https://www.scirp.org/journal/jbise

J. Biomedical Science and Engineering, 2025, Vol. 18, (No. 10), pp: 393-400

Glycidic Cues for Tissue Engineering: Synthesis and Characterization

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Keywords: Collagen, Glycidic Cue, Multifunctional Biomolecule, Bioconjugation, Tissue Engineering

Received: August 26, 2025 **Accepted:** October 26, 2025 **Published:** October 29, 2025

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ABSTRACT

The bioactivity of materials can be enhanced by incorporating adhesive cues and regulatory molecules. Carbohydrates are essential for numerous biological recognition processes. Recent evidence suggests that collagen glycosylation is crucial for maintaining the equilibrium between collagen deposition and turnover, with several implications for healthy and pathological conditions. In this study, we synthesized small glycidic cues for enrichment with collagen. A relevant factor for successful biomaterial decoration pertains to the selection of appropriate chemistry. This research is strongly motivated by the need for innovative biomaterials in cartilage tissue engineering, especially for repairing osteoarthritis defects.

1. INTRODUCTION

Osteoarthritis (OA) [1] is the most prevalent form of degenerative joint disease and a primary cause of pain typically linked with aging [2]. It affects over 50 and 25 million individuals in the EU and USA, accounting for approximately 25% of all visits to primary care physicians and half of the Nonsteroidal Anti-Inflammatory Drug (NSAID) prescriptions. Globally, these figures are striking, and projections indicate that the prevalence of OA-related disability will double by 2050, exacerbating its already considerable economic impact [3]. Despite centuries of scientific and medical advancements, a universally accepted and successful treatment for damaged articular cartilage remains elusive [4]. Present pharmacological treatments are often limited in efficacy and are associated with substantial side effects or high costs. Furthermore, surgical interventions are frequently necessitated to repair cartilage and bone injuries, highlighting the imperative for novel and effective treatments [5]. Tissue engineering presents a comprehensive strategy for the structural and functional restoration of tissues. This field typically employs a combination of cells, biomaterials, and bioactive factors (signaling cues/regulators) [6] to foster the regeneration of damaged or lost tissue, influencing cellular differentiation, proliferation, and tissue morphogenesis [7]. Repair of articular cartilage represents a formidable challenge in musculoskeletal medicine owing to the limited intrinsic repair capacity of

the tissue.

Biomaterials crafted for cartilage tissue engineering are examined for their physical attributes, such as porosity and mechanical compressive strength, as well as their chemical properties, including degradation rates [8]. Recent advances in the design of these biomaterials have incorporated signaling cues within the synthetic microenvironment [6, 9]. In the fields of tissue engineering and regenerative medicine, the development of biomaterial matrices with covalently attached biomolecular cues that can influence cellular carbohydrate cues onto surfaces to confer specific biofunctionalities is a promising approach.

Collagen is the most abundant protein in the body, serving as a principal element of the extracellular matrix (ECM). It forms fibrillar meshes and interacts with a multitude of adhesion proteins including fibronectin, integrins, and laminin. The biosynthesis of collagen initiates intracellularly at the ribosomal membranes and continues extracellularly [10, 11]. Owing to its dualistic properties, collagen can be characterized as a "block" copolymer, identified with favorable properties for tissue engineering [12-14] and cartilage repair [15]. The process of collagen glycosylation is highly conserved across the animal kingdom, observed in organisms ranging from simple sponges to mammals. It plays a critical role in ECM breakdown and remodeling, influencing the dynamic equilibrium between turnover and collagen deposition in healthy and pathological states [16, 17]. The saccharidic residues predominantly identified were β-galactosides or α-(1→2)-glucosyl-β-galactosides [18].

Recent studies have demonstrated that lectin domains directly interact with glycosylated collagens [17]. Lectins, proteins that bind with sugars, are implicated in signal transduction and carbohydrate recognition across various biological processes [19]. Small saccharidic motifs are reportedly attached to material surfaces [20]. The versatility of this approach enables the ligation of diverse reducing sugars to adhesive groups or lipids without the need for protecting group chemistry, considerably expediting the development of new coating entities. This methodology applies to the synthesis of coating molecules that can be thoroughly characterized before their employment in surface functionalization.

