Carbohydrate Chemistry | Proven Synthetic Methods Series

Carbohydrate Chemistry

Proven Synthetic Methods

Volume 1

Edited by
Pavol Kováč

CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an Imprint of the
Taylor & Francis Group, an **Informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number: 978-1-4398-6689-4 (Hardback)

Library of Congress Cataloging-in-Publication Data

Carbohydrate chemistry : proven synthetic methods / edited by Pavol Kovac.
p. cm.
ISBN 978-1-4398-6689-4 (hardcover : alk. paper)
1. Carbohydrates--Synthesis. I. Kovác, Pavol, 1938- II. Title.

QD322.S95C37 2011
547'.27--dc22 2011010495

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26 Stereoselective Synthesis of α-*C*-Sialyl Compounds

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INTRODUCTION

Sialic acids (or neuraminic acids) are often found at the outmost ends of the oligosaccharide components of cell-surface glycoproteins and glycolipids. They are involved in a number of important biological events including cell recognition and interaction, neuronal transmission, ion transport, reproduction, differentiation, epitope masking, and protection. They are also involved in pathological processes including infection, inflammation, cancer, neurological, cardiovascular, endocrine, and autoimmune diseases.[1–4] Cell surfaces containing sialic acids interact with receptors, hormones, enzymes, toxins, and viruses and other pathogens that use them to localize on the surface of cells they infect.[5] The linkage of sialic acid to oligosaccharide is among the most labile glycosidic linkages and is cleaved in vitro under mildly acidic conditions.[6] In vivo, sialic acid–containing glycoconjugates are catabolized through the removal of the terminal sialic acid residue by the action of hydrolase-type enzymes called neuraminidases.[7] A nonhydrolyzable glycosidic linkage to sialic acid is an attractive approach to design reagents for glycobiology and immunology. The replacement of the interglycosidic oxygen atom with a hydroxymethylene group using SmI_2 chemistry affords hydrolytically and metabolically inert α-*C*-sialyl analogues of natural glycoconjugates. This stable linkage is being studied to improve our understanding of biological recognition and to enhance or suppress biological events at the molecular level.

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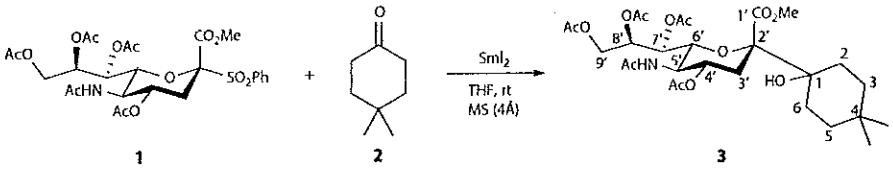


SCHEME 26.1 Stereoselective synthesis of 4,4-dimethyl-1-α-*C*-sialylcyclohexanol.

A method for the stereoselective preparation of α-*C*-sialyl compounds was pioneered in our laboratory.[8a] Since 1997, this method has been applied for the diastereocontrolled synthesis of α-*C*-sialyl compounds, using samarium iodide under Barbier conditions,[8] a method that had been previously used to prepare *C*-glycosyl compounds.[9–11] This approach is tolerant of a wide variety of protecting groups.[8–11] The reducing potential of SmI_2 is exploited through the in situ generation of a neuraminyl samarium (III) species and its coupling to carbonyl compounds. Through a simple, high-yielding reaction, this same chemistry could be used to couple different ketones or aldehydes with peracetylated sialic acid sulfone and form α-*C*-sialyl compounds (Scheme 26.1).

EXPERIMENTAL METHODS

General Methods

All chemicals were purchased from commercial suppliers and used without further purification, unless otherwise noted. Column chromatography was performed on silica gel 60 (EM Science, 70-230 mesh). Reaction was monitored by TLC on Kieselgel $60F_{254}$ (EM Science) and the compounds were detected by UV light and visualized by dipping the plates in a cerium sulfate-ammonium molybdate solution followed by heating. Solutions in organic solvents were concentrated by rotary evaporation below 40°C under reduced pressure. ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker, 600 MHz instrument. When reporting NMR data, nuclei associated with the sugar are denoted with a prime (′). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Data are presented as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = double of doublet, ddd = doublet of doublet of doublet, dt = double of triplet, m = multiplet and/or multiple resonances), integration, and coupling constant in Hertz (Hz). High-resolution mass spectra were run in a JMS SX/SX102A tandem mass spectrometer, equipped with FAB source. The matrix used was DHB and the internal standards ultramark 1621 and PEG. SmI_2 solution was purchased from Aldrich.

