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Finely selective protections and deprotections of multifunctional chitin and chitosan to synthesize key intermediates for regioselective chemical modifications

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ABSTRACT

Site-selective protection of chitin and chitosan has been studied in detail in order to distinguish the three kinds of functional groups, which would make possible finely controlled regiospecific structural modifications. To allow reliable chemical manipulations and to establish stable protection and facile deprotection at high selectivity, benzyl was evaluated for the C-3 protection in combination with other protective groups including triphenylmethyl (trityl) for C-6 and acetyl or phthaloyl for C-2. Chitin was first tritylated and then benzylated to give 3-*O*-benzyl-6-*O*-trityl-chitin, of which each of the trityl, benzyl, and acetyl groups could be removed selectively with dichloroacetic acid, hydrogen-Pd/C, and aqueous sodium hydroxide, respectively, affording three kinds of derivatives having a reactive group at C-6, C-3, or C-2. 2-*N*-Phthaloyl-chitosan was also tritylated at C-6 and benzylated at C-3; the resulting fully protected product was detritylated, debenzylated, or dephthaloylated, similarly giving rise to three kinds of precursors having a reactive group only at one position. The extents of all the substitution and removal reactions proved quantitative under appropriate conditions to give structurally well-defined derivatives. They exhibited improved solubility in organic solvents, indicating high potential of these derivatives as novel convenient intermediates for designing diversified molecular architectures through regiospecific chemical modifications.

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1. Introduction

Because of the presence of amino groups, polysaccharides chitin and chitosan are expected to be particularly useful biopolymers in various fields (Domard, Guibal, & Vårum, 2007; Uragami, Kurita, & Fukamizo, 2001; Uragami & Tokura, 2006). Although they are abundant and easily accessible, and therefore attracting much attention, their utilization has been quite limited. This is primarily due to the difficulty in fabrication and structural transformation, which is ascribed to the lack of solubility in suitable solvents. The various distinctive biological and physicochemical functions of chitin and chitosan suggest the prospect of synthesizing intelligent polymeric materials having medicinal and pharmaceutical activities by appropriate chemical modifications (Kurita, 1997, 2001, 2006a, 2006b; Nishimura, Kohgo, Kurita, & Kuzuhara, 1991; Roberts, 1992).

For precise and well-controlled structural modifications of these polysaccharides to develop advanced materials with desirable bioactivities, it is necessary to clearly distinguish the three kinds of functional groups in their repeating units. In this respect, 2-*N*-phthaloyl-chitosan is the practical derivative currently used, since it is organosoluble and useful for the regioselective chemical modifications (Nishimura et al., 1991). Several kinds of sugar branches can be incorporated at the C-6 position to synthesize non-natural branched chitins and chitosans (Kurita, Akao, Kobayashi, Mori, & Nishiyama, 1997; Kurita, Shimada, Nishiyama, Shimojoh, & Nishimura, 1998; Kurita, Kojima, Nishiyama, & Shimojoh, 2000; Kurita, Akao, Yang, & Shimojoh, 2003). Many other substituents have also been introduced for various purposes using 2-*N*-phthaloyl-chitosan (Holappa et al., 2004, 2005; Kurita, Hayakawa, Nishiyama, & Harata, 2002; Nishimura et al., 1993, 1998; Nishiyama et al., 2000; Ouchi, Nishizawa, & Ohya, 1998; Yoksan, Akashi, Hiwatari, & Chirachanchai, 2003; Yoksan, Matsusaki, Akashi, & Chirachanchai, 2004).

In the above procedures, the C-3 hydroxy was protected by acetylation, but the resulting ester linkage is somewhat vulnerable and may undergo hydrolysis and/or acetyl migration under certain reaction conditions, which limits its utility as a precursor. To further expand the scope of structural modifications of chitin and chitosan, stable protection and facile deprotection of the C-3 hydroxy group are undoubtedly key issues. In view of the reliability for *O*-protection in chemical manipulations, benzyl would be a promising candidate. It has, however, not been used for chitin and

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Table 1
Benzylation of 6-*O*-trityl-chitin (**1**)[a].

Base	Base/pyranose[b]	BnCl/pyranose[b]	Repetition of reaction[c]	ds for Bn[d]	Yield (%)
NaOH	2	6	2	0.85	65
NaOH	6	12	2	0.80	72
NaH	2	6	1	1.00	75

[a] **1**, 0.30 g; DMSO, 4.5 mL; temp, rt; time, 24 h.
[b] Mole ratio.
[c] Number of repetition under the same reaction conditions.
[d] Degree of substitution calculated from the C/N of elemental analysis.

chitosan, and we have thus examined the possibility of benzyl as a protecting group for C-3 in terms of both protection and deprotection in the presence of other protective groups to synthesize versatile intermediates for site-selective chemical modifications at the three different fictional groups.

2. Experimental

2.1. General procedures

IR spectra were taken on a Shimadzu FTIR-8900 spectrometer. ^{1}H NMR spectra were recorded with a JEOL JNM-LA400D FT-NMR in deuterated dimethyl sulfoxide (DMSO-d_6) at 90 °C. Elemental analysis was conducted with a Perkin-Elmer 2400 II instrument. Conductometric titration was carried out with a DKK·TOA CM-20J. HPLC was performed with a Waters 486 equipped with a Waters Controller 800, SIM Chromatocorder 21, and a Bondasphere column (5 μm, C18, 100A) with a mobile phase of acetonitrile/water (4/1). Chemicals were of reagent grade and used after drying. Dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF) were dried with calcium hydride and molecular sieves, respectively, and distilled. Pyridine was refluxed with potassium hydroxide and distilled. All the solvents were stored over molecular sieves.