Biocompatible materials such as synthetic Carbonate Hydroxyapatite (CHA) and Hydroxyapatite (HA) are extensively utilized in biomedical applications [21]. HA, the natural mineral component of bones, teeth, and calcified tissues in vertebrates, along with synthetic HA and CHA, is employed for human implant coatings owing to its osteoconductivity. The geometry of these materials can profoundly affect specific tissue responses, as observed in vascular in-growth [22, 23]. Therefore, this study aimed to engineer a novel natural nanofibrous scaffold with surface-bound galactose ligands to augment the bioactivity and mechanical stability of primary hepatocytes in culture for liver regeneration.

A distinct strategy was employed for carbohydrate grafting on polycaprolactone substrates. Aliphatic polyesters, among synthetic polymers, are favored as biomaterials for scaffold design to support the regeneration of various tissue-engineered organs, attributed to their unique biodegradability and biocompatibility [17, 24, 25]. However, similar to other synthetic polymers, they lack inherent molecular motifs for cellular biological recognition. Cell adhesion is intimately associated with the surface characteristics of biomaterials, influenced by surface charge, topography, wettability, roughness, etc. Introducing glucosamine is an innovative approach to enhance scaffold biocompatibility by increasing hydrophilicity. Notably, given the ubiquity of this monosaccharide in nature, including in humans, and its inclusion in biomedical formulations for osteoarthritis treatment, its application in biomaterial surface modification is considered a safe and promising strategy.

The bioactivity of materials can be enhanced by incorporating adhesive cues and regulatory molecules. Carbohydrates are essential in numerous biological recognition processes. Recent findings indicate that collagen glycosylation is crucial for regulating the equilibrium between collagen deposition and turnover, with profound implications for healthy and pathological states [17, 25]. However, only a handful of studies have investigated the impact of small carbohydrate epitopes on collagen [26]. Consequently, this study aims to augment collagen with small glycidic cues (vide infra). Present investigations at the host institution are assessing the effects of collagen glycosylation. The selection of appropriate chemistry is critical for the successful modification of biomaterials. We propose straightforward, dependable, and gentle bioconjugation

steps, facilitating a chemoselective reaction between cues (multifunctional biomolecules) and the collagen matrix. This method utilizes a Michael reaction between a thiol-terminated peptide/carbohydrate and a maleimido-modified scaffold [27].

This study has undertaken the design and synthesis of biologically relevant glycidic structures. By focusing on the design and synthesis of collagen patches functionalized with such innovative signaling microenvironment cues, future research will be directed toward developing smart biomaterials based on collagen matrices for the repair of cartilage defects. This research is strongly motivated by the need for novel, promising, biomaterial-based cartilage tissue engineering strategies for the treatment of OA defects. The glycidic structures providing specific biological signals were characterized using spectroscopic methods (^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR), FTIR, mass spectrometry).

2. EXPERIMENTAL SECTION

2.1. Materials, Instrumentation, and Characterization

All reagents were procured commercially and utilized without modification. Column chromatography was conducted using silica gel G-60 (Merck 7734), while thin-layer chromatography employed silica gel 60 with a fluorescent indicator F_{254} on precoated aluminum plates measuring 20 × 20 cm^2 (Merck 5554). Organic solvents were evaporated under reduced pressure at low temperatures.

NMR spectra were acquired at 400 MHz for ^{1}H and 100 MHz for ^{13}C using a mercury FT NMR spectrometer (Varian AS 400+, Varian Inc., Palo Alto, CA, USA) at room temperature, with $CDCl_3$ as the solvent and Tetramethylsilane (TMS) as the reference. Fourier-transform infrared (FT-IR) spectra were obtained within the wavenumber range of 400 - 4000 cm^{-1} using KBr disks on a PerkinElmer 100 FTIR Model instrument (PerkinElmer, Norwalk, CT, USA).

