(49%). Compound **2a** was shown to be stable towards transformation into **2b** under similar irradiation conditions, and this implies the photochemical route selectively forms **2b** from **1**. Compounds **2a** and **2b** were not interconvertible upon prolonged heating at 80 °C, that is, no intermetal movement of the isocyanide ligand occurs in these clusters.

In conclusion, we have demonstrated the first transformation of the bonding mode of C_{60} from μ_3-η^2,η^2,η^2 (π) to μ_3-η^1,η^2,η^1 (σ) on an Os_3 framework induced by an external ligand (**1** → **2a** + **2b**). We have shown that the selective formation of isomer **2b** can be accomplished by UV irradiation. Efforts are currently underway to understand the thermal and photochemical conversion pathways of the π and σ C_{60}–metal interactions. Reactivity studies and selective functionalization of the C_{60} ligand of **2a** and **2b** are also in progress.

Experimental Section

Details on the synthesis as well as full spectroscopic characterization of **1**, **2a**, and **2b** are given in the Supporting Information. For the X-ray structure analyses, data were collected on a CCD diffractometer with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) by using ω scans. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-151706 (**1**), CCDC-151707 (**2a**), and CCDC-151708 (**2b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

2a: Analysis calcd for $C_{85}H_{14}N_2O_8S_2Os_3$ (**2a**·CS_2): C 55.92, H 0.77, N 1.53, S 3.51; found: C 55.50, H 0.68, N 1.29, S 3.57; IR (C_6H_{12}): $\tilde{\nu} = 2079$ (s), 2068 (s), 2019 (s), 1986 cm^{-1} (s) (CO); $\tilde{\nu} = 2189$ (w), 1634 cm^{-1} (vw) (CN); ^1H NMR (400 MHz, CS_2/$CDCl_3$, 298 K): $\delta = 7.49$–6.98 (m, 10H; Ph), 5.50 (d, 1H, $J_{H,H} = 13$ Hz; CH_2), 4.95 (br s, 2H; CH_2), 4.87 (d, 1H, $J_{H,H} = 13$ Hz; CH_2); ^{13}C NMR (carbonyl region, 100 MHz, $C_6H_4Cl_2$/$C_6D_5CD_3$, 298 K): $\delta = 179.96$, 179.00, 178.32, 176.74, 175.74, 174.55, 173.39, 168.95; MS (FAB^+): m/z: 1754 [M^+].

X-ray data for **2a**: Brown crystals were obtained by slow diffusion of hexane into a solution of **2a** in CS_2 at room temperature. A crystal of dimensions $0.12 \times 0.14 \times 0.42$ mm was used for data collection: $C_{84}H_{14}N_2O_8Os_3 \cdot CS_2$, $M_r = 1825.7$; monoclinic, space group $P2_1/c$, $Z = 4$, $\rho_{calcd} = 2.105$ g cm^{-3}, $a = 19.4334(2)$, $b = 10.6922(2)$, $c = 29.0892(2)$ Å, $\beta = 107.615°$, $V = 5760.9(1)$ Å^3. The structure was solved by direct methods and refined by full-matrix least-squares analysis to give $R = 0.0448$ and $R_w = 0.0695$ (based on F^2) for 878 variables and 11 490 observed reflections with $I > 2\sigma(I)$ and $1.47 < \theta < 26.23$. Data collection at $T = 293(2)$ K.

2b: Analysis calcd for $C_{84}H_{14}N_2O_8Os_3$: C 57.66, H 0.81, N 1.60; found: C 56.76, H 0.61, N 1.22; IR (C_6H_{12}): $\tilde{\nu} = 2085$ (vs), 2052 (s), 2026 (vs), 2015 (w), 1992 (w), 1982 (w), 1968 cm^{-1} (m) (CO); $\tilde{\nu} = 2185$ (w), 1629 cm^{-1} (vw) (CN); ^1H NMR (400 MHz, CS_2/$CDCl_3$, 298 K): $\delta = 7.49$–7.19 (m, 10H; Ph), 5.66 (d, 1H, $J_{H,H} = 13$ Hz; CH_2), 5.48 (d, 1H, $J_{H,H} = 16$ Hz; CH_2), 5.41 (d, 1H, $J_{H,H} = 16$ Hz; CH_2), 4.88 (d, 1H, $J_{H,H} = 13$ Hz; CH_2); ^{13}C NMR (carbonyl region, 100 MHz, $C_6H_4Cl_2$/$C_6D_5CD_3$, 223 K): $\delta = 181.9$, 176.9, 176.1, 175.8, 175.5, 174.5, 173.2, 169.2; MS (FAB^+): m/z 1754 [M^+].

