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Substantial Refinement of the Photochemical Synthesis of (+)-Aspicilin[1]

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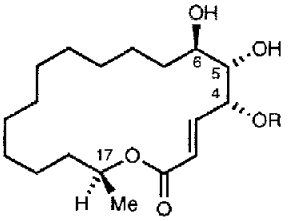
Abstract: *The photochemical synthesis of the 18-membered lichen macrolide (+)-aspicilin (***1a***), reported earlier, is characterized by the successful use of a photolactonization as a key reaction and by diastereoselective generation of stereogenic centers C(4), C(5), and C(6). In comparison with an especially designed reference synthesis, where all the stereogenic centers came from the chiral pool, the photochemical synthesis of* **1a** *needs further refinement. This has been achieved now by the use of* ortho-*formyl benzoic acid as a nucleophile in a Pd(0)-mediated epoxide ring opening furnishing an ester which is known easily to be hydrolyzed by morpholine catalysis.*

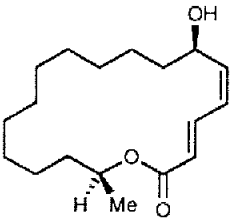
The 18-membered lichen macrolide (+)-aspicilin (**1a**) has been synthesized using the recently developed photolactonization[2] as a key reaction[3,4]. The hydroxy diene lactone **2**, already provided with the correct sense of chirality at stereogenic centers C(6) and C(17), is easily available and plays the role of an essential synthetic intermediate. Its direct transformation (with OsO_4 under the appropriate conditions) selectively into **1a** suffers from a low chemical yield (40%)[3]. Attempts to reach **1a** from **2** via the readily accessible epoxide **4** were only partially successful. Pd(0)-mediated ring opening of the *lyxo*-epoxide[5] **4** in THF in the presence of CO_2, AcOH, and $ClCH_2CO_2H$ afforded the *lyxo*-compounds[5] **3** (73%), **1b** (76%), and **1c** (slightly above 50%) respectively. Hydrolysis of the ring opening products in each case furnished **1a** in an overall yield (relative to **2**) too low to be satisfactory[4]: it is the result of the hydrolysis[6] that falls behind expectation.

Almost three decades ago *M.L. Bender* and *M.S. Silver*[7] have shown, that *ortho*-formyl benzoates undergo an exceedingly fast hydrolysis by neighboring group participation[8]. When epoxide **4** was subjected to Pd(0)-mediated ring opening in the presence of *ortho*-formyl benzoic acid (**5**), compound **1d**[9] successively was formed and hydrolyzed under the very mild *Bender/Silver* conditions producing **1a** in an overall yield of 79% (relative to **4** or 74% relative to **2**).

By smooth conversion of epoxide **4** via ester **1d**[9] into **1a** the total yield of (−)-aspicilin (**1a**) goes up to 15% (relative to phenol as starting material) and exceeds former figures (8%[3] or 4%[4]) substantially. It leaves even the total yield of a previously reported reference synthesis[10] of **1a** (13% relative to D-mannose) behind[11].



1a : R = H
1b : R = Ac
1c : R = $ClCH_2CO$
1d : ROH = 5



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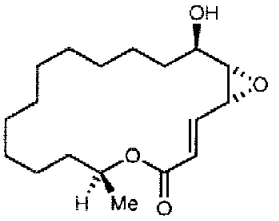

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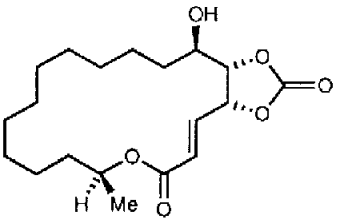

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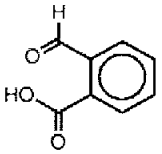

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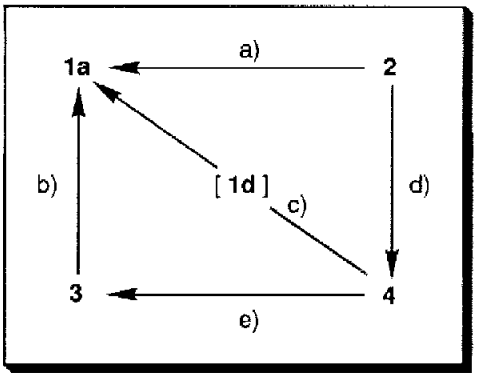

a) lit.[3] : Exper. 2.3
b) lit.[4] : Exper. 2.3.4.1
c) vide infra
d) lit[4] : Exper. 2.1.1
e) lit[4] : Exper. 2.3.3.1

