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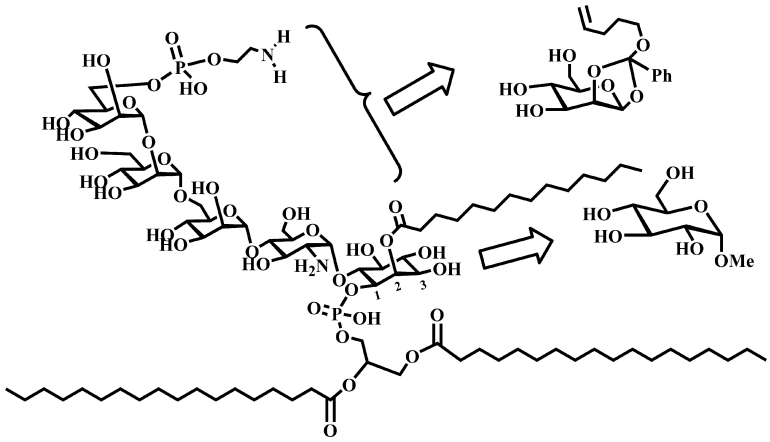

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Synthesis of a Malaria Candidate Glycosylphosphatidylinositol (GPI) Structure: A Strategy for Fully Inositol Acylated and Phosphorylated GPIs

Jun Lu, K. N. Jayaprakash, Urs Schlueter, and Bert Fraser-Reid*

Contribution from the Natural Products and Glycotechnology Research Institute, Inc., 4118 Swarthmore Road, Durham, North Carolina 27707

Received September 30, 2003; E-mail: dglucose@aol.com

Abstract: A congener of the glycosylphosphatidylinositol (GPI) membrane anchor present on the cell surface of the malaria pathogen *Plasmodium falciparum* has been synthesized. This GPI is an example of a small number of such membrane anchors that carry a fatty acyl group at O-2 of the inositol. Although the acyl group plays crucial roles in GPI biosynthesis, it rarely persits in mature molecules. Other notable examples are the mammalian GPIs CD52 and AchE. The presence of bulky functionalities at three contiguous positions of the inositol moiety creates a very crowded environment that poses difficulties for carrying out selective chemical manipulations. Thus installations of the axial long-chain acyl group and neighboring phosphoglyceryl complex were fraught with obstacles. The key solution to these obstacles in the successful synthesis of the malarial candidate and prototype structures involved stereoelectronically controlled opening of a cyclic ortho ester. The reaction proceeds in very good yields, the desired axial diastereomer being formed predominantly, even more so in the case of long-chain acyl derivatives. The myoinositol precursor was prepared from methyl α-D-glucopyranoside by the biomimetic procedure of Bender and Budhu. For the glycan array, advantage was taken of the fact that (a) *n*-pentenyl ortho ester donors are rapidly and chemospecifically activated upon treatment with ytterbium triflate and *N*-iodosuccinimide and (b) coupling to an acceptor affords α-coupled product exclusively. A strategy for obtaining the GPI's α-glucosaminide component from the corresponding α-mannoside employed Deshong's novel azide displacement procedure. Thus all units of the glycan array were obtained from a *β*-D-*manno*-*n*-pentenyl ortho ester, this being readily prepared from D-mannose in three easy, high-yielding steps. The "crowded environment" at positions 1 and 2, noted above, could conceivably be relieved by migration of the acyl group to the neighboring *cis*-*O*-3-hydroxyl in the natural product. However, study of our synthetic intermediates and prototypes indicate that the O-2 acyl group is quite stable, and that such migration does not occur readily.

Introduction

The insurgence of cerebral malaria that traditionally claims 2−3 million lives annually, mainly in tropical "Third World" nations,[1,2] now threatens the northern and southern temperate zones.[3,4] Attention has thereby been drawn to the causative parasite, *Plasmodium falciparum*.[5] This circumstance has prompted unraveling of the mosquito's genome,[6] and development of various drugs and vaccine candidates.[7] Seminal 1992 publications by Playfair and co-workers implicated phosphoinositide antigens,[8] and subsequent studies by Schofield[9] and others[10] culminated in the assignment of the glycosylphosphatidylinositol (GPI) candidate structure(s) **1** by Schwarz and co-workers.[11] Subsequent investigations by Gowda, Gupta, and Davidson[12] have shown that the lipid residues of **1** can vary widely in structure, with profound consequences for biological