X-ray crystal data for **2b**: Brownish black crystals were obtained by slow diffusion of methanol into a solution of **2b** in toluene at room temperature. A crystal of dimensions $0.41 \times 0.29 \times 0.11$ mm was used for data collection: $C_{84}H_{14}N_2O_8Os_3$, $M_r = 1749.6$; monoclinic, space group $P2_1/c$, $Z = 4$, $\rho_{calcd} = 2.024$ g cm^{-3}, $a = 19.9376(8)$, $b = 23.0770(9)$, $c = 12.8318(5)$ Å, $\beta = 103.462(1)°$, $V = 5741.7(4)$ Å^3. The structure was solved by direct methods and refined by full-matrix least-squares analysis to give $R = 0.0779$ and $R_w = 0.1995$ (based on F^2) for 851 variables and 8192 observed reflections with $I > 2\sigma(I)$ and $1.37 < \theta < 23.34$. Data collection at $T = 193(2)$ K.

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Expanding the Pyrimidine Diphosphosugar Repertoire: The Chemoenzymatic Synthesis of Amino- and Acetamidoglucopyranosyl Derivatives**

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An extensive body of in vivo genetic evidence indicates that the glycosyltransferases involved in secondary metabolism are extremely promiscuous with respect to their nucleotide diphosphosugar (NDP-sugar) donor.[1] Yet, in vitro experiments in this area are limited to only a few examples, partly because of the lack of the required NDP-sugar substrates for

