Chemistry
A European
Journal

Chemistry Europe
European Chemical Societies Publishing

Accepted Article

Title: Total Synthesis of a Partial Structure from Arabinogalactan and its Application for Allergy-Prevention

Authors: Matthias Krumb, Maximilian Jäger, Alice Voss, Loreen Immig, Karin Peters, Danuta Kowalczyk, Albrecht Bufe, Till Opatz, Otto Holst, Christian Vogel, and Marcus Peters

To be cited as: *Chem. Eur. J.* 10.1002/chem.202002287

Link to VoR: https://doi.org/10.1002/chem.202002287

WILEY-VCH

10.1002/chem.202002287

WILEY-VCH

COMMUNICATION

Total Synthesis of a Partial Structure from Arabinogalactan and Its Application for Allergy Prevention

Matthias Krumb,[b] Maximilian Jäger,[a] Alice Voss,[c] Loreen Immig,[a] Karin Peters,[a] Danuta Kowalczyk,[b] Albrecht Bufe,[a] Till Opatz,*[b] Otto Holst,[d] Christian Vogel,[c] and Marcus Peters*[a]

[a] Dr. M. Jäger, MSc L. Immig, Dr. K. Peters, Prof. Dr. A. Bufe, Dr. M. Peters
Department of Experimental Pneumology
Ruhr-University Bochum
Universitätsstr. 150, 44801 Bochum, Germany
E-mail: marcus.peters@rub.de

[b] MSc M. Krumb, D. Kowalczyk, Prof. Dr. T. Opatz
Department of Chemistry
Johannes Gutenberg-University
Duesbergweg 10-14, 55128 Mainz, Germany
E-mail: opatz@uni-mainz.de

[c] A. Voss, Prof. Dr. C. Vogel
Department of Chemistry
University of Rostock
Albert-Einstein-Str. 3a, 18051 Rostock, Germany

[d] Prof. Dr. O. Holst
Division of Structural Biochemistry
Research Center Borstel, Leibniz Lung Center, Airway Research Center North (ARCN)
Parkallee 1-40, 23845 Borstel, Germany

Supporting information for this article is given via a link at the end of the document.

Abstract: Arabinogalactan, a microheterogeneous polysaccharide occurring in plants, is known for its allergy-protective activity, which could potentially be used for preventive allergy treatment. New treatment options are highly desirable, especially in a preventive manner, due to the constant rise of atopic diseases worldwide. The structural origin of the allergy-protective activity of arabinogalactan is, however, still unclear and isolation of the polysaccharide is not feasible for pharmaceutical applications due to a variation of the activity of the natural product and contaminations with endotoxins. Therefore, a pentasaccharide partial structure was selected for total synthesis and subsequently coupled to a carrier protein to form a neoglycoconjugate. The allergy-protective activity of arabinogalactan could be reproduced with the partial structure in subsequent *in vivo* experiments. This is the first example of a successful simplification of arabinogalactan with a single partial structure while retaining its allergy-preventive potential.

The negative impact on human health of allergic diseases, often overrepresented in first world countries, has been increasing unimpededly. However, studies have shown that growing up and living in a traditional farming environment can decrease the risk of developing these allergies significantly, which is known as the "farm effect" in literature.[1-4] Nevertheless, the connection between living in a farming environment and allergy protection is not yet fully understood.[5] Arabinogalactan (AG), an immune-modulating natural polysaccharide, has recently received considerable attention as one potential origin for this phenomenon.[5, 6]

The polysaccharide occurs frequently in grasses that are present in a farming environment and can be isolated therefrom.[6, 7] Unfortunately, the composition of the structurally microheterogeneous AG is very complex and difficult to analyse.[8, 9] There is literature evidence that the allergy-protective activity of AG could originate from recognition of particular (terminal) arabinose containing epitopes by the immune system, since it is known that a cleavage of these significantly reduced the allergy-protective activity of the polysaccharide.[6] Moreover, it was shown in the same work that AG from other plants, namely Acacia or Larix, does not show allergy-protective activity. This is probably based on a differing molecular structure, however, the exact chemical structure of the different AG is unknown. Fortunately, pioneering work by Brecker et al. shed light on the structural composition of AG isolated from Timothy grass (*Phleum pratensis*) by deciphering arabinose and galactose containing partial structures (Figure 1, A).[7] The latter consist of a β-(1→6)-linked D-galactopyranosyl backbone with L-arabinofuranosyl-α-(1→5)- or α-(1→3)- and β-(1→3)-linked side chains. It was revealed in previous studies that isolated AG from meadow foxtail (*Alopecurus pratensis*), which contains these partial structures, is allergy-protective.[6]

