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Stereospecific Synthesis of Cryptophycin 1

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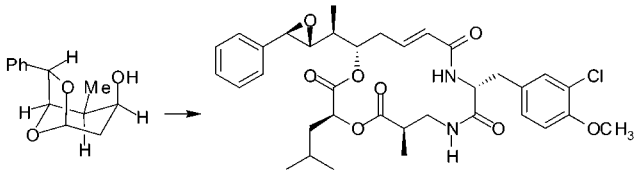
ABSTRACT



cryptophycin 1

A brief stereospecific synthesis of cryptophycin 1 is described in which (*R*)-mandelic acid serves as the sole source of asymmetry for unit A. The key step is a hetero-Diels–Alder cycloaddition.

A systematic effort to collect, culture, and screen extracts from cyanophytes (blue-green algae) was initiated in the 1980s by Richard E. Moore and Gregory M. L. Patterson in the University of Hawaii Chemistry Department.[1] During the time that this program was active, a large number of potent cytotoxins, many of which possessed unique, unprecedented structures, were discovered. The most potent selectively cytotoxic compound to emerge from this program, cryptophycin 1, was isolated from a crude lipophilic extract of *Nostoc* sp. GSV 224.[2] Some years earlier, researchers at Merck had isolated the same compound from *Nostoc* sp. ATCC 53789.[3,4] Although the Merck group elucidated the gross structure, no details of the relative or absolute stereochemistry were disclosed. Our group published the first total synthesis of the cryptophycins in 1995.[5] The total synthesis also served to correct the structure of cryptophycin 1. Since then, the realization that the cryptophycins represent a new class of extraordinarily potent, solid tumor-selective cytotoxins[6] led to the development of a number of total syntheses, as well as syntheses of cryptophycin analogues and fragments.[7]

The cryptophycins can be logically divided into four units. Unit A is polyketide-derived, whereas units B−D are derived from amino acids. The first obvious retrosynthetic step is removal of the epoxide function. This leads to cryptophycin 3, a naturally occurring congener. This approach is appealing,

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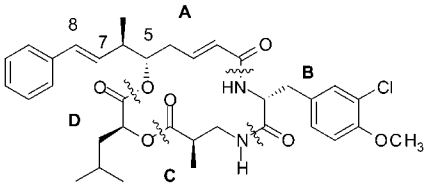
because it installs the labile styrene oxide function at the very end of the sequence. The problem is that the epoxidation of cryptophycin 3 produces at best a 3/1 mixture of cryptophycin 1 and the diastereomeric α-epoxide. Moreover, the diastereomers are only separable with difficulty by HPLC. Attempts by our group[5] and by others[7a,i,k] to optimize the epoxidation reaction have failed to improve the ratio of diastereomers.

Leahy and Gardinier's beautiful synthesis of cryptophycin 1 was the first to control the epoxide stereochemistry. They used an Evans asymmetric aldol reaction with the TIPS derivative of (*R*)-mandelaldehyde to control the stereochemistry at C6−8.[7c] A second solution to the problem was described in the context of a synthesis of cryptophycin 52,



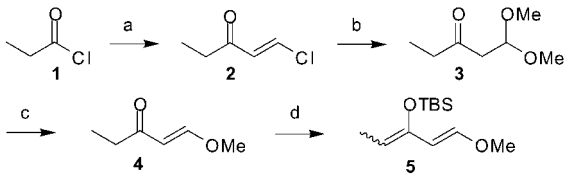
cryptophycin 3

a synthetic analogue of the natural product.[8] The Sharpless AD was used to install a C7−C8 syn diol in a seco compound that was subsequently cyclized. Diol to epoxide conversion was accomplished through a modification of Sharpless' protocol.[9] More recently, a synthesis of unit A based on a diastereoselective addition of acetylide to methyl mandelate coupled with a Sharpless epoxidation has been described.[7m]

In this Letter, we describe a stereospecific synthesis of cryptophycin 1 that relies on (*R*)-mandelic acid as the sole source of asymmetry for unit A. A C7−C8 syn diol was installed early in the sequence and was converted to the epoxide in the last step of the synthesis. We have been able to control the stereochemistry of the four contiguous asymmetric centers in unit A through application of the Danishefsky hetero-Diels−Alder cycloaddition.[10] Stereochemical induction in these reactions depends on the solvent, additives, diene geometry, and in the present case, the oxygen protecting group of the dienophile.

