1. Graphical Abstract
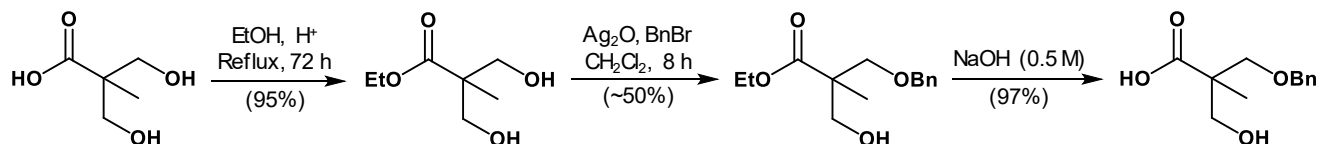
Selective Mono-benzylation of 2,2-Bis(hydroxymethyl)propionic Acid (bis-MPA) to Yield an AB Linear Monomer and Analogous Linear Polymers

Leave this area blank for abstract info.

Joseph A. Giesen and Scott M. Grayson

Selective Monobenzylation of 2,2-Bis(hydroxymethyl)propionic Acid (bis-MPA) to Yield an AB Linear Monomer and Analogous Linear Polymers

Joseph A. Giesen[a] and Scott M. Grayson[a*]

[a] Department of Chemistry, Tulane University, 2015 Stern Hall, 6400 Freret St., New Orleans, LA 70118, USA
* Corresponding author
E-mail address: sgrayson@tulane.edu

ARTICLE INFO

ABSTRACT

The synthesis of a mono-benzylated AB monomer (**2**) based on bis-MPA (**1**) is explored and accomplished via a three-step synthesis without column chromatography. This optimized synthesis utilizes a generic acid-catalyzed esterification of **1** to the ethyl ester (**12**). Subsequently, a selective mono-benzylation mediated by silver(I) oxide affords the monobenzyl ether of the ethyl ester (**13**). Finally, a simple base hydrolysis of **13** yields 3-(benzyloxy)-2-(hydroxymethyl)-2-methylpropanoic acid (**2**). This synthesis was utilized to generated gram quantities of the linear monomer for the linear polymer analog. Although there are many branched analogs of bis-MPA, this is the first linear polymer that has been confirmed.

1. 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.[2,3,4] 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] (**Figure 1**).
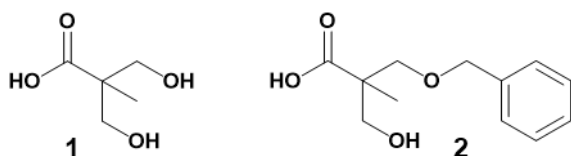
Figure 1: Bis-MPA (**1**) and the proposed mono-benzylated linear AB monomer (**2**)

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 structurally perfection. 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 polymer 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.

$$DB = 2D/(2D+L)$$

In order to assess differences in structure between these three architectures, we consider the degree of branching (DB) of a polymer, previously defined by Hölter, *et al*. (**Equation 1**),[11] to compare the relative quantities of linear (L) and dendritic (D) units. Applying the Hölter equation to linear polymers we find a DB of 0.0 because the linear polymer possesses no D units. Conversely, when applied to dendrimers that lack L units, they have a DB equal to one (2D/2D = 1.0). Linear polymers represent the purely unbranched repeating units, whereas dendrimers exhibit the perfectly branched repeating units. All other branched polymers (e.g. HBP) fall somewhere between these two morphologies making them an attractive intermediate for the study of how the DB affect the final properties. To that end several articles have investigated the effect branching has on the properties of these polymers.[12,13,14] 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, it is important that each of the polymers have an identical repeat unit. Controlling the composition and macromolecular size will allow for the most accurate assessment of the effects of DP on the resulting polymers thus limiting variation by only architecture. 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 across the varied range of branching. To this end, bis-MPA represents an extremely attractive monomer with well-defined synthetic routes to the dendrimer[17,18] and the HBPs[19,20,21] 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 (**Figure 1**).

2. Results and Discussion

2.1. 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. In order to completely understand how the DB affects a polymer's properties there is a critical need for both linear analog (DB = 0.0 or completely unbranched) as well as the dendrimers (DB = 1.0 or perfectly branched). These two architectures thus provide information about the extremes or book ends of polymer branching. The HBPs (DB = 0.01-0.99) intrinsically exist between these extremes but a number of these can be made in a single one-pot reaction. Additionally, large quantities of the linear monomer are required to produce the amount of polymer for bulk material studies of some physical and chemical properties. Therefore, 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
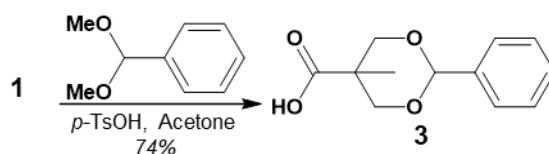

Scheme 1: Synthesis is benzylidene protected bis-MPA (BpbMPA, **3**) from bis-MPA and benzylidene dimethoxy acetal in the presence of catalytic acid (*p*-TsOH*).

