Pergamon

Tetrahedron Letters 40 (1999) 7761–7764

TETRAHEDRON LETTERS

CARBONYL TO METHYLENE CONVERSIONS AT THE TRICARBONYL-PORTION OF ASCOMYCIN DERIVATIVES

Karl Baumann,* H. Knapp, G. Strnadt, G. Schulz, M. A. Grassberger

Department of Chemistry and Pharmacology, Novartis Forschungsinstitut
Brunner Strasse 59, A-1235 Vienna, Austria

Received 27 July 1999; accepted 23 August 1999

Abstract: Treatment of ascomycin or its O-TBDMS-derivatives with hydrogen sulfide and pyridine in dimethylformamide solution results in deoxygenation reactions at the tricarbonyl sequence of the binding domain. 9-deoxo-ascomycins (**5a-c**) are obtained in high yields (75-85%) together with small amounts (2-14% yield) of 10-deoxo-ascomycins (**6a-c**). The novel derivative 10-deoxo-ascomycin (**6a**) is accessible in excellent yield (85%) from the 10-amino-analog of ascomycin upon reaction with hydrogen sulfide in the absence of base.

Ascomycin (**1**) is a macrolactam isolated from the fermentation broth of *Streptomyces hygroscopicus var. ascomyceticus*.[1] Derivatives of ascomycin have shown interesting anti-inflammatory activities in animal models[2] and in man.[3] SDZ ASM 981 (33-epi-chloro-ascomycin, **2**) is the first representative in clinical development for the treatment of inflammatory skin diseases.[4] Ascomycin and related macrolactams feature in the "binding domain" (Fig.1)[5] the unusual pattern of three adjacent carbonyl groups (C8-C10), whereby one carbonyl group is involved in hemiketal formation with the secondary hydroxyl group at C-14.

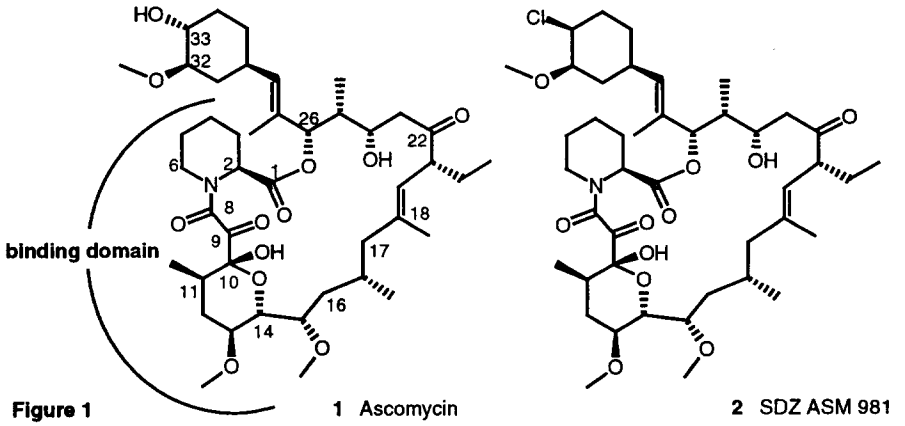

Figure 1 **1** Ascomycin **2** SDZ ASM 981

It was of interest to investigate the impact of chemical modifications at the tricarbonyl-sequence on the biological activity of ascomycin. In a previous paper we reported on the conversion of ascomycin into its 9-imino- and 10-amino-analogs.[6] Here we present a simple, high yield, one step synthesis of 9-deoxo- and 10-deoxo-ascomycin starting from ascomycin or its 9-imino- or 10-amino derivative.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01622-6

Treatment of ascomycin (**1**) or its O-TBDMS derivatives (**3**,**4**) with gaseous dihydrogen sulfide in the presence of pyridine in DMF solution provided the corresponding 9-deoxy-ascomycins (**5a-c**) in high yield (85-75%) together with lower amounts (2-14% yield) of the 10 deoxo-derivatives[7] (**6a-c**, Fig.2, Table 1).