Scheme 1 summarizes our synthesis of diene **5**. Friedel−Crafts reaction of propionyl chloride with dry acetylene leads to 1-chloro-1-penten-3-one **2** in 81% yield.[11] Addition of methanol to vinylogous acid chloride **2** gave 1,1-dimethoxy-3-pentanone **3** (89% yield). Elimination of methanol from **3** took place in excellent yield upon heating in toluene with catalytic sodium methoxide.[12] After methanol was distilled off, the desired product was isolated by vacuum distillation of the residue (85% yield). Conversion of **4** to silyl enol ether **5** was accomplished by treatment with TBS triflate and

Scheme 1[a]

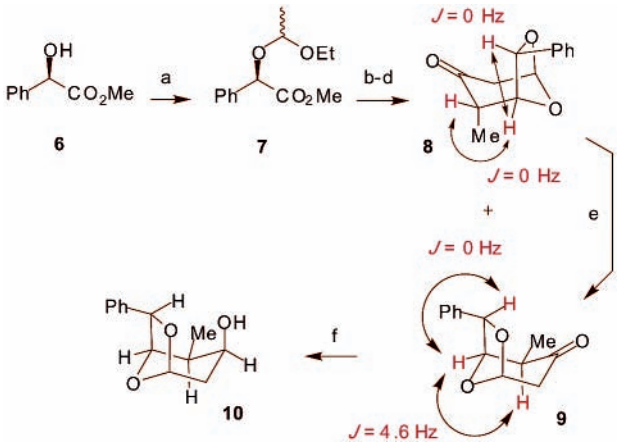


[a] Reaction conditions: (a) acetylene, CCl_4, $AlCl_3$, rt, 81%; (b) K_2CO_3, anhyd MeOH, rt, 89%; (c) PhMe, NaOMe, bath temperature 160 °C, distillation of MeOH, 85%; (d) Et_3N, TBSOTf, from −78 °C to 0 °C, 78%, (*E*,*Z*)/(*E*,*E*) = 9/1.

triethylamine at −78 °C, followed by slow warming to 0 °C. These conditions led to a 9/1 mixture of (*E*,*Z*) and (*E*,*E*) dienes in 78% yield. Ordinarily, separation of the geometrical isomers of the diene would be desirable, since each isomer can be expected to lead to a different diastereomer of the hetero-Diels−Alder product.[13] As will be shown, separation of the isomers of **5** was unnecessary.[14]

Scheme 2 shows the stereospecific synthesis of unit A. (*R*)-Methyl mandelate was first protected as the ethoxyethyl

Scheme 2[a]



[a] Reaction conditions: (a) ethyl vinyl ether, PPTS; (b) DIBAL, ether, −78 °C; (c) $MgBr_2$, THF, **5**, 36−42 °C; (d) TFA, THF, **8**/**9** = 10/1; (e) KF, alumina, MeCN, **8**/**9** = 1/4, 48% overall from **6**; (f) L-Selectride, THF, −78 °C, 93%.

ether **7**[15] and then reduced with DIBAL. Mandelate ester **7** was formed as a ca. 1/1 mixture of acetal isomers, as judged by the ^{1}H NMR spectrum at 300 MHz. The protected mandelaldehyde was dissolved in THF and treated sequentially with $MgBr_2$ and diene **5**.[16] The mixture was heated to

