coordination can also be detected (eq 3). That the paramagnetic

$$Cp'_2Eu + \| \rightleftharpoons Cp'_2Eu \leftarrow \| \quad (3)$$

shift direction (*downfield*) of the olefinic protons is opposite to that observed in H_2 is in accord with complexation of the olefin π system and delocalization through the ligand framework of polarization-derived, carbon-centered unpaired spin density.[12] The opposite, *upfield* displacement of the methyl signal in an analogous experiment with propylene is further support for this mechanism.[12] In regard to saturated hydrocarbons, negligible preferential interaction is observed between Cp'_2Eu and methane. However, in the case of more basic[11c] cyclopropane, substantial broadening and upfield displacement of the hydrocarbon ^1H signal is observed.[15]

Efforts to extract[16] accurate bound shift (Δ) and binding constant (K) information from shift/stoichiometry data are complicated by the large line widths and limitations in solubility. A preliminary analysis[17] indicates that $\Delta/K \approx 1$ for eq 1 and 2, which, in view of the large anticipated values of Δ,[12] implies small binding constants. Further studies are in progress.

Acknowledgment. We are grateful to the NSF for support of this research under Grant CHE-8800813.

(14) $Cp'_2Yb(\mu\text{-}C_2H_4)Pt(PPh_3)_2$ is isolable as a solid, but significantly dissociated into Cp'_2Yb and $(C_2H_4)Pt(PPh_3)_2$ in solution: Burns, C. J.; Andersen, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 915-917.

(15) For comparable concentrations, paramagnetic shifts are roughly comparable to those observed for $Cp'_2Eu + H_2$.

(16) (a) Reference 9b, Chapter 4. (b) Inagaki, F.; Miyazawa, T. *Prog. Nucl. Magn. Reson. Spectrosc.* **1981**, *14*, 67-111. (c) Inagaki, F.; Miyazawa, T. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1427-1430. (d) Shapiro, B. L.; Johnston, M. D., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 8185-8191.

(17) Least-squares analysis of $1/\Delta$ vs $1/[Eu]$ data at constant concentration of substrate assuming 1:1 complexes.

n-Pentenyl Glycosides Facilitate a Stereoselective Synthesis of the Pentasaccharide Core of the Protein Membrane Anchor Found in *Trypanosoma brucei*[1]

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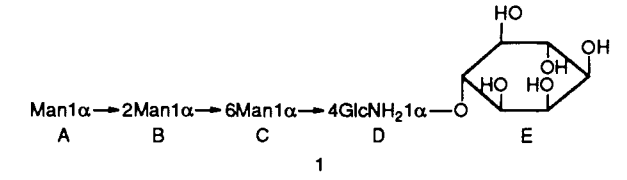
Received June 9, 1989

Recent investigations in this laboratory have revealed that *n*-pentenyl glycosides (NPGs) offer some remarkable advantages for processes that require activation of the anomeric center of sugars. Glycosyl donors commonly in use[3] may possess one or another of the following attributes, but NPGs are unique in that they possess all seven: (1) direct preparation from an aldose by modified Fischer glycosidation procedures,[4] (2) stability to diverse chemical manipulations and compatibility with standard protecting groups,[4a,5] (3) mild, chemospecific, and nontoxic activation of the anomeric center,[4-6] (4) direct use in saccharide coupling,[5-7] (5) control of the α,β selectivity in glycosidation by choice of solvent,[5] and by other methods,[6,8] (6) ready conversion into glycosyl halides for Koenigs-Knorr reactions,[9] and (7) *most uniquely, the ability to "arm" or "disarm" these glycosyl donors by means of the protecting group on the C2 oxygen.*[7]

