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Selective monobenzylation of 2,2-bis(hydroxymethyl)propionic acid (bis-MPA) to yield an AB linear monomer and analogous linear oligomers

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ABSTRACT

The synthesis of a mono-benzylated AB monomer based on bis-MPA is explored and accomplished via a three-step synthesis without column chromatography. This optimized synthesis utilizes a generic acid-catalyzed esterification of bis-MPA to the ethyl ester. Subsequently, a selective mono-benzylation mediated by silver(I) oxide affords the monobenzyl ether of the ethyl ester. Finally, a simple base hydrolysis of monobenzyl ether ethyl ester yields 3-(benzyloxy)-2-(hydroxymethyl)-2-methylpropanoic acid, the AB monomer. This synthesis was utilized to generate gram quantities of the linear monomer (47% yield) and this monomer was used to produce a small amount of the linear polymer analogs. Although there are many branched analogs of bis-MPA, this is the first linear oligomer that has been confirmed.

Introduction

First described by Vögtle in 1978 [1], dendritic polymers are characterized by perfectly defined concentric layers of branched monomers, or generations, yielding monodisperse polymers with a high number of peripheral functionalities. The remarkable amount of functional end groups, combined with their biocompatibility and biodegradability, has caused dendrimers to be of increasing interest in recent years for a number of biological applications [2–4]. Consequently, in order to achieve this prefect branching and symmetry, these materials require a multi-step synthesis. Nonetheless dendrimers have been commercialized with particular focus on two major types: poly(amidoamine) (PAMAMs) [5] and polyesters based on 2,2-bis(hydroxymethyl)propionic acid (bis-MPA, **1**) [6] (Fig. 1).

Hyperbranched polymers (HBPs) offer an attractive alternative to dendrimers due to a single step, one-pot synthesis. While this significantly simplifies the synthetic requirements, it comes at the cost of sacrificing structural perfection. Thus, HBPs do not have perfect branching, possessing both linear and branched sections, but still maintain a similarly dense functional surface and globular structure [7,8].

The third structure that incorporates the same monomer are linear polymers. Such polymers must have one branch protected and the second branch able to be functionalized via a linear polymerization. While these are rare, a few samples were obtained for the poly(benzyl esters) [9] and polyglycerol [10] monomers.

It is known that the structural variation of polymers plays a critical role in a material's physical and chemical properties. The variation in branching has been defined by Hölter, et al. [11] as the degree of branching (DB) comparing the relative quantities of linear (L) and dendritic (D) units (DB = 2D/2D + L). Linear polymers represent the purely unbranched repeating units (DB = 0), whereas dendrimers exhibit the perfectly branched repeating units (DB = 1). All other branched polymers (e.g. HBP) fall somewhere between these two morphologies. Additionally, several articles have investigated the effect branching has on the properties of these polymers [12–14]. However, the vast majority of these investigations have been limited in scope; comparing only two architectures; i.e. linear and dendritic [13,14], or linear and HBPs [15,16]. Similarly many these investigation have also been limited in effect of DB on one or a few properties. Thus, limiting the conclusions that can be made for these various materials. The most comprehensive studies, by Wooley et al. [9] and Morikawa [12] importantly compare the linear, HBPs and dendritic architectures of poly(benzyl ester)s and poly(aryl ether ketones), respectively.

In order to comprehensively study, assess and predict the effect DB on the final material, it is important that each of the polymers have an identical repeat unit and macromolecular size. Furthermore, the linear monomer should have the ability to polymerize and then have the protecting group easily removed post-polymerization. Lastly, synthetic access to both the purely linear and purely dendritic morphologies is required for a given monomer to provide a complete evaluation. To this end, bis-MPA represents an

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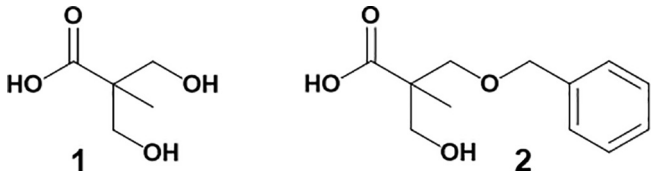


Fig. 1. Bis-MPA (**1**) and the proposed mono-benzylated linear AB monomer (**2**).

extremely attractive monomer with well-defined synthetic routes to the dendrimer [17,18] and the HBPs [19–21] leading to commercialization by Polymer Factory (dendrimer) and Boltorn™ (HBPs) [22]. Unfortunately, while the HBPs and dendrimers of bis-MPA, **1**, have been commercialized, to our knowledge, no attempts to produce a linear AB monomer based on bis-MPA have been made, and no linear polymerizations have been achieved. Therefore, a linear AB monomer analogue (**2**), is proposed and synthesized herein, via the selective mono-functionalization of one of bis-MPA monomers hydroxy groups (Fig. 1).