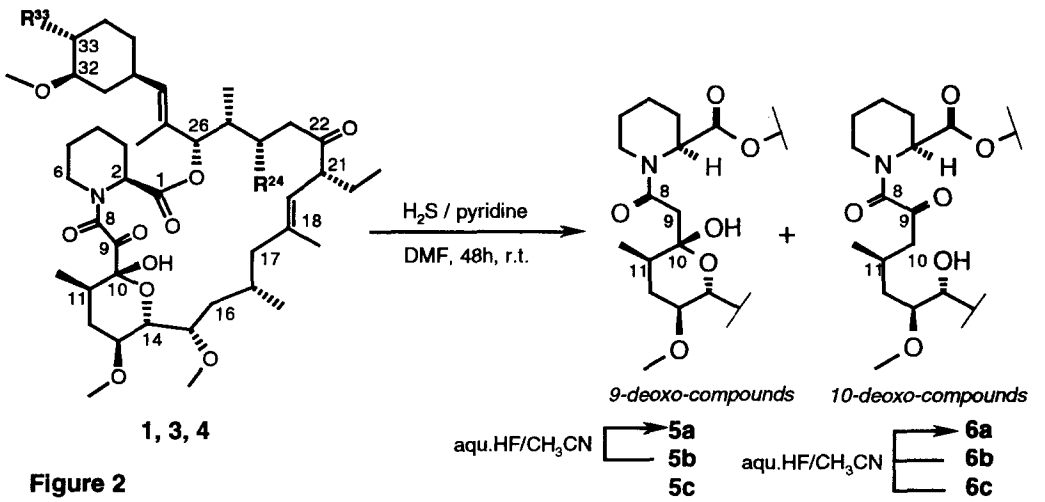

Figure 2

Table 1 Deoxygenation of ascomycin derivatives

entry	educt	R^{24}	R^{33}	9-deoxo (%)[a]	10-deoxo (%)[a]	ratio 9/10-deoxo[b]
1	**1**	OH	OH	**5a** (85%)	**6a** (2%)	95 : 5
2	**3**	TBDMSO[c]	TBDMSO	**5b** (78%)	**6b** (11)	85 : 15
3	**4**	TBDMSO	OH	**5c** (75%)	**6c**(14%)	80 : 20

[a] isolated yields; [b] determined by H NMR, [c] TBDMSO = *tert.*butyldimethylsilyloxy

The NMR data of **5a-c** are in accordance with the data published for **5a**.[8] The protected derivatives **5b** and **5c** were easily converted into **5a** by desilylation using standard conditions (5% HF / acetonitrile, 8h-r.t.; 89% yield of isolated product). The structures of the novel derivative **6a-c** was assigned unambiguously by 2D-NMR analysis.[9] Deprotection of both, **6b** and **6c** provided **6a** (91% and 88% yield of isolated product, respectively) as expected.

Examples of carbonyl to methylene conversion with dihydrogen sulfide are rare,[10a] and the mechanism of the reaction is not fully understood. Although the transient formation of numerous products was observed, when monitoring the course of the reaction by TLC, all attempts to isolate these putative intermediates were unsuccessful. Only starting material or the end products were isolated upon work-up. Taking into consideration the known reactivity of ketones towards dihydrogen sulfide in basic media[10b,c], the following sequence of reactions might take place: (a) thionation of the 9- or 10-carbonyl group; (b) 1,4-addition of a thiolate-anion to give a disulfide; (c) fragmentation of the disulfide to the deoxo derivative and sulfur (Fig.3).