(1) For a brief introduction, see: Lopez-Antinano, F. J.; Schmunis, G. A. Plasmodia of Humans. In *Parasitic Protozoa*; Academic Press: New York, 1993; Vol. 5, pp 146−169.
(2) *MALARIA: and Obstacles and Opportunities*; National Academy Press: Washington, DC, 1991.
(3) Martin, P. H.; Lefebvre, M. G. *Ambio* **1996**, *24*, 200−209.
(4) See, for example: *The New York Times*, Jan 8, 1997, p 1; *The Wall Street Journal*, May 7, 2001, p B12; *The Globe and Mail*, June 18, 1977, p 1; *Business Week*, Sept 21, 1998, p 70; *The Ottawa Citizen*, Sept 28, 1997, p A3.
(5) See, for example: Miller, L. H.; Good, M. F.; Milon, G. *Science* **1994**, *264*, 1878−1883.
(6) Gardner, M. J.; Hall, N.; Fung, E.; White, O.; Berriman, M.; Hyman, R. W.; Carlton, J. M.; Pain, A.; Nelson, K. E.; Bowman, S.; Paulsen, I. T.; James, K.; Eisen, J. A.; Rutherford, K.; Salzberg, S. L.; Craig, A.; Kyes, S.; Chan, M.-S.; Nene, V.; Shallom, S. J.; Suh, B.; Peterson, J.; Angiuoli, S.; Pertea, M.; Allen, J.; Selengut, J.; Haft, D.; Mather, M. W.; Vaidya, A. B.; Martin, D. M. A.; Fairlamb, A. H.; Fraunholz, M. J.; Roos, D. S.; Ralph, S. A.; McFaddeb, G. I.; Cummings, L. M.; Subramanian, G. M.; Mungall, C.; Venter, J. C.; Carucci, D. J.; Hoffmann, S. L.; Newbold, C.; Davis, R. W.; Fraser, C. M.; Barrel, B. *Nature* **2002**, *419*, 498−511.
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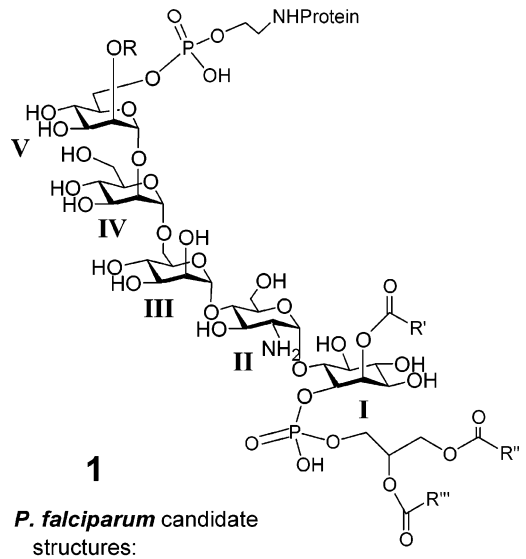
Scheme 1



activity.[13] These observations clearly have crucial implications for the design of therapeutic agents, and therefore justify the development of synthetic strategies.

Accordingly, in this paper, we report the synthesis and properties of a malarial GPI prototype, **35a**, and one variant, i.e., **35b**, of the candidate structures summarized as **1** (Scheme 1).[11] The approach addresses the crucially important (vide infra) O-2 acylation of the inositol moiety, an unusual feature which also occurs in other heavily lipidated GPIs such as CD52[14] and AchE.[15] While this paper was being prepared, two important contributions by Guo and co-workers relating to this challenging feature, in the context of CD52, were published.[16,17] Apart from the issue of inositol acylation, the synthetic strategy described herein also overcomes additional obstacles related to the phosphodiacyl−glycerolipid residues, without which GPI constructs cannot function as "membrane anchors".

Background and Significance

Although GPIs have a conserved core comprising units **I**−**V** of **1**, there are significant differences in how it is assembled by various organisms. By using cell free systems to study the most readily available GPI, the variant surface glycoprotein (VSG) of *Trypanosoma brucei*, Guther and Ferguson have established a parasite biosynthetic pathway[18] that makes it possible to draw comparisons with the mammalian pathway deduced by Kinoshita and co-workers.[19] Ferguson's summary of these pathways, reproduced in Figure 1,[20] shows that crucial differences exist between both pathways. Thus as indicated by asterisks 1 and 2, inositol acylation (via Acyl-T) *necessarily* precedes the first mannosylation (via MT-1) in mammals. However, in the case of *T. brucei*, the mannosylation does not require prior inositol acylation.

Inositol acylation therefore enforces a subtle distinction between mammalian and parasitic biosynthetic pathways, thereby presenting a window of opportunity for therapeutic intervention. Indeed, Kinoshita has already exploited this successfully in the case of African sleeping sickness.[21]

Interestingly, removal of the acyl group (asterisk 3) is also an important biosynthetic step in that it precedes critical processes involving "fatty acid remodeling" of the lipidation at the sn1 and sn2 positions of the glyceryl moiety (asterisk 4). McConville and Menon have suggested that these remodeling procedures are specifically designed to facilitate translocation of the growing GPI between the cytosolic and lumenal faces of the endoplasmic reticulum.[22]

The glycerolipid residues are essential for anchoring the glycoconjugate to the cell membrane, but the structural requirements, such as length, and functionality (e.g., acyl versus alkyl) of these lipid residues are as yet unclear.

In view of the inositol deacylation step in Figure 1, it is not surprising that most mature GPIs do not carry an acyl group on inositol.[23] It is therefore of interest that reacylation is sometimes seen, notable examples being the human derived GPI-anchored proteins CD52[14] and AchE.[15] Acylated modifications have also been harvested from *T. brucei* procyclins.[24]

In light of the paramount importance of inositol acylation, it is interesting to note that assignment of this functionality is usually based on formation of a cyclic phosphate, e.g., **3** → **4**, upon treatment with phospholipase C (PLC)[25] (Scheme 2). However, the specter of acyl migration to the cis-related C3-OH, e.g., **2** → **3**, is worrisome since such an occurrence would result in a positive, but compromised, PLC diagnosis. Notable in this context is the fact that Puzo and co-workers have recently isolated a 3-*O*-acyl phosphoinositide from *Mycobacterium tuberculosis* extracts.[26]

Ferguson and co-workers have used O-2 alkyl groups as biosynthetic probes with some success.[27] However, such O-alkylated substrates cannot be used to study phenomena such as deacylation and migration, hence the importance of the compounds described herein.

Results and Discussion

The representation of compound **1** in Scheme 3 emphasizes the fact that the intersaccharide linkages are all α-D. Although this anomeric option is favored in mannosides owing to the

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(13) Gowda, D. C. *Microbes Infect.* **2002**, *4*, 983−990. Naik, R. S.; Branch, O. H.; Woods, A. S.; Vijaykumar, M.; Perkins, D. J.; Nahlen, B. L.; Lal, A. A.; Cotter, R. J.; Costello, C. E.; Ockenhouse, C. F.; Davidson, E. A.; Gowda, D. C. *J. Exp. Med.* **2000**, *192*, 1563−1575.
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(16) For a recent synthesis of a GPI with the C2 acyl (but *not* the phospholipid), see: Xue, J.; Shao, N.; Guo, Z. *J. Org. Chem.* **2003**, *68*, 4020−4029.
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(27) Smith, T. K.; Sharma, D. K.; Crossman, A.; Dix, A.; Brimacombe, J. S.; Ferguson, M. A. J. *EMBO J.* **1997**, *16*, 6667−6675.

