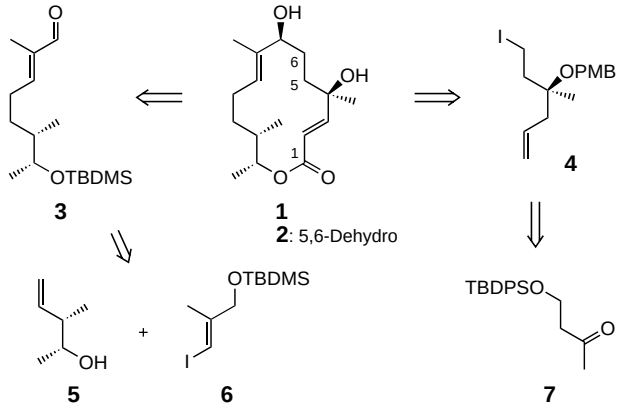
Total Synthesis of the Macrolide Antibiotic 5,6-Dihydrocineromycin B**

Lutz F. Tietze* und Ludwig Völkel

Dedicated to Professor Burchard Franck on the occasion of his 75th birthday

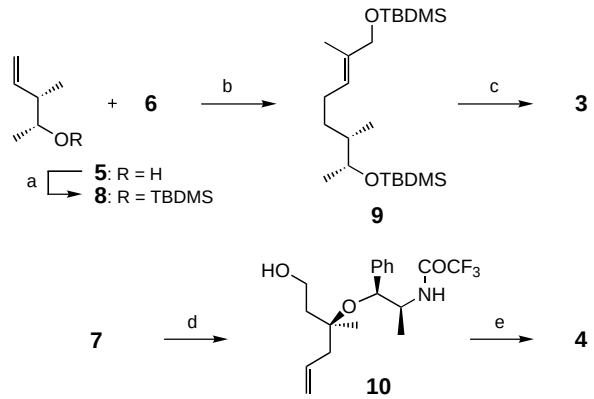
5,6-Dihydrocineromycin B (**1**) belongs to the group of macrolide antibiotics with a 14-membered lactone functionality and has been isolated recently from *Streptomyces* sp. Gö 40/10 together with cineromycin B (**2**) and other metabolites by Zeeck et al.[1] The group of cineromycins and albocyclins—18 compounds are currently known—are particularly important due to their antibiotic activity against staphylococci. To date only one report has appeared in which the syntheses of this class of compounds is described.[2] Here we outline the first total synthesis of 5,6-dihydrocineromycin B (**1**) as well as that of the 7-*epi* diastereomer **17** and of the corresponding 2,3,5,6-tetrahydro compound **14**.

The retrosynthesis of **1** leads to the chiral building blocks **3** and **4** (Scheme 1). Compound **3** can be obtained from the known homoallyl alcohol **5**[3] and the vinyl iodide **6**;[4] the tertiary homoallyl ether **4** is accessed through a facial selective allylation[5] of the ketone **7**.



Scheme 1. Retrosynthesis of 5,6-dihydrocineromycin B (**1**). TBDMS = *tert*-butyldimethylsilyl, PMB = 4-methoxybenzyl, TBDPS = *tert*-butyldiphenylsilyl.

The alcohol **5** was converted into the silyl-protected compound **8** and then intermediary by reaction with 9-BBN into the corresponding borane for the cross coupling with **6** (Scheme 2).[6] In the subsequent reaction with **6**, a small variation of the reaction conditions usually applied for such couplings, led to a considerable increase in the yield and rate



Scheme 2. a) TBDMSCl, imidazole, DMF, DMAP, RT, 100%; b) **8**, 9-BBN, THF, 0°C→RT, then **6**, DMF, 2.8 equiv H_2O, K_3PO_4, 5 mol% [$PdCl_2$(dppf)], RT, 85%; c) 1. 40% HF(aq)/pyridine 1:10, RT, 89%; 2. MnO_2, CH_2Cl_2, RT, 96%; d) 1. 2 equiv **7**, 2 equiv allyltrimethylsilane, 1 equiv of the trimethylsilyl ether of *N*-trifluoroacetamidonorpseudoephedrine, 0.2 equiv TfOH, CH_2Cl_2, −78°C, 17 h; 2. crude product, 40% HF(aq), CH_3CN, RT, crystallization from pentane/*t*BuOMe, 73%, *ds* > 99:1; e) 1. Li, NH_3/THF, −78°C, then NH_4Cl, 90%; 2. TBDPSCl, DMAP, imidazole, DMF, RT, 99%; 3. PMBO(NH)CCl_3, cat. TfOH, Et_2O, 0°C; 4. crude product, TBAF·$3H_2O$, THF, 50°C, 66%; 5. I_2, imidazole, PPh_3, CH_2Cl_2, RT, 90%. DMAP = 4-dimethylaminopyridine, 9-BBN = 9-borabicyclo[3.3.1]nonane, Tf = trifluoromethanesulfonyl, TBAF = tetrabutylammonium fluoride.

