Tetrahedron Letters 50 (2009) 1787–1790

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Access to the core structure of aurisides by a ring-closing metathesis/transannular ketalisation sequence

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ARTICLE INFO

Article history:
Received 3 December 2008
Revised 21 January 2009
Accepted 28 January 2009
Available online 1 February 2009

Keywords:
Transannular cyclization
Metathesis
RCM
Macrolactones
Tetrahydropyrans
Reduction of epoxy ketones
Auriside

ABSTRACT

A short access to the macrocyclic structure of aurisides has been achieved by combining a ring-closing metathesis leading first to a 14-membered ring and a subsequent transannular ketalisation to build the tetrahydropyran subunit.

Aurisides A and B, respectively **1** and **2**, have been isolated in 1996 from the sea hare *Dolabella auricularia* and their structures elucidated by extensive NMR studies (Fig. 1).[1]

Structurally, these two macrolides differ from the sugar residue R_1 or R_2 attached on carbon 5. As other secondary metabolites as dolastatin 19 **3** identified from the same natural source,[2] they present very promising and important biological activities. Aurisides **1** and **2** are cytotoxic against HeLa S_3 cells with IC_{50} values of 0.17 and 1.2 μg/mL respectively. Unfortunately, all these compounds are obtained in very low quantities; for example, only 0.8 mg of **1** was isolated from 278 kg of the wet marine organism. Therefore, intense efforts have been made to prepare these compounds and analogues. Two years after the identification of aurisides, the Yamada group confirmed the structure of the aglycon moiety by synthesis.[3] Since 2005, two total syntheses of both aurisides A and B appeared in the literature. Paterson et al. reported the first total synthesis based on highly stereoselective aldolisations.[4] Shortly after, Kigoshi and Yamada groups published jointly a second synthesis by using (*R*)-pantolactone as chiron.[5] Olivo et al. made intensive research in the auriside area culminating recently by a formal synthesis of the aglycon part.[6] Interestingly, in all these approaches, the formation of the 14-membered lactone was accomplished by a Yamaguchi type macrocyclisation.[7] Recently, Hoye

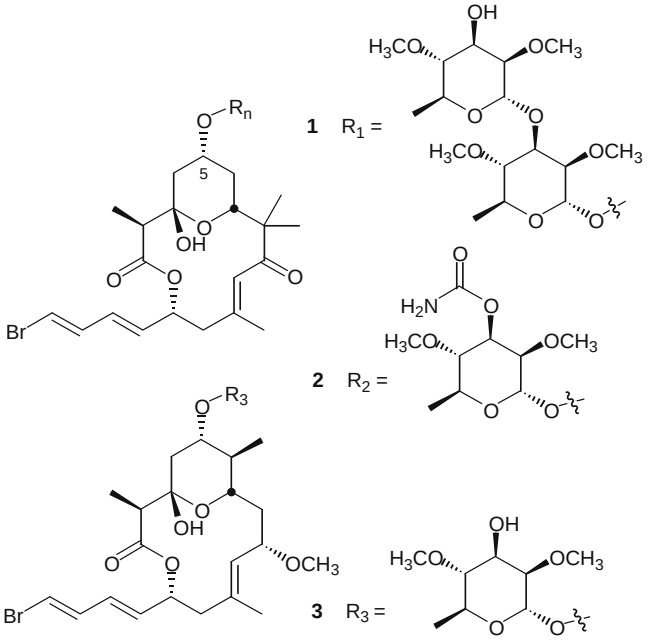

Figure 1. Structure of aurisides and dolastatin **19**.

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doi:10.1016/j.tetlet.2009.01.139

et al. reported a very elegant access to the core structure of similar macrolactones by a tandem macrocyclization/hemiketal formation from readily available dioxinones.[8]

In connection with studies devoted to the synthesis of aurisides and analogues, we have investigated the access to the macrolide core structure according to an original disconnection as disclosed in Scheme 1. We envisioned the formation of the 14-membered ring by a ring-closing metathesis[9–11] of an unsaturated β-hydroxyester followed after few functional modifications by a subsequent transannular ketalisation (Scheme 1).[12] While ring-closing metathesis has been widely applied for the synthesis of macrocycles since the discovery of efficient catalysts, few related cyclizations have been combined with transannular reactions.[13,14]