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 bioproducts (**Scheme 3**). The initial reduction yielded the acetal aldehyde **4**, and a second reaction followed almost immediately to form the mono-hydroxy acetal **5**. The preference of reduction of the aldehyde even over that of the acid was evident by the nearly 10-fold excess of **5** to **4** in all samples. Increasing equivalents (>5 eq.) of the reducing agent did eventually cause the desired 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** 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 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
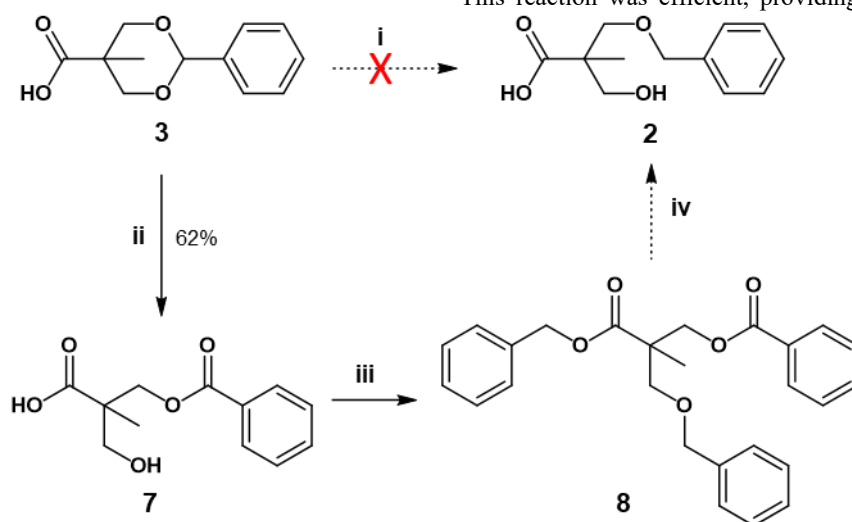
Scheme 2: Synthesis of linear AB monomer **2** from the benzylidene acetal via reductive and oxidative ring-opening. i) DIBAL-H (2-10 eq.), dry THF, N$_2$ atmosphere. ii) NBS (1.1 eq), 2:1 CCl$_4$:H$_2$O, N$_2$, light, 2 h. iii) BnBr (xs), NaH (2 eq), 2 h. iv) NaOH (0.5 M), overnight.
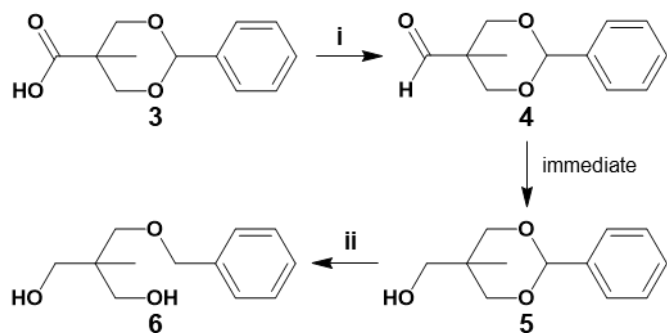
Scheme 3: Reduction of **3** with i) DIBAL-H (2-5 eq.), and ii) DIBAL-H (>5 eq.). These lead to the formation of a number of undesired biproducts. This is due to the preferential reduction of the carbonyl over that of the acetyl group. The first reduction yields the acetal aldehyde **4**, which is then 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**.

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 then they 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. Large-scale synthesis would require significant amounts of this hazardous solvent, so the reusability of the solvent was tested. It was determined that recycling of the solvent for an additional reaction did not negatively impact the reaction and would be a viable option for reducing the potential environmental impact. 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 a straightforward base-catalyzed hydrolysis of **8**, which would then yield **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 biproduct, 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 **Figure 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**). Through incremental addition of NaH and BnBr, 1 eq. at a time, the more acidic carboxylic acid functionality should be protected first via esterification. A subsequent addition of NaH and BnBr (1 eq.) should deprotect one of the alcohols to form the benzyl ether. 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

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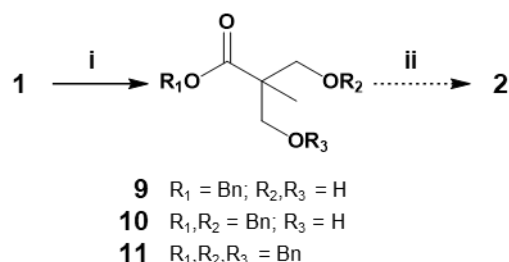
Scheme 4: Direct but nonselective Williamson benzyl etherification of bis-MPA. i) BnBr (2 eq), NaH (2 eq.), THF, 2 h. ii) NaOH (0.5 M), overnight.

