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Facile Acyl Migration in 6-*O*-Acylcastanospermine

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Abstract: *6-O-Acylcastanospermine derivatives undergo ready acyl migration under physiological temperature and pH leading to the formation of a mixture of 6-, 7- and 8-O-acylcastanospermines*

Castanospermine **1** (1*S*,6*S*,7*R*,8*R*,8a*R*)-1,6,7,8-tetrahydroxyindolizidine, has been shown to act as an inhibitor of glycosylation[1] and HIV replication.[2] The clinical utility of **1** is limited by its low potency *in vitro* and *in vivo*.[3] However, this can be partially circumvented by increasing the lipophilicity of the compound; 6-*O*-butanoylcastanospermine has been reported[4] to be almost 20 times more potent than castanospermine. Since the first report on the increased potency of esters of castanospermine, mono derivatives of castanospermine, in particular esters are gaining more synthetic importance.[5]

A recent disclosure from our laboratories reported application of tin mediated regioselective acylations, leading to the synthesis of a number of 6-*O*-acylcastanospermine derivatives.[6] We undertook a systematic hydrolysis of these esters to correlate the observed biological activity to their chemical reactivity. In a typical experiment, 5 mg of 6-*O*-(2'-methoxybenzoyl)castanospermine **2a** was dissolved in methanol (1mL) and diluted with 4mL of 0.2M phosphate buffer of pH 7.4 and maintained at 37 °C for 15 h. Analysis of the reaction sample by HPLC[7] revealed the formation of two compounds in addition to the starting 6-benzoate (Scheme 1). The formation of corresponding benzoic acid was not detected and negligible amount of methylbenzoate was present in the mixture. This led us to examine the possibility of acyl migration in this polyhydroxy indolizidine derivative. Inspection of the ^{1}H NMR spectrum of the reaction mixture (reaction performed in D_2O as the solvent) revealed the presence of 7-benzoate **3a**, 8-benzoate **4a**, and the starting 6-benzoate **2a** as indicated by the marked downfield shift for the corresponding H-7'and H-8'. This was further confirmed by comparing the retention time of authentic isomeric esters by HPLC. A change of the buffer to an organic amine-trishydroxyethylaminomethane (pH: 7.4) or a change of pH did not affect the rate of acyl migration significantly.

Scheme 1

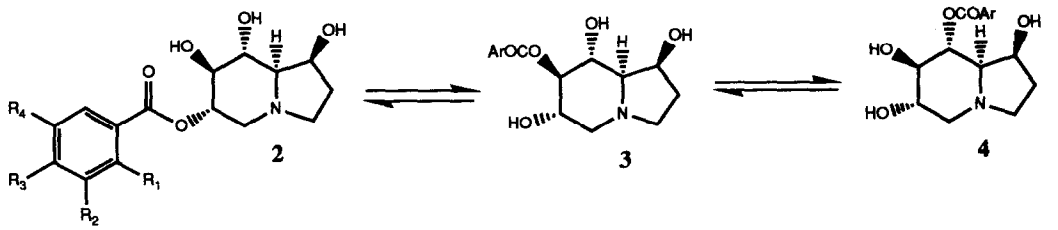

Table 1. Acyl Migration in 6-*O*-Acylcastanospermines

Entry	R_1	R_2	R_3	R_4	Ratio of **6**:**7**:**8**
a	OCH_3	H	H	H	2.6:1.8:1.0
b	H	OCH_3	H	H	2.0:1.6:1.0
c	H	H	OCH_3	H	2.5:2.1:1.0
d	H	H	OCH_3	OCH_3	2.0:2.0:1.0
e	H	OCH_3	H	OCH_3	2.4:2.3:1.0
f	H	H	CH_3	H	2.5:1.9:1.0
g	H	H	H	H	3.9:2.3:1.0
h	H	H	NO_2	H	1.8:2.3:1.0
i	H	H	CN	H	1.0:2.1:1.0
j	H	H	Cl	H	2.0:2.2:1.0
k	H	H	CF_3	H	***

*** insoluble in the solvents employed

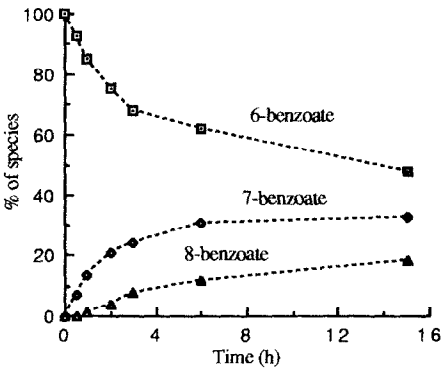

Fig.1

Species concentrations versus time profile for 6-*O*-(2'-methoxybenzoyl)castanospermine **2a** are shown in the Fig. 1. It is clear from the data that the 6-benzoyl derivative **2a** is not completely converted to the 7- or 8-derivative (**3a** or **4a**) and they exist in equilibrium. This was confirmed by subjecting the 7-benzoate (**3g**) to the identical reaction conditions, wherein both 6- and 8-benzoates (**2g** and **4g**) were formed. Elevated temperature or longer reaction time did not bring about complete conversion to any one of the isomers. As seen from the Table 1, it was found to be a general trend irrespective of the nature of the substituents present on the benzoyl moiety, although the rate of migration was slightly faster for the electron withdrawing substituents (**2h**-**2j**) compared to the electron releasing groups (**2a**-**2f**). The reaction was found to be facile even in the case of aliphatic esters like 6-*O*-acetyl and 6-*O*-butanoylcastanospermines.[8] Although acyl migration has been demonstrated in some prodrugs,[9] the rigid bicyclic system combined with the *trans* disposition of the hydroxyl groups in the case of castanospermine facilitates this process.

This observation highlights the possibility of 7- or the 8- isomer being the active form of the parent compound, although the 6-esters are gaining attention in the biological evaluation as α-glucosidase inhibitors.

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7. Reverse Phase, C-18 BondaPak; Mobile phase: 70% Water, 25% Methanol and 5% Acetonitrile; Flow-1.8mL/min; UV- 254nm.
8. The reaction was monitored by ^{1}H NMR in the case of aliphatic esters.
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