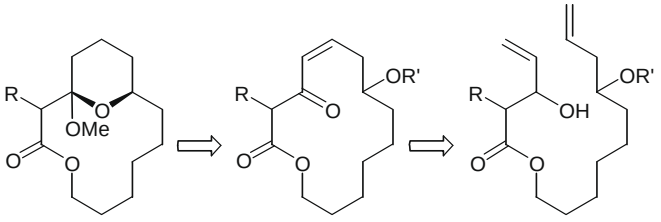
The required substrates for our studies were easily prepared from 1,7-heptanediol. After monoesterification with acetyl or propionyl chloride, the alcohol was oxidized with PCC into the corresponding aldehydes. Allylation and protection of the hydroxyl group by a silyl residue delivered unsaturated esters **6a–b** in good overall yield. A carefully made aldolisation[15] with acrolein led to the required β-hydroxyesters **7a–b** (see Scheme 2).

Ring-closing metathesis was performed in the presence of a catalytic amount of second generation Grubbs catalyst (2.5 mol %) and under high dilution conditions to prevent oligomerizations (Scheme 3). The reactions occurred nicely in term of yields and selectivities; the *E* configuration was assigned to the newly created double bond by measurement of the *J* coupling value (15.5 Hz) between the two olefinic protons. This selectivity in favour of the *E* isomer has been already reported in the literature for the formation of parent structures.[10a] Oxydation of allylic alcohols **8** occurred nicely with Dess Martin periodinane while other reagents tested were less efficient. Hydrogenation in methanol and under moderate acidic conditions allowed the reduction of the C=C bond, the cleavage of the silyl ether and a subsequent transannular ketalisation. This three step sequence furnished macrolides **10** in good overall yields.

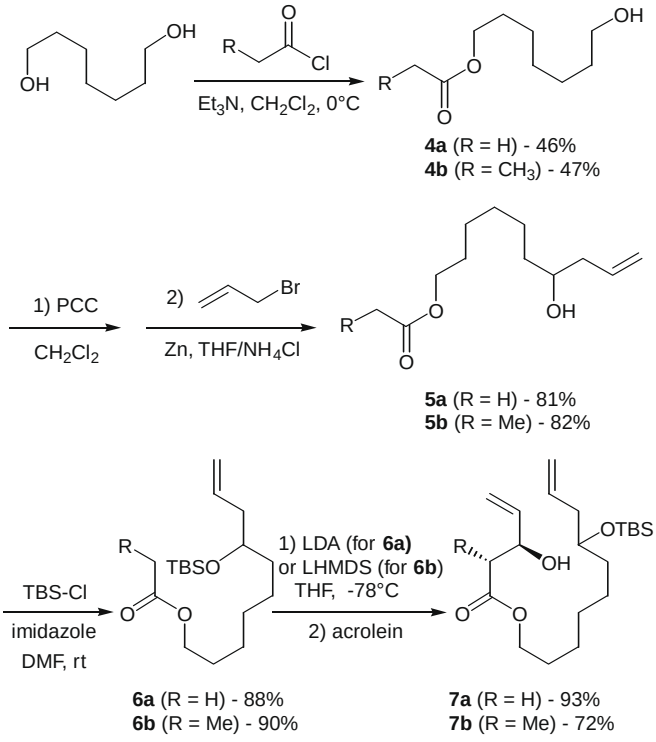
The relative configuration of the two substituents attached on carbon 3 and 7 of the oxa-ring was unambiguously attributed after NOE experiments performed on compound **10a** (Fig. 2). Based on these results, this relative configuration was also assigned to the parent compound **10b** which was isolated as a 1:1 mixture of stereoisomers.

