

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-derivatives⁷ (**6a-c**, Fig.2, Table 1).

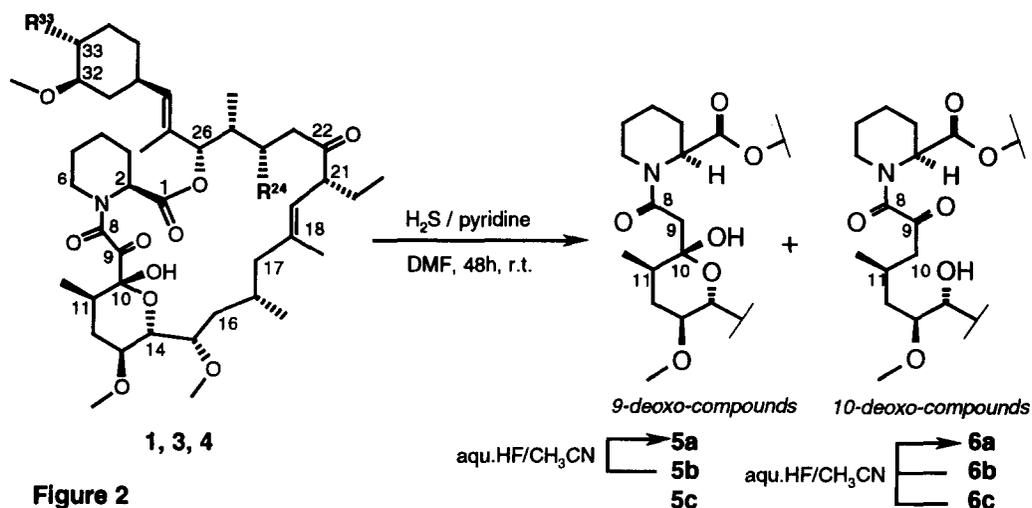


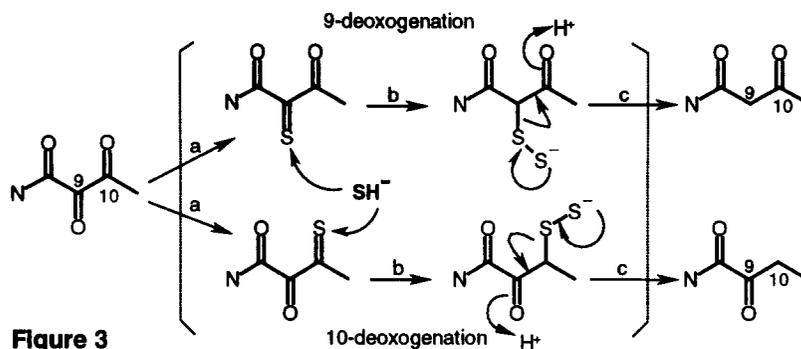
Table 1 Deoxygenation of ascomycin derivatives

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

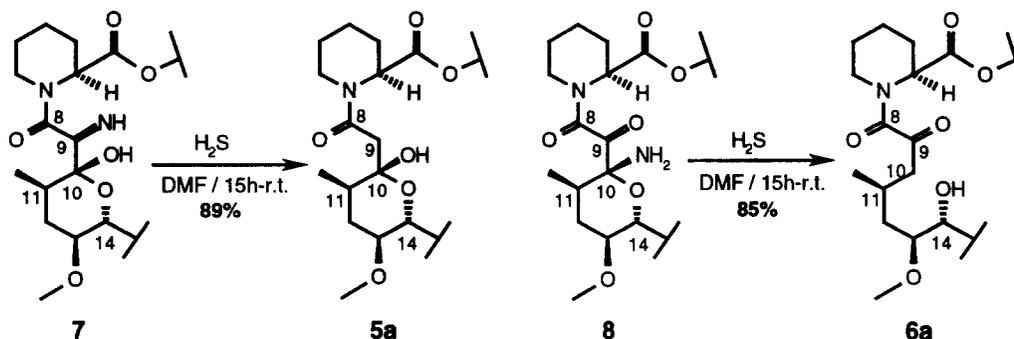
^a) isolated yields; ^b) determined by H NMR, ^c) TBDMSO = *tert*.butyldimethylsilyloxy

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).



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).



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

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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: ¹³C NMR (CDCl₃): 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-CH₃); 9,53 (25-methyl).
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11. The methodology is applicable to ascomycin-, FK 506- and rapamycin derivatives bearing an intact tricarbonyl domain.