SmI_2-Mediated *C*-Sialylation: 4,4-Dimethyl-1-[Methyl (5-Acetamido-4,7,8,9-Tetra-*O*-Acetyl-3,5-Dideoxy-D-*Glycero*-α-D-*Galacto*-Non-2-Ulopyranosyl)onate]cyclohexanol (3)

To a solution of sulfone donor **1**[12] (308 mg, 0.5 mmol) and 4,4-dimethylcyclohexanone **2** (94 mg, 0.75 mmol) in anhydrous THF (7.5 mL) was added molecular sieves (4 Å,

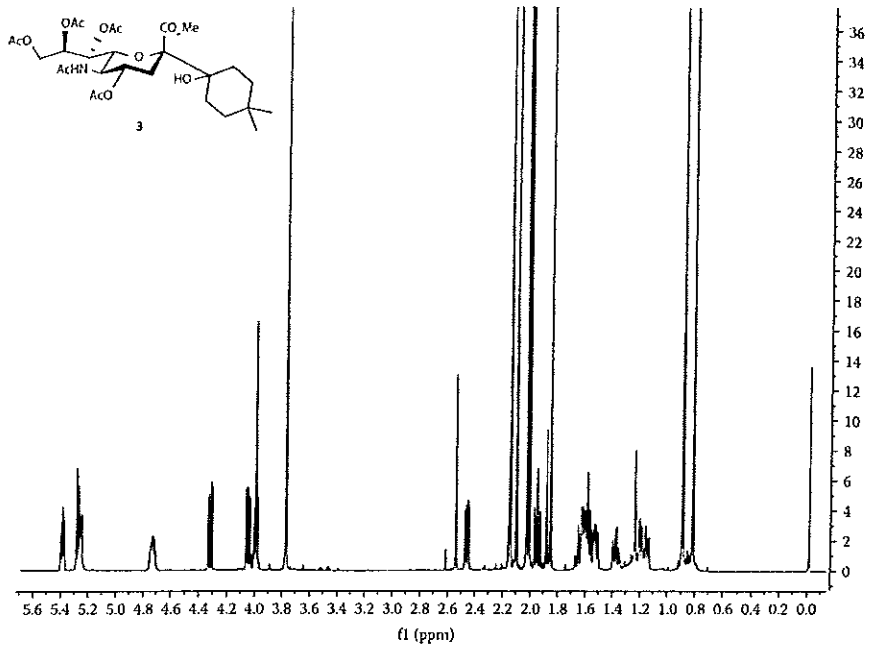
500 mg).* After stirring for 2 h at room temperature under a positive pressure of Argon, SmI_2 solution (30.0 mL, 0.1 M in THF, 3.0 mmol)† was added to the reaction mixture and stirring was continued for 1 h under argon. During initial addition of the SmI_2, the solution decolorized and the mixture turned yellow but when the addition was complete the reaction mixture turned dark green and maintained that color for ~1 h.‡ TLC (3:2 hexane-acetone) then showed reaction to be complete.§ The mixture was diluted with Et_2O (50 mL), and washed successively with aqueous 1 N HCl (50 mL), aqueous 0.1 M $Na_2S_2O_3$ (50 mL), and saturated aqueous $NaHCO_3$ (50 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, the filtrate was concentrated, and chromatography (2:1 hexane–acetone) afforded **3** (219 mg, 73%): R_f=0.4 (3:2 hexane–acetone), c.f. R_f=0.3 for the starting material; $[\alpha]_D$=−19° (c=0.7, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.41 (ddd, 1H, J=8.8, 6.5, 2.7 Hz, H-8′), 5.35–5.24 (m, 2H, H-7′, NH), 4.78–4.73 (m, 1H, H-4′), 4.35 (dd, 1H, H-9′a, J=12.4, 2.7 Hz), 4.07 (dd, 1H, J=12.4, 6.4 Hz, H-9′b), 4.03–3.98 (m, 2H, H-5′, H-6′), 3.79 (s, 3H, CO_2CH_3), 2.56 (s, 1H, OH), 2.48 (dd, 1H, J=12.8, 4.6 Hz, H-3′eq), 2.17 (s, 3H, Ac), 2.12 (s, 3H, Ac), 2.05 (s, 3H, Ac), 2.03 (s, 3H, Ac), 1.97 (t, 1H, J=12.4 Hz, H-3′ax), 1.88 (s, 3H, NAc), 1.68–1.16 (m, 8H, 4×CH_2), 0.92 (s, 3H, CH_3), 0.84 (s, 3H, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.1, 170.70, 170.68, 170.35, 170.18, 170.02, 86.0 (C-2′), 74.9 (C-1), 73.2 (C-6′), 70.4 (C-4′), 68.7 (C-8′), 67.8 (C-7′), 62.6 (C-9′), 52.3 (CO_2CH_3), 49.5 (C-5′), 34.1, 33.9 (C-3, 5), 32.9 (C-3′), 32.5 (CH_3), 29.3 (C-4), 27.6, 27.3 (C-2, 6), 23.2 (CH_3), 23.1 (NAc), 21.2 (Ac), 20.9 (Ac), 20.74 (Ac), 20.72 (Ac); HR MALDI-TOF MS: *m/z*: calcd for $C_{28}H_{43}NNaO_{13}$ $[M + Na]^+$: 624.2627; found: 624.2624. Anal. Calcd for $C_{28}H_{43}NO_{13}$: C, 55.90; H, 7.20; N, 2.33; O, 34.57. Found: C, 56.07; H, 7.23; N, 2.42.