In order to obtain a closer core structure of the aurisides, we decided before the crucial ketalisation step, to take advantage of the allylic alcohol subunit to introduce at the expected position the hydroxyl group present on the target molecules (Scheme 4). Compound **8a** was then diastereoselectively epoxided[16] with *t*-BuOOH/VO(acac)$_2$ while the corresponding epoxy alcohol **11** was smoothly oxidized with Dess–Martin periodinane. The reduction of the epoxyketone with sodium phenylselenolate gave the corresponding β-aldol **13**.[17]

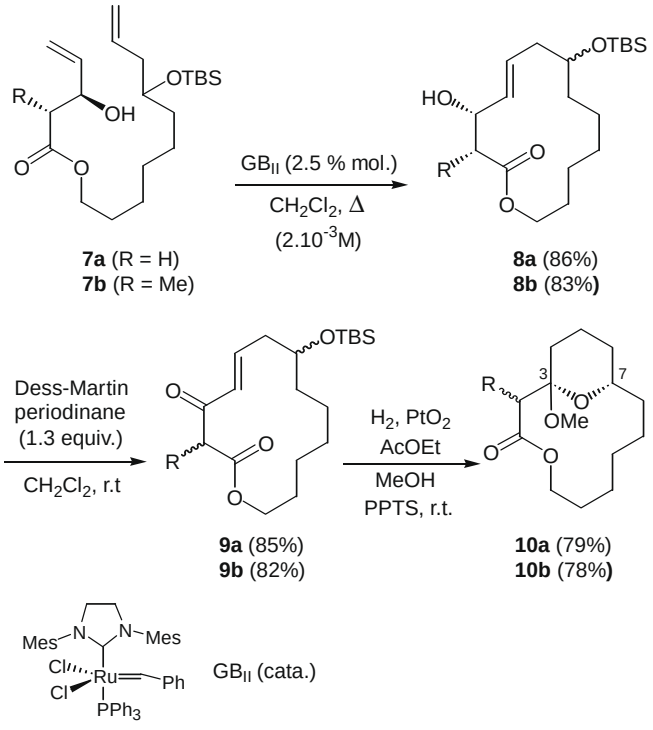
The deprotection of the silylether was achieved by treatment with catalytic amounts of CSA in MeOH[18] and was followed by the in situ formation of the tetrahydropyran ring.[19] Fortunately,



Scheme 1. Retrosynthetic analysis.



Scheme 2. Preparation of substrates **7a–b**.



Scheme 3. Three-step synthesis of macrolactones **10a–b**.

the 1:1 mixture of the two macrolides **14** and **14′** was separated after carefully made chromatography on silica. They differ themselves by the relative configuration on center C-5 bearing the hydroxy group. NOESY studies revealed for both compounds the same relative configuration between C3 and C7 as observed for lac-

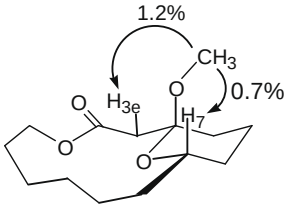
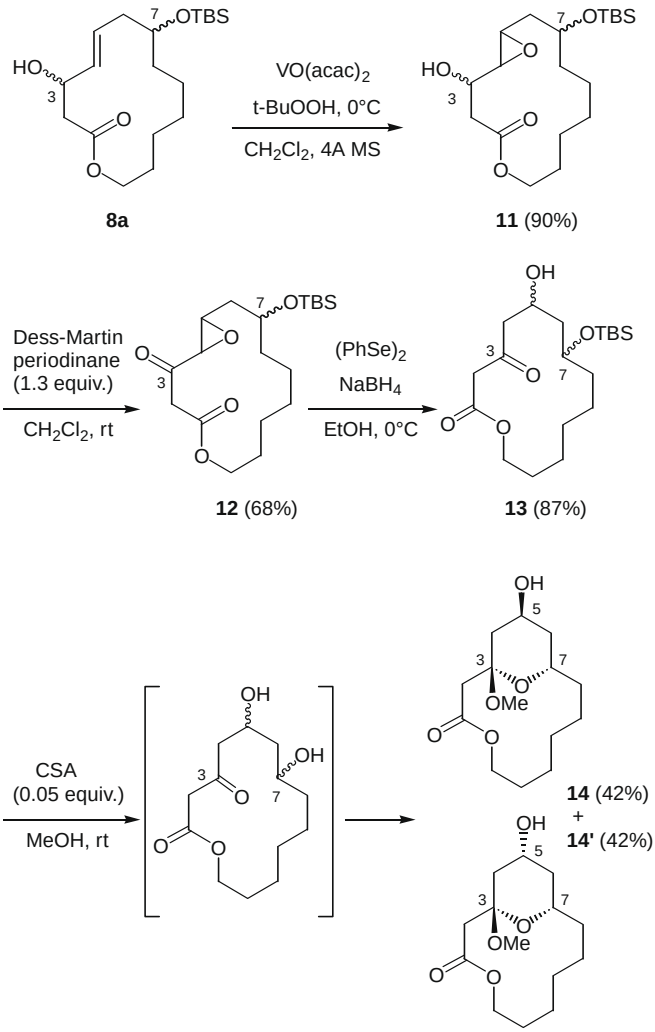


Figure 2. NOE experiments on compound **10a**.



