Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 5915–5917
Tetrahedron Letters

Model studies on the ring construction of the auriside macrolactone

Rodolfo Tello-Aburto, Adrián Ochoa-Teran and Horacio F. Olivo*

Division of Medicinal and Natural Products Chemistry, The University of Iowa, Iowa City, IA 52242, United States

Received 19 May 2006; revised 5 June 2006; accepted 8 June 2006
Available online 30 June 2006

Abstract—The preparation of a 12-membered ring macrolactone model of auriside that contains a pendant diene chain bearing a bromide was investigated employing two approaches. The first approach utilized an oxidative rearrangement of a tertiary allylic alcohol on a 12-membered ring. The second approach was based on a 1,4-methylation of an ynone followed by macrolactonization.

Aurisides A and B are cytotoxic marine polyketides isolated from the Japanese sea hare *Dolabella auricularia* by Yamada and co-workers in 1996.[1] These two molecules exhibited significant cytotoxicity against HeLa S_3 cervical cancer cell lines. The aurisides are glycosylated 14-membered macrolactones, bridged through a hemiketal moiety, possessing a brominated conjugated diene side chain on C13, and bearing different rhamnose derived sugars on C5. Their unusual structure and significant cytotoxicity have attracted interest in their synthesis.[2–4] We envisioned a highly convergent approach that involves building two fragments, the C1–C9 northern fragment possessing an aldehyde and an ester,[5] and the C10–C17 southern fragment containing a brominated diene.[6] Herein, we present our synthetic studies to assemble the C10–C17 fragment with a simple aldehyde in a 12-membered model macrolactone (Fig. 1).

We envisioned beginning the construction of the macrolactone with a bromodiene already in place. We examined two different strategies to combine and convert the C1–C9 and C10–C17 fragments into the desired model macrocycle, Figure 2. The first strategy relies on an oxidative rearrangement of a tertiary alcohol to furnish the desired α,β-unsaturated ketone **1** (path a). The second strategy focuses on a 1,4-alkylation to an ynone followed by macrolactonization (path b). These two strategies employ two similar C10–C17 fragments containing the conjugated bromodiene side chain **4** and **6**, both of them prepared from the versatile acyl imide **7**.[6,7] The tertiary alcohol **2** could be obtained by selective Grignard 1,2-addition to an enone, and the macrolactone could be prepared utilizing Yamaguchi's reagent. The propargylic ketone **5** could be accessed via addition of the acetylide of **6** to aldehyde **3** followed by oxidation of the resulting alcohol.

The oxidative tertiary allylic alcohol rearrangement strategy is illustrated in Figure 3. The synthesis starts from aldol product **7**,[6] which was protected as the triethylsilyl ether. Chiral thiazolidinethione auxiliaries are easily displaced by several nucleophiles.[7,8] The thiazolidinethione group of **8** was displaced with methyl (bismethoxy)phosphonate and butyl lithium to furnish β-ketophosphonate **9** in excellent yield.[9] Coupling of ketophosphonate **9** and aldehyde **3**[10] was accomplished using barium hydroxide in THF in 85% yield.[11] Selective methylation of ketone **10** was carried out with excess methyl Grignard reagent at low temperature to afford **11** in 53% yield (75% based on recovered starting material). Concurrent desilylation of the TES group and ester hydrolysis of compound **11** occurred smoothly with lithium hydroxide and provided **12** in 88% yield. Formation of the 12-membered ring lactone **2** was accomplished using Yamaguchi's reagent in 81% yield.[12]

With tertiary allylic alcohol **2** in hand, we investigated appropriate conditions to carry out the desired oxidative rearrangement to α,β-unsaturated ketone **1**. A recent report showed that this rearrangement can be carried out effectively with five and six-membered cyclic tertiary alcohols to β-disubstituted α,β-unsaturated ketones using IBX in DMSO at 55 °C.[13] Unfortunately, no product was observed in our more challenging 12-membered ring system using hypervalent iodine reagents.

