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Substrate-dependent fluorinations of highly functionalized cycloalkanes

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ABSTRACT

Substrate-dependent fluorinations of several highly functionalized cycloalkanes with multiple stereocentres were investigated. The synthetic transformations were based on selective functionalization of the ring C=C bonds of the readily available bicyclic β-lactams by epoxidation and regioselective nucleophilic oxirane opening with azide or cyanide, followed by hydroxy–fluorine exchange with Deoxofluor. Depending on the substituents and their relative steric arrangement, the attempted fluorinations produced different types of substituted cycloalkanes. These selective, substrate-directed synthetic procedures and their presumed pathways towards interesting highly functionalized fluorinated cycloalkane scaffolds were investigated.

1. Introduction

Great interest has been expressed in highly functionalized alicyclic amino acid derivatives in the fields of synthetic and medicinal chemistry during the past decade. The six-membered oseltamivir (tamiflu),[1–7] and the five-membered peramivir,[8–10] for instance, are two illustrative examples of densely functionalized antiviral cycloalkanes. As a consequence of the significance of these bioactive products, a number of Tamiflu,[11–20] or peramivir[21–25] analogues have been synthesized and investigated in the past fifteen years (Fig. 1).

As a result of the considerable importance of fluorinated organic products in medicinal chemistry and drug design (25% of pharmaceuticals contain at least one fluorine atom), the synthesis of fluorine-containing organic molecules has become of great interest to synthetic and medicinal chemists, and as a consequence the number of fluorinated substances has recently been increasing continuously.[26–36]

Although less abundant than the α- or γ-analogues, cycloalkane β-amino acids (cispentacin, icofungipen, oryzoxymycin, etc.; Fig. 1), are biologically relevant molecules in medicinal chemistry and peptide research.[37–47]

The present work is intended to offer an insight into the preparation by fluorination of various densely functionalized

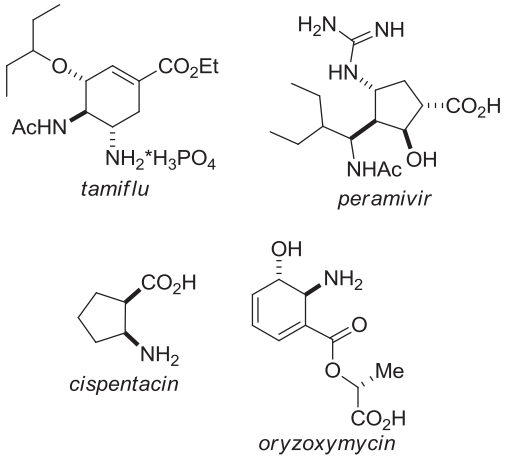

Fig. 1. Structures of some highly substituted bioactive cycloalkanes.

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cycloalkanes with multiple stereocentres. We set out to accomplish synthetic transformations by the fluorination of a number of multisubstituted six- or five-membered representatives of this class of valuable biomolecules. Relatively few methods are currently available for access to fluorine-containing five- or six-membered cyclic β-amino acid derivatives.[48–57]

2. Results and discussion

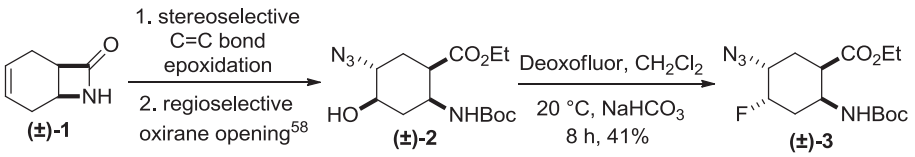
For the synthesis of fluorine-containing polyfunctionalized cycloalkanes, we first selected several six-membered HO-containing cyclic β-amino acids derivatives as starting molecules. The synthetic pathway was based on the transformation of the ring C=C bond of the corresponding bicyclic β-lactams. Accordingly, highly functionalized hydroxylated amino ester (±)**-2**, obtained from lactam (±)**-1** by ring C=C bond functionalization,[58] was subjected to fluorination with Deoxofluor; through inversion, this gave the expected fluorinated product (±)**-3** in 22% yield, whose stereochemistry was assigned on the basis of 2D NMR data. (For similar hydroxy–fluorine exchanges with inversion on a cycloalkane ring, see Refs. 48–50 and 57) It was found that the presence of $NaHCO_3$ had a beneficial effect on this fluorination, increasing the yield to 41% (Scheme 1).