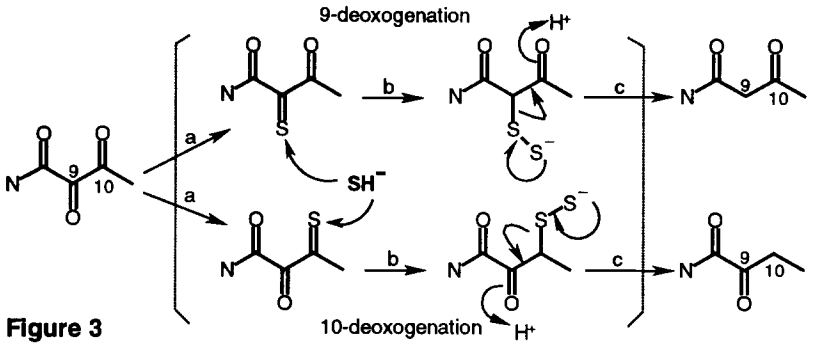

Figure 3

Assuming that a positively charged imonium species should be more reactive towards nucleophilic attack than an inactivated carbonyl group, we hypothesized that the 9- or 10-aza analogues of ascomycin, should readily and regioselectively react with hydrogen sulfide to deoxo-ascomycins in the absence of a base. For experimental proof, the easily accessible aza-analogs 9-imino-ascomycin (**7**) and 10-imino-ascomycin (**8**, masked via aminal-formation with the hydroxyl group at C-14)[6] were treated with dihydrogen sulfide in DMF solution in the absence of pyridine (Fig.4).

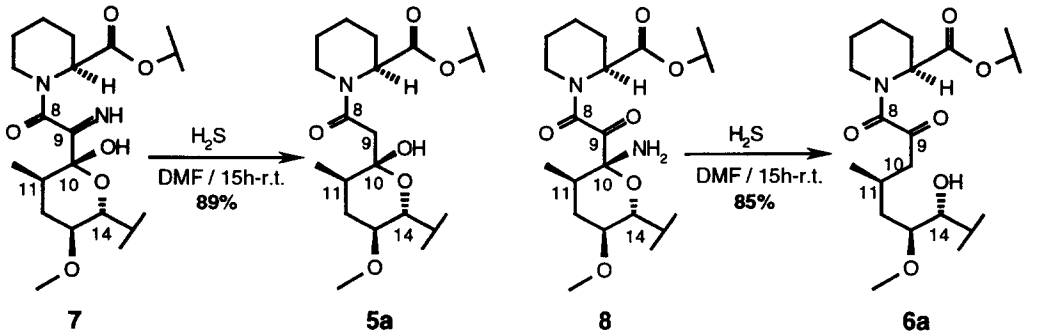

Figure 4 (only partial structures shown)

The reaction yielded, as expected, the 9-deoxo-ascomycin derivative **5a** (from **7**), and more importantly the 10-deoxo derivative **6a** (from **8**) as the single products in excellent yields.

In summary, the synthesis of ascomycin derivatives deoxygenated at C-10 was shown for the first time. In addition, an alternative and easy access to 9-deoxo-ascomycin derivatives was detected. Follow-up experiments indicate that the deoxygenation protocol, described herein, is applicable to a broad range of related macrolactams.[11] Due to their good availability, the deoxo derivatives are versatile starting materials for further modifications.

References and Notes

1. (a) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *109*, 5031. (b) Hatanaka, H.; Kino, T.; Miyata, S.; Inamura, N.; Kuroda, A.; Goto, T.; Tanaka, H.; Okuhara, M. *J. Antibiot.* **1988**, *41*, 1592. (c) Morisaki, M.; Arai, T. *J. Antibiot.* **1992**, *45*, 126.

2. (a) For a review, see: Stuetz, A.; Grassberger, M.A.; Baumann, K.; Edmunds, A.J.F.; Hiestand, P.: Meingassner, J.G.; Nussbaumer, P.; Schuler, W.; Zenke, G. in *Perspectives in Medicinal chemistry,* Testa, B.; Kyburz, E,; Fuhrer, W.; Giger, R. (Eds.), Verlag Helv. Chim. Acta, Basle and VCH, Weinheim, **1993**, Chapt. 27, 427-44.

3. Rappersberger, K.; Meingassner, J. G.; Fialla, R.; Fodinger, D.; Sterniczky, B.; Rauch, S.; Putz, E.; Stuetz, A.; Wolff, K. *J. Invest. Dermatol.* **1996**, *106*, 701.

