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Bioreduction of (*R*)-Carvone and Regioselective Baeyer-Villiger Oxidations: Application to the Asymmetric Synthesis of Cryptophycin Fragment A

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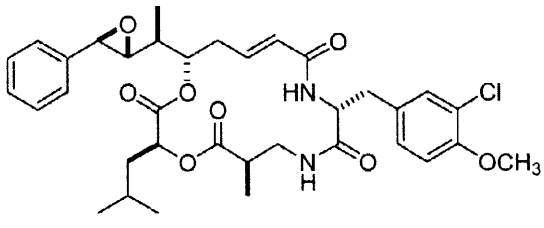
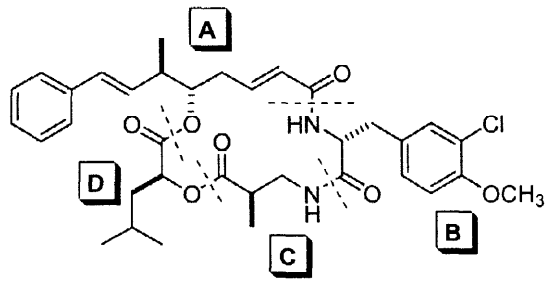
Abstract: Cryptophycin fragment A (**1**) was prepared in high enantiomeric purity in 10 steps from (*R*)-carvone. A stereoselective bioreduction of (*R*)-carvone to neodihydrocarveol and a regioselective Baeyer-Villiger oxidation of cyclohexanone **8** with pertrifluoroacetic acid were employed in this synthesis.

Cryptophycins, which are depsipeptides derived from terrestrial blue-green algae, exhibit high activity against a broad spectrum of solid tumors. The major cytotoxic component of the algal extracts, cryptophycin A, was first isolated from a *Nostoc* cyanobacterium by Schwartz and co-workers in 1990.[1] Later, Moore and co-workers isolated several cryptophycins, including cryptophycin A, from *Nostoc* sp GSV 224[2] as part of a program aimed at screening extracts for anti-tumor activity. Following the report of the total synthesis of cryptophycin A by Tius *et al*,[3] several syntheses of cryptophycins were reported.[4] Herein we report a novel asymmetric synthesis of a key portion of the cryptophycin framework, fragment A (**1**), from readily available (*R*)-carvone (**3**).

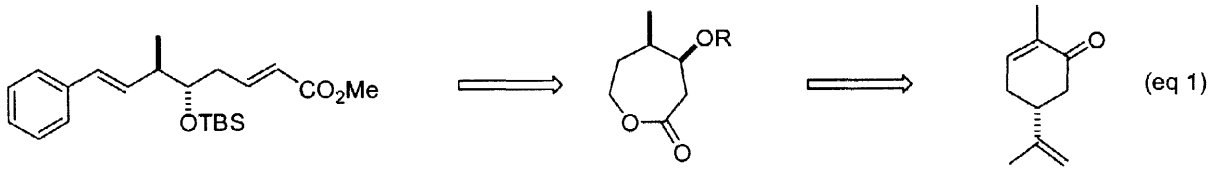


Cryptophycin A



Cryptophycin C

Retrosynthetic disconnection of cryptophycin A provides four fragments (**A-D**). The most challenging synthetic target is fragment A. One strategy for the synthesis of the cryptophycin macrocycle (e.g. cryptophycin C) utilizes fragment A styrene **1**,[3,4a-e] which contains two of the four required fragment A stereocenters. Our strategy for the preparation of **1** (eq 1) requires a stereoselective reduction of carvone, isopropenyl group oxidation, a regioselective Baeyer-Villiger oxidation, and chain elongation. We envisioned generation of lactone **2** by a regioselective Baeyer-Villiger reaction as the key to successfully implementing this strategy.