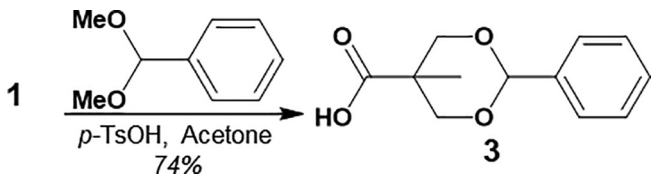
Results and discussion

Synthesis of an AB linear monomer

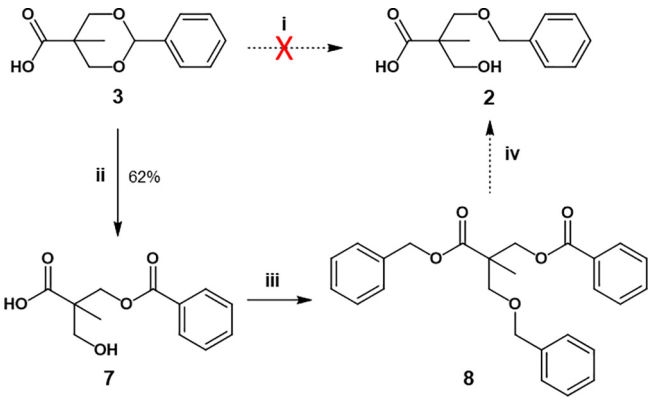
The synthesis of a linear (monoprotected) AB monomer is of unique importance, though very few have actually been achieved. Bis-MPA was selected as a viable starting point for the selective monofunctionalization, because of its cost and commercial availability. The synthetic design focused on numerous factors including: high yield, little to no purification, and overall synthetic ease.

While a number of pathways were described (full scheme in supplemental, Scheme S1), the first attempts focused on utilizing the benzylidene protected dendritic monomer **3**, because the synthesis of kilogram quantities [17,18] has been achieved with relative ease in our labs (Scheme 1). This acetal, **3** potentially affords two unique routes of producing the desired product (Scheme 2). First the direct reductive ring opening of the acetal **3**, utilizing varying equivalents of diisobutylaluminum hydride (DIBAL-H) in tetrahydrofuran (THF), has been performed previously without the acid [23,24]. Unfortunately (though expectedly) the presence of the carboxylic acid proved troublesome due to preferential reactivity of DIBAL-H toward the carbonyl forming a number of by products (Scheme 3). The initial reduction yielded the acetal aldehyde **4**, and a second reaction followed almost immediately to form the mono-hydroxy acetal **5**. Increasing equivalents (>5 eq.) of the reducing agent eventually caused the acetyl ring-opening but only after complete conversion to the mono-hydroxy thus forming a di-hydroxy benzyl ether product **6**.

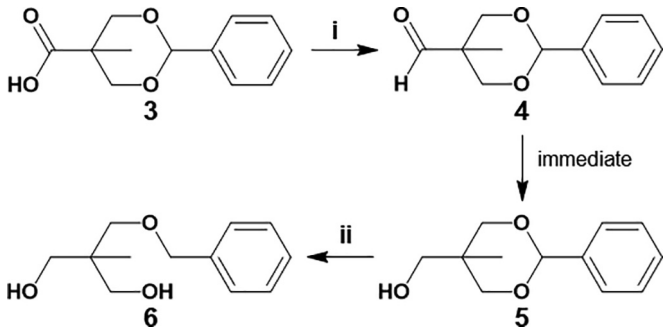
Alternatively, a three-step synthesis via an oxidative ring opening of **3** (Scheme 2) with *N*-bromosuccinimide (NBS) and light to form the benzoyl ester (**7**) was carried out similarly to work by Hanessian, et al. [25,26], Hullar, et al. [27,28] and Binkley, et al. [29] This achieved via the addition of **3** and NBS (1.1 eq) to a 2:1 solution of carbon tetrachloride (CCl_4) and water. This flask was then sealed and purged with N_2 for 1 h with stirring before being



Scheme 1. Synthesis is benzylidene protected bis-MPA (BpbMPA, **3**) from bis-MPA and benzylidene dimethoxy acetal in the presence of catalytic acid (*p*-TsOH).