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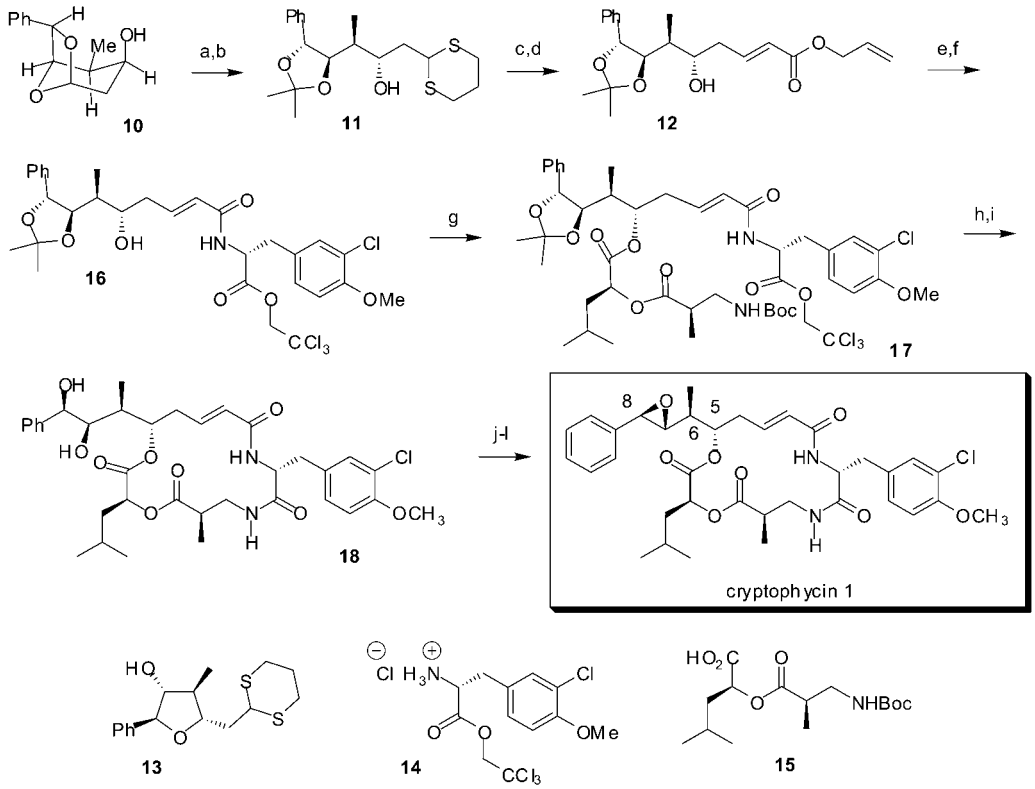
Scheme 3[a]



[a] Reaction conditions: (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, $HS(CH_2)_3SH$, 0 °C, 85%; (b) $Me_2C(OMe)_2$, TsOH, acetone, 93%; (c) MeI, $CaCO_3$, MeCN, H_2O, 70 °C; (d) $LiClO_4$, Hünig's base, MeCN, $(EtO)_2POCH_2CO_2CH_2CH{=}CH_2$, 68% from **11**; (e) $Pd(PPh_3)_4$, morpholine, 100%; (f) **14**, Et_3N, EDCI, CH_2Cl_2, from 0 °C to room temperature, 81%; (g) **15**, DCC, DMAP, CH_2Cl_2, 81%; (h) TFA, CH_2Cl_2, 0 °C; (i) 2-hydroxypyridine, PhMe, rt, 62% from **17**; (j) $(MeO)_3CH$, PPTS, CH_2Cl_2, rt; (k) AcBr, CH_2Cl_2, rt; (l) $KHCO_3$, 6/4/1 DME/EtOH/MeOH, 40 °C, 70% from **18**.

42 °C for 4.5 h and then kept at 36 °C for another 12 h. Exposure to aqueous TFA, followed by workup gave a 10/1 mixture of **8** and **9**. Epimerization took place by stirring with KF/alumina in acetonitrile for 48 h, leading to a 1/4 mixture of axial and equatorial isomers **8** and **9** in 48% overall yield for the five steps from **6**.[17] Stereochemistry in **8** and **9** was assigned on the basis of $^1H-^1H$ coupling constants as indicated in the structures shown in Scheme 2.

There are several observations regarding the hetero-Diels–Alder cycloaddition that deserve mention. Both diastereomeric forms of the protected mandelaldehyde derived from **7** participated in the cycloaddition; therefore, we had no reason to examine the reactions of the individual isomers. Although the cycloaddition reaction between diene **5** and *O*-methoxymethyl mandelaldehyde was also stereoselective, the subsequent hydrolytic removal of the acetal protecting group led to inferior yields of **8** and **9**. The TBS derivative of mandelaldehyde failed to undergo cycloaddition with diene **5** under a wide variety of reaction conditions in which the Lewis acid, solvent, and temperature were varied. Cycloaddition between the *O*-trimethylsilyl diene analogous to **5** with either the TBS or the TIPS derivative of mandelaldehyde took place unselectively and led to diastereomeric mixtures of products that were of no preparative value. These results suggest a requirement for a chelating oxygen protecting group in the mandelaldehyde-derived heterodienophile. Temperature control of the hetero-Diels–Alder reaction appears to be critical to its success. At ambient temperature, the reaction is very slow, proceeding to less than 30% conversion overnight. At reflux the reaction is predictably faster; however, acid-catalyzed loss of the ethoxyethyl ether protecting group competes with the desired cycloaddition. Optimum conditions for the hetero-Diels–Alder reaction were developed through trial and error.