Fragment A (**1**) **2** *R*-Carvone (**3**) (eq 1)

In our initial work, (*R*)-carvone (98% ee) was reduced with Zn/EtOH[5] to provide an 82:18 *trans:cis* (equilibrium) mixture of dihydrocarvone diastereomers (**4**)[6] as shown in Scheme 1. The major diastereomer

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(***trans*-4**) was easily separated by chromatography and reduced with Li(*s*-Bu)$_3$BH[7] to provide alcohol **5** (neodihydrocarveol) in >99% de. Seeking a more scaleable process, we examined the bioreduction of carvone with a variety of microorganisms.[8] *Trigonopsis variablis* (ATCC 10679) was shown to reduce (*R*)-carvone (*via* ***trans*-4**)[9] to **5** with >98% de (GC assay), in 50-62% isolated yields without chromatography. Alcohol **5** was treated with *t*-butyldimethylsilyl chloride, *t*-butyldiphenylsilyl chloride, or pivaloyl chloride to give oxygen protected compounds **6a-c**. Ozonolysis of **6a-c** followed by Criegee rearrangement[10] conditions provided alcohols **7a-c**. The desired ketones **8a-c** were then obtained by oxidation of **7a-c** with bleach and catalytic TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) free radical.[11]

Scheme 1. Synthesis of Lactones **2a-c** from (*R*)-Carvone.

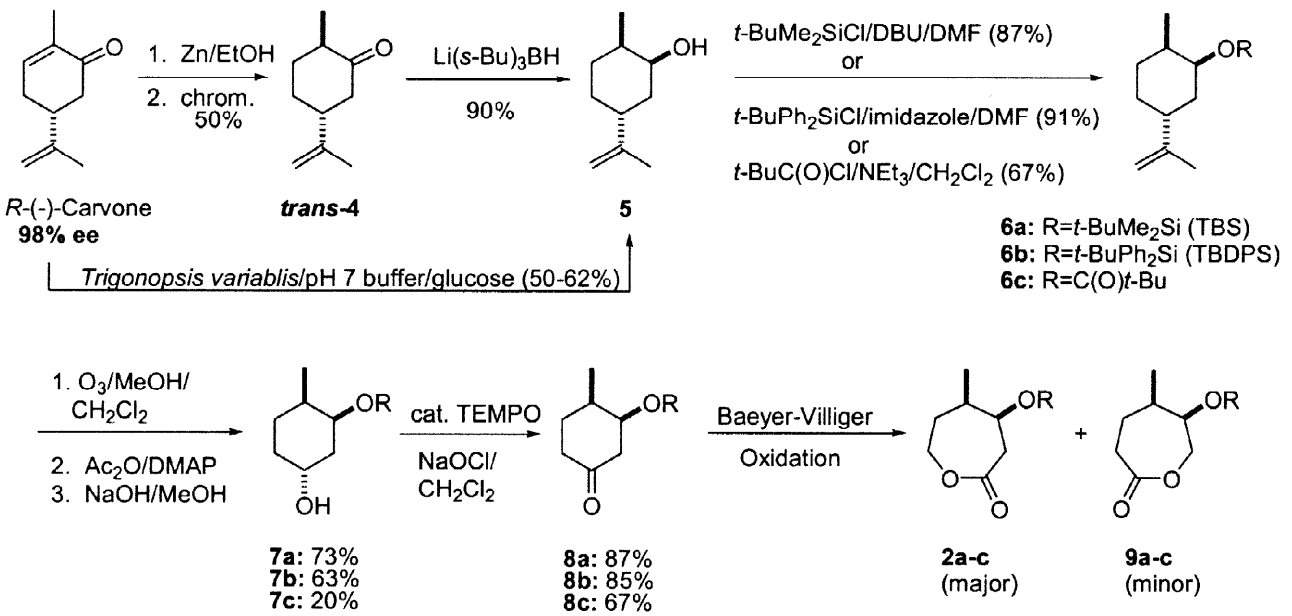

Table 1. Baeyer-Villiger Oxidation of Ketones **8a-c**.