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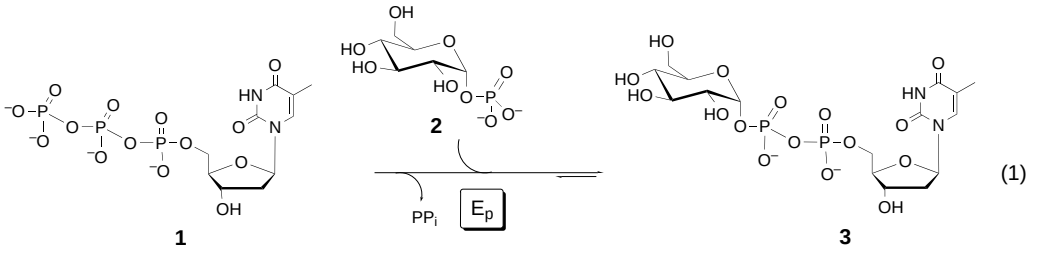
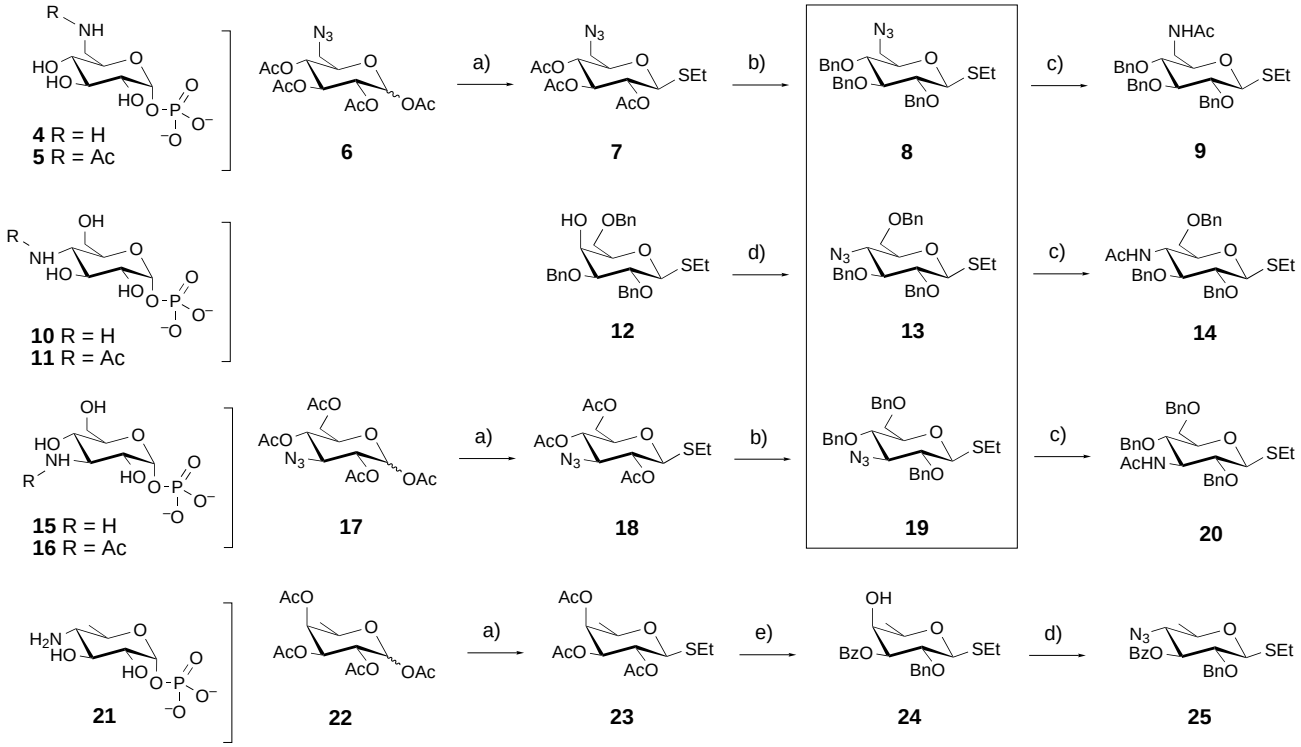
these experiments.[2] Thus, the reliance of these unique glycosyltransferases on pyrimidine diphosphosugars (uridine (UDP)/thymidine (dTDP)) has revitalized interest in methods to expand the repertoire of UDP/dTDP-sugars.[3] We recently reported that *Salmonella enterica* LT2 α-D-glucopyranosyl phosphate thymidylyltransferase (E_p),[4] which catalyzes the reaction shown in Equation (1), can convert a



(1)

wide array of α-D-hexopyranosyl phosphates into their corresponding dTDP- *and* UDP-nucleotide sugars.[3] Herein we expand this methodology to include glycosides that are common to biological systems, namely aminodeoxy-α-D-hexopyranosyl phosphates and acetamidodeoxy-α-D-hexopyranosyl phosphates. A general chemoenzymatic method to rapidly generate these reagents is presented. This method is significant because it provides a substrate set for developing in vitro glycosylation systems. Furthermore, a direct comparison between a series of aminodeoxy-α-D-glucopyranosyl phosphate series and their corresponding acetamidodeoxy analogues provides insight into the ability of the active site of E_p to accommodate additional steric bulk.

Only two of the aminodeoxy-α-D-glucopyranosyl phosphates examined, 2-amino-2-deoxy-α-D-glucopyranosyl phosphate (**26**; see Figure 1) and 2-acetamido-2-deoxy-α-D-glucopyranosyl phosphate (**27**; Figure 1), were commercially available. The syntheses of the remaining analogues diverged from the key intermediates **8**, **13**, and **19** (Scheme 1). 1-Ethylthio-β-D-pyranosides **8** and **19** were derived from the previously reported glycosides **6**[5] and **17**,[6] respectively, whereas **13** was synthesized from the previously reported **12**,[7] in a manner strategically similar to the synthesis of deoxy-α-D-glucopyranosyl phosphate.[3] Specifically, this effective strategy invoked a protection scheme to selectively expose the position of substitution, followed by activation (with TsCl or Tf_2O; Ts = *para*-toluenesulfonyl, Tf = trifluoromethanesulfonyl) and S_N2 displacement by sodium azide. From the divergent point (**8**, **13**, and **19**), an efficient and selective reduction of the azide group with $SnCl_2$, followed by acetylation, gave the desired 1-ethylthio-β-D-pyranoside precursors **9**, **14**, and **20**. Finally, **9**, **14**, and **20**