10.1002/chem.202002287
WILEY-VCH

COMMUNICATION

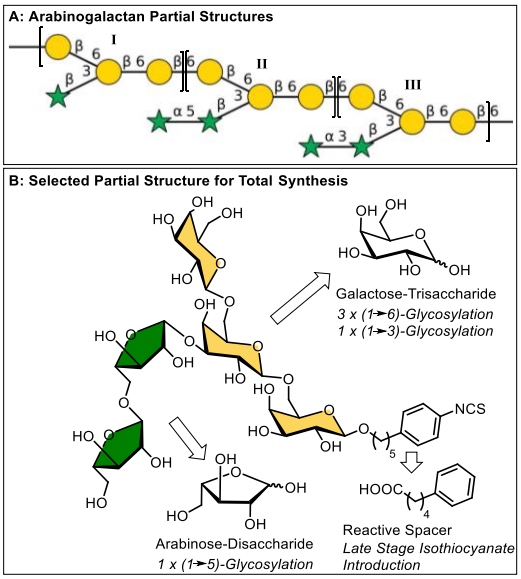
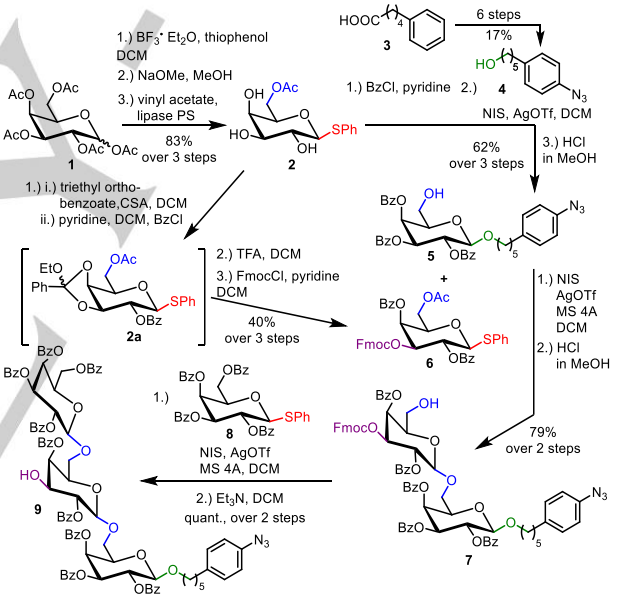


Figure 1. Illustration of partial structures of AG identified by Brecker and co-workers using symbol nomenclature for glycans (A).[7, 10] Partial structure of arabinogalactan selected for total synthesis and its retrosynthetic analysis (B).

Preventive and prophylactic approaches with a promising perspective are still rare, despite a huge research effort in the search for new treatment options for allergic diseases.[11] While the use of natural polysaccharides for prophylaxis could be envisioned, the size and complexity of AG precludes the production of chemically well-defined species with consistent biological activity. In addition, the separation of natural polysaccharides from other immune-modulating contaminants, such as endotoxins, is, at least, highly challenging, especially under the good manufacturing practice conditions required for pharmaceutical applications. Gratifyingly, the prime example of fondaparinux, a synthetic pentasaccharide used as an anticoagulant, showcases that the total synthesis of carbohydrate pharmaceuticals can be cost-effective, despite their intrinsic high complexity and polyfunctionality.[12-15] In terms of AG, there are a few examples for the synthesis of related oligosaccharides but structure-activity relationships are unfortunately missing.[16-21]

Thus, we selected a partial structure of arabinoglactan, namely a pentasaccharide containing two L-arabinose and three D-galactose units (Ara*f*$_2$Gal*p*$_3$) as the target for total synthesis to match one of the partial structures in AG (Figure 1, A (structure II) and Figure 1, B)[7] which were shown to be biologically active in earlier studies.[6] Our overall goal for this project was to gain a better understanding of the role of glyco-epitopes in AG and to achieve a strategic simplification of the polysaccharide while the useful allergy-protective activity is retained.

