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A Formal Synthesis of the Auriside Aglycon

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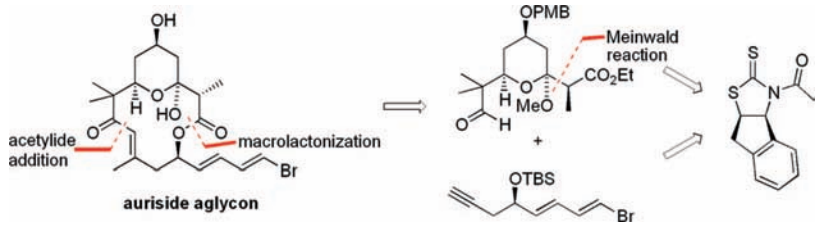
ABSTRACT



A highly convergent formal synthesis of the auriside aglycon was achieved. An indene-based thiazolidinethione chiral auxiliary was used for the construction of both the C1−C9 and C10−C17 fragments via acetate aldol reactions. A Meinwald reaction was utilized to install the stereocenter at C2, and a conjugated addition to an ynone was used to construct the C9−C11 enone.

Aurisides A and B are two glycosidated macrolactones isolated in minute amounts from *Dolabella auricularia*,[1] a sea hare that has proved to be a rich source of biologically active and structurally unique natural products (Figure 1).[2] The structure and absolute configuration of the aurisides was established on the basis of spectroscopic data as well as degradation experiments. Both aurisides A and B exhibit cytotoxicity against human cervical cancer HeLa-S3 cells, with IC_{50} values of 0.17 and 1.2 μg/mL, respectively. Both natural products share a common aglycon attached to different rhamnose-derived sugars; the aglycon contains five stereogenic centers, a brominated conjugated diene side chain, a 14-membered macrolactone, and a hemiketal moiety.

Due to their important activity, unique structure, and scarce availability from the natural source, the aurisides have been attractive synthetic targets. Paterson's group accomplished the first enantioselective synthesis of both natural products[3] using asymmetric Mukaiyama and vinylogous Mukaiyama

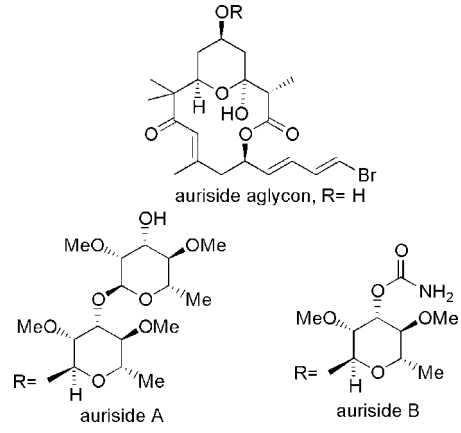


Figure 1. Structure of aurisides A and B.

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aldol reactions as key steps. On the basis of the synthesis of the aglycon previously reported by Yamada,[4] Kigoshi's group published a total synthesis[5] using (*R*)-pantolactone as chiral starting material, featuring a Nozaki−Hiyama−Kishi reaction and a late-stage installation of the vinyl bromide moiety. On continuation of our research program aimed at the synthesis of biologically important natural products, we became interested in the synthesis of the aurisides and the structurally related callipeltosides.[6,7] Our synthetic approach had to be highly convergent, efficient, and provide flexibility for the development of analogues. Recently, we developed an indene-based thiazolidinethione chiral auxiliary which allows efficient control of asymmetric aldol reactions, a key transformation for the construction of polyketide-derived natural products.[8,9] Herein, we present the application of this methodology to the synthesis of macrolide **21**, a valuable advanced intermediate in Paterson's synthesis of the aurisides.

