrazoles we wished to develop

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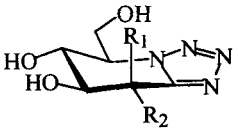
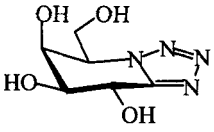
a more convenient synthesis from readily available starting materials. One of the classical syntheses of tetrazoles is based on the reaction of an azide with an imidoyl chloride. Imidoyl chlorides are readily prepared by treating the corresponding amides with phosphorus(V) chloride.[5] We now report the high-yielding transformation of glyconolactams into the corresponding tetrazoles using trifluoromethanesulfonic anhydride (Tf_2O) and sodium azide in acetonitrile.[6]

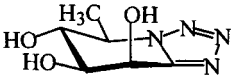
Figure 1



1 $R_1 = H, R_2 = OH$
2 $R_1 = OH, R_2 = H$
3 $R_1 = H, R_2 = NHAc$



4



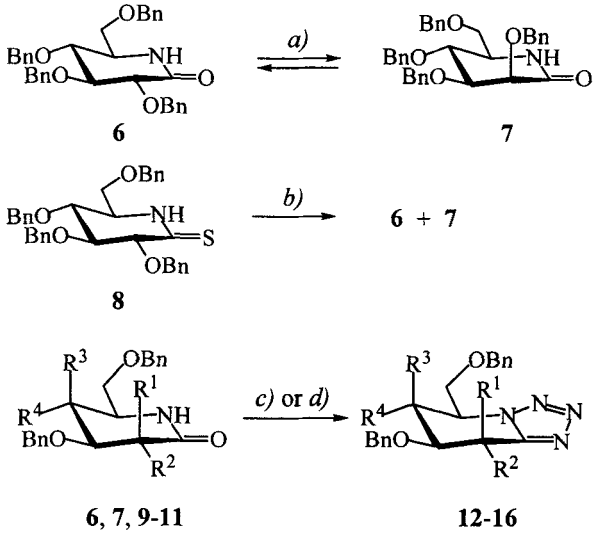
5

Results and Discussion. — The required glyconolactams are readily accessible. The gluconolactam **6** has been prepared from 2,3,4,6-tetra-*O*-benzyl-glucopyranose in 4 steps on a 100 gram scale.[7,8] The D-mannono-δ-lactam **7** [8-10] was obtained by equilibration of the *gluco*-configurated lactam **6** in toluene/piperidine or, more rapidly, in pyridine containing either trifluoroacetic acid (TFA) or pyridinium *p*-toluenesulfonate (PPTS) (*Scheme 1*). This gave a 3:2 mixture (>95%) of the *gluco*- and *manno*-isomers **6** and **7**, easily separated by flash chromatography. The same product distribution was obtained from the mannonolactam **7**. Alternatively, the mannonolactam **7** was obtained by the $Hg(OAc)_2$-assisted epimerising hydrolysis of the *gluco*-configurated thionolactam **8** [11] in aq. THF. This procedure yielded 85% of a 1:1.1 mixture of the glyconolactams **6** and **7**, respectively. Overall the synthesis is less advantageous as it requires the preparation of the thionolactam **8** from the lactam **6**.[11]

The galactonolactam **9** [8,12], the cellobionolactam **10** [13] and the *N*-acetyl-D-glucosamine-derived lactam **11** [14] were prepared in a similar way as the gluconolactam **6**.