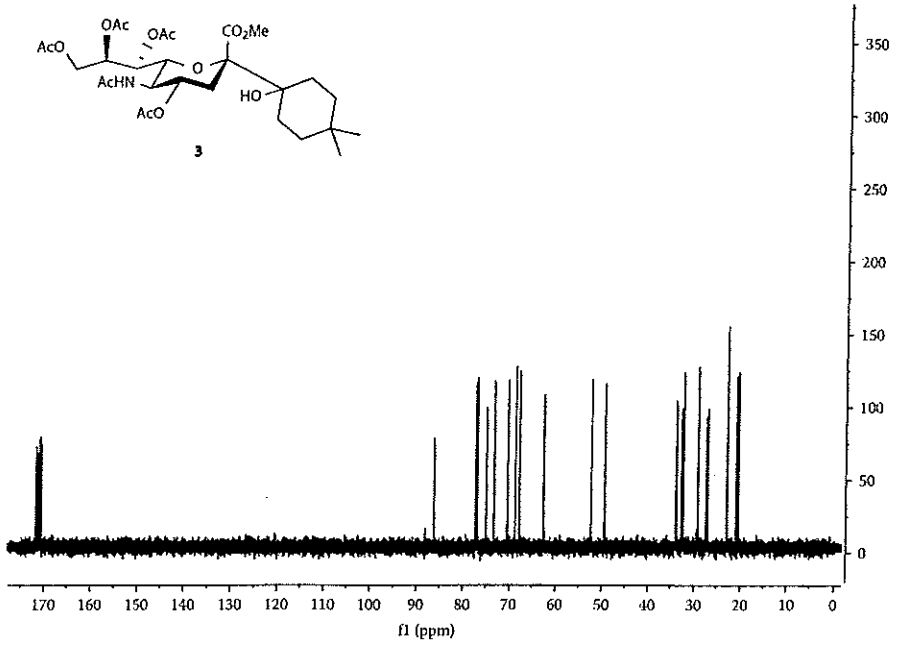
* Molecular sieves (4 Å) were crushed and activated in vacuo >160°C for 5 h before use.

† Commercial 0.1 M samarium iodide solution in THF should be clear blue with only small amount of solid samarium present, which is used as stabilizer.

‡ Blue, instead of green color was observed when the reaction was carried out on much smaller scale.

§ Frequent monitoring of progress of the reaction by TLC is not recommended, to prevent the mixture from exposure to atmospheric air and moisture.





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