The pentasaccharide selected requires construction of a trigalactose (Gal*p*$_3$) backbone with two β-(1→6)-glycosylations and an additional β-(1→3)-glycosylation for the attachment of the arabinose side chain. The latter required the construction of an α-(1→5)-glycosidic linkage. Additionally, a reactive isothiocyanate spacer was needed for covalent coupling to a carrier protein. The synthesis of the pentasaccharide Ara*f*$_2$Gal*p*$_3$ started with the construction of the trigalactose (Gal*p*$_3$) backbone; the (1→6)-connections desired were furnished using a combination of regioselective enzymatic acetylation and chemoselective deacetylation in the presence of benzoyl groups (Scheme 1). An orthogonally stable Fmoc-protecting group was introduced to enable glycosylation of the Ara*f*$_2$-disaccharide later in the synthesis. In detail, the synthetic route for Gal*p*$_3$ (**9**) started from peracetylated D-galactose (**1**) to give the 6-*O*-acetyl-protected thioglycoside **2** through a reaction with thiophenol, Zemplén deprotection and regioselective acetylation using a lipase to selectively furnish the 6-*O*-protected galactose **2** in an 83 % yield over three steps.[22] Subsequently, galactose **2** was benzoylated and glycosylated with spacer **4**, which was synthesized in six steps from 5-phenylvaleric acid (**3**, details can be found in the SI). The 6-*O*-acetyl group was then removed using methanolic HCl to give intermediate **5**. The free hydroxyl group obtained in **5** was then glycosylated with an orthogonally protected galactose **6**. The latter was synthesized from galactose **2** through orthoester formation with triethyl orthobenzoate, benzoylation, regioselective cleavage of the orthoester intermediate **2a** and, subsequent Fmoc-protection in a 40 % yield over three steps.[23] Both building blocks, galactose **5** and galactose **6,** were glycosylated, 6-*O*-deprotected and again glycosylated with thioglycoside **8** to synthesize a Gal*p*$_3$ building block **9** in four further steps.

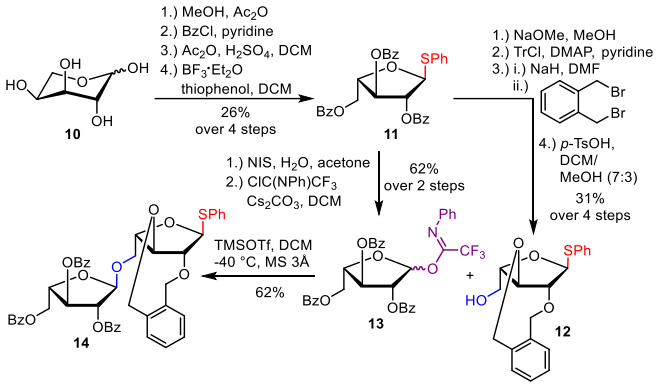


Scheme 1. Synthesis of Gal*p*$_3$ intermediate **9** over nine linear steps starting from peracetylated D-Galactose (**1**).

The synthesis of the Ara*f*$_2$ side chain **14** required a (1→5) linkage between the L-arabinose units, which was furnished using the established tritylation-detritylation approach (Scheme 2).[24] The *cis*-glycosidic linkage in the first galactose-connected arabinose required the use of non-participating *O*-protection, while the latter arabinose has a trans-glycosidic linkage and, therefore, requires participating *O*-protection for synthesis.[25] According to a report by Lowary and co-workers, the cis-glycosylation is possible when a conformationally restricted *O*-xylylene-protected donor is used.[26, 27] We adapted this approach and started the synthesis from L-arabinose (**10**) in a Fischer glycosylation in methanol, the product of which was subsequently benzoylated. Thioarabinoside **11** was subsequently prepared from a 1-*O*-acetyl-intermediate in four steps and a 26 % yield. Next, the 5-*O*-deprotected

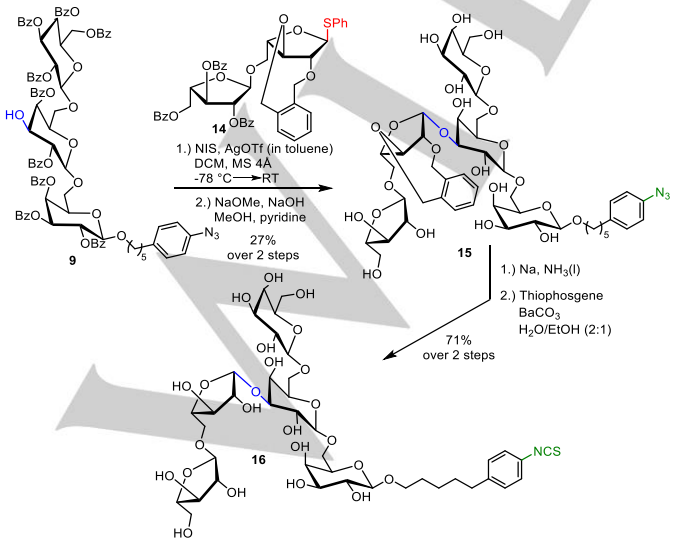
10.1002/chem.202002287

arabinose **12** was produced in a sequence of debenzoylation, 5-*O*-tritylation, introduction of the 2,3-*O*-xylylene ether, according to Lowary et al., and detritylation to give glycosyl acceptor **12** in a 31 % yield over four steps. The thioglycoside in arabinose **12** should be used afterwards for glycosylation to trigalactose **9**. Thus, an orthogonal glycosylation, which leaves the thioglycoside untouched, was required to introduce the second arabinose unit. Gratifyingly, using the *N*-phenyltrifluoroacetimidate donor **13**,[28] synthesized through cleavage of thioglycoside **11** to its hemi-acetal and reaction with 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride, furnished the Ara*f*$_2$ intermediate **14** desired in a 62 % yield in a modified procedure based on Andersen et al.[29]



Scheme 2. Synthesis of Ara*f*$_2$ intermediate **13** over eight linear steps starting from L-arabinose (**9**).

