Tetrahedron 70 (2014) 2944–2950

Contents lists available at ScienceDirect

Tetrahedron

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

A highly stereoselective route to medium-ring-sized *trans*-alkenolides via oxidative fragmentation of bicyclic oxycyclopropane precursors: application to the synthesis of (+)-recifeiolide

Dzmitry M. Zubrytski, Dzmitry G. Kananovich *, Oleg G. Kulinkovich

Department of Organic Chemistry, Belarusian State University, Nezalezhnasci Av. 4, 220030 Minsk, Belarus

ARTICLE INFO

Article history:
Received 1 December 2013
Received in revised form 23 February 2014
Accepted 11 March 2014
Available online 15 March 2014

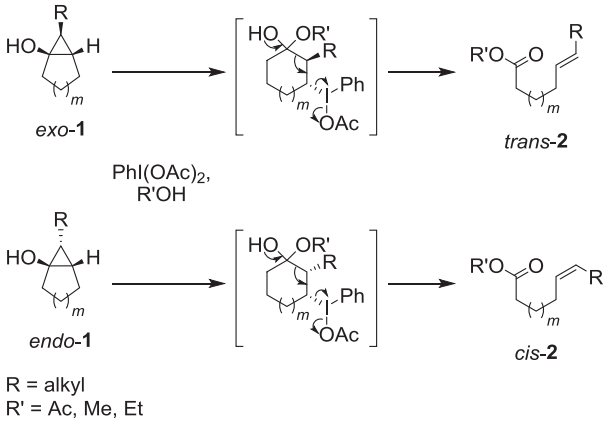
Keywords:
Alkenolides
Cyclopropanols
Hypervalent iodine compounds
Stereoselective synthesis
(+)-Recifeiolide

ABSTRACT

A new approach to the synthesis of medium-ring-sized *trans*-alkenolides, based on the oxidative fragmentation of a three-carbon ring in hydroxyalkyl substituted bicyclo[*n*.1.0]alkan-1-ols readily available from 2-alkylidenecycloalkanones, is described. This methodology was applied to the six-step transformation of cyclooctanone to the natural 12-membered *trans*-alkenolide antibiotic (+)-recifeiolide.

1. Introduction

Oxycyclopropanes are reactive, easily available compounds that are used as intermediates in the synthesis of other organic compounds owing to their ability to undergo synthetically useful transformations based upon the cleavage of the strained cyclopropane ring. Cleavage of either of the two adjacent to alcohol group bonds of the cyclopropane usually results in the formation of corresponding carbonyl compounds, whereas cleavage of the opposite carbon–carbon bond of the ring leads to allylic alcohols or related compounds.[1] Oxidative fragmentation of the substituted cyclopropanols with $Pb(OAc)_4$ or $PhI(OAc)_2$, occurring via the splitting of both carbon–carbon bonds adjacent to oxygen and leading to the corresponding carboxylic acids and alkenes, is also known.[2,3] An essential feature of the latter transformations is its high diastereoselectivity. This occurs, particularly, in the transfer of the relative configuration of substituents at the cyclopropane ring in bicyclic cyclopropanols **1** to the stereochemistry of the disubstituted carbon–carbon double bond in the products of their fragmentation, for example, *exo*-**1** is exclusively converted into *trans*-alkene **2**, whereas *endo*-**1** converts to *cis*-alkene **2** (Scheme 1).[2–4] This sort of substrate diastereocontrol has made it possible to efficiently use this oxidative fragmentation of the cyclopropane ring in appropriate bicyclic precursors to perform the stereoselective generation of carbon–carbon double bonds in the syntheses of the alkaloid (−)-pinidine,[3b] capsaicin[4] and some monoene insect pheromones.[5]



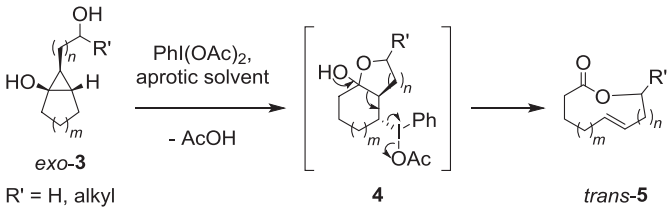
Scheme 1.

Since hydroxylic solvents are involved in the formation of a carbon–oxygen bond in this reaction (Scheme 1), we assumed that the oxidation of bicyclo[*n*.1.0]alkan-1-ols **1**, bearing a hydroxyl

* Corresponding author. E-mail address: kananovich82@tut.by (D.G. Kananovich).

0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.03.032

group in alkyl substituent R, in aprotic solvents would afford the corresponding lactones. In this case, the less sterically hindered *exo*-diastereomers of bicyclo[*n*.1.0]alkan-1-ols **3** might form the corresponding fused bicyclic intermediates **4**, and the fragmentation of the bridge carbon–carbon bond in the latter should provide alkenolides **5** with *trans*-configuration of the double bond (Scheme 2).



Scheme 2.

Similar diastereocontrol in the formation of *trans*-alkenolides was observed during the oxidation of fused oxabicycloalkenes,[6–9] as well as trialkylstannyl-substituted bicyclic lactols.[10] However, the formation of the double bond in these transformations was not highly regioselective or the required substrates for the oxidation were not readily available. At the same time, macrolactonization or ring-closing methathesis, which are both frequently employed in the synthesis of natural bioactive *trans*-alkenolides, quite often gave products in low yields or with low stereoselectivity, which required optimization of the reaction conditions.[11,12] In this work, we report a convenient method for the preparation of oxy-substituted *exo*-bicyclo[*n*.1.0]alkan-1-ols **3** and their application to the synthesis of medium-ring *trans*-alkenolides **5**.

