8: A solid sample of **2** (72 mg, 0.10 mmol) was mixed with $[HNMe_2Ph][B(C_6F_5)_4]$ (80 mg, 0.10 mmol) and treated at $-80\,^{\circ}C$ with of CD_2Cl_2 (2 mL). According to the NMR spectra, the generated yellow solution contained exclusively complex **8**. ^1H NMR (200 MHz, CD_2Cl_2, $-60\,^{\circ}C$): $\delta = 7.32-6.97$ (m, 5H, Ph-H), 3.0 (br s, 6H, NCH_3), 2.39–1.24 (m, 69H, PCy_3 and $RuCCH_3$), -6.33 (t, $^2J(P,H) = 15$ Hz, 1H, RuH); ^{31}P NMR (162 MHz, CD_2Cl_2, $-70\,^{\circ}C$): $\delta = 56.6$ (s); ^{13}C NMR (100.6 MHz, CD_2Cl_2, $-70\,^{\circ}C$): $\delta = 311.9$ (br s, Ru*C*CH_3), 147.4 (d, $^1J(C,F) = 239$ Hz, C_6F_5), 137.7 (d, $^1J(C,F) = 245$ Hz, C_6F_5), 135.7 (d, $^1J(C,F) = 247$ Hz, C_6F_5), 129.0 (s, NPh), 123.2, 118.1 and 113.4 (all br s, NPh), 41.5 (br s, NCH_3), 40.2 (s, Ru*C*CH_3), 34.0 (vt, $N = 23$ Hz, C_1 of PCy_3), 30.6, 28.9, 26.7, 26.4, and 25.3 (all s, PCy_3).

9: Analogous to the synthesis of **8**, compound **9** was prepared in quantitative yield from **2** (20 mg, 0.028 mmol) and $[H(OEt_2)_2][B\{C_6H_3(CF_3)_2\}_4]$ (28 mg, 0.028 mmol) in CD_2Cl_2 and characterized spectroscopically at room temperature. ^1H NMR (200 MHz, CD_2Cl_2): $\delta = 7.75$, 7.59 (both m, 12H, $B\{C_6H_3(CF_3)_2\}_4$), 3.36 (q, $^3J(H,H) = 6.6$ Hz, 8H, OCH_2CH_3), 2.7–1.2 (m, 69H, PCy_3 and $RuCCH_3$), 1.19 (t, $^3J(H,H) = 6.6$ Hz, 12H, OCH_2CH_3), -6.57 (t, $^2J(P,H) = 15$ Hz, 1H, RuH); ^{31}P NMR (81 MHz, CD_2Cl_2): $\delta = 57.2$ (s).

Selective ROM of cyclopentene with methyl acrylate: A solution of **2** (56 mg, 0.077 mmol) in a mixture of CH_2Cl_2 (2 mL), Et_2O (2 mL), and 0.5 mL of a 1.6 M solution of HBF_4 in Et_2O was added to a mixture of methyl acrylate (50 mL, 0.552 mol) and cyclopentene (4 mL, 0.045 mol) at room temperature. After the solution was stirred for 2 h at room temperature, the solvent and excess of substrate were distilled off at normal pressure, the remaining residue was treated with pentane (10 mL), and upon addition of Et_2O (60 mL) the solution was filtered through aluminum oxide (neutral, activity grade III). After removal of the solvent, a colorless liquid (2.5 g) was obtained, the composition of which was investigated by GC/MS. The liquid contained the first members of a homologous series of long-chain multiply unsaturated esters $C_7H_{11}CO_2CH_3$, $C_{12}H_{19}CO_2CH_3$, and $C_{17}C_{27}CO_2CH_3$ in ratios of 50, 40, and 10%.