Scheme 2. Synthesis of linear AB monomer **2** from the benzylidene acetal via reductive and oxidative ring-opening. i) DIBAL-H (2–10 eq.), dry THF, N_2 atmosphere. ii) NBS (1.1 eq), 2:1 CCl_4:H_2O, N_2, light, 2 h. iii) BnBr (xs), NaH (2 eq), 2 h. iv) NaOH (0.5 M), overnight.



Scheme 3. Reduction of **3** with i) DIBAL-H (2–5 eq.), and ii) DIBAL-H (>5 eq.). These lead to the formation of a number of undesired byproducts. This is due to the preferential reduction of the carbonyl over that of the acetyl group. The first reduction yields the acetal aldehyde **4**, which is then subsequently and rapidly converted to the monohydroxy acetyl **5**. Once the carbonyl is fully converted, additional equivalents of DIBAL-H causes reduction of the acetal generating the dihydroxy benzyl ether **6**.

placed into a UV reactor for 2 h. The organic layer is removed and the product **7** readily extracted from water with diethyl ether. This reaction was efficient, providing pure product and with a reasonable yield (>60%) of **7**. This product affords a monoprotected AB monomer that could be used as linear monomer for the condensation polymerization. Additionally, the removal of the aqueous layer from the reaction could be used to isolate the bromo product rather than the hydroxy acid. This reaction however has two significant drawbacks. The first is the use of carbon tetrachloride (CCl_4), which is considered to be an ozone depleting compound, so special care is required to minimize evaporation and re-collection of any used solvent. Second and of greater importance to this work is the presence of the benzoyl ester. Polymerization of this monomer will yield a polyester backbone, however, any attempt to remove the protecting benzoyl ester group will degrade the polymer as well. This lack of orthogonality between the polymer backbone and protecting group may limit the ability to further study the linear polymer in a direct comparison with the deprotected dendrimer or the hydroxylated HBPs. Ultimately, the removal of this side group is critical to the accuracy of any comparative study or post-polymerization modification.

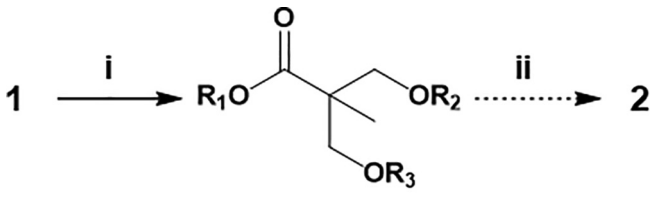
A potential remedy to this incompatibility is the subsequent exhaustive benzylation of **7** with excess sodium hydride (NaH) and benzyl bromide (BnBr) in THF will afford the diester monobenzyl ether (**8**) [30,31]. The reaction can be quenched via the addition of water and the organic layer extracted with water to remove the

salts. This is followed by the base-catalyzed hydrolysis of **8**, affording **2**. The benzylation of this compound was carried out with relative ease, and the presence of residual benzyl alcohol (BnOH) from the etherification or hydrolysis is readily removed via liquid–liquid extraction with organic solvent from water at pH ~7. Unfortunately, the other hydrolytic byproduct, benzoic acid, is exceedingly difficult to remove via extraction, due to the relative pKa's of benzoic acid (4.20) and the AB monomer **2**, determined to be 4.43 (supplemental Fig. S1). This would require purification via liquid column chromatography (LCC) requiring an undesirable amount of time and large volume of waste.

Another route that was considered was the direct benzylation of bis-MPA with NaH, (2 eq.) and BnBr (1.8–2 eq.) (Scheme 4). The NMR of the crude product shows the formation of the desired monobenzyl ether protected compound of the benzyl ester (**10**). However, without a means to control the mono-functionalization, the reaction contains byproducts of the unprotected diol (**9**) and dibenzyl ether (**11**), each with a benzyl ester. Ultimately, this pathway requires LCC for purification and removes it as a viable option for large scale synthesis due to the time intensive purification.

There are a few methods for the selective mono-benzylation of unprotected diols [32], the most attractive is the selective mono-benzylation with BnBr in the presences of silver(I) oxide (Ag_2O) [33,34]. In order to attempt this selective mono-benzylation the carboxylic acid was first converted to the ethyl ester (**12**) via a Fischer acid catalyzed esterification (Scheme 5). Bis-MPA (**1**) was added to ethanol with catalytic Dowex® resin, containing a sulfonic acid moiety, in a Soxhlet extractor containing 4 Å molecular sieves and heated to reflux. The resulting ester **12**, was isolated in gram quantities at high yield and purity (>95%) by removal of the catalyst via filtration and subsequent evaporation of the solvent. Attempts at further purification by chromatography or extraction greatly reduced yield with minimal increase in purity.

