

Tetrahedron Letters 39 (1998) 8771-8774

TETRAHEDRON LETTERS

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

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Received 27 July 1998; revised 15 September 1998; accepted 18 September 1998

Abstract: Acyclic and a highly efficient stereoselective C-C bond formation of aldehyde 3 with the crotylboron reagent 4, derived from  $(-)-\alpha$ -pinene, provided a homoallylic alcohol 6 in  $\geq$ 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. © 1998 Elsevier Science Ltd. All rights reserved.

Cryptophycin A, a novel 16-membered depsipeptide macrolide, was first isolated from *Nostoc* cyanobacterium in 1990 by Schwartz and co-workers.<sup>1</sup> Later, Moore and co-workers<sup>2</sup> isolated a number of cryptophycin macrolides from *Nostoc* sp GSV 224. Subsequently, Tius *et al*<sup>3</sup> reported the first total synthesis of cryptophycin A. These cryptophycins exhibit a broad range of anti-tumor activity.<sup>2,3</sup> A number of synthetic strategies have been developed<sup>4</sup> 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.



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 with four of the six chiral centers of cryptophycin proved most challenging. Many of the cryptophycin syntheses reported hitherto<sup>4</sup> 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,<sup>5</sup> 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)<sup>6</sup> 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)<sup>7</sup> 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 (-)- $\alpha$ pinene of 81% ee.<sup>5,8</sup> 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).<sup>9</sup> 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.<sup>10</sup>



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<sup>7</sup> provided an essentially quantitative yield of hydroxy aldehyde 8, which upon Horner-Emmons-Wadsworth (HEW) reaction followed by hydrolysis provided the desired  $\alpha_{\beta}$ -unsaturated hydroxy acid 10 in 85% isolated yield over 4 steps (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.<sup>3</sup> Standard 1,3-dicyclohexylcarbodiimide (DCC)<sup>3</sup> mediated esterification of fragments C<sup>12</sup> and D provided CD-allyl ester fragment from which the allyl group was quantitatively removed by treatment with catalytic Pd(0)<sup>13</sup> to provide a desired CD-acid fragment (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  $[Ph_2P(O)CI]^{14}$  provided coupled product 11 in 65% yield. The hydroxyl moiety of 11 was subjected to esterification mediated by DCC<sup>3</sup> 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,<sup>15</sup> 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<sup>16</sup> 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  $\alpha$ -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 (-)- $\alpha$ -pinene. This Fragment A was later convergently transformed into the desired cryptophycin derivatives in a good overall yield.<sup>17</sup> 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.



Acknowledgments. We gratefully acknowledge the efforts of Mr. Joseph Turpin for GC analyses of the various intermediates and products and Drs. Eric Moher, Andrew Fray, Tony Zhang, Mr. Dave Varie, and Professors William Roush, and Marcus Tius for helpful discussions. We are also grateful to the Lilly Physical Chemistry group for providing analytical and spectral data.

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