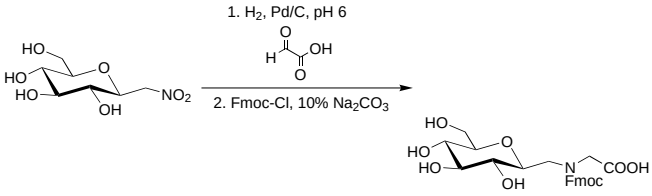


Scheme 3. Synthesis of a glycopeptoid building block.

[10] The building blocks **15**–**22** were made as Fmoc derivatives, and were as such used under standard solid-phase conditions with TBTU/HOBt [R. Knorr, A. Trzeciak, W. Bannwarth, D. Gillessen, *Tetrahedron Lett.* **1989**, *30*, 1927–1930].

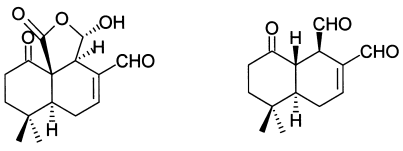
[11] a) R. Haubner, H. J. Wester, R. Senekowitsch-Schmidtke, B. Diefenbach, H. Kessler, G. Stöcklin, M. Schwaiger, *J. Labelled Compd. Radiopharm.* **1998**, *40*, 853–856; b) R. Haubner, H. J. Wester, R. Senekowitsch-Schmidtke, B. Diefenbach, H. Kessler, G. Stöcklin, M. Schwaiger, *J. Nucl. Med.* **1999**, *40*, 1061–1071.

A Short Total Synthesis of Kuehneromycin A**

Johann Jauch*

Dedicated to Professor Volker Schurig on the occasion of his 60th birthday

The kuehneromycins were isolated from the fermentation broth of the basidiomycete *Kuehneromyces* sp. 8758 in 1995.[1] Kuehneromycin A (**1**) is a noncompetitive inhibitor of avian myeloblastosis virus reverse transcriptase[2] as well as moloney murine leukemia virus reverse transcriptase.[2] Kuehneromycin B (**2**) is a strong inhibitor of platelet aggregation and both compounds show cytotoxic and antimicrobial activities. Structurally, the kuehneromycins are related to the mniopetals,[3] which inhibit HIV reverse transcriptase.



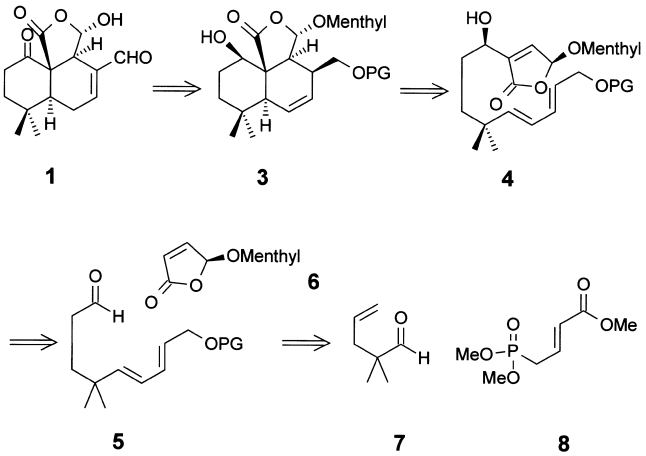
1 **2**

[*] Dr. J. Jauch
Institut für Organische Chemie und Biochemie
Technische Universität München
Lichtenbergstrasse 4, 85747 Garching (Germany)
Fax: (+49) 89-289-13-329
E-mail: jjauch@nucleus.org.chemie.tu-muenchen.de

[**] This work was generously supported by the Deutsche Forschungsgemeinschaft and the Fazit-Stiftung. We are grateful to Prof. W. Steglich, Ludwig-Maximilians-Universität München, for copies of spectra of natural kuehneromycin A and for recording 600 MHz ^{1}H NMR spectra of our synthetic sample. We thank BASF AG, Ludwigshafen, Germany, Pfizer AG, Karlsruhe, Germany, Haarmann & Reimer GmbH, Holzminden, Germany, Wacker GmbH, Burghausen, Germany, DEGUSSA AG, Frankfurt a. M., Germany and Bayer AG, Leverkusen, Germany, for chemicals and laboratory equipment.