The final steps of the synthesis started with the glycosylation of Ara*f*$_2$ donor **14** with Gal*p*$_3$ acceptor **9** (Scheme 3). After a successful *cis*-glycosylation and Zemplén deprotection, protected Ara*f*$_2$Gal*p*$_3$ **15** was synthesized in a 27 % yield. In the two final steps, the 2,3-*O*-xylylene protecting group was removed under Birch conditions using liquid ammonia and sodium. This also led to the reduction desired of the azide to an amino group at the same time. Conversion of the latter to the reactive isothiocyanate with thiophosgene under mildly basic conditions using $BaCO_3$ as a mild base in a water/ethanol mixture gave the target structure Ara*f*$_2$Gal*p*$_3$ **16** in a 71 % yield over two steps.



Scheme 3. Synthesis of the AG partial structure Ara*f*$_2$Gal*p*$_3$ **15** over four linear steps from the key intermediates Gal*p*$_3$ **8** and Ara*f*$_2$ **13**.

The pentasaccharide was coupled to bovine serum albumin (BSA) as the carrier protein to create a neoglycoconjugate (Ara*f*$_2$Gal*p*$_3$-BSA, Figure S1) for biological evaluation. Coupling was accomplished using the reactive isothiocyanate group, which reacts readily with BSA's free amino groups. The neoglycoconjugate created was subsequently evaluated for allergy-protective activity in a mouse model of allergic asthma (Figure 2). The treatment of mice with Ara*f*$_2$Gal*p*$_3$-BSA led to reduced allergic inflammation in the airways upon sensitization and challenge with ovalbumin (OVA) as a model allergen. This can be seen by the reduction of eosinophilic granulocytes, lymphocytes and macrophages (Figure 2, A). Moreover, immunoglobulin E (IgE) production (Figure 2, B) and the Th2 response determined by measuring the *in vitro* production of interleukin (IL)-5 and IL-13 by spleen cells is significantly reduced (Figure 2, C), as well as the goblet cell metaplasia (Figure 2, D and Figure S2). The efficacy of treatment was comparable to AG, shown to be allergy-protective in former studies.[6] Another hallmark of allergic asthma is airway hyperreactivity (AHR) towards provocation with cholinergic stimuli, such as methacholine. Therefore, the AHR of mice was tested in the asthma model by measuring the airway mechanics. As seen for airway inflammation, the AHR is also significantly reduced in mice treated with Ara*f*$_2$Gal*p*$_3$-BSA (Figure S4).

