SYNTHETIC STUDIES ON TULEARIN MACROLIDES

M.Montserrat Martínez, Luis A. Sarandeses, José Pérez Sestelo

Departamento de Química Fundamental, Universidade da Coruña, E-15071
A Coruña, Spain
E-mail: mmartinezc@udc.es

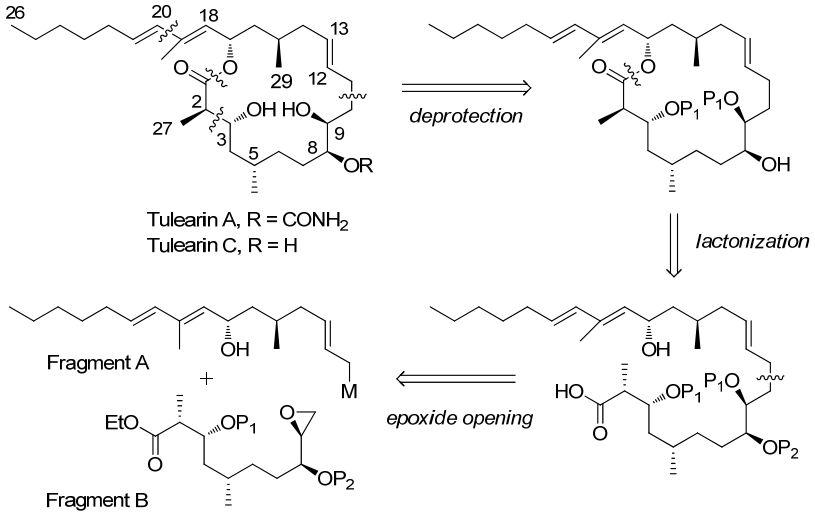
■ ABSTRACT

In this communication we present our initial synthetic studies to the natural product tulearin A. The total synthesis relies on the assembly of two chiral building blocks through regioselective nucleophilic epoxide opening and macrolactonization for the construction of 18-membered lactone skeleton. In this initial contribution we report the partial synthesis of the fragment C_1-C_7 containing three stereogenic centers where the key step is an asymmetric aldol condensation.

■ INTRODUCTION

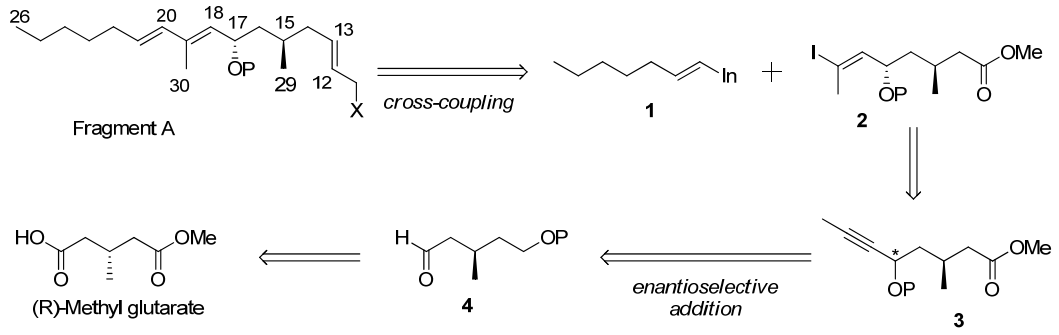
Tulearin A is a marine natural product, isolated from a sponge *Fascaplysinopsis* by Kashman et al. in 2008,[1] that exhibits potent antiproliferative activity against human leukemic cell lines K562 and UT7. The structure was elucidated by interpretation of MS and 1D and 2D NMR spectroscopic analysis, although the stereochemistry remained unknown until 2009.[2] From a structural point of view, tulearin A is a macrolide forming an 18-membered lactone with seven stereogenic centers and functionalized with two hydroxyl groups (on C_3 and C_9), a carbamate moiety (on C_8) and a *E*,*E* defined diene (on C_{18} and C_{20}).

The synthesis of tulearin A represents a considerable synthetic challenge that have attracted the attention of research groups. However, only the synthesis of one stereoisomer of tulearin A[3] and tulearin C, a non-natural isomer, has been synthetized.[4] In this communication we present our synthetic strategy and the initial studies towards tulearin A. The total synthesis was envisaged following the retrosynthetic analysis shown in the figure bellow. The strategy was based in the construction of the 18-membered lactone skeleton between the union of the fragment A (C_{13}-C_{26}) and fragment B (C_1-C_{10}) by a regioselective nucleophilic ring-epoxide opening and lactonization as the key steps.