In the course of our project towards the synthesis of new sesquiterpenoids[4] with interesting biological activities we decided to synthesize kuehneromycin A and here we report the first synthesis of naturally occurring (−)-kuehneromycin A.

Retrosynthetic analysis of kuehneromycin A (**1**) leads to the protected alcohol **3** which should readily be obtainable from the trienolide **4** in an *endo*-selective intramolecular Diels–Alder reaction (IMDA reaction; Scheme 1). Trienolide **4** is the result of a Baylis–Hillman reaction of aldehyde **5** and Feringa's butenolide **6**.[5] Aldehyde **5** is disconnected into aldehyde **7** and phosphonate **8** through retrosynthetically applying a hydroboration/oxidation Horner–Wadsworth–Emmons sequence.

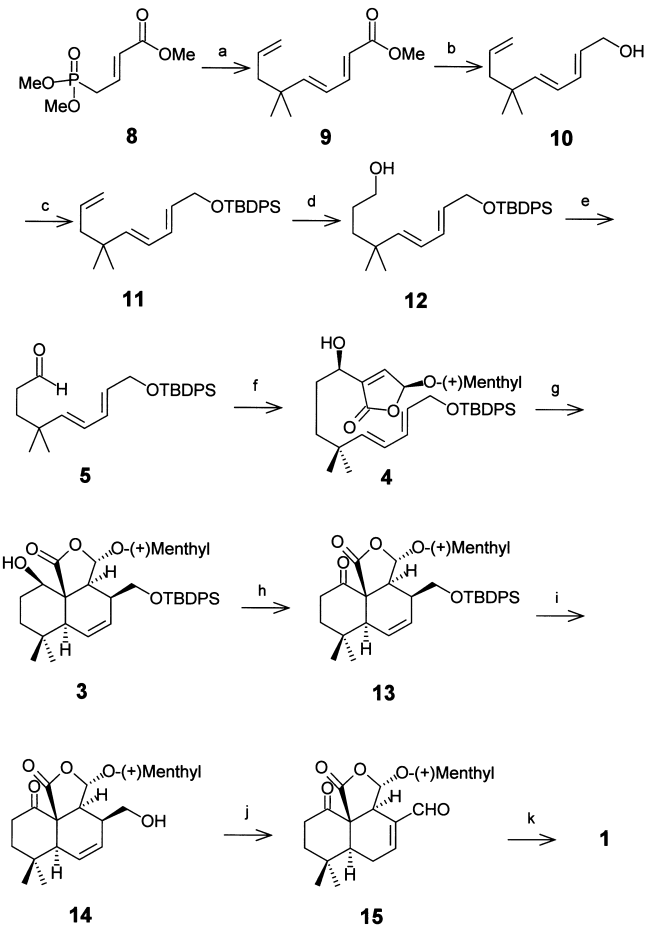


Scheme 1. Retrosynthetic analysis of kuehneromycin A (**1**). PG = protecting group.

Our synthesis (Scheme 2) started with a Horner–Wadsworth–Emmons reaction[6] of 2,2-dimethyl-4-pentenal (**7**)[7] and phosphonate **8**[8] from methyl *E*-4-bromobutenoate, which afforded a mixture of triene esters (*trans*:*cis* > 20:1) from which **9** was readily separated in 85% yield by flash chromatography. Reduction of the ester functionality with diisobutylaluminum hydride (DIBALH)[9] gave the alcohol **10** in 97% yield, which subsequently was protected as the *tert*-butyldiphenylsilyl (TBDPS) ether **11**[10] in quantitative yield. Hydroboration[11] with 9-borabicyclo[3.3.1]nonane (9-BBN), followed by oxidation with H_2O_2/NaOH under standard conditions led regioselectively to alcohol **12** in 91% yield. Oxidation of the primary alcohol with 2,2,6,6-tetramethylpiperidin-*N*-oxyl (TEMPO)/diacetoxyiodobenzene[12] gave exclusively the aldehyde **5**, which served as the starting material for the planned Baylis–Hillman reaction.[13]