10.1002/chem.202002287

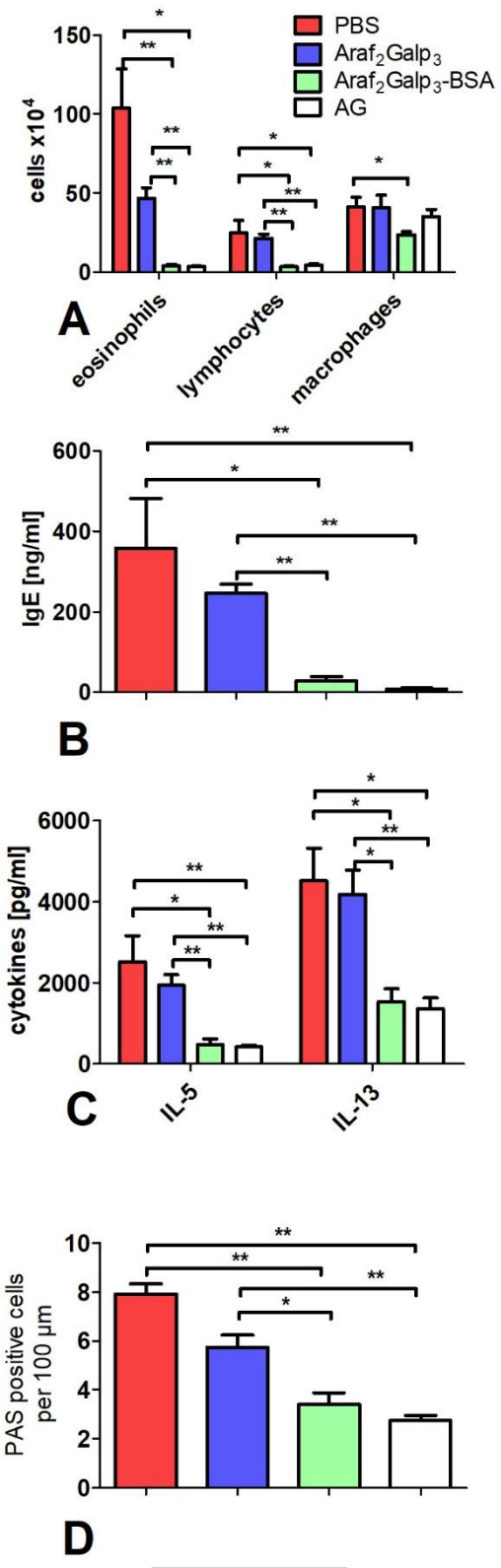
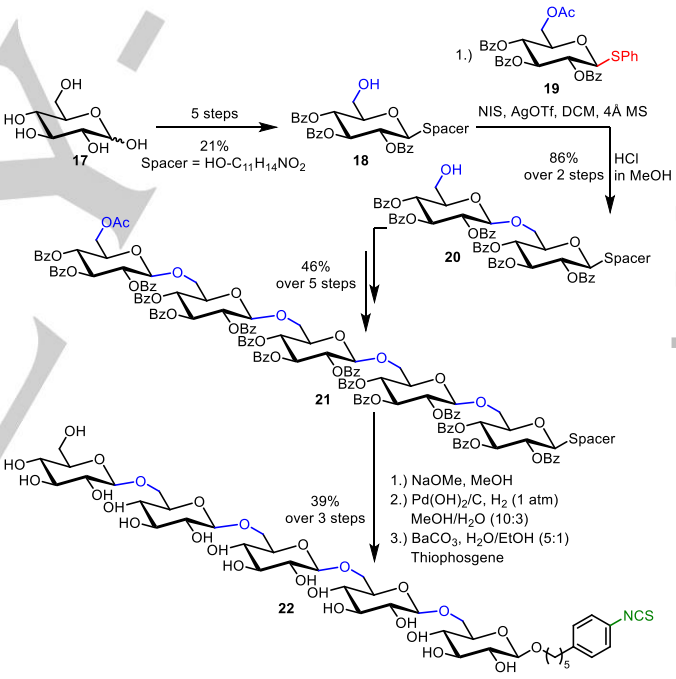


Figure 2. Ara*f*$_2$Gal*p*$_3$-BSA reduces the allergic airway inflammation and sensitization. (A). immunoglobulin E (IgE) was measured in BAL fluid (B). Production of IL-5 and IL-13 was determined in spleen cell supernatants after the restimulation of cells with OVA (C). Goblet cells were counted from five different bronchi of each mouse and expressed as the number of cells per 100 µm basement membrane (D). One-way ANOVA was used to analyse the data for statistical differences. * $p < 0.05$ and ** $p < 0.01$.

Next, a neutral control structure was needed to clarify that the biological activity of pentasaccharide **16** observed results from the actual recognition of the structure by the immune system and not from unspecific glycosylation. Hence, we synthesized a glucose pentamer (Glc*p*$_5$) equal in size and presence of multivalent carbohydrate ligands to pentasaccharide **12** to form a robust control structure (Scheme 4). D-glucose (**17**) was converted to intermediate **18** over five steps in a 21 % yield using standard operations. Glycosylation with thioglycoside **19** and deprotection gave disaccharide **20** over two steps. This process was repeated to obtain the pentaglucose **21** over five steps in 46 % in an iterative manner (details can be found in the SI). After global deprotection, reduction and conversion of the amine to the isothiocyanate using the established procedure, pentaglucose **22** was synthesized in a 39 % yield. It was subsequently coupled to BSA to give the neoglycoconjugate Glc*p*$_5$-BSA (Figure S1). No significant protection against allergic airway disease was found using Glc*p*$_5$-BSA as a neutral control structure (Figure S3). These results underline that the allergy-protective activity depends on the specific composition of the pentasaccharide and is not due to the unspecific glycosylation of BSA.



Scheme 4. Synthesis of the glucose pentamer (**22**, Glc*p*$_5$).

