Published in final edited form as:

Angew Chem Int Ed Engl. 1996 January 19; 35(1): 74–76. doi:10.1002/anie.199600741.

A Convergent, Enantioselective Total Synthesis of Hapalosin: A Drug with Multidrug-Resistance Reversing Activity

Prof. Arun K. Ghosh, Wenming Liu, Yibo Xu, and Zhidong Chen

Department of Chemistry, University of Illinois at Chicago 845 West Taylor Street, Chicago, IL 60607 (USA)

Keywords

chemotherapy; hapalosin; natural products; total syntheses

Hapalosin (**1**), a novel cyclodepsipeptide isolated recently^[1] from the blue-green alga *Hapalosiphon welwilschii*, has shown important multidrug-resistance reversing activity.^[2] The term multidrug-resistance (MDR), is defined as the ability of tumor cells exposed to one drug to develop cross resistance to seemingly unrelated drugs. This phenomenon is apparently caused by an overexpression of P-glycoprotein, a 170–200 kDa transmembrane protein that acts as an ATP-dependent drug efflux pump.^[3] As a consequence, chemotherapy very often becomes ineffective. Thus, the agents that are capable of reversing this P-glycoprotein-induced MDR effect, may have therapeutic potential for patients undergoing cancer chemotherapy. Preliminary biological studies indicated that hapalosin inhibits the P-glycoprotein efflux pump.^[1] Also, hapalosin has already been shown to have better MDR-reversing activity than verapamil which is currently under active investigation to test the MDR-reversing hypothesis in the clinic.^[4] The structure of hapalosin was assigned by Moore et al.^[1] through spectroscopic and degradation studies. Besides important MDR-reversing activity, one of the intriguing features of hapalosin is that the molecule exists as a mixture of two conformers, as shown by ¹H and ¹³C NMR spectroscopy. Perhaps, only one of these conformers is responsible for the potent MDR-reversing activity. In order to study the structure–function relationships as well as to gain information regarding the bioactive conformation, we sought a flexible, enantioselective synthesis of hapalosin. We describe here a convergent and stereocontrolled first total synthesis of hapalosin.

The synthesis of (3*R*,4*S*-4-(*N*-benzyloxycarbonyl-*N*-methy-amino)-3-methoxymethoxy-5-phenylpentanoic acid **5** was carried out stereoselectively starting from Weinreb amide **2** (Fig. 1)^[5] Treatment of **2** with allylmagnesium bromide (2.2 equiv) in THF at –20 °C afforded the corresponding ketone, which was subsequently reduced with sodium borohydride in propanol at 0 °C to provide the alcohol **3** as a mixture (5:1) of diastereomers in 73 % yield.^[6] The isomers were separated by chromatography (silica gel, 15% ethyl acetate/hexane). Protection of the major isomer **3** as a methoxymethyl (MOM) ether followed by *N*-methylation with sodium hydride (2 equiv) and methyl iodide (3 equiv) in a mixture of THF/DMF (10:1) at 23 °C afforded the protected amino alcohol **4** in 68 % yield after silica gel chromatography.^[7] The cleavage of the double bond in **4** with ruthenium trichloride and

excess of sodium periodate in a mixture of acetonitrile, carbon tetrachloride, and water at 23 °C for 12 h provided the acid **5** in 84% yield.^[8]