Scheme 1. An overview of the key steps in the described syntheses of analogues of E_p substrates. The box highlights the point from which the aminodeoxy-α-D-glucose phosphate series and the acetamidodeoxy-α-D-glucose phosphate series diverge. Reaction conditions: a) Me_3SiSEt, ZnI_2 (84.2% overall yield); b) 1) MeONa, 2) NaH, BnBr (77.3% average overall yield, two steps); c) 1) $SnCl_2$, PhSH, Et_3N, 2) Ac_2O, py (84.0% average overall yield, two steps); d) 1) Tf_2O, py, 2) NaN_3 (87.7% average overall yield, two steps); e) 1) NaOMe, 2) $CH_3C(OCH_3)_2CH_3$, TsOH, 3) NaH, BnBr, 4) HCl/MeOH, 5) BzCl, DMAP, Et_3N (87.3% average overall yield, five steps); final steps (not shown): 1) phosphorylation, 2) reductive deprotection, 3) cation exchange to give the Na^+ salt (44.4% average overall yield, three steps). Bn = benzyl, Bz = benzoyl, DMAP = 4-dimethylaminopyridine, py = pyridine.

were phosphorylated by the reaction with dibenzyl phosphate as previously described,[3] and reductively deprotected to form **5**, **11**, and **16**, respectively. The same procedure also led to the conversion of azides **8**, **13**, and **19** into the desired amines **4**, **10**, and **15**, respectively. An aminodideoxy sugar, 4-amino-4,6-dideoxy-α-D-glucopyranosyl phosphate (**21**), was also synthesized from peracetylated D-fucose (**22**) by using a similar strategy (Scheme 1).

To evaluate the synthetic utility of our thymidylyltransferase,[8] E_p, α-D-glucopyranosyl phosphate, Mg^{2+}, nucleotide triphosphate (NTP), and inorganic pyrophosphatase[9] were incubated at 37 °C for 30 min, and the extent of product formation was determined by HPLC (Figure 1).[10] For each assay, confirmation of the product was based on high-resolution mass spectrometry (HR-MS) of the HPLC-isolated products, and in some cases also on HPLC coelution with commercially available standards.[11] Control reactions showed that no product formation was observed in the absence of E_p, glucopyranosyl phosphate, Mg^{2+}, or NTP. The fundamental goal of this work was to assess the utility of E_p in simplifying the synthesis of nucleotide sugar pools. Figure 1 clearly illustrates that E_p is advantageous for this task: of the nine substrate analogues tested, seven with thymidine triphosphate (dTTP) and four with uridine triphosphate (UTP) provide appreciable amounts of product (more than 50% conversion) under the conditions described.

