

TETRAHEDRON LETTERS

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

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Chemical Process R&D, Lilly Research Laboratories, A Division of Eli Lilly and Co., Indianapolis, Indiana 46285 Received 10 July 1998; revised 17 August 1998; accepted 18 August 1998 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.

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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 224² 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.



In our initial work, (R)-carvone (98% ee) was reduced with Zn/EtOH⁵ 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 $Li(s-Bu)_3BH^7$ 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 rearrangement¹⁰ 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)
	89 (t-BuMe-Si)	<i>m</i> -CPBA (2)	CH_CL	22	72	67:33	36 (50%)
2	8a $(t$ -BuMe ₂ Si)	m-CPBA (3) + BF.•Ft O (3)	CH_2Cl_2 CH_2Cl_2	0	4	80:20	75
3	8a (t-BuMe ₂ Si)	<i>m</i> -CPBA (1.6)	CH ₂ Cl ₂	-15	90	72:28	(94%)
4	8c (C(O)t-Bu)	<i>m</i> -CPBA (2)	CH ₂ Cl ₂	-15	48	90:10	(10%)
5	8a (t-BuMe ₂ Si)	CF ₃ CO ₃ H (2.5) ^b	CH ₂ Cl ₂	-15	3	94:6	67
6	8c (C(O)t-Bu)	$CF_{3}CO_{3}H(3.2)^{b}$	CH ₂ Cl ₂	-15	24	93:7	70
7	8a (t-BuMe ₂ Si)	CF ₃ CO ₃ H (2.5) ^c	$CH_2Cl_2/TFA(4:1)$	0	2	94:6	79
8	$8a (t-BuMe_2Si)$	$CF_{3}CO_{3}H(1.6)^{c}$	$CH_2Cl_2/TFA(4:1)$	-15	2	98:2	83
9	8c (C(O)t-Bu)	$CF_{3}CO_{3}H(2.5)^{c}$	$CH_2Cl_2/TFA(4:1)$	-15	18	96:4	70
10	8a (t-BuMe ₂ Si)	$CF_{3}CO_{3}H(2.5)^{c}$	CH ₂ Cl ₂ /TFA(1:1)	-15	2	98:2	80
11	8b (t-BuPh ₂ Si)	$CF_{3}CO_{3}H(2.5)^{c}$	CH ₂ Cl 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 complex¹⁴ (entries 5-6) or 30% aqueous hydrogen peroxide¹⁵ (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 diastereometric 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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References and Notes

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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 CF₃CO₃H in the presence of excess NaHCO₃ (no free CF₃CO₂H present) was much slower (23% conversion/10 h/-15 °C) than the reaction in the presence of CF₃CO₃H. The 2a:9a ratio was only slightly diminished to 90:10. The regioselectivity difference between oxidations using *m*-CPBA and CF₃CO₃H 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.