In order to maximize the convergence of our approach, we envisioned a synthesis of the auriside aglycon to arise from the coupling of two fragments, the C1−C9 fragment,[10] containing four stereocenters, a hemiacetal moiety, and a propionate unit, and a C10−C17 fragment,[11] containing one stereocenter and a conjugated diene with a vinyl bromide already in place, Figure 2. We have previously disclosed the use of a biocatalytically generated bicyclic lactone as chiral starting material for the synthesis of the C1−C9 fragment.[10,12] In this work, we describe a more efficient, scalable, and economical second-generation synthesis for this fragment, utilizing an indene-based thiazolidinethione chiral auxiliary[8] to control the stereochemistry at C7 by means of a key acetate aldol reaction.

The synthesis of the C1−C9 fragment is depicted in Schemes 1 and 2. Known aldehyde **2**[13] was subjected to aldol reaction[8,9] with *N*-acetyl thiazolidinethione **1** to afford **3**.

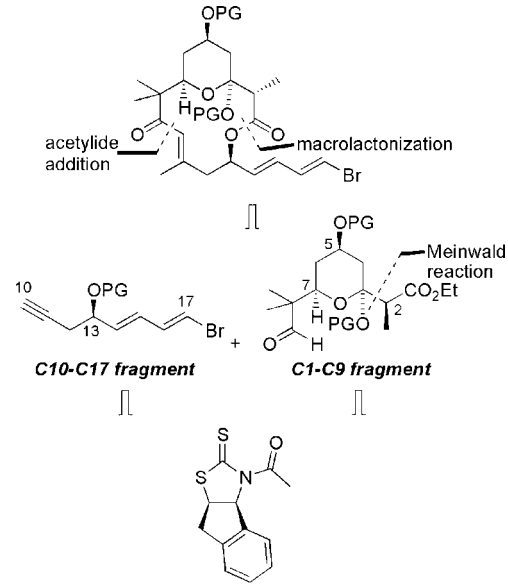
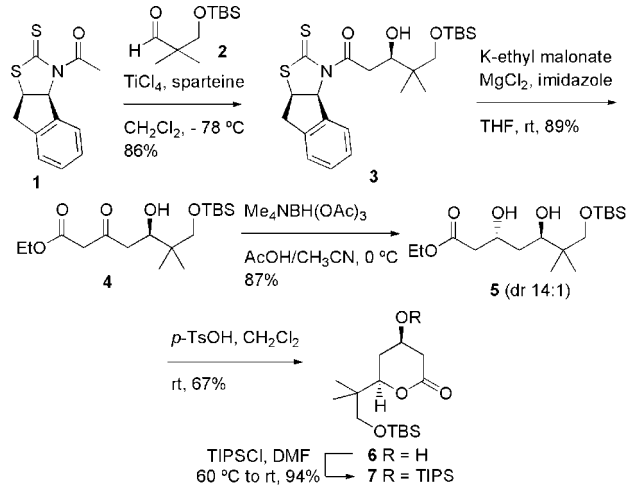


Figure 2. Retrosynthesis of the aglycon core.

Scheme 1



Optimized conditions developed by Crimmins delivered aldol product **3** as a single diastereomer.[14]The configuration of the created stereogenic center was confirmed later in the sequence by correlation with our previously described lactone **7**.[10]

Direct displacement of the chiral auxiliary[15] with potassium ethyl malonate gave keto ester **4** which was subjected to hydroxyl-directed reduction[16] to give *anti*-diol **5** in good

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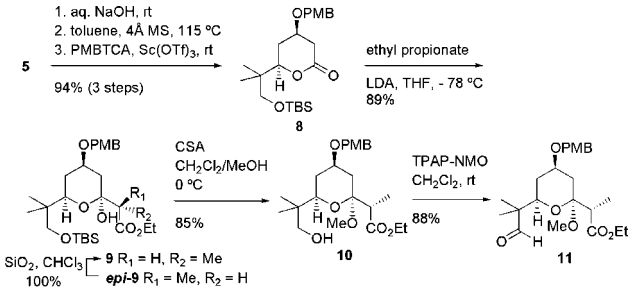
yield and diastereoselectivity (87%, 14:1 dr). The relative stereochemistry of **5** was confirmed by conversion to the corresponding acetonide and applying Rychnovsky's method.[17,18] Acid-catalyzed cyclization of *anti*-diol **5** provided hydroxyvalerolactone **6**. At this stage, correlation with known lactone **7**[10] was carried out by protection of **6** as the TIPS derivative, whose characterization data are identical to our previously described intermediate **7**, thus confirming the stereochemical outcome of the key aldol reaction between **1** and **2**.

