Tetrahedron Letters, Vol.32, No.46, pp 6771-6774, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

A Novel Stereoselective Synthesis of (+)-Cerulenin and (+)-Tetrahydrocerulenin

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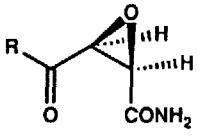
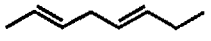
Key Words: Cerulenin synthesis; antibiotic; imide; C_2-symmetry; Grignard addition.

Abstract: *An antibiotic natural (+)-cerulenin and (+)-tetrahydrocerulenin have been synthesized, based on successive alkylation and reduction of chiral cyclic imide with C_2-symmetry derived from D-tartaric acid.*

Cerulenin (**1b**), an antifungal antibiotic first isolated from the culture filtrate of *Cephalosporium caerulens*,[1] has attracted considerable attention since this compound was shown to inhibit lipid biosynthesis of *Escherichia coli* by irreversibly binding β-ketoacyl-acyl carrier protein synthetase, the enzyme which catalyzes the acylation of a malonyl thioester for the chain lengthening reaction of fatty acid synthesis in a variety of yeast cells[2] and also found to be inhibitory for a number of bacteria, fungi, and yeasts.[3] The inhibition mechanism is assumed to be an S-C bond formation between the C-2 of **1b** and cysteine-SH as the enzyme active site.[4]

