

# Articles

## C-Glucuronide from O-Glucuronyl Trichloroacetimidate

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From O-glucuronyl trichloroacetimidate (4) and  $\Delta^6$ -tetrahydrocannabinol (5), the C-glucuronide of  $\Delta^6$ -tetrahydrocannabinol ( $\Delta^6$ -THC) (7) was obtained using mild Lewis acid catalysis. The known method for the synthesis of C-glucuronide from 1-O-protected glucuronide provided low chemical yields. The C-glucuronide of  $\Delta^6$ -THC was obtained through inversion of configuration at the anomeric center in O-glucuronyl trichloroacetimidate (4).

### Introduction

O-Glycosyl trichloroacetimidates were obtained directly in high chemical and stereochemical yield from 1-O-protected carbohydrates and trichloroacetonitrile under base catalysis. Reaction of these activated species with different alcohols in the presence of acid catalyst afforded O-glycosides, di-, tri- and tetrasaccharides mainly by inversion of configuration at the anomeric center<sup>1</sup>.

The existence of C-glycosides in nature has generally been limited to non-mammalian systems although such derivatives are widely distributed in plants and micro organisms. The possibilities of rare C-glucuronide formation in normal mammalian metabolism are based in part on the observation that aromatic C-substitution of phenolic compounds occurs preferentially to aromatic O-substitution in certain activated systems including cannabinoids<sup>3-6</sup>. A number of approaches have led to the synthesis of the C-glucuronide of  $\Delta^6$ -tetrahydrocannabinol ( $\Delta^6$ -THC)<sup>7-9</sup>.

We report now that when  $\text{BF}_3 \cdot \text{OEt}_2$  is used as condensing reagent the reaction of (3) and (4) with (5) on a 0.1 mmole scale, leads to (7) as the major product, in 26% and

44% yields as chromatographically pure crystalline material.

This known product (7) was identified by comparison of its physical data (tlc, ir, ms, nmr) with those published or by direct comparison (Scheme 1).

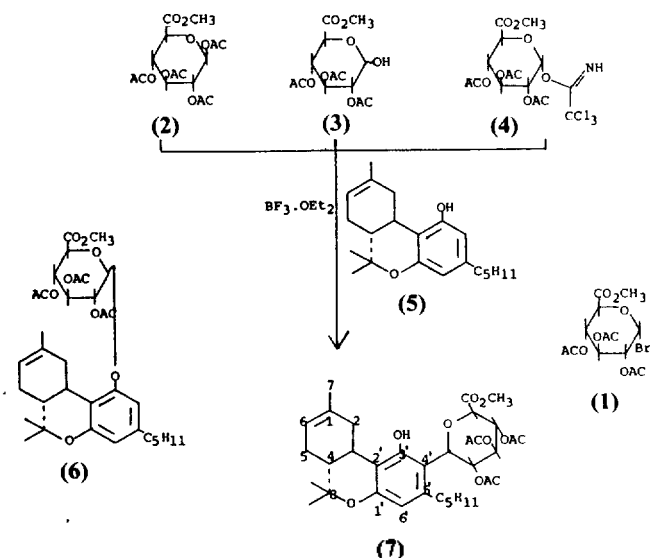
### Experimental

IR spectra were recorded on a Perkin-Elmer 457 Grating Infrared Spectrophotometer. <sup>1</sup>H-NMR spectra were obtained on a Bruker WH-60, and WH-300 pulsed FT spectrometer. Chemical shifts are given in part per million downfield from Me<sub>4</sub>Si internal standard. Mass spectra were recorded on a Varian Mat, CH-5 Mass Spectrometer and LKB 2091-Gas Chromatograph-Mass Spectrometer. Mp. is uncorrected and measured in open capillary in a Thomas Hoover instrument. Chromatograph; Analytical TLC was performed by using commercially available silica plate. Polygram sil N-HR/UV<sub>254</sub> and the plates were visualized with Fast Blue phenol reagent or charring with a solution of MeOH : H<sub>2</sub>SO<sub>4</sub> (1 : 1). Preparative TLC was carried on home-made 20×20 cm<sup>2</sup> glass plates using silica gel 60 PF<sub>254</sub>. Medium pressure liquid chromatography was performed by ALTEX glass column, 1 meter long, internal diameter 9 mm using FMI pump and silica gel 60 (230-400 mesh) purchased from Merck, collective fraction with LKB 2070 or LKB 7000 fraction collectors of 2-10 ml/min.