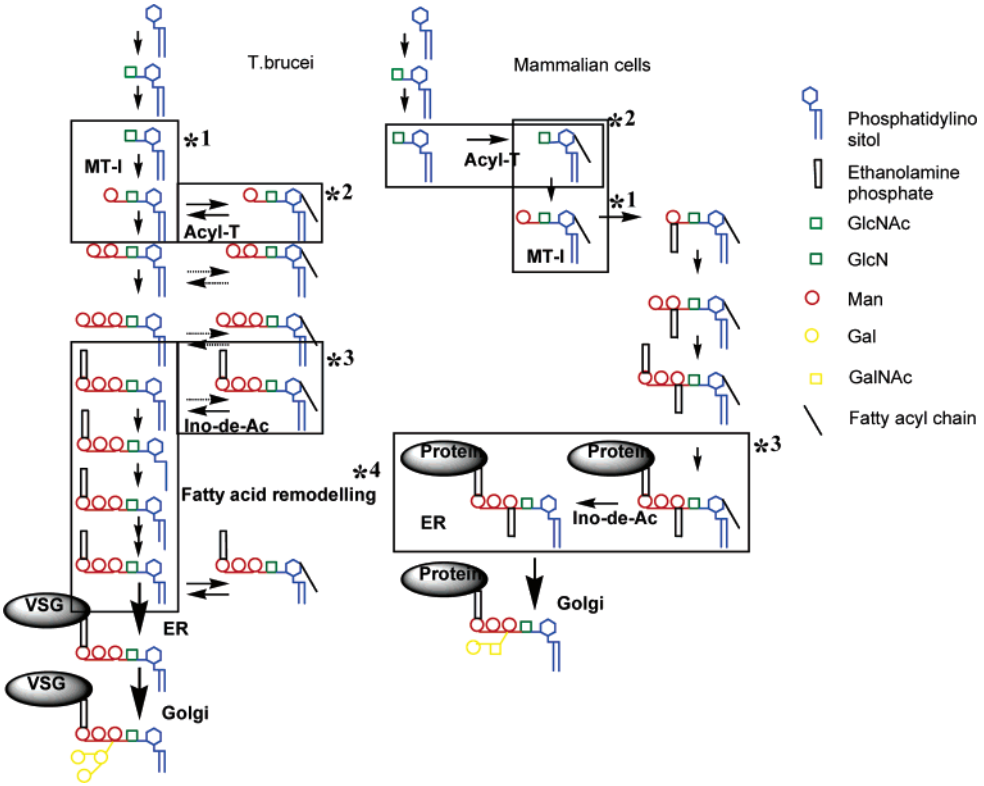
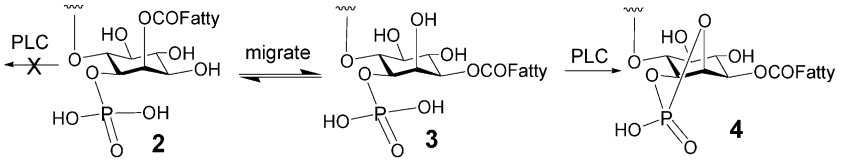


Figure 1. Parasite versus mammalian biosynthetic pathways for assembly of glycosylphosphatidyinositol membrane anchors.[20]

Scheme 2



PLC = phospholipase C

kinetic anomeric effect,[28] *n*-pentenyl ortho ester (NPOE) donors have the advantage that α-oriented products are usually formed exclusively.[29] Furthermore, converting C2-OH into C2-NH_2 with inversion of configuration transforms an α-mannoside into an α-glucosaminide. Thus, as indicated in the retrosynthetic plan (Scheme 3), the entire glycan array of **1** can be derived from the *manno*-orthobenzoate **5**, which can be prepared from D-mannose in three easy steps.[29]

The attractiveness of the strategy is further enhanced by recent investigations which have shown that use of ytterbium triflate ($Yb(OTf)_3$) as activator for *N*-iodosuccinimide (NIS) induces chemospecific reaction of NPOEs, while leaving armed and disarmed NPG donors untouched.[31] Additional valuable nuances concerning choice of activators for use with NIS are the incompatibility of *p*-methoxybenzyl groups with both boron trifluoride etherate and *tert*-butyldimethylsilyl triflate, while cyclohexylidene acetals tolerate the former, but not the latter.

For the myoinositol moiety, the route developed to compound **6** from methyl α-D-glucopyranoside by Bender and Budhu[30] has been the most convenient in our hands.

Several total syntheses of GPIs have been reported,[16,17,32] none of which has had to confront phosphodiacylglycero lipidation as well as inositol acylation. Anticipating that the latter feature would present new challenges, we carried out model studies on the inositol moiety by itself.[33]

Nearly 40 years ago, Angyal and Tate had shown that the vicinal hydroxyl groups of diol **10** could be differentiated by chemoselective reactions with alkylating and acylating agents giving rise to **9** and **11** respectively as major products.[34] The desired axial acyl derivative therefore could not be achieved directly from such a diol, so protection/deprotection steps featuring tin-mediated chemistry[35] were applied to give **12** and thence **13** and **14**.[33] However, as is clear from Scheme 4, this