Scheme 2

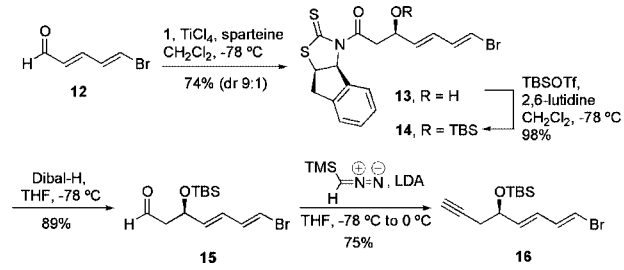


To continue the sequence of the C1−C9 fragment **11**, we found it to be more convenient the use of a PMB protecting group at position C5 (auriside numbering), Scheme 2. Lactone **8** could be obtained from **5** by cyclization and protection of hydroxyvalerolactone **6**; however, better results were obtained when diol **5** was taken into a three-step sequence of hydrolysis, cyclization, and protection[19] to give lactone **8** in excellent yield. Meinwald reaction of **8** with the lithium enolate of ethyl propionate afforded a separable ∼2:1 mixture of C2 diastereomers, from which the major product **9** was identified as the required (2*S*)-isomer.[20] Upon prolonged exposure to silica (∼72 h), the minor diastereomer epimerized completely to give **9** in 89% overall yield.[21]

Protection of the hemiketal **9** as the methyl ketal occurred under acidic conditions with concomitant cleavage of the TBS group at C9 to give alcohol **10**. Oxidation of **10** using Ley's protocol[22] gave aldehyde **11**.

The synthesis of fragment C10−C17 **16** started with the aldol reaction between known aldehyde **12**[23,11a] and *N*-acetyl thiazolidinethione **1** again using Crimmins' protocol,[14] Scheme 3. The aldol product **13** was obtained in good yield and good diastereoselectivity (74%, dr 9:1). Protection of

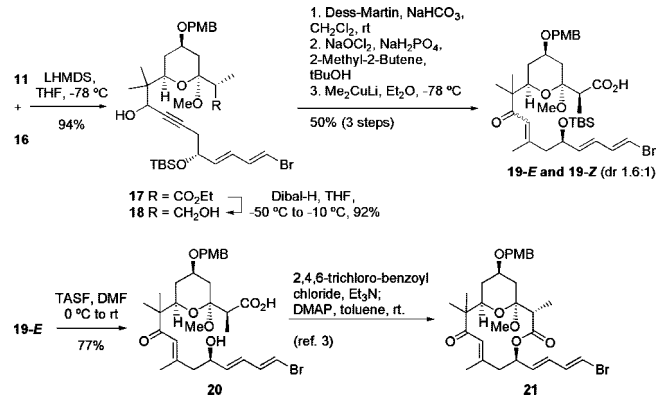
Scheme 3



the aldol product **13** as the TBS ether and reductive cleavage of the chiral auxiliary afforded aldehyde **15**. Direct homologation of aldehyde **15** to alkyne **16**[11b] could be carried out using the Ohira-Bestmann reagent[24] at low temperature, but we found this transformation easier to scale up when using TMS-diazomethane[25] to give gram quantities of **16** in good yield.

