Tetrahedron 68 (2012) 8994–9003

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

Enantiodivergent synthesis of (+)- and (−)-isolaurepan

Gonzalo Pazos, Manuel Pérez, Zoila Gándara, Generosa Gómez *, Yagamare Fall *

Departamento de Química Orgánica, Facultad de Química, Universidad de Vigo, 36200 Vigo, Spain

ARTICLE INFO

Article history:
Received 5 June 2012
Received in revised form 21 June 2012
Accepted 29 August 2012
Available online 4 September 2012

Keywords:
Marine toxins
Enantioselective synthesis
Claisen rearrangement
2,6-*syn*-Disubstituted tetrahydropyrans

ABSTRACT

The enantiodivergent synthesis of (+)-and (−)-isolaurepan was achieved from a common chiral template easily available from tri-*O*-acetyl-D-glucal, using as key step a diastereoselective thermal Claisen rearrangement, combined with a ring expansion reaction using trimethylsilyldiazomethane.

1. Introduction

A large number of marine natural products contain a medium ring ether in their structures and present a wide range of biological activities.[1] The synthesis of these unique structures constitutes a considerable challenge for organic chemists.[2] (+)-Isolaurepinnacin (**1**)[3] and (+)-neoisoprelaurefucin (**2**),[4] which were both isolated from species of the genus *Laurencia* and contain a 2,7-disubstituted oxepane core (Fig. 1), have received much attention as synthetic targets. (+)-Isolaurepan (**3**) and (−)-isolaurepan (**4**) are fully saturated analogues of **1** and **2**, respectively, and of other chiral oxepene and oxepane derivatives.[5]

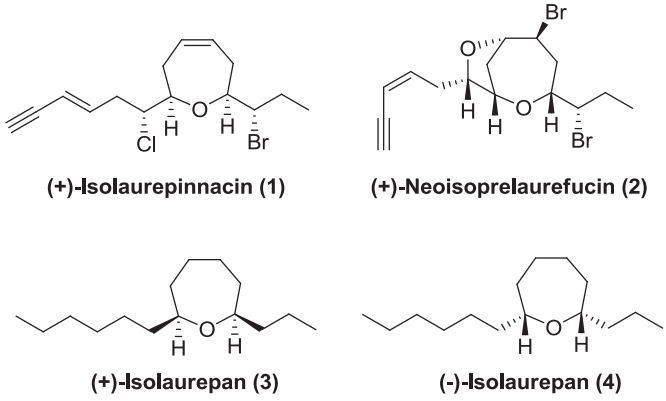


Fig. 1. Structures of representative *Laurencia* acetogenin metabolites.

Several reports of the stereoselective construction of racemic *cis*-2,7-disubstituted oxepanes have appeared,[2e,6] but there are very few syntheses of nonracemic species such as (+)-isolaurepan[7] and only one for the synthesis of (−)-isolaurepan.[8]

The work proposed in this paper is part of the overall objective of our research group directed toward the synthesis of ether rings as components of a large number of natural products.[9] In a preliminary communication we reported an enantioselective synthesis of (+)-isolaurepan.[10]

2. Results and discussion

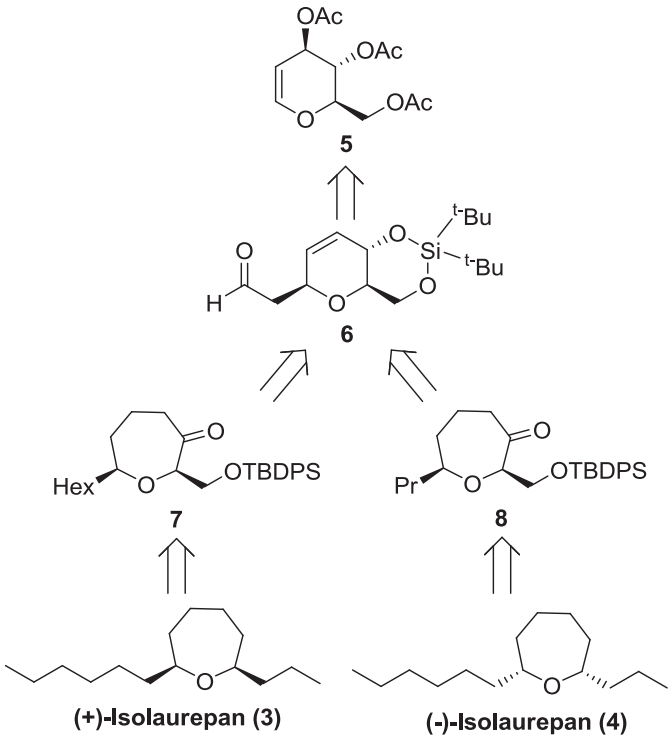
In this paper, we describe the enantioselective synthesis of (+)-isolaurepan and (−)-isolaurepan, both obtained from commercially available tri-*O*-acetyl-D-glucal (**5**) (Scheme 1). Our synthetic strategy is based in the intermediate 2,6-*cis*-disubstituted tetrahydropyran **6**, obtained through a thermal Claisen rearrangement.[11] From this compound and following analogues synthetic route were afforded oxepanes **7** and **8** by ring expansion with trimethylsilyldiazomethane.[12] A subsequent Wolf–Kishner reaction and side chain manipulation afforded (+)-isolaurepan (**3**) and (−)-isolaurepan (**4**).