(28) *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Kirby, A. J., Ed.; Springer-Verlag: New York, 1983.
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(32) See, for example: Pakari, K.; Schmidt, R. R. *J. Org. Chem.* **2003**, *68*, 1295−1308. Campbell, A. S.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1995**, *117*, 10387−10388. Baeschlin, D. K.; Chaperon, A. R.; Green, L. G.; Hahn, M. G.; Ince, S. J.; Ley, S. V. *Chem. Eur. J.* **2000**, *6*, 172−186. Ogawa, T. *Chem. Rev.* **1994**, *23*, 397.
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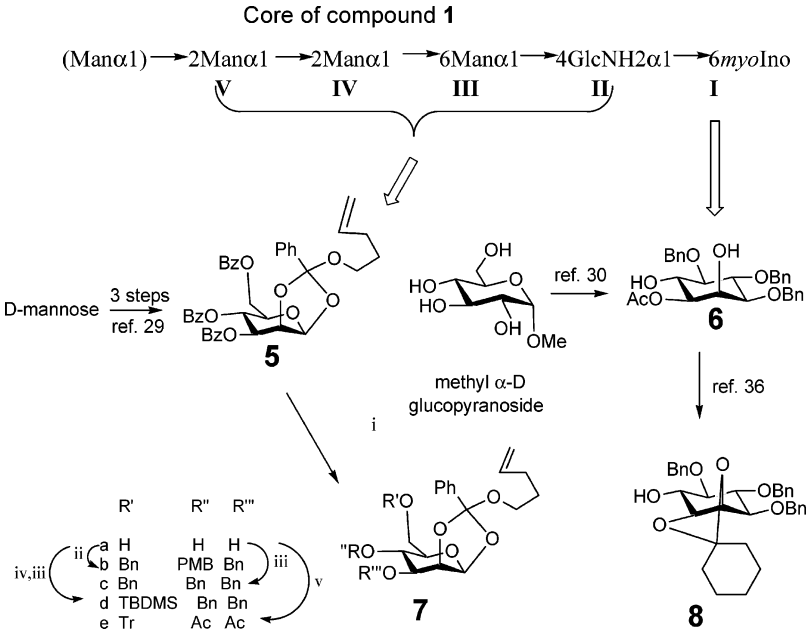
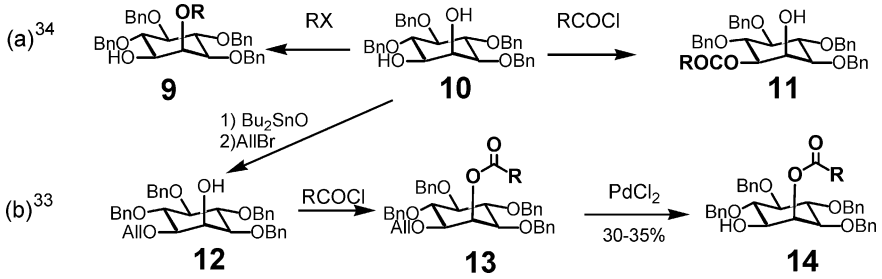
Scheme 3 [a]



[a] (i) NaOMe/MeOH/CH_2Cl_2. (ii) (a) ($^nBu_3Sn)_2O$, benzene; (b) $PhCH_2Br/Bu_4NI$/benzene; (c) *p*-$MeOC_6H_4CH_2Cl$/DMF/NaH/TBAI. (iii) $PhCH_2Br$/NaH/Bu_4NI/DMF. (iv) TBDMSCl/THF/imidazole. (v) Ph_3CCl/pyridine/Ac_2O/DMAP/Et_3N.

Scheme 4



strategy, which has also been explored by Guo,[16] met with only modest success.[33]

Testing was therefore carried out on a more advanced substrate as outlined in Scheme 5. In keeping with the retrosynthetic plan in Scheme 3, the *n*-pentenyl ortho ester (NPOE) **7b** was chosen as the donor. Preparation of this material took advantage of the fact that the NPOE triol **7a** undergoes tin-mediated selective double alkylation of the C6- and C3-OHs, thereby making the C4-OH available for *p*-methoxybenzylation. Acceptor **8** was prepared from the Bender−Budhu product, **6**, as described previously by us.[36] Coupling of **7b** (3 equivalents) with **8** under the agency of ytterbium triflate ($Yb(OTf)_3$)[31] and *N*-iodosuccinimide (NIS) gave a pseudodisaccharide, **15a**. The lone benzoate was replaced by triflate under routine conditions to give **15b** in 77% yield over two steps. Deshong's novel azide displacement[37] was then employed.

Unfortunately, the yield of the glucosaminyl synthon **16** was much lower than with our previously tested substrates.[38] The ^1H parameters of compound **16** (5.60 ppm, $J_{12} = 3.6$ Hz) are distinctive, and this knowledge would be valuable in making assignments as the synthesis progressed.

