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A Versatile Route to the Tulearin Class of Macrolactones: Synthesis of a Stereoisomer of Tulearin A

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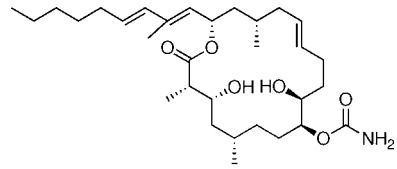
ABSTRACT



stereoisomer of tulearin A

A versatile synthetic approach to the tulearin class of macrolactones has been developed and deployed to make a stereoisomer of tulearin A. The knowledge gained about structure and synthesis will expedite the assignment of the stereostructure of this new anticancer agent.

In 2008, Kashman et al. reported the isolation of tulearin A (**1**) (Figure 1) from the marine sponge Madagascar *Fascaplysinopsis* sp. collected in the Salary Bay north of Tulear.[1a] The structure of **1** was elucidated through interpretation of MS, IR, and various one-dimensional and two-dimensional NMR experiments. However, the relative and absolute stereochemistry of **1** were unknown until recently.[1b] Tulearin A (**1**) exhibited potent antiproliferative activity against human leukemic cell lines K562 and UT7. Activity against K562 cells was notably better; a 0.5 μg/mL solution of **1** inhibited ~60% of proliferation vs 35% inhibition against the UT7 cells.[1a]

Due to its promising biological activity and lack of a three-dimensional structure, we designed a synthetic strategy that was capable of producing any stereoisomer of tulearin A (**1**).

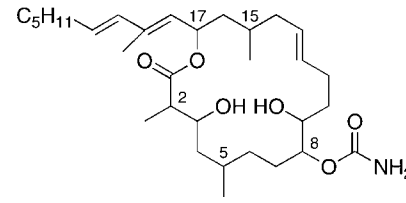


Figure 1. Proposed two-dimensional structure of tulearin A.

These stereoisomers could be used to help assign the stereochemistry and to provide information about the stereostructure/activity relationship. Here, we describe the synthesis of the single stereoisomer of tulearin, compound **2**.

Our retrosynthetic plan was to construct the complete structure through the union of three fragments: stannane **25** (the C20−C26 fragment), an acid of type **I** (the C1−C12 fragment), and vinyl iodide **20** (the C13−C19 fragment) through an esterification, ring-closing metathesis, and Stille coupling (Figure 2).

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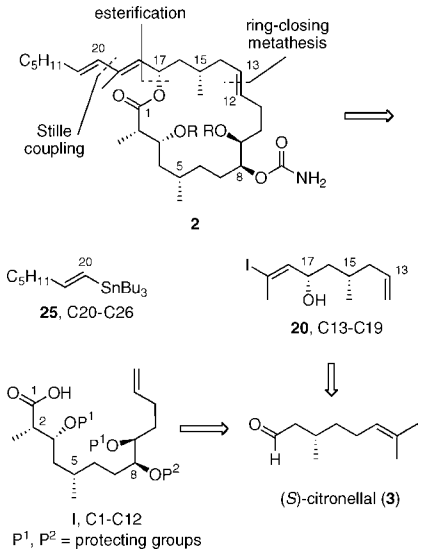


Figure 2. Target stereoisomer **2** and retrosynthetic plan.