2.2. Structurally uniform chitin and chitosan

Squid chitin with a degree of acetylation of 0.8–0.9 was *N*-acetylated with acetic anhydride in methanol, and a small amount of *O*-acetyl groups were selectively removed by treating with potassium hydroxide/methanol to give white powdery chitin with a degree of *N*-acetylation of 1.00 as determined by conductometric titration (Kurita, Ishii, Tomita, Nishimura, & Shimoda, 1994).

Pulverized shrimp chitin was deacetylated repeatedly with 40% aqueous sodium hydroxide to give fully deacetylated chitosan as a white powder. Conductometric titration indicated the degree of deacetylation to be 1.00 (Nishimura, Matsuoka, & Kurita, 1990).

2.3. 6-*O*-Trityl-chitin

Trimethylsilylated chitin with a degree of substitution (ds) 2.00 was treated with chlorotriphenylmethane to introduce triphenylmethyl (trityl) group at C-6 according to the method reported previously (Kurita, Sugita, Kodaira, Hirakawa, & Yang, 2005). The ds was 1.00 for the trityl as confirmed by spectroscopy and elemental analysis. IR (KBr): ν 3408 (OH and NH), 3057 (arom), 1670 (amide I), 1522 (amide II), 1150–1000 (pyranose), and 748 and 706 cm^{-1} (arom).

Anal. Calcd for $C_{27}H_{27}NO_5 \cdot 1.4H_2O$: C, 68.89; H, 6.38; N, 2.98. Found: C, 68.72; H, 6.31; N, 2.92

2.3.1. Benzylation of 6-*O*-trityl-chitin

6-*O*-Trityl-chitin (0.30 g, 0.67 mmol) obtained above was dissolved in 4.5 mL of DMSO, and 0.03 g (1.34 mmol) of sodium hydride was added. After stirring the mixture in nitrogen at room temperature for 2 h, 0.51 g (4.04 mmol) of benzyl chloride (BnCl) was added dropwise. The mixture was stirred at room temperature for 24 h, and the resulting solution was poured into 30 mL of methanol to precipitate the product. It was washed with water and methanol and dried to give 0.27 g (75%) of 3-*O*-benzyl-6-*O*-trityl-chitin as a pale tan powdery material. IR (KBr): ν 3420 (NH), 3058 (arom), 1682 (amide I), 1150–1000 (pyranose), and 746 and 706 cm^{-1} (arom).

Anal. Calcd for $C_{34}H_{33}NO_5 \cdot 0.5H_2O$: C, 74.98; H, 6.29; N, 2.57. Found: C, 75.04; H, 6.39; N, 2.53.

2.3.2. Detritylation of 3-*O*-benzyl-6-*O*-trityl-chitin

To 3 mL of a dichloroacetic acid/DMSO (1/1) mixed solvent was added 30 mg (0.056 mmol) of 3-*O*-benzyl-6-*O*-trityl-chitin, and the mixture was stirred at room temperature for 1 h. It was poured into 10 mL of acetonitrile/water (4/1), and the precipitate was washed with water and methanol. After drying, 13 mg (79%) of 3-*O*-benzyl-chitin was obtained as a pale tan powdery material. IR (KBr): ν 3406 (OH and NH), 3059 (arom), 1653 (amide I), 1523 (amide II), 1150–1000 (pyranose), and 768, 748, and 702 cm^{-1} (arom).

Anal. Calcd for $C_{15}H_{19}NO_5 \cdot 0.4H_2O$: C, 59.95; H, 6.64; N, 4.66. Found: C, 59.94; H, 6.47; N, 4.60.

2.3.3. Deacetylation of 3-*O*-benzyl-6-*O*-trityl-chitin

A mixture of 20 mg (0.037 mmol) of 3-*O*-benzyl-6-*O*-trityl-chitin in 10 mL of 12 mol/L sodium hydroxide was stirred at 80 °C for 8 h. After cooling to room temperature, the precipitate was washed by repeated decantations with water until neutral, filtered, and dried to give 15 mg (81%) of 3-*O*-benzyl-6-*O*-trityl-chitosan. IR (KBr): ν 3411 (NH_2), 3059 (arom), 1599 (NH_2), 1150–1000 (pyranose), and 746 and 700 cm^{-1} (arom).

Anal. Calcd for $C_{32}H_{31}NO_4 \cdot 0.5H_2O$: C, 76.47; H, 6.42; N, 2.79. Found: C, 76.35; H, 6.41; N, 2.78.

2.3.4. Debenzylation of 3-*O*-benzyl-6-*O*-trityl-chitin

To a solution of 3-*O*-benzyl-6-*O*-trityl-chitin (30 mg, 0.056 mmol) in 6 mL of DMSO/acetic acid (10:1) was added 30 mg of 5% Pd/C. The mixture was stirred under an atmosphere of hydrogen at 70 °C for 24 h and filtered with Celite 545. The filtrate was concentrated under reduced pressure. The product was precipitated in water, washed with water and methanol, and dried to give 20 mg (80%) of 6-*O*-trityl-chitin. The spectral data were identical with those of the authentic sample.

Anal. Calcd for $C_{27}H_{27}NO_5 \cdot 0.4H_2O$: C, 71.63; H, 6.19; N, 3.09. Found: C, 71.70; H, 6.05; N, 3.08.

2.4. 2-*N*-Phthaloyl-6-*O*-trityl-chitosan

Chitosan was subjected to *N*-phthaloylation with phthalic anhydride in DMF/water (Kurita, Ikeda, Yoshida, Shimojoh, & Harata, 2002) followed by tritylation with chlorotriphenylmethane in pyridine as reported (Nishimura et al., 1991). IR (KBr): ν 3472 (OH), 3058 (arom), 1775 and 1716 (imide C=O), 1150–1000 (pyranose), and 743 and 700 cm^{-1} (arom).

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