The ethyl ester (**12**), was then selectively protected to the monobenzyl ether of the ethyl ester (**13**) via a silver mediated etherification. The Ag_2O acts as a Lewis acid to both oxygens of the two alcohol groups helping to catalyze the reaction without the need of NaH or another base. Once the first protection occurs, the activity of the second hydroxyl is sufficiently reduced preventing a second benzylation. There are a few aspects to consider when contemplating this method. Firstly, the cost of silver on a large scale required for gram-scale quantities is not feasible without reclaiming most of the catalytic silver. This was addressed by isolating the silver via centrifugation of the reaction mixture, pelleting the silver, and allowing for easy isolation of the product in the supernatant. The isolated silver pellet weighs more than the original silver used (presumably a combination of the product Ag_4O_4 as well as the starting material Ag_2O). While it is doubtful this pellet can be immediately reused, its recovery is important



9 R_1 = Bn; R_2,R_3 = H
10 R_1,R_2 = Bn; R_3 = H
11 R_1,R_2,R_3 = Bn

Scheme 4. Direct but nonselective Williamson benzyl etherification of bis-MPA. i) BnBr (2 eq), NaH (2 eq.), THF, 2 h. ii) NaOH (0.5 M), overnight.

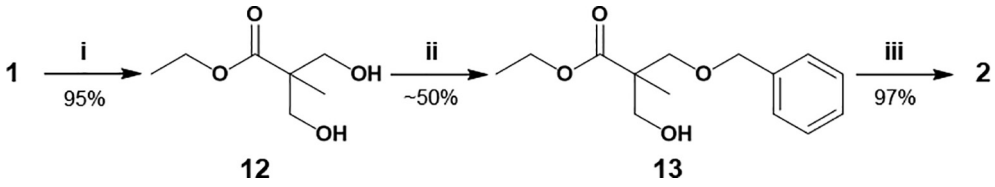
in limiting the cost of the overall reaction. Once recovered it can be reduced back to Ag_2O according to literature [35]. Unfortunately, the overall yield of this reaction is only about 50% if purified by LCC, with a notable presence of the unreacted **12** and residual BnBr in the crude product. This need for LCC might be of concern, however, the presence of these impurities/byproducts *do not* affect the subsequent hydrolysis of **13** and were easily removed post hydrolysis via simple purification.

Rather serendipitously the ensuing hydrolysis actually reduces the complexity by converting residual BnBr quantitatively to BnOH, while the unreacted **12** is hydrolyzed back to **1**. BnOH and ethanol are easily removed from the reaction mixture by organic extraction at neutral pH, due to the relatively high pKa's. The AB monomer **2**, can then be isolated via acidification of the aqueous solution to a pH $\leq$4 followed by organic extraction with no evidence of contamination from residual **1**. This is not unexpected and undoubtedly the result of the miniscule solubility of **1** in chloroform especially when compared to that of water. Ultimately, this three-step synthesis proved be the most efficient route for producing gram quantities of **2** at high purity, confirmed by NMR. The resulting total synthesis has an overall yield of 47% (0.954 × ~0.5 × 0.974 = 0.465) and purification achieved by liquid–liquid extraction. Most notably this pathway requires absolutely ***no*** column chromatography for purification. Unfortunately, the highly efficient (>95% yields) of the esterification to **12** and hydrolysis (>97% yield) to **2** are hurt by the less efficient monobenzylation to **13**.

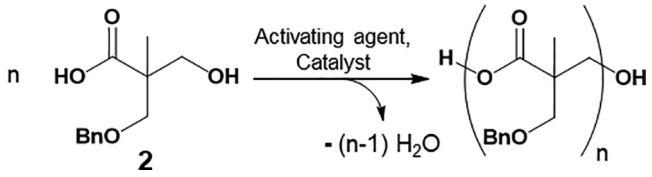
Polymerization to linear oligomers

Once **2** was isolated a number of attempts were made to polymerize linear polymers via a variety of activated esterification chemistries analogous to those used in the dendronization (Scheme 6). Utilizing *N,N′*-dicyclohexylcarbodiimide (DCC) or *N*-ethyl-*N′*-(3-dimethylaminopropyl)carbodiimide (EDC) in the presence of catalytic 4-dimethylaminopyridine (DMAP) were added to a neat solution of **2** and allowed to react. They were monitored with MALDI-TOF regularly to assess the DP. Variations to the rate at which the activating agent was added to **2** were attempted, including the reaction either by single addition, multiple aliquoted additions or slow drop-wise addition of the activating agent. This first direct A – B (carboxylic acid/alcohol) approach yielded relatively small oligomers and cyclics which is somewhat expected from this type of step growth condensation polymerization.