Scheme 4. Synthesis of 5-hydroxymacrolactones **14** and **14′**.

tone **10a**. Further investigations performed also on the acetate derived from **14′** confirm this attribution.

In conclusion, we have developed a short access to the core structure of aurisides and related marine macrolides. Work is now in progress to apply this strategy to the total synthesis of auriside A and will be reported in due course.

Acknowledgments

E.B. thanks the 'Ministère de l'Education Nationale, de la Recherche et de la Technologie' for a doctoral fellowship. This work was partly supported by European Union FP6 Integrated Project No. 503467 on protein kinases.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.139.

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19. *Data for selected compounds*: Compound **7a** (1:1 mixture of dia-stereoisomers): ^{1}H NMR ($CDCl_3$): δ 0.04 (6H, s), 0.88 (9H, s), 1.27–1.41 (8H, m), 1.60–1.64 (2H, m), 2.20 (2H, dd, J = 7.0, 6.8 Hz), 2.47–2.64 (2H, m), 3.67 (1H, quint, J = 5.5 Hz), 4.11 (2H, t, J = 6.8 Hz), 4.49–4.55 (1H, m), 5.00–5.05 (2H, m), 5.17 (1H, dd, J = 10.5, 1.3 Hz), 5.32 (1H, dd, J = 17.3, 1.3 Hz), 5.74–5.94 (2H, m). IR (neat): ν = 1738 cm^{-1}. MS: (ESI) m/z = 407.3 (M+Na$^+$, 100). HRMS: (ESI) Found: 407.2594 (M+Na$^+$); calcd for $C_{21}H_{40}O_4SiNa$: 407.2594. Compound **9a**: ^{1}H NMR ($CDCl_3$): δ 0.06 (3H, s), 0.07 (3H, s), 0.89 (9H, s), 1.22–1.63 (10H, m), 2.33–2.44 (2H, m), 3.53 (2H, s), 3.77–3.84 (1H, m), 4.12 (1H, ddd, J = 10.6, 7.4, 3.2 Hz), 4.27 (1H, ddd, J = 10.6, 7.4, 2.9 Hz), 6.26 (1H, d, J = 15.7 Hz, H_4), 6.93 (1H, dt, J = 15.7, 7.5 Hz, H_5). ^{13}C NMR: δ −4.6 ($2CH_3$), 18.1 (C), 21.7 (CH_2), 23.4 (CH_3), 25.9 ($2CH_3$), 26.0 (CH_2), 27.9 (CH_2), 34.0 (CH_2), 40.2 (CH_2), 48.8 (CH_2), 65.3 (CH_2), 70.1 (CH), 130.8 (CH), 145.8 (CH), 167.3 (C=O), 191.2 (C=O). IR: ν = 1739, 1698, 1633 cm^{-1}. MS: (ESI) m/z = 377.2 (M+Na$^+$, 100), 731.2 (2M+Na$^+$, 86). HRMS: (ESI) 377.2124 (M+Na$^+$); calcd for $C_{19}H_{34}O_4SiNa$: 377.2124. Compound **10a**: ^{1}H NMR (acetone-d_6): δ 1.16–1.97 (16 H, m), 2.80 (1H, d, J = 10.2 Hz), 2.88 (1H, d, J = 11.7 Hz), 3.21 (3H, s), 3.65–3.76 (2H, m), 4.53 (1H, ddd, J = 11.0, 9.9, 3.9 Hz). ^{13}C NMR (acetone-d_6): δ 19.8 (CH_2), 