The steps in the unexpected transformation of (±)**-6** are depicted in Scheme 3. Intermediates **T1** and **T2** underwent E2 elimination to give **T3**. Subsequent deprotonation through the active hydrogen at C-1, followed by double bond reorganization, led through **T4** to the conjugated cyclic diene **9** (Scheme 3).

The fluorination of hydroxylated nitrile (±)**-7** (derived from lactam (±)**-4**) with Deoxofluor was next attempted. The presence of the nitrile group in (±)**-7**, however, determined the formation of the unsaturated conjugated product (±)**-10** in 53% isolated yield. The formation of (±)**-10** might be a result of the deprotonation of intermediate **T5** through the acidic hydrogen on C-4, followed by stabilization of the anion **T6** through olefin bond formation by elimination (Scheme 4).

We next investigated the action of Deoxofluor on multisubstituted cyclopentanes. Analogous to the six-membered derivatives, the HO-containing cyclopentane azido ester (±)**-13**[59] (prepared from unsaturated bicyclic lactam (±)**-11** through (±)**-12** by stereoselective epoxidation and regioselective oxirane opening) underwent inversion to afford the fluorinated multisubstituted cyclopentane (±)**-15** in 45% yield (Scheme 5).

Treatment of cyclopentane nitrile (±)**-14** (Fig. 2; from (±)**-11** via (±)**-12** in the reaction with Et_2AlCN, according to the earlier described literature procedure for the six-membered derivatives[58])



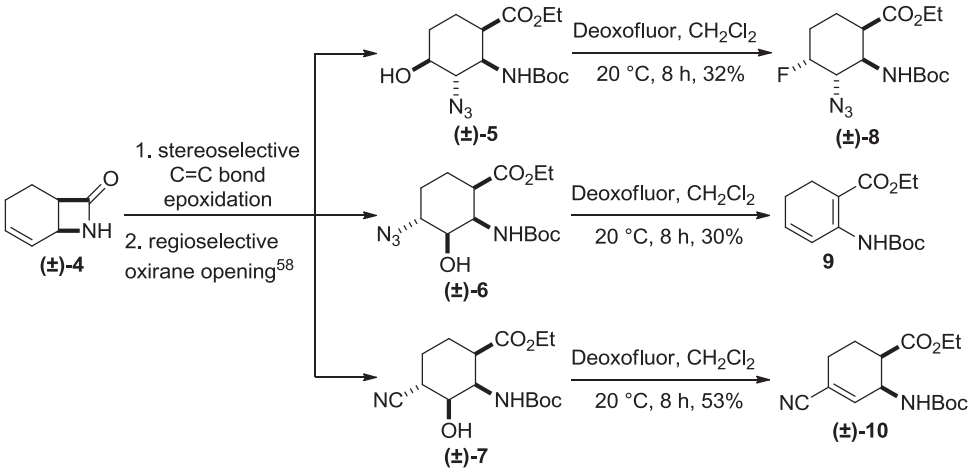
Scheme 1. Fluorination of amino ester (±)**-2**.

With the aim to access to novel isomers of (±)**-3**, cyclohexane hydroxylated azido esters (±)**-5**,[58] and (±)**-7**,[58] (derived from bicyclic lactam (±)**-4**, a regioisomer of (±)**-1**, by ring olefin bond functionalization through stereoselective epoxidation and regioselective oxirane opening), were subjected to fluorination conditions. Interestingly, while (±)**-5** reacted with Deoxofluor to furnish the expected multifunctionalized fluorinated cyclohexane (±)**-8** in 32% isolated yield, the attempted fluorination of its regio- and stereoisomer (±)**-6** did not give a fluorine-containing product, but a highly unsaturated cyclic β-amino ester **9** (Scheme 2).

with Deoxofluor led to the corresponding elimination product (±)**-16** in 56% yield (Scheme 5), similarly as in the case of the cyclohexene analogue (Scheme 4).

A series of other multifunctionalized cyclopentanes, such as (±)**-19**, (±)**-20** and (±)**-23** (Scheme 6) as stereo- or regioisomers of (±)**-13** or (±)**-14** (Scheme 5), were next subjected to treatment with Deoxofluor.

These substrates were synthesized from *trans* epoxy amino ester (±)**-18** (derived from lactam (±)**-11** via *trans* ester (±)**-17**). Azidolysis of (±)**-18** by a published procedure,[59] gave regioisomers



Scheme 2. Attempted fluorination of amino esters (±)**-5**, (±)**-6** and (±)**-7**.