Additional, polymerizations were attempted utilizing an initiator to preventing the cyclization of small oligomers by producing a polymer with a single reactive end. This was performed by the incremental addition of **2** to a solution of activating agent containing of a small amount ethanol or **13** as an "initiator" for the polymerization, in an effort to prevent unwanted intramolecular cyclization and thus yield higher M_n polymers. Unfortunately, these attempts also yielded predominately small oligomers with all samples displaying multiple polymers initiated from water, ethanol, and DMAP as determine by matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (supplemental Fig. S2). It is clearly evident from this data and confirmed by GPC (supplemental Fig. S3) that the vast majority of the sample is oligomers of <1 K Da. The cyclics and smaller oligomers were removed via GPC fractionation, in order to isolate larger oligomers initiated from water, DMAP and ethanol (Fig. 2). The MALDI shown in Fig. 2 was obtained from the 18.0 to 18.5 min retention time fraction of the crude linear bis-MPA sample yielding the orange GPC trace (supplemental Fig. S3). The linearity and low DP was confirmed by MALDI-TOF *m*/*z* analysis, with the three samples averaging to a DP of 10, with an M_n of 2070 and M_w 2130. This is in agreement with the GPC data (supplemental Fig. S3), with the



Scheme 5. Three-step synthesis wherein 1 is first esterified to 12, before undergoing a selective silver(I) oxide mediated mono-benzylation to give 13. The ethyl ester is cleaved via hydrolysis to give the linear AB monomer 2. i) Dowex H^+ resin, ethanol, reflux, 72 h in Soxhlet apparatus equipped with 4 Å molecular sieves. ii) BnBr (1.1 eq.), Ag_2O (1.5 eq.) CH_2Cl_2, 8 h. iii) NaOH (0.5 M), 8 h.



Scheme 6. Polymerization of a linear bis-MPA polymer utilizing the monomer **2** neat with either DCC or EDC as an activating agent in the presence of catalytic DMAP.

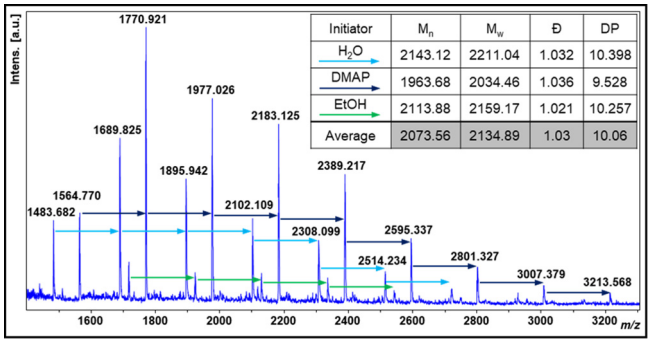


Fig. 2. MALDI-TOF mass spectra of GPC fractionated linear (orange GPC trace in Fig. S3) polymer synthesized from **12**, DCC and DMAP with ethanol as an initiator with dithranol matrix and Na^+ cation. This yielded three major distributions resulting from initiation off water (H_2O) and ethanol charged with Na^+ cation, and DMAP ($C_7H_{10}N_2$) which is natively charged when in the activated ester form.

fraction calculated to have an M_n of 1523 and an M_w of 1528 using a polystyrene reference. While these initial polymerization attempts yielded only small amount of these polymers, they are the first example of a linear polymerization from the bis-MPA monomer.

Conclusions

In this work a number of synthetic pathways were explore for the production of gram quantities of a mono-protected linear AB monomer, **2**. The synthesis of **2** was achieved through a multi-step pathway that maintains an overall 47% yield while requiring minimal purification and absolutely *no column chromatography*. Furthermore, the monomer **2** has been shown to produce linear polymers and we expect that larger polymers will be achieved in the future. As such, **2** critically allows access to the completely unbranched linear analog of the already commercially produced hyperbranched and dendritic bis-MPA polymers; thus providing for a thorough investigation of the role and degree to which branching effects the properties of polymers based on bis-MPA. This is a critical step in fully understanding and then predicting the properties of branched synthetic polymers.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152016.

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