The protected β -hydroxy acid **7** was conveniently prepared by an asymmetric aldol reaction utilizing an (1S,2R)-aminoindan-2-ol derived chiral auxiliary.^[9] Thus, reaction of *n*-octanaldehyde and the corresponding chiral propionimide using di-*n*-butylboryl trifluoromethanesulfonate and triethylamine at –78 °C furnished the aldol product **6** in 90% yield after silica gel chromatography.^[10, 11] The hydroxyl group was protected as the tetrahydropyranyl ether by treatment with dihydropyran (2 equiv) and a catalytic amount of pyridinium *p*-toluenesulfonate in CH₂Cl₂ at 23 °C for 6 h. The removal of chiral auxiliary was effected with lithium hydroperoxide under standard reaction conditions^[12] to provide the acid **7** in 84 % yield'. Alcohol **8** was prepared by diazotization^[13] of L-valine and subsequent esterification with benzyl alcohol in the presence of dicyclohexylcarbodiimide (DCC) (2 equiv) and dimethylaminopyridine (DMAP) (2 equiv) in CH₂Cl₂.^[14] The acid **7** was esterified by reaction with 2,4,6-trichlorobenzoyl chloride (1.0 equiv), triethylamine (1.2 equiv), and alcohol **8** (1.2 equiv) to afford the diester **9** in 91 % yield.^[15] The removal of the THP protecting group of **9** with *p*-toluenesulfonic acid in methanol followed by esterification of the resulting alcohol with acid **5** using an analogous procedure to that described above furnished the tri-ester derivative **10** in 76 % yield.^[16] Catalytic hydrogenation of **10** over Pearlman's catalyst in ethyl acetate under a hydrogen filled balloon for 5 h provided the requisite precursor **11** for macrocyclization.^[17] The amino acid **11** was subjected to macrocyclization conditions without further purification. Thus, the desired cyclization was effected by slow addition of a solution of **11** in DMF with a syringe pump to a mixture of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (1.5 equiv) and HOBt (1.5 equiv) in the presence of triethylamine (3 equiv) in DMF (0.01 molar solution) at 60 °C to furnish the macrolactam **12** ($[\alpha]_D^{23} = -80.8$, $c = 0.7$, CH₂Cl₂; 30–37% yield after silica gel chromatography). Attempts to improve the yield of the cyclization step by using a variety of reagents and reaction conditions have so far been unsuccessful. Interestingly, the ¹H NMR (400 MHz) spectrum of macrolactam **12** (CDC 13) revealed the presence of a 2:1 mixture of conformers at 23 °C. Removal of the MOM protecting group^[18] of **12** by exposure to tetra-*n*-butylammonium bromide (5 equiv) and trimethylsilyl chloride (5 equiv) in CH₂Cl₂ at 23 °C for 24 h furnished the synthetic (–)-hapalosin **1** ($[\alpha]_D^{23} = -40.9$, $c = 0.1$, CH₂Cl₂; ref.^[1], $[\alpha]_D^{23} = -49.2$, $c = 0.35$, CH₂Cl₂) as a mixture (2:1) of conformers at 23 °C. Spectral data (IR and 400 MHz ¹H NMR) for the major conformer is identical to that reported for the natural product.^[1] The *R*_f value (0.3 in MeOH/H₂O 9/1) is also identical to the reported value. Thus, the synthesis of hapalosin has provided confirmation of the absolute configurational assignments. To gain insight into the bioactive conformation of hapalosin, we are currently studying the design and synthesis of conformationally restricted structural variants of hapalosin.

Acknowledgments

We thank Prof. Robert Moriarty for helpful discussions. Financial support of this project was provided by the University of Illinois at Chicago and Merck Research Laboratories.