2.2. Synthesis of Allyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-*β*-D-galactopyranoside (2)

To a stirred solution of 1,2-di-O-acetyl-3,4,6-tri-O-benzyl-D-galactopyranose (**1**) (2.7 g, 5.0 mmol) in dry acetonitrile (50 mL) were added allyl alcohol (0.4 mL, 6 mmol) and BF_3OEt (2.4 mL, 25 mmol) at −20˚C under an atmosphere of argon. The reaction mixture was stirred for 18 h at −20˚C and then it was neutralized with sat. Na_2CO_3 solution. Afterward, acetonitrile was evaporated and the water layer was extracted with EtOAc (3 × 100 mL). The organic layer was dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, Petroleum Ether:EtOAc, 4:1) to afford compound **2** (1.94 g, 70%) as a colorless syrup. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 - 7.24 (15H, m), 5.80 (1H, m), 5.39 (2H, dd, J = 12.0, 8.0 Hz), 5.25 (1H, dd, J = 16.0, 4.0 Hz), 5.13 (1H, dd, J = 12.0, 4.0 Hz), 4.93 (1H, d, J = 11.6 Hz), 4.68 (1H, d, J = 12.0 Hz), 4.60 (1H, d, J = 12.0 Hz), 4.55 (1H, d, J = 12.0 Hz), 4.43 (1H, d, J = 4.0 Hz), 4.40 (2H, d, J = 4.0 Hz), 4.31 (1H, dd, J = 12.0, 4.0 Hz), 4.04 (1H, dd, J = 12.0, 4.0 Hz), 3.95 (1H, d, J = 4.0 Hz), 3.65 (2H, dd, J = 8.0, 4.0 Hz), 3.55 (1H, dd, J = 12.0, 4.0 Hz), 2.05 (3H, s). ^{13}C ($CDCl_3$, 100 MHz): δ 170.1, 138.4, 138.0, 137.8, 133.9, 128.5, 128.5, 128.4, 128.4, 128.3, 128.2, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.4, 116.9, 100.2, 80.3, 77.8, 76.7, 74.4, 73.6, 73.6, 72.5, 71.9, 71.3, 69.3, 21.1. m/z calculated for $[M+Na]^+$ $C_{32}H_{36}O_7$ 555.6, found 555.2.

2.3. Synthesis of Allyl 2-Hydroxy-3,4,6-tri-*O*-benzyl-*β*-D-galactopyranoside (3)

To a stirred solution of compound **2** (1.7 g, 3.0 mmol) in dry MeOH (30 mL) was added Na metal (69.0 mg, 3.0 mmol) under an atmosphere of argon. The reaction mixture was stirred for 2 h at r.t. Thereafter, the reaction mixture was quenched by the addition of Amberlite IR-120 (H+) resin and the resulting mixture was filtered. The filtrate was then concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, Petroleum Ether:EtOAc, 1:1) to afford compound **3** (1.24 g, 81%) as a colorless syrup. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.26 (15H, m), 5.94 (1H, m), 5.30 (1H, dd, J = 16.0, 1.2 Hz), 5.20 (1H, d, J = 12.0, 1.2 Hz), 4.90 (1H, d, J = 11.6 Hz), 4.70 (1H, dd, J = 12.0, J = 14.0 Hz), 4.68 (1H, d, J = 14.0 Hz), 4.62 (1H, d, J = 12.0 Hz), 4.46 (2H, d, J = 6.8 Hz), 4.38 (1H, dd, J = 10.0, 4.8 Hz), 4.31 (1H, d, J = 7.6 Hz), 4.10 (1H, dd, J