Entry	Ketone (R)	Oxidant (equiv.)	Solvent	T (°C)	Time (h)	Ratio 2:9[a]	%Yield of 2+9 (conversion)
1	**8a** (*t*-BuMe$_2$Si)	*m*-CPBA (2)	CH_2Cl_2	22	72	67:33	36 (50%)
2	**8a** (*t*-BuMe$_2$Si)	*m*-CPBA (3) + BF_3•Et_2O (3)	CH_2Cl_2	0	4	80:20	75
3	**8a** (*t*-BuMe$_2$Si)	*m*-CPBA (1.6)	CH_2Cl_2	-15	90	72:28	(94%)
4	**8c** (C(O)t-Bu)	*m*-CPBA (2)	CH_2Cl_2	-15	48	90:10	(10%)
5	**8a** (*t*-BuMe$_2$Si)	CF_3CO_3H (2.5)[b]	CH_2Cl_2	-15	3	94:6	67
6	**8c** (C(O)t-Bu)	CF_3CO_3H (3.2)[b]	CH_2Cl_2	-15	24	93:7	70
7	**8a** (*t*-BuMe$_2$Si)	CF_3CO_3H (2.5)[c]	CH_2Cl_2/TFA(4:1)	0	2	94:6	79
8	**8a** (*t*-BuMe$_2$Si)	CF_3CO_3H (1.6)[c]	CH_2Cl_2/TFA(4:1)	-15	2	98:2	83
9	**8c** (C(O)t-Bu)	CF_3CO_3H (2.5)[c]	CH_2Cl_2/TFA(4:1)	-15	18	96:4	70
10	**8a** (*t*-BuMe$_2$Si)	CF_3CO_3H (2.5)[c]	CH_2Cl_2/TFA(1:1)	-15	2	98:2	80
11	**8b** (*t*-BuPh$_2$Si)	CF_3CO_3H (2.5)[c]	CH_2Cl_2/TFA(1:1)	-15	2	98:2	86

[a] NMR assay of crude reaction mixture. [b] Prepared from hydrogen peroxide urea and TFAA.[14] [c] Prepared from 30% aqueous hydrogen peroxide and TFAA.[15]

We anticipated that the electron withdrawing effect of the β-alkoxy substituent in ketone **8** would favor rearrangement to the desired lactone regioisomer (**2**) under Baeyer-Villiger oxidation conditions.[12] Oxidation of ketone **8a** with *m*-CPBA at room temperature proceeded very slowly (50% conversion after 72 h) and gave a disappointing 2:1 mixture of lactone regioisomers **2a** and **9a** respectively (Table 1, entry 1).[13] However, oxidation with pertrifluoroacetic acid (-15 °C/2 h) gave a 98:2 ratio of lactones in 83% chromatographed yield (entry 8). Pertrifluoroacetic acid was generated by reaction of trifluoroacetic anhydride (TFAA) with 30% hydrogen peroxide urea complex[14] (entries 5-6) or 30% aqueous hydrogen peroxide[15] (entries 7-11). Employing the latter procedure, sufficient TFAA was used to consume the water. Trifluoroacetic acid thus comprised 20-50% of the reaction mixture volume. Consistently higher ratios of ketone regioisomers **2:9** were obtained with use of this procedure (e.g. 98:2 vs. 94:6 for **2a:9a**, entries 5 and 10). The origin of this apparent solvent effect may be increased protonation of the β-oxygen by the trifluoroacetic acid.[16]

Oxidation of ketone **2c**, which has the β-oxygen protected as the more electron withdrawing pivaloyl ester group, provided a >90:10 ratio of lactones **2c:9c** regardless of the oxidant (entries 4, 6, and 9). However, oxidations of **2c** were significantly slower those of the *O*-silyl protected ketones. Lactone **2a** was viewed as the most desirable analog for downstream chemistry and was thus carried forward.

Lactone **2a** was reduced with DIBAL at -78 °C and the resulting aldehyde/lactol mixture was treated with trimethylphosphonoacetate and tetramethyl guanidine to provide alcohol **10a** as a single geometric isomer (Scheme 2). Oxidation of alcohol **10a** to the aldehyde followed by addition of phenylmagnesium bromide at -78 °C gave carbinol **11a** in 67% overall yield as a 1:1 mixture of diastereomers.

Scheme 2. Conversion of Lactone **2a** to Cryptophycin Fragment A.

