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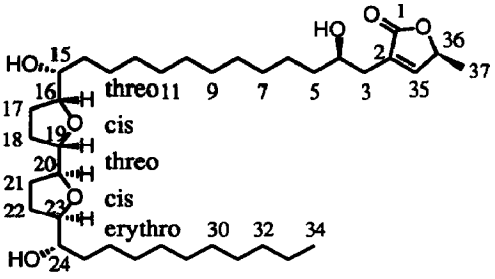
Total Synthesis of (+)-Rolliniastatin 1

Ulrich Koert

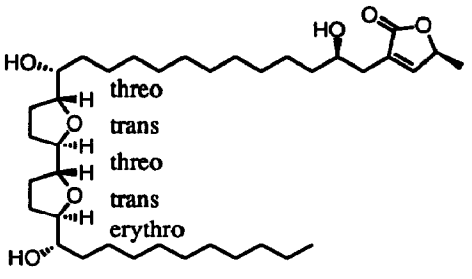
Fachbereich Chemie der Philipps Universität
D-35032 Marburg, Germany

Abstract: The first total synthesis of the naturally occurring acetogenin (+)-rolliniastatin 1 (1) has been achieved. A high degree of stereochemical control in the construction of the bis-THF system was accomplished by chelation controlled addition of functionalized organo-metallic reagents derived from **5** and **11** to α-alkoxy-aldehydes.

(+)-Rolliniastatin 1 (**1**) belongs to the Annonaceous acetogenins,[1] a growing class of natural products with promising antitumor and pesticidal properties. Its isolation from seeds of *rollina mucosa* and structural characterisation was first reported in 1987.[2] The relative configuration was established by X-ray structure analysis.[2] From a structural point of view, rolliniastatin 1 (**1**) possesses a rare *cis-threo-cis* stereostrucure in the bis-tetrahydrofuran (bis-THF) system compared to the more common *trans-threo-trans* pattern found e.g. in (+)-bullatacin **2**.[3] The crucial part in the synthesis of any of these natural products is the stereoselective elaboration of the bis-THF diol moiety. While we had already developed a stereoselective approach to related oligo-tetrahydrofurans with the relative configuration *trans-threo-trans*,[4] we focus here on the *cis-threo-cis* stereostructure. So far in the class of bis-THF natural products the non-natural (-)-enantiomer of bullatacin[5] and a non-natural diastereomer of uvaricin[6] have been synthesized by other groups.[7] In addition, a few chiral building blocks suitable for the preparation of acetogenins have been reported.[8] Described here is the first synthesis of (+)-rolliniastatin 1 (**1**).



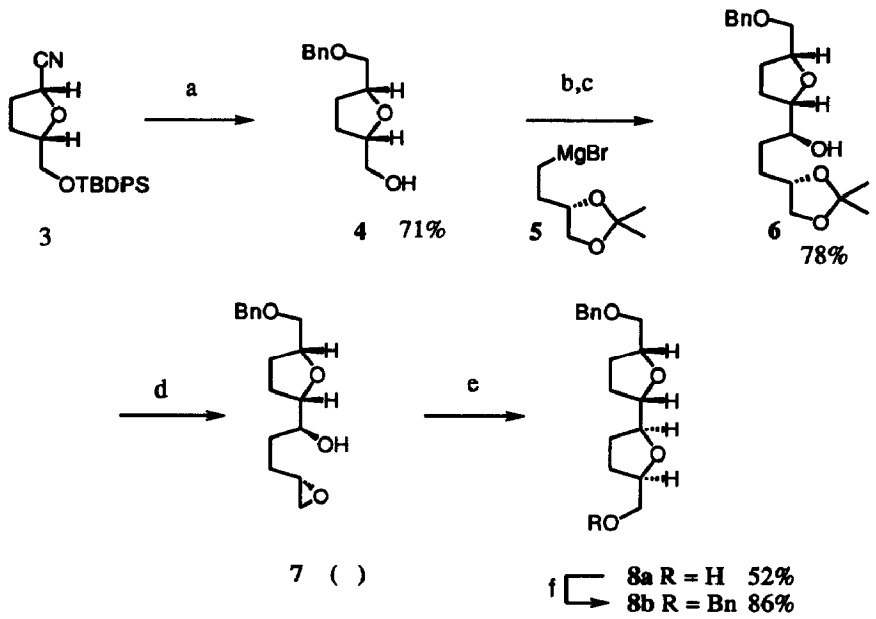
1
(+)-Rolliniastatin 1



2
(+)-Bullatacin

The synthesis starts with the enantiomerically pure *cis* nitrile **3** available in 5 steps from L-glutamic acid.[4] The nitrile **3** was converted into the corresponding methyl ester, which was reduced to the alcohol. Benzylation and desilylation gave access to the alcohol **4** (scheme 1). After oxidation to the corresponding