The Baylis–Hillman reaction under standard conditions using 1,4-diazabicyclo[2.2.2]octane (DABCO) as a nucleophile was not applicable in our case since Feringa's butenolide[5] **6** is highly base sensitive and the DABCO-catalyzed reaction only works well for β-unsubstituted acrylic acid derivatives. Therefore we developed a new and highly diastereoselective variant[14] of the Baylis–Hillman reaction that used lithium phenylselenide as a strong but only weakly basic nucleophile. PhSeLi was readily prepared from diphenyl diselenide through reductive cleavage with either *n*BuLi[15] or

  1433-7851/00/3915-2764 $ 17.50+.50/0



Scheme 2. Synthesis of kuehneromycin A (**1**). a) LiHMDS, **7**, THF, $-40\,^{\circ}C$, 85%, *trans:cis* > 20:1; b) DIBALH, Et_2O, $0\,^{\circ}C$, 30 min, 97%; c) TBDPSCl, imidazole, DMF, RT, 2 h, quant.; d) 9-BBN, THF, RT, 4 h, H_2O_2, NaOH, EtOH, $0\,^{\circ}C$, 4 h, 91%; e) TEMPO/diacetoxyiodobenzene, CH_2Cl_2, RT, 90 min, 98%; f) PhSeLi, THF, **6**, $-60\,^{\circ}C$, 6 h, 88%; g) xylene, silylated flask, $140\,^{\circ}C$, 60 h, 68%; h) PDC, MS 3 Å, 2 h, 95%; i) TBAF, THF, RT, 1 h, 93%; j) DMSO, $Py \cdot SO_3$, NEt_3, RT, 14 h, 69%; k) TFA/H_2O, (80/20 v/v) 4 h, 94%. LiHMDS = lithium 1,1,1,3,3,3-hexamethylsilazide.

elemental lithium, catalyzed by benzophenone under sonication.[16] Reaction of PhSeLi with aldehyde **5** and **6** at $-60\,^{\circ}C$ for 6 h gave trienolide **4** in a highly diastereoselective tandem-Michael-aldol-retro-Michael reaction in 88% yield. The configuration of the newly formed secondary alcohol is the result of chirality transfer from the acetal carbon atom in **6** to the new chirality center via a Zimmermann–Traxler like transition state in the aldol addition step.[17]

The IMDA reaction[18] of **4** gave after 60 h at $140\,^{\circ}C$ in xylene the desired cyclization product **3** (68%) along with some unidentified side products and about 20% recovered starting material. The structure of **3** was determined by NMR spectroscopy (TOCSY, HMQC, and NOESY).

In the next step, **3** was oxidized to the ketone **13** by pyridinium dichromate (PDC) in the presence of 3 Å molecular sieves in 95% yield. Deprotection of the primary alcohol by tetrabutylammonium fluoride (TBAF; 93%) was followed by Parikh–Doering oxidation[19] with concomitant double bond shift leading to the α,β-unsaturated aldehyde **15** (69%). To obtain reproducible good yields it is important to conduct the reaction under an inert atmosphere and to add the pyridine–sulfur trioxide complex very slowly with a syringe pump.

In the last step, the menthyl residue was removed through action of trifluoroacetic acid (TFA)/H_2O[20] to give kuehneromycin A (**1**) in 94% yield, identical in all respects with the natural product.[21] Thus, we were able to synthesize kuehneromycin A (**1**) in a total of 11 steps in 25–26% yield. Furthermore, our synthesis confirms the absolute configuration of kuehneromycin A (**1**) as determined already by Steglich et al.[1, 3c] for structurally related substances.

Received: March 10, 2000 [Z14830]

[1] G. Erkel, K. Lorenzen, T. Anke, R. Velten, A. Gimenez, W. Steglich, *Z. Naturforsch. C* **1995**, *50*, 1–10.

[2] *Retroviruses* (Eds.: J. M. Coffin, S. H. Hughes, H. E. Varmus), Cold Spring Harbor Laboratory Press, New York, **1997**.

[3] a) A. Kuschel, T. Anke, R. Velten, D. Klostermeyer, W. Steglich, B. König, *J. Antibiot.* **1994**, *47*, 733–739; b) R. Velten, D. Klostermeyer, B. Steffan, W. Steglich, A. Kuschel, T. Anke, *J. Antibiot.* **1994**, *47*, 1017–1024; c) R. Velten, W. Steglich, T. Anke, *Tetrahedron: Asymmetry* **1994**, *5*, 1229–1232.

