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COMMUNICATION

A programmable "build–couple" approach to the synthesis of heterofunctionalized polyvalent molecules†

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A maximally divergent "build–couple" synthesis of heterofunctionalized polyvalent molecules is described. This strategic approach enables the synthesis of highly diverse polyvalent structures from a pre-programmed combinatorial set of modules.

Polyvalent interactions play a critical role in a large number of biochemical processes, including protein–nucleic acid and protein–protein interactions.[1] Traditional small molecules (MW < 800 Daltons) regulate a small number of such interactions. In contrast, the overwhelming majority of polyvalent biochemical processes, which utilize large surface areas and "flat" topologies, are largely resistant to traditional small molecule-dependent regulation.[2]

In an effort to expand beyond the traditional small molecule paradigm, researchers have begun to synthesize and evaluate new materials and molecules designed to interact with polyvalent targets. Various molecular architectures, including dendrons and dendrimers, have recently emerged as a potential solution to recognizing polyvalent systems.[3] While the large surface area spanned by these molecules is a critical component for recognizing complex polyvalent surfaces, highly selective binding typically requires spatially-defined interactions involving diverse functional groups. For example, heterofunctionalized polyvalent molecules that display functional groups precisely matching the electrostatic signature of their polyvalent target would be expected to have higher target affinity, binding selectivity and therapeutic utility, in comparison to polyvalent molecules that display a single functional group. However, in comparison to homofunctionalized polyvalent molecules, general approaches for the programmed synthesis of heterofunctionalized polyvalent molecules are limited.[4]

Unlike strategies that rely on iterative steps to grow or diversify a polyvalent molecule, we envisaged a "build–couple" approach, wherein pre-programmed heterofunctionalized modules are first synthesized, then selectively coupled to a multi-podal core. The general "build–couple" concept is illustrated in Fig. 1.[5] This maximally divergent strategic choice allows for the preparation of highly diverse polyvalent structures from a combinatorial set of modules. In order to avoid the generation of racemic molecules, our approach focuses on modules that contain a programmable combination of two identical and one different functional group.

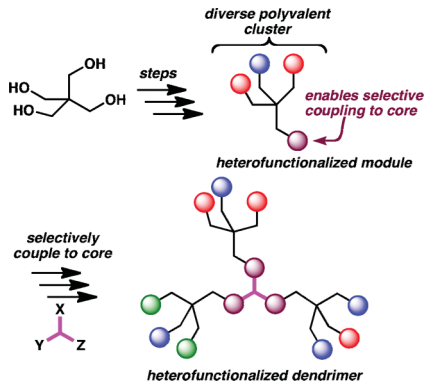

Fig. 1 A programmable and convergent "build–couple" strategy yielding a hetero-functionalized dendrimer.

As a proof-of-concept, we prepared a small library of heterofunctionalized modules, beginning with the preparation of triol **1** from pentaerythritol, which proceeded in 91% overall yield, over three steps. Triol **1** was then reacted with propargyl bromide to generate di- and tri-propargylated compounds **2** and **3**, respectively. The highest yield (55%) of di-propargyl compound **2** was obtained when six equivalents of propargyl bromide were used.[6] Unlike compound **3**, the primary alcohol and terminal alkynes in compound **2** can be orthogonally functionalized. In order to utilize tri-yne **3**, it was converted into a ~1 : 2 ratio of mono- (29%) and di-TMS (52%) alkynes **4** and **5**, by addition of trimethylsilyl trifluoromethansulfonate and zinc triflate.[7,8] Taken together, three module precursors (**2**, **4** and **5**) were synthesized in 83% overall yield from **1** in either one or two steps (Scheme 1).

