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Synthesis of polysaccharide derivatives bearing bromobenzoate pendants for use as chiral auxiliaries

Tomoyuki Ikai *, Kazuma Kimura, Katsuhiro Maeda, Shigeyoshi Kanoh

Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

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ABSTRACT

Cellulose and amylose derivatives bearing bromobenzoate pendants were synthesized as chiral auxiliaries to create optically active biaryl compounds through Suzuki–Miyaura cross-coupling with naphthalen-1-ylboronic acids. The regioselectively substituted polysaccharide derivatives bearing 2-bromobenzoate pendants at the 6-position of the glucose unit exhibited higher diastereoselectivity than did the corresponding monosaccharide-based chiral auxiliary and the non-regioselectively substituted polysaccharide derivative bearing 2-bromobenzoates at the 2,3,6-positions. These results suggest that the chiral induction by the regioselectively substituted polysaccharide-based auxiliaries is mainly based on regular higher-order structures, such as one-handed helical structures.

1. Introduction

Many compounds of biological and pharmacological interest consist of chiral molecules, and their enantiomers often possess different biological properties, including unique pharmacodynamic, pharmacokinetic, protein binding, and toxic effects [1–6]. Therefore, the acquisition of single enantiomers has become increasingly important in the pharmaceutical, agrochemical, food, and fragrance industries. Optically active compounds have also become relevant to the development of functional chiral materials, such as ferroelectric liquid crystals, nonlinear optical materials, and circularly polarized luminescent materials [6–12]. Asymmetric synthesis using chiral auxiliaries is a potential method for obtaining optically active compounds [13–17]. Chiral auxiliaries are preferentially prepared from readily available and inexpensive natural products because a stoichiometric amount of chiral template is required in asymmetric reactions. Since a practical chiral auxiliary using D-ribose as a chiral source was reported in 1977 [18], a wide variety of monosaccharide-based chiral auxiliaries have been reported for asymmetric reactions, including Strecker- and Mannich-type reactions [19–21], 1,4-conjugate additions [22–24], alkylations [25–27], cyclopropanations [28,29], Diels–Alder cycloadditions [30–33], aza-Friedel–Crafts reactions [34], 1,3-dipolar cycloadditions [35–37], and many others [38–42].

On the other hand, polysaccharides such as cellulose and amylose are the most abundant and renewable resources on earth. These polysaccharides are optically active not only owing to the stereogenic centers of the constituent sugar units but also because of their regular higher-order structures, such as one-handed helices. To date, various polysaccharide derivatives have been successfully applied to chiral stationary phases [43–46] and asymmetric catalysts [47–52]. These polysaccharide-based chiral materials often exhibit better performance than the corresponding monosaccharide- and oligosaccharide-based materials, which only display chirality at their stereogenic centers [47,53].

In view of their attractiveness as a resource and their potential as chiral materials, polysaccharides exhibiting helical chirality appear to be intriguing candidates for superior chiral auxiliaries compared to conventional monosaccharides. However, to the best of our knowledge, polysaccharides have never been utilized as scaffolds for chiral auxiliaries. In the present study, we synthesized cellulose and amylose derivatives bearing bromobenzoate pendants and investigated their abilities as chiral auxiliaries to provide optically active biaryl compounds through Suzuki–Miyaura cross-coupling with naphthalen-1-ylboronic acids.

2. Experimental

2.1. Materials

Anhydrous solvents, such as pyridine, *N*,*N*-dimethylacetoamide (DMA), and tetrahydrofuran (THF), as well as lithium chloride and

* Corresponding author. Tel./fax: +81 76 234 4781.
E-mail address: ikai@se.kanazawa-u.ac.jp (T. Ikai).