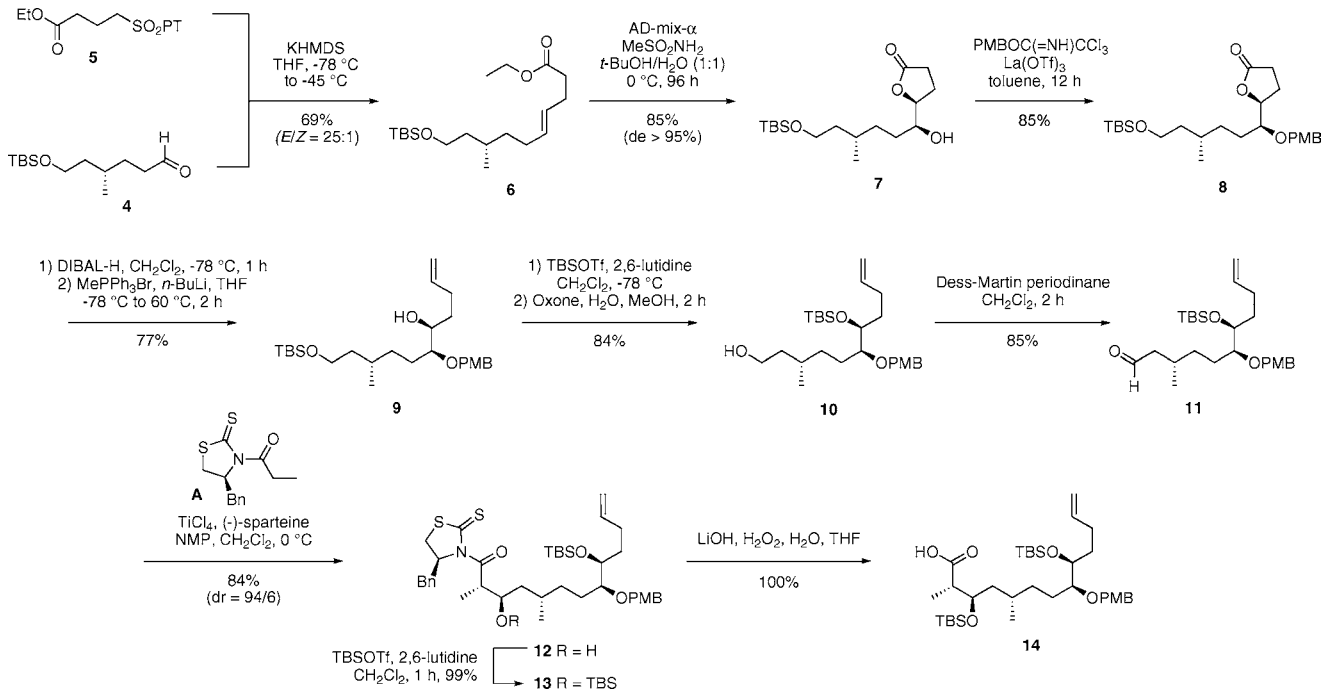
Both acid **I** and iodide **20** originate from readily available (*S*)-citronellal (**3**), which already contains the methyl stereochemistry at C5 and C15. The stereocenters at C2 and C3 come from an asymmetric aldol reaction, while the substituents at C8 and C9 are installed through a Sharpless asymmetric dihydroxylation.

The alcohol at C17 is formed through a Noyori reduction. The carbamate is challenging because the alcohols at C8 and C9 have to be orthogonally protected to allow its installation before the final deprotection. We envisioned that all of the fragments could be adjusted by choice of reagents to give any stereoisomer.

The synthesis of the C1−C12 fragment **I** began with known aldehyde **4**[2] derived from (*S*)-citronellal (Scheme 1). Aldehyde **4** and phenyltetrazolylsulfonyl ester **5** were joined in a Julia−Kociensky reaction[3] (KHMDS, THF, −78 °C to −45 °C, 69%) to provide alkene **6** with excellent *E* selectivity. Sharpless asymmetric dihydroxylation[4] of **6** with AD-mix-α in the presence of methanesulfonamide (*t*-BuOH/H_2O 1:1, 0 °C, 96 h) gave rise to a diol that spontaneously cyclized to form the five-membered lactone **7** exclusively in 85% yield. Thus, the hydroxy groups at C8−C9 (tulearin A numbering) were differentiated, and the C8 group was protected as a *p*-methoxybenzyl ether [PMBOC(═NH)CCl_3, La$(OTf)_3$, toluene, 12 h, 85%] to give lactone **8**. The *p*-methoxybenzyl (PMB) group was chosen because it can later be removed in the presence of silyl protecting groups installed on the hydroxy groups present at C3 and C9.