#### Methyl-2,3,4-tri-O-acetyl-D-glucopyranuronate. (3)<sup>11,12</sup>.

To Methyl-2,3,4-tri-O-acetyl-1-bromo- $\beta$ -D-glucopyranuronate. (1) (4 g, 10.1 mmol) in anhydrous acetone (25 ml), water (0.18 ml) and silver carbonate (3.0 g) were added at room temperature. The mixture was shaken for 12 h, the precipitate was filtered off and washed with warm acetone, and the combined C-Glucuronide from O-Glucuronyl Trichloroacetimidate washings were concentrated to give a syrup which solidified on standing. The process was speeded up by seeding, and gave the ester (3.34 g, 100%), mp. 104-107°;  $[\alpha]_D^{20} +75.4^\circ$  (c 1.1, in H<sub>2</sub>O) +67.4° (c 1.1, CHCl<sub>3</sub>)<sup>14</sup> (lit, mp. 113°);  $[\alpha]_D^{20} +72^\circ$  (c 1.0, in CHCl<sub>3</sub>) +75° (c 1.0, in H<sub>2</sub>O); NMR( $\delta$ ) (CDCl<sub>3</sub>), 2.04(2×3H, s, OCOCH<sub>3</sub>), 2.09(3H, s, OCOCH<sub>3</sub>), 3.76(3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.00-5.61(5×1H, m, C-1, C-2, C-3, C-4, C-5H); IR(KBr), 3475, 2974, 1735, 1440, 1380, cm<sup>-1</sup>; MS(180), m/e 318(M<sup>+</sup>-16, 25), 275(14), 257(16), 245(41), 215(100).

#### Methyl-2,3,4-tri-O-acetyl- $\beta$ -D-glucopyranosyl trichlo-



Scheme 1

**roimidate. (4)**<sup>1,14</sup>. Trichloroacetonitrile (3.3 ml) and sodium hydride (10 mmol) are added to a solution of methyl-2,3,4-tri-O-acetyl-D-glucopyranuronate (3) (3.34 g, 10 mmol) in dichloromethane (50 ml) at room temperature. After stirring for 20 min the reaction mixture was dissolved in 100 ml of ethylacetate and the organic layer was washed with brine. After drying the ethylacetate with anhydrous sodium sulfate the mixture was filtered. Solvent was removed under reduced pressure (water pump, 10-20 mm, bath temp. 60°C). Compound was also purified by medium pressure liquid chromatography (elution with ethylacetate to petroleum ether bp. 60-80°C) to yield the title compound (4) (1.77 g, 37%), mp. 105-108°C; NMR( $\delta$ ) (CDCl<sub>3</sub>), 2.02(3H, s, OCOCH<sub>3</sub>), 2.05(2 × 3H, s, OCOCH<sub>3</sub>), 3.75(3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.47(1H, brd,  $J=8.0$  Hz, C-5H), 5.00-5.74(3 × 1H, m, C-2, C-3, C-4H), 6.60(1H, brd,  $J=4.0$  Hz, C-1H), 8.75(1H, brs, NH); MS(220),  $m/e$  370(M<sup>+</sup>-8, Cl<sup>+</sup>, 29%), 428(10), 417(26), 410(8), 440(9), 375(23), 362(100); IR(KBr), 3300, 1755, 1630, 1230, 833 cm<sup>-1</sup>.

**Procedure A.** To a solution of  $\Delta^6$ -tetrahydrocannabinol (31.4 mg, 0.10 mmol) (5) in dry acetonitrile (10 ml)<sup>17</sup>, methyl-2,3,4-tri-O-acetyl-D-glucopyranuronate (37.6 mg, 0.112 mmol) (3)<sup>1</sup> and BF<sub>3</sub>-etherate (0.35 ml) *via* syringe were added sequentially. The reaction mixture was kept with stirring under a nitrogen atmosphere for overnight at room temperature. Ethylacetate was added to the reaction mixture. Reaction mixture was washed concentrated sodium chloride (50 ml). Aqueous phase was extracted with an additional ethylacetate (50 ml). Combined organic layer was dried over anhydrous sodium sulfate, filtered through a celite filter in the hood, and volatiles were removed under reduced pressure. The product (7) was purified by preparative thin layer chromatography. Compound (7) was found to be identical with authentic sample (16.4 mg, 26%)<sup>7</sup>.