Treating the gluconolactam **6** with Tf_2O and sodium azide in CH_3CN gave the *gluco*-tetrazole **12** [1] in 87% yield (*Scheme 1*).[15,16] Similarly, the *manno*- and the

Scheme 1

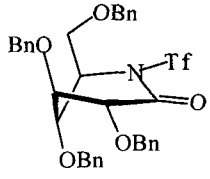


Lactam	R^1	R^2	R^3	R^4	Tetrazole
6	H	OBn	H	OBn	**12** (87%)
7	OBn	H	H	OBn	**13** (77%)
9	H	OBn	OBn	H	**14** (82%)
10	H	OBn	H	β-D-Glc*p*2,3,4,6Bn$_4$	**15** (79%)
11	H	NHAc	H	OBn	**16** (30%)

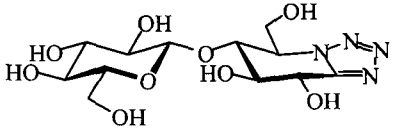
a) Piperidine, toluene, 96 h, Δ or Pyridine, PPTS or TFA, 24 h, Δ; 97% of **6**/**7** 3:2. *b)* $Hg(OAc)_2$, THF:H_2O (95:5), 16 h, 20°; 85% of **6**/**7** 1:1.1. *c)* (for **6**, **7**, **9**, **10**) Tf_2O, NaN_3, CH_3CN, 50–60 mim, –15°. *d)* (for **11**) PCl_5, $TMSN_3$, CH_2Cl_2, 24 h, –15°.

galacto-tetrazoles **13** [2] and **14** [4] were prepared from the glyconolactams **7** and **9** in 77% and 82% yield, respectively. Surprisingly, no reaction was observed when the cellobionolactam **10** was treated with Tf_2O and NaN_3 in CH_3CN unless Tf_2O was added first, and NaN_3 only after 30 min. This difference is best rationalised by assuming a reduced nucleophilicity of the cellobionolactam **10** [17] resulting in a slower formation of an imidoyl triflate as obligatory intermediate. The monosaccharide-derived lactams **6**, **7**, and **9** could conceivably react with Tf_2O or with *in situ* generated TfN_3, while **10** would be inert to TfN_3. No reaction, however, was observed when **6** was treated with TfN_3 in CH_3CN. The sulfonamide **17** was isolated as by-product (6%) of the transformation of the gluconolactam **6** to the tetrazole **12**, and upon treatment of **6** with Tf_2O in the absence of NaN_3 (23%).[18]

Hydrogenolysis of the new tetrazole **15** yielded 91% of the cellobionotetrazole **18**.



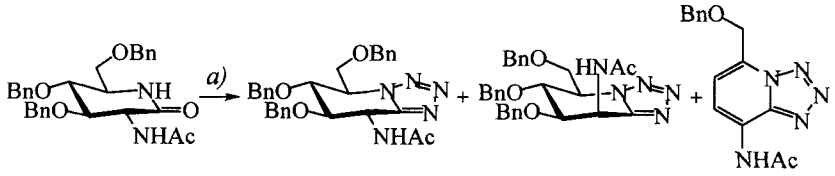
17



18

Attempts to prepare the *N*-acetyl-glucosamine-derived tetrazole **16** [4] from the *N*-acetyl-D-gluconolactam **11** [14] by the Tf_2O/NaN_3 method failed. However, **16** (30%) was obtained along with the known *manno*-epimer **19** [4] (15%) and the aromatised product **20** [4] (40%) when **11** was treated with PCl_5 and $TMSN_3$ in CH_2Cl_2 at 15° (*Scheme 2*).[19] Conducting the reaction at 0° suppressed the formation of **20**, but led to a slow and only partial conversion of **11**.

Scheme 2



11 **16** **19** **20**

a) PCl_5, $TMSN_3$, CH_2Cl_2, 24 h, 15°.

