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A new, enantioselective synthesis of (+)-isolaurepan

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ABSTRACT

A highly enantioselective synthesis of 2,6-*syn*-disubstituted tetrahydropyrans from commercially available tri-*O*-acetyl-D-glucal, based on a thermal Claisen rearrangement, allows enantioselective synthesis of (+)-isolaurepan when combined with a ring expansion reaction using trimethylsilyldiazomethane.

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Polycyclic ether toxins are potent bioactive agents with skeletons consisting of ladder-like chains of fused, mostly 6–9-membered oxacycles; many are found in marine organisms.[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 intermediate synthetic targets. (+)-Isolaurepan (**3**) is a fully saturated analogue of **1** and of other chiral oxepene and oxepane derivatives.[5]

Several reports of the stereoselective construction of racemic cis-2,7-disubstituted oxepanes have appeared,[2e,6] but very few syntheses of nonracemic species such as (+)-isolaurepan.[7] A general strategy for enantioselective functionalisation of the oxepane ring is lacking.

Here we describe the new, enantioselective synthesis of (+)-isolaurepan that is outlined retrosynthetically in Scheme 1. We anticipated that the latent allylic alcohol of tri-*O*-acetyl-D-glucal (**6**) would undergo a thermal Claisen rearrangement,[8] to 2,6-cis-disubstituted tetrahydropyran **5**, which would afford oxepane **4** by ring expansion with trimethylsilyldiazomethane.[9] A subsequent Wolf-Kishner reaction and side chain manipulation would then afford (+)-isolaurepan (**3**).

Following the procedure described by Mori and Hayashi,[10] compound **7** was prepared in two steps from **6**[11] in 85% yield (Scheme 2).

The preparation of aldehyde **5** from allylic alcohol **7** via ester **8** was at first frustrated by the yield of **8** being only 30% when ob-

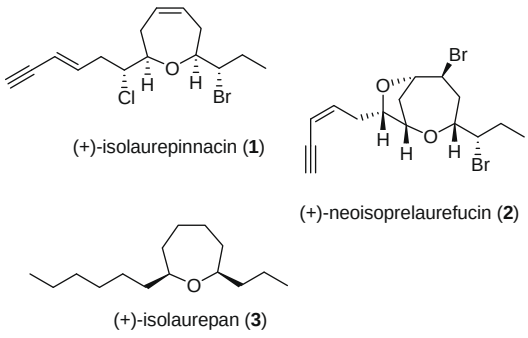
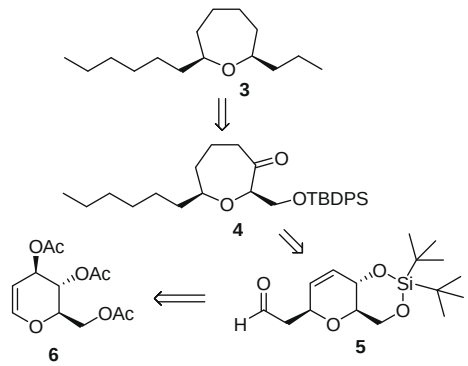


Figure 1. Structures of representative *Laurencia* acetogenin metabolites.



Scheme 1. Retrosynthetic analysis.

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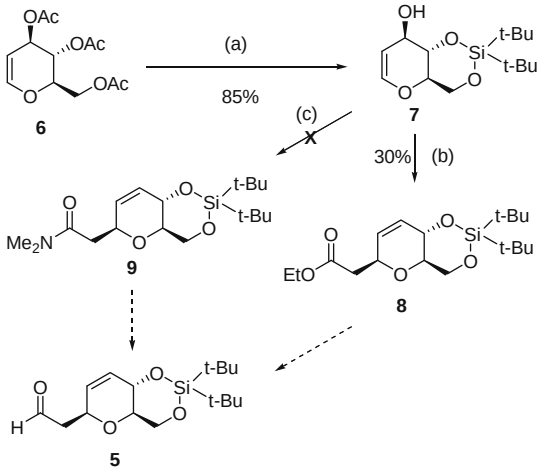


Scheme 2. Reagents and conditions: (a) (i) K_2CO_3, MeOH; (ii) *t*-$Bu_2Si(OTf)_2$, DMF, Pyr; (b) $MeC(OMe)_3$, TMBA, 160 °C; (c) $MeC(OMe)_2NMe_2$, toluene, 120 °C.

tained by acid-catalysed orthoester Claisen rearrangement.[12] The Eschenmoser [3,3]-sigmatropic rearrangement of alcohol **7** to amide **9**[13] was also unsuccessful.

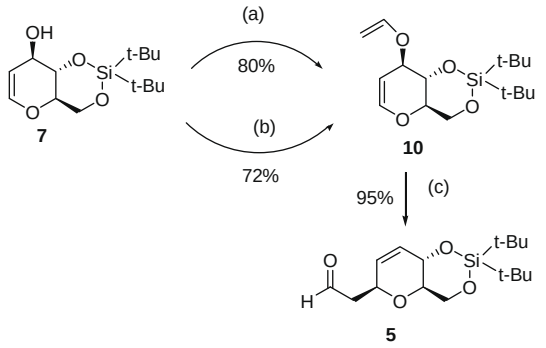
As the Johnson orthoester rearrangement and the Eschenmoser variant involve the in situ generation of an allyl vinyl ether, we decided to change our strategy and use the classical Claisen rearrangement following preparation of allyl vinyl ether **10** (Scheme 3).