4. (a) Grassberger, M.A.; Baumruker, T.; Enz, A.; Hiestand, P.; Kalthoff, F.; Schuler, W.; Schulz, M.; Werner, F.-J.: Winiski, A.; Wolff, B.; Zenke, G. *Br. J. Dermatol* in press.(b) Van Leent, E. J. M.; Graber, M.; Thurston, M.; Wagenaar, A.; Spuls, P. I.; Bos, J. D. *Arch. Dermatol.* **1998**, *134*, 805. (c) Graul, A.; Castaner, J. *Drugs Future* **1998**, *23*, 508. (d) Meingassner, J. G.; Grassberger, M.; Fahrngruber, H.; Moore, H. D.; Schuurman, H.; Stuetz, A. *Br. J. Dermatol.* **1997**, *137*, 568. (e) Paul C., Ho V.C. *Seminars in Cutaneous Medicine and Surgery* **1998**, *17*, 1-5.

5. (a) Van Duyne, G. D.; Standaert, R. F.; Karplus, P. A.; Schreiber, S. L.; Clardy, J. *Science* **1991**, 252, 839, and references cited therein. (b) For a review, see: Grassberger, M. A.; Baumann, K. *Current Opinion in Therapeutic Patents*, **1993**, 931. (c) Griffith, J. P.; Kim, J. L.; Kim, E.; Sintchak, M. D.; Thomson, J. A.; Fitzgibbon, M. J.; Fleming, Mark A.; Caron, P. R.; Hsiao, K.; Navia, M. A. *Cell* **1995**, *82*, 507.

6. Nussbaumer, P.; Grassberger, M. A.; Schulz, G. *Tetrahedron Lett.* **1992**, 33, 3845.

7. In a typical run, a solution of the starting material (1mmol of **1,3** or **4**) and 3ml pyridine (37mmol) in 30ml dimethyl formamide was treated with a stream of dihydrogen sulfide at room temperature for three hours. After additional twenty hours at ambient temperature, the mixture was concentrated at reduced pressure and partitioned between brine and ethyl acetate. The organic layer was dried over sodium sulfate, filtered and evaporated to dryness. The residual oil was subjected to column chromatography (silica gel, eluent: n-heptane : ethyl acetate = 1:3 => 1:5 for **5a/6a**; 1:1 =>1 : 2 for **5b/6b** and 4 : 1 => 2 : 1 for **5c/6c**) to give the title compounds according table 1.

8. A multi-step synthesis of 9-deoxo-ascomycin (**5a**) utilizing radical chemistry has been described earlier, see: Emmer, Gerhard; Weber-Roth, Sabine. *Tetrahedron* **1992**, *48*, 5861.

9. Analytical data for **6a**: mixture of conformers 2.1, major conformer: ^{13}C NMR ($CDCl_3$): 212,41 (C-22); 201,73 (C-9); 169,45 (C-1); 167,45 (C-8); 138,32 (C-19); 135,03 (C-29); 131,45 (C-28); 124,87 (C-20); 84,20 (C-32); 83,66 / 79,45 / 76,84 (C-13 / C-15 / C-26); 74,19 (C-14); 73,47 (C-33); 66,40 (C-24); 57,50 / 57,07 / 56,44 (3x methoxy); 54,72 (C-21); 51,66 (C-2); 48,33 (C-18); 47,22 (C-10); 46,28 (C-23); 44,20 (C-6); 40,32 (C-25); 38,01 (C-16); 34,99 / 34,57 / 34,40 (C-12 / C-30 / C-31); 31,24 (C-34); 30,30 (C-35); 27,84 (C-11); 26,89 (C-17); 25,23 / 25,00 (C-3 / C-5); 24,37 (C-36); 21,42 / 21,24 / 21,04 (C-4 / 17-methyl / 11-methyl); 16,47 (19-methyl); 11,85 / 11,60 (C-37 / 28-CH_3); 9,53 (25-methyl).

10. (a) Mayer, R.; Hiller G. *Angew. Chem.* **1963**, *21*, 1001. For reviews, see: (b) Campaigne, E. *Chem. Carbonyl Group.* **1966**, 917. (c) Mayer, R. *Organosulfur Chem.* **1967**, 219.

11. The methodology is applicable to ascomycin-, FK 506- and rapamycin derivatives bearing an intact tricarbonyl domain.