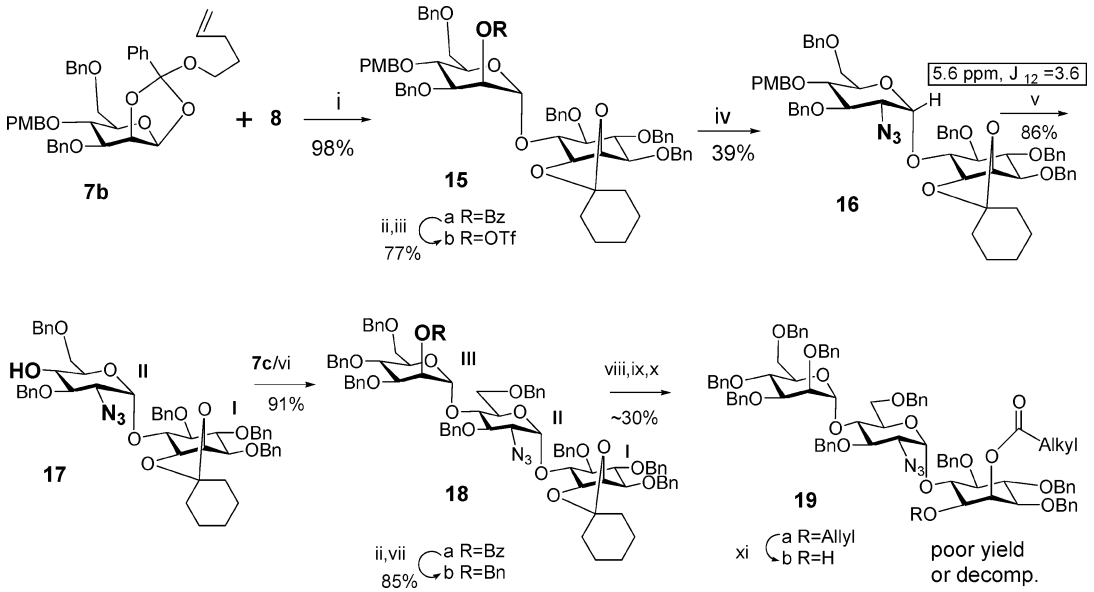
Removal of PMB gave acceptor **17**, which coupled efficiently (91%) with NPOE **7c** (4 equiv) to give the pseudotrisaccharide **18a**, which was converted into the perbenzylated counterpart **18b** in the usual way. Removal of the cyclohexylidene acetal with camphorsulfonic acid led to the corresponding diol, to which the protocol in Scheme 4 (**10** → → **14**) was applied. However, the O-1-allylation step went poorly, and additional problems were experienced with the subsequent deallylation using palladium chloride in water and acetic acid. Thus short-chain models of **19** gave poor yields, and with long-chain analogues the situation became worse in that there was gross decomposition.

A more reliable approach was therefore needed, and in view of previous frustrations, we decided that the best "model" would be the actual precursor. Accordingly, acceptor **17** was coupled with the silylated NPOE **7d** (5 equiv) to give pseudotrisaccharide **20a** in 79% yield. As before, the lone benzoate was replaced by benzyl in two steps, and desilylation of the resulting product, **20c**, then gave the acceptor **20d**. Coupling with previously used NPOE **7c** (3 equiv) gave pseudotetrasaccharide **21a**, and subsequent debenzoylation afforded acceptor **21b**.

Problems intensified with the next step. We had hoped to use the 6-O-silylated NPOE **7d** again, but for reasons which are unclear, coupling of **7d** with acceptor **21b** failed to give the desired pseudopentasaccharide **22**.

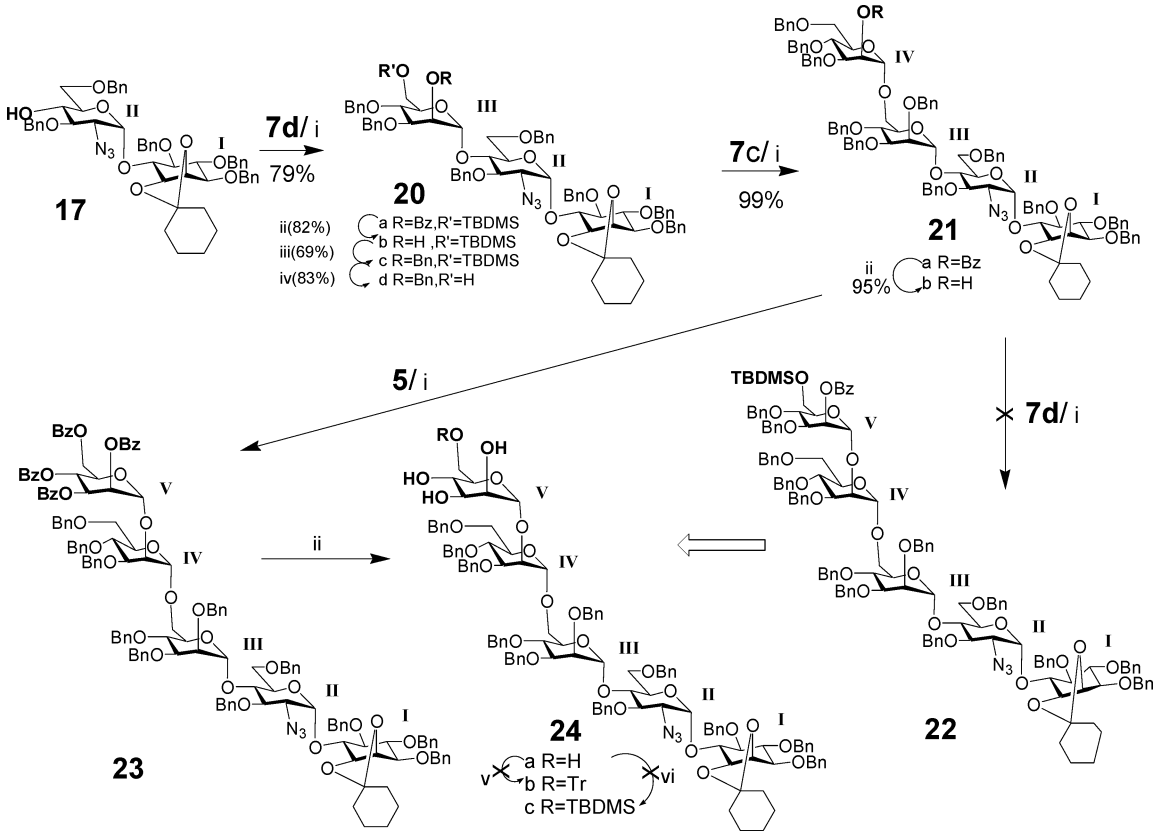
(36) Jia, Z. J.; Olsson, L.; Fraser-Reid, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 631−632.
(37) Soli, E. D.; Manoso, A. E.; Satterson, M. C.; DeShong, P.; Favor, D. A.; Hirschmann, R.; Smith, A. B., III. *J. Org. Chem.* **1999**, *64*, 3171−3177.
(38) Anilkumar, G.; Nair, L. G.; Olsson, L.; Danield, J. K.; Fraser-Reid, B. *Tetrahedron Lett.* **2000**, *41*, 7605−7608.