Experimental Part

(*3*S,*4*S,*5*R,*6*R)-3,4,5-Tris(benzyloxy)-6-[(benzyloxy)methyl]piperidin-2-one (7)

a) *From* **6** *with piperidine*: A soln. of **6** [7] (0.3 g, 0.6 mmol) in toluene (5ml) and piperidine (0.1 ml) was heated to reflux. After 96 h the solvent was evaporated *i.v.* and the residue was purified by FC (silica gel; hexane/EtOAc 3:1) to afford **6** (0.18 g, 59%) and **7** (0.11 g, 37%).

b) *From* **6** *with pyridine and PPTS or TFA*: A soln. of **6** (0.3 g, 0.6 mmol) and pyridinium *para*-toluenesulfonate (0.1 g) or trifluoroacetic acid (0.05 ml) in pyridine (5 ml) was heated to reflux for 24 h and worked up as described above to afford **6** (0.17 g, 57%) and **7** (0.11 g, 36%).

c) *From* **8**: A suspension of **8** [11] (0.8 g, 1.4 mmol) and $Hg(OAc)_2$ (0.6 g, 1.9 mmol) in 95% aq. THF (15 ml) was stirred for 16 h at 20°. After filtration through *Celite*, the filtrate was concentrated *i.v.*, the residue was dissolved in CH_2Cl_2 (20 ml) and washed with sat. aq. $NaHCO_3$ soln. Drying of the org. phase ($MgSO_4$), evaporation, and FC (silica gel; hexane/EtOAc 3:1) afforded **6** (0.30 g, 38%) and **7** (0.33 g, 42%).

Data of **6**:[7,8] R_f (hexane/EtOAc 1:1) 0.45.

Data of **7**:[8] R_f (hexane/EtOAc 1:1) 0.40. ^{13}C-NMR ($CDCl_3$, 50 MHz): 54.28 (*d*); 71.15 (*t*); 72.61 (*t*); 72.88 (*t*); 73.09 (*t*); 73.18 (*t*); 74.80 (*d*); 74.87 (*d*); 77.72 (*d*); 127.69–128.39 (several *d*); 137.40 (*s*); 137.53 (*s*); 137.88 (*s*); 137.92 (*s*); 169.56 (*s*). FAB-MS (3-NOBA): 554.2 (8), 538.2 (100, $[M + H]^+$), 90.8 (38).

(*5*R,*6*R,*7*S,*8*S)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydro-tetrazolo[1,5-a]pyridine (12)

At –15°, a suspension of **6** [7] (2.70 g, 5 mmol) and sodium azide (390 mg, 6 mmol)

in anhydrous CH_3CN (50 ml, dist. from CaH_2) was treated with triflic anhydride (1.23 ml, 7.5 mmol). After 50 min, the colourless solution was treated with a sat. aq. $NaHCO_3$ soln. (20 ml), the product extracted with CH_2Cl_2 (2x40 ml) and the org. phase washed with brine and dried ($MgSO_4$). Evaporation gave a pale yellow oil (2.8 g) which was purified by FC (silica gel; hexane/EtOAc 4:1) to afford **12** (2.5 g, 87% after crystallisation from MeOH) and **17** (0.18 g, 6%).

Data of **12**:[1] *Rf* (hexane/EtOAc 2:1) 0.50. M.p. 92–92.5° (oil [1]).

(5R,6R,7S,8R)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydro-tetrazolo[1,5-a]pyridine (13)

At –15°, a suspension of **7** (40 mg, 74 μmol) and sodium azide (5.8 mg, 90 μmol) in anhydrous CH_3CN (1 ml) was treated with triflic anhydride (18 μl, 0.11 mmol). After 50 min, the colourless solution was worked up as described for **12**. Purification by FC (silica gel; hexane/EtOAc 7:3) afforded **13** [2] (32 mg, 77%) as a colourless oil.

(5R,6S,7S,8S)-6,7,8-Tris(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydro-tetrazolo[1,5-a]pyridine (14)

At –15°, a suspension of **9** [12] (270 mg, 0.5 mmol) and sodium azide (39 mg, 0.6 mmol) in anhydrous CH_3CN (5 ml) was treated with triflic anhydride (0.12 ml, 0.75 mmol). After 1 h, the colourless solution was worked up as described for **12**. Purification by FC (silica gel; hexane/EtOAc 4:1) afforded **14** [4] (235 mg, 82%) as a colourless solid.