References

- [1]. Stratmann K, Burgoyne DL, Moore RE, Patterson GML, Smith CD, J. org. Chem 1994, 59, 7219.
- [2]. Endicott JA, Ling V, Annu. Rev. Biochem 1989, 58, 137. [PubMed: 2570548]
- [3]. a)Pastan I, Gottesman MM, Annu. Rev. Med 1991, 42, 277 [PubMed: 2035973] b)Kartner N, Riordan JR, Ling V, Science 1983, 221, 1285. [PubMed: 6137059]
- [4]. Ozols RF, Cunnion RE, Klecker RW, Hamilton TC, Ostchega Y, Parrillo JE, Young RC, J. Clin. Omi 1987, 5, 641.
- [5]. Nahm S, Weinreb SM, Tetrahedron Lett. 1981, 32 3815.
- [6]. The stereochemistry of the major isomers was assigned based upon comparison of the corresponding BOC derivative of 3 with the sample derived from opening the known epoxide [7] 3 (S) – azido-1,2(R)-epoxy-4-phenylbutane with vinylmagnesium bromide (2 equiv) and cuprous cyanide (catalytic) at -20°C to 0°C followed by hydrogenation of the azide with 10% Pd-C in ethyl acetate in the presence of BOC2O (overall isolated yield 20–22%). The resulting 4(R)hydroxy-5(S)-tert-butyloxycarbonylaminophenylhexane is identical with the hydrogenated BOC derivative of 3.
- [7]. Ghosh AK, Thompson WJ, Holloway MK, McKee SP, Duong TT, Lee HY, Munson PM, Smith AM, Wai JM, Darke PL, Zugay JA, Emini EA, Schleif WA, Huff JR, Anderson PS, J. Med. Chem 1993 36, 2300. [PubMed: 8360874]
- [8]. Carlsen PJ, Katsuki T, Martin V, Sharpless KB. J. org. Chem 1981, 46, 3936.
- [9]. a)Available from Sepracor Inc., Marlborough, MA 01752 (USA). For convenient synthesis and resolution see Ghosh AK, McKee SP, Sanders WM, Tetrahedron Lett. 1991, 32, 711b)Thompson WJ, Fitzgerald PMD, Holloway MK, Emini EA, Darke PL, McKeever BM, Schleif WA, Quintero JC, Zugay JA, Tucker TI, Schwering JE, Homnick CF, Nunberg J, Springer JP, Huff JR, J. Med. Chem 1992, 35, 1685. [PubMed: 1588551]
- [10]. Ghosh AK, T, T. Duong S McKee P, J. Chem. soc. Chem. Commun 1992, 1673 For other asymmetric aldol reactions with suitable chiral auxiliaries, see ref [11].
- [11]. a)Evans DA, Asymmetric Synth. 1984, 3, 1b)Heathcock CH, ibid. 1984 3, 111c)Oppolzer W, Blagg J, Rodriguez I, Walther E. J. Am. Chem. Soc 1990, 112, 2767c) Roder H, Helmchen G, Peters E-M, Peters K, von Schnering HG, Angew. Chem 1984, 96, 895;Angew. Chem. Int. Ed. Engl. 1984, 23, 898d)Gardillo G, Orena M, Romero M, Sandri S, Tetrahedron 1989, 45, 1501e)Sankhavasi W, Yamamoto M, Kohmoto S, Yamada K. Bull. Chem. Soc. Jpn 1991, 64, 1425f)Drewes SE, Malissar DS. G. P. Roos. Chem. Ber 1991, 124, 2913, and references therein.
- [12]. Evans DA, Britton TC, Ellman JA, Tetrahedron Lett. 1987 28, 6141.
- [13]. Mori K, Tetrahedron 1976, 32, 1101.
- [14]. Neises B, Steglich W, Angew. Chem 1978, 90, 556;Angew. Chem. Int. Ed. Engl 1978, 17, 522.
- [15]. Inanaga J, Hirata K, Saeki H, Katsuki T, Yamaguchi M, Bull. Chem. Soc. Jpn 1979, 52, 1989.
- [16]. All new compounds were fully characterized by spectroscopic and analytical methods.
- [17]. An analytical sample of compound II was obtained after chromatography over silica gel (10% MeOH/CHCl₃): $[\alpha]_{\text{D}}^{23} = -5.1$ ($c = 0.93$, CHCl₃); ^1H NMR (400 MHz): $\delta = 0.88$ (t, 3H, $J = 6.9$ Hz, CH_3), 0.98 (d, 3H, $J = 7.0$ Hz, CH_3), 1.02 (d, 3H, $J = 7.1$ Hz, CH_3), 1.18 (d, 3H, $J = 7.0$ Hz, CH_3), 1.17–1.31 (m, 10H, $(\text{CH}_2)_5$), 1.51 (m, 1H, CH_2), 1.72 (m, 1H, CH_2), 2.29 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.47 (dd, 1H, $J = 4.0$, 16.2 Hz, $\text{CH}_2\text{-C=O}$), 2.66 (s, 3H, N-CH_3), 2.71–2.82 (m, 2H, $\text{CH}_2\text{-C=O}$, MeCHC=O), 3.00 (dd, 1H, $J = 5.2$, 14.2 Hz, CH_2Ph), 3.18 (dd, 1H, $J = 8.8$, 14.2 Hz, CH_2Ph), 3.35 (s, 3H, CH_3O), 3.55 (br, s, 1H, CH-NHMe), 3.66 (br, 1H, NHMe), 4.43 (m, 1H, CH-OMOM), 4.73 (ABq, 2H, $J = 6.4$, 9.5 Hz, $\text{O-CH}_2\text{-OMe}$), 4.79 (d, 1H, $J = 4.1$ Hz, O-CH-CHMe_2), 5.34 (dt, 1H, $J = 3.1$, 7.6 Hz, CH-O-CO-CH_2), 7.20–7.38 (m, 5H, Ph); ^{13}C NMR (100 MHz): $\delta = 9.81$ (CH_3), 14.04 (CH_3), 17.29 (CH_3), 19.28 (CH_3), 22.58 (CH_2), 25.65 (CH_2), 29.11 (CH_2), 29.31 (CH_2), 29.74 (CHMe_2), 30.42 (CH_2), 30.98 (CH_2), 31.73 (CH_2Ph), 39.22 (CH_2), 40.43 (CHMeCO), 41.04 (NCH_3), 56.20 (OCH_3), 68.46 (CHNMe), 75.27 (CHOMOM), 77.17 (OCHCHMe_2), 78.66 ($\text{CH}_2\text{CHOC=O}$), 96.50 (OCH_2OMe), 126.82 (CH), 128.77 (CH), 128.72 (CH), 129.18 (CH), 129.37 (CH), 137.2 (C=CH), 169.7 (C=O), 170.0 (C=O), 173.5 (C=O); IR (neat): $\tilde{\nu} = 3660$, 3621, 3020, 2975, 1730, 1716, 1527 cm^{-1} ; MS (70 eV): m/z : 551 (M^+)

- [18]. Hanessian S, Delorme D, Dufresne Y, Tetrahedron Lett. 1984, 23, 2515

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Fig. 1.
The compounds employed and synthesized in this work.