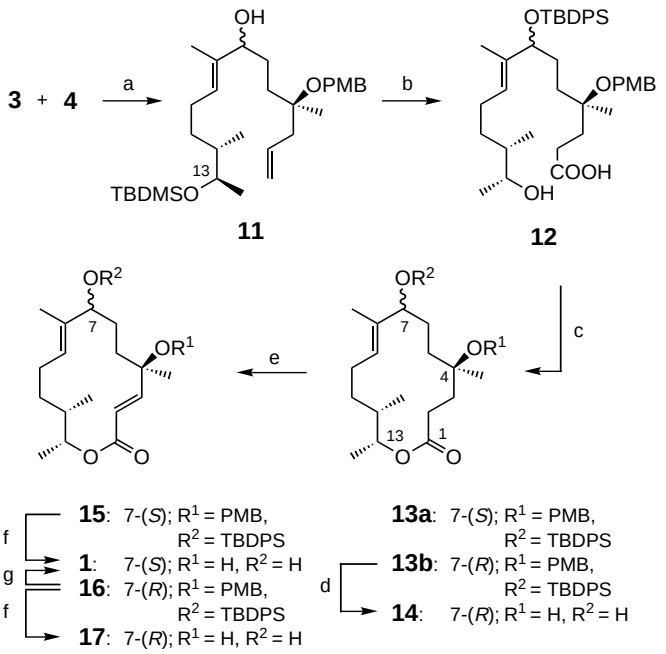
of reaction: The reaction with K_3PO_4 as base and DMF as solvent at 50°C for 6–24 h under dry conditions in the presence of catalytic amounts of [$PdCl_2$(dppf)] (dppf = bis-(diphenylphosphanyl)ferrocene) gave **9** with a moderate yield of 18–37%. On the other hand, addition of a small amount of water to the reaction mixture led, after 5 h at 25°C, to a yield of 85%. The selective cleavage of the primary silyl ether unit in **9** with HF(aq)/pyridine, followed by oxidation with manganese dioxide gave **3** in 85% yield. The building block **4** was generated by converting the ketone **7**, in accordance with our previously described method,[5] followed by cleavage of the silyl ether, into the diastereomerically pure homoallyl ether **10**. Removal of the auxiliaries from **10**, followed by introduction of a 4-methoxybenzyl group at the tertiary hydroxy group and the replacement of the primary hydroxy group with an iodine substituent gave the desired product with an *ee* value of >99%.

We have also carried out this synthesis sequence with a *tert*-butyldimethylsilyl group at the tertiary hydroxy group; unfortunately on deprotection of the 2,3,5,6-tetrahydro derivative of cineromycin B (**2**) at the end of the synthesis, a complete rearrangement of the 14-membered lactone ring to give a γ-lactone occurred, forcing us to choose another protecting group. For the 1,2-addition to the α,β-unsaturated aldehyde **3**, the iodide **4** was allowed to react with *sec*-butyllithium at −78°C 10 min (Scheme 3). (With longer reaction times or use of *tert*-butyllithium, deprotonation of the 4-methoxybenzyl group at C-4 and subsequent Wittig rearrangement become more pronounced.[7]) The addition on **3** gave the allyl alcohol **11** as a 1:1 mixture: attempts to carry out the reaction selectively according to the method developed by Knochel et al.,[8] failed because the corresponding organozinc compound was unaccessible. Protection of the

[*] Prof. Dr. h.c. L. F. Tietze, Dipl.-Chem. L. Völkel
Institut für Organische Chemie der Universität
Tammannstrasse 2, 37077 Göttingen (Germany)
Fax: (+49) 551-39-9476
E-mail: ltietze@gwdg.de

[**] This work was supported by the DFG (SFB 416) and the Fonds der Chemischen Industrie. We thank Prof. Dr. A. Zeeck for supplying data of the title compound, as well as BASF, Degussa-Hüls and Wacker-Chemie for donations of chemicals.

  1433-7851/01/4005-0901 $ 17.50+.50/0



Scheme 3. a) **4**, 1.8 equiv *s*BuLi, Et_2O, $-78\,^{\circ}C$, 10 min, then **3**, Et_2O, 10 min, then MeOH, 68%; b) 1. TBDPSCl, imidazole, DMAP, DMF, $50\,^{\circ}C$, 90%; 2. 9-BBN, THF, $50\,^{\circ}C$, then H_2O_2, NaOH, 78%; 3. IBX, THF/DMF 1:1, RT; 4. $NaClO_2$, NaH_2PO_4, *t*BuOH, 2-methyl-2-butene, H_2O, RT, then crude product, 40% HF(aq)/pyridine 1:1, EtCN, RT, 67%; c) 2,4,6-trichlorobenzoyl chloride, iPr_2NEt, THF, $0\,^{\circ}C$, then toluene, DMAP, RT, 86%; d) 1. HF · pyridine/pyridine 1:3, $60\,^{\circ}C$, 73%; 2. DDQ, CH_2Cl_2/H_2O 30:1, $0\,^{\circ}C$, 5 min, ca. 60%; e) LHMDS, TMSCl, THF, $-78\,^{\circ}C$, then CH_3CN, MS 3 Å, $Pd(OAc)_2$, RT, **15**: 38%, **16**: 59%; f) 1. as (d), step 2, 15 min; 2. as (d), step 1, two steps, **1**: 49%, **17**: 50%; g) 1. as (d), step 1, 72%; 2. as (b), step 3, 90%; 3. (*S*)-BINAL-H, see ref. [11], 72%; 4. as (d), step 2, 15 min, 51%. LHMDS = lithium hexamethyldisilazide, TMS = trimethylsilyl.