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potassium hydroxide were purchased from Kanto Kagaku (Tokyo, Japan). Cellulose (Avicel, DP ~200) was purchased from Merck (Darmstadt, Germany). Amylose (DP ~300), 3,5-dimethylphenyl isocyanate, and Chiralcel OD-H (25 × 0.46 cm ID) were kindly supplied by Daicel Chemical Industries (Tokyo, Japan). 2-Bromobenzoyl chloride, 2-bromo-3-methylbenzoic acid, 4-methoxyphenyl isocyanate, *m*-tolyl isocyanate, *p*-tolyl isocyanate, and phenyl isocyanate were from Tokyo Kasei (Tokyo, Japan). 4-Phenoxyphenyl isocyanate and 4-*tert*-butylphenyl isocyanate were from Aldrich (Milwaukee, WI, USA). Potassium carbonate and D-glucose were obtained from Nacalai (Kyoto, Japan). Tetrakis(triphenylphosphine)palladium(0) $Pd(PPh_3)_4$ and 4-bromo-3-methylbenzoic acid were purchased from Wako (Osaka, Japan). 2-Bromo-3-methylbenzoyl chloride and 4-bromo-3-methylbenzoyl chloride were prepared through the reaction of the corresponding carboxylic acids with oxalyl chloride in toluene. The regioselectively protected cellulose derivative Ce—Tr [54], 2-methylnaphthalen-1-ylboronic acid **8a** [55], and 2-methoxylnaphthalen-1-ylboronic acid **8b** [55] were prepared according to literature procedures.

2.2. Synthesis of polysaccharide derivatives

*Synthesis of Ce-**a**:* Cellulose (DP ~200, 0.50 g, 3.09 mmol) was dispersed in pyridine (15 mL) and was allowed to react with 2-bromobenzoyl chloride (3.05 g, 13.9 mmol) at 80 °C. After 24 h, the reaction mixture was cooled to room temperature and poured into a large amount of methanol. The target cellulose derivative Ce-**a** (1.92 g, 87%) was isolated by centrifugation. ^{1}H NMR (500 MHz, $CDCl_3$, 55 °C): δ 3.38 (br, 1H, glucose proton), 3.77 (br, 1H, glucose proton), 3.92 (br, 1H, glucose proton), 4.25 (br, 1H, glucose proton), 4.60 (br, 1H, glucose proton), 5.33 (br, 1H, glucose proton), 5.62 (br, 1H, glucose proton), 6.9–7.7 (m, 12H, aromatic). IR (KBr): 1742 cm^{-1} ($\nu_{C=O}$). Elemental analysis calcd. (%) for $C_{27}H_{19}Br_3O_8$: C, 45.60; H, 2.69. Found: C, 45.52; H, 2.75.

*Synthesis of Ce-**1a**′:* Cellulose (0.50 g, 3.09 mmol) was first dissolved in a mixture of DMA (17 mL), lithium chloride (1.50 g), and pyridine (8.5 mL). Then, 3,5-dimethylphenyl isocyanate (0.68 g, 4.63 mmol) was added, and the mixture was stirred for 18 h at 80 °C. Subsequently, 2-bromobenzoyl chloride (0.68 g, 3.09 mmol) was added and allowed to react for 18 h at 80 °C. Finally, the remaining hydroxyl groups of cellulose were treated with an excess amount of 3,5-dimethylphenyl isocyanate (1.14 g, 7.73 mmol) for 24 h at 80 °C. After the reaction, the target cellulose derivative Ce-**1a**′ (1.77 g, 90%) was isolated as the methanol-insoluble fraction. The ratio of the 3,5-dimethylphenylcarbamate (R^1) and 2-bromobenzoate (R^{Br}) pendants (R^1/R^{Br}) was determined to be 64/36 by elemental analysis. ^{1}H NMR (500 MHz, $CDCl_3$, 55 °C): δ 1.7–2.5 (br, 11.46H, Ph—CH_3), 3.1–5.5 (br, 7H, glucose protons), 6.3–8.0 (br, 12H, aromatic and —NH). IR (KBr): 3365 cm^{-1} (ν_{NH}), 1736 cm^{-1} ($\nu_{C=O}$). Elemental analysis calcd. (%) for $C_{30.82}H_{30.46}Br_{1.09}N_{1.91}O_8$: C, 57.60; H, 4.78; N, 4.16. Found: C, 57.63; H, 4.90; N, 4.33.