Scheme 5 [a]



[a] (i) NIS/Yb(OTf)$_3$/0.3 equiv/CH_2Cl_2/0 °C (98%). (ii) NaOMe/MeOH/CH_2Cl_2. (iii) Tf_2O/Py/DMAP/CH_2Cl_2. (iv) $TMSN_3$/TBAF/THF (39%). (v) BF_3·Et_2O/CH_2Cl_2 (86%). (vi) NIS/BF_3·Et_2O/CH_2Cl_2/0 °C (91%). (vii) BnBr/NaH/Bu_4NI. (viii) CSA/ethylene glycol (68%). (ix) Bu_2SnO, toluene, then DMF, −10 °C allyl bromide, CsF, 18 h (54%). (x) Alkyl-COCl, pyridine. (xi) $PdCl_2$, HOAc, H_2O, NaOAc.

Scheme 6 [a]

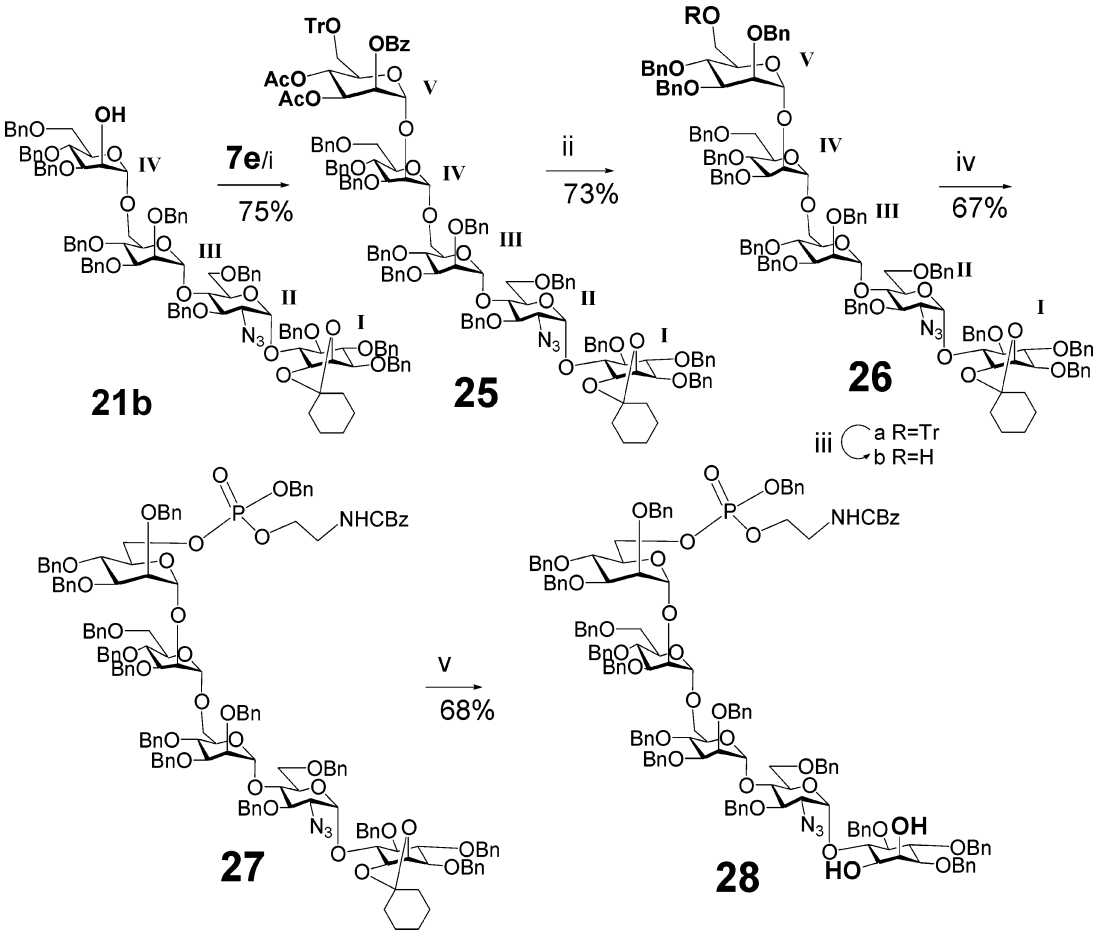


[a] (i) NIS/BF_3·Et_2O/CH_2Cl_2/0 °C. (ii) NaOMe/MeOH/CH_2Cl_2 (82%). (iii) BnBr/NaH/Bu_4NI (69%). (iv) TBAF/MS(4 Å)THF (83%). (v) Ph_3CCl/pyridine/DMAP/Et_3N. (vi) TBDMSCl/THF/imidazole.

We have recently observed that acylated NPOEs frequently give higher coupling yields than their alkylated counterparts,[39] so the tribenzoylated NPOE **5** was tried. Indeed the expected tetrabenzoate **23** was obtained in acceptable yield, paving the way to corresponding tetrol **24a**. Surprisingly, however, attempts to selectively tritylate or silylate the latter, using the same conditions as in Scheme 3, failed to give **24b** or **24c**. Silylation

(39) Fraser-Reid, B.; Lopez, J. C.; Radhakrishnan, K. V.; Mach, M.; Schlueter, U.; Gomez, A.; Uriel, C. *Can. J. Chem.* **2002**, *80*, 1075−1087.