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[1] a) S. T. Nguyen, L. K. Johnson, R. H. Grubbs, *J. Am. Chem. Soc.* **1992**, *114*, 3974–3975; b) G. C. Fu, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1993**, *115*, 9856–9857; c) S. T. Nguyen, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1993**, *115*, 9858–9859; d) P. Schwab, M. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem.* **1995**, *107*, 2179–2181; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039–2041; e) P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
[2] Reviews: a) M. Schuster, S. Blechert, *Angew. Chem.* **1997**, *109*, 2124–2144; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036–2055; b) A. S. K. Hashmi, *J. Prakt. Chem.* **1997**, *339*, 195–199; c) A. Fürstner, *Top. Catal.* **1997**, *4*, 285–299.
[3] Representative examples: a) R. R. Schrock, *Pure Appl. Chem.* **1994**, *66*, 1447–1454; b) J. H. Oskam, R. R. Schrock, *J. Am. Chem. Soc.* **1993**, *115*, 11831–11845; c) R. R. Schrock, *Acc. Chem. Res.* **1990**, *23*, 158–165.
[4] a) M. B. France, R. H. Grubbs, D. V. McGrath, R. A. Paciello, *Macromolecules* **1993**, *26*, 4742–4747; b) M. A. Hillmyer, S. T. Nguyen, R. H. Grubbs, *Macromolecules* **1996**, *30*, 718–721; c) J. C. Marmo, K. B. Wagener, *Macromolecules* **1995**, *28*, 2602–2606.
[5] a) M. F. Schneider, N. L. Lucas, J. Velder, S. Blechert, *Angew. Chem.* **1997**, *109*, 257–259; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 257–259; b) W. E. Crowe, Z. J. Zhang, *J. Am. Chem. Soc.* **1993**, *115*, 10998–10999; c) W. E. Crowe, D. R. Goldberg, *J. Am. Chem. Soc.* **1995**, *117*, 5162–5163; d) W. E. Crowe, D. R. Goldberg, Z. J. Zhang, *Tetrahedron Lett.* **1996**, *37*, 2117–2120; e) P. O. Nubel, H. B. Yokelson, R. B. Moreland, V. Bagheri, S. A. Cohen, W. G. Bouslog, R. T. Behrends, J. P. Nelson (Amoco Corp.), EP-B 626402, **1994** [*Chem. Abstr.* **1995**, *123*, 10201p].
[6] *Kationische Rutheniumkomplexe, Verfahren zu ihrer Herstellung und ihre Verwendung*, BASF AG, NAE19980187.
[7] a) J. Wolf, W. Stüer, C. Grünwald, H. Werner, P. Schwab, M. Schulz, *Angew. Chem.* **1998**, *110*, 1165–1167; *Angew. Chem. Int. Ed.* **1998**, *37*, 1124–1126; b) *Verfahren zur Herstellung von Rutheniumkomplexen*, BASF AG, O.Z. 0050/48279.
[8] M. L. Christ, S. Sabo-Etienne, B. Chaudret, *Organometallics* **1994**, *13*, 3800–3804.
[9] M. Oliván, O. Eisenstein, K. G. Caulton, *Organometallics* **1997**, *16*, 2227–2229.
[10] D. Huang, W. E. Streib, O. Eisenstein, K. G. Caulton, *Angew. Chem.* **1997**, *109*, 2096–2098; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2004–2006.
[11] M. Brookhart, B. Grant, A. F. Volpe, *Organometallics* **1992**, *11*, 3920–3922.
[12] a) M. Bourgault, A. Castillo, M. A. Esteruelas, E. Oñate, N. Ruiz, *Organometallics* **1997**, *16*, 636–645; b) J. Espuelas, M. A. Esteruelas, F. J. Lahoz, L. A. Oro, N. Ruiz, *J. Am. Chem. Soc.* **1993**, *115*, 4683–4689; c) G. J. Spivak, J. N. Coalter, M. Oliván, O. Eisenstein, K. G. Caulton, *Organometallics* **1998**, *17*, 999–1001.
[13] Dr. A. Schäfer, BASF AG, unpublished results.
[14] W. Stüer, Dissertation, Universität Würzburg, to be submitted, **1998**.
[15] Some examples of alkyne metathesis reactions with a carbyne- or alkylidynemetal complex as catalyst are known: a) R. R. Schrock, *Acc. Chem. Res.* **1986**, *19*, 342–348; b) R. R. Schrock, *Polyhedron* **1995**, *14*, 3177–3195; c) K. Weiss in *Carbyne Complexes* (Eds.: H. Fischer, P. Hofmann, F. R. Kreissl, R. R. Schrock, U. Schubert, K. Weiss), VCH, Weinheim, **1988**, pp. 205–228.
[16] a) K. Weiss, A. Michel, E.-M. Auth, U. H. F. Bunz, T. Mangel, K. Müllen, *Angew. Chem.* **1997**, *109*, 522–525; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 506–509; b) A. Fürstner, G. Seidel, *Angew. Chem.* **1998**, *110*, 1758–1760; *Angew. Chem. Int. Ed.* **1998**, *37*, 1734–1736.
[17] M. A. Gallop, W. R. Roper, *Adv. Organomet. Chem.* **1986**, *25*, 121–198.
[18] a) W. A. Herrmann, W. C. Schattenmann, O. Nuyken, S. C. Glander, *Angew. Chem.* **1996**, *108*, 1169–1170; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1087–1088; b) A. Fürstner, M. Picquet, C. Bruneau, P. H. Dixneuf, *Chem. Commun.* **1998**, 1315–1316.

Rapid Assembly of Oligosaccharides: Total Synthesis of a Glycosylphosphatidylinositol Anchor of *Trypanosoma brucei***

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Glycoproteins and glycolipids are major components of the outer surface of eukaryotic cells and play a vital role in fundamental biological processes such as viral, bacterial, and parasitic infections, immune defence, and inflammation.[1] Intensive research into the biological role of carbohydrates has led to an increased need for the synthesis of natural and modified glycoconjugates. Although remarkable progress has been made in the field of oligosaccharide synthesis,[2] further innovations are still required since the synthesis of complex oligosaccharides remains a highly specialized and time con-

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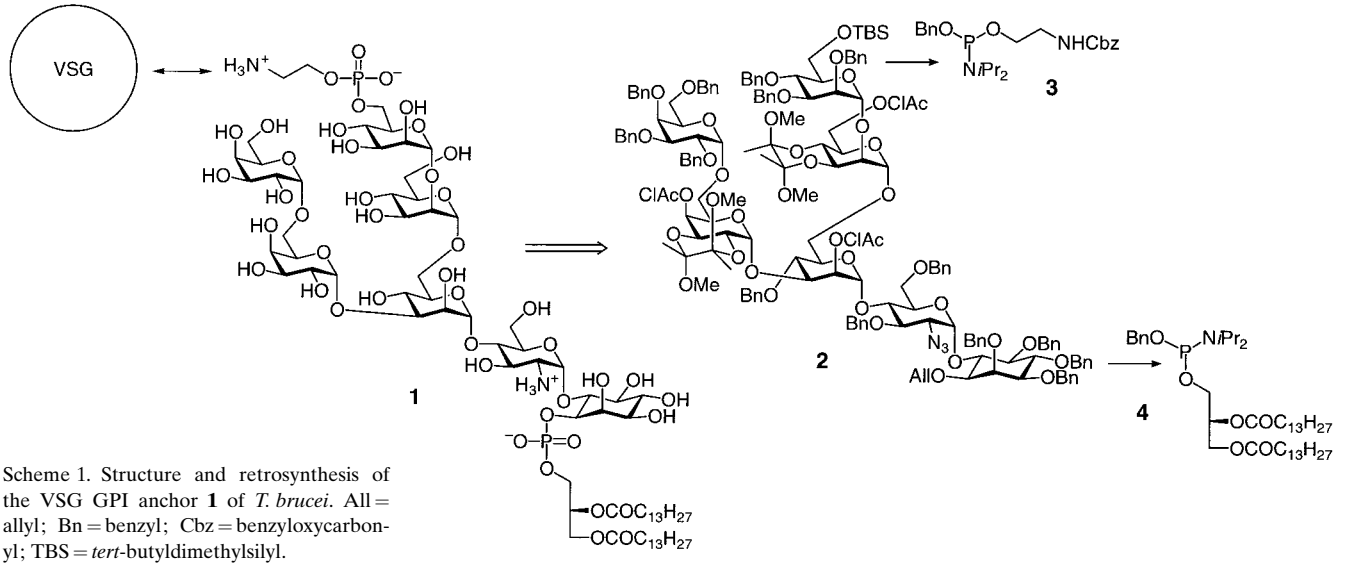


Scheme 1. Structure and retrosynthesis of the VSG GPI anchor **1** of *T. brucei*. All = allyl; Bn = benzyl; Cbz = benzyloxycarbonyl; TBS = *tert*-butyldimethylsilyl.