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.

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
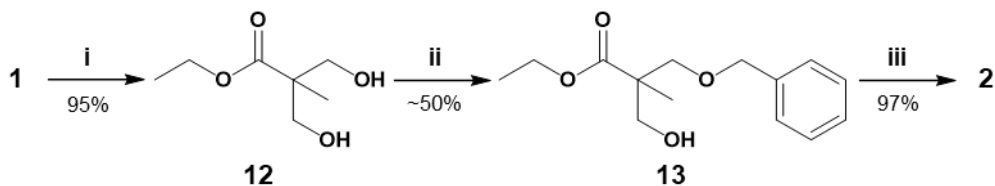

Scheme 5: Three-step synthesis wherein **1** is first esterified to **12**, before undergoing a selective silver(I) oxide mediated mono-benzylation to give **13**. The ethyl ester is cleaved via hydrolysis to give the linear AB monomer **2**. i) Dowex H⁺ resin, ethanol, reflux, 72 h in Soxhlet apparatus 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.

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 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 <u>do not</u> 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 quantitively 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 ≤ 4 followed by organic extraction with no evidence of contamination from residual **1**. This is not unexpected and undoubtably 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**. The resulting total synthesis has an overall yield of 47% (0.954 x ~0.5 x 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 mono-benzylation to **13**.

2.2. Polymerization to linear polymers

Once **2** was isolated a number of attempts were made to polymerize linear polymers via a variety of activated esterification chemistries (**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
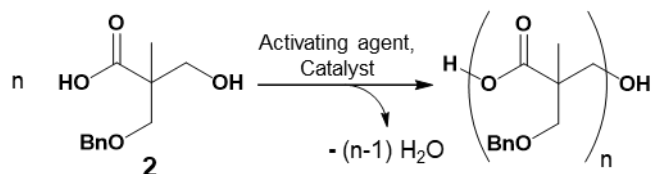
Scheme 6: Polymerization of a linear bis-MPA polymer utilizing the monomer **2** neat with either DCC or EDC as an activating agent in the presence of catalytic DMAP.

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 predominantly 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 **Figure S2**). It is clearly evident from this data that the vast majority of the sample is oligomers of < 1K Da. This relatively small DP is confirmed by the GPC data (supplemental **Figure S3**). However, the small cyclics and oligomers can be removed via GPC fractionation, in order to isolate larger oligomers initiated from water, DMAP and ethanol (**Figure 3**). The MALDI shown in **Figure 3** was obtained from the 18.0 – 18.5 min retention time fractionation of the linear bis-MPA yielding the orange GPC trace (supplemental **Figure S3**). While these initial polymerization attempts yielded only small amount of these polymers, they are the first example of a linear
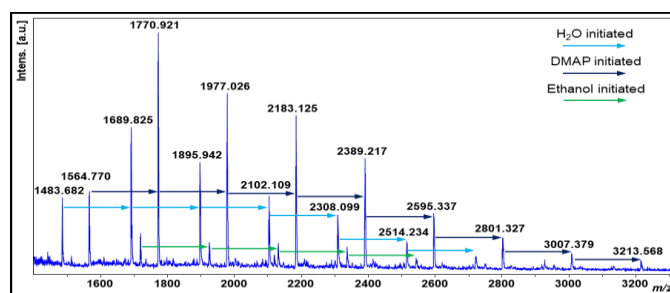
Figure 3: MALDI-TOF mass spectra of GPC fractionated linear (orange GPC trace in **Figure S3**) polymer synthesized from **12**, DCC and DMAP with ethanol as an initiator with dithranol matrix and Na+ cation. This yielded three major distributions resulting from initiation off water (H_2O) and ethanol charged with Na+ cation, and DMAP ($C_7H_{10}N_2$) which is natively charged when in the activated ester form.

polymerization from the bis-MPA monomer.

3. Conclusions

In this work a number of synthetic pathways were explore for the production gram quantities of a mono-protected linear AB monomer, **2**. The synthesis of **2** was achieved through a multi-step pathway that maintains relatively high yields 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.