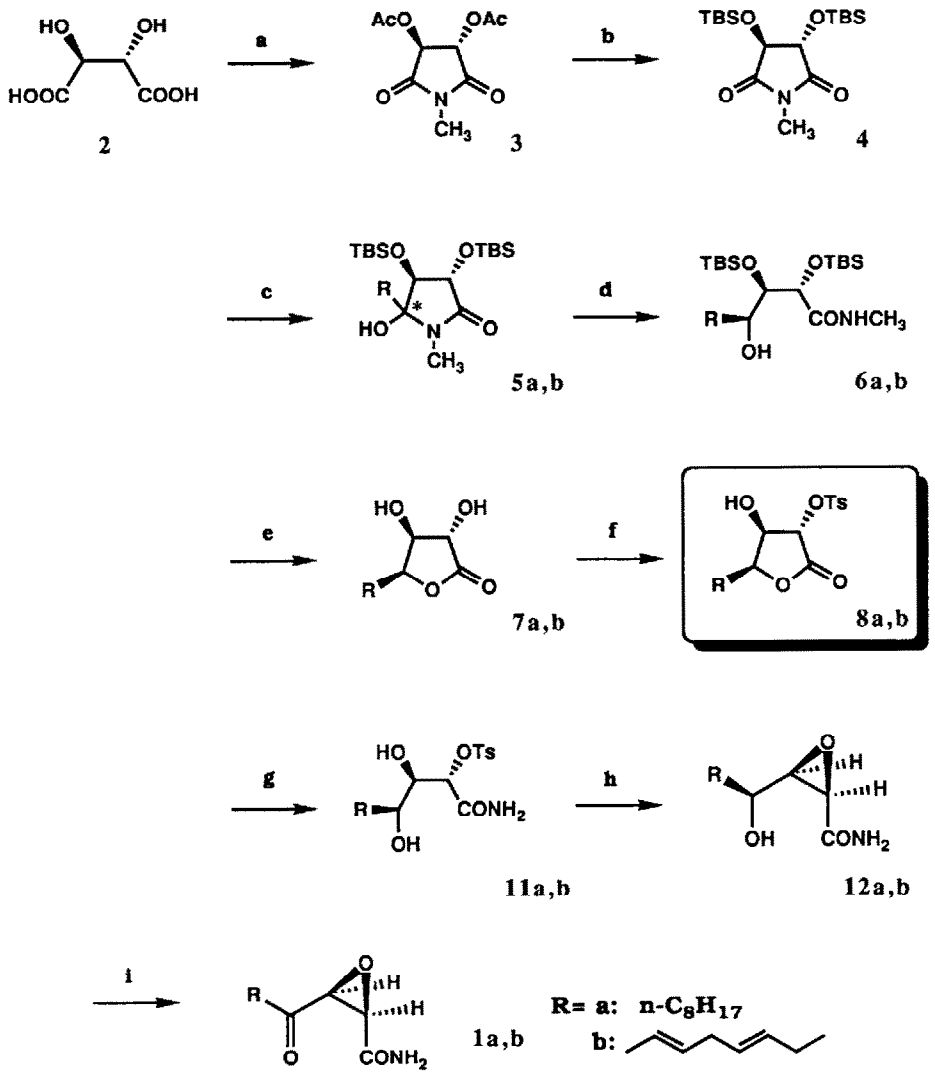


1a: R= n-C_8H_{17}

1b: 

Due to its interesting activity as well as unique structural features such as the keto *cis*-epoxy amide moiety and *trans, trans*-1,4-diene system, **1b** has been the subject of extensive synthetic efforts which have culminated in numerous syntheses of racemic **1b** [5] and chiral syntheses of tetrahydrocerulenin (**1a**).[6] Natural (+)-**1b**,[7] however, has only been synthesized from D-glucose[8] or by using Sharpless' epoxidation.[9] These methods generally required multistage and were not necessarily satisfactory.

Scheme 1



Reagents: (a) 1, AcCl, reflux; 2, CH_3NH_2; 3, AcCl, reflux; (b) 1, AcCl, 60 °C; 2, TBSCl, imidazole, DMF; (c) RMgBr, THF, -78 °C to room temperature; (d) $NaBH_4$, EtOH; (e) 3M HCl, dioxane, 80 °C; (f) TsCl, pyridine, 0 °C; (g) NH_4OH, MeOH, 0 °C; (h) K_2CO_3, MeOH; (i) pyridinium chlorochromate, sodium acetate, CH_2Cl_2.

In this communication we describe a novel chiral syntheses of (+)-**1a** and (+)-**1b** by means of the method recently developed from this laboratory[10] in which asymmetric alkylation and reduction of chiral cyclic imide with C_2-symmetry (**4**) is the essential step for introducing the side chain of **1**.

As shown in scheme 1, C_2-symmetrical imide **4**, $[\alpha]^{25}_D$-134.3° (c 1.68, $CHCl_3$), obtained from D-tartaric acid in 88% yield, was treated with octyl and 3,6-octadienyl Grignard reagents, the latter prepared from 3-butyn-1-ol[9] followed by bromination with Ph_3P-CBr_4 in 65% overall yield, to provide labile carbinolamides **5**, which were successively submitted to reduction with $NaBH_4$ without isolation to afford exclusive diastereomers **6a**, $[\alpha]^{26}_D$-55.98° (c 1.40, $CHCl_3$), in 86% and **6b**, $[\alpha]^{23}_D$-53.99° (c 1.49, $CHCl_3$), in 73% yields, respectively after isolation.[11]

Cyclization and concomitant deprotection of silyl groups of **6** were effected simultaneously by using 3M HCl in refluxing dioxane for 2 h to furnish γ-lactones **7a**, $[\alpha]^{23}_D$-71.90° (c 1.21, $CHCl_3$); mp 68-70 °C, in 87% and **7b**, $[\alpha]^{24}_D$-66.67° (c1.20, $CHCl_3$), in 83% yields containing three contiguous stereogenic centers. Then, **7** were transformed regioselectively into synthetically useful mono-α-sulfonates **8a**, $[\alpha]^{25}_D$-4.94° (c 1.59, $CHCl_3$), in 60% and **8b**, $[\alpha]^{22}_D$-6.19° (c 2.13, $CHCl_3$), in 62% yields in pyridine at 0 °C for 2 days.[12] Accompanying formation of a small amount of mono-β-sulfonates **9** and olefinic mono-α-sulfonates **10**, the latter compounds probably resulted from elimination of the bissulfonates, was observed in this reaction.[13]

