Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 17 Sep 2007.

To cite this article: Yulan Wang , Jianmin Mao & Mengshen Cai (1999) Stereoselective Synthesis of a New Kind of Natural Glyco-Cyclophane, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:12, 2093-2097, DOI: 10.1080/00397919908086202

To link to this article: http://dx.doi.org/10.1080/00397919908086202

SYNTHETIC COMMUNICATIONS, 29(12), 2093-2097 (1999)

STEREOSELECTIVE SYNTHESIS OF A NEW KIND OF NATURAL GLYCO-CYCLOPHANE

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ABSTRACT : A new kind of natural glyco-cyclophane, clemochinenoside-A (**1**), has been stereoselectively synthesized from 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose. 4-Dimethylaminopyridine and dicyclohexylcarbodiimide were first used to catalyze the glyco-cycloesterification.

During the last few years, the important biological implication of the attachment of sugar moieties to an aglycon are becoming more and more obvious, creating a growing interest in searching for new biological active glycoside from wild plants. As a result, many new natural glycosides were discovered. The roots of *Clematis chinensis Osbeck* were used for treatment of arthritis, arthralgia, headache and inflammatory disease, respectively, in Chinese medicine[1]. From the roots a new kind of natural glyco-cyclophane, clemochinenoside-A (**1**) was recently found[2].

The structure of the natural compound is attractive and very interesting. In the present work we reported its total stereoselective synthesis.

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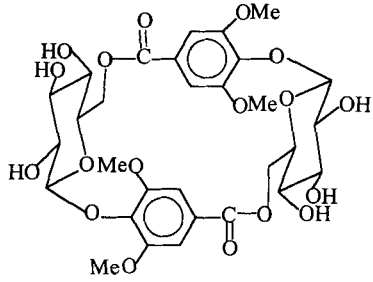
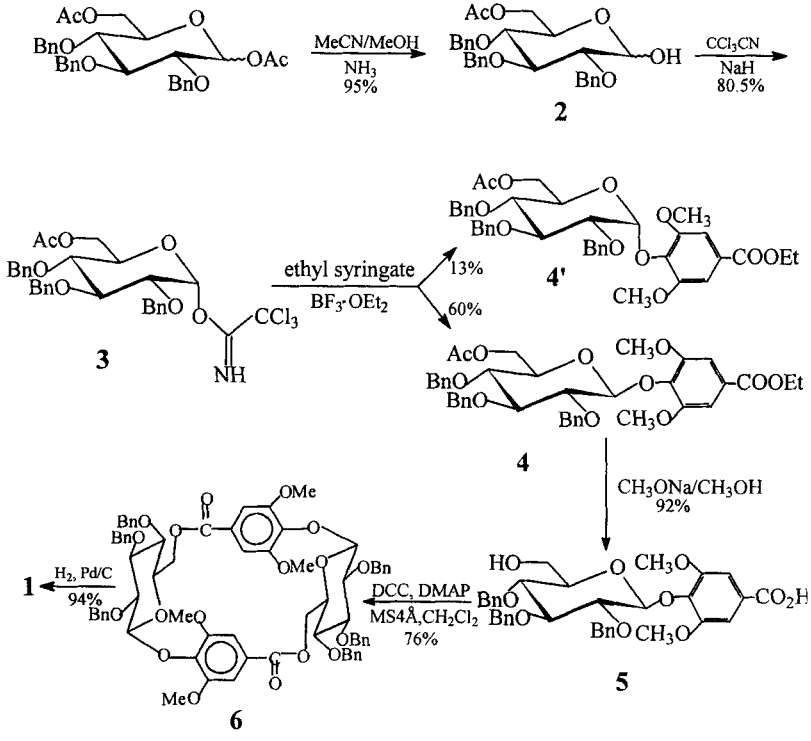


Clemochinenoside-A (1)

RESULTS AND DISCUSSION

The reactions of the synthesis of the new kind of natural glyco-cyclophane (1) can be represented by the following equations:



1,6-Di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose[3] was dissolved in 4:1 (v/v) MeCN/MeOH, NH_3 was introduced and the mixture was stirred at room temperature for 24 hours. Only one new elliptical spot was observed on TLC in the reaction. Purification of the crude product with column chromatography gave compound **2** in very high yield (95%). Compound **3** was easily obtained under the Schmidt conditions.[4] Without further purification, **3** reacted with syringic acid ethyl ester in dichloromethane at -15 ~ -10 °C in the presence of $BF_3{\cdot}OEt_2$, a mixture of **4** and its α-isomer (**4'**) was obtained in the ratio of 4:1. The isomers were separated by fractional crystallization from ethanol, and the β-isomer was obtained in 60% yield, α-isomer was obtained in 13% yield.[5] Compound **4** was treated with CH_3ONa/CH_3OH and then was neutralized to give intermediate **5** in 92% yield. In anhydrous dichloromethane and in the existence of MS 4Å, 4-dimethylaminopyridine (DMAP) and dicyclohexylcarbodiimide (DCC) catalyzed cyclic esterification of intermediate **5** to give the glyco-cyclophane **6**. **6** was hydrogenized to afford the new kind of natural glyco-cyclophane (**1**) in 94% yield.