The addition of Me_2CuLi to an ynone system is a strategy that has proved to be useful for the synthesis of trisubstituted enones.[26] The required ynone was thus synthesized by coupling of the C9−C11 (**11**) and C10−C17 (**16**) fragments with LHMDS at low temperature to give propargylic alcohol **17** as an inconsequential mixture of diastereomers in excellent yield, Scheme 4. Attempts to hydrolyze ethyl ester **17**

Scheme 4



always resulted either in recovery of starting material, elimination of the methyl ketal, and/or cleavage of the silyl protecting group. Therefore, we followed a reduction−oxidation sequence to obtain the corresponding carboxylic acid.

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(26) See, for example: (a) Marshall, J. A.; Crooks, S. L.; DeHoff, B. S. *J. Org. Chem.* **1988**, *53*, 1616–1623. (b) Marshall, J. A.; Andersen, M. A. *J. Org. Chem.* **1992**, *57*, 2766–2768. (c) Dounay, A. B.; Urbanek, R. A.; Frydrychowsky, V. A.; Forsyth, C. J. *J. Org. Chem.* **2001**, *66*, 925–938. (d) Balnalves, A. S.; McGowan, G.; Shapland, P. D. P.; Thomas, E. J. *Tetrahedron lett.* **2003**, *44*, 2713–2716. (e) Houghton, T. J.; Choi, S.; Rawal, V. H. *Org. Lett.* **2001**, *3*, 3615–3617.

Reduction of **21** with Dibal-H gave diols **18** in excellent yield. Oxidation of both the primary and propargylic alcohols was then accomplished by using $NaHCO_3$-buffered Dess−Martin reagent.[27] Lindgren−Pinnick oxidation[28] of the keto-aldehyde intermediate followed to afford the corresponding ynone-acid, that was subjected to 1,4 addition of Me_2CuLi to produce **19** as a 1.6:1 mixture of *E* and *Z* enones in 50% overall yield over three steps.[29] Similar diatereomeric ratios were observed in model systems.[11b] Better diastereomeric ratios favoring the *E*-olefins have been observed in cyclic systems when quenching the reaction with *i*-PrSH.[26b] Isomerization of the *Z*-olefin can also be achieved by treating the olefin with LiS-*i*-Pr in cyclic systems.[26a] Quenching our Gilman reagent addition with other than NH_4Cl solution resulted in lower diastereoselectivities. At this stage, the required **19-*E*** could be isolated in 31% over three steps from **18** and then treated with TASF[30] in wet DMF to promote cleavage of the TBS group, giving hydroxy acid **20**.

As previously reported by Paterson,[3] hydroxy acid **20** underwent macrolactonization using Yamaguchi's protocol[31] to afford macrolide **21**. The spectral data for compounds **20** and **21** matched Paterson's intermediates. Macrolide **21** is a valuable advanced intermediate for the synthesis of the aurisides; therefore, our efforts represent a formal synthesis of these natural products. Our approach features the use of a propionate Meinwald reaction to install the stereocenter at C2 and makes use of a chemoselective addition of an acetylide to aldehyde **11** and 1,4-addition of Me_2CuLi to an ynone system to construct the C9−C11 enone. Following Paterson's work, Yamaguchi's macrolactonization gave the 14-membered macrolide **21**. The synthesis of **21** proceeded in 17 steps (longest linear sequence) and 8.04% overall yield from known aldehyde **2**. The synthesis is highly convergent and highlights the versatility and efficiency of an indene-based thiazolidinethione chiral auxiliary in the context of polyketide-derived natural product synthesis.

Acknowledgment. We thank Prof. Ian Paterson (University of Cambridge) and Prof. Gordon. J. Florence (University of St. Andrews) for kindly providing us with detailed characterization data for compounds **20** and **21** as well as for useful comments. We thank the Center for Biocatalysis and Bioprocessing at The University of Iowa for a predoctoral fellowship (RTA). This work was supported by a research grant from the National Science Foundation (CHE-0111292).

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds (**3**−**6** and **8**−**21**) and copies of ^1H and ^{13}C NMR spectra (**3**−**21**). This material is available free of charge via the Internet at http://pubs.acs.org.

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