*Synthesis of Ce-**1a**:* To a solution of Ce—Tr (0.82 g, 1.89 mmol) in pyridine (10 mL) was added 3,5-dimethylphenyl isocyanate (0.83 g, 5.66 mmol), and then the mixture was heated to 80 °C. After 40 h, the reaction mixture was poured into a large amount of methanol, and the resulting precipitate was collected by centrifugation. The obtained white solid was dispersed in methanol containing 0.1 M hydrochloric acid at room temperature to deprotect the 4-methoxytriphenylmethyl groups. After 24 h, the cellulose derivative bearing 3,5-dimethylphenylcarbamate groups at the 2,3-positions of the glucose unit was isolated by centrifugation. The obtained derivative was reacted with 2-bromobenzoyl chloride (0.68 g, 3.09 mmol) in pyridine (7.5 mL) at 80 °C. After 24 h, the target cellulose derivative Ce-**1a** (R^1/R^{Br} = 62/38) was isolated as the methanol-insoluble fraction (0.91 g, 75%), in which a small amount of R^{Br} group appeared to be reluctantly introduced at the 2,3-positions of the glucose unit. ^{1}H NMR (500 MHz, $CDCl_3$, 55 °C): δ 1.8–2.4 (br, 11.22H, Ph—CH_3), 3.0–5.4 (br, 7H, glucose protons), 6.4–7.9 (br, 12H, aromatic and —NH). IR (KBr): 3358 cm^{-1} (ν_{NH}), 1743 cm^{-1} ($\nu_{C=O}$). Elemental analysis calcd. (%) for $C_{30.74}H_{30.22}Br_{1.13}N_{1.87}O_8$: C, 57.32; H, 4.73; N, 4.07. Found: C, 57.34; H, 4.60; N, 4.24.

*Synthesis of Ce-**1b**:* The title compound was prepared from Ce—Tr in the same way as Ce-**1a** and obtained in 77% yield. R^1/R^{Br}: 65/35. ^{1}H NMR (500 MHz, $CDCl_3$, 55 °C): δ 1.9–2.5 (br, 14.85H, Ph—CH_3), 3.3–5.4 (br, 7H, glucose protons), 6.4–7.6 (br, 10.95H, aromatic and —NH). IR (KBr): 3365 cm^{-1} (ν_{NH}), 1743 cm^{-1} ($\nu_{C=O}$). Elemental analysis calcd. (%) for $C_{31.95}H_{32.80}Br_{1.05}N_{1.95}O_8$: C: 58.50; H: 5.04; N: 4.16. Found: C, 58.48; H, 5.14; N, 4.31.

*Synthesis of Ce-**1c**:* The title compound was prepared from Ce—Tr in the same way as Ce-**1a** and obtained in 76% yield. R^1/R^{Br}: 65/35. ^{1}H NMR (500 MHz, $CDCl_3$, 55 °C): δ 1.9–2.5 (br, 14.88H, Ph—CH_3), 3.2–5.3 (br, 7H, glucose protons), 6.3–7.8 (br, 10.96H, aromatic and —NH). IR (KBr): 3347 cm^{-1} (ν_{NH}), 1742 cm^{-1} ($\nu_{C=O}$). Elemental analysis calcd. (%) for $C_{31.96}H_{32.84}Br_{1.04}N_{1.96}O_8$: C: 58.56; H, 5.05; N, 4.19. Found: C, 58.52; H, 5.06; N, 4.42.

*Synthesis of Ce-**2a**:* The title compound was prepared from Ce—Tr in the same way as Ce-**1a** and obtained in 93% yield. R^2/R^{Br}: 62/38. ^{1}H NMR (500 MHz, $CDCl_3$, 55 °C): δ 2.0–2.4 (br, 5.61H, Ph—CH_3), 3.0–5.4 (br, 7H, glucose protons), 6.6–7.9 (br, 13.87H, aromatic and —NH). IR (KBr): 3365 cm^{-1} (ν_{NH}), 1743 cm^{-1} ($\nu_{C=O}$). Elemental analysis calcd. (%) for $C_{28.87}H_{26.48}Br_{1.13}N_{1.87}O_8$: C: 56.12; H, 4.32; N, 4.24. Found: C, 56.11; H, 4.28; N, 4.52.