23.6 (CH_2), 23.7 (CH_2), 26.8 (CH_2), 27.3 (CH_2), 28.3 (CH_2), 31.9 (CH_2), 32.8 (CH_2), 42.8 (CH_2), 48.0 (OCH_3), 63.5 (CH_2), 72.0 (CH), 99.5 (C), 170.7 (C=O). IR: ν = 1732 cm^{-1}. MS: (ESI) m/z = 279.1 (M+Na$^+$, 100). HRMS: (ESI) 279.1571 (M+Na$^+$); calcd for $C_{14}H_{24}O_4Na$: 279.1572. Compound **10b** (1:1 mixture of two epimers): ^{1}H NMR ($CDCl_3$): δ 1.06 (1.5H, d, J = 7.2 Hz), 1.17 (1.5H, d, J = 7.2 Hz), 1.26–1.91 (16H, m), 2.67 (0.5H, q, J = 7.2 Hz) and 2.95 (0.5H, q, J = 7.2 Hz), 3.18 (1.5H, s) and 3.33 (1.5H, s,), 3.68–3.92 (2H, m), 4.59–4.70 (1H, m). ^{13}C NMR ($CDCl_3$): δ 11.2 (CH_3), 11.9 (CH_3), [18.8, 19.1, 22.4, 22.8, 22.9, 23.0, 25.5, 26.4, 26.5, 26.7, 27.0, 27.1] (2×6 CH_2), 30.1 and 31.1 (CH_2), 33.0 and 34.7 (CH_2), 43.6 and 47.1 (CH), 49.8 and 50.0 (OCH_3), 62.8 and 64.2 (CH_2), 71.1, and 72.3 (CH), 100.0 and 100.7 (C), 174.6 and 175.2 (C=O). IR: ν = 1732 cm^{-1}. MS: (ESI) m/z = 293.1 (M+Na$^+$, 100). HRMS: (ESI) 293.1726 (M+Na$^{+)}$; calcd for $C_{15}H_{26}O_4Na$: 293.1729. Compound **14**: ^{1}H NMR (C_6D_6, 500 MHz): δ 1.03–1.46 (9H, m), 1.52–1.64 (2H, m), 1.77–1.81 (2H, m), 1.90 (1H, d, J = 11.7 Hz, H_2), 2.32 (1H, dd, J = 14.5, 3.5 Hz, H_4), 2.65 (1H, d, J = 11.7 Hz, H_2), 2.79 (3H, s), 3.53 (1H, dt, J = 11.4, 4.4 Hz), 3.74 (1H, –OH); 3.89 (1H, ddd, J = 12.0, 6.0, 3.2 Hz, H_7); 4.01–4.02 (1H, m, H_5), 4.63 (1 H, dt, J = 3.2, 11.0 Hz, H_{13}). ^{13}C NMR ($CDCl_3$): δ 22.6, 22.7, 26.0, 26.4, 29.9, 34.2, 37.2 (7 CH_2); 42.2 (CH_2, C_2); 47.8 (OCH_3); 63.6 (CH_2); 64.9 (CH, C_5); 65.7 (CH, C_7); 100.5 (C_{IV}, C_3); 170.2 (C=O, C_1). IR: ν = 1728 cm^{-1}. Compound **14′**: ^{1}H NMR (C_6D_6, 500 MHz): δ 1.23–1.44 (7H, m); 1.50–1.65 (4H, m); 1.78–1.87 (1H, m), 2.04–2.09 (3H, m, H_2 and H_4), 2.80 (1H, d, J = 11.7 Hz, H_2), 2.92 (3H, s, OCH_3), 3.46–3.50 (1H, m, H_7); 3.60 (1H, dt, J = 11.1, 4.7 Hz, H_{13}), 4.00–4.05 (1H, m, H_5), 4.64 (1H, dt, J = 3.4, 10.4 Hz, H_{13}). ^{13}C NMR ($CDCl_3$): δ 22.7 (CH_2), 22.8 (CH_2), 25.7 (CH_2), 26.4 (CH_2), 30.0 (CH_2), 37.3 (CH_2), 41.7 (CH_2), 42.1 (CH_2), 47.9 (OCH_3), 63.4 (CH_2); 65.1 (CH); 70.0 (CH); 100.0 (C); 170.4 (C=O). MS: (ESI) m/z = 295.2 (M+Na$^+$, 100). HRMS: (ESI) 295.1521 (M+Na$^+$); calcd for $C_{14}H_{24}O_5Na$: 295.1521.