* Corresponding author. Tel.: +1 319 335 8849; fax: +1 319 335 8766; e-mail: horacio-olivo@uiowa.edu

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.06.041

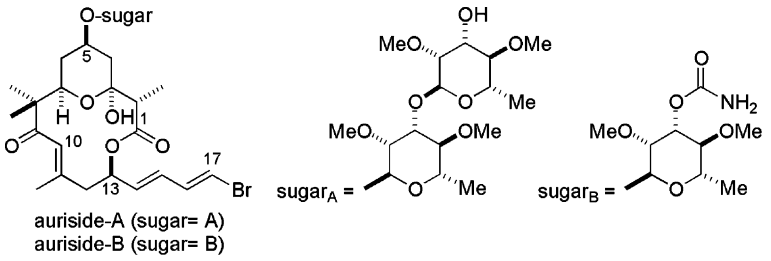

Figure 1. Aurisides A and B.

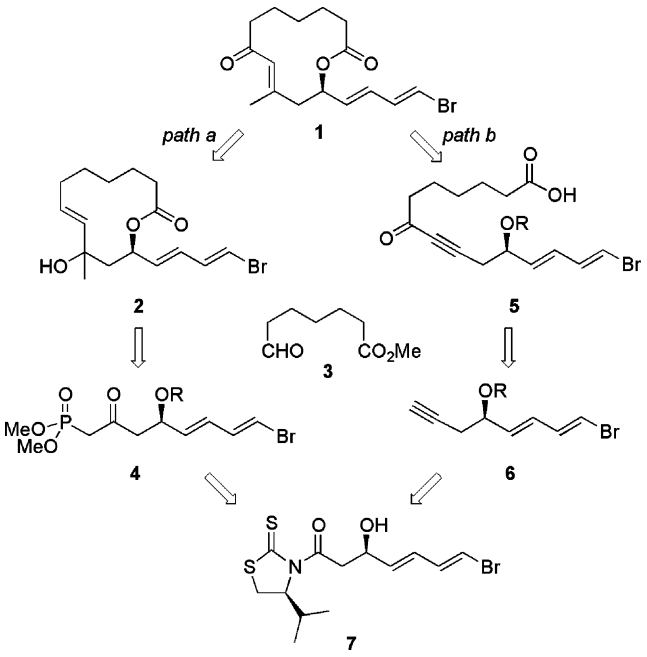

Figure 2. Strategies for the coupling of C1–C9 and C10–C17 fragments.

However, the desired product was formed as a single isomer using PCC and excess *p*-TsOH in CH_2Cl_2, albeit in low 30% yield and no starting material isolated.[14] We believe the acidic conditions needed for the rearrangement might not be compatible with the allylic lactone present in the molecule, but no other product could be identified.

In our alternate strategy, ketone C9 is already in place, Figure 4. The thiazolidinethione aldol product **7** was protected with a TBS group. The thiazolidinethione **13** was reduced directly to aldehyde **14** using dibal-H at low temperature. Homologation of the aldehyde was accomplished with Ohira's reagent at low temperature to avoid β-elimination.[6] Coupling of alkyne **15** with aldehyde **3** was accomplished with LDA at low temperature to give an inconsequential diastereomeric mixture of alcohols **16**. Compound **16** was subjected to hydrolysis, oxidation with Dess–Martin reagent, and addition of Gilman's reagent to the corresponding ynone.[15] An inseparable mixture of isomeric enones **17**-*E*/*Z* was isolated in 74% yield. The ratio of isomers was determined by ^{1}H NMR and NOE experiments of the mixture (*E*/*Z*, 1.5:1). Cleavage of the silyl group was successful when TAS-F was added to **17** in wet DMF.[16,17] Interestingly, we observed that the *E*-isomer **17** was deprotected faster than the more hindered *Z*-isomer. Thus, alcohol **18** was isolated uncontaminated from the *Z*-isomer. Yonemitsu's modification[18] of the Yamaguchi's protocol gave the desired 12-membered lactone **1** in 45% yield.