= 12.8, 6.4 Hz), 4.00 (1H, dd, J = 8.0, 8.0 Hz), 3.94 (1H, d, J = 2.4 Hz), 3.62 (2H, m), 3.58 (1H, dd, J = 5.2, 5.2 Hz), 3.45 (1H, dd, J = 9.6, 2.8 Hz), 2.23 (1H, br s). ^{13}C ($CDCl_3$, 100 MHz) δ 138.5, 138.0, 137.8, 134.0, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 128.2, 127.9, 127.9, 127.8, 128.8, 127.7, 127.7, 127.6, 117.1, 102.1, 82.0, 77.4, 76.7, 73.9, 72.5, 71.6, 70.9, 69.9, 69.3, 68.6. *m/z* calculated for $[M + Na]^+$ $C_{30}H_{34}O_6$ 513.6, found 513.2.

2.4. Synthesis of Allyl 3,4,6-Tri-*O*-benzyl-*β*-D-galactopyranosyl-(1→2)-2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranoside (5)

To a stirred solution of compound **3** (1.54 g, 3.0 mmol) in dry DCM (30 mL), a TMSOTf solution in DCM (c = 0.05 M, 0.06 mmol) was added at −20˚C under an atmosphere of argon. The reaction mixture was stirred for 10 minutes at −20˚C. Thereafter, the reaction mixture was added to a stirred solution of compound **4** (2.7 g, 3.9 mmol) in dry DCM (20 mL) at −20˚C under an atmosphere of argon. Afterward, the reaction mixture was stirred for 30 minutes at −20˚C and was neutralized with sat. Na_2CO_3 solution. The water layer was extracted with DCM (3 × 100 mL). The organic layer was dried with Na_2SO_4 and concentrated in vacuo at 35˚C. The residue was purified by flash chromatography (SiO_2, Petroleum Ether:EtOAc:Et_3N, 7:3:0.1) to afford compound **5** (1.8 g, 60%) as a colorless syrup. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 - 7.07 (35H, m), 5.89 (1H, m), 5.28 (1H, d, J = 16.0 Hz), 5.12 (2H, d, J = 12.0), 5.03 (1H, d, J = 4.0), 5.00 (1H, d, J = 16.0), 4.88 (1H, d, J = 8.0 Hz), 4.81 (2H, d, J = 12.0 Hz), 4.78 (1H, d, J = 4.0), 4.75 (2H, d, J = 12.0 Hz), 4.73 (2H, d, J = 16.0 Hz), 4.65 (1H, d, J = 16.0 Hz), 4.58 (2H, d, J = 8.0 Hz), 4.48 (1H, d, J = 8.0 Hz), 4.47 (2H, d, J = 7.6 Hz), 4.35 (1H, dd, J = 12.0, 4.0 Hz), 4.30 (2H, d, J = 12.0 Hz), 3.94 (1H, d, J = 2.4 Hz), 4.20 (1H, dd, J = 12.0, 4.0 Hz), 4.10 (1H, dd, J = 12.0, 4.0 Hz), 4.04 (1H, d, J = 2.4 Hz), 4.02 (2H, d, J = 2.4 Hz), 3.99 (1H, d, J = 4.0 Hz), 3.67 (1H, t, J = 4.0 Hz), 3.58 (1H, dd, J = 5.2, 5.2 Hz), 3.40 (1H, dd, J = 9.6, 2.8 Hz). ^{13}C ($CDCl_3$, 100 MHz) δ 138.9, 138.8, 138.7, 138.4, 138.2, 137.9, 134.1, 134.1, 128.7, 128.5, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 128.1, 128.1, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 127.5, 127.5, 127.4, 127.3, 118.3, 106.7, 102.4, 101.5, 100.8, 95.4, 95.1, 95.0, 94.4, 84.9, 83.0, 82.2, 79.0, 77.7, 77.5, 77.4, 77.1, 76.8, 76.8, 74.8, 74.7, 73.7, 73.6, 73.3, 73.2, 71.8, 71.7, 70.1, 69.5, 69.4, 68.7, 68.7, 67.8. *m/z* calculated for $[M + Na]^+$ $C_{64}H_{68}O_{11}$ 1035.2, found 1035.2.

