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A Novel Approach for Total Synthesis of Cryptophycins via Asymmetric Crotylboration Protocol

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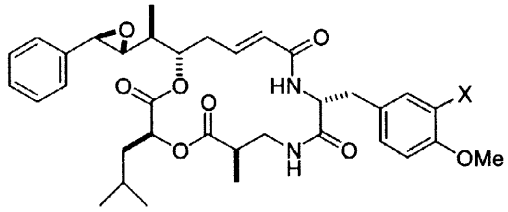
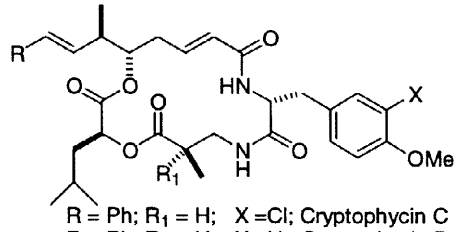
Abstract: Acyclic and a highly efficient stereoselective C-C bond formation of aldehyde **3** with the crotylboron reagent **4**, derived from (–)-α-pinene, provided a homoallylic alcohol **6** in ≥99% enantio-(ee) and diastereomeric excess (de). The alcohol **6** was linearly converted into the desired Fragment A **10** of cryptophycins in seven steps. This enantiomerically pure Fragment A was conveniently and efficiently coupled with the other three fragments, namely B, C and D, and provided the desired cryptophycin A derivative (**LY404291**). The terminal double bond in **LY404291** was further elaborated to provide a terminal epoxide **LY404292**, and cryptophycins **51** and **52**.

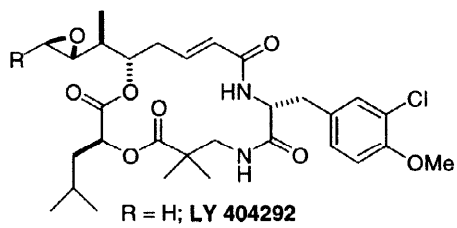
Cryptophycin A, a novel 16-membered depsipeptide macrolide, was first isolated from *Nostoc* cyanobacterium in 1990 by Schwartz and co-workers.[1] Later, Moore and co-workers[2] isolated a number of cryptophycin macrolides from *Nostoc* sp GSV 224. Subsequently, Tius *et al*[3] reported the first total synthesis of cryptophycin A. These cryptophycins exhibit a broad range of anti-tumor activity.[2,3] A number of synthetic strategies have been developed[4] to probe structure-activity relationships in search of more potent compounds. Indeed, representative synthetic cryptophycin analogs have demonstrated superior activities and properties to their natural counterparts, resulting in the development of Cryptophycin 52.



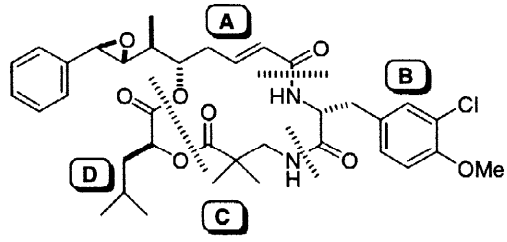
X = Cl; Cryptophycin A
X = H; Cryptophycin B



R = Ph; R_1 = H; X =Cl; Cryptophycin C
R = Ph; R_1 = H; X =H; Cryptophycin D
R = H; R_1 = Me; X =Cl; **LY404291**
R = Ph; R_1 = Me; X =Cl; Cryptophycin 51



R = H; **LY 404292**
R = Ph; Cryptophycin 52



Straightforward retrosynthetic analysis of the cryptophycin nucleus reveals four fragments A through D. Although syntheses of fragments B, C and D are achieved in 2-6 steps, stereodefined synthesis of fragment A