The cyclization of compound **18** to build model macrolactone **1** occurred in modest yield (45%). Interestingly, macrolactonization of the seco-acid of the auriside aglycon by Paterson occurred cleanly in 86% yield.[3]

In summary, we have investigated two approaches to construct a model macrolactone ring that should be applied successfully to our synthesis of aurisides. The two approaches make use of an aldehyde (the northern fragment) and two similar C10–C17 fragments (southern fragment) that were prepared from a common aldol product. Although the two approaches present some problems, the 1,4-methyl-addition-macrolactonization seems to be a more appealing alternative, since the late-stage steps of the synthesis require mild conditions.

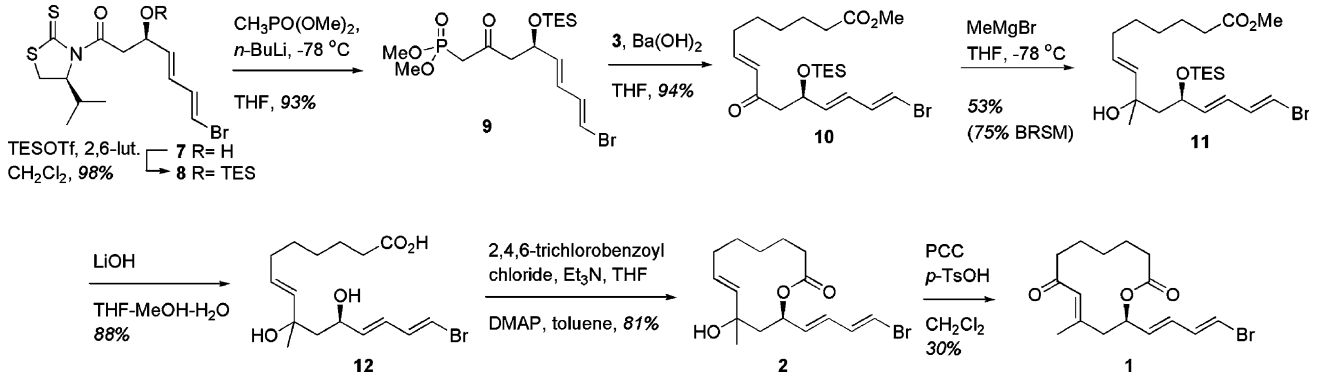

Figure 3. Oxidative tertiary allylic alcohol rearrangement.

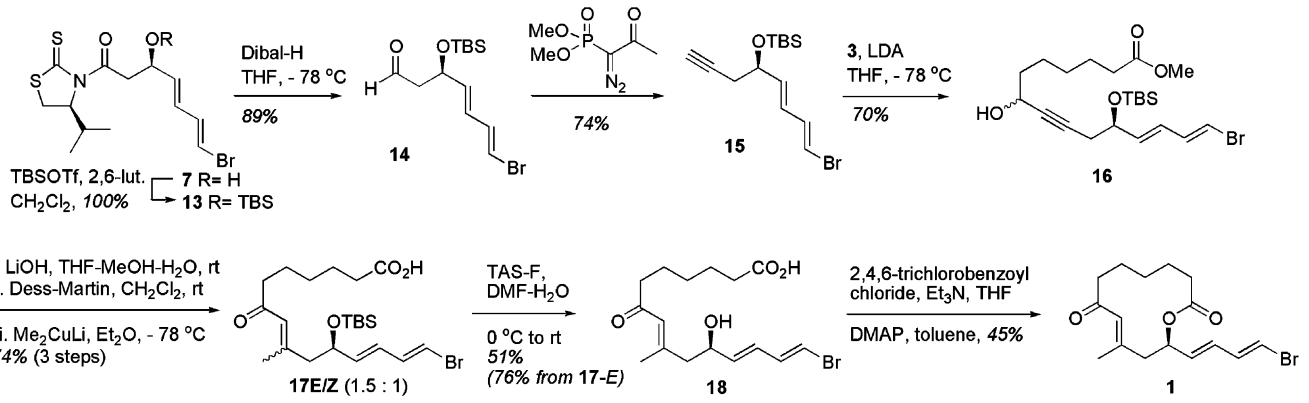

Figure 4. 1,4-Methyl addition—macrolactonization.

