Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 3177–3180

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

ENANTIOSELECTIVE SYNTHESIS OF A 3′-DEPHENYLCRYPTOPHYCIN SYNTHON[1]

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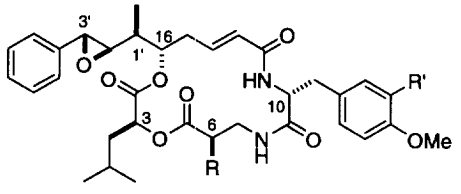
Received 3 September 1998; accepted 29 September 1998

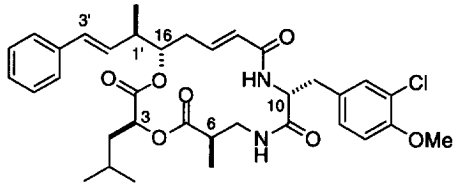
Abstract: An enantioselective synthesis of *tert*-butyl (*5S,6R*)-(*E*)-5-*tert*-butyldimethylsilyloxy-6-methyl-2,7-octadienoate, a precursor for the synthesis of the antimitotic macrolides cryptophycin A and arenastatin A (cryptophycin-24), is presented. The key step in the reaction sequence features 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.

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



R = H, R' = H, Arenastatin A (**1**)
R = Me, R' = Cl, Cryptophycin-1 (**2**)



Cryptophycin-3 (**3**)

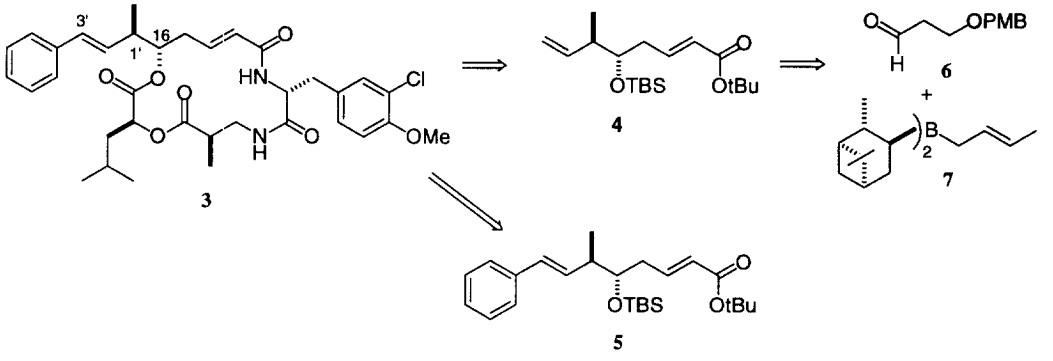
Initial knowledge of the structure–activity relationships (SAR) of the cryptophycins was obtained from natural products isolated from *Nostoc.*[5,6] Although natural variation occurred on the substituents of the macrocycle, alterations were absent from the C3′ aromatic moiety. Through synthetic approaches,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

0960-894X/98/$ - see front matter
PII: S0960-894X(98)00557-5

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**.

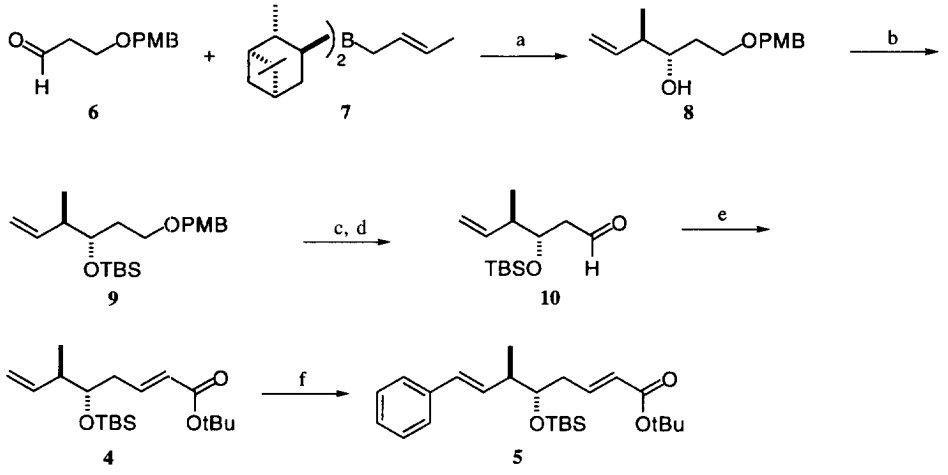
Scheme 1



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 boration[18] 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

oxidation[21] 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 **4**[22] proceeded cleanly using *tert*-butyl diethylphosphonoacetate, DBU and LiCl. The octadienoate **4** was converted to the key synthon **5**[23] using a Heck reaction[24] with iodobenzene in 84% yield.

Scheme 2



a) THF, Et_2O, -78 °C, 2 h, then $HOCH_2CH_2NH_2$, 55%, (91% ee); b) TBSOTf, 2,6-lutidine, THF, -78 °C, 10 min, 92%; c) DDQ, CH_2Cl_2, H_2O, 0 °C, 15 min; d) TPAP, NMO, CH_2Cl_2, rt, 15 min, 74% over two steps; e) $(EtO)_2P(O)CH_2C(O)OtBu$, DBU, LiCl, CH_3CN, rt, 2 h, 89%; f) PhI, $Pd(OAc)_2$, Et_3N, CH_3CN, 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.

Acknowledgments: We gratefully acknowledge support from the National Institutes of Health (RO1 CA 70369) and the Department of the Army for a postdoctoral fellowship for MariJean Eggen (DAMD 17-97-1-7051).

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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**: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{19}H_{37}O_3Si$ (M + H) 341.2512, found 341.2514.
23. Compound **5** was also synthesized by an alternate route [see ref 17, $[\alpha]_D$ +69° (*c* 0.73, $CHCl_3$)]: $[\alpha]^D$ +64° (*c* 0.73, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{25}H_{41}O_3Si$ (M + H) 417.2825, found 417.2848.
24. (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.