We next prepared six azide or alkyne building blocks **6–9b**[9] (Scheme 2A), which contain protein-compatible hydrophobic, anionic (protected as the *t*-butyl ester) or cationic groups (Boc protected). As a proof-of-concept, we prepared four heterofunctionalized modules from precursors **2**, **4** and **5** and building blocks **6–9b**, (Scheme 2B). Module precursor **2** was first reacted with two equivalents of azide **6** using Huisgen–Sharpless 1,3-dipolar cycloaddition conditions.[9] The remaining primary alcohol was next converted to the mesylate, then to the corresponding azide by reacting with sodium azide at 110 °C for 72 h. A 1,3-dipolar

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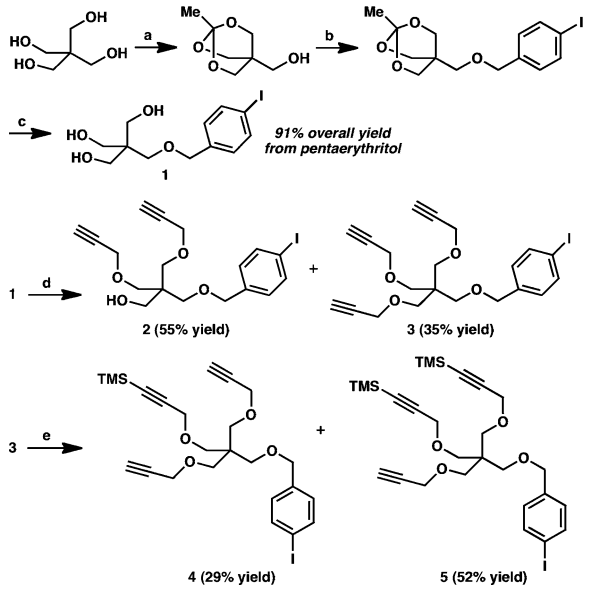


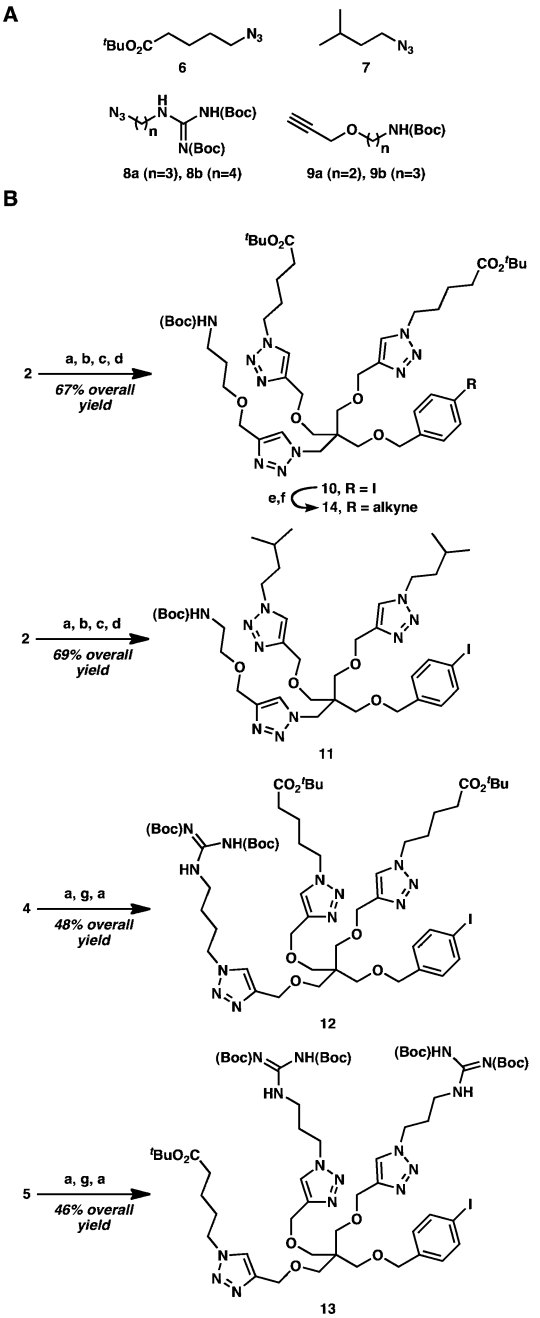
Scheme 1 Synthesis of module precursors **2**, **4** and **5**. a = $MeC(OEt)_3$, PTSA (0.1 equiv.), toluene, 100 °C, 3 days, 95% yield; b = *p*-iodobenzyl bromide, NaH/DMF, 25 °C, 2 h, 98% yield; c = HCl (0.1 equiv.)/MeOH, 50 °C, 4 h, 98% yield; d = propargyl bromide (6 equiv.), NaOH, $DMSO/H_2O$, 25 °C, 18 h; e = TMS-OTf, $Zn(OTf)_2$, Et_3N, DCM, 25 °C, 20 h.