**Procedure B.** To a solution of  $\Delta^6$ -tetrahydrocannabinol (31.4 mg, 0.10 mmol) (5) in dry dichloromethane (10 ml), methyl-2,3,4-tri-O-acetyl- $\beta$ -D-glucopyranosyl trichloroacetimidate (47.8 mg, 0.10 mmol) (4)<sup>18</sup> and BF<sub>3</sub>-etherate (0.35 ml) *via* syringe were added sequentially. The reaction mixture was kept with stirring under a nitrogen atmosphere for overnight at room temperature. Ethylacetate was added to the reaction mixture. Reaction mixture was stirred till the volution of bubbles ceased, separated into the organic layer and extracted from the aqueous layer with an additional ethylacetate (50 ml). Combined organic layer was dried over anhydrous sodium sulfate, and filtered through a celite filter in the hood, and volatiles were removed under reduced pressure. The product (7) was purified by preparative thin layer chromatography. Compound (7) was found to be identical with authentic sample (22.7 mg, 44%)<sup>17</sup>.

## Results and Discussion

In several chemical reactions, including glucosidation, the C-4 aromatic position in some cannabinoids is substituted in preference to the free phenolic group<sup>7</sup>. On this basis we assumed that C-glucuronidation could take place on that carbon atom. Indeed it took place in the reaction of (5) with O-glucuronyl trichloroacetimidate (4) and 1-O-unprotected glucuronide (3).

Richard. R. Schmidt *et al.*<sup>1</sup>, have obtained O-glycosyl tri-

chloroacetimidate directly in high chemical and stereochemical yield from 1-O-unprotected carbohydrate and trichloroacetonitrile under base catalyst. The observed high reactivity of this O- $\alpha$ -D-glucopyranosylimidate should also admit a stereoselective  $\alpha$ -D-glycosides from O-glycosyl trichloroacetimidates by inversion of configuration at the anomeric center.

The synthetic routes available<sup>7,8,10</sup> are not of practical value because they lead to the known compound (7) and (6) in low yields. The best route to C-glucuronide of  $\Delta^6$ -tetrahydrocannabinol ( $\Delta^6$ -THC) described so far is the condensation of methyl (2,3,4-tri-O-acetyl- $\beta$ -glucopyranosyl bromide) uronate (1) or methyl-tetra-O-acetyl- $\beta$ -glucopyranuronate (2) with  $\Delta^6$ -tetrahydrocannabinol in the presence of mercuric cyanide or weak acids<sup>7</sup>.

$\Delta^6$ -THC is expected to react as a nucleophile. O-glucuronyl trichloroacetimidate (4) reacts with  $\Delta^6$ -THC to result in the inversion of configuration at the anomeric center. The glucuronyl transfer to  $\Delta^6$ -THC in a Friedel-Craft type reaction is of interest for the synthesis of C-glucuronide of  $\Delta^6$ -THC (7)<sup>19</sup>. We consider that  $\Delta^6$ -THC attack the oxonium ion generated from methyl-2,3,4-tri-O-acetyl-D-glucopyranuronate (3).

The present synthesis may be of interest, in the cannabinoid field since C-glucuronide formation was shown to be a general metabolic pathway<sup>2,10</sup>, and synthetic method leading to C-glucuronides seems to be further investigated to improve the efficiency.

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## Electronic Structures and Properties of the Charged Model Clusters Relating to High- $T_c$ Superconductor $\text{YBa}_2\text{Cu}_3\text{O}_{7-x}$

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We have carried out an extended Hückel calculation to rationalize the role of  $\text{CuO}_3$  chains and the size effect of the charged model clusters for the following charged model clusters:  $\text{Cu}_6\text{O}_{21}^{28-}$ ,  $\text{Cu}_8\text{O}_{22}^{30-}$ ,  $\text{Cu}_9\text{O}_{30}^{39-}$ ,  $\text{Cu}_6\text{O}_{32}^{43-}$ ,  $\text{Cu}_{12}\text{O}_{38}^{48-}$ ,  $\text{Cu}_{15}\text{O}_{50}^{65-}$ ,  $\text{Cu}_{18}\text{O}_{54}^{66-}$ ,  $\text{Cu}_{18}\text{O}_{55}^{68-}$ ,  $\text{Cu}_{24}\text{O}_{70}^{84-}$ , and  $\text{Cu}_{27}\text{O}_{78}^{83-}$  for high- $T_c$  superconductor  $\text{YBa}_2\text{Cu}_3\text{O}_7$ ;  $\text{Cu}_6\text{O}_{18}^{22-}$ ,  $\text{Cu}_9\text{O}_{26}^{31-}$ ,  $\text{Cu}_{12}\text{O}_{32}^{36-}$ ,  $\text{Cu}_{15}\text{O}_{42}^{49-}$ ,  $\text{Cu}_{18}\text{O}_{46}^{50-}$ ,  $\text{Cu}_{24}\text{O}_{60}^{64-}$ , and  $\text{Cu}_{27}\text{O}_{66}^{69-}$  for insulator  $\text{YBa}_2\text{Cu}_3\text{O}_6$ . The results show that the electronic structures and properties of the charged model clusters relating to high- $T_c$  superconductor are very sensitive to the size change of the clusters with various environmental effects, whereas those of the charged model clusters for insulator  $\text{YBa}_2\text{Cu}_3\text{O}_6$  are monotonous to the size change. The  $\text{CuO}_3$  chains along the  $b$ -direction may yield cooperative electronic coupling with the  $\text{CuO}_2$  layers in determining both conducting and superconducting properties of  $\text{YBa}_2\text{Cu}_3\text{O}_{7-x}$  system.