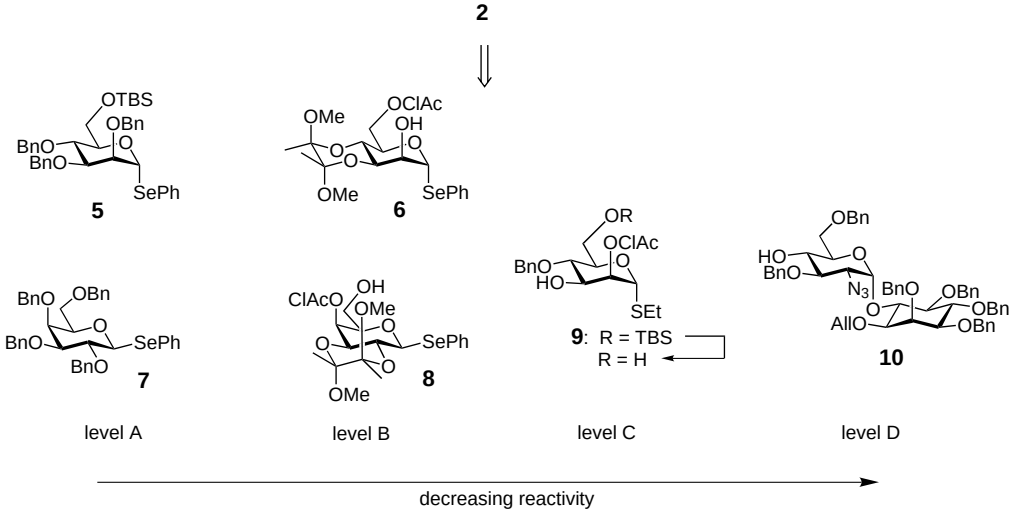
suming task relative to the synthesis of peptides or oligonucleotides. The 1,2-diacetal methodology recently developed in our laboratory can in many cases greatly simplify the assembly of oligosaccharides by considerably reducing the number of steps required.[3]

The African parasite *Trypanosoma brucei* is the cause of human sleeping sickness and a similar disease in domestic animals. As such it represents a serious problem in the tropical areas of Africa.[4] The parasite is able to survive in the host's bloodstream by virtue of a dense cell-surface coat that consists of variant surface glycoproteins (VSG) anchored to glycosylphosphatidylinositol (GPI) groups.[5] GPI anchors not only exist in *T. brucei* but are ubiquitous in eukaryotic cells. Their principal function is to attach proteins to the plasma membrane. Various proteins have been found to be GPI anchored and their role in biological recognition processes has attracted a great deal of attention.[6]

The structures of VSG GPI anchors of *T. brucei* were elucidated in 1988 (Scheme 1).[7] Since then the structures of other protein GPI anchors have been determined and the trimannose-glucoseamine-inositol backbone has been shown to be conserved in every known case. The biosynthetic pathways of GPI anchors have partly been elucidated and have given rise to some potential targets for chemotherapeutic agents.[8] Rapid synthetic access to VSG GPI anchors of *T. brucei*, other GPI anchors, and derivatives would aid investigations into the biosynthetic pathways of these molecules and into their role as protein anchors. Three total syntheses of GPI anchors have previously been reported[9] along with the syntheses of various partial structures.[10]

We report here a highly efficient and versatile synthesis of GPI anchor **1** by employing methods developed by our group.

A highly convergent strategy was chosen to allow the synthesis of various derivatives and to minimize the number of manipulations on the growing oligosaccharide. The GPI anchor **1** arises from the carbohydrate core **2** and the two phosphate linkers **3** and **4** (Scheme 1). The core **2** may be derived from six building blocks **5**–**10** (Scheme 2). We anticipated that the reactivity of the glycosyl donors **5**–**9** could be tuned by the use of 2,3-butanediacetal (BDA) protecting groups[11] and appropriate anomeric leaving groups to give four levels of descending reactivity (A, B, C, and D). This would allow assembly of the carbohydrate core in only six steps. The phosphoramidites **3** and **4** are easily accessible: **3** is available from literature methods,[9a] while **4** can be prepared by a desymmetrization of glycerol with chiral bis(dihyropyran) **11**, which was recently reported by our group (Scheme 3).[12] The pseudodisaccharide **10** should be accessible from suitably protected monomers: a glycosyl donor and a D-*myo*-inositol.



Scheme 2. Disconnection of **2** to building blocks **5**–**10**, which are grouped in four levels of reactivity. Level A: most reactive glycosyl donor; level B: the diacetal ring reduces donor reactivity; level C: change of Se to S reduces reactivity; level D: inert.