Ammonolysis of **8** with ammonium hydroxide in methanol cleanly opened the lactones to single isomers of **11a**, $[\alpha]^{26}_D$-20.04° (c 1.43, MeOH); mp 130-131 °C, and **11b**, $[\alpha]^{24}_D$-22.19° (c 1.11, MeOH); mp 118-120 °C, in nearly quantitative yields. Subsequent treatment of **11** with K_2CO_3 in methanol at room temperature immediately cyclized leading to the chiral *cis*-epoxy amides **12a**, $[\alpha]^{25}_D$-5.09° (c 0.54, MeOH) mp 135-137 °C, in 88% and **12b**, $[\alpha]^{21}_D$-3.75° (c 1.16, MeOH); mp 120-121 °C, in 91% yields stereoselectively after chromatographic isolation.

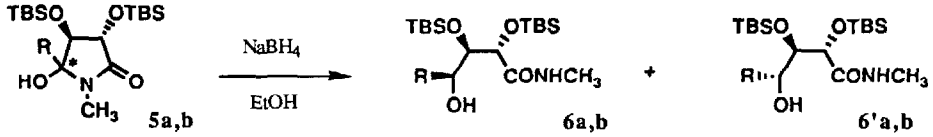
Finally, **12** were effected by oxidation with pyridinium chlorochromate in the presence of sodium acetate to produce (**2R,3S**)-tetrahydrocerulenin (**1a**), $[\alpha]^{21}_D$+57.6° (c 1.51, MeOH after 24 h); mp 90 °C (lit.[6c] $[\alpha]^{20}_D$+57.5° (c 1, MeOH after 24 h); mp 90 °C), in 65% and natural (**2R,3S**)-cerulenin (**1b**), $[\alpha]^{22}_D$+61.8° (c 0.24, MeOH after 24 h); mp 93 °C (lit.[8a] $[\alpha]^{20}_D$+62.0° (c 0.15, MeOH); mp 93 °C), in 63% yields, respectively.[14] The spectral data of the synthetic **1** were identical with those of reported compounds.[7]

In summary, an efficient method for the stereoselective syntheses of (+)-cerulenin and (+)-tetrahydrocerulenin has been developed from D-tartaric acid. We anticipate that chiral C_2-symmetrical imide **4** will serve as a template for the synthesis of the other natural products.

References and notes

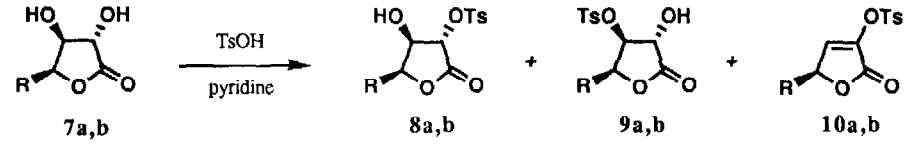
1. Hata, T.; Sano, Y.; Matsumae, A.; Kanio, Y.; Nomura, S.; Sugawara, R. *Nippon Saikingaku Zasshi* **1960**, *15*, 1075.
2. (a) Nomura, S.; Horiuchi, T.; Omura, S.; Hata, T. *J. Biochem.* **1972**, *71*, 783. (b) Vance, D.; Goldberg, I.; Mitsuhashi, O.; Bloch, K.; Omura, S.; Nomura, S. *Biochem. Biophys. Res. Commun.* **1972**, *48*, 649. (c) Nomura, S.; Horiuchi, T.; Hata, T.; Omura, S. *J. Antibiotics*, **1972**, *25*, 365. (d) D'Agnolo, G.; Rosengold, I. S.; Awaya, J.; Omura, S.; Vagelos, P. R. *Biochem. Biophys. Acta*, **1973**, *326*, 155.
3. Matsumae, A.; Nomura, S.; Hata, T. *J. Antibiot.* **1964**, *17*, 1.