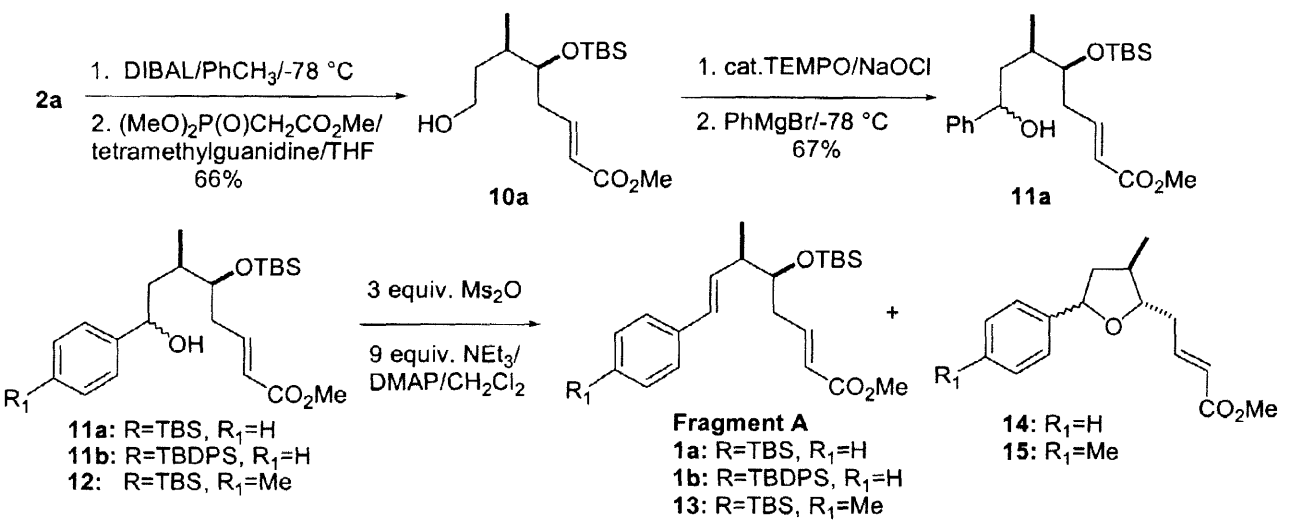

Table 2. Mesylation/Elimination Reactions of Alcohols **11** and **12**.

Compound	Reaction Time (h)	Ratio of Fragment A:14/15	%Yield of Fragment A
11a	42	80:20	53
11b	120	>99:1	41
12	16	97:3	71

To complete the synthesis, alcohol **11a** was converted to the mesylate (methanesulfonic anhydride/triethylamine/DMAP)[17] which eliminated *in situ* to give fragment A (**1a**) in 53% chromatographed yield (97.3% ee, HPLC assay). A by-product, tetrahydrofuran **14,** was also isolated in 14% yield. When alcohol **11b**, which had the less labile *t*-butyldiphenylsilyl protecting group, was subjected to the same mesylation/elimination reaction conditions, **14** was not observed. However, formation of the mesylate was extremely slow (5 d vs. 2 d for **11a**) and **1b** was isolated in 41% yield. Interestingly, reaction of the 4-methyl

phenyl analog (**12**) under identical conditions gave an improved (97:3) ratio of the fragment A analog **13** and the tetrahydrofuran **15** (Table 2). Compound **13** was also formed at approximately three times the rate of the parent compound (**1a**). Apparently, increased electron density at the benzylic carbon of **12** increases the rate of mesylation/elimination relative to the rate of formation of the tetrahydrofuran by-product.

In summary, cryptophycin fragment A (**1a**) was prepared in high enantio- and diastereomeric purity in 7% overall yield from (*R*)-carvone employing a stereoselective bioreduction of carvone and a regioselective Baeyer-Villiger oxidation of the derived β-alkoxy cyclohexanones (**8a, b**). Further details and variations of this chemistry will be the subject of future reports.

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9. In the presence of *Trigonopsis variablis*, ***trans*-4** was independently reduced to **5** with 99% de; ***cis*-4** was reduced under similar conditions to give a 1:1 mixture of the two possible dihydrocarveol diastereomers.
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13. Compounds **2a-c** and **9a-c** were separated by chromatography and distinguished by 500 MHz proton NMR decoupling and HETCOR experiments. Regioisomer ratios in the crude lactone mixtures were determined by integration of the methine proton signals α to the oxygen.
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16. Oxidation of **8a** with 1.5 equiv. of CF_3CO_3H in the presence of excess $NaHCO_3$ (no free CF_3CO_2H present) was much slower (23% conversion/10 h/-15 °C) than the reaction in the presence of CF_3CO_3H. The **2a:9a** ratio was only slightly diminished to 90:10. The regioselectivity difference between oxidations using *m*-CPBA and CF_3CO_3H cannot be fully explained by simple protonation of the β-oxygen. A more detailed study of this reaction will be reported separately.
17. The intermediate mesylate was not observed in any of the reactions. When methanesulfonyl chloride was used, in additon to a 4:1 mixture of **1a:14**, a 25% yield of the benzylic chloride was isolated. The chloride did not eliminate under the reaction conditions.