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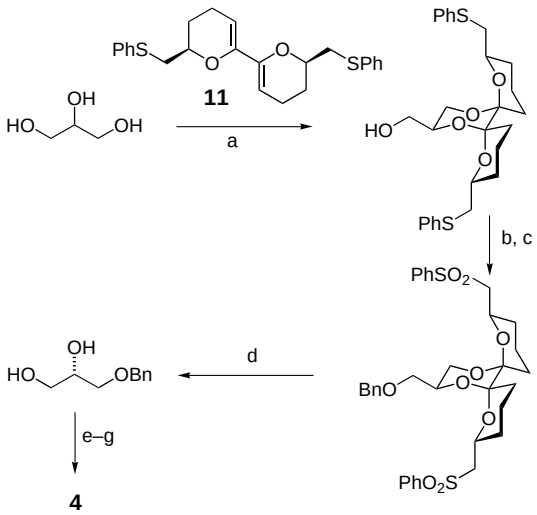
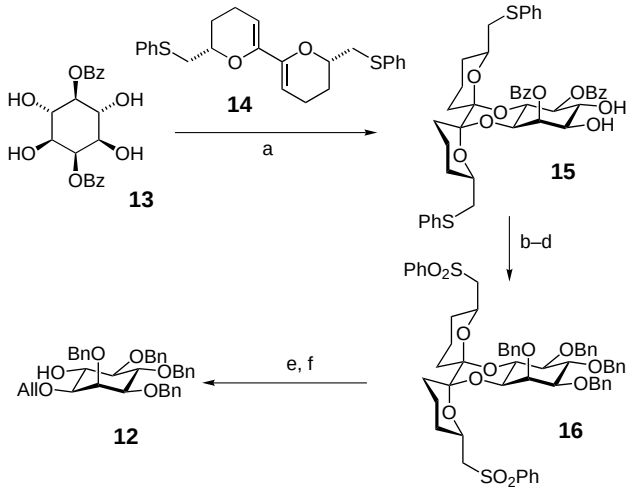


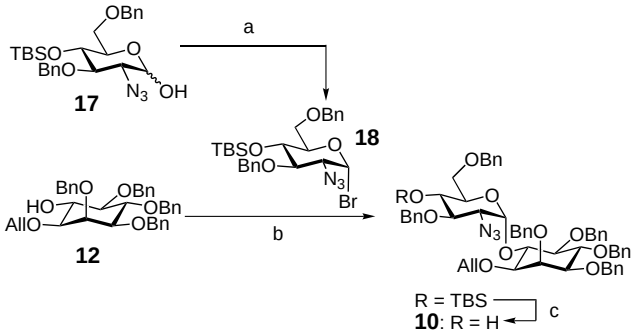
Scheme 3. Desymmetrization of glycerol. a) **11**, (±)-camphorsulfonic acid (CSA), $CHCl_3$, △, 88% (*ee* ≥ 98%); b) BnBr, NaH, DMF, 90%; c) mCPBA, CH_2Cl_2, 98%; d) $LiN(TMS)_2$, THF, 0 °C, 93%; v) $CH_3(CH_2)_{12}COCl$, pyridine, 84%; e) 10% Pd/C, H_2, EtOAc, 80%; f) $BnOP(NiPr_2)_2$, tetrazole, CH_2Cl_2, 85%. mCPBA = *meta*-chloroperbenzoic acid; TMS = trimethylsilyl.

The desymmetrization of *myo*-inositol has remained a problem despite the tremendous interest in the biological role of inositolphosphates as secondary messengers.[13] Most syntheses of *myo*-inositols include a chiral resolution or a low-yielding desymmetrization step.[14] We have reported a route to chiral L-*myo*-inositols that employs a chiral bis(dihydropyran).[12] The same strategy was used here to provide access to D-*myo*-inositol **12** (Scheme 4). One of the two enantiotopic



Scheme 4. Desymmetrization of *myo*-inositol **13**. a) **14**, $PPh_3 \cdot HBr$, $CHCl_3$, △, 71% (*ee* ≥ 98%); b) K_2CO_3 (aq), MeOH; c) NaH, BnBr, DMF, 56% over two steps; d) mCPBA, CH_2Cl_2, 93%; e) $LiN(TMS)_2$, THF, 0 °C, 93%; f) $Bu_2Sn(OMe)_2$, toluene, △, then allylbromide, tetrabutylammonium iodide (TBAI), 65%.

diol pairs in **13**[15] was selectively protected with chiral bis(dihyrdopyran) **14**[16] to give exclusively the dispiroketal **15** in 71% yield (*ee* ≥ 98%). Debenzoylation, per-O-benzylation, and oxidation led to sulfone **16**. Removal of the dispiroketal moiety with lithium hexamethyldisilazide (LHMDS) proceeded in excellent yield (93%). Selective allylation *via* the tin acetal furnished the desired alcohol **12** along with a minor amount of the undesired 6-O-allyl protected isomer, which could be isolated and recycled. The known glucose azide **17**[10c] was converted into the bromide **18** with thionylbromide and imidazole (Scheme 5).[17] Crude **18** was then coupled to inositol **12** using Leumieux's inversion protocol[18] to give the desired α-linked product with excellent selectivity.[19] Desilylation with tetrabutylammonium fluoride (TBAF) furnished pseudodisaccharide **10**.

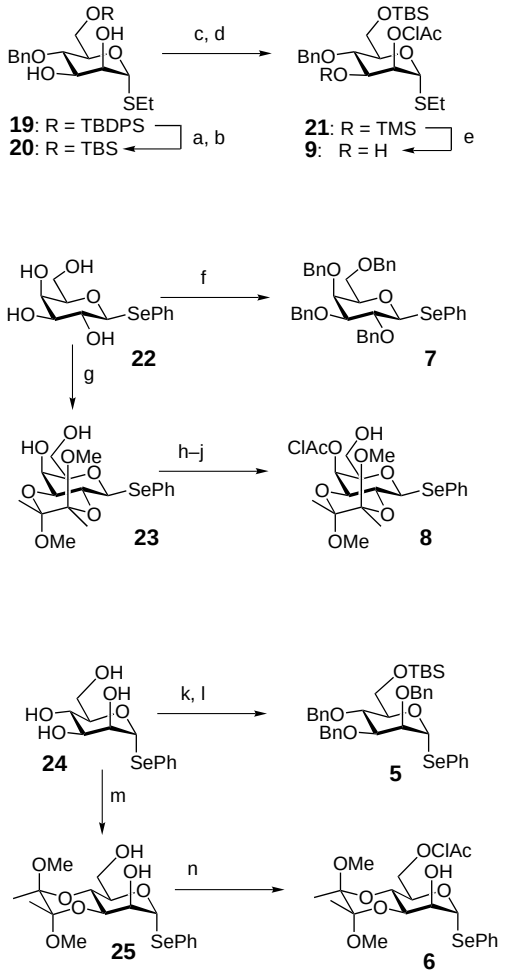


Scheme 5. Synthesis of pseudodisaccharide **10**. a) $SOBr_2$, imidazole, THF; b) **18** (1.5 equiv), TBAI, CH_2Cl_2, molecular sieves (4 Å), 3 d, 65%; c) TBAF, THF, 95%.

