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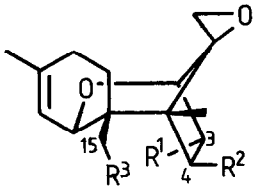
CONVERSION OF ANGUIDINE INTO CALONECTRIN AND 3-DEACETYL-CALONECTRIN [1]

Nicolas Jeker, Peter Mohr & Christoph Tamm*

Institute of Organic Chemistry, University of Basel,
St. Johanns-Ring 19, CH-4056 Basel, Switzerland

ABSTRACT: Anguidine (diacetoxyscirpenol, 2) was converted into calonectrin (3) in 7 steps using the Barton deoxygenation as key reaction.

The trichothecenes are a class of natural products produced by moulds, especially various species of Fungi imperfecti. Many members of the family display a wide range of biological activities [3]. Both the simple sesquiterpenes and their macrocyclic di- and triesters have attracted much attention from the synthetic, biosynthetic and pharmacological view point. It seems now well established that not only the sesquiterpene moiety in the naturally occurring metabolites, most often verrucarol (1), but also the polyfunctionalized macrocyclic portion is relevant for the biological activity. In connection with our interest in preparing novel, unnatural macrocycles, we studied the functional group interchange of anguidine (diacetoxyscirpenol, 2) [4]. In this communication we report a relatively efficient conversion of this metabolite readily available from various Fusarium strains into 3-deacetyl-calonectrin (3) and calonectrin (4) [5].



1	R^1=H,	R^2=OH,	R^3=OH	Verrucarol
2	R^1=OH,	R^2=R^3=OAc		Anguidine
3	R^1=OH,	R^2=H,	R^3=OAc	3-Deacetyl-calonectrin
4	R^1=R^3=OAc,		R^2=H	Calonectrin
5	R^1=H,	R^2=OH,	R^3=H	Trichodermol

Our strategy was analogous to that of Tulshian and Fraser-Reid which they followed in the transformation of 2 into verrucarol (1) and trichodermol (5) [6]. Key reaction was a Barton-deoxygenation via the corresponding thiocarbonyl--imidazole derivative [7]. The yield was nearly quantitative. Another crucial step was the chemical differentiation of the C(4)- and C(15)-hydroxyl groups. Whereas silylation (TBDMS-Cl/DMAP/NEt_3) [8] gave erratic results, acetylation

proceeded with fairly good selectivity comparable to that observed in the verrucarol series [6,9]. The scheme summarizes the reaction sequence leading to 3-deacetyl-calonectrin (3) and calonectrin (4) in 6, respectively 7 steps with 30% overall yield for 4. The final products were characterized and identified as follows [10]. Deacetylcalonectrin (3): m.p. 142.5-148° (hygr.), Lit. 144-145°, microanalysis (found C 65.92%, H 7.92%; calc. C 66.21%, H 7.85%); IR (KBr): 3460 (br), 3060, 3020, 2975, 2945, 1740, 1680, 1245; MS (EI, 10eV): 308 (M^+, 0.3%), 265 (5.0%), 249 (18%), 248 (100%), 220 (98%); NMR spectra see Table 1 and 2. Calonectrin (4): m.p. (82.8-85.3°, Lit. 83-85°), $[\alpha]_D^{27}$ = +5.8° (Lit. +14.6°, authentic reference sample +6.2°, $CHCl_3$), microanalysis (found C 64.85%, H 7.44%; calc. C 65.12%, H 7.48%). IR (KBr): 2980, 2940, 2895, 1745, 1730, 1680, 1245. MS (EI, 50eV): 351 (MH^+ 4.26%), 307 (1.3%), 291 (18.5%), 262 (13.5%), 41 (100%); NMR spectra see Table 1 and 2.

Experimental Procedures: 3-O-THP,15-O-acetyl-scirpentriol: 2.00 g (5.46 mmol) of diol 6 was dissolved in 40 ml of CH_2Cl_2 and treated with 2.64 ml of pyridine and 1.03 ml of Ac_2O (2 eq.). After standing at RT for 14 h, the reaction mixture was diluted with ether, washed with 1N HCl and sat. $NaHCO_3$, dried over Na_2SO_4 and evaporated i.v. column chromatography of the residue (SiO_2/ether) yielded 1.296 g of the 15-monoacetylated product.