2.5. Synthesis of 1-*O*-(3-Acetylthiopropane)-3,4,6-tri-*O*-benzyl-*β*-D-galactopyranosyl-(1→2)-2,3,4,6-tetra-*O*-benzyl-*α*-D-glucopyranoside (6)

To a stirred solution of compound **5** (1.2 g, 1.2 mmol) and thioacetic acid (0.17 mL, 2.4 mmol) in dry 1,4-dioxane (0.3 mL), 2,2'-azobisisobutyronitrile (AIBN; 0.98 g, 6.0 mmol) was added at 50˚C under an atmosphere of argon. The reaction mixture was stirred for 3 h at 80˚C, then cooled to room temperature. Cyclohexene (0.64 mL, 6.3 mmol) was added, and the reaction mixture was stirred at room temperature for 30 min. After evaporation, the residue was purified by flash chromatography (SiO_2, Petroleum Ether:EtOAc, 8:2) to afford compound **6** (0.13 g, 10%) as a yellow syrup. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36 - 7.06 (35H, m), 5.64 (1H, d, J = 3.6 Hz), 4.96 (1H, d, J = 14.8 Hz), 4.86 (1H, d, J = 11.6), 4.83 (1H, d, J = 10.8), 4.80 (1H, d, J = 12.0), 4.78 (1H, d, J = 8.0 Hz), 4.68 (1H, d, J = 12.0 Hz), 4.65 (1H, d, J = 8.0), 4.58 (1H, d, J = 12.0 Hz), 4.56 (2H, d, J = 12.0 Hz), 4.51 (1H, d, J = 8.0 Hz), 4.48 (2H, d, J = 6.0 Hz), 4.42 (2H, d, J = 11.6 Hz), 4.29 (2H, t, J = 12.0 Hz), 4.12 (2H, d, J = 8.0 Hz), 3.98 (1H, d, J = 2.4 Hz), 3.97 (1H, d, J = 12.0 Hz), 3.88 (1H, m), 3.70 (1H, d, J = 8.0 Hz), 3.59 (6H, m), 3.36 (1H, d, J = 8.0 Hz), 2.86 (3H, m), 2.24 (3H, s). ^{13}C ($CDCl_3$, 100 MHz) δ 204.2, 139.2, 138.8, 138.8, 138.6, 138.3, 137.9, 137.2, 128.8, 128.8, 128.8, 128.8, 128.8, 128.8, 128.8, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.3, 128.3, 128.3, 128.3, 128.3, 128.3, 128.3, 128.2, 128.1, 128.1, 128.1, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.7, 127.4, 103.1, 102.7, 97.2, 96.5, 90.0, 89.7, 83.5, 83.2, 78.0, 77.3, 77.3, 76.7, 75.0, 74.1, 73.4, 70.2, 69.9, 68.6, 68.3, 67.3, 29.8, 29.7, 25.3. *m/z* calculated for $[M+Na]^+$ $C_{66}H_{72}O_{12}S$ 1102.3, found 1102.1.

2.6. Synthesis of 1-*O*-(3-Mercaptopropyl)-*β*-D-galactopyranosyl-(1→2)-*α*-D-glucopyranoside (G1)

To a stirred solution of compound **6** (100 mg, 0.092 mmol) in dry MeOH (2 mL) were added Pd/carbon