The central building block **9** was synthesized from the known mannoside **19**[10c] (Scheme 6). Treatment of **20** with trimethylsilyl chloride (TMSCl) and triethylamine (TEA) in CH_2Cl_2 led to selective silylation of the equatorial alcohol and was followed by acylation to give the fully protected mannoside **21** in 79% yield. Other attempts to distinguish between the 2 and 3-hydroxyl groups in **20**, such as by acylation under phase-transfer conditions, failed. The trimethylsilyl group was removed with one equivalent of aqueous HF to give acceptor **9**.[20]

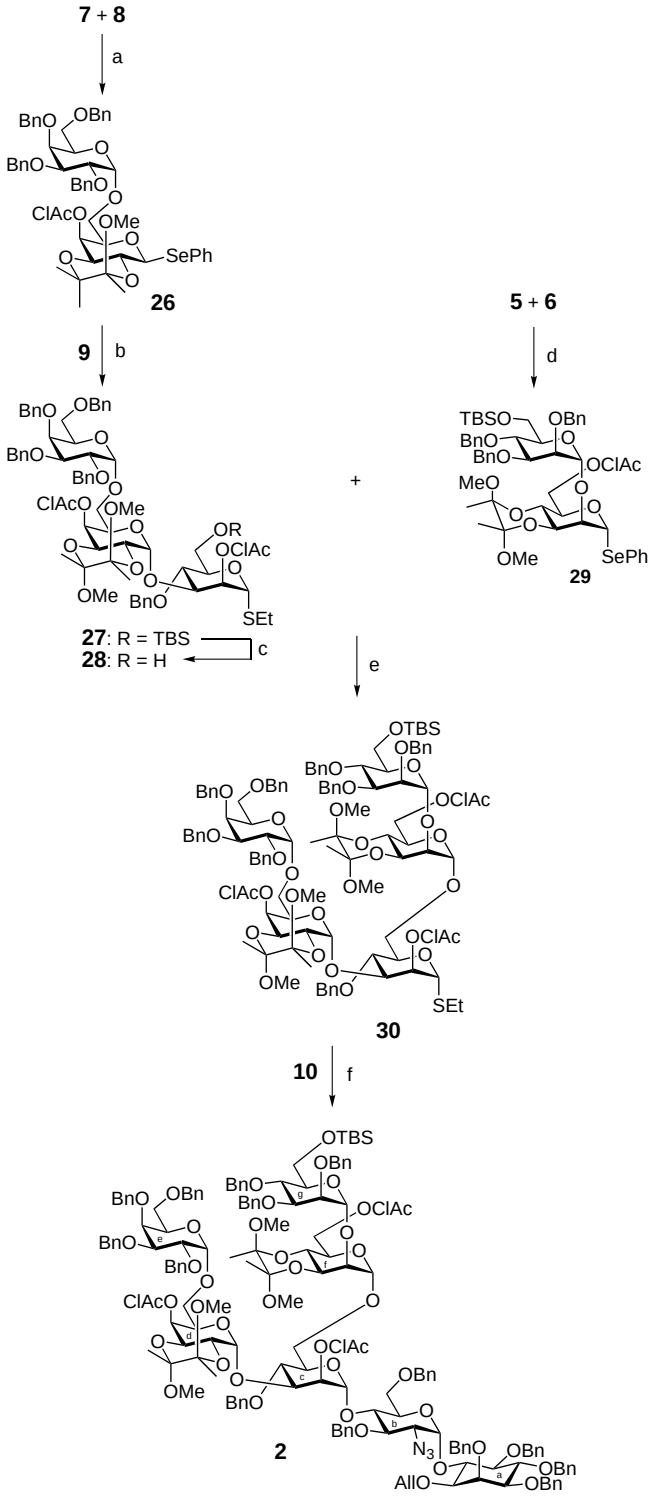
The galactosides **7** and **8** were synthesized from the common, readily available starting material **22**[21] (Scheme 6). The *trans*-diol of **22** was protected in one step to give diacetal **23** in 67% yield, subsequent selective silylation, acylation, and desilylation furnished acceptor **8**. Per-O-benzylation of **22** gave donor **7**. The mannosides **5** and **6** were accessible in a similar fashion from the common readily available selenide **24**.[3c] Selective protection of the *trans*-diol in **24** afforded the diacetal **25** in 80% yield. Acylation of the primary alcohol *via* the tin acetal furnished the desired acceptor **6**. Silylation of the primary hydroxyl group in **24** followed by per-O-benzylation yielded the required donor **5**.