Following the initial observation of the allergy-protective effect of Ara*f*$_2$Gal*p*$_3$-BSA, the mechanism of protection was investigated. During the treatment of mice with Ara*f*$_2$Gal*p*$_3$-BSA, a significant increase of BSA-specific immunoglobin G 1 (IgG1) in serum was observed, which was absent when mice were treated with unmodified BSA. By contrast, treatment with Glc*p*$_5$-BSA did not lead to a significantly increased antibody production (Figure 3, A). Interestingly, the titre of BSA-specific IgG1 shows a strong negative correlation with the number of eosinophilic granulocytes and OVA-specific IgE, suggesting a causative relationship between these parameters (Figure 3, B and C). The galactosylation of the IgG produced was analysed since it is

10.1002/chem.202002287

known that the modification of the Fc-part of IgG with galactose confers immune-regulatory properties,[30-32]. It was found that the treatment of mice with Araf_2Galp_3-BSA causes a significant increase of galactosylated IgG1 (Figure 3, D). The IgG produced was, therefore, suspected of being involved in the regulation of airway inflammation. However, an interference with the induction of eosinophilic airway inflammation by adoptive transfer of IgG1 was not observed (details can be found in the SI, Figure S5), which hints at a more complex mechanism. In addition to antibodies, B-lymphocytes produce cytokines that may affect immune regulation. The so-called regulatory B cells are releasing IL-10 and provide several other mechanisms of down-regulation of inflammatory immune responses.[33, 34] Thus, IL-10 production of B cells from the lung tissue of mice treated with Araf_2Galp_3-BSA was confirmed (Figure S6). The activity of IL-10 was blocked by intranasal administration of a blocking antibody binding to the IL-10 receptor to analyse whether the IL-10 produced is involved in the regulation of the allergic immune response. As expected, mice that were treated with Araf_2Galp_3-BSA and an isotype control antibody showed a significantly reduced allergic inflammation (Figure 3, E). By contrast, the allergic airway inflammation and sensitization in mice that received Araf_2Galp_3-BSA and an IL-10R blocking antibody showed no significant difference from the phenotype observed in mice that were not treated with the glycoconjugate. This shows that IL-10 signalling is probably involved in the mechanism of immune modulation mediated by Araf_2Galp_3-BSA- (discussion can be found in the SI).

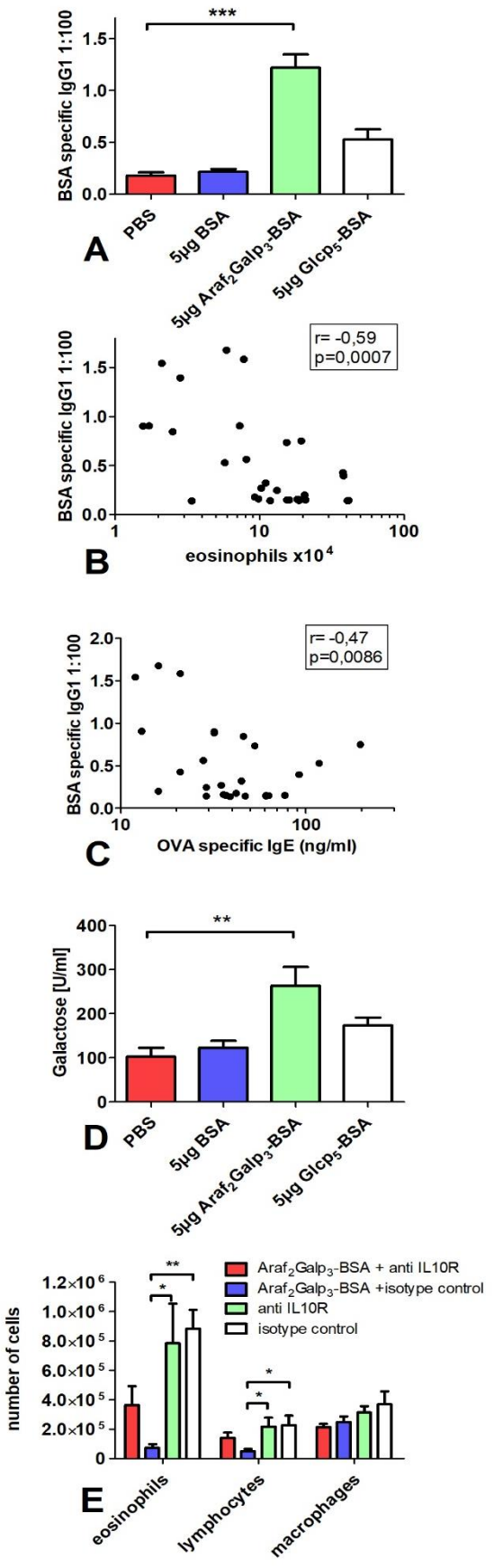


Figure 3. Araf_2Galp_3-BSA-induced production of specific IgG1. The BSA-specific IgG1 antibodies were detected by ELISA (A). Antibody titre was

correlated to the number of eosinophilic granulocytes (B) and the concentration of IgE (C). Galactose modification of IgG was measured in a lectin-binding test by using the galactose-specific *Erythrina crista-galli* lectin (D). The immune-regulatory activity of IL-10 is also involved in Ara*f*$_2$Gal*p*$_3$-BSA-mediated allergy protection. This was shown by blocking the IL-10 receptor by using an antibody, leading to the inhibition of the anti-inflammatory action of Ara*f*$_2$Gal*p*$_3$-BSA (E). One-way ANOVA was used to analyse the data for statistical differences. Correlation analysis was done by Spearman's rank correlation. * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$.