Experimental procedure for the conversion of **4** *via* **1d**[9] *into* **1a**: A 100 ml *Löwenthal* flask equipped with a magnetic stirrer, a dropping funnel, and a nitrogen inlet was charged under nitrogen atmosphere with 198 mg (1.32 mmol, 1.25 eq) of compound **5** (crystallized from ether/pentane) and 30 ml of THF (freshly distilled under nitrogen over sodium/benzophenone) and cooled to 0°C. 36 mg of $Pd(PPh_3)_4$ (0.032 mmol, 3 mol%) was added under nitrogen and a solution of 327 mg (1.054 mmol) **4** in 10 ml of THF was added through the dropping funnel over 2 hr at 0°C. The solution was stirred at 0°C for 2 hr and for additional 2 hr at room temperature. After cooling to 0°C 0.49 ml (4.2 mmol, 4 eq) of 2,6-lutidine, 3 ml of water, and 0.18 ml (2.1 mmol, 2 eq) of morpholine was added and stirred for another 1 hr. Then 200 ml of ethyl acetate (cooled in an icebath) was added and rapidly extracted with 120 ml of 0.05 M aqueous sodium carbonate (cooled in an icebath). The aqueous layer was extracted 4 times with ethyl acetate. The combined organic layers were washed with 100 ml of 1% aqueous phosphoric acid, the aqueous layer was extracted 4 times with ethyl acetate. The combined organic layers were washed with 200 ml of saturated aqueous sodium bicarbonate, the aqueous layer was extracted 4 times with ethyl acetate. The combined organic layers were dried over magnesium sulfate and concentrated with a rotary evaporator. The residue was purified by *flash*-chromatography on 120 g of silica gel, using a 1:1 mixture of hexane and ethyl acetate as eluent, to afford 291 mg (0.885 mmol, 84%) of a colorless solid. Recrystallization from ethyl acetate/hexane furnished 275 mg (0.834 mmol, 79%) of *(2E,4R,5S,6R,17S)-4,5,6-trihydroxyoctadeca-2-en-17-olid* = *(3E,5R,6S,7R,18S)-5,6,7-trihydroxy-18-methyloxacyclooctadec-3-en-2-one*, (**1a**): mp 154-156°C (ethyl acetate/hexane); mixed mp with an authentic sample of **1a** (isolated from lichen; lit.[3]) 154-156°C. $[\alpha]_{589}^{20} = +39.4°$ ($c = 0.868$, chloroform); $[\alpha]_{578}^{20} = -41.3°$; $[\alpha]_{546}^{20} = +46.8°$; $[\alpha]_{436}^{20} = +79.4°$; $[\alpha]_{365}^{20} = +121.6°$. $[\alpha]_{589}^{20} = +43.0°$ ($c = 0.706$, methanol); $[\alpha]_{578}^{20} = +44.8°$; $[\alpha]_{546}^{20} = +50.9°$; $[\alpha]_{436}^{20} = +86.4°$; $[\alpha]_{365}^{20} = +133.8°$. TLC (hexane/ethyl acetate 1:1): R_f 0.19. UV (trifluoroethanol): λ_{max} 207 (12980). The IR- and ^{1}H-NMR data were identical with those ones published before[3]. Anal. Calcd. for $C_{18}H_{32}O_5$ (328.5): C, 65.81; H, 9.82. Found: C, 65.77; H, 9,68.

REFERENCES AND NOTES

1. The work reported here was generously supported by the Deutsche Forschungsgemeinschaft (Project Qu 15/24-1), the Bundesminister für Forschung und Technologie (Project 0318801A+B), the Bundesminister für Wirtschaft (Project 7882 AIF), the Fonds der Chemischen Industrie, and Hoechst AG.
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4. G. Quinkert, U. Döller, M. Eichhorn, F. Küber, H.P. Nestler, H. Becker, J.W. Bats, G. Zimmermann, G. Dürner, *Helv. Chim. Acta* **1990**, *73*, 1999.
5. The stereochemical descriptor *lyxo* is used here to indicate the relative configuration at the three stereogenic centers C(4), C(5), and C(6) according to the convention of the *Fischer* projection pattern (cf. lit.[4]: footnote 11).