Scheme 7 [a]



[a] (i) NIS/BF_3·Et_2O/CH_2Cl_2/0 °C (75%). (ii) (a) NaOMe/MeOH/CH_2Cl_2; (b) BnBr/NaH/Bu_4NI (73%). (iii) HCOOH/Et_2O (60%). (iv) CbzNH$(CH_2)_2$OP(OBn)-N(^{i}Pr)$_2$/1*H*-tetrazole/CH_2Cl_2, −40 °C/MCPBA (60−70%). (v) CSA/ethylene glycol.

with TBDMSOTf could not be tried, because as noted above, the cyclohexylidene ring would not have survived.

Fortunately, the tritylated diacetylated NPOE **7e** (8 equiv) worked well to give **25** (Scheme 7), and deacetylation followed by benzylation gave the elusive pseudopentasaccharide **26a** in 73% overall yield. Mild cleavage of the trityl group afforded **26b**, to which the phosphoethanolamine complex[40] was attached leading to **27**. Removal of the cyclohexylidene was then readily accomplished to give diol **28**.

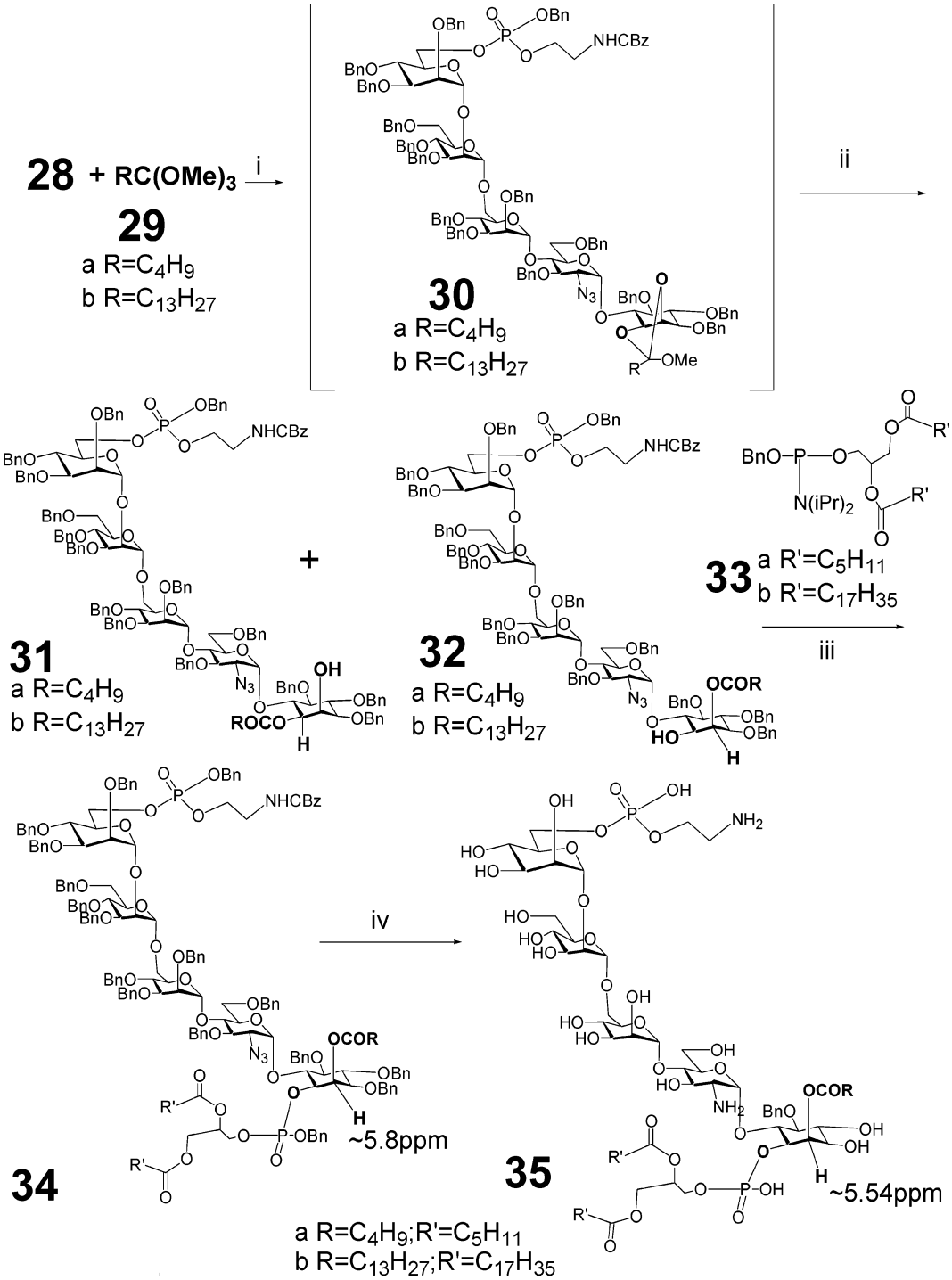
Given the poor yields for converting **18** into **19** (Scheme 4), a different strategy for installing the axial acyl entity was needed. The stereoelectronically controlled opening of cyclic ortho esters pioneered by King and Albutt[41] was an attractive option. In an exploratory experiment with a short-chain model, Scheme 8, treatment of diol **28** with trimethyl orthovalerate **29a** afforded the cyclic ortho ester **30a**. This material was usually not isolated, but was treated directly with ytterbium(III) triflate[31] to give the regioisomeric β-hydroxy esters **31a** and **32a** in acceptable yield (75%), but a disappointing 1:2 ratio. However, reaction with the readily prepared[40] diacylated glycerylphosphoamidite **33a** proceeded well to give the fully lipidated glycan **34a**. The latter structure was supported by FAB (3010.4 M + Na), by signal(s) at 5.89 ppm for the inositol's H2, and by carbon signals at 172.31, 172.58, and 172.99 ppm for the three ester carbonyl groups. Debenzylation of **34a** by atmospheric hydrogenolysis over Pearlman's catalyst finally gave **35a**, confirmed by MALDI (1385.7 M + H, 1407.9 M + Na) and NMR (5.54 ppm for inositol's H2).