Current efforts in our laboratory are focused on applying this methodology to the total synthesis of the aurisides.

Acknowledgements

This work was supported by research grants from the National Science Foundation (CHE-0111292 and ECC-0310689).

Supplementary data

Copies of ^{1}H and ^{13}C NMR of compounds **1**–**3**, and **7**–**18**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.041.

References and notes

1. Sone, H.; Kigoshi, H.; Yamada, K. *J. Org. Chem.* **1996**, *61*, 8956–8960.
2. Synthesis of the auriside aglycone: Sone, H.; Suenaga, K.; Bessho, Y.; Kondo, T.; Kigoshi, H.; Yamada, K. *Chem. Lett.* **1998**, 85–86.
3. First total syntheses of aurisides A and B: Paterson, I.; Florence, G. J.; Heimann, A. C.; MacKay, A. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1130–1133.
4. Synthetic Studies: (a) Vakalopoulos, A.; Smits, R.; Hoffman, H. R. M. *Eur. J. Org. Chem.* **2002**, 1538–1545; (b) Sneddon, H. F.; Gaunt, M. J.; Ley, S. V. *Org. Lett.* **2003**, *5*, 1147–1150.
5. Ríos, M. Y.; Velázquez, F.; Olivo, H. F. *Tetrahedron* **2003**, *59*, 6529–6536.
6. Romero-Ortega, M.; Colby, D. A.; Olivo, H. F. *Tetrahedron Lett.* **2002**, *43*, 6439–6441.
7. (a) Hodge, M. B.; Olivo, H. F. *Tetrahedron* **2004**, *60*, 9397–9403; (b) Osorio-Lozada, A.; Prisinzano, T.; Olivo, H. F. *Tetrahedron: Asymmetry* **2004**, *15*, 3811–3815.
8. Velázquez, F.; Olivo, H. F. *Curr. Org. Chem.* **2002**, *6*, 303–340.
9. Crimmins, M. T.; Siliphaivanh, P. *Org. Lett.* **2003**, *5*, 4641–4644.
10. Suzuki, M.; Kawagishi, T.; Yanagisawa, A.; Suzuki, T.; Okamura, N.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1299–1312.
11. (a) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774–776; (b) Alvarez Ibarra, C.; Arias, S.; Fernández, M. J.; Sinisterra, J. V. *J. Chem. Soc., Perkin Trans. 2* **1989**, 503–508.
12. (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993; (b) Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911–939.
13. Shibuya, M.; Ito, S.; Takahashi, M.; Iwabuchi, Y. *Org. Lett.* **2004**, *6*, 4303–4306.
14. (a) Carnell, A. J.; Casy, G.; Gorins, G.; Kompany-Saeid, A.; McCague, R.; Olivo, H. F.; Roberts, S. M.; Willets, A. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3431–3439; (b) Baeckström, P.; Okecha, S.; De Silva, N.; Wijekoon, D.; Noria, T. *Acta. Chem. Scand. B* **1982**, *36*, 31–36; (c) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682–685.
15. Dounay, A. B.; Urbanek, R. A.; Frydrychowski, V. A.; Forsyth, C. J. *J. Org. Chem.* **2001**, *66*, 925–938.
16. TASF: tris-(dimethylamino)sulfonium difluorotrimethylsilicate, $(Me_2N)_3$–$S^+F_2SiMe_3^-$.
17. Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436–6437.
18. Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7–9.