To cleave the lactone and introduce the double bond for the eventual ring-closing metathesis (RCM), lactone **8** was reduced (DIBAL-H, CH_2Cl_2, −78 °C, 96% yield) and the resulting hemiacetal was treated with the methylphosphonium ylide ($MePPh_3Br$, *n*-BuLi, THF, −78 °C to +60 °C, 2 h, 80%) to give alkene **9**. The liberated hydroxy group at C9 was protected with TBSOTf (2,6-lutidine, CH_2Cl_2, 1 h, 96%), and the primary alcohol was deprotected selectively with Oxone[5] (MeOH, H_2O, 2 h) to yield alcohol **10** (88%). The free alcohol was then oxidized to aldehyde **11** with Dess−Martin periodinane (CH_2Cl_2, 2 h, 85%). To construct the final two stereogenic centers with the carboxylic acid already in place, the versatile Crimmins chiral auxiliary **A**[6] was chosen and conditions were used to provide the *syn*

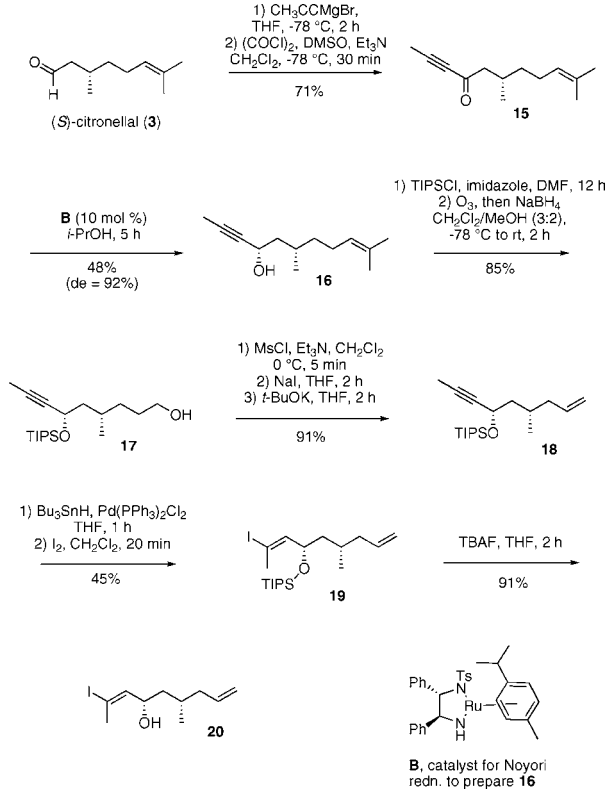
Scheme 1. Synthesis of C1−C12 Fragment **14**



product. Reagent **A** was treated with $TiCl_4$, (−)-sparteine, and *N*-methylpyrrolidinone (CH_2Cl_2, 0 °C) to give an enolate intermediate that was reacted with aldehyde **11** to afford the aldol product **12** in good yield (84%) and with good diastereoselectivity (dr = 94/6). After protection (TBSOTf, 2,6-lutidine, CH_2Cl_2) and saponification[7] (LiOH, H_2O_2, THF), compound **13** was transformed into acid **14** in 99% yield (over the two steps). Thus, the C1−C12 fragment **14** was obtained in 21.7% yield from (*S*)-citronellal (**3**) over 14 steps.

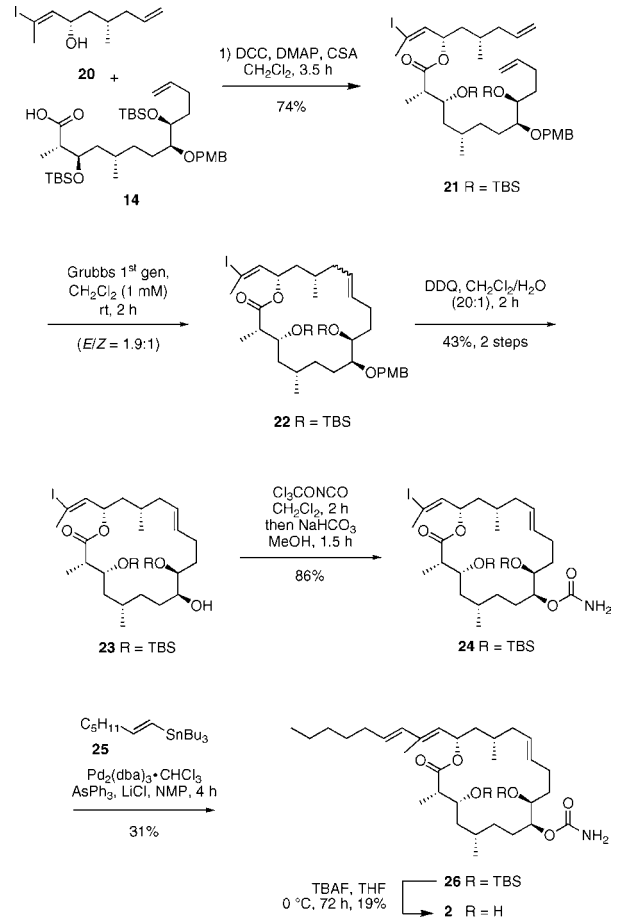
Alcohol **20**, representing the C13−C19 fragment of target **2**, was also prepared from (*S*)-citronellal (**3**) (Scheme 2).