3-Deacetyl-3-O-THP-calonectrin (7): 201 mg (0.49 mmol) of the above prepared alcohol were refluxed for 6.5 h in 6 ml of 1.2-dichloromethane containing 211 mg (1.19 mmol) of N,N-thiocarbonyldiimidazole. After cooling, CH_2Cl_2 was added and washed with 1N HCl, sat. $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness (253 mg). 238 mg of this crude product were dissolved in 11 ml of toluene and added dropwise during 0.5 h in an Argon atmosphere to 0.243 ml (0.92 mmol) of nBu_3SnH. After additional 2 h at 110° the reaction mixture was cooled and evaporated i.v. column chromatography of the residue (SiO_2/ether) yielded 170 mg of 6.

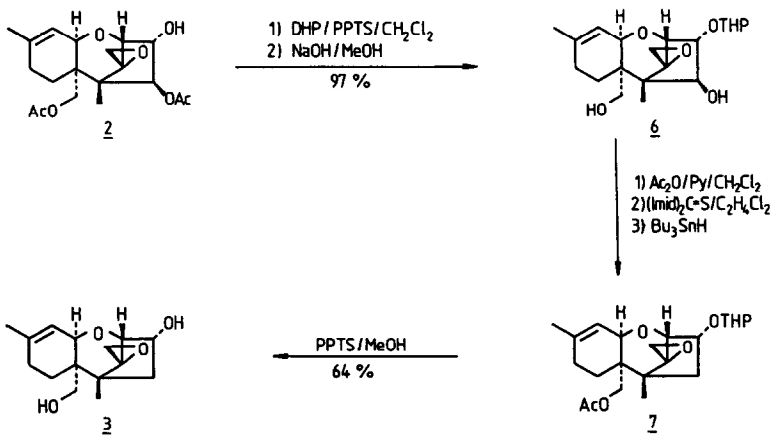


Table 1: ^{1}H NMR (200 MHz, $CDCl_3$)

	3-Deacetylcalonectrin (3)	Calonectrin (4)
2-H	3.53 (d, J = 4.5, 1 H)	3.76 (d, J = 5, 1 H
3-H	4.47 (m, 1 H), dxdxd: after exchange with D_2O	5.17 (dxdxd, 1 H)
4-H	1.5 - 2.3 (m)	1.5 - 2.3 (m)
7-H	1.5 - 2.3 (m)	1.5 - 2.3 (m)
8-H	1.5 - 2.3 (m)	1.5 - 2.3 (m)
10-H	5.51 (d (br), J = 5, 1 H)	5.47 (d (br), J = 5, 1 H)
11-H	4.15 (d (br), J = 5, 1 H)	4.03 (d (br), J = 5, 1 H)
13-H	2.86 and 3.09 (2xd, J = 4, 2 H)	2.86 and 3.10 (2xd, J=4, 2 H)
14-H	0.82 (s, 3 H)	0.83 (s, 3 H)
15-H	3.85 and 4.09 (2xd, J = 12, 2 H)	3.85 and 4.09 (2xd, J=12, 2 H)
16-H	1.73 (s (br), 3 H)	1.73 (s (br), 3 H)
OAc	2.06 (s, 3 H)	2.05 (s, 3 H)
OAc	--	2.12 (s, 3 H)

Table 2: ^{13}C NMR (22,63 MHz, $CDCl_3$)

	3-Deacetylcalonectrin (3)	Calonectrin (4)
C-2	68.4 (d)	68.3 (d)
C-3	69.1 (d)	71.4 (d)
C-4	42.4 (t)	39.6 (t)
C-5	45.9 (s)	45.5 (s)
C-6	43.1 (s)	43.2 (s)
C-7	21.2 (t)	21.0 (t)
C-8	28.4 (t)	28.3 (t)
C-9	140.1 (s)	140.1 (s)
C-10	119.3 (d)	119.2 (d)
C-11	80.0 (d)	78.2 (d)
C-12	65.6 (s)	65.1 (s)
C-13	48.4 (t)	48.5 (t)
C-14	12.3 (q)	12.2 (q)
C-15	62.8 (t)	63.8 (t)
C-16	23.2 (q)	23.1 (q)
$OCO\underline{C}H_3$	21.0 (q)	21.2 (2xq)
$O\underline{C}OCH_3$	170.6 (s)	170.5 (s) 170.2 (s)

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