(120 mg) and dry HCO_3NH_4 (400 mg, 6.44 mmol) at r.t. under an atmosphere of argon. The reaction mixture was stirred and heated for 10 h at 100˚C. Afterward, the resulting mixture was filtered through Acrodise * Premium 25 mm Syringe Filter with a 0.45 μm Nylon Membrane. The filtrate was concentrated in vacuo to afford compound **G1** (10 mg, 26%) as a colorless syrup. ^1H NMR (D_2O, 400 MHz) δ 5.40 (1H, d, J = 3.6 Hz), 5.15 (1H, d, J = 3.6 Hz), 4.43 (1H, d, J = 8.0 Hz), 3.95 (1H, m), 3.86 (2H, m), 3.77 - 3.45 (10H, m), 3.30 - 3.22 (1H, m), 2.80 (1H, t, J = 7.2 Hz), 2.58 (1H, t, J = 7.2 Hz), 2.05 - 1.84 (2H, m). ^{13}C ($CDCl_3$, 100 MHz) δ 110.4, 111.2, 83.6, 81.5, 81.2, 76.8, 76.0, 74.1, 71.8, 71.5, 67.4, 62.9, 62.2, 30.3, 20.9. *m/z* calculated for $[M+Na]^+$ $C_{15}H_{28}O_{11}S$ 416.4, found 416.2.

3. RESULTS AND DISCUSSION

The synthesis of glycidic cues poses a considerable challenge. Unlike proteins and nucleic acids, carbohydrate derivatives are complex to synthesize because of the absence of generalized methods for their routine preparation, often necessitating multiple selective protection and deprotection steps. The selection of glycidic cues is informed by their natural occurrence in collagen; the synthesis of relevant glycidic structures eliciting specific biological signals has been accomplished. Concurrently, the production of suitable linkers for the biodecoration process is underway. These heterobifunctional linkers are designed to attach to the material on one end and to the cues on the other.

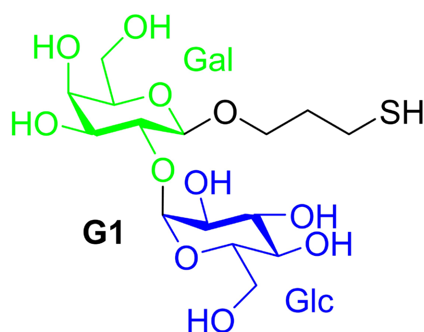

Figure 1. The structure of the glycidic clue G1.

Considerably, the glycidic cue **G1** (**Figure 1**) has been selected for biomaterial functionalization. **G1**, a disaccharide present in embryonic collagen, has been suitably modified for conjugation to materials via an appropriate linker. The synthesis of individual monosaccharides is undertaken to elucidate the specific role of each sugar unit. Moreover, the synthesis of the target disaccharidic cue **G1** (**Figure 2**) is particularly demanding. The critical synthesis aspects include 1) protection/deprotection steps, leading to a glycosyl acceptor (Gal unit) with selective deprotection at the 2-position for the glycosylation reaction; 2) formation of glycosidic bond with alpha-stereoselection, necessitating a nonparticipating protecting group at the 2-OH of the glucose unit.

Dedicated to the development of intelligent biomaterials based on collagen matrices for repairing cartilage defects, with a focus on designing and synthesizing collagen patches functionalized with innovative signaling microenvironment cues, such as biologically pertinent glycidic structures. The impetus for this research is the demand for novel and effective biomaterial-based strategies for OA defect repair. The relevant glycidic structures that provide specific biological signals were characterized using spectroscopic techniques (^1H and ^{13}C NMR, FTIR, mass spectrometry).

In the ^1H NMR spectra of the synthesized glycidic cue **G1**, the anomeric protons are discernible at 5.40 and 5.15 ppm. The remaining sugar protons are evident at 4.43 - 3.45 ppm. Notably, the characteristic aromatic peaks of compound **6** are absent in the ^1H NMR spectra of the synthesized glycidic cue **G1**, following the hydrolysis reaction, indicating the successful synthesis of glycidic cue **G1**. In the ^{13}C NMR spectrum, anomeric carbons C-1 of glycidic cue **G1** are observed at 111.1 and 110.4 ppm. Additionally, the alkyl group

carbon peaks of glycidic cue **G1** are present at 30.3 - 20.4 ppm.