A comparison of the aminodeoxy-α-D-glucopyranosyl phosphate/dTTP assay results (Figure 1, **4**, **10**, **15** and **26**) with the native reaction of E_p (Figure 1, **3**/dTTP) reveals that the position of the amino substituent has absolutely no effect on product formation, and, with the exception of **4**, a similar phenomenon is observed in the presence of UTP. The divergence of **4** from this trend is consistent with our previous observations of a UTP-dependent E_p "adverse cooperation" in the presence of certain hexopyranosyl phosphates,[3] perhaps a result of allosteric activation by dTTP.[12] An evaluation of the acetamidodeoxy-α-D-glucopyranosyl phosphate/dTTP assays (Figure 1, **5**, **11**, **16**, and **27**), in comparison to their non-acetylated counterparts (Figure 1, **4**, **10**, **15**, and **26**, respectively), revealed that a bulky *N*-acetyl group at C2 or C3 (**16** and **27**) is tolerated, whereas the identical substituent at C4 or C6 (**5** and **11**) results in a complete loss of activity. Given that these effects most likely derive from unfavorable steric interactions, it follows that the active site of E_p is able to accommodate additional C2/C3 bulk, whereas steric interactions limit the allowed C4/C6 substitutions. To our surprise, product formation from **5**/UTP was eight times that from **5**/dTTP. This is the first example that contradicts the typical adverse UTP-dependent effect on yields, as illustrated by **4** and **16** in the present study. Finally, a comparison of aminodideoxy-α-D-glucopyranosyl phosphate (**21**)[13] with **10** reveals that C6 deoxygenation does not affect dTTP-dependent E_p catalysis, but greatly diminishes UTP-dependent conversion (Figure 1). Given that independent deoxygenation at C6[3] or amino substitution at C4 (**10**) have no effect on product yield (in the context of our assay conditions), data from independent substitutions may not be reliable in predicting the effects of multiple substitutions on product yield.

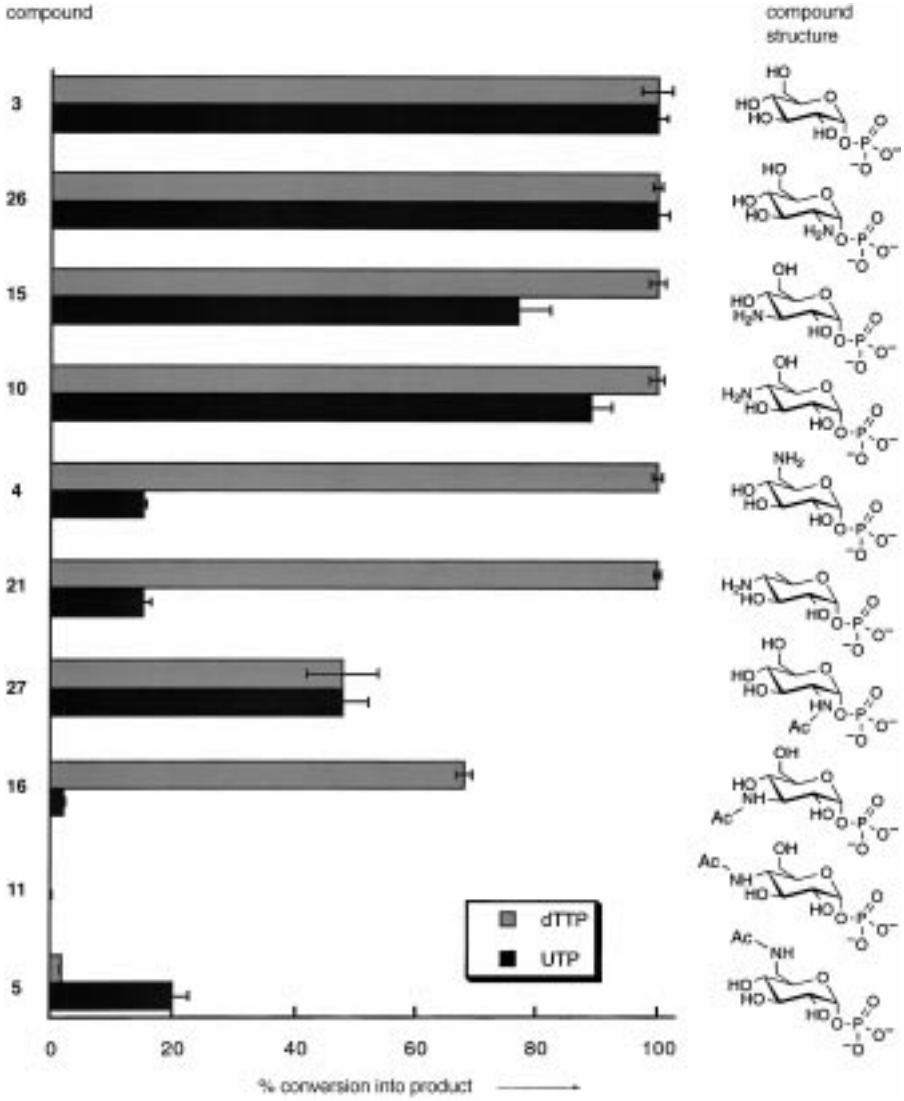


Figure 1. The E_p-catalyzed conversion of "unnatural" substrates. Percent conversion $= [A_P/(A_P + A_T)] \times 100$ (A_P = the NDP-sugar product peak integration, A_T = the NTP peak integration). The composition of all the products was confirmed by HR-MS.