Acknowledgments

Supplementary Material

Supplementary data for this article can be found online at:

References and notes

1. E. Buhleier, W. Wehner, F. Vögtle, Synthesis. 2 (1978) 155-158.
2. P. Kesharwani, K. Jain, N.K. Jain, Prog. Polym. Sci. 39 (2014) 268-307.
3. S. Svenson, D.A. Tomalia, Adv. Drug Deliv. Rev. 57 (2005) 2106-2129.
4. E. Nance, S.P. Kambhampati, E.S. Smith, Z. Zhang, F. Zhang, S. Singh, M.V. Johnston, R.M. Kannan, M.E. Blue, S. Kannan, J. Neuroinflammation. 14 (2017) 252/1-252/19.
5. D.A. Tomalia, H. Baker, J. Dewald, M. Hall, G. Kallos, S. Martin, J. Roeck, J. Ryder, P. Smith, Polymer Journal, 17, (1985) 117-132.
6. H. Ihre, A. Hult, E. Söderlind, J. Am. Chem. Soc. 118 (1996) 6388-6395.
7. B.I. Voit, A. Lederer, Chem. Rev. 109 (2009) 5924-5973.
8. Y.C. Zheng, S.P. Li, Z.L. Weng, C. Gao, Chem. Soc. Rev. 44 (2015) 4091-4130.
9. K.L. Wooley, J.M.J. Fréchet, C.J. Hawker, Polymer, 35 (1994) 4489-4495.
10. S.-E. Stiriba, H. Kautz, H. Frey, JACS 124 (2002) 9698-9699.
11. D. Hölter, A. Burgath, H. Frey, Acta Polym. 48 (1997), 30-35.
12. A. Morikawa, Molecules. 21 (2016) 219/1-219/13.
13. G.R. Newkome, C.N. Moorefield, J.D. Epperson, Eur. J. Org. Chem. 18 (2003) 3666-3672.
14. E.M. Harth, S. Hecht, B. Helms, E.E. Malmstrom, J.M.J. Frechet, C.J. Hawker, J. Am. Chem. Soc. 124 (2002) 3926-3938.
15. M, Wang, D. Gan, K.L. Wooley, Macromolecules. 34 (2001) 3215-3223.
16. H.Y. Lee, S.Y. Kwak, Polymer. 42 (2000) 1375-1382.
17. H. Ihre, A. Hult, J.M.J. Fréchet, I. Gitsov, Macromolecules. 31 (1998) 4061-4068.
18. H. Ihre, O.L. Padilla de Jesús, J.M.J. Fréchet, J. Am. Chem. Soc. 123 (2001) 5908-5917.
19. E. Malström, F. Lui, R.H. Boyd, A. Hult, U.W. Gedde, Polym. Bull. 32 (1994) 679-685.
20. E. Malström, M. Johansson, A. Hult, Macromolecules. 28 (1995) 1698-1703.
21. H. Magnusson, E. Malmström, A. Hult, Macromolecules. 33 (2000), 3099-3104.
22. A. Carlmark, E. Malmström, M. Malkoch, Chem. Soc. Rev. 42 (2013) 5858-5879.
23. S. Takano, M. Akiyama, S. Sato, K. Ogasawara, Chem. Lett. 12 (1983)-1593-1596.
24. K.A. Willham, B.A. Laurent, S.M. Grayson. Tetrahedron Lett. 49 (2008) 2091-2094.
25. S. Hanessian. Carbohydr. Res. 2 (1966) 86-88.
26. S. Hanessian, N.R. Plessas, J. Org. Chem. 34 (1969) 1035-1058.
27. D.L. Failla, T.L. Hullar, S.B. Siskin, Chem. Comm. (London). 20 (1966) 716-717.
28. T.L Hullar, S.B. Siskin, J. Org. Chem. 35 (1970) 225-228.
29. R.W. Binkley, G.S. Goewey, J.C. Johnston, J. Org. Chem. 49 (1984) 992-996.
30. R. Mazitschek, A. Huwe, A. Giannis, Org. Biomol. Chem. 3 (2005) 2150-2154.
31. A. Fürstner, O.R. Thiel, J. Org. Chem. 65 (2000) 1738-1742.
32. W. Muramatsu, J. Org. Chem. 77 (2012) 8083-8091.
33. A. Bouzide, G. Sauvé, Tetrahedron Lett. 38, (1997) 38, 5945-5948.
34. A. Bouzide, G. Sauvé, Org. Lett. 4 (2002) 2329-2332.
35. M. Tanabe, R.H. Peters, Org. Synth. 60 (1981) 92-10.