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ENANTIOSELECTIVE SYNTHESIS OF A 3'-DEPHENYLCRYPTOPHYCIN SYNTHON¹

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Abstract: An enantioselective synthesis of *tert*-butyl (5S,6R)-(E)-5-*tert*-butyldimethylsilyloxy-6-methyl-2,7-octadienoate, a precursor for the synthesis of the antimitotic macrolides cryptophycin A and arenastatin A (cryptophycin-24), is presented. The key step in the reaction sequence features a crotyl boration that sets both stereocenters that become the C16 hydroxyl and C1' methyl in the cryptophycins. Homologation of the terminal olefin via a Heck reaction is presented. © 1998 Elsevier Science Ltd. All rights reserved.

The cryptophycins (Figure 1) are 16-membered macrolides isolated from the blue-green algae (cyanobacteria) *Nostoc* sp. GSV 224.^{2,3} Arenastatin A (1, Figure 1), cryptophycin-24, had previously been isolated from the Okinawan marine sponge *Dysidea arenaria.*⁴ Thus far, 25 compounds of this class have been identified.^{5,6} Cryptophycin-1 (2), the most abundant component, was found to have significant tumor selective cytotoxicity against drug- and multiple drug-resistant tumor cells.³ When administered intravenously, depsipeptide 2 was also very effective against subcutaneously transplanted solid tumors in mice.³ The cytotoxic activity of cryptophycins is derived from their inhibition of tubulin polymerization into microtubules.^{7,8} Additionally, they inhibit microtubule dynamics making them somewhat unique in their activity.^{9,10}

Figure 1



Initial knowledge of the structure-activity relationships (SAR) of the cryptophycins was obtained from natural products isolated from *Nostoc.*^{5,6} Although natural variation occurred on the substituents of the macrocycle, alterations were absent from the C3' aromatic moiety. Through synthetic approaches, it has become

clear that the epoxide and the absolute and relative stereochemistry at the epoxide and at C16 and C1' are necessary for activity.^{10,11} For example, compound **3**, a common intermediate in most of the total syntheses, is essentially inactive.⁵ However, until recently nothing was known about the terminal aromatic group.¹¹ Several syntheses and formal syntheses from our group and others have been presented,¹²⁻¹⁷ but none have addressed the practical modification of the C3' aromatic moiety.

Our approach (Scheme 1) involved development of a concise method in which both stereocenters were incorporated in a single step utilizing a readily scalable method such as the crotyl boration. Fragment 4, as we envisioned, would allow for incorporation of a variety of aryl groups after macrocyclization for thorough SAR studies. In addition, it could be utilized for the direct synthesis of 5 for ongoing studies probing other regions of the cryptophycin structure. Herein we report our synthesis of synthon 4 originating from aldehyde 6 and (E)-crotyl borane 7 (Scheme 1) amenable to structure-activity studies at the C3' aromatic side chain. Additionally, we present the highly convergent and concise synthesis of building block 5.

Scheme 1



The synthesis of octadienoate 4 was accomplished in seven steps from 1,3-propanediol (Scheme 2). The key step in our reaction sequence of segment 4 utilizes the crotyl boration¹⁸ of aldehyde 6^{19} with 7 (prepared from (+)-*B*-methoxydiisopinocampheylborane) to generate the desired stereochemistry at the two chiral centers of 8 in 55% yield (91% ee).²⁰ Silyl protection of the secondary alcohol 8 with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and 2,6-lutidine proceeded at low temperature in 92% yield. Rapid deprotection of the *p*-methoxybenzyl ether with DDQ at 0 °C, followed by flash chromatography provided a mixture of *p*-methoxybenzaldehyde and the desired primary alcohol. The mixture was subjected to TPAP

oxidation²¹ conditions in the presence of NMO producing aldehyde 10 after chromatography in 74% yield over two steps. The Horner–Emmons homologation to form the α,β -unsaturated *tert*-butyl ester 4²² proceeded cleanly using *tert*-butyl diethylphosphonoacetate, DBU and LiCl. The octadienoate 4 was converted to the key synthon 5²³ using a Heck reaction²⁴ with iodobenzene in 84% yield.