cycloaddition between the newly formed azide and terminal alkyne on **9b** was used to generate heterofunctionalized module **10** in 67% overall yield, in four steps from **2**. Heterofunctionalized module **11** was prepared similarly in 69% overall yield from **2**, using building blocks **7** and **9a**. A synthetic sequence involving a 1,3-dipolar cycloaddition, removal of TMS from the remaining alkyne(s), and an additional 1,3-dipolar cycloaddition was employed to synthesize heterofunctionalized modules **12** and **13**, in three steps, from precursors **4** and **5** in 48% and 46% overall yield, respectively.

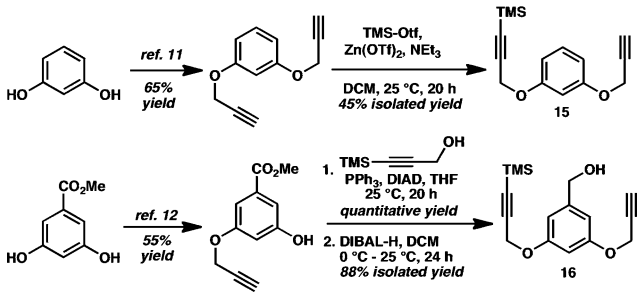
An orthogonal coupling strategy[10] was used to chemoselectively attach modules to a core scaffold. We envisaged utilizing either a palladium-catalyzed Sonogashira reaction between the iodobenzene moiety present on modules **10–13** and a pendant terminal alkyne on a core structure, or a Huisgen–Sharpless 1,3-dipolar cycloaddition reaction between a module equipped with a terminal alkyne and pendant azide on a core structure. In order to test the latter approach, *p*-ethynyl module **14** was prepared in two steps from **10** in 66% overall yield (Scheme 2B, steps e–f).

With this orthogonal coupling strategy in mind we prepared two previously unreported di- and tri-podal cores **15**[11] and **16**,[12] respectively (Scheme 3), which can be programmably decorated with modules **10–14**. The synthesis of a heterofunctionalized dendron was initiated by coupling module **10** to di-podal core **15** using a Sonogoshira reaction, which proceeded in 95% yield. Removal of the TMS group on the remaining alkyne was next achieved by the addition of cesium fluoride. The resulting terminal alkyne was then coupled to module **12** in 62% yield, using an additional Sonogashira reaction.[13]

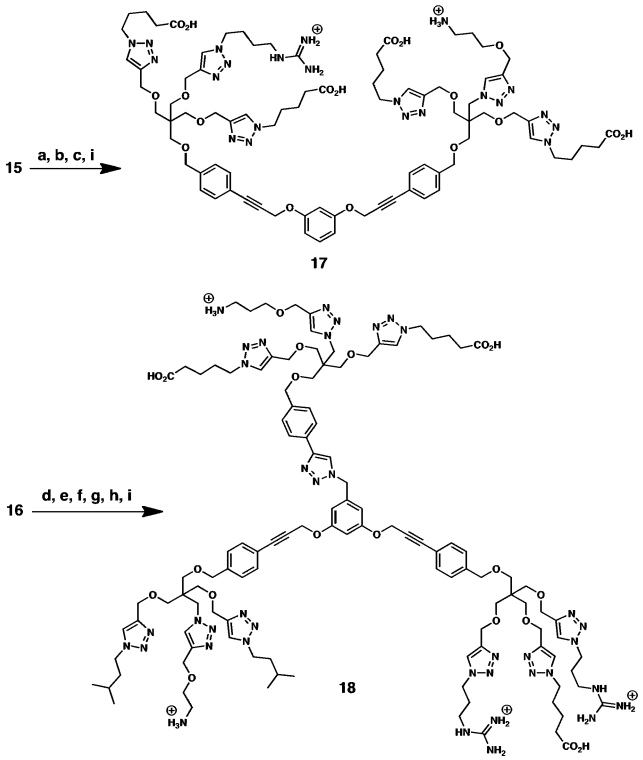
A tri-podal heterofunctionalized dendrimer was prepared by first performing a Sonogashira reaction between core **16** and module **11**. Our initial efforts to convert the benzyl alcohol on the Sonogashira reaction product to the corresponding azide by mesylation and displacement with sodium azide were unsuccessful. However, a recently reported variation[14] on the Mitsunobu reaction, which employs DDQ as the activating reagent, was used to successfully install an azide in 65% yield. A subsequent 1,3-dipolar cycloaddition between the newly generated core azide and alkyne on module **14** was achieved in 74% yield. Following removal of the TMS group from the remaining alkyne, module **13** was attached *via* a Sonogashira reaction. For both the di- and tri-podal molecules, global deprotection of *t*-butyl ester and Boc groups