The successful conversion of **9** to cryptophycin 1 confirmed the stereochemical assignment. Treatment of the epimeric mixture of **8** and **9** with 1 equiv of L-Selectride per equiv of **9** at −78 °C gave alcohol **10** as a single isomer in 93% yield, based on recovered starting material. Under these conditions, little or no reduction of ketone **8** took place, since reduction of axial isomer **8** by L-Selectride at −78 °C is very slow. The recovered ketone **8** was recycled by treatment with KF/alumina to give the same 1/4 mixture of **8** and **9** in >90% yield. Alcohol **10** has all four asymmetric carbon atoms of unit A.

The ratio of **8** to **9** that was obtained from the cycloaddition reflects the ratio of geometrical isomers of diene **5**. Although

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the cycloaddition reaction is likely to be mechanistically distinct from the classical Diels−Alder reaction, the stereochemistry of **8** and **9** can be rationalized on the basis of an exo transition state in a chelation-controlled process (see Figure 1).[16]

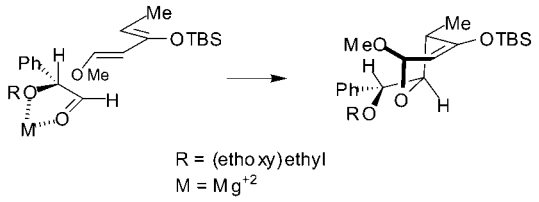

Figure 1. Stereochemistry of the cycloaddition.

Scheme 3 summarizes the conversion of **10** to cryptophycin 1. Careful exposure of **10** to 1,3-propanedithiol in the presence of $BF_3{\cdot}Et_2O$ at 0 °C led to the anticipated ring-opened dithioketal (85% yield).[18] If this reaction was carried out at higher temperature, or if it was not quenched promptly upon consumption of the starting material, tetrahydrofuran **13** was formed in up to 30% yield. Diol to acetonide conversion furnished **11** (93% yield). Dithioketal hydrolysis, followed by Horner−Emmons reaction led to allyl ester **12** in 68% yield for the two steps.[19] The overall yield of **12** from (*R*)-methyl mandelate was 24%.

Palladium-catalyzed cleavage of the allyl group in **12** (100% yield)[20] was followed by coupling with *O*-methyl-D-chlorotyrosine derivative **14**[5] in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and triethylamine to give **16** in 81% yield.[5] The free C5 hydroxyl group in **16** was esterified with the carboxylic acid of C−D unit **15**[5] to produce protected seco derivative **17** (81% yield). Exposure of this material to TFA in dichloromethane cleaved both Boc and acetonide protecting groups. Macrocyclization took place very easily according to the conditions developed by the Lilly group.[21] Treatment with 2-hydroxypyridine in toluene at room-temperature overnight led to **18** in 62% yield for the two steps. The trichloroethyl ester group in unit B thus serves two complementary roles in the synthesis. It protects the carboxylate during the coupling with **15**, and then it activates the same carboxylate during the ring-closure step.

The last task, conversion of diol to epoxide, was accomplished in three steps in 70% overall yield. Treatment of **18** with trimethyl orthoformate and PPTS, followed by acetyl bromide, led to the anticipated bromohydrin formate, which was taken on to the last step without purification. Exposure to powdered $KHCO_3$ in a 6/4/1 mixture of DME/ethanol/methanol at 40 °C for 24 h led to cryptophycin 1. The synthetic product was spectroscopically indistinguishable from natural material. The conditions for the last step were optimized carefully. A small amount of methanol is necessary to partially dissolve the bicarbonate. If a high proportion of methanol is used in the solvent mixture, methanolysis of the unit C-unit D link takes place.

In summary, an efficient (6.8% overall yield) and stereospecific synthesis of cryptophycin 1 from (*R*)-methyl mandelate has been described. The key feature of this work is the stereoconvergent hetero-Diels−Alder strategy for the control of unit A stereochemistry.

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Supporting Information Available: Synthetic procedures for **2**−**5**, **7**−**12**, **16**−**18**, and cryptophycin 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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