Scheme 2



a) THF, Et₂O, -78 °C, 2 h, then HOCH₂CH₂NH₂, 55%, (91% ee); b) TBSOTf, 2,6-lutidine, THF, -78 °C, 10 min, 92%; c) DDQ, CH₂Cl₂, H₂O, 0 °C, 15 min; d) TPAP, NMO, CH₂Cl₂, rt, 15 min, 74% over two steps; e) (EtO)₂P(O)CH₂C(O)OtBu, DBU, LiCl, CH₃CN, rt, 2 h, 89%; f) PhI, Pd(OAc)₂, Et₃N, CH₃CN, sealed tube, 83 °C, 18 h, 84%.

In conclusion, we have developed a convenient enantioselective route to the 3'-dephenyl synthon 4 of the cryptophycins. We also applied this approach to the rapid synthesis of fragment 5. Application of octadienoate 4 to the total synthesis and structure-activity studies at the aromatic side chain will be reported in due course.

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- 20. The enantiomeric excess was determined by chiral HPLC comparing alcohol 8, derived from (+)-*B*-methoxydiisopinocampheylborane (purchased from Aldrich chemical company) with alcohol ent-8 derived from reaction with the (-)-borane: Chiralcel OD-H, 254 nm, 99:1 hexanes: isopropyl alcohol, 0.5 mL/min, retention time: ent-8 = 32.2 min, 8 = 34.6 min.
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- 22. Compound 4: ¹H NMR (400 MHz, CDCl₃) δ 6.82–6.75 (dt, J = 8, 16 Hz, 1 H), 5.80–5.71 (buried, 1H), 5.74–5.70 (br d, J = 16 Hz, 1H), 5.03 (br s, 1H), 5.01-4.99 (br d, J = 9 Hz, 1H), 3.67–3.63 (m, 1H), 2.29–2.23 (m, 3H), 1.46 (s, 9H), 1.00–0.99 (d, J = 6.8 Hz, 3H), 0.88 (s, 9H), 0.033 (s, 3H), 0.027 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.7, 145.1, 140.1, 125.0, 115.1, 80.0, 74.9, 43.3, 36.8, 28.1 (3C), 25.8 (3C), 18.1, 15.3, -4.4, -4.6; HRMS (FAB) calcd for C₁₉H₃₇O₃Si (M + H) 341.2512, found 341.2514.
- 23. Compound **5** was also synthesized by an alternate route [see ref 17, $[\alpha]_D + 69^\circ$ (*c* 0.73, CHCl₃)]: $[\alpha]^D + 64^\circ$ (*c* 0.73, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.37–7.17 (m, 5 H), 6.86–6.76 (dt, J = 8, 16 Hz, 1 H), 6.38–6.33 (d, J = 16 Hz, 1H), 6.18–6.10 (dd, J = 8, 16 Hz, 1H), 5.74–5.69 (d, J = 16 Hz, 1H), 3.74–3.69 (app q, J = 6 Hz, 1H), 2.47–2.40 (m, 1H), 2.32–2.27 (m, 2H), 1.45 (s, 9H), 1.09–1.06 (d, J = 7 Hz, 3H), 0.88 (s, 9H), 0.033 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 165.8, 144.8, 137.6, 132.0, 130.4, 128.5 (2C), 127.0, 126.0 (2C), 125.1, 80.0, 75.1, 42.8, 37.3, 28.1 (3C), 25.9 (3C), 18.1, 16.1, -4.4, -4.5; HRMS (FAB) calcd for C₂₅H₄₁O₃Si (M + H) 417.2825, found 417.2848.
- (a) For review, see: Heck, R. F. Palladium Reagents in Organic Syntheses; Academic: London, 1985. (b) de Meijere, A.; Meyer, F. E. Angew Chem. Int. Ed. Engl. 1994, 33, 2379.