Carbohydrate Research 415 (2015) 12–16

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Stereoselective synthesis and molecular modeling of chiral cyclopentanes

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ARTICLE INFO

Article history:
Received 21 May 2015
Received in revised form 22 June 2015
Accepted 1 July 2015
Available online 23 July 2015

Keywords:
Asymmetric synthesis
Cyclopentane
Molecular modeling
Molecular dynamics

ABSTRACT

The reaction of 3-methyseleno-2-methylselenomethyl-propene with benzyl 2,3-anhydro-4-*O*-triflyl-β-L-ribopyranoside provides a major convenient enantiomeric product of 1-methylene-(benzyl3, 4-dideoxy-α-D-arabinopyranoso)-[3,4-c]-cyclopentane, with benzyl-2,3-anhydro-4-deoxy-4-*C*-(2-methyl- propen-3-yl)-α-D-lyxopyranoside as a minor product. While the reaction of 3-methyseleno-2-[methylselenomethyl]-propene with benzyl 2,3-anhydro-4-*O*-triflyl-α-D-ribopyranoside produces a good yield of benzyl-2,3-anhydro-4-deoxy-4-*C*-(2-methylpropen-3-yl)-α-D-lyxo-pyranoside. Molecular modeling and molecular dynamics simulations indicate that the intermediate in the reaction of the β-L sugar frequently occupies an optimal conformation that leads to the formation of cyclopentane, while the intermediate in the reaction of the α-D sugar has a very small probability. The results point to the dominant role of the β-L sugar intermediate in controlling the cyclopentane formation.

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1. Introduction

The construction of asymmetric cyclopentanemoieties has received much attention in recent years due to their diversity and frequency of multifunctional five-membered carbocyclic structures in natural products and their interesting biological activities.[1–3] Moreover, the significance of the development of new synthetic strategies leading to construct such diverse complex molecular structures arises due to their essential need in total synthesis of natural products and the high demand for synthetic strategies, which can provide alternative and practical methods for the synthesis of pharmaceuticals and agrochemicals. Pactamycin (**1**) and pactamycin derivative (**2**) have been shown to possess antitumor and antibacterial activities[4] whereas CCR5 (**3**) has been reported as an anti-HIV drug candidate.[5] Viridenomycin (**4**) have shown potent antimicrobial activities[6] against Gram positive and negative organisms (Fig. 1).

Although, many methods for the construction of cyclopentane rings onto preexisting cyclic compounds are reviewed,[7–11] one of the most straightforward methods, the annelation of a cyclopentane ring on a pyranoside nucleus has not been reported, to the best of our knowledge. In the present work, we describe a one-step regio- and stereo-selective annelation of highly functionalized cyclopentane on pyranoside ring.

We have previously reported several methods for the asymmetric synthesis of heterocyclic systems; e.g. piperazines,[12] morpholines,[13] cyclic trithiocarbonates[14] and thiazolidines[15] using carbohydrates as chiral scaffolds. Our basic strategy involves stereospecific nucleophilic substitution of the triflate group followed by intramolecular nucleophilic opening of the adjacent epoxy group. In continuation of our efforts on the development of novel synthetic strategies for asymmetric construction of complex molecular structures, we utilized the reaction of 3-methyseleno-2-[methylselenomethyl]-propene[16] (**5**, Scheme 1), as a valuable reagent, able to transfer a four carbon unit to various derivatives with the β-L-anhydro triflate **6** and its α-D isomer **7**.

2. Results and discussion

2.1. Synthesis

The synthesis of β-L-anhydro triflate **6** was successfully achieved in six steps,[17] starting from the commercially available L-arabinose and following a multi-step synthetic strategy including benzylation, selective protection, tosylation, deprotection, intramolecular S_N2 reaction, and triflation. On the other hand, the synthesis of the α-D-isomer **9** was prepared in eight steps following an alternative procedure[18] which includes benzoylation, S_N2 reaction, deprotection,