With all the building blocks in hand the carbohydrate core **2** was assembled (Scheme 7). Galactosyl donor **7** was activated with *N*-iodosuccinimide (NIS) and catalytic amounts of triflic acid (TfOH) or trimethylsilyltriflate (TMSOTf)[22] in the presence of acceptor **8** to furnish the desired α-linked digalactoside **26** in 75% yield along with a minor amount of the separable β-linked isomer (14%). The deactivating effect of the BDA and the chloroacetate in acceptor **8** allowed selective activation of donor **7** and prevented any homocoupling. Digalactoside **26** was then used as a donor, by activation with methyl triflate (MeOTf),[23] and treated with the manno-



Scheme 6. Synthesis of building blocks **5**–**9**. a) TBAF, THF; b) TBSCl, imidazole, THF, 91% over two steps; c) TMSCl, TEA, CH_2Cl_2; d) $(ClAc)_2O$, pyridine, CH_2Cl_2, 0°C, 79% over two steps; e) 48% HF (aq), CH_3CN, 95%; f) BnBr, NaH, DMF, 75%; g) butanedione, $HC(OCH_3)_3$, CSA, MeOH, △, 67%; h) TBSCl, imidazole, THF; i) $(ClAc)_2O$, pyridine, CH_2Cl_2, 0°C, 80% over two steps; j) 48% HF (aq), CH_3CN, 95%; k) TBSCl, imidazole, THF, 91%; l) BnBr, NaH, DMF, 82%; m) butanedione, $HC(OCH_3)_3$, CSA, MeOH, △, 80%; n) $(Bu_3Sn)_2O$, toluene, △, then $(ClAc)_2O$, CH_2Cl_2, O°C, 95%. TBDPS = *tert*-butyldiphenylsilyl; TEA = triethylamine.

side **9** to afford trisaccharide **27** in 75% yield. In this case it is the higher reactivity of the selenophenyl leaving group in **26** that allows selective activation in the presence of the thioethyl group of acceptor **9**. The silyl ether was then removed with HF to allow for further glycosidation on alcohol **28**. Dimannoside **29** was obtained from building blocks **5** and **6** as a single anomer in excellent yield upon NIS/TMSOTf activation. As in the above galactoside case, the BDA and chloroacetate group tuned the reactivity of acceptor **6** and prevented homocoupling. The trisaccharide **28** was 6-O-glycosidated with selenophenyl donor **29** under MeOTf conditions to produce the pentasaccharide **30** in 75% yield. An excess of donor **29** (four equivalents), which was fully recovered, was used to supress formation of the anhydrosugar of **28**, which arises from intramolecular glycosidation of the 6-hydroxyl group in **28**. Activation of the thioethyl donor **30** with NIS/TfOH led to glycosidation of the inositol fragment **10** and furnished the heptasaccharide core **2** in 51% yield.



Scheme 7. Assembly of the carbohydrate core **2**. a) NIS (1 equiv), TMSOTf (cat.), Et_2O/CH_2Cl_2 (6/1), molecular sieves (4 Å), 75%; b) **9** (1 equiv), TfOMe (5 equiv), Et_2O, molecular sieves (4 Å), 75%; c) 48% HF (aq), CH_3CN, 89%; d) NIS (1 equiv), TMSOTf (cat.), Et_2O/CH_2Cl_2 (1/1), molecular sieves (4 Å), 87%; e) **29** (5 equiv), MeOTf (5 equiv), CH_2Cl_2, molecular sieves (4 Å), 12 h, 75%; f) **30** (1.4 equiv), NIS, TfOH (cat.), Et_2O/CH_2Cl_2 (3/1), molecular sieves (4 Å), 51%.

The carbohydrate core **2** was elaborated to the fully protected GPI anchor by well established phosphoramidite chemistry, which had been successfully applied in other GPI

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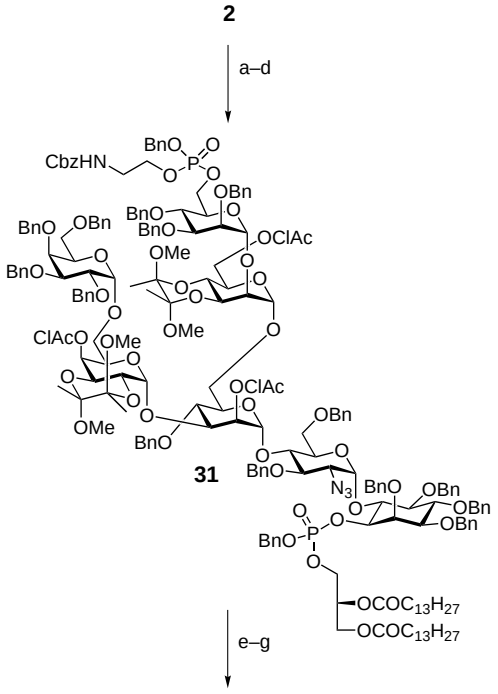
syntheses (Scheme 8).[9] The ethanolamine linker was introduced after desilylation by phosphorylation with phosphoramidite **3** followed by oxidation with chloroperbenzoic acid (*m*CPBA). Deallylation with $PdCl_2$[24] followed by phosphorylation with **4** and oxidation furnished the fully protected GPI anchor **31**.



Scheme 8. Phosphorylations and deprotection. a) 48% HF (aq), CH_3CN, 75%; b) **3** (10 equiv), tetrazole (20 equiv), CH_3CN/CH_2Cl_2 (1/1), then mCPBA (−40→25 °C), 85%; c) $PdCl_2$, NaOAc, HOAc/H_2O (19/1), 66% (81% based on recovered starting material); d) **4** (10 equiv), tetrazole (20 equiv), CH_3CN/CH_2Cl_2 (1/1), then mCPBA (−40→25 °C), 81%; e) Pd/C, H_2, $CHCl_3$/MeOH/H_2O (3/3/1); f) $H_2NNHC(S)SH$, 2,6-lutidine/AcOH (3/1); g) TFA/H_2O (9/1), 2 min, 90% over three steps.

A final deprotection sequence involving hydrogenation, deacylation, and deacetalisation was planned. Studies on the deprotection of diacetals had shown that the hydrolysis of BDA groups gave better results if performed after debenzylation. Hydrogenation of **31** with Pd/C removed the benzyl ethers, the benzyloxycarbonyl (Cbz) group, and transformed the azide into the amine. Treatment with hydrazinedithiocarbonate[25] allowed the selective deacylation of the chloroacetates, whilst leaving the alkyl esters intact. Final rapid hydrolysis of the BDAs with aqueous trifluoroacetic acid (TFA) gave the GPI anchor **1** in 90% yield over the three steps. Selected physical data for **1**, **2**, and **31** are listed in Table 1.