6. Total hydrolysis followed by internal *Michael* addition and lactonization of the resulting product leads to a hetereo bicyclic compound described earlier (cf. lit.[4]: compound **33**). For improvement, a leaving group is needed removable under virtually neutral conditions.
7. M.L. Bender, M.S. Silver, *J. Am. Chem. Soc.* **1962**, *84*, 4589; M.L. Bender, J.A. Reinstein, M.S. Silver, R. Mikulak, *J. Am. Chem. Soc.* **1965**, *87*, 4545.
8. A very useful application of *ortho*-formyl benzoates as reactive intermediates has been reported by J.B. Chattopadhyaya, C.B. Reese, A.H. Todd, *J. Chem. Soc., Chem. Comm.* **1979**, 987.
9. Because of its high reactivity ester **1d** usually is not isolated. This can be done, however, suffering heavy losses. The physical properties of *(2E,4R,5S,6R,17S)-4-(2'-formyl)benzoyloxy-5,6-dihydroxyoctadeca-2-en-17-olid* (= *(3E,5R,6S,7R,18S)-o-formylbenzoicacid-(6,7-dihydroxy-18-methyl-2-oxo-1-oxacyclooctadec- 3-en-5-yl)ester*) (**1d**) are as follows: mp 76-76.5°C (ethyl acetate/hexane). $[\alpha]_{589}^{20}$ = +41.6° (*c* = 0.916, chloroform); $[\alpha]_{578}^{20}$ = +43.8°; $[\alpha]_{546}^{20}$ = +50.2°; $[\alpha]_{436}^{20}$ = +93.2°; $[\alpha]_{365}^{20}$ = non-transparent. TLC (hexane/ethyl acetate 2:1): R_f 0.22. UV (trifluoroethanol): λ = 288.0 (2060); λ = 246.5 (8600); λ_{max} = 209.4 (35525). FT-IR (KBr): 3468*s* (br., OH); 2754*w* (C-H, arom. aldehyde); 1708*s* (C=O); 1663*m* (C=C); 992*m* (H-C=C-H, *trans*); 751*m* (arom.). ^{1}H-NMR (DMSO-d$_6$): 1.10–1.64 (*m*, 2H-C(7) – 2H-C(16)); 1.25 (*d*, *J*(H-C(18), H-C(17)) = 6.3, 3H-C(18)); 3.30 (*m*, H-C(6)); 3.78 (*m*, H-C(5)); 4.66 (*d*, *J*(OH-C(6), H-C(6)) = 5.1, OH-C(6)); 5.02 (*m*, H-C(17)); 5.37 (*d*, *J*(OH-C(5), H-C(5)) = 5.0, OH-C(5)); 5.76 (*dd*, *J*(H-C(4), H-C(3)) = 8.3, *J*(H-C(4), H-C(5)) = 1.7, H-C(4)); 6.27 (*d*, *J*(H-C(2), H-C(3)) = 15.8, H-C(2)); 7.02 (*dd*, *J*(H-C(3), H-C(2)) = 15.8, *J*(H-C(3), H-C(4)) = 8.3, H-C(3)); 7.82–7.94 and 8.06–8.13 (2*m*, 4 arom. H); 10.51 (*s*, H-aldehyde). ^{13}C-NMR (DMSO-d$_6$): 20.11 (C(18)); 22.47, 24.43, 25.41, 25.96, 26.43, 27.00, 27.21, 28.05, 31.12, 34.46 (C(7)-C(16)); 69.12 (C(6)); 70.53 (C(17)); 74.50 (C(5)); 75.47 (C(4)); 125.17 (C(2)); 128.22, 130.23, 131.80, 132.66, 133.28, 136.49 (arom. C); 140.92 (C(3)); 164.79, 165.14 (C-benzoyloxy, C(1)); 192.48 (C-aldehyde). Assignment of resolved resonance lines was provided by (^{1}H,^{1}H)- and (^{1}H,^{13}C)-*COSY* spectroscopy (DMSO-d$_6$). Anal. Calcd. for $C_{26}H_{36}O_7$ (460.6): C, 67.80; H, 7.88. Found: C, 67.73; H, 7.95.
10. G. Quinkert, E. Fernholz, P. Eckes, D. Neumann, G. Dürner, *Helv. Chim. Acta* **1989**, *72*, 1753.
11. It ought to be mentioned that the non-natural enantiomer, (–)-aspicilin (*ent*-**1a**), has been synthesized in two laboratories: P.P. Waanders, L. Thijs, B. Zwanenburg, *Tetrahedron Lett.* **1987**, *28*, 2409; G. Solladie, I. Fernandez, C. Maestro, *Tetrahedron Asymmetry* **1991**, *2*, 801.

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