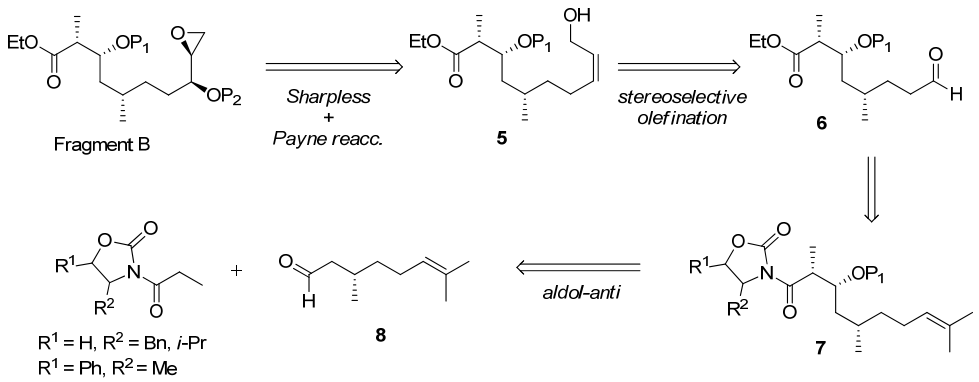
Scheme 1. Retrosynthetic analysis for Tulearins.

The fragment A (C_{13}-C_{26}) possessing two stereogenic centers and a *E*,*E*-diene was envisaged by palladium-catalyzed cross-coupling reaction using the alkenylindium organometallic **1** and vinyl iodide **2** (Scheme 2).[5] The enantioselective synthesis vinyl iodide **2** was devised using commercial (*R*)-methyl glutarate as chiral building block. The versatility of the strategy should allow the synthesis of the four possible stereoisomers.



Scheme 2. Retrosynthetic plan of fragment A.

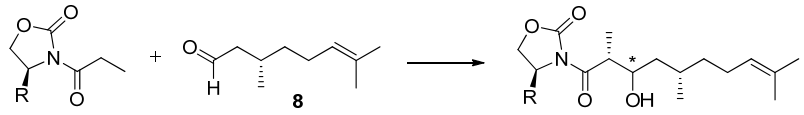
To construct the fragment B (C_1-C_{10}) with five stereogenic centers we planned an asymmetric aldol reaction starting from available (*S*)-citronellal using a chiral oxazolidinone for generation of the stereocenters at C_2 and C_3 (Scheme 3). A stereoselective olefination followed by reduction should lead the allylic alcohol **5**. Finally, the stereocenters at C_8 and C_9 of fragment B would come from an asymmetric epoxidation followed by a Payne rearrangement starting from allylic acohol **5**.



Scheme 3. Retrosynthetic plan of fragment B.

■ RESULTS AND DISCUSSION

The synthesis of fragment B began with an asymmetric aldol reaction using the readily available (*S*)-citronellal and *N*-acyloxazolidinone. Initially, we explored the reactivity of different oxazolidinones with (*S*)-citrollenal (**8**) to obtain the *anti*-aldol product **7b**. Unfortunately, under several reactions conditions the *anti*-aldol product **7b** was obtained only in very low yields (entries 1-3, table 1) and isopulegone (byproduct from a acid-catalyzed rearrangement) was obtained as major reaction product. For this reason we decided to optimize the synthesis of **7a-*syn*** to later convert it into **7b-*anti***. In this research, the reaction of chiral oxazolidinone furnished with a benzyl group with 8 using $TiCl_4$, (–)-sparteine and *N*-methylpyrrolidine (table 1, entry 7) afforded the *syn*-aldol product **7a** in 97% yield as the only diastereoisomer detected by ^1H NMR (97% yield, *dr* = 95:5).[6]