The key step in the total synthesis of the new kind of natural glyco-cyclophane **1** was the cyclic esterification of intermediate **5**, which was easily polymerized into chain compound, and the cyclic esterification failed in many cases we have tried. 4-Dimethylaminopyridine (DMAP) and dicyclohexyl-carbodiimide (DCC) are often used in synthesis of peptides, in this research work we found that they also can effectively catalyze the glyco-cycloesterification.

EXPERIMENTAL

General methods.— IR spectra were recorded using a Perkin-Elmer 983 infrared spectrophotometer in a KBr pellet. FAB-MS spectrum was recorded on a ZAB-HS mass spectrograph. ^1H NMR spectrum was recorded on an INOVA-500 instrument, Elemental analyses were performed on Perkin-Elmer 240C instrument. Melting points were recorded on a X-4 micro-melting point instrument and the temperature uncorrected. Analytical Thin-Layer Chromatography (TLC) was performed by using 2.5 cm × 10 cm plates coated with a 0.25 mm thickness of silica gel GF 254 (Hai Yang Chemical Factory,

Qingdao, Shandong, P.R. China). Column chromatography was performed on silica gel H (10 ~ 40 mm) (Hai Yang Chemical Factory, Qingdao, Shandong, P.R. China). The solvent systems indicated are volume-volume ratios. Components were detected by means of ultraviolet irradiation and /or by spraying with 20% sulfuric acid in ethanol and heating at 120°C. All chemicals were used directly as obtained commercially and all reactions and manipulations were conducted at room temperature unless otherwise indicated.

(2,6-Dimethoxyl-4-carbonyl)phenyl 2,3,4-O-benzyl-β-D-glucopyranoside (**5**). — 67.5 mg (1.25 mmol) of CH_3ONa was dissolved in 5 ml of CH_3OH, and 0.175g (0.25 mmol) of compound **4** was added. The reaction mixture was stirred for 24 h at room temperature. TLC (eluent: petroleum ether : acetone = 3 : 1) showed that the reaction was complete. The mixture was neutralized and then column chromatography of the crude product gave 0.145 g of **5** (92%), white crystals, mp. 194~195 °C, ^1H NMR (200Mz, $CDCl_3$) δ 7.30~7.37 (m, 17H, ArH), 3.44~5.15 (m, 13H, CHO, CH_2O), 3.85 (S, 6H, OCH_3), 6.10 (br, 2H, OH and COOH) which disappeared when D_2O was added, 5.21 (d, 1H, J=6.4, H-1α, β). Elemental analysis: cal. C: 68.50, H: 6.33. Found. C: 68.75, H: 6.38.

Glyco-cyclophane **6**. — A mixture of 0.126 g (0.2 mmol) of **5**, 15 mg DMAP and 100 mg of MS 4 Å in 10 ml of anhydrous dichloromethane was stirred for 0.5 h at -5 °C and then 152 mg of DCC was added. The reaction mixture was stirred at room temperature until the spot of **5** was disappeared on TLC. The MS 4 Å was filtered off and the filtrate was purified by preparative TLC (eluent: petroleum ether : acetone = 5 : 1) to give 93 mg of **6** (76%), light yellow solid, mp. 206°C. Elemental analysis: calc. C: 68.56, H: 6.07. Found: C: 68.50, H: 6.09. FAB-MS (m/z): 1263 [M+K] calc. for $C_{72}H_{72}O_{18}$ [M+39], 1263; ^1H NMR (500 MHz, CD_3COCD_3) δ 7.21-7.46 (m, 34 H, ArH), 5.3 (d, 2H, J = 8Hz, H-1α, β), 3.04-5.32 (m, 26H, CHO, CH_2O), 3.77 (s, 6H, OCH_3), 3.72 (s, 6H, OCH_3). IR (KBr): 2924 (m), 2846 (m), 1714 (s), 1588 (s), 1529 (m), 1449 (s), 1342 (s), 1215 (s), 1131 (vs), 1074 (vs), 986 (s), 730 (s), 697 (s) cm^{-1}.

Clemochinenoside-A (**1**). —10% Pd/C was added to the solution of 98 mg (0.08 mmol) of **6** in anhydrous dichloromethane. The mixture was stirred under 0.3 MPa of hydrogen pressure at room temperature for 16 h. The catalyst was

removed and the solvent was evaporated. The residue was purified by Column chromatography (eluent: $CHCl_3$: MeOH = 5 : 1) to give 51 mg of **1** (94%), white crystals, mp.276.5 ~ 8 °C (lit.[2] mp.276 ~ 8 °C).

Acknowledgment

This program was financially supported by the starting research fund for the Returned Scholar of the National Educational Committee.

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(Received in Japan 7 September 1998)