### Introduction

The recent dramatic increases<sup>1,2</sup> of  $T_c$  have given reason to believe that some totally new mechanism for superconductivity is operating in the high- $T_c$  superconductor,  $\text{YBa}_2\text{Cu}_3\text{O}_{7-x}$ . One significant conclusion about the new oxide superconductors is that there is a short coherence length for the electron pair.<sup>3</sup> Also sleight suggested this pair as existing in real space instead of momentum space.<sup>4</sup> In real space the structure of the high- $T_c$  materials is very important. The structure of high- $T_c$  superconductor,  $\text{YBa}_2\text{Cu}_3\text{O}_{7-x}$ , has been determined and confirmed by many different groups.<sup>4-8</sup> The distinct structural unit in  $\text{YBa}_2\text{Cu}_3\text{O}_{7-x}$  superconducting system in Figure 1 contains 2 copper atoms (called Cu(2)) with a square pyramidal coordination by 5 oxygen atoms and 1 copper atom (called Cu(1)) with a square planar coordination by 4 oxygens. There are O(1)-Cu(1) chains along the  $b$ -direction. These chains and planes form a sub-lattice of repeating  $\text{CuO}_2$ - $\text{CuO}_3$ - $\text{CuO}_2$  units along the  $c$ -direction. Magnetic rare-earth substitution studies<sup>9</sup> and the lack of copper-oxygen chains in the  $(\text{La}_{1-x}\text{M}_x)_2\text{CuO}_{4-x}$  ( $\text{M}=\text{Sr}$  or  $\text{Ba}$ ) superconducting system<sup>10</sup> led some to believe that the  $\text{CuO}_3$  chains were responsible for the much higher transition temperatures in the new Y-Ba-Cu-O system. However, recent Zn and Ga substitution studies,<sup>11</sup> as well as the discovery of the  $(\text{AO})_m\text{-ACa}_{n-1}\text{Cu}_n\text{O}_{2n+2}$  phases<sup>4,12</sup> where A is Bi or Tl, indicate that the  $\text{CuO}_3$  chains are not essential to high-temperature superconductivity. Their role is not yet clear.

One of the problems that make it difficult to study the

**Table 1.** Atomic Parameters Used in the Calculation<sup>16</sup>

	$H_i$ (eV)			Exponents		
	$s$	$p$	$d$	$s$	$p$	$d$
Cu	-11.4	-6.06	-14.0	2.2	2.2	5.9533(0.5933) 2.30(0.5744)
O	-32.3	-14.8		2.275	2.275	

high- $T_c$  superconductor  $\text{YBa}_2\text{Cu}_3\text{O}_{7-x}$  is that the single crystals,<sup>13</sup> which can now be routinely produced, are twinned. The twinned structure precludes the possibility of measurement to distinguish between the  $a$ - and  $b$ -directions that are particularly important in this system because of the on-going discussion as to where the  $\text{CuO}_3$  chains along the  $b$ -direction play an important role in the superconducting process. It has recently become possible to detwin single crystals.<sup>14</sup> Recently a Brillouin scattering study<sup>15</sup> shows the anisotropy of the surface wave velocity in the  $a$ - $b$  plane of an untwinned crystal but the isotropy of that in the  $a$ - $b$  plane of twinned crystal. Band structure and cluster calculations of varying degrees of sophistication have been reviewed on the high-temperature oxide superconductors.<sup>12b</sup> In order to better understand the high- $T_c$  superconductor  $\text{YBa}_2\text{Cu}_3\text{O}_{7-x}$ , it is important to correlate the structure with the physical properties of both superconducting  $\text{YBa}_2\text{Cu}_3\text{O}_7$  and nonsuperconducting  $\text{YBa}_2\text{Cu}_3\text{O}_6$ . The purpose of this work is to understand whether the  $\text{CuO}_3$  chains play any role in determining superconductivity, and to study the size effect of the model clusters along the  $a$ -,  $b$ -direction, and both the  $a$ - and  $b$ -directions. We have carried out extended Hückel cluster calcula-

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