(5R,6R,7S,8S)-6-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyloxy)-7,8-bis-(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydrotetrazolo[1,5-a]pyridine (15)

At –15°, a suspension of hepta-*O*-benzyl-D-cellobionolactam **10** [13] (0.27 g, 0.28 mmol) in anhydrous CH_3CN (3 ml) was treated with triflic anhydride (0.1 ml, 0.61 mmol). After 30 min, sodium azide (30 mg, 0.46 mmol) was added and stirring was continued at –15° for 50 min. Work-up as described for **12** and HPLC (silica gel; hexane/EtOAc 5:1) afforded **15** (0.22 g, 79%). Colourless oil. *Rf* (hexane/EtOAc 7:3) 0.65. $[\alpha]_D^{25}$ = +27.9 (*c* = 0.5, $CHCl_3$). IR (CH_2Cl_2): 3089*w*, 3033*w*, 2870*m*, 1955*w*, 1876*w*, 1812*w*, 1605*w*, 1496*m*, 1454*m*, 1362*m*, 1071*s* (br.). 1028*m*, 913*m*. ^{1}H-NMR ($CDCl_3$, 500 MHz): 3.36 (*dd*, *J* = 8.9, 7.9, H–C(3')); 3.37 (*ddd*, *J* = 9.4, 4.4, 1.9, H–C(5')); 3.56 (*t*, *J* ≈ 8.5, H–C(2')); 3.58 (*t*, *J* ≈ 8.2, H–C(4')); 3.61 (*dd*, *J* = 10.9, 4.6, H–C(6')); 3.66 (*dd*, *J* = 10.9, 2.2, H'–C(6')); 3.91 (*dd*, *J* = 9.9, 6.5, CH–C(5)); 4.04 (*dd*, *J* = 9.9, 4.1, CH'–C(5)); 4.28 (*dd*, *J* =

5.7, 4.2, 1 H); 4.45–4.51 (*m*, 7 H); 4.54 (*d*, *J* = 11.7, PhC*H*); 4.55 (*d*, *J* = 10.9, PhC*H*); 4.65 (*d*, *J* = 11.6, PhC*H*); 4.64–4.68 (*m*, PHC*H*, H–C(6)); 4.78 (*d*, *J* = 11.0, PhC*H*); 4.79–4.82 (*m*, H–C(2), 2 PhC*H*); 4.87 (*d*, *J* = 11.0, PhC*H*); 4.95 (*d*, *J* = 11.6, PhC*H*)); 6.97–7.04 (*m*, 1 arom. H); 7.17–7.36 (*m*, 34 arom. H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 59.91 (*d*); 67.50 (*t*); 68.87 (*t*); 69.56 (*d*); 72.55 (*d*); 72.61 (*t*); 73.47 (*t*, 3 C); 74.96 (*t*, 2 C); 75.18 (*d*); 75.66 (*t*); 76.96 (*d*); 78.55 (*d*); 81.94 (*d*); 84.61 (*d*); 102.51 (*d*); 127.71–128.64 (several *d*); 137.01 (*s*); 137.27 (*s*, 2 C); 137.40 (*s*); 138.03 (*s*); 138.25 (*s*); 138.54 (*s*); 150.27 (*s*). FAB-MS (3-NOBA): 1085.5 (29), 995.5 (100, $[M + H]^+$), 887.4 (63), 563.2 (33), 473.2 (21), 91.1 (100). Anal. calc. for $C_{61}H_{62}N_4O_9$ (995.18): C 73.62, H 6.28, N 5.63; found: C 73.35, H 6.30, N 5.68.