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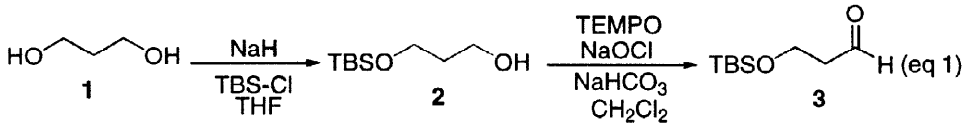
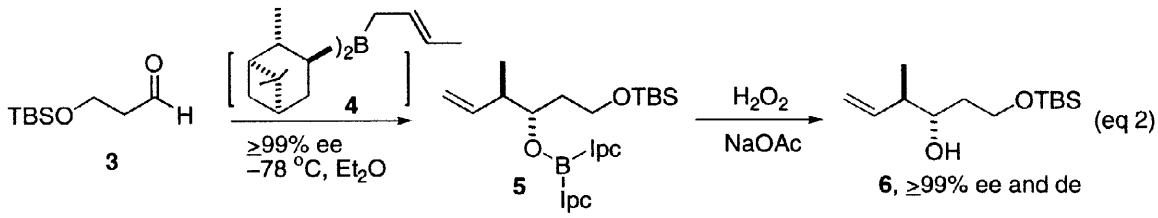
with four of the six chiral centers of cryptophycin proved most challenging. Many of the cryptophycin syntheses reported hitherto[4] were focused on Fragment A. We envisaged an enantio- and diastereoselective crotylboration protocol for the formation of Fragment A. We also anticipated that elaboration of a terminal double bond in macrocycle **LY404291** would provide immediate access to potentially useful cryptophycin analogs. In this communication, we report a highly efficient, stereospecific synthesis of Fragment A based upon Brown's asymmetric crotylboration reaction,[5] with elaboration to structurally unique cryptophycin analogs, namely **LY404291, 404292**, and cryptophycins **51** and **52**.

Aldehyde **3** was viewed as the requisite partner for the key crotylboration process. Thus, an exclusive monoprotection of 1,3-propanediol (**1**) was achieved in 95% yield by the treatment of **1** with sodium hydride and *tert*-butyldimethylsilyl chloride (TBS-Cl)[6] in THF at 0 °C. The resultant 3-(*tert*-butyldimethylsilyloxy)-1-propanol (**2**) was subjected to TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy free radical)[7] catalyzed oxidation with bleach at pH = 9.0-9.2 to provide the requisite propanal derivative **3** in 91% yield (eq 1).

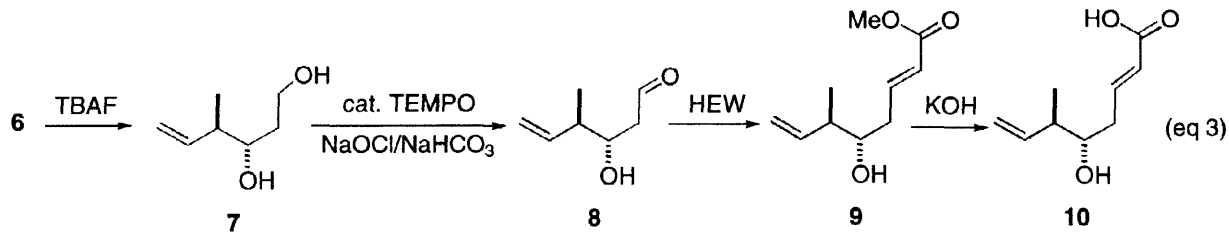


Aldehyde **3** was then subjected to an acyclic enantio- and diastereocontrolled C-C bond formation process with the enantiomerically pure crotylboron reagent **4**, which was readily generated *in situ* from (–)-α-pinene of 81% ee.[5,8] Reaction of **4** with the aldehyde **3** at –78 °C provided intermediate **5**, which was oxidized with alkaline peroxide to provide the desired homoallylic alcohol **6** of ≥99% ee and de in 67% isolated yield (eq 2).[9] The enantio- and diastereoselectivities achieved in this reaction were determined by analyzing alcohol **6** in comparison with the racemic and diastereomeric alcohols of **6** by chiral column and capillary GC, respectively. These racemic alcohols were synthesized by crotylboration utilizing a 9-BBN derived achiral crotylboron reagent.[10]



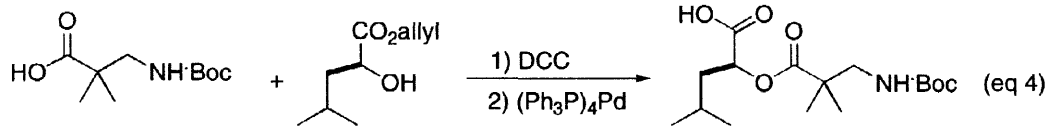
The next task of converting homoallylic alcohol **6** to the desired intermediate **10** was achieved in a very simple and efficient four step reaction sequence in high overall yield. Thus, the removal of TBS-protecting group of **6** with tetrabutylammonium fluoride (TBAF)[11] provided diol **7** in quantitative yield. Further, selective oxidation of the primary hydroxyl moiety of the diol **7** with bleach in the presence of a catalytic

amount of TEMPO[7] provided an essentially quantitative yield of hydroxy aldehyde **8**, which upon Horner-Emmons-Wadsworth (HEW) reaction followed by hydrolysis provided the desired α,β-unsaturated hydroxy acid **10** in 85% isolated yield over 4 steps (eq 3).