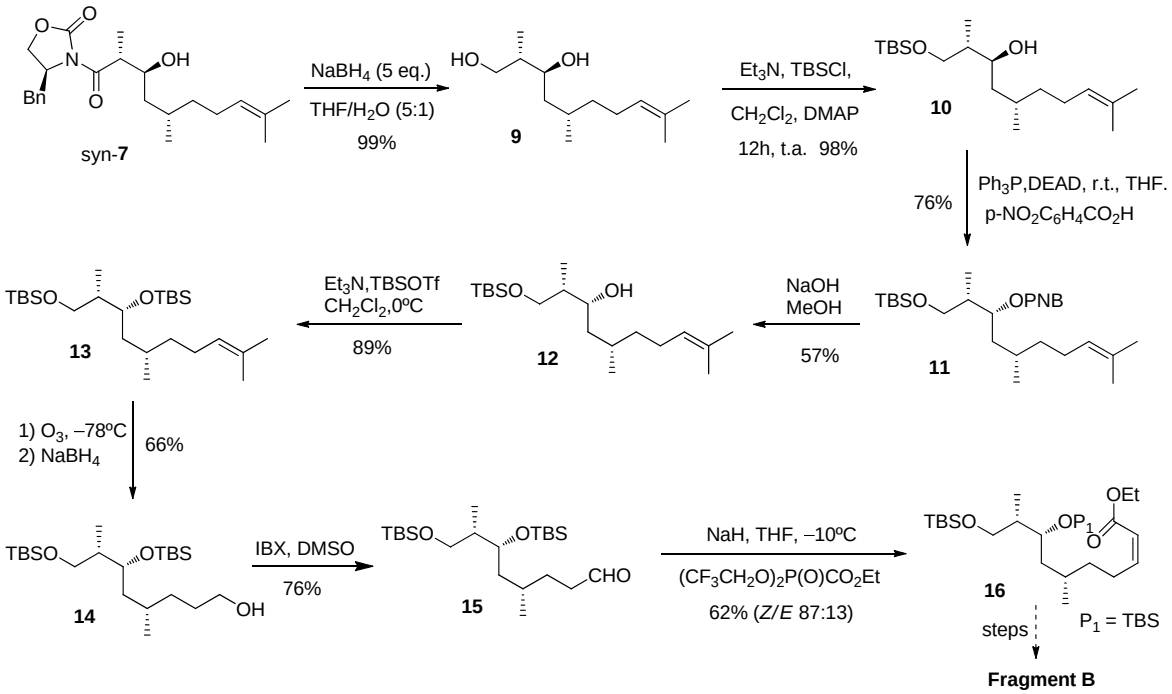
Entry	R	Reagent (eq.)	Amine (eq.)	Aditive (eq.)	T[a]	t (h)	Product	Yield (%)
1	*i*-Pr	*n*-Bu_2BOTf (1.1)	Et_3N (1.2)	Et_2AlCl (3.0)	0–78ºC	12		–
2	*i*-Pr	*n*-Bu_2BOTf (1.1)	*i*-Pr_2NEt (1.5)	Et_2AlCl (3.0)	0–78ºC	12	**7b**	40[a]
3	*i*-Pr	*c*-HexBOTf (1.2)	Et_3N (1.5)	none	0–78ºC	12		–
4	Bn	*n*-Bu_2BOTf (1.1)	Et_3N (1.5)	*none*	0ºC	2	**7a**	24
5	*i*-Pr	$TiCl_4$ (1.0)	(–)-sp (2.5)	none	0ºC	1	**7a**	72
6	Bn	$TiCl_4$ (1.0)	(–)-sp (2.5)	none	0ºC	1	**7a**	95
7	Bn	$TiCl_4$ (1.0)	(–)-sp (1.1)	*N*-Metylpyrroline (1.1)	0ºC	1	**7a**	97

[a]. The byproduct isopulegone was also obtained.

Table 1. Synthesis of compound **7** by asymmetric aldol reaction.

According to our synthetic plan, the reduction of oxazolidinone moiety with NaH and protection of primary alcohol as TBSether gave **10** in good yield (97%, two steps). The inversion of configuration under Mitsunobu conditition's using of DIAD, PH_3P and 4-NBA in THF at room temperature provided **11** in 76% yield. After hydrolysis with NaOH, the *p*-

nitrobenzoate ester **11** was converted to alcohol **12** (57% yield). Protection of **12** as TBSether (**13**) and reductive ozonolysis gave alcohol **14** in 66% overall yield. Then, careful oxidation of alcohol **14** by using IBX in DMSO led the aldehyde **15** in good yield. Finally, the stereoselective olefination of **15** under Still-Gennari conditions (NaH in THF at −10 ºC followed by addition of $CF_3CH_2O)_2P(O)CO_2Et$) provided α,β-unsaturated ester **16** in 62% as a separable mixture of olefins (*Z*/*E* 87:13).



Scheme 4. Synthetic studies on fragment B.

In this way the C1-C7 piece of tulearin containing three stereogenic centers of tulearin was synthetized. Now, for the synthesis of fragment B only remains: (i) reduction of α,β-unsaturated ester (ii) asymmetric epoxidation followed by Payne rearrangement to generate the chiral centers at C_8 and C_9 (iii) protection of secundary alcohol (iv) deprotection of primary alcohol followed by oxidation and esterification to the corresponding ester.