Scheme 2. Synthesis of C13−C19 Fragment **20**



Treatment of **3** with the propynyl Grignard reagent (THF, −78 °C), followed by a Swern oxidation [$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C], afforded ketone **15** in 71% yield over the two steps.

Scheme 3. Endgame for the Synthesis of **2**



Noyori reduction[8] with (*S*,*S*)-Noyori catalyst **B** (10 mol % in *i*-PrOH) gave alcohol **16** in moderate yield (48%).[9] Alcohol **16** was transformed into the alkyne **18**, precursor of **20**, through a facile five-step sequence (Scheme 3). To begin, the hydroxy group in **16** was protected (TIPSCl, imidazole, DMF), and then the double bond was oxidatively cleaved with ozone followed by in situ reduction with $NaBH_4$ (CH_2Cl_2/MeOH (3:2), −78 °C to rt) to give alcohol **17** in 85% yield (two steps). A three-step sequence[10] involving mesylation (MsCl, Et_3N, CH_2Cl_2), iodination (NaI, THF), and elimination (*t*-BuOK, THF) produced alkyne **18** in good yield (91%). Finally, the alkyne was converted to the desired vinyl iodide **19** through the (*E*)-selective hydrostannylation (Bu_3SnH, $Pd(PPh_3)_2Cl_2$, THF), followed by tin−iodine exchange with iodine (I_2, CH_2Cl_2, 45% yield).[11] Deprotection of the C17 hydroxy group proceeded smoothly to furnish iodide **20** (TBAF, THF) in 72% yield. Thus, the C13−C19 fragment **20** was obtained in 10.6% yield from (*S*)-citronellal (**3**) over 11 steps.

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(4) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M. *J. Org. Chem.* **1992**, *57*, 2768–2771.

(5) Sabitha, G.; Syamala, M.; Yadav, J. S. *Org. Lett.* **1999**, *1*, 1701–1703.

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(7) Crimmins, M. T.; Slade, D. J. *Org. Lett.* **2006**, *8*, 2191–2194.

(8) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739. Selectivity was confirmed by formation of a MPA-ester and ^1H NMR analysis. See: Seco, J. M.; Quiñoa, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17–118.

(9) Catalyst **B** (1%) gave **16** in only 10% yield. A high catalyst loading was used, however some starting material could still be recovered from this reaction (39%).

(10) Tu, Y. Q.; Hübener, A.; Zhang, H.; Moore, C. J.; Fletcher, M. T.; Hayes, P.; Dettner, K.; Francke, W.; McErlean, C. S. P.; Kitching, W. *Synthesis* **2000**, 1956–1978.

(11) Marshall, J. A.; Bourbeau, M. P. *J. Org. Chem.* **2002**, *67*, 2751–2754.

With both major fragments **14** and **20** in hand, the fragment couplings were undertaken. Several avenues were explored, and we present in Scheme 3 the optimum strategy for both yield and RCM (*E*) to (*Z*) selectivity. Coupling of acid **14** with alcohol **20** (DCC, DMAP, CSA, CH_2Cl_2)[12] produced ester **21** in 74% yield. The RCM with Grubbs' first-generation metathesis catalyst gave macrocyclic lactone **22** as a 1.9:1 (*E*/*Z*) mixture.[13] Without separation, **22** was deprotected with DDQ[14] (CH_2Cl_2/H_2O 20/1, rt). A single flash chromatography purification on silica gel gave (*E*)-macrocycle **23** in 43% yield (over two steps). The free C8 hydroxy group was converted to the carbamate using a milder base that had been described[15] (Cl_3CONCO, CH_2Cl_2, then $NaHCO_3$, MeOH) to afford macrocycle **24** in 86% yield. The Stille coupling with the easily prepared stannane **25**, based on conditions reported by Marshall et al.[16] [$Pd_2(dba)_3$·$CHCl_3$, $AsPh_3$, LiCl, NMP], proceeded in moderate yield (31%) to provide compound **26**. Finally, the latter was deprotected with TBAF at 0 °C to minimize basic saponification of the carbamate moiety,[17] and compound **2**[18] was recovered after HPLC purification.[19]