4. Funabashi, H.; Iwasaki, S.; Okuda, S.; Omura, S. *Tetrahedron Lett.*, **1983**, *24*, 2673.
5. (a) Boeckman, R. K. Jr.; Thomas, E. W. *J. Am. Chem. Soc.* **1977**, *99*, 2805. (b) Boeckman, R. K. Jr.; Thomas, E. W. *ibid.* **1979**, *101*, 987. (c) Jakubowski, A. A.; Guziec, F. S. Jr.; Tishler, M. *Tetrahedron Lett.* **1977**, 2399. (d) Corey, E. J.; Williams, D. R. *ibid.* **1977**, 3847. (e) Jakubowski, A. A.; Guziec, F. S. Jr.; Sugiura, M.; Tam, C. C.; Tishler, M. *J. Org. Chem.* **1982**, *47*, 1221. (f) Ohta, T.; Tsuchiyama, H.; Nozoe, S. *Heterocycles*, **1986**, *24*, 1137.
6. (a) Ohrui, H.; Emoto, S. *Tetrahedron Lett.*, **1978**, 2095. (b) Pougny, J-R.; Sinay, P. *ibid.*, **1978**, 3301. (c) Vigneron, J. P.; Blanchard, J. M. *ibid.*, **1980**, *21*, 1739.
7. (a) Omura, S.; Katagiri, M.; Nakagawa, A.; Sano, Y.; Nomura, S.; Hata, T. *J. Antibiotics*, A 20, **1967**, *10*, 349. (b) Arison, B. H.; Omura, S. *ibid.*, **1974**, *27*, 28.
8. (a) Sueda, N.; Ohrui, H.; Kazuhara, H. *Tetrahedron lett.*, **1979**, 2039. (b) Pietraszkiewicz, M.; Sinay, P. *ibid.*, **1979**, 4741.
9. Furukawa, J.; Funabashi, H.; Morisaki, N.; Iwasaki, S.; Okuda, S. *Chem. Pharm. Bull.*, **1988**, *36*, 1229.
10. (a) Yoda, H.; Shirakawa, K.; Takabe, K. *Tetrahedron Lett.*, **1991**, *32*, 3401. (b) Yoda, H.; Shirakawa, K.; Takabe, K. *Chem. Lett.*, **1991**, 489.
11. The minor diastereomers **6'a**, $[\alpha]^{26}_{D}$-18.84° (c 1.15, $CHCl_3$), and **6'b**, $[\alpha]^{23}_{D}$-19.44° (c 2.10, $CHCl_3$), were easily separated on silica-gel column chromatography and the ratio of the products was determined after isolation. The reaction mechanisms in asymmetric induction were also previously discussed: see ref. 10a.



a: 94 : 6
b: 91 : 9

12. (a) Barton, D. H. R.; Bénéchie, M.; Khuong-Huu, F.; Dotier, P.; Reyna-Pinedo, V. *Tetrahedron Lett.*, **1982**, *23*, 651. (b) Fleming, P. R.; Sharpless, K. B. *J. Org. Chem.*, **1991**, *56*, 2869.
13. The two side products were separated without difficulty by using flash chromatography to give **9a**, $[\alpha]^{23}_{D}$-58.23° (c 1.84, $CHCl_3$); mp 112-114 °C, **10a**, $[\alpha]^{21}_{D}$+32.56° (c 2.40, $CHCl_3$), **9b**, $[\alpha]^{22}_{D}$-58.15° (c 1.71, $CHCl_3$); mp 101-102 °C, and **10b**, $[\alpha]^{22}_{D}$+32.22° (c 1.80, $CHCl_3$), respectively.



	8a,b	9a,b	10a,b
a:	60%	25%	10%
b:	62%	20%	12%

14. Purification of **1** by normal chromatographic workup eluting with CH_2Cl_2, then ethyl acetate: hexane (1:1) provided a mixture of **1** and the corresponding equilibrated hydroxy lactams.[5a,b,d]

(Received in Japan 5 August 1991)