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Synthesis of Diverse Ethoxyformacetal Oligomers. Toward Libraries of Metal-Coordinating Unnatural Biopolymers

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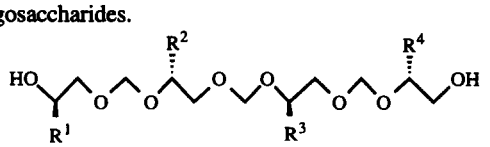
Abstract: An expedient two-step iterative protocol for the solution-phase elaboration of ethoxyformacetal oligomers is described. A set of four O,S-thioformacetal donor monomers, with diverse chiral side-chains, were coupled using NIS/TfOH activation to afford three model tetramers.

Recently, there has been considerable interest in the synthesis and screening of libraries of novel chemical structures for applications as biological ligands and small-molecule receptors.[2] In particular, there have been numerous efforts toward the development of libraries of novel "unnatural biopolymers"[3] including oligocarbamates,[4] peptoids,[5] oligoureas,[6] oligopyrrolinones,[7] oligosulfonamides,[8] and β-peptides.[9] Because these oligomeric compounds can be assembled, like peptides, from a set of diverse building blocks, large molecular libraries can be rapidly generated. In contrast to peptides, the properties of the backbone, including solubility, proteolytic stability, conformation and hydrogen bonding ability, can be chemically "tuned" to improve bioavailability or to create novel secondary and tertiary structures.

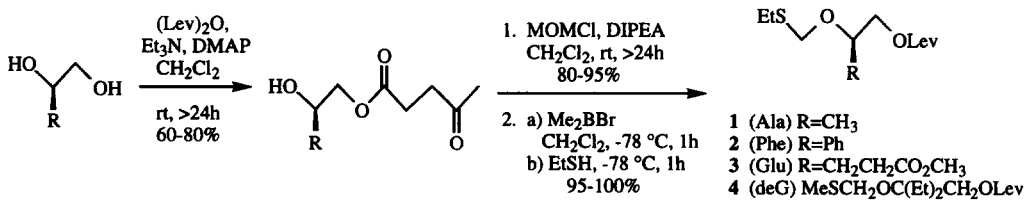
As part of our ongoing efforts toward the development and exploration of the physical, chemical, and biological properties of unnatural biopolymers, we wished to design a non-amide scaffold capable of selective metal ion coordination. Based on the seminal work on cyclic (crown) and acyclic (podand) ethers,[10] we chose to elaborate libraries of acyclic oligoethers. The use of a backbone consisting of oxygen atoms should confer to the oligomer the ability to bind hard metal cations (Li^+, Na^+, Ca^{2+}, Mg^{2+}) and may result in interesting secondary structures or novel functions such as ion transporters or solid electrolytes. Although lacking the conformational restriction of cyclic receptors, one might identify ligands that fold into stable, ordered metal ion complexes by screening large libraries of linear oligomers.[11]

Synthetic routes to oligoethers that involve the displacement of alkyl halides with metal alkoxides require harsh reaction conditions. The alternative approach described herein exploits the formacetal linkage to assemble glycol units bearing diverse chiral side-chains. The resulting poly(ethoxymethoxy) backbone can be viewed as a truncated mimetic of 1,6-oligosaccharides.



In general, the formation of substituted acetals involves milder conditions and several methods derived from oligosaccharide chemistry are potentially available. The formacetal function is very stable to basic conditions and appreciably resistant to aqueous acid (to pH 2-3). Although two atoms longer than an ethylene glycol unit, the formacetal linkage still offers some conformational rigidity through the anomeric effect,[12] and the acetal oxygens should show comparable basicity to ethers. Indeed, some natural products such as the ionophoric antibiotic monensin are known to bind metals through acetal functions.[13]