Analysis of the α_D data and ^1H and ^{13}C NMR spectra of **2** showed that it was a stereoisomer of tulearin A. The J^3 coupling constant between H_2 and H_3 was significantly smaller in the spectrum of the natural product (2.9 Hz) than in isomer **2** (6.9 Hz) (the natural product has the 1,2-*anti* configuration).[1b] Other resonances in the ^1H NMR spectrum of compound **2** tended to be similar to those of the natural product in both chemical shifts and coupling constants, but because the stereocenters of tulearin are somewhat isolated from each other, further conclusions about stereochemistry were premature.[1b]

In summary, a stereoisomer of tulearin A, compound **2**, has been prepared in 0.34% overall yield from (*S*)-citronellal (20 steps for the longest linear sequence) in a total of 32 steps. The synthesis takes into account stereochemical flexibility, so the work paves the way to make other isomers and analogues of tulearin in an expeditious fashion.

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Supporting Information Available: Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Other catalysts such as Grubbs second-generation and Hoveyda–Grubbs second-generation were unreactive or, when forced, produced byproducts. Understanding that protecting groups can also alter the outcome of methatheses, alternately protected compounds were tried with all of the catalysts but gave poorer selectivities and yields. See: Yamamoto, K.; Biswas, K.; Gaul, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2003**, *44*, 3297–3299.

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(16) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **2002**, *67*, 733–740.

(17) Under the conditions used for the deprotection step, two byproducts were formed: one appeared to be the macrocyclic lactone wherein the carbamate was cleaved and the other compound corresponds to an allylic rearrangement of the macrocycle producing a 22-membered ring lactone.

(18) Compound **2**: $R_f \sim 0.21$ (Hex/EtOAc 1/4); $[\alpha]^{20}_D = +13$ ($c = 0.04$, $CHCl_3$); IR 3361, 2950, 2923, 1707, 1604, 1456, 1394, 1380, 1325, 1250, 1066, 1040, 968, 935 cm^{-1}; ^1H NMR (600 MHz, $(CD_3)_2CO$) δ 6.09 (d, $J = 15.5$ Hz, 1H), 5.77 (dt, $J = 15.5$ and 7.0 Hz, 1H), 5.72 (br s, 2H), 5.60 (td, $J = 9.3$ and 5.2 Hz, 1H), 5.49 (dt, $J = 15.2$ and 6.5 Hz, 1H), 5.43 (dt, $J = 15.3$ and 6.8 Hz, 1H), 5.23 (d, $J = 9.3$ Hz, 1H), 4.58 (dt, $J = 6.5$ and 5.1 Hz, 1H), 3.81 (m, 1H), 3.67 (m, 1H), 3.61 (d, $J = 6.8$ Hz, 1H), 3.52 (d, $J = 6.2$ Hz, 1H), 2.44 (p_{app}, $J = 6.9$ Hz, 1H), 2.22−1.96 (m, 6H), 1.86 (d, $J = 1.1$ Hz, 3H), 1.72−1.34 (m, 11H) 1.31 (m, 7H), 1.12 (d, $J = 7.0$ Hz, 3H), 0.95 (d, $J = 6.3$ Hz, 3H), 0.92 (d, $J = 6.7$ Hz, 3H), 0.88 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 174.2, 158.0, 138.3, 134.9, 132.6, 131.5, 129.5, 129.0, 77.5, 70.9, 70.7, 70.7, 47.6, 42.5, 41.2, 40.8, 33.9, 33.5, 33.4, 32.2, 30.1, 30.0, 30.0, 29.5, 28.6, 23.2, 20.2, 20.0, 14.3, 13.4, 13.1; HRMS $[M + Na]^+$ calcd = 558.3765, found 558.3757.

(19) HPLC using a Waters (USA) Xterra MS C_{18} 7 μm reversed-phase column measuring 7.8 mm × 300 mm with a gradient from 55% MeCN/H_2O to 95% MeCN/H_2O over 25 min.