In summary we have reported a highly convergent and efficient synthesis of GPI anchor **1**. The diacetal protection protocols have allowed us to desymmetrize *myo*-inositol and glycerol, as well as to conveniently protect monomers and tune the reactivity of the resulting glycosyl donors. This strategy is clearly adaptable to other syntheses of GPI anchors and their derivatives.

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Table 1. Selected physical data for compounds **1**, **2**, and **31**.[a]

1: ^{1}H NMR (600 MHz, [D$_6$]DMSO/D$_2$O (50/1), 60 °C): $\delta = 4.67$(s, 1H; 1Man-H), 4.83(s, 1H; 1Man-H), 4.87(d, ^3J(H,H) = 3.4 Hz, 1H; 1Gal-H), 4.91(d, ^3J(H,H) = 3.5 Hz, 1H; 1Gal-H), 4.94(s, 1H; 1Man-H), 5.35(s, 1H; 1Glu-H); ^{31}P NMR (243 MHz, CD_3CN/D_2O (3/1), 50 °C): $\delta = 9.24, 1.36$; matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) MS (matrix: trihydroxyacetophenone, negative-ion mode): *m/z*(%): 1864 (100) [M^- − H].

2: ^{1}H NMR (600 MHz): $\delta = 4.58$(s, 1H; 1f-H), 4.85(s, 1H; 1e-H), 5.19(s, 1H; 1d-H), 5.27(s, 1H; 1g-H), 5.42(s, 1H; 1c-H), 5.70(d, ^3J(H,H) = 3.7 Hz, 1H; 1b-H); FAB-MS *m/z*(%): 3062 (95) [M^++Na], 2947.6 (100).

31 (as two separable pairs of diastereoisomers): **31a**: ^{31}P NMR (262 MHz): $\delta = 7.82, 7.79, -0.02, -0.12$; **31b**: ^{31}P NMR (243 MHz): $\delta = 6.89, 6.88, 0.00, -0.12$; FAB-MS *m/z*(%): 3913 (45) [M^++H], 3800 (100) [M^+ − Cbz+H].

[a] ^{1}H and ^{31}P NMR spectra were recorded in $CDCl_3$ at 26 °C, and FAB-MS with acidified 3-nitrobenzyl alcohol matrix in positive-ion mode unless otherwise indicated.

Keywords: acetals · glycosylations · inositolphosphates · oligosaccharides · protecting groups

[1] a) R. A. Dwek, *Chem. Rev.* **1996**, *96*, 683–720; b) A. Varki, *Glycobiology* **1993**, *3*, 97–130.
[2] a) H. Paulsen, *Angew. Chem.* **1995**, *107*, 1562–1564; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1432–1433; b) K. Toshima, K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503–1531, and references therein.
[3] a) L. Green, B. Hinzen, S. J. Ince, P. Langer, S. V. Ley, S. L. Warriner, *Synlett* **1998**, 440–442; b) N. L. Douglas, S. V. Ley, U. Lücking, S. L. Warriner, *J. Chem. Soc. Perkin Trans. 1* **1998**, 51–65; c) P. Grice, S. V. Ley, J. Pietruszka, H. M. I. Osborn, H. W. M. Priepke, S. L. Warriner, *Chem. Eur. J.* **1997**, *3*, 431–440, and references therein.
[4] I. Roditi in *Modern Synthetic Methods* (Eds.: B. Ernst, C. Leumann), Helvetica Chimica Acta, Basel, **1995**, pp. 259–279.
[5] a) M. A. J. Ferguson, *Philos. Trans. R. Soc. London B* **1997**, *352*, 1295–1303; b) M. J. McConville, M. A. J. Ferguson, *Biochem. J.* **1993**, *294*, 305–324.
[6] S. Udenfriend, K. Kodukula, *Annu. Rev. Biochem.* **1995**, *64*, 563–591.
[7] M. A. J. Ferguson, S. W. Homans, R. A. Dwek, T. W. Rademacher, *Science* **1988**, *239*, 753–759.
[8] a) T. Kinoshita, K. Ohishi, J. Takeda, *J. Biochem.* **1997**, *122*, 251–257; b) M. A. J. Ferguson, *Parasitology Today* **1994**, *10*, 48–52, and references therein.
[9] a) A. S. Campbell, B. Fraser-Reid, *J. Am. Chem. Soc.* **1995**, *117*, 10387–10388; b) T. G. Mayer, B. Kratzer, R. R. Schmidt, *Angew. Chem.* **1994**, *106*, 2289; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2177–2181; c) C. Murakata, T. Ogawa, *Carbohydr. Res.* **1992**, *235*, 95–114; for corrections see d) T. Ogawa, *Chem. Soc. Rev.* **1994**, *23*, 397–407.
[10] a) P. J. Garegg, P. Konradsson, S. Oscarson, K. Ruda, *Tetrahedron* **1997**, *53*, 17727–17734; b) A. Crossman, J. S. Brimacombe, M. A. J. Ferguson, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2769–2774; c) G. J. Boons, P. Grice, R. Leslie, S. V. Ley, L. L. Yeung, *Tetrahedron Lett.* **1993**, *34*, 8523–8526, and references therein.
[11] a) N. L. Douglas, S. V. Ley, H. M. I. Osborn, D. R. Owen, H. W. M. Priepke, S. L. Warriner, *Synlett* **1996**, 793–795; b) J.-L. Montchamp, F. Tian, M. E. Hart, J. W. Frost, *J. Org. Chem.* **1996**, *61*, 3897–3899; c) U. Berens, D. Leckel, S. C. Oepen, *J. Org. Chem.* **1995**, *60*, 8204–8208.
[12] S. V. Ley, S. Mio, B. Meseguer, *Synlett* **1996**, 791–792.
[13] B. V. L. Potter, D. Lampe, *Angew. Chem.* **1995**, *107*, 2085–2125; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1933–1972.
[14] a) D. C. Billington, *Chem. Soc. Rev.* **1989**, *18*, 83–122; b) Y. Watanabe, M. Nakatomi, *Tetrahedron Lett.* **1998**, *39*, 1583–1586; c) B. Kratzer, T. G. Mayer, R. R. Schmidt, *Tetrahedron Lett.* **1993**, *34*, 6881–6884.
[15] Y. Watanabe, M. Mitani, T. Morita, S. Ozaki, *J. Chem. Soc. Chem. Commun.* **1989**, 482–483.
[16] S. V. Ley, S. Mio, B. Meseguer, *Synlett* **1996**, 787–788.
[17] Modified Darzen's procedure: *The Merck Index, 9th ed.*, Merck, Rahway, NJ, **1976**, p. ONR-22.