aldehyde, a Cu(I) catalyzed reaction with the Grignard compound **5** [9] afforded the acetonide alcohol **6** (stereoselectivity: 93/7). The stereochemical outcome of this reaction corresponds to our results in the *trans* THF series,[4] and can be rationalized by a chelation controlled reaction pathway. Stereoselective conversion of the acetonide into an epoxide, and intramolecular epoxide opening gave the tetrahydrofuran-dimer monoalcohol **8a**. The *cis-threo-cis* stereostructure of **8a** was proved by conversion to the C-2 symmetric dibenzyl ether **8b**, the symmetry of which was evident from the NMR spectra.



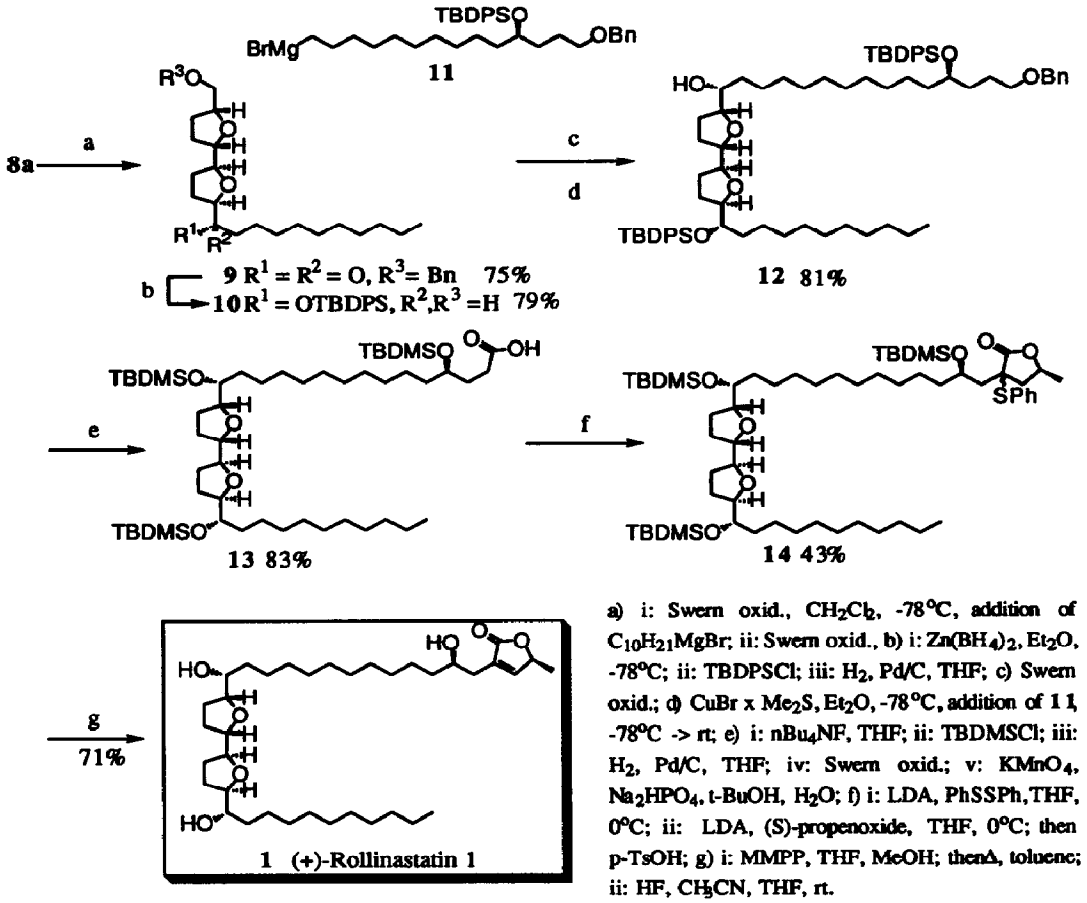
scheme 1

a) i: NaOMe, MeOH; ii: $LiAlH_4$, THF; iii: BnBr, NaH; iv: nBu_4NF, THF; b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C; c) 5, CuBr • Me_2S, -78°C, Et_2O, then addition of aldehyde, -78°C -> rt; d) i: HOAc, THF/H_2O: ii: $MesitylSO_2Cl$, pyridine, 0°C; iii: K_2CO_3, MeOH; e) HOAc, CH_2Cl_2, rt; f) BnBr, DMF.

Having completed the stereoselective construction of the bis-THF system, we focussed on the attachment of the lower side chain next. Swern oxidation of alcohol **8a** followed by *in situ* reaction with decyl magnesium bromide and a second Swern oxidation produced the ketone **9** (scheme 2). This was stereoselectively reduced to the *erythro* alcohol with $Zn(BH_4)_2$ (stereoselectivity: 82/18). Subsequent t-butyldiphenylsilyl (TBDPS) protection and debenzylation provided access to alcohol **10** with the lower side chain now in place.

Finally, the stereoselective introduction of the upper side chain was addressed. After oxidation of **10** to the corresponding aldehyde, a Cu(I) catalyzed reaction with the Grignard compound **11** [10] afforded the *threo* alcohol **12** (stereoselectivity: 95/5). The di-TBDPS ether monoalcohol **12** was desilylated and reprotected to yield the corresponding tri-t-butyldimethylsilyl (TBDMS) ether. The latter was debenzylated and the resulting alcohol was oxidized, via the aldehyde, to the acid **13**. Next, the unsaturated γ-lactone moiety was introduced. Towards this end, the dianion of the acid **13** was allowed to first react with PhSSPh, and then with (S)-