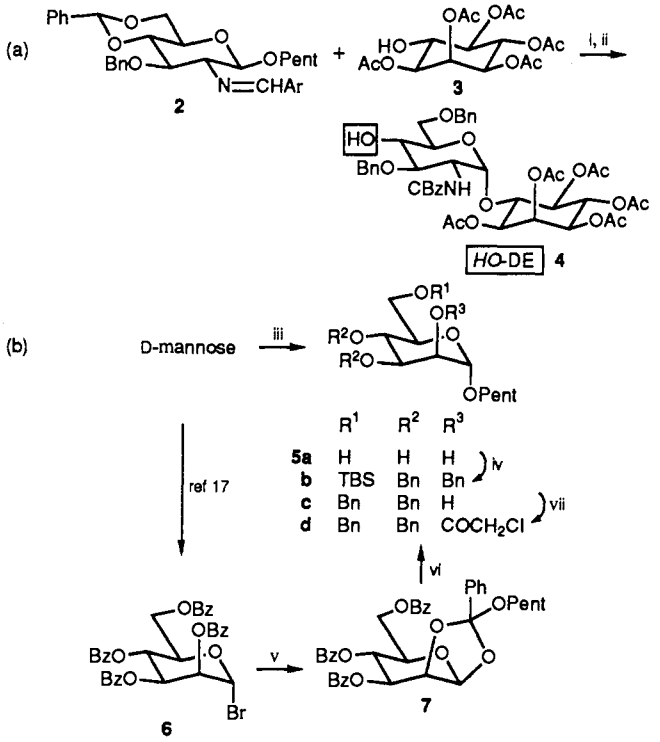
These attributes offer much promise for meeting the daunting demands of oligosaccharide syntheses,[3,10] and as an appropriate testing ground, we have addressed the synthesis of the mannan-rich pentasaccharide **1** from the core oligosaccharide of the variant surface glycoprotein[11] found in *Trypanosoma brucei*[12,13] (Scheme

Scheme I



1

Scheme II[a]



[a] (i) $I(collidine)_2ClO_4/CH_2Cl_2$/4A molecular sieves, then 10% MeOH in HOAc/$TsNHNH_2$/room temperature, then $Et_3N/CBzCl$/0 °C, 65%; (ii) $NaBH_3(CN)$/THF-Et_2O/HCl/4A molecular sieves, 75%; (iii) $CH_2{=}CH(CH_2)_3OH$/DMSO/camphorsulfonic acid/90 °C/24 h,[3] 65%; (iv) *tert*-butyldiphenylsilyl chloride/Et_3N/DMAP/CH_2Cl_2, then $PhCH_2Br$/NaH, DMF, 62%; (v) $CH_2{=}CH(CH_2)_3OH$/lutidine/CH_2Cl_2, 90%; (vi) NaOMe, then $PhCH_2Br$/NaH/DMF, then camphorsulfonic acid/CH_2Cl_2, 64%; (vii) $(ClCH_2CO)_2O$/pyridine, 65%.

(1) We are gratetul to the National Science Foundation (CHE 8703916) and Glaxo Laboratories, Inc. (Durham, NC), for financial support of this work.

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(6) The use of *N*-iodosuccinimide and trifluoromethanesulfonic acid (NIS/TfOH) as a source of iodonium ions has been developed in this laboratory. The details, which will be published elsewhere, are available in the supplementary material.

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(11) These intriguing substances reveal a novel mechanism for how proteins are anchored to cell membranes and hence are thought to be implicated in signal transduction. For example, see: (a) Schmitz, B.; Klein, R. A.; Duncan, I. A.; Egge, H.; Gunawan, J.; Peter-Katalinic, J.; Dabrowski, Y.; Dabrowski, J. *Biochem. Biophys. Res. Commun.* **1987**, *146*, 1055. (b) Cross, G. A. M. *Cell* **1987**, *48*, 179. (c) Low, M. G. *Biochem. J.* **1987**, *244*, 1. (d) Saltiel, A. R.; Cuatrecasas *Am. J. Physiol.* **1988**, *255*, C1.