2.1. Synthesis of (+)-isolaurepan

The procedure started with the synthesis of compound **9**, following the procedure described by Mori and Hayashi,[13] in two steps

* Corresponding author. Fax: +34 986 81 22 62; e-mail addresses: ggomez@uvigo.es (G. Gómez), yagamare@uvigo.es (Y. Fall).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.08.094

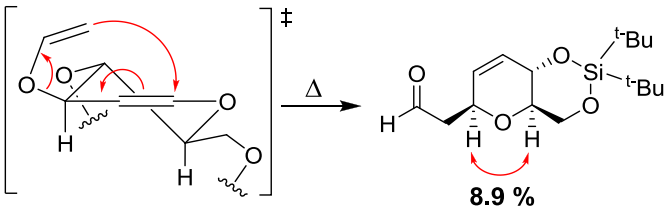


Scheme 1. Retrosynthetic analysis.

from **5**[14] in 85% yield (Scheme 2). This compound presents a latent allylic alcohol, which underwent a thermal Claisen rearrangement. The preparation of aldehyde **6** from allylic alcohol **9** via ester **11** was at first frustrated, by the yield of **11** being only 30% when obtained by Johnson rearrangement.[15] The Eschenmoser [3,3]-sigmatropic rearrangement of alcohol **9** to amide **10**[16] was also unsuccessful, recovering only part of the starting material without conversion.

As the Johnson orthoester rearrangement and the Eschenmoser variant involve the in situ generation of an allyl vinyl ether, we decided to change our strategy and use the classical Claisen rearrangement, by previous preparation of allyl vinyl ether **12**. This compound was successfully obtained by two alternative routes, which differed in the catalyst used. Thus, the reaction of allylic alcohol **9** with ethyl vinyl ether gave enolether **12** in 80% and 72% yields by catalysis with $Hg(OAc)_2$[17] or $Pd(OAc)_2$,[18] respectively. Following purification by column chromatography, compound **12** underwent a Claisen rearrangement when heated in toluene at 185 °C, giving aldehyde **6** in 95% yield.

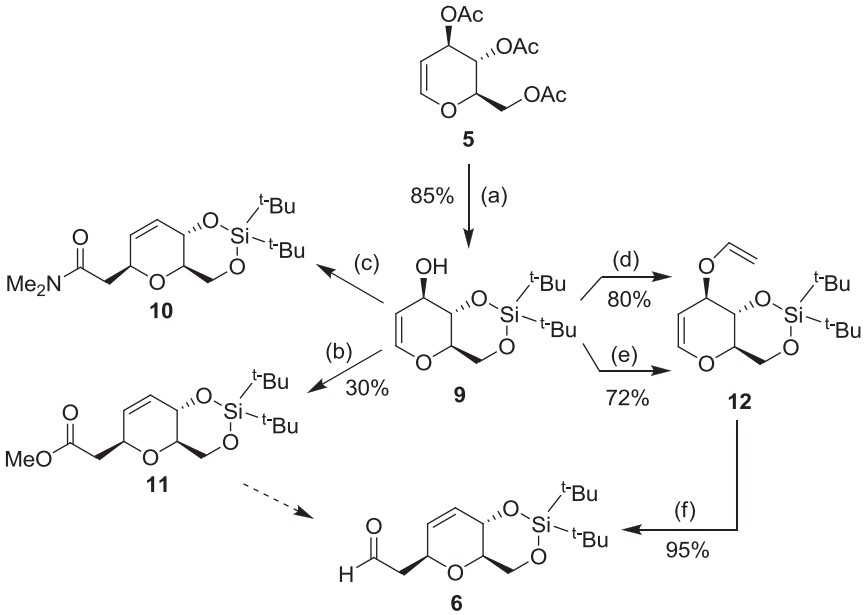
NMR spectroscopy confirmed the presence of single diastereoisomer as a reaction product. The high stereoselectivity obtained can be explained by conformational effects of the ring substituents in equatorial position. The stereochemistry of **6** was confirmed by NOE experiments (Scheme 3).



Scheme 3. NOE-NMR of aldehyde **6**.

With aldehyde **6** in hand, we addressed the transformation of its side chains and the expansion of its ring (Scheme 4).

Wittig reaction over **6** afforded an 80% yield of diene **13**, which upon hydrogenation on Pd/C gave **14** in nearly quantitative yield. Removal of the silyl protecting group of **14**, followed by selective protection of the primary alcohol provided alcohol **15**, which was converted into ketone **16** in 80% yield. The crucial oxepane formation was accomplished by reaction of **16** with trimethylsilyldiazomethane in the presence of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −78 °C, which gave the seven-membered ketone **7** in 60%. In this reaction was also isolated 8% of its isomeric ketone after acidic hydrolysis of the intermediary trimethylsilyl enolether. Wolf–Kishner reaction of **7** afforded oxepane **17** in 58% yield.[19] Removal of the silyl protecting group of **17** with TBAF gave the known alcohol **18**,[7a,c] which was transformed into alkyne **19** by alkylation of the corresponding triflate. Finally, alkyne **19** was uneventfully converted into the



Scheme 2. Reagents and conditions: (a) i. K_2CO_3, MeOH; ii. $^tBu_2Si(OTf)_2$, DMF, Py; (b) $MeC(OMe)_3$, TMBA, 160 °C; (c) $MeC(OMe)_2NMe_2$, toluene, 120 °C; (d) ethyl vinyl ether, $Hg(OAc)_2$, 65 °C; (e) ethyl vinyl ether, $Pd(OAc)_2$, Bipy, CF_3CO_2H, Et_3N, 80 °C; (f) toluene, 185 °C, 5 h.