(5R,6R,7R,8S)-8-Acetamido-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydrotetrazolo[1,5-a]pyridine (16), (5R,6R,7R,8R)-8-acetamido-6,7-bis-(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydrotetrazolo[1,5-a]pyridine (19) and 8-acetamido-5-[(benzyloxy)methyl]tetrazolo[1,5-a]pyridine (20)

At 15°, a soln. of **11** [14] (0.25 g, 0.5 mmol) in anhydrous CH_2Cl_2 (5 ml, dist. from CaH_2) was treated with PCl_5 (0.11 g, 0.55 mmol) and trimethylsilyl azide (0.5 ml, 3.8 mmol). After 24 h at 15°, the mixture was diluted with CH_2Cl_2 (10 ml) washed with a sat. aq. $NaHCO_3$ soln. (20 ml), and dried ($MgSO_4$). Evaporation gave a pale yellow oil (0.25 g) which was purified by FC (silica gel; hexane/EtOAc 1:1 → 1:2) to afford **16** (80 mg, 30%), **19** (38 mg, 15%) and **20** (60 mg, 40%).

Data of **16**:[2] R_f (hexane/EtOAc 1:4) 0.20.

Data of **19**:[2] R_f (hexane/EtOAc 1:4) 0.25.

Data of **20**:[2] R_f (hexane/EtOAc 1:4) 0.60. ^{13}C-NMR ($CDCl_3$, 200 MHz): 24.59 (*q*); 65.60 (*t*); 73.69 (*t*); 115.94 (*d*); 117.37 (*d*); 125.68 (*s*); 128.00 (*d*, 2 C); 128.28 (*d*); 128.70 (*d*, 2 C); 130.45 (*s*); 137.02 (*s*); 143.14 (*s*); 169.55 (*s*).

(3S,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-[(benzyloxy)methyl]-1-(trifluoromethyl-sulfonyl)piperidin-2-one (17)

At –15°, a suspension of **6** (0.13 g, 0.24 mmol) in anhydrous CH_3CN (4 ml) was treated with triflic anhydride (60 µl, 0.37 mmol). After 1 h at 0°, the pale yellow solution was worked up as described for **12**. Purification by FC (silica gel; hexane/EtOAc 9:1) afforded **6** (92 mg, 71%) and **17** (32 mg, 23%). R_f (hexane/EtOAc 2:1) 0.85. Pale yellow oil. IR (CH_2Cl_2): 3033*m*, 2871*m*, 1755*s*,

1576*m*, 1497*m*, 1455*s*, 1406*s*, 1357*s*, 1207*s*, 1094*s*, 610*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.65 (*dd*, *J* = 9.7, 4.4, CH–C(6)); 3.78 (*dd*, *J* = 9.7, 7.8, CH'–C(6)); 3.90 (*ddd*, *J* = 7.2, 2.5, 1.6, H–C(4)); 3.98 (*t*, *J* ≈ 2.7, H–C(5)); 4.39 (*d*, *J* = 7.2, H–C(3)); 4.45–4.57 (*m*, 7 H); 4.59 (*d*, *J* = 11.5, PhC*H*); 4.99 (*d*, *J* = 11.2, PhC*H*); 7.20–7.40 (*m*, 20 arom. H). ^{1}H-NMR (C_6D_6, 300 MHz): 3.47 (*dd*, *J* = 9.7, 5.0, CH–C(6)); 3.55 (*dd*, *J* = 9.4, 8.7, CH'–C(6)); 3.86–3.89 (*m*, 2 H); 4.07 (*s*, 2 H); 4.12 (*m*, 2 H); 4.23–4.30 (*m*, 2 H); 4.32 (*d*, *J* = 11.5, PhC*H*); 4.33 (*d*, *J* = 11.5, PhC*H*); 4.66 (*m*, H–C(6)); 4.96 (*d*, *J* = 11.2, PhC*H*); 7.00–7.33 (*m*, 20 arom. H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 62.00 (*d*); 69.08 (*t*); 71.60 (*t*); 73.09 (*t*); 73.50 (*t*); 74.14 (*t*); 74.58 (*d*); 80.16 (*d*); 81.99 (*d*); 127.85–128.68 (several *d*); 136.80 (*s*); 137.10 (*s*); 137.20 (*s*); 137.40 (*s*); 169.48 (*s*). ^{19}F-NMR ($CDCl_3$, 282 MHz): –71.43.