We were encouraged by these results, but would **35a**, with its short alkyl chains, be able to mimic naturally occurring long-chain GPI anchors in its ability to be embedded into the cell membrane? Accordingly, O-2 myristoylation was effected via the trimethyl ortho ester **29b**, the latter being prepared from the corresponding myristonitrile by the method of Presova and Smrt.[42] The derived cyclic ortho ester **30b** was rearranged efficiently (86%) by treatment with Yb$(OTf)_3$, and gratifyingly with greater regioselectivity than had been achieved with the short-chain analogue **30a**, there being a 5:1 ratio of axial (**32b**) and equatorial (**31b**) esters.

Longer chains were also placed on the glyceryl moiety in the form of phosphoramidite **33b**, the use of which led to the perbenzylated GPI **34b** smoothly in 72% overall yield. The structure was confirmed by MALDI (3471.01 M + Na), and the parameters for proton (5.88 ppm) and carbon (172.34, 172.55, and 172.96 ppm) NMR spectra were in excellent agreement with the short-chain analogue **34a**.

(40) Campbell, A. S.; Fraser-Reid, B. *Bioorg. Med. Chem.* **1994**, *2*, 1209−1219.
(41) King, J. F.; Allbutt, A. D. *Can. J. Chem.* **1970**, *48*, 1754−1759.
(42) Presova, M., Smrt, J. *Collect. Czech. Chem. Commun.* **1989**, *54*, 487−497.

Scheme 8 [a]



[a] (i) CSA 0.5 h, CH_3CN. (ii) $Yb(OTf)_3$; CH_2Cl_2. (iii) 1*H*-Tetrazole/CH_2Cl_2, −40 °C/MCPBA (60−70%). (iv) $CHCl_3$/MeOH (1:1) HOAc(trace)/Pd/C (10%) room temperature slightly over atmospheric pressure 12 h; add H_2O (0.3), room temperature 12 h.

The final global debenzylation step proved to be extremely frustrating. Procedures that had succeeded with previous GPI syntheses in our lab and elsewhere,[32] and even with the short-chain prototype[43] of **34a**, failed with the more lipophilic substrate **34b**. The presence of the myristoyl ester on inositol of **34b** clearly presented unprecedented problems. First, after 12 h of hydrogenolysis at 70 psi in chloroform−methanol−water mixture (3:3:1) over palladium hydroxide on carbon, some benzyl groups were still present. However, there had been partial loss of the glyceryl acyl group(s)—but notably the myristoyl ester was not affected.

Second, we tried palladium on carbon (10%) in methanol: chloroform (1:1) mixture with a trace of acetic acid using a balloon of hydrogen for 12 h. The isolated product, upon TLC in butanol:ethanol:water (1:1:1), indicated the presence of more polar material, but ^1H NMR showed that, while there was no more starting material (**34b**), there were still some benzyl groups present.

(43) Lu, J.; Jayaprakash, K. N.; Frasaer-Reid, B. *Tetrahedron Lett.* **2004**, *45*, 879−882.

Third, the recovered marterial was redissolved in methanol: chloroform:water (1:1:0.3) mixture and hydrogenolysis was continued for a further 12 h. This gave and even more polar material—which proved to be **35b**.

Fourth, in view of the preceding observation, we tried to use the last solvent mixture, methanol:chloroform:water (1:1:0.3), with **34b** right from the beginning. Unfortunately, the desired product was not obtained after 12 h!

Finally, further prodigious experimentation revealed that the best strategy for hydrogenolytic deprotection of **34b** was to start with methanol:chloroform (1:1) mixture and acetic acid (trace) with balloon pressure for 12 h. At this time the experiment was briefly interrupted, water (0.3) was added, the apparatus was reassembled, and hydrogenolysis was continued for a further 12 h. This ensured complete debenzylation to give **34b**.

The product was purified by chromatography using a Sephadex G-15 column with chloroform:methanol:water (1:1:0.3) as eluent. Electrospray mass spectroscopy of the product, **35b**, in methanol/formic acid gave *m*/*z* 1937.1 (M + 2HCOOH). The ^{1}H NMR spectrum showed a 6-proton signal at 2.29 ppm for the three methylene groups α to carboxyl, nine-proton overlapping triplets at 0.91 ppm for the three fatty acyls, and the telling one-proton signal at 5.54 ppm for the inositol H-2.

With respect to the crucial question of migration of the inositol's acyl group, we have examined three substrates: (1) *O*-2-pentanoylmyoinositol obtained by hydrogenolysis of **14**, (2) the fully lipidated pseudodisaccharide corresponding to units **I** and **II** of **15**, and (3) the synthetic prototype **35a**. In the first, ^{1}H NMR easily gave no evidence of any acyl migration over several months. The same conclusions were reached for the other two substrates, based on the signal at 5.43 ppm that is assignable to the equatorial proton α to the acyl group. This conclusion could be reached by comparing the intensity of this signal to that of the well-resolved anomeric protons at 5.03, 5.12, and 5.22 ppm. (As a point of interest, we have also synthesized the diastereomer of **35a** with the inositol's C1 and C2 functionalities reversed. The axial proton α to the acyl group comes to a much higher field, ~4.7 ppm.)

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Supporting Information Available: Synthesis of **7b,e**, **15a,b**, **16**, **17**, **18b**, **20a−d**, **21a,b**, **26a,b**, **27**, **28**, **31a**, **32a,b**, **34a,b**, **35a,b**; NMR spectra of **18e**, **19a**, **22b**, **24a**, **24b**, and **25a**.This material is available free of charge via the Internet at http://pubs.acs.org.

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