In summary, a convergent total synthesis of a partial structure of AG was accomplished by synthesis of a trigalactose backbone and an arabinose disaccharide sidechain and their subsequent combination. Late-stage introduction of a reactive isothiocyanate and covalent coupling to BSA led to a neoglycoconjugate. It was shown for the first time that this construct can reduce the allergic airway inflammation in a mouse model of allergic asthma in comparable potency as natural AG. The allergy-protective activity was specific for the composition of the partial structure and does not result from unspecific glycosylation of BSA, as shown by the synthesis and investigation of the pentaglucose control structure. Additionally, the mode of action of the synthesized glyco-epitope was investigated, where induction of B-cells that produce galactosylated antibodies and IL-10 was identified, which was found to regulate the allergic response. Gratifyingly, we did not observe any negative side effects accompanying the treatment with Ara*f*$_2$Gal*p*$_3$-BSA and, therefore, believe strongly that this compound is an interesting candidate for a pharmaceutical approach to prevent allergic sensitization in future work.

Acknowledgements

This study was supported by Deutsche Forschungsgemeinschaft (INST 213/950-1 FUGG, PE 1813/2-1), collaborative research centre 1066 of Johannes Gutenberg-University, intramural research funding of Ruhr-University Bochum F659-2009 and F797-2013 and a grant provided by the Gesellschaft für Pädiatrische Allergologie. We thank Dr. Johannes C. Liermann (Mainz) for NMR Spectroscopy, Dr. Christopher Kampf (Mainz) for mass spectrometry, and Petra Bonowitz (Bochum) and Sandra Busse (Bochum) at Experimental Pneumology, Ruhr-University Bochum, for excellent technical assistance. We like to thank Mr. Philip Saunders (Language Support Services, Berlin) for proofreading our manuscript.

Keywords: Arabinogalactan • Total Synthesis • Carbohydrates • Allergy Protection • Airway Inflammation

[1] R. P. Lauener, T. Birchler, J. Adamski, C. Braun-Fahrländer, A. Bufe, U. Herz, E. von Mutius, D. Nowak, J. Riedler, M. Waser, F. H. Sennhauser, *Lancet* **2002**, *360*, 465.

[2] M. J. Ege, I. Herzum, G. Büchele, S. Krauss-Etschmann, R. P. Lauener, M. Roponen, A. Hyvärinen, D. A. Vuitton, J. Riedler, B. Brunekreef, J.-C. Dalphin, C. Braun-Fahrländer, J. Pekkanen, H. Renz, E. von Mutius, *J. Allergy Clin. Immunol.* **2008**, *122*, 407.

[3] V. Ehrenstein, V. Mutius, V. Kries, *Clin. Exp. Allergy* **2000**, *30*, 187.

[4] J. Riedler, C. Braun-Fahrländer, W. Eder, M. Schreuer, M. Waser, S. Maisch, D. Carr, R. Schierl, D. Nowak, E. Von Mutius, *Lancet* **2001**, *358*, 1129.

[5] L. Gorelik, M. Kauth, K. Gehlhar, A. Bufe, O. Holst, M. Peters, *Innate Immun.* **2008**, *14*, 345.

[6] M. Peters, M. Kauth, O. Scherner, K. Gehlhar, I. Steffen, P. Wentker, E. von Mutius, O. Holst, A. Bufe, *J. Allergy Clin. Immunol.* **2010**, *126*, 648.

[7] L. Brecker, D. Wicklein, H. Moll, E. C. Fuchs, W.-M. Becker, A. Petersen, *Carbohydr. Res.* **2005**, *340*, 657.

[8] G B Fincher, a. B A Stone, A. E. Clarke, *Annu. Rev. Plant Physiol.* **1983**, *34*, 47.

[9] W. Qi, C. Fong, D. T. A. Lamport, *Plant Physiol.* **1991**, *96*, 848.

[10] K. Cheng, Y. Zhou, S. Neelamegham, *Glycobiology* **2016**, *27*, 200.

[11] A. Nieto, U. Wahn, A. Bufe, P. Eigenmann, S. Halken, G. Hedlin, A. Høst, J. Hourihane, J. Just, G. Lack, *Pediatr. Allergy Immunol.* **2014**, *25*, 516.