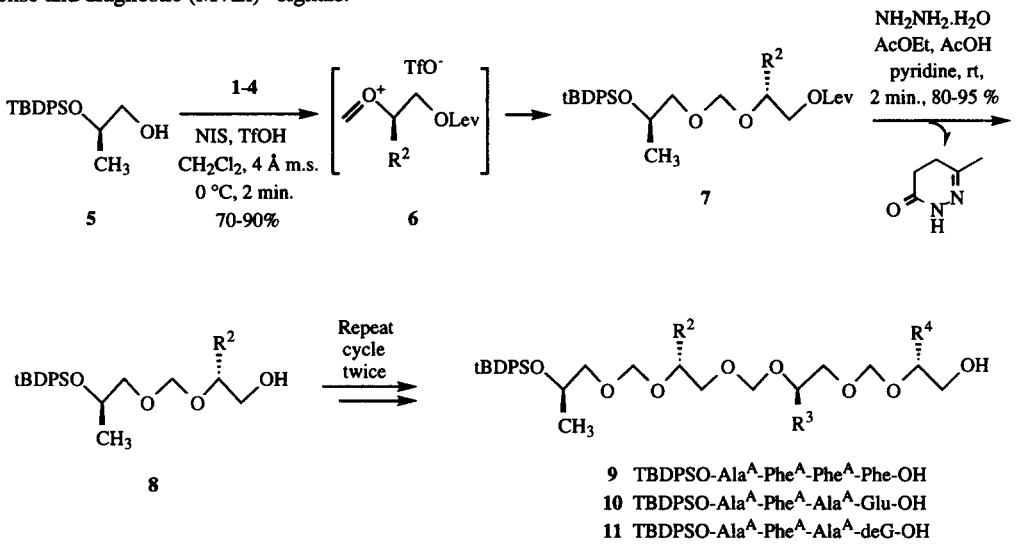
Herein, we describe an expedient iterative solution-phase synthetic cycle to assemble functionally diverse 1,2-diol units through formacetal coupling. Several chiral vicinal diols (glycols) are commercially available in both enantiomeric forms. Alternatively, they are readily accessible through synthetic methods such as the Sharpless asymmetric dihydroxylation.[14] Given the mildness and effectiveness (rates and yields) of thioglycoside coupling methods, we wished to extend the use of the van Boom variant[15] to the construction of formacetals through the generation of transient oxonium ions. The levulinyl ester[16] (Lev), which can be rapidly removed under relatively mild conditions (hydrazine, pH 5), was selected as an orthogonal protecting group for the terminal hydroxyl group. As shown in general Scheme 1, the three-step monomer synthesis route starts with the mono-esterification of a chiral glycols, affording the secondary alcohols as the major products in variable yields (60-80%) depending on the nature of the side chain (R). The free hydroxyl is then alkylated with MOMCl in high yield (80-95%). The method of Morton and Guindon,[17] which involves the one-pot sequential treatment of MOM ethers with Me_2BBr and thioethanol, was found the most practical one to complete the synthesis of the desired O,S-thioformacetal monomers in very high yield (95-100%). Using this route, four model monomers structurally analogous to amino acids were prepared; the alanine analog (Ala, **1**), phenylalanine (Phe, **2**) as a hydrophobic side-chain capable of π-cation interactions, methyl-protected glutamic acid (Glu, **3**) for metal ion complexation, and the conformationally restrained diethyl glycine monomer (deG, **4**).[18]



Scheme 1.

The iterative two-step coupling cycle is illustrated in Scheme 2.[20] Starting from TBDPS-protected alanine acceptor **5**, a typical sequence involves mixing the primary alcohol and one of the donor monomers (**1-4**) in methylene chloride/tetrahydrofuran (THF) containing molecular sieves at 0 °C. The coupling reaction was triggered by the addition of a THF solution of N-iodosuccinimide (NIS) and catalytic trifluoromethanesulfonic acid (TfOH), and stopped after 2 min.[21] The adduct **7** could be isolated in satisfactory isolated yield (70-90%), and then subjected to levulinyl ester cleavage with hydrazine in pyridine/ethyl acetate/acetic acid at room temperature for 2 min., affording the alcohol **8** in high yields (80-95%) after flash-chromatography, which is required to eliminate the levulinic acid cyclic by-product. This cycle was repeated twice with different monomers, as demonstrated by the synthesis of three tetrameric sequences (**9-11**). The short reaction times required make this two-step protocol quite practical. It is also noteworthy that the methyl-protected glutamate side chain remained untouched under the hydrazinolysis conditions. A control coupling reaction was performed

with monomer **2**, indicating that epimerization through oxonium intermediate **6** does not occur. Indeed, the resulting adduct was degraded back to 1-phenyl-1,2-ethanediol and showed no loss of optical activity. The tetramers (**9-11**) were obtained in high purity and were characterized by ^{1}H, ^{13}C NMR, and mass spectroscopy (MS).[20] Under FAB ionization with a LiCl-containing matrix, fragmentation was minimal and resulted in very intense and diagnostic $(M+Li)^+$ signals.



Scheme 2. (NOTE. A:formacetal linkage)

This study shows the applicability of O,S-thioacetal oxidative activation for formacetal coupling. As exemplified in the synthesis of compounds **9-11**, this protocol allows the facile and expedient construction of glycomimetic ethoxyformacetal oligomers. The mildness of the NIS/TfOH activation method is compatible with the use of diverse chiral side chains. We are currently attempting to apply this iterative protocol to solid-support for the elaboration of large libraries directed toward screening for metal ion ligands.

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18. The starting S-(+) enantiopure 1,2-diols were purchased from Aldrich Chemical Co. 1,1-Diethyl glycol was made from the osmium catalyzed dihydroxylation of 2-ethyl-1-butene. The thioacetalization step to make **4** was carried out using the method of Yamada[19] (DMSO, Ac_2O).
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20. **Typical coupling cycle and characterization of tetramers 9-11.** To a stirred solution of donor alcohol (1.00 mmol) and acceptor O,S-acetal (1.25 mmol) in a 2:1 methylene chloride/tetrahydrofuran mixture (3 mL) containing 4 Å molecular sieves, at 0 °C, was quickly added a solution of NIS (1.25 mmol) and TfOH (0.15 mmol) in THF (1 mL) cooled to 0 C. The solution became increasingly dark purple and was stirred for 2 min. A dilute aqueous solution of sodium thiosulfate was added (5 mL), followed by methylene chloride (50 mL) and the mixture was stirred for 15 min. or until it becomes uncolored. The separated organic layer was further washed with aq. dilute $Na_2S_2O_3$, brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash-chromatography over a short silica gel column.