Scheme 2 (A) Azide and alkyne building blocks. (B) Synthesis of heterofunctionalized modules. a = azide building block, CuI (10 mol%), DIPEA, THF, 25 °C, 15 h; b = MsCl, Et_3N, DCM, 25 °C, 4 h; c = NaN_3, DMF, 110 °C, 72 h; d = alkyne building block, CuI (10 mol%), DIPEA, THF, 70 °C, 15 h; e = ethynyltrimethylsilane, $PdCl_2(PPh_3)_2$ (10 mol%), CuI (20 mol%), NEt_3, DMF, 25 °C, 8 h; f = CsF, MeCN, 25 °C, 3 h; g = K_2CO_3, MeOH, 25 °C, 1.5 h.



Scheme 3 Synthesis of di- and tri-podal cores **15** and **16**.



Scheme 4 Programmed synthesis of di- and tri- hetero-functionalized polyvalent compounds. a = **10**, $PdCl_2(PPh_3)_2$ (10 mol%), CuI, (20 mol%), NEt_3, DMF, 25 °C 12 h (95% yield); b = CsF, MeCN, 25 °C, 14 h (77% yield); c = **12**, $PdCl_2(PPh_3)_2$ (10 mol%), CuI, (20 mol%), NEt_3, DMF, 25 °C 14 h (62% yield); d = **11**, $PdCl_2(PPh_3)_2$ (10 mol%), CuI, (20 mol%), NEt_3, DMF, 25 °C 12 h (98% yield); e = Bu_4NN_3, DDQ, PPh_3, DCM, 25 °C, 1 h (65% yield); f = **14**, CuI (20 mol%), DIPEA, 25 °C, 8 h (74%); g = CsF, MeCN, 25 °C, 3 h (99% yield); h = **13**, $PdCl_2(PPh_3)_2$ (10 mol%), CuI, (20 mol%), NEt_3, DMF, 25 °C, 14 h (52% yield); i = 20% TFA/1% TES, DCM, 25 °C, 1 h.

was performed at room temperature with 20% trifluoroacetic acid/1% triethylsilane in dichloromethane. The fully deprotected compounds were then precipitated by the addition of cold diethyl ether (summarized in Scheme 4). Precipitated products **17** and **18** were obtained as TFA salts in ~95% yield from the *t*-butyl ester and Boc-protected precursors. The completeness of deprotection was assessed by ^{1}H NMR spectroscopy by the disappearance of *t*-butyl protons at 1.48–1.49 ppm (Boc) and 1.41 ppm (*t*-butyl ester) for **17**, and 1.48 ppm (Boc) and 1.42 ppm (*t*-butyl ester) for **18**.

Conclusions

In conclusion, we have developed a programmable "build–couple" method for the synthesis of heterofunctionalized polyvalent molecules. This approach was used to prepare a diverse heterofunctionalized dendron and dendrimer. We demonstrated the effectiveness of pairing the Huisgen–Sharpless 1,3-dipolar cycloaddition and Sonogashira coupling reaction with pre-programmed modular components to synthesize these complex molecules. While the functional groups we chose to utilize herein are inspired by amino acid side chains, the functional group tolerance demonstrated by these coupling reactions[15] likely makes this approach well suited for the synthesis functional group diverse heterofunctionalized polyvalent molecules.

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