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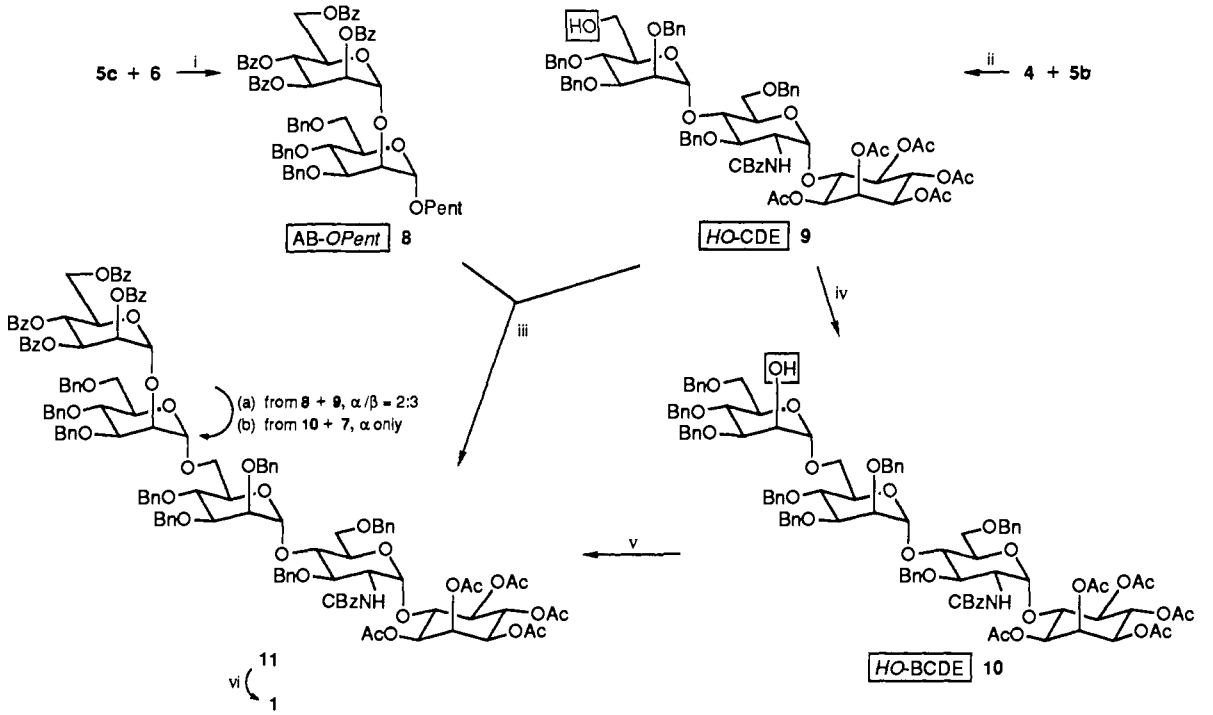
Scheme III[a]



[a] (i) $AgOTf/CH_2Cl_2/(Me_2N)_2CO$/4A molecular sieves, 76%; (ii) NIS–TfOH/CH_2Cl_2/4A molecular sieves, HF/pyridine/THF, 67%; (iii) NIS–TfOH/CH_2Cl_2/4A molecular sieves, 73%; (iv) **5d**/NIS–TfOH/CH_2Cl_2/4A molecular sieves, thiourea/EtOH/Δ, 53%; (v) **7**/NIS–TfOH, CH_2Cl_2/4A molecular sieves, 68%; (vi) NaOMe/MeOH, Pd on carbon/HCOOH/MeOH, 69%.

I). Related glycosylphosphatidylinositol residues have been implicated in a second messenger hypothesis for insulin signal transduction.[11d]

A block (i.e., convergent) approach to the target would be obviously beneficial, and in view of the high α (or β) selectivity that we have already found for NPGs in glucosaminide syntheses,[8] the glucosylinositol residue D-E was an obvious launching point for the synthesis. Preparation of this block from precursors **2**[8] and **3**,[14,15] modeled after the pioneering work of Lemieux and co-workers[16] as outlined in Scheme II, part a, furnished **4** in 65% overall yield.

With **4** in hand, two options for high convergency were to divide **1** into (a) ABC+DE or (b) AB+CDE subunits. Option b was our initial choice, since a primary hydroxyl group would be involved in the final coupling process.[3a]

The pentenylated mannosides required for this study were prepared either via the Fischer glycosidation[4b] product **5a** or the pentenylated ortho ester **7**,[17,18] by the routine procedures outlined in Scheme II, part b. For the AB block, compounds **6** and **5c** were coupled to give the dimannan **8** (Scheme III). For the CDE block, we took advantage of previously reported work,[7] which showed that C2-O-alkylated pentenyl mannosides exhibited high α selectivity in coupling reactions.[5] Thus, the previously prepared DE segment **4** was coupled with the pentenyl mannoside **5b** to give **9** in 67% yield.

Coupling of the pentenylated dimannan **8** with trisaccharide **9** was mediated by iodosuccinimide/triflic acid.[6] The reaction was complete in 20 min at room temperature and afforded the pentasaccharide in 73% yield. However, the *Achilles' heel* of higher reactivity of the primary hydroxyl was poor selectivity. Indeed, the α,β ratio was 2:3, with the undesired coupling product predominating.

A C2 ester on the B segment would have ensured α selectivity in forging the B-C linkage via the well-known neighboring-group participation.[19] However, this possibility had been sacrificed in the decision for greater convergency using the AB block. On the other hand, if *convergency* was sacrificed, a stepwise synthetic plan could evolve around the ester **5d**, prepared by proton-induced rearrangement[17b] of ortho ester **7**, followed by acylation with chloroacetic anhydride. Indeed, the tetrasaccharide **10** was obtained in 53% yield by reaction of **9** with **5d**, the α anomer being the only product detected.