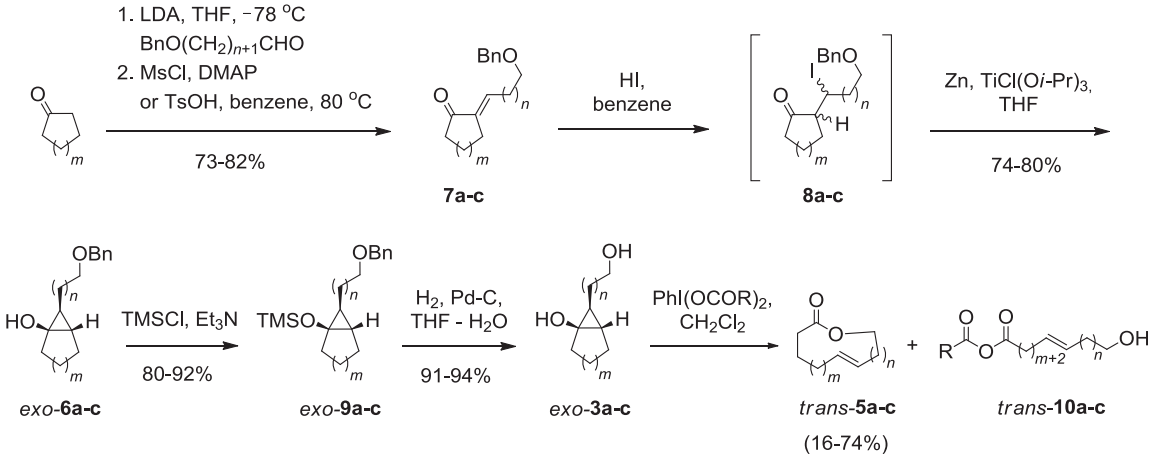
2. Results and discussion

Bicyclic cyclopropanols **6a**–**c**, bearing benzyl-protected hydroxyalkyl substituents, were obtained from unsaturated ketones **7a**–**c**, which are readily available via aldol condensation (Scheme 3). The treatment of unsaturated ketones **7a**–**c** with hydrogen iodide in dry benzene, followed by the reaction of intermediate β-iodoketones **8a**–**c** with zinc dust in the presence of $TiCl(Oi\text{-}Pr)_3$, under the previously described conditions,[4] led to the formation of the corresponding bicyclic cyclopropanols **6a**–**c** in high (74–91%) overall yields.[13] It is noteworthy that, unlike the transformations of 2-alkylidenecycloalkanones without functional groups in the side chain,[4] the reductive cyclization of compounds **7a**,**b** led to *exo*-bicyclo[*n*.1.0]alkan-1-ols **6a**,**b** exclusively.[14] In the case of ketone **7c**, which contains a remote benzyloxy substituent, a chromatographically readily separable mixture of *exo*/*endo*-isomers **6c** in the ratio of 82:18 was obtained. We suggest that the exclusive formation of *exo*-isomers **6a**,**b** was favored due to the intramolecular chelation of a metal atom with oxygen of the benzyloxy group in intermediate β-metaloketones.[15]

Debenzylation of compounds **6a**–**c** by hydrogenolysis was performed in the presence of 5 mol % of Pd–C following a silyl protection of the tertiary hydroxyl group. The benzyl group in TMS-protected cyclopropanols **9a**–**c** was smoothly removed in aq tetrahyfrofuran with the retention of a three-carbon ring, and was accompanied by the removal of the TMS-protecting group to give hydroxyalkyl substituted cyclopropanols **3a**–**c**. It is noteworthy that unprotected cyclopropanols **6** were involved in Pd-catalyzed three-carbon ring opening reactions[16] and yields of the target products **3** did not exceed 50%.

The oxidative fragmentation of *exo*-bicyclo[*n*.1.0]alkan-1-ol **3b** with phenyliodine(III) diacetate in anhydrous dichloromethane or deuterochloroform was completed in 1 h to give *trans*-alkenolide **5b**[9] in 70% yield (Scheme 3). The signals of the olefinic protons in the homodecoupled ^{1}H NMR spectrum of *trans*-**5b** displayed mutual splitting with a coupling constant of 15.4 Hz,[17] which corresponded to the *trans*-configuration of the double bond. The presence of an absorption band at 975 cm^{-1} in the IR spectrum of *trans*-**5b** provided further support for the stereochemistry assignment. The more reactive phenyliodine(III) bis(trifluoroacetate), as was shown by ^{1}H NMR inspection, reacted with diol *exo*-**3b** significantly faster to complete the reaction within 12 min. However, only a minor increase in the yield of lactone *trans*-**5b** (to 74%) was observed.[18] Under the same conditions, *exo*-bicyclo[*n*.1.0]alkan-1-ol **3a** gave the corresponding *trans*-alkenolide **5a** in 60% isolated yield.[19] At the same time, according to ^{1}H NMR spectroscopy, *exo*-bicyclo[*n*.1.0]alkan-1-ol **3c** in reaction with $PhI(OCOCF_3)_2$ in $CDCl_3$ was converted to the target macrolactone *trans*-**5c** in 23% yield (16% isolated yield).

^{1}H NMR analysis of the reaction mixtures also indicated the formation of mixed anhydrides **10a**–**c**[20] of the corresponding *trans*-ω-hydroxyalkenoic acids as initial side products, which were transformed gradually to acyclic *trans*-ω-acyloxyalkenoic acids as a result of the cross-acylation reactions. As an example, in the reaction *exo*-**3c** with $PhI(OCOCF_3)_2$ in $CDCl_3$, the primary reaction



Scheme 3.