propenoxide to give, after acid treatment, the lactone **14**. Oxidation of the thioether **14** to the sulfoxide and thermal elimination were used to introduce the double bond. The thioether oxidation was best accomplished with magnesium monoperoxophthalate (MMPP). Oxidation with m-chloro-perbenzoic acid (MCPBA)[6] gave considerable amounts of sulfone byproduct. At last, deprotection with 5 % HF in CH_3CN/THF afforded the target compound (+)-rolliniastatin 1 (**1**).



a) i: Swern oxid., CH_2Cl_2, -78°C, addition of $C_{10}H_{21}MgBr$; ii: Swern oxid., b) i: $Zn(BH_4)_2$, Et_2O, -78°C; ii: TBDPSCl; iii: H_2, Pd/C, THF; c) Swern oxid.; d) CuBr x Me_2S, Et_2O, -78°C, addition of **11**, -78°C -> rt; e) i: nBu_4NF, THF; ii: TBDMSCl; iii: H_2, Pd/C, THF; iv: Swern oxid.; v: $KMnO_4$, Na_2HPO_4, t-BuOH, H_2O; f) i: LDA, PhSSPh, THF, 0°C; ii: LDA, (S)-propenoxide, THF, 0°C; then p-TsOH; g) i: MMPP, THF, MeOH; then Δ, toluene; ii: HF, CH_3CN, THF, rt.

scheme 2

Our synthetic **1** (mp. 78-80 °C from acetone), $[\alpha]_D^{20} = +25^\circ$ (c = 0.51, CH_2Cl_2); lit[2]: mp. 81-83 °C from acetone), $[\alpha]_D^{28} = +25.2^\circ$ (c = 1.03, CH_2Cl_2) was found by TLC, ^{1}H-NMR and ^{13}C-NMR[10] to be identical to the naturally occurring compound.[11] The *threo-cis-threo-cis-erythro* stereostructure of the bis-THF diol moiety is reflected by its characteristic ^{13}C-NMR data. The six oxygen bearing carbons of this moiety in **1** show resonances at δ = 74.00 (C-15), 71.97 (C-24), **80.95, 81.11**, 82.90, 83.04 (C-16,19,20,23). In comparison to that, the ^{13}C-NMR spectrum of bullatacin **2** [3] with the *threo-trans-threo-trans-erythro*

stereostructure shows six resonances at δ = 74.08 (C-15), 71.34 (C-24), **82.17, 82.44**, 82.75, 83.20 (C-16,19,20,23).