The final coupling involved the relatively hindered C2-OH highlighted in **10**, and hence, it was wise to choose a highly reactive partner for segment A. Accordingly, the pentenylated ortho ester **7** was utilized, *since treatment with halonium ion should generate the corresponding dioxolenium ion. Indeed, in the presence of* ***10****, pentasaccharide* ***11*** *was obtained as a single substance in 68% yield.* This material was identical with the minor product obtained by coupling of **8** and **9**. Full deprotection of **11** now afforded **1**.

The transformations described above illustrate one or more of the seven attributes of *n*-pentenyl glycosides noted at the beginning of this paper. Of special note are (i) the easy preparation of precursors, such as those in Scheme II, part b, particularly with regard to the formation, rearrangement, and high reactivity of

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(13) Other structures for the variant surface glycoprotein of *Trypanosoma brucei* had been suggested earlier than that in ref 12. For example, see ref 11a.

(14) The required inositol aglycon **3** was prepared from 6-*O*-benzyl-2,3:4,5-di-*O*-cyclohexylidene-L-*myo*-inositol (**13**) via standard procedures for acid hydrolysis, acetylation, and hydrogenolysis.

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(19) (a) Isbell, H. S.; Frush, H. L. *J. Res. Natl. Bur. Stand. (U.S.)* **1949**, *43*, 161 and papers cited therein. (b) For a convenient review, see: Bochkov, A. F.; Zaikov, G. E. *Chemistry of the O-glycosidic Bond*; Pergamon Press: Elmsford, NY; Chapter 2.

the ortho ester **7**, *under neutral conditions*,[17] and (ii) the mildness of the activation procedure.

Developmental studies are continuing and will be reported in due course.[20]

Supplementary Material Available: Experimental details of the preparation of compounds **1-4**, **5c,d**, **8-10**, **11α/β**, and **11α** (12 pages). Ordering information is given on any current masthead page.

(20) An invention disclosure has been filed to cover the use of *n*-pentenyl glycosides as glycosyl donors.

A Slow Proton Transfer from Trifluoroacetic Acid to Tribenzylamine in DMSO Solution

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We have discovered a remarkably small rate constant of 2.8×10^2 M^{-1} s^{-1} for the proton transfer from trifluoroacetic acid ($pK_a = 3.50$) to tribenzylamine ($pK_a = 3.64$ for the conjugate acid) in DMSO-d_6 (dimethyl sulfoxide-d_6) solution at 20 °C.

Since the work by Eigen and his co-workers[1] in the early 1960s, it has been believed that proton transfer reactions between nitrogen and oxygen acids and bases in solution occur at, or near, the diffusion-controlled limit. There have been occasional reports of such reactions occurring well below the diffusion limits, but these have all been thought to be highly unusual in some respect. For example, Bernasconi[2] and Ritchie[3] have reported rate constants of less than 10^6 M^{-1} s^{-1} for thermodynamically favorable proton transfers from several large, presumably sterically hindered, tertiary amines to amine and oxygen bases in DMSO solution. Kreevoy and Wang[4] studied the rates of protonation of ring-substituted tribenzylamines by the solvated proton in DMSO-d_6 and found rate constants ranging from 2.2×10^3 M^{-1} s^{-1} for tris(3-chlorobenzyl)amine to 1.8×10^4 M^{-1} s^{-1} for tribenzylamine. They also found that the *N,N*-dimethylbenzylamine protonation rate constant of 4.2×10^6 M^{-1} s^{-1} fit on the Brønsted correlation line for protonations of the tribenzylamines, indicating that the tribenzylamine protonations were not appreciably slowed by a steric effect. The slow protonations were rationalized as being due to the solvation of the proton in DMSO. Delpuech[5] has reported rate constants near diffusion limited for protonations of ammonia and of trimethylamine, but much lower than diffusion limited (6.7×10^5 M^{-1} s^{-1}) for protonation of *cis*-2,6-dimethyl-*N*-methylpiperidine, all in DMSO solution.