    The coupling adduct was then stirred in a 4:1 pyridine/ethyl acetate mixture (3 mL). A solution of hydrated hydrazine (10 mmol) in a 3:2 pyridine/acetic acid mixture (2 mL) was added and the solution was stirred for 2 min. Water (5 mL) was added and the mixture was extracted with methylene chloride (5x10 mL). The combined organic layers were washed with water, aq. $NaHCO_3$ (2x), dried with anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by flash-chromatography over a short silica gel column.

    TBDPSO-Ala^A-Phe^A-Phe^A-Phe-OH (9) Clear oil: IR (neat) 3495 (br), 3040-3070, 2950, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (3H, d, J=7.0 Hz, $-CH_3$), 1.04 (9H, s, $-C(CH_3)_3$), 3.48-3.70 and 3.79-3.90 (9H, m, 4x $-CH_2O-$ + $-OCH(CH_3)-$), 4.50-4.90 (9H, m, 3x $-OCH_2O-$ + 3x $-OCH(Ph)-$), 7.20-7.45 (21H, m, ArH), 7.65 (4H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 16.5, 19.2, 26.9, 67.2, 67.7, 71.4, 71.6, 72.8, 76.8, 80.5, 91.8, 93.2, 93.6, 126.9, 127.1, 127.1, 127.4, 127.6, 127.7, 128.0, 128.0, 128.2, 128.4, 128.4, 129.5, 129.6; MS (FAB) m/z 771 $(M+Li)^+$; HRMS (FAB) m/z 771.3895 (calcd for $C_{46}H_{56}O_8SiLi$ 771.3905).

    TBDPSO-Ala^A-Phe^A-Ala^A-Glu-OH (10) Clear oil: IR (neat) 3465 (br), 3100-3000, 2925, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (3H, d, J=6.5 Hz, $-CH_3$), 1.05 (9H, s, $-C(CH_3)_3$), 1.06 (3H, d, J=6.5 Hz, $-CH_3$), 1.82 (2H, m, $-CH_2CH_2CO_2CH_3$), 2.40 (2H, t, J = 7.5 Hz, $-CH_2CO_2CH_3$), 3.30-3.80 (10H, m, 4x $-CH_2O-$ + 2x $-OCH(CH_3)-$), 3.66 (3H, s, $-CO_2CH_3$), 3.84 (1H, m, + $-OCH(CH_2-)-$), 4.60-4.88 (7H, m, 3x $-OCH_2O-$ + $-OCH(Ph)-$), 7.20-7.45 (11H, m, ArH), 7.65 (4H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 16.4, 16.9, 19.1, 26.6, 26.7, 29.9, 51.5, 65.1, 67.7, 71.5, 71.8, 72.8, 76.5, 81.0, 91.7, 94.1, 95.6, 127.1, 127.4, 127.6, 127.7, 128.2, 129.4, 129.5, 133.5, 135.5, 135.8, 139.1, 173.7; MS (FAB) m/z 719 $(M+Li)^+$; HRMS (FAB) m/z 719.3819 (calcd for $C_{39}H_{56}O_{10}SiLi$ 719.3803).

    TBDPSO-Ala^A-Phe^A-Ala^A-deG-OH (11) Clear oil: IR (neat) 3495 (br), 3100-3000, 2940 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (6H, t, J=7.0 Hz, $-C(CH_2CH_3)_2-$), 0.96 (3H, d, J=6.5 Hz, $-CH_3$), 1.04 (9H, s, $-C(CH_3)_3$), 1.05 (3H, d, J=6.5 Hz, $-CH_3$), 1.40-1.60 (4H, m, $-C(CH_2CH_3)_2-$), 3.37-3.55 (6H, m) + 3.60-3.75 (3H, m) (4x $-CH_2O-$ + $-OCH(CH_3)-$), 3.87 (1H, dd, J=6.0, 6.0 Hz, $-OCH(CH_3)-$), 4.60-4.85 (7H, m, 3x $-OCH_2O-$ + $-C(Ph)H-O-$), 7.25-7.45 and 7.60-7.70 (15H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 7.4, 7.5, 16.5, 16.8, 19.2, 23.8, 24.2, 26.8, 65.2, 67.8, 71.7, 72.9, 76.8, 82.2, 89.0, 91.8, 94.0, 127.2, 127.4, 127.6, 127.6, 127.8, 128.3, 129.5, 129.6, 135.6, 135.6, 135.8, 139.2; MS (FAB) m/z 689 $(M+Li)^+$; HRMS (FAB) m/z 689.4062 (calcd for $C_{39}H_{58}O_8SiLi$ 689.4061).
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