In conclusion, the presented work further substantiates the promiscuous nature of E_p and the advantages of exploiting this unique characteristic to synthesize an incredible array of valuable nucleotide diphosphosugar reagents. Thus, these studies will broadly impact efforts to understand and exploit the biosynthesis of glycosylated

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bioactive natural products.[1] Moreover, this work suggests that E_p can accept greater C2/C3 steric bulk in the substrate (relative to **3**), which opens the door to even more imaginative substitutions at these positions. Efforts are in progress to further expand the scope of this methodology.

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[10] The reaction of a mixture containing NTP (2.5 mM), sugar phosphate (5.0 mM), $MgCl_2$ (5.5 mM), and inorganic pyrophosphatase (10 U; 1 U = the amount of protein needed to produce 1 μmol min^{-1} of TDP-D-glucose) in potassium phosphate buffer (pH 7.5, 50 mM, 50 μL) at 37 °C was initiated by the addition of E_p (3.52 U). The reaction was incubated with slow agitation for 30 min at 37 °C, quenched with MeOH (50 μL), centrifuged (5 min, 14000 × *g*), and the supernatant was stored at −20 °C until analysis by HPLC. Samples (30 μL) were resolved on a Sphereclone 5 μ SAX column (150 × 4.6 mm) fitted with a SecurityGuard cartridge (Phenomenex, Torrance, CA) by using a linear gradient (potassium phosphate buffer, pH 5.0, 50 – 200 mM, 1.5 mL min^{-1}, A_{275nm}).
[11] HPLC product fractions from the assay described in ref. [10] were lyophilized and submitted directly for HR-MS (fast-atom bombardment (FAB)) analysis.
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Note added in proof: The three-dimensional structure of E_p and the structure-based engineering of E_p to expand the methodology reported here have recently been reported (W. A. Barton, J. Lesniak, J. B. Biggins, P. D. Jeffrey, J. Jiang, K. R. Rajashankar, J. S. Thorson, D. B. Nikolov, *Nat. Struct. Biol.* **2001**, in press).

$[Ru(N_2)(P\mathit{i}Pr_3)(\text{'}N_2Me_2S_2\text{'})]$: Coordination of Molecular N_2 to Metal Thiolate Cores under Mild Conditions**

Dieter Sellmann,* Barbara Hautsch, Annette Rösler, and Frank W. Heinemann

Dedicated to Professor Ernst-Gottfried Jäger on the occasion of his 65th birthday

X-ray crystallography has revealed the structure of FeMo nitrogenase and its FeMo cofactors, however, the molecular mechanism of biological N_2 fixation has remained as unknown as low-molecular weight compounds catalyzing the reduction of N_2 under mild and biologically compatible conditions.[1] These conditions rule out the use of alkali metals or comparably strong reductants at any stage in the design of a nonenzymatic chemical system for modeling the biological N_2 reduction. This includes the first stage, the synthesis of N_2 complexes.

All mechanisms postulated for biological N_2 fixation consider the coordination of N_2 to the metal sulfur core of the Fe_7MoS_9 cofactors as the first key step.[1] However, *metal sulfur complexes* that bind N_2 under mild conditions are unknown, in spite of numerous intensive efforts.[2] There are only 12 N_2 complexes with sulfur coligands,[3] only two of which could be prepared directly from molecular N_2.[3a,f] Their preparation, however, required strong reductants or precursors prepared by use of strong reductants. None of these complexes meets the severe constraints with regard to mild conditions.

Our attempts to tackle this problem have focussed on sulfur ligand complexes of iron and its congener ruthenium. They

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