We have determined the proton transfer rates to tribenzylamine by ^1H NMR line-shape fitting using the Kaplan-Fraenkel density matrix method.[6] The pertinent parts of the NMR spectra in DMSO-d_6 solution are a doublet, $J = 5.2$ Hz, for the six equivalent benzyl protons of the tribenzylammonium ion centered at δ 4.32 ppm (1728 Hz) and a singlet for the six equivalent protons of tribenzylamine at δ 3.50 ppm (1401 Hz) in the 400-MHz spectrum. The T_2 relaxation time for the benzyl protons of tribenzylamine in DMSO-d_6 was found to be 0.93 s; the T_2 for the benzyl protons of the tribenzylammonium-d_1 ion in DMSO-d_6 was determined to be 1.06 s under conditions of very slow exchange in the presence of 1.6 M CF_3COOD. The J value for the protons was determined for the tribenzylammonium ion in the presence of 0.04 M CF_3SO_3H and found to be the same as that observed in $CDCl_3$ solution containing 0.06 M tribenzylamine plus 0.2 M CF_3SO_3H. Spectra of dilute solutions, typically 5×10^{-4} to 2×10^{-3} M of the amine, were obtained by using supression of the residual solvent protons in the purified "99.9%" DMSO-d_6 (Cambridge Isotope Laboratories). The solvent was purified as described by Bordwell[7] for the nondeuterated material; water content of the purified solvent was determined, typically, to be slightly less than 10^{-3} M by NMR analysis. All solutions were prepared and kept under argon atmospheres; normally capped NMR tubes of the purified solvent showed no increase in water content over periods of several days. The pK_a's were determined by Bordwell's indicator techniques;[8] the value of 3.5 for CF_3COOH is in good agreement with that of 3.45 reported by Bordwell,[9] and that of 3.6 for the tribenzylammonium ion is in good agreement with that of 3.65 reported by Kreevoy.[4]

Kinetic studies were carried out in solutions buffered by trifluoroacetic acid-trifluoroacetate ion prepared by partial neutralization of trifluoroacetic acid solutions with dimsylpotassium solution. Concentrations of trifluoroacetate ion were varied from 9.8×10^{-3} M to 1.0×10^{-1} M, and concentrations of tribenzylamine varied from 3.4×10^{-4} to 9.8×10^{-4} M. At low concentrations of trifluoroacetate, the benzyl proton doublet of the tribenzylammonium ion collapses to a singlet, and at higher concentrations, both this peak and the one due to the benzyl protons of tribenzylamine are considerably broadened, but not coalesced. Simulations of the spectra require two adjustable parameters: the $1/\tau_{BH^+}$ value and the amine/ammonium ion concentration ratio. It was observed that the concentration ratio required for fitting was not equal to that calculated from the buffer ratio and the pK values. This was found to be an ionic strength effect on the equilibrium constant, as is expected for this type of reaction involving neutral acid plus neutral base producing ionic conjugate base and ionic conjugate acid. The apparent pK_a of tribenzylammonium ion measured with 2,4-dinitro-4-chlorophenol varies with ionic strength, adjusted with sodium perchlorate, in quantitative accord with the NMR observations of the amine concentration ratios in the trifluoroacetate buffers at the same ionic strengths. A plot of Log K_{app} for the amine-phenol reaction vs the square root of the ionic strength of solutions is nicely linear with a slope of 1.44 (note that limiting Debye-Hückel theory gives a slope of 2.40).

The plot of $1/\tau_{BH^+}$ vs concentration of trifluoroacetate ion is linear with a slope of 2.0×10^2 M^{-1} s^{-1} and an intercept of 2.4 s^{-1}. The intercept corresponds to the rate of deprotonation of tribenzylammonium ion by solvent and is in reasonable agreement with the value of 4.0 ± 1.5 s^{-1} obtained by Kreevoy[4] as the intercept of plots of rates of deprotonation of tribenzylammonium ion by solvent vs water concentration. The value $1/\tau_{BH^+} = 4.3$ s^{-1} obtained at a trifluoroacetate ion concentration of 9.8×10^{-3} M is the same for tribenzylamine concentrations of 3.9×10^{-4} and 9.8×10^{-4} M; we conclude that the direct proton transfer from tribenzylammonium ion to tribenzylamine must have a second-order rate constant of much less than 10^3 M^{-1} s^{-1}.

These extremely slow proton transfers are similar to those found for strongly intramolecularly hydrogen bonded acids in aqueous solution[10] and could be due to hydrogen bonding of acids to solvent in DMSO solution. It seems less likely, but still conceivable, that steric effects are large enough, even for the small carboxylate ion or solvent, to severely decrease rates of reactions of tribenzylammonium ions. We are currently studying rates of other nitrogen and oxygen acid-base reactions in DMSO in hopes of defining the factors responsible for the slowness of the reactions.

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