*Synthesis of Ce-**3a**:* The title compound was prepared from Ce—Tr in the same way as Ce-**1a** and obtained in 85% yield. R^3/R^{Br}: 66/34. ^{1}H NMR (500 MHz, $CDCl_3$, 55 °C): δ 1.9–2.4 (br, 5.94H, Ph—CH_3), 3.0–5.4 (br, 7H, glucose protons), 6.3–8.0 (br, 13.98H, aromatic and —NH). IR (KBr): 3347 cm^{-1} (ν_{NH}), 1735 cm^{-1} ($\nu_{C=O}$). Elemental analysis calcd. (%) for $C_{28.98}H_{26.92}Br_{1.02}N_{1.98}O_8$: C: 56.83; H, 4.43; N, 4.53. Found: C, 56.82; H, 4.50; N, 4.78.

*Synthesis of Ce-**4a**:* The title compound was prepared from Ce—Tr in the same way as Ce-**1a** and obtained in 84% yield. R^4/R^{Br}: 64/36. ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C): δ 3.4–5.4 (br, 12.79H, glucose protons and —OCH_3), 6.3–7.7 (br, 12H, aromatic), 8.3–9.2 (br, 1.93H, —NH). IR (KBr): 3366 cm^{-1} (ν_{NH}), 1735 cm^{-1} ($\nu_{C=O}$). Elemental analysis calcd. (%) for $C_{28.93}H_{26.72}Br_{1.07}N_{1.93}O_{9.93}$: C: 53.80; H, 4.17; N, 4.19. Found: C, 53.78; H, 4.14; N, 4.24.

*Synthesis of Ce-**5a**:* The title compound was prepared from Ce—Tr in the same way as Ce-**1a** and obtained in 91% yield. R^5/R^{Br}: 65/35. ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C): δ 3.4–5.3 (br, 7H, glucose protons), 6.7–7.7 (br, 13.94H, aromatic), 8.4–9.5 (br, 1.94H, —NH). IR (KBr): 3347 cm^{-1} (ν_{NH}), 1747 cm^{-1} ($\nu_{C=O}$). Elemental analysis calcd. (%) for $C_{27}H_{22.88}Br_{1.06}N_{1.94}O_8$: C: 55.23; H, 3.93; N, 4.63. Found: C, 55.23; H, 3.91; N, 4.49.

*Synthesis of Ce-**6a**:* The title compound was prepared from Ce—Tr in the same way as Ce-**1a** and obtained in 90% yield. R^6/R^{Br}: 60/40. ^{1}H NMR (500 MHz, pyridine-d_5, 80 °C): δ 1.0–1.4 (br, 16.20H, —$C(CH)_3$), 3.3–5.9 (br, 7H, glucose protons), 6.8–8.1 (br, 12H, aromatic), 8.8–10.4 (1.80H, —NH). IR (KBr): 3365 cm^{-1} (ν_{NH}), 1750 cm^{-1} ($\nu_{C=O}$). Elemental analysis calcd. (%) for $C_{34.20}H_{37.00}Br_{1.20}N_{1.80}O_8$: C: 58.92; H, 5.35; N, 3.62. Found: C, 58.88; H, 5.27; N, 3.60.

*Synthesis of Ce-**7a**:* The title compound was prepared from Ce—Tr in the same way as Ce-**1a** and obtained in 89% yield. R^7/R^{Br}: 63/37. ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C): δ 3.3–5.4 (br, 7H, glucose protons), 6.4–7.8 (br, 21.40H, aromatic), 8.6–9.8 (br, 1.88H, —NH). IR (KBr): 3391 cm^{-1} (ν_{NH}), 1748 cm^{-1} ($\nu_{C=O}$). Elemental analysis calcd. (%) for $C_{38.28}H_{30.28}Br_{1.12}N_{1.88}O_{9.88}$: C: 60.17; H, 3.99; N, 3.45. Found: C, 60.17; H, 4.00; N, 3.55.

*Synthesis of Am-**1a**:* The title compound was synthesized by a similar procedure to that used for Ce-**1a**. R^1/R^{Br}: 58/42. ^{1}H NMR (500 MHz, $CDCl_3$, 55 °C): δ 1.6–2.4 (br, 10.38H, Ph-CH_3), 3.7–5.8