SYNTHETIC STUDIES ON TULEARIN MACROLIDES

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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 C1-C7 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 C3 and C9), a carbamate moiety (on C8) and a E,E defined diene (on C18 and C20).

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 (C13-C26) and fragment B (C1-C10) by a regioselective nucleophilic ring-epoxide opening and lactonization as the key steps.
The fragment A (C\textsubscript{13}-C\textsubscript{26}) possessing two stereogenic centers and a \textit{E,E}-diene was envisaged by palladium-catalyzed cross-coupling reaction using the alkenylindium organometallic 1 and vinyl iodide 2 (Scheme 2). 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.

To construct the fragment B (C\textsubscript{1}-C\textsubscript{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\textsubscript{2} and C\textsubscript{3} (Scheme 3). A stereoselective olefination followed by reduction should lead the allylic alcohol 5. Finally, the stereocenters at C\textsubscript{8} and C\textsubscript{9} of fragment B would come from an asymmetric epoxidation followed by a Payne rearrangement starting from allylic alcohol 5.
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)-citronellal (8) to obtain the anti-aldol product 7b. Unfortunately, under several reaction conditions the anti-aldol product 7b was obtained only in very low yields (entries 1-3, table 1) and isopulegone (byproduct from an 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 TiCl4, (−)-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).

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

| Entry | R        | Reagent (eq.) | Amine (eq.) | Additive (eq.) | T°C | t(h) | Product Yield (%) |
|-------|----------|---------------|-------------|----------------|-----|------|-------------------|
| 1     | i-Pr     | n-Bu3BOTf (1.1) | Et3N (1.2) | Et3AlCl (3.0) | 0-78 | 12   | -                 |
| 2     | i-Pr     | n-Bu3BOTf (1.1) | i-PrNEt (1.5) | Et3AlCl (3.0) | 0-78 | 12   | 7b 40a             |
| 3     | i-Pr     | n-Bu3BOTf (1.2) | Et3N (1.5) | none           | 0-78 | 12   | -                 |
| 4     | Bn       | n-Bu3BOTf (1.1) | Et3N (1.5) | none           | 0°C  | 2    | 7a 24              |
| 5     | i-Pr     | TiCl4 (1.0)    | (−)-esp (2.5) | none           | 0°C  | 1    | 7a 72              |
| 6     | Bn       | TiCl4 (1.0)    | (−)-esp (2.5) | none           | 0°C  | 1    | 7a 95              |
| 7     | Bn       | TiCl4 (1.0)    | (−)-esp (1.1) | N-Methylpyrrolidine (1.1) | 0°C  | 1 | 7a 97 |

a. The byproduct isopulegone was also obtained.

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 condition’s using of DIAD, PH3P 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 CF₃CH₂O)₂P(O)CO₂Et) 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 synthesized. 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 C₈ and C₉ (iii) protection of secondary 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 CH₂Cl₂ was cooled to 0ºC. TiCl₄ (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 CH₂Cl₂ dropwise. The mixture was stirred 1h at −78ºC, gradually warmed to 0ºC, and stirred for 1h. The reaction was quenched with half-saturated NH₄Cl
and warmed to 25°C. The layers were separated, and the aqueous layer was extracted twice with CH$_2$Cl$_2$. The combined extracts were washed with brine, dried over MgSO$_4$, filtered and concentrated in vacuum. Purification by flash chromatography (1:1 Hexanes/Et$_2$O) afforded, after concentration and high-vacuum drying, 1.60 g (97%) of 7a-syn product.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$/ppm: 0.90 (d, $J = 7.1$ Hz, 3H), 1.02–1.24 (m, 1H), 1.27 (d, $J = 7.5$ Hz, 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$_3$) $\delta$/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 (ESI TOF): 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$_2$Cl$_2$ at 0°C, was added Et$_3$N (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$_2$O and warmed to 25°C. The layers were separated and the aqueous layer was extracted twice with CH$_2$Cl$_2$. 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$_3$) $\delta$/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), 3.32–3.65 (m, 2H), 3.80–3.95 (m, 1H), 5.04–5.15 (m, 1H).

HRMS (ESI TOF): calcd.: 444.3743 for C$_{25}$H$_{55}$NO$_2$Si$_2$ [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 −10°C. A solution of (CF$_3$CH$_2$O)$_2$P(O)(O)CO$_2$Et (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 25°C slowly. The reaction was quenched with saturated NH$_4$Cl. The layers were separated and the aqueous layer was extracted twice with CH$_2$Cl$_2$ (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$_3$) $\delta$/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 (ESI TOF): calcd.: 488.3642 for C$_{26}$H$_{55}$O$_4$Si$_2$ [M + H]+; found: 488.3644.
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