[12] C.-H. Chang, L. S. Lico, T.-Y. Huang, S.-Y. Lin, C.-L. Chang, S. D. Arco, S.-C. Hung, *Angew. Chem. Int. Ed.* **2014**, *53*, 9876.

[13] Y. Ding, C. V. N. S. Vara Prasad, H. Bai, B. Wang, *Bioorg. Med. Chem. Lett.* **2017**, *27*, 2424.

[14] T. Li, H. Ye, X. Cao, J. Wang, Y. Liu, L. Zhou, Q. Liu, W. Wang, J. Shen, W. Zhao, P. Wang, *ChemMedChem* **2014**, *9*, 1071.

[15] F. Lin, G. Lian, Y. Zhou, *Carbohydr. Res.* **2013**, *371*, 32.

[16] M. P. Bartetzko, F. Schuhmacher, H. S. Hahm, P. H. Seeberger, F. Pfrengle, *Org. Lett.* **2015**, *17*, 4344.

[17] F. W. D'Souza, T. L. Lowary, *Org. Lett.* **2000**, *2*, 1493.

[18] A. Fekete, A. Borbás, S. Antus, A. Lipták, *Carbohydr. Res.* **2009**, *344*, 1434.

[19] H. Huang, L. Han, Y.-M. Lan, L.-L. Zhang, *J. Asian Nat. Prod. Res.* **2014**, *16*, 640.

[20] K. S. Kim, B.-Y. Lee, S. H. Yoon, H. J. Jeon, J. Y. Baek, K.-S. Jeong, *Org. Lett.* **2008**, *10*, 2373.

[21] Y. Wu, D.-C. Xiong, S.-C. Chen, Y.-S. Wang, X.-S. Ye, *Nat. Commun.* **2017**, *8*, 14851.

[22] X. Zhang, T. Kamiya, N. Otsubo, H. Ishida, M. Kiso, *J. Carbohydr. Chem.* **1999**, *18*, 225.

[23] R. Lemieux, H. Driguez, *J. Am. Chem. Soc.* **1975**, *97*, 4069.

[24] B. Helferich in *Advances in Carbohydrate Chemistry*, Vol. 3 (Eds.: W. W. Pigman, M. L. Wolfrom, S. Peat), Academic Press, Cambridge, MA, **1948**, pp. 79-111.

[25] D. R. Mootoo, P. Konradsson, U. Udodong, B. Fraser-Reid, *J. Am. Chem. Soc.* **1988**, *110*, 5583.

[26] L. Zhang, K. Shen, H. A. Taha, T. L. Lowary, *J. Org. Chem.* **2018**, *83*, 7659.

[27] A. Imamura, T. L. Lowary, *Org. Lett.* **2010**, *12*, 3686.

[28] B. Yu, H. Tao, *Tetrahedron Lett.* **2001**, *42*, 2405.

[29] M. C. Andersen, S. K. Kračun, M. G. Rydahl, W. G. Willats, M. H. Clausen, *Chem. Eur. J.* **2016**, *22*, 11543.

[30] R. M. Anthony, F. Nimmerjahn, D. J. Ashline, V. N. Reinhold, J. C. Paulson, J. V. Ravetch, *Science* **2008**, *320*, 373.

[31] N. Washburn, I. Schwab, D. Ortiz, N. Bhatnagar, J. C. Lansing, A. Medeiros, S. Tyler, D. Mekala, E. Cochran, H. Sarvaiya, *PNAS* **2015**, *112*, E1297.

[32] G. Dekkers, T. Rispens, G. Vidarsson, *Front. Immunol.* **2018**, *9*, 553.

[33] B. Peng, Y. Ming, C. Yang, *Cell Death Dis.* **2018**, *9*, 109.

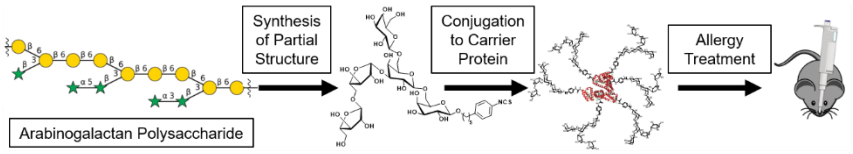
[34] T. F. Tedder, *J. Immunol.* **2015**, *194*, 1395.

10.1002/chem.202002287

WILEY-VCH

COMMUNICATION

Entry for the Table of Contents



Total synthesis of a pentasaccharide containing L-arabinose- and D-galactose was accomplished and covalently coupled to a carrier protein to form a neoglycoconjugate that mimics partial structures of allergy-preventive arabinogalactan. Inhalative treatment of mice with the neoglycoconjugate protects them against allergic inflammation by the induction of immune regulation involving antibodies and interleukin-10.