[4] J. Jauch, *Synlett* **1999**, 1325–1327.

[5] B. L. Feringa, J. C. de Jong, *Bull. Soc. Chim. Belg.* **1992**, *101*, 627–640, and references therein.

[6] W. R. Roush, *J. Am. Chem. Soc.* **1980**, *102*, 1390–1404.

[7] a) K. C. Brannock, *J. Am. Chem. Soc.* **1959**, *81*, 3379–3383; b) G. Salomon, S. Ghosh, *Org. Synth.* **1984**, *62*, 125–133.

[8] P. Baeckström, U. Jacobsson, T. Norin, C. R. Unelius, *Tetrahedron* **1988**, *44*, 2541–2548.

[9] E. Winterfeldt, *Synthesis* **1975**, 617–630.

[10] S. Hanessian, P. Lavallee, *Can. J. Chem.* **1975**, *53*, 2975–2977.

[11] a) A. Pelter, K. Smith, H. C. Brown, *Borane Reagents*, Academic Press, London, UK, **1988**; b) M. J. Kurth, J. O'Brien, H. Hope, M. Yanuck, *J. Org. Chem.* **1985**, *50*, 2626–2632.

[12] A. De Mico, R. Margarita, L. Parlanti, A. Vescovi, G. Piacantelli, *J. Org. Chem.* **1997**, *62*, 6974–6977.

[13] E. Ciganek in *Organic Reactions*, *Vol. 51* (Ed.: L. A. Paquette), Wiley, New York, **1997**, pp. 201–350, and references therein.

[14] J. Jauch, *J. Org. Chem.* in press.

[15] H. J. Reich, R. R. Dykstra, *Organometallics* **1994**, *13*, 4578–4585.

[16] S. V. Ley, I. A. O'Neil, C. M. R. Low, C. *Tetrahedron* **1986**, *42*, 5363–5368.

[17] Vgl. z. B. P. Arya, H. Qin, *Tetrahedron* **2000**, *56*, 917–947, and references therein.

[18] W. R. Roush in *Comprehensive Organic Synthesis*, *Vol. 5* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 513–550, and references therein.

[19] T. T. Tidwell in *Organic Reactions Vol. 39* (Ed.: L. A. Paquette), Wiley, New York, **1990**, pp. 297–572, and references therein.

[20] J. W. J. F. Thuring, G. H. L. Nefkens, R. Schaafstra, B. Zwanenburg, *Tetrahedron* **1995**, *51*, 5047–5056.

[21] ^{1}H NMR (600 MHz, [D$_6$]benzene, TMS): $\delta = 8.90$ (s, 1H), 6.46 (br. s, 1H), 5.85 (d, $^3J(H,H) = 6.8$ Hz, 1H), 5.47 (s, 1H), 3.35 (m, 1H), 2.42 (ddd, $^3J(H,H) = 15.9$, 11.5, 4.6 Hz, 1H), 1.89 (ddd, $^3J(H,H) = 3.6$, 7.0, 15.2 Hz, 1H), 1.82 (ddt, $^3J(H,H) = 2.7$, 12.5, 19.1 Hz, 1H), 1.54 (ddd, $^3J(H,H) = 3.7$, 7.0, 19.1 Hz, 1H), 1.50 (ddd, $^3J(H,H) = 4.6$, 7.0, 13.9 Hz, 1H), 1.19 (s, 3H), 1.03 (ddd, $^3J(H,H) = 3.7$, 11.4, 14.8 Hz, 1H), 0.90 (dd, $^3J(H,H) = 3.4$, 12.5 Hz, 1H), 0.54 (s, 3H); ^{13}C NMR (90 MHz, [D$_6$]benzene, TMS): $\delta = 209.6$, 191.5, 170.5, 151.8, 137.5, 101.5, 62.1, 47.6, 46.3, 37.6, 36.0, 31.7, 31.1, 24.9, 22.9; $[\alpha]_D^{21} = -53$ ($c = 0.2$ in ethanol); (ref. [1] $[\alpha]_D^{21} = -55$ ($c = 0.2$ in ethanol)).