In summary, the first total synthesis of (+)-rolliniastatin 1 (**1**) has been accomplished. This work unequivocally proves the absolute configuration of the natural product and confirms the assigment made on the basis of NMR measurements.[13] The synthetic strategy presented here provides a convenient entry into other members of this class of biologically active compounds.

Acknowledgement: Financial support by the Deutsche Forschungsgemeinschaft as well as the Fonds der Chemischen Industrie and Wacker AG is gratefully acknowledged.

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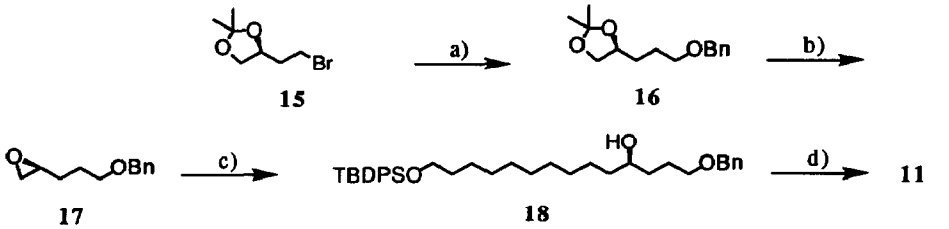
10. The Grignard compound **11** was prepared from the enantiomerically pure bromide **15** [9] using the following reaction sequence:



a) NaCN, DMSO, 94%; ii: NaOH; $LiAlH_4$, 78% iii: BnBr, NaH, DMF 83%; b) i: HOAc, 97%; ii: TsCl, Py; K_2CO_3, MeOH, 77% c) $TBDPSO(CH_2)_9MgBr$, CuBr x Me_2S, 91%; b) i: TBDPSCl, 95%; ii: nBu_4NF, THF, rt, 88%; iii: TsCl, pyridine, 93%; iv: LiBr, THF, 93%; v: Mg, Et_2O.

11. All new compounds gave satisfactory analytical and spectral data according to their structures. Spectral information for synthetic (+)-rolliniastatin 1 (**1**):
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.86 (t, J = 7.4 Hz, 3H, CH_3-34), 1.10-1.45 (m, CH_2-(7-13, 26-33)), 1.41 (d, J = 6.9 Hz, 3H, CH_3-37), 1.74-1.96 (m, 8H, CH_2-17,18,21,22), 2.18 (bs, 1H, OH), 2.38 (ddt, J = 15.1/8.2/1.2 Hz, 1H, CHH-3), 2.51 (ddt, J = 15.1/3.5/1.2 Hz, 1H, CHH-3), 2.80 (bs, 1H, OH), 2.92 (bs, 1H, OH), 3.38-3.40 (m, 1H, CH-15), 3.80-3.91 (m, 6H, CH-4,16,19,20,23,24), 5.03 (dq, J = 6.9/1.5 Hz, 1H, CH-36), 7.17 (d, J = 1.3 Hz, CH-35).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.10 (C-34), 19.12 (C-37), 22.68, 23.75, 25.56, 25.77, 26.01, 27.91, 28.45, 28.78, 29.33, 29.48, 29.51, 29.54, 29.57, 29.62, 29.71, 31.91 (C-(6-13), (26-33), overlapping of signals at 29.5-29.7), 32.79, 33.36, 34.29, 37.43 (C-3,5,14,25), 70.02 (C-4), 71.97 (C-24), 74.00 (C-15), 77.94 (C-36), 80.95, 81.11, 82.90, 83.04 (C-16,19,20,23), 131.24 (C-2), 151.71 (C-35), 174.53 (C-1). The NMR spectra of synthetic (+)-rolliniastatin 1 (**1**) were identical with the NMR spectra of a natural sample[12] recorded with the same NMR spectrometer and corresponded to the literature data.[2]
12. We are indebted to Prof. G. R. Pettit/Arizona State University for kindly providing a sample of natural (+) rolliniastatin 1.
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