(5R,6R,7S,8S)-6-(β-D-Glucopyranosyloxy)-5-hydroxymethyl-5,6,7,8-tetrahydro-tetrazolo[1,5-a]pyridine-7,8-diol (18)

A soln. of **15** (70 mg, 70 μmol) in MeOH (10 ml) containing AcOH (0.05 ml) was hydrogenated for 48 h at 1 atm and at 22° in the presence of 10% Pd/C (40 mg). The suspension was diluted with MeOH and filtered. The filter paper was washed twice with MeOH and the filtrate was evaporated and dried *i.v.* Crystallisation from methanol gave **20** (23 mg, 91%). Colourless solid. *Rf* (EtOAc/MeOH/H_2O 4:2:1) 0.75. M.p. 230–235° (dec.). IR (KBr): 3342*s* (br.), 2921*m*, 1569*m*, 1465*m*, 1409*m*, 1371*m*, 1252*m*, 1165*m*, 1085*s*, 1024*m*, 906*w*, 894*w*, 849*m*, 595*m*. ^{1}H-NMR (CD_3OD, 500 MHz): 3.29 (*dd*, *J* = 9.1, 7.9, 1 H); 3.31–3.41 (*m*, 4 H); 3.70 (*dd*, *J* = 11.9, 5.3, H–C(6')); 3.89 (*dd*, *J* = 12.0, 2.1, H'–C(6')); 4.01 (*dd*, *J* = 8.9, 7.7, 1 H); 4.31 (*dd*, *J* = 12.2, 2.4, CH–C(5)); 4.39 (*dd*, *J* = 8.9, 8.7, 1 H); 4.44 (*dd*, *J* = 12.2, 3.1, CH'–C(5)); 4.56 (*d*, *J* = 7.8, H–C(1')); 4.55-4.59 (*m*, H–C(5)). ^{13}C-NMR (CD_3OD, 50 MHz): 59.30 (*t*); 62.41 (*t*); 63.26 (*d*); 66.88 (*d*); 71.23 (*d*); 74.40 (*d*); 74.78 (*d*); 77.23 (*d*); 77.74 (*d*); 78.34 (*d*); 104.78 (*d*); 156.08 (*s*). FAB-MS (3-NOBA): 483.3 (16), 461.3 (24), 387.2 (15), 365.2 (26, [*M* + H]$^+$).

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12. Heightman, T.D., Galley, C., Vasella, A. *unpublished results*.
13. Pipelier, M. and Vasella, A. *unpublished results*.
14. Granier, T., Vasella, A. *unpublished results*.
15. Known compounds were identified on the basis of their reported physical and spectroscopic data.
16. Contrary to the literature procedure the addition of Hünig's base did not improve the yield nor did it accelerate the reaction.
17. Cf. the reduced reactivity of di- and oligosaccharide-derived glycosyl donors; Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155.
18. The structure of the sulfonamide **17** is evidenced by the strong IR absorption at 1755 cm^{-1} (**6**, 1685 cm^{-1}) and the ^{19}F-NMR signal for a CF_3 group at –71.4 ppm. The ^{1}H-NMR signals for H–C(3) at 4.39 ppm (**6**, 4.00 ppm) and H–C(6) at ca. 4.50 ppm (**6**, 3.55 ppm) are shifted to lower-field; the J values $J_{4,5} = J_{5,6} \approx 2.7$ Hz and the long-range coupling (W coupling) between H–C(4) and H–C(6) are best rationalised by assuming a $^4H_5$ conformation; cf. Glänzer, B.I., Györgydeák, Z., Bernet, B., Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 343.

19. Meanwell, N.A., Hewawasam, P., Thomas, J.A., Wright, J.J.K., Russell, J.W., Gamberdella, M., Goldenberg, H.J., Seiler, S.M. and Zavoico, G.B. *J. Med. Chem.* **1993**, *36*, 3251.

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