Thorough investigation of the latter step showed that reaction of allylic alcohol **7** with ethyl vinyl ether could give enolether **10** in 80% and 72% yields when catalysed by $Hg(OAc)_2$[14] and $Pd(OAc)_2$,[15] respectively.

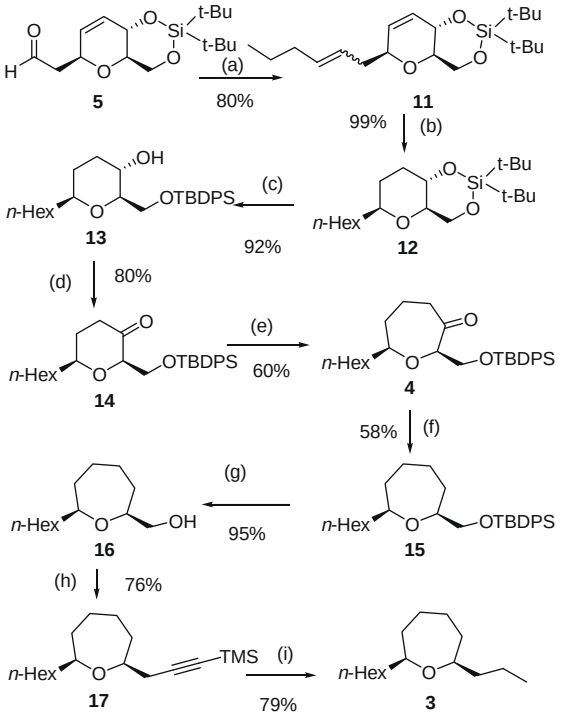
Following purification by column chromatography, compound **10** underwent a Claisen rearrangement when heated in toluene at 185 °C, giving aldehyde **5** in 95% yield. The stereochemistry of **5** was determined by NOE experiments.

With aldehyde **5** in hand, we addressed the transformation of its side chains and the expansion of its ring (Scheme 4).

Wittig reaction of **5** afforded an 80% yield of diene **11,** which upon hydrogenation on Pd/C gave **12** in nearly quantitative yield. Removal of the silyl protecting group of **12**, followed by selective protection of the primary alcohol of the resulting diol, then provided alcohol **13**, which was converted into ketone **14** in 80% yield. The crucial oxepane formation was accomplished by reaction of **14** with trimethylsilyldiazomethane in the presence of BF_3OEt_2 in CH_2Cl_2 at −78 °C, which gave the seven-membered ketone **4** in 60% yield along with an 8% yield of its isomeric ketone after acidic hydrolysis of the intermediary trimethylsilyl enol ether. Wolf-Kishner reaction of **4** then afforded oxepane **15** in 58% yield,[16]



Scheme 3. Reagents and conditions: (a) ethyl vinyl ether, $Hg(OAc)_2$, 65 °C; (b) ethyl vinyl ether, $Pd(OAc)_2$, bipyridine, CF_3CO_2H, Et_3N, 80 °C; (c) toluene, 185 °C, 5 h.



Scheme 4. Reagents and conditions: (a) *n*-$BuPPh_3Br$, *n*-BuLi, THF, 0 °C; (b) H_2, Pd/C (10%), MeOH; (c) (i) TBAF, THF, rt; (ii) TBDPSCl, imidazole, DMAP, DMF; (d) TPAP, NMO, CH_2Cl_2, molecular sieves; (e) (i) $TMSCHN_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C; (ii) PPTS, MeOH; (f) (i) NH_2NHTs, MeOH, 70 °C, molecular sieves; (ii) $NaBH_3CN$, DMF, 130 °C; (g) TBAF, THF; (h) (i) Tf_2O, CH_2Cl_2, pyridine, −15 °C; (ii) TMSCCH, *n*-BuLi, THF/DMPU, 0 °C; (i) (i) TBAF, THF; (ii) H_2, Pd/C(10%), MeOH.

and removal of the silyl protecting group of **15** with TBAF gave the known alcohol **16**,[7a,c] which was transformed into alkyne **17** by alkylation of the corresponding triflate. Finally, alkyne **17** was uneventfully converted into the target (+)-isolaurepan **3** in 79% yield. All attempts to obtain **3** directly from alcohol **16** by the method described in the literature[7a] were unsuccessful.

In conclusion, we have achieved a new and enantioselective synthesis of (+)-isolaurepan. Furthermore, intermediate **5** is a valuable building block. It will allow us not only to synthesise (−)-isolaurepan, the enantiomer of **3**, by sequential side chain modification, but also to extend our work on racemic polyoxacyclic compounds[17] to the enantioselective synthesis of polyoxacycles with trans–cis–trans stereochemistry. These developments are currently underway in our laboratories.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.041.

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