(eq 3)

Having accomplished a highly stereodefined synthesis of **10**, attention was focused on the synthesis of the other fragments of the target cryptophycin molecule. Fragments B and D were synthesized starting from *D*-tyrosine and *L*-leucic acid in 6 and 2 steps, respectively, according to the literature procedure.[3] Standard 1,3-dicyclohexylcarbodiimide (DCC)[3] mediated esterification of fragments C[12] and D provided CD-allyl ester fragment from which the allyl group was quantitatively removed by treatment with catalytic Pd(0)[13] to provide a desired CD-acid fragment (eq 4).

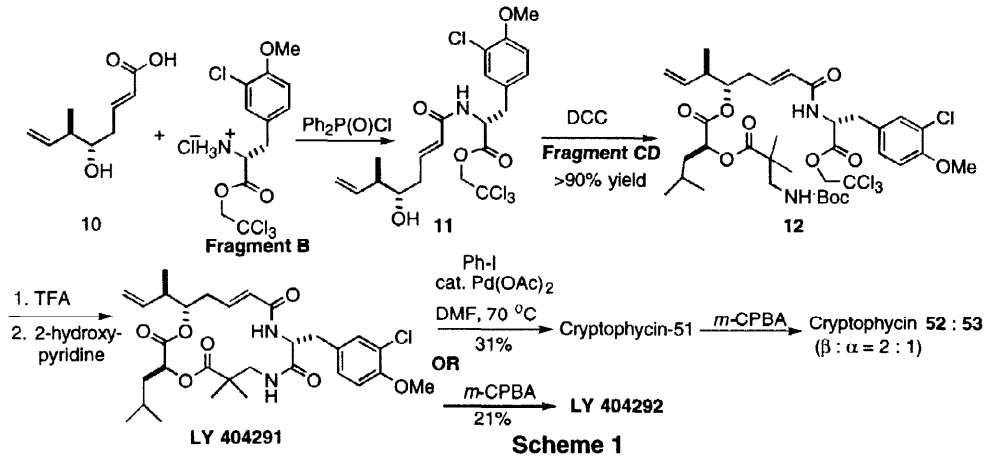


(eq 4)

With the requisite portions of the cryptophycin core structure in hand, the remaining construction of the desired macrolide **LY404291** was efficiently achieved in three steps. Amidation of the carboxyl function of Fragment A with Fragment B using diphenylphosphinic chloride [$Ph_2P(O)Cl$][14] provided coupled product **11** in 65% yield. The hydroxyl moiety of **11** was subjected to esterification mediated by DCC[3] with the carboxylic acid group of preassembled Fragment CD to provide *seco*-ABCD fragment **12** in nearly quantitative yield. Macrolactamization of **12** was effected by removal of the *tert*-butyloxy carbonyl (Boc) group of **12** followed by the treatment of the resulting amino ester intermediate with 2-hydroxypyridine,[15] providing the desired macrocyclic product (**LY404291**) in 35% yield. The terminal double bond in **LY404291** was readily epoxidized with *m*-chloroperbenzoic acid (*m*-CPBA) or subjected to the Heck reaction[16] to provide the desired **LY404292** as an ~1:1 mixture of diastereomers and cryptophycin **51**, respectively in good yields. Further epoxidation of cryptophycin **51** with *m*-CPBA provided a mixture of cryptophycins **52** and **53** (undesired α–epoxide) in a 2 : 1 ratio, respectively (Scheme 1).

In conclusion, the synthesis of intermediate **10** of cryptophycin was achieved in seven steps in good overall yield using a highly stereodefined asymmetric crotylboration approach based upon inexpensive and abundantly available (–)-α-pinene. This Fragment A was later convergently transformed into the desired cryptophycin derivatives in a good overall yield.[17] The noteworthy feature of this protocol is the stereoselective formation of **LY404291** with a highly versatile terminal double bond. This double bond

serves as a handle for the introduction of structural diversity, thus providing a source for an array of useful compounds to probe the structure-activity relationships.



Scheme 1

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