  1433-7851/98/3724-3427 $ 17.50+.50/0

[18] R. U. Lemieux, K. B. Hendriks, R. V. Stick, K. James, *J. Am. Chem. Soc.* **1975**, *97*, 4056 – 4062.
[19] Trace amounts of the β-linked product were easily separated after the next step.
[20] This building block was always freshly prepared because migration of the chloroacetate to the 3-hydroxyl group was observed upon prolonged standing even at $-20\,^{\circ}C$.
[21] A. Mallet, J.-M. Mallet, P. Sinaÿ, *Tetrahedron: Asymmetry* **1994**, *5*, 2593 – 2608.
[22] a) P. Konradsson, U. E. Udodong, B. Fraser-Reid, *Tetrahedron Lett.* **1990**, *31*, 4313 – 4316; b) G. H. Veeneman, S. H. van Leeuwen, J. H. van Boom, *Tetrahedron Lett.* **1990**, *31*, 1331 – 1334.
[23] H. Lönn, *Carbohydr. Res.* **1985**, *139*, 105 – 113.
[24] T. Ogawa, H. Yamamoto, *Carbohydr. Res.* **1985**, *137*, 79 – 88.
[25] C. A. A. van Boeckel, T. Beetz, *Tetrahedron Lett.* **1983**, *24*, 3775 – 3778.

Synthesis of Enantiopure α-Alkoxy-α-Trifluoromethyl Aldehydes and Carboxylic Acids from Trifluoromethyl Ketones**

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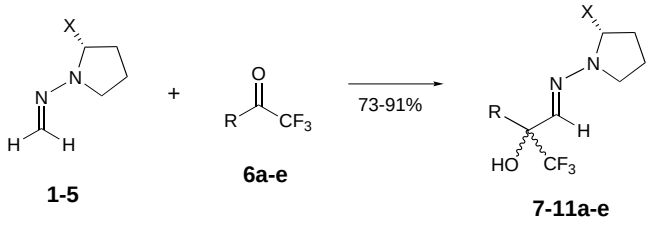
The unique properties conferred to organic compounds by the introduction of one or more fluorine atoms have recently found many applications in a variety of fields including pharmaceuticals, material science, and agrochemistry.[1] This fact, combined with the lack of appropriate fluorinated building blocks from natural sources, has evoked in the last few years the development of new synthetic methods for such compounds; the synthesis of enantiomerically enriched trifluoromethyl-containing building blocks is of particular significance in medicinal chemistry[2] and material science.[3] In this context, easily available trifluoromethyl ketones[4] appear as appropriate starting materials, but their reactions with d^1 reagents for the synthesis of interesting α-hydroxy-α-trifluoromethyl carbonyl compounds have been scarcely investigated.[5]

We have recently reported on the use of formaldehyde dialkylhydrazones as a new class of neutral formyl anion and cyanide equivalents, and this new methodology has been successfully applied to the formylation of several electrophilic substrates, including conjugated nitroalkenes,[6] α,β-unsaturated ketones,[7] and aldehydes.[8] As a natural extension of the method, we now report the nucleophilic 1,2-addition of these compounds to trifluoromethyl ketones, which provides a straightforward, short route to both racemic or enantiomerically pure α-alkoxy-α-trifluoromethyl aldehydes and carboxylic acids.

All tested couples of formaldehyde hydrazones **1** – **5** and a variety of trifluoromethyl ketones (**6a** – **e**) easily reacted in the absence of any catalyst or promoter, giving rise to the expected α-hydroxy-α-trifluoromethylhydrazones **7** – **11** in excellent yields, even when less reactive aromatic trifluoromethyl ketones (**6c**, **e**) were used as substrates (Scheme 1; selected results are collected in Table 1). Racemic adducts were best synthesized with the more reactive pyrrolidine-containing hydrazone **1**,[8] as this reagent led to the corresponding adducts **7a** – **e** in better yields and shorter reaction times than the simple formaldehyde dimethylhydrazone. Concerning the asymmetric version of the reaction, we found that use of the chiral formaldehyde SAMP-hydrazone **2**[6c] (SAMP = (*S*)-1-amino-2-(methoxymethyl)pyrrolidine) resulted in very low inductions under all tested reaction conditions; the selectivity of these additions was only slightly or not at all affected by temperature. Under the assumption that the origin of selectivity should be steric in nature, hydrazones **3** – **5**, in which the modified chiral auxiliaries are more sterically demanding than SAMP units, were synthesized. The influence by the tuned auxiliaries was analyzed from the results of the addition to compound **6b** (Table 1, entries 4 – 7). These experiments indicated a direct correlation between size and selectivity: The benzhydryl-containing reagent **3** gave slightly better results (d.r. 64:36) than **2**, while the asymmetric inductions effected by **4** and **5**, having bigger (quaternary) groups on position 2 of the pyrrolidine ring, were higher (d.r. 71:29 and 81:19, respectively). Nevertheless, crystalline derivative **5** proved to be the reagent of choice for practical



	1,7	2,8	3,9	4,10	5,11
X	H	CH_2OMe	$CHPh_2$	CEt_2OMe	CPh_2OMe

6-15	a	b	c	d	e
R	Me	Bn	Ph	n-C_7H_{15}	

Scheme 1. Synthesis of α-hydroxyhydrazones **7** – **11**.

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