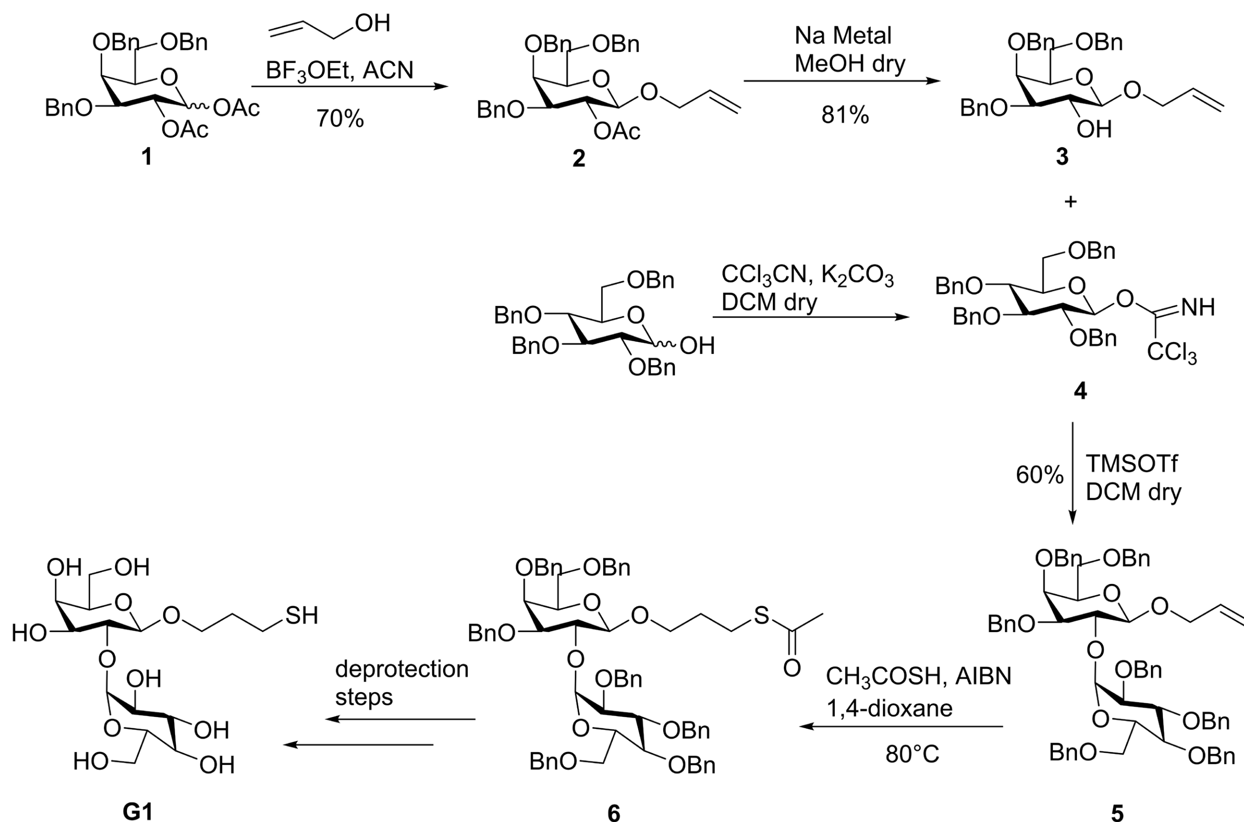

Figure 2. **Synthesis of glycidic cluue G1.**

4. CONCLUSION

This investigation executed the design and synthesis of glycidic structures with biological relevance. Focusing on the design and synthesis of collagen patches, functionalized with such pioneering signaling microenvironment cues, will guide subsequent research toward the creation of intelligent biomaterials derived from collagen matrices for the remediation of cartilage defects. The driving force behind this endeavor is the necessity for inventive and promising biomaterial-based strategies in cartilage tissue engineering to address OA defects.

ACKNOWLEDGEMENTS

I received a grant from the TUBITAK (Scientific and Technical Research Council of Türkiye) BIDEB-2219 Programme for a postdoctoral fellowship.

CONFLICTS OF INTEREST

The author declares no conflicts of interest regarding the publication of this paper.

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