■ EXPERIMENTAL PROCEDURE

Synthesis of 7a-*syn*. A solution of the *N*-acyloxazolidinone (1.0 g, 4.29 mmol) in 30 mL of CH_2Cl_2 was cooled to 0ºC. $TiCl_4$ (4.5 mL, 4.5 mmol) was added, and the mixture was stirred for 5 minutes. (−)-Sparteine (0.98 mL, 4.28 mmol) was added dropwise slowly. After complete addition, the mixture was stirred at 0 ºC for 20 minutes. The mixture was cooled to −78ºC and *N*-methyl-2-pyrrolidinone (0.42 mL, 4.28 mmol) was added. The mixture was stirred for 10 minutes followed by addition of (*S*)-citronellal (0.85 mL, 4.71 mmol) in 5 mL of CH_2Cl_2 dropwise. The mixture was stirred 1h at −78ºC, gradually warmed to 0ºC, and stirred for 1h. The reaction was quenched with half-saturated NH_4Cl

and warmed to 25ºC. The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuum. Purification by flash chromatography (1:1 Hexanes/Et_2O) afforded, after concentration and high-vacuum drying, 1.60 g (97%) of **7a-*syn*** product.

^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm: 0.90 (d, *J* = 7.1 Hz, 3H), 1.02–1.24 (m, 1H), 1.27 (d, *J* = 7.5Hz, 3H), 1.39–1.62 (m, 4H), 1.62 (s, 3H), 1.69 (s, 3H), 1.93–2.05 (m, 2H), 2.81 (dd, *J* = 9.5 Hz, 1H), 2.89 (broad s, 1H), 3.26 (dd, *J* = 3.2 Hz, 1H), 3.73 (q, *J* = 7.1, 2.5 Hz, 1H), 4.08–4.11 (m, 1H), 4.19–4.26 (m, 2H), 4.70–4.4.74 (m, 1H), 5.11 (t, *J* = 1.4 Hz, 1H), 7.21–7.37 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ/ppm: 10.3 (CH_3), 17.7 (CH), 20.7 (CH_3), 25.4 (CH_2), 25.7 (CH_3), 29.2 (CH_3), 36.6 (CH_2), 37.8 (CH_2), 41.1 (CH_2), 42.1 (CH), 55.1 (CH), 66.2 (CH_2), 69.3 (CH), 124.8 (CH), 127.5 (CH), 129.0 (2 × CH), 129.4 (2 × CH), 131.2 (C), 135.0 (C), 153.0 (C), 177.7 (C).

HRMS (ESITOF): calcd.: 388.2482 for $C_{23}H_{34}NO_4$ $[M + H]^+$; found:388.2481.

Synthesis of 13. To alcohol **12** (1.03 g, 3.13 mmol) in 20 mL of anhydrous CH_2Cl_2 at 0ºC, was added Et_3N (650 μL, 4.7 mmol) followed by TBSOTf (1.1 mL, 4.7 mmol). The resultant mixture was stirred for 30 minutes. The reaction was quenched by the addition of H_2O and warmed to 25ºC. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered and concentrated in vacuum. Purification by flash chromatography (Hexanes) afforded, after concentration and high-vacuum drying, 1.23 g (89%) of **13**.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.06 (s, 6H), 0.09 (s, 6H), 0.74–1.02 (m, 28H), 1.28–1.30 (m, 2H), 1.60 (s, 3H), 1.70 (s, 3H), 1.78–2.08 (m, 2H), 3.32–3.56 (m, 2H), 3.81–3.91 (m, 1H), 5.04–5.15 (m, 1H).

HRMS (ESITOF): calcd.: 444.3743 for $C_{25}H_{55}NO_2Si_2$ $[M + H]^+$; found:444.3740.

Synthesis of 16. A suspension of HNa (43 mg, 1.03 mmol) in 5 mL of dry THF was cooled to −10ºC. A solution of $(CF_3CH_2O)_2P(O)CO_2Et$ (330 μL, 1.0 mmol) was added dropwise and the mixture was stirred for 30 minutes at the same temperature. Aldehyde **15** (36 mg, 0.86 mmol) in 2 mL of THF was added dropwise and the reaction was warmed to 25ºC slowly. The reaction was quenched with saturated NH_4Cl. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2 (20 mL). The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuum. Purification by flash chromatography (Hexanes) afforded, after concentration and high-vacuum drying, 260 mg (62%) of **16**.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.06 (s, 6H), 0.08 (s, 6H), 0.75-0.96 (m, 21H), 1.16–1.35 (m, 10H), 1.59–1.71 (m, 1H), 2.54–2.78 (m, 2H), 3.27–3.65 (m, 3H), 3.80–3.95 (m, 1H), 4.05–4.24 (m, 2H), 5.71 (dt, *J* = 11.5, 1.6 Hz, 1H), 6.13–6.23 (m, 1H).

HRMS (ESITOF): calcd.: 488.3642 for $C_{26}H_{55}O_4Si_2$ $[M + H]^+$; found:488.3644.

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