allyl hydroxy group in **11**, followed by rearrangement of the double bond and selective cleavage of the protecting group of the secondary hydroxy group on C-13 gave the acyclic carbonic acid **12**, from which the lactone **13** was obtained by Yamaguchi lactonization[9] on reaction with 2,4,6-trichlorobenzoyl chloride. The synthesized diastereomeric macrocycles **13a** and **13b** can be separated easily by column chromatography on silica gel. The diastereomers were assigned by comparison of the data of **1** produced from **13a** with the literature data.[1a]

The 2,3-double bond was introduced in **13a** and **13b** by using a modified procedure from Saegusa et al.[10] by conversion into the silyl enol ether followed by oxidation with $Pd(OAc)_2$. This gave the 7-*epi* derivative **16** and the diastereomer **15** in yields of 59 and 38%, respectively, under identical reaction conditions. The formation of the α-silylated macrolactone in a competing reaction was responsible for the latter result; remarkably its formation proceeds in a stereochemically uniform manner. The final transformation of **15** into the natural product **1** was achieved by removal of the two protecting groups with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) and with the HF · pyridine complex in pyridine at $60\,^{\circ}C$ in 46% yield. The 7-*epi* derivative **17** was obtained from **16** in a similar manner. Moreover, the 2,3,5,6-tetrahydro derivative **14** was synthesized from **13b**; however, this compound is only stable for a short time at room temperature due to its tendency to rearrange to the γ-lactone. The synthetic compound **1** is identical to the natural product.[1a]

An improvement of the selectivity in the formation of **1** occurs on removal of the silyl protecting group in **16** and oxidation with IBX (*o*-iodoxybenzoic acid; 1-hydroxy-1,2-benziodoxol-3(1*H*)-one-1-oxide).[11] The resulting enone can be reduced in a 6:1 selectivity to the corresponding *S*-configured allyl alcohol on reaction with (*S*)-BINAL-H[12] and be converted into **1** by oxidative deprotection.

The presented concept for the first total synthesis of 5,6-dihydrocineromycin B (**1**) offers a flexible and convergent access to the cineromycins. The key step hereby is our selective synthesis of enantiomerically pure tertiary alcohols by allylation of ketones.

Received: September 28, 2000 [Z15865]

[1] a) H. J. Schiewe, A. Zeeck, *J. Antibiot.* **1999**, *52*, 635–642; b) A. Taddei, A. Zeeck, *J. Antibiot.* **1997**, *50*, 526–528; c) N. Miyairi, M. Takashima, K. Shimizu, H. Sakai, *J. Antibiot.* **1966**, *19*, 56–62.

[2] D. Tanner, P. Somfai, *Tetrahedron* **1987**, *43*, 4395–4406.

[3] a) H. C. Brown, K. S. Bath, *J. Am. Chem. Soc.* **1986**, *108*, 293–294; b) H. C. Brown, K. S. Bath, *J. Am. Chem. Soc.* **1986**, *108*, 5919–5923.

[4] C. L. Rand, D. E. Van Horn, M. W. Moore, E. Negishi, *J. Org. Chem.* **1981**, *46*, 4096–4097.

[5] a) L. F. Tietze, C. Wegner, C. Wulff, *Chem. Eur. J.* **1999**, *4*, 2885–2889; b) L. F. Tietze, C. Wegner, C. Wulff, *Eur. J. Org. Chem.* **1998**, 1639–1644.

[6] N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh, A. Suzuki, *J. Am. Chem. Soc.* **1989**, *111*, 314–321.

[7] U. Azzena, L. Pilo, A. Sechi, *Tetrahedron* **1998**, *54*, 12389–12398.

[8] C. Lutz, P. Knochel, *J. Org. Chem.* **1997**, *62*, 7859–7898.

[9] a) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993; b) K. C. Nicolaou, F. Nincovic, D. Sarabia, F. Vourloumis, Y. He, H. Vollberg, M. R. V. Finlay, Z. Yang, *J. Am. Chem. Soc.* **1997**, *119*, 7974–7991.

[10] a) Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011–1013; b) K. Shimamoto, M. Ishida, H. Shinozaki, Y. Ohfune, *J. Org. Chem.* **1991**, *56*, 4167–4176.

[11] M. Frigerio, M. Santagostino, S. Sputore, G. Palmisano, *J. Org. Chem.* **1995**, *60*, 7272–7276.

[12] a) R. Noyori, I. Tomino, Y. Tanimoto, M. Nishizawa, *J. Am. Chem. Soc.* **1984**, *106*, 6709–6716; b) R. Noyori, I. Tomino, Y. Tanimoto, M. Nishizawa, *J. Am. Chem. Soc.* **1984**, *106*, 6717–6725.

  1433-7851/01/4005-0902 $ 17.50+.50/0