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http://dx.doi.org/10.1016/j.carres.2015.07.012
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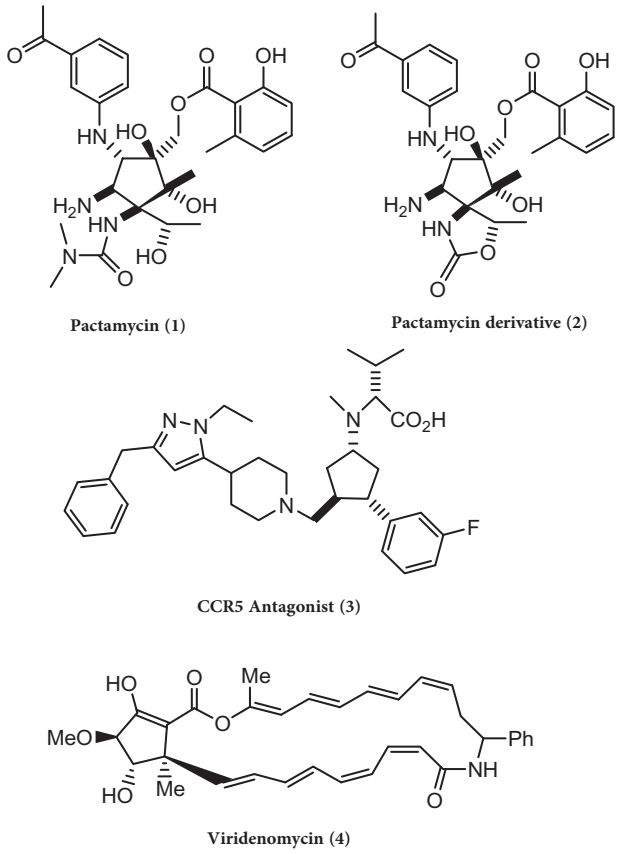
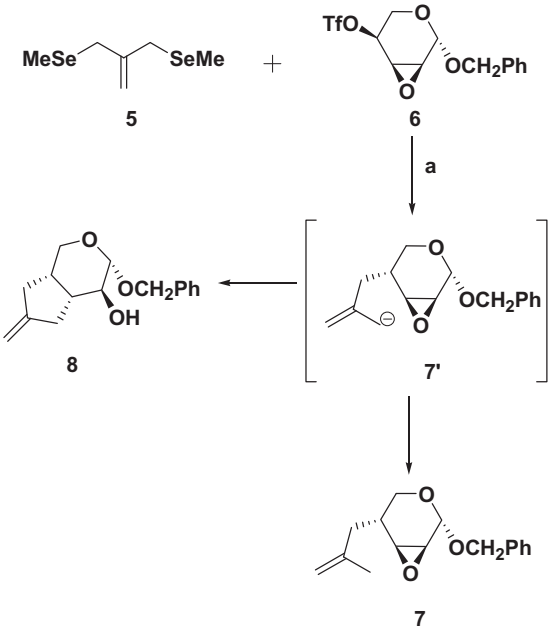
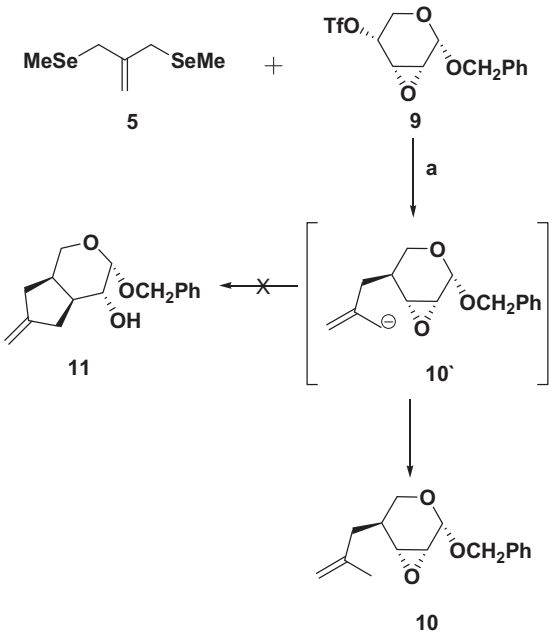


Fig. 1. Representative structures of cyclopentane-containing natural products.

intramolecular S_N2 reaction, and triflation. The reaction of the intermediary reagent 3-lithio-2-[lithiomethyl]-propene (formed from the sequential addition of two equivalents of *sec*-BuLi to **5** in THF at –78 °C) with the sugar triflate **6** at the same temperature leads to the formation of 1-methylene-(benzyl3,4-dideoxy-α-D-arabino-pyranoso)-[3,4-c]- cyclopentane (**8**) and benzyl-2,3-anhydro-4-deoxy-4-*C*-(2-methyl-propen-3-yl)-α-D-lyxo-pyranoside (**7**), in 77 and 5% yield, respectively (Scheme 1).



Scheme 1. Synthesis of **7** and **8** (a) *sec*-BuLi, THF, –78 °C.



Scheme 2. Synthesis of **10** and **11** (a) sec-BuLi, THF, –78 °C.

Surprisingly when the same reaction conditions were applied to the α-D-anhydro triflate isomer **9**, the major product was the non-cyclized product **10** in 60% yield and there were no traces for the formation of the expected cyclopentane derivative **11** as shown in Scheme 2. We tried several reaction conditions, but did not detect any traces of **11**. These included changing the equivalents of sec-BuLi (one to five equivalents), changing the solvent of the reaction (diethylether) and changing the temperature of the reaction (from –78 °C to room temperature), after the formation of the carbanion intermediate at –78 °C.

Despite all attempts to vary the reaction conditions, the major product in the reaction of α-D- isomer **9** is always the non-cyclized compound **10**. The combined use of 2D homo- and hetero-nuclear chemical shift correlation spectroscopy allowed the unambiguous and complete assignment of the proton and carbon chemical shifts of the new cyclopentane derivative **8**. Thus, in the ^{1}H NMR spectrum of **8**, H-1 appears as a doublet with (J = 4.3 Hz) at δ = 4.27 ppm, representing diequatorial relationship with H-2. The predominant conformation is therefore $^4C_1$. Successful transformation of the sugar triflate **6** into the cyclopentane derivative **8** is manifested in the disappearance of the two oxirane ring peaks in the ^{13}C NMR spectrum (normally appear at around 50–52 ppm in the sugar triflate **6**) and the appearance of two upfield peaks at δ = 39.4 and 43.5 ppm, correlated to C-3 and C-4, respectively. In the ^{13}C NMR spectrum of **7**, the two oxirane ring peaks resonate at δ = 50.1 and 54.2 ppm and the appearance of a singlet methyl peak at δ = 1.75 ppm in the ^{1}H NMR spectrum prove the proposed structure of this minor product.

2.2. Theoretical modeling

We obtained average heats of formation (ΔH^0_f) for the four compounds at 298 K from 10 ns of semiempirical QM molecular dynamics data (Table 1). The expected two reaction products **8** and **11** are found to have very similar heats of formation, to within the calculation uncertainty. In contrast, the reaction intermediates **7′** and **10′** exhibit different ΔH^0_f values. **7′**, the intermediate through

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