metal are reduced to those of the "electron in a box" problem (the nanometer range) the electronic states in the metal become discrete in their energy distribution. To a very simple approximation, the energy gap ΔE between the electron states in a small metal particle can be estimated by $\Delta E = E/N$, where E is the width of the energy band in the metal and N is the number of atoms per cluster.[10] For $E = 10$ eV[11] and $N = 100$ an energy separation of the order of 0.1 eV is obtained. This, of course, is a rather crude estimation, but it demonstrates that overpotentials (in this case in the thermodynamic sense) of 50 or 180 mV, as observed in the experiment, can result from quantum effects. Consider a redox potential, that is, the Fermi level of the redox system, lying within the energy gap of the metal cluster. Dissolution of the metal would only start after the energy states in the cluster have been shifted by a change in the electrode potential to match the redox potential. We thus propose that the stability range of our tip-induced copper clusters of at least 50 mV versus Cu/Cu^{2+} (which is quite significant in electrochemical terms) might be a consequence of quantum effects. An obstacle for such an interpretation is the fact that the copper clusters are on a metal rather than on an insulator surface, which raises the question of a quantum confinement normal to the surface. However, since the contact between copper cluster and the gold(111) substrate represents a discontinuity in structural as well as in electronic terms, this interface may well provide the necessary barrier for the electrons in the cluster.

Experimental Section

Both fabrication and imaging of the Cu clusters were performed with a PicoSPM (Molecular Imaging Corp., Tempe, Arizona). The electrolyte used in this study was 0.05 M H_2SO_4 with concentrations of Cu^{2+} between 0.05 and 1 mM, prepared from H_2SO_4 (Merck, 96%), $CuSO_4 \cdot 5H_2O$ (Fluka, >99%) and Milli-Q water (Millipore). Sample and tip potentials were controlled independently from each other by a bipotentiostat. As reference electrode, a Cu or a Pt wire was used, and the counter electrode was a Pt wire. The tip was made from a 0.25 mm diameter Pt/Ir (80/20) wire by electrochemical etching. All potentials are quoted against Cu/Cu^{2+} in the same solution. Other technical details are given in references [2, 3, 12].

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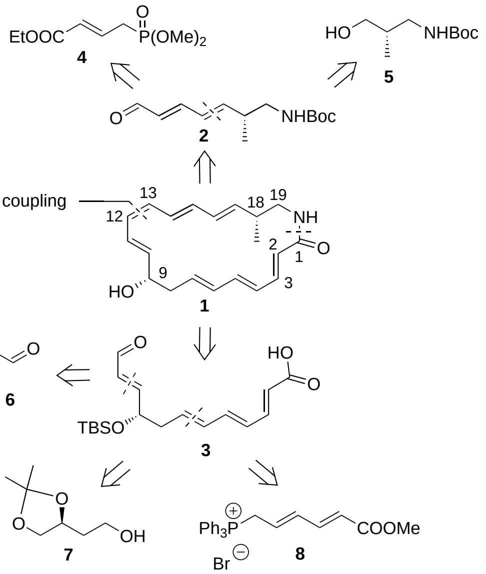
Synthesis of the (9*S*,18*R*) Diastereomer of Cyclamenol A**

Marc Nazaré and Herbert Waldmann*

A key event in the humoral response to inflammation, tissue injury, and infection is the transport of leukocytes to the site of injury. It is facilitated by adhesion of the leukocytes to endothelial cells and their subsequent transmigration from the bloodstream through the wall of the blood vessel and the surrounding tissue.[1] Over-recruitment of these blood cells can result in the establishment of various diseases and disorders ranging from chronic autoimmune diseases to acute inflammation. Intervention of leukocyte recruitment by inhibiting their adhesion to endothelial cells is considered to be a new strategy for the development of antiinflammatory agents. This approach may offer entirely new and alternative opportunities for the treatment of, for example, reperfusion injuries, strokes, asthma, and arthritis. Thus, the development of peptide and carbohydrate derivatives as inhibitors of the selectin/sialyl Lewis X interaction has attracted considerable interest.[2] However, non-peptide and non-carbohydrate natural products have not been investigated so far.

Cyclamenol A (**1**) (Scheme 1), a macrocyclic polyene lactam isolated from *Streptomyces spec.* MHW 846 by chem-



Scheme 1. Retrosynthetic analysis of cylamenol A (**1**). Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl.

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[*] Prof. Dr. H. Waldmann, Dr. M. Nazaré[+]
Max-Planck-Institut für Molekulare Physiologie
Department of Chemical Biology
Otto-Hahn-Strasse 11, 44227 Dortmund (Germany)
Fax: (+49) 231-133-2499
E-mail: herbert.waldmann@mpi-dortmund.mpg.de
and
Universität Dortmund
Fachbereich 3, Organische Chemie (Germany)

[+] Further address: Universität Karlsruhe
Institut für Organische Chemie (Germany)

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ists at Bayer,[3] is one of the very few natural products known to inhibit adhesion of leukocytes to endothelial cells.[4] It blocks this process in an ex vivo model and completely inhibits adhesion of leukocytes to arterioles in hamsters (i.e. in vivo). Its mode of action and the structural parameters influencing its biological activitiy including the absolute configuration of the two stereogenic centers incorporated into cyclamenol A are unknown.

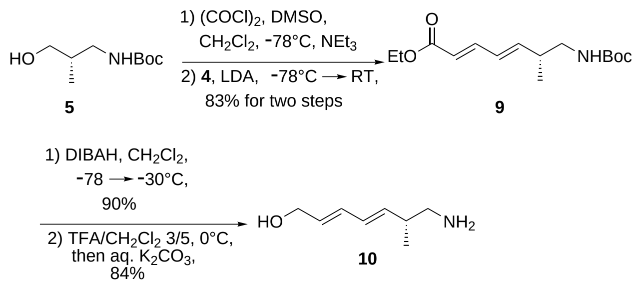
In the light of these important and unsolved medicinal and biological questions and as part of a study to develop tools for unravelling the biological activity of cyclamenol A we have embarked on syntheses of this natural product and analogues thereof with modified biological properties. Herein we report on the synthesis of (9*S*, 18*R*)-cyclamenol A.

In developing a strategy for the synthesis of (9*S*, 18*R*)-cyclamenol A particular attention was paid to the polyene system, which embodied one *Z* and six *E* double bonds. Thus, once the entire backbone was assembled it was feared it would react further to give a fully conjugated octaene system or that the *Z* double bond would isomerize. In addition, force field calculations indicated that a final ring closure by amide bond formation would be difficult to achieve since the triene and the tetraene system incorporated into cyclamenol A seco acid induce a conformation of the acyclic precursor in which the amine and the acid are not close to each other. Therefore, we planned to construct the sensitive polyene system in the final steps of the synthesis and to establish the entire backbone by a transformation that allows both ends of the acyclic precursor to be tied together under template control. The formation of pinacols from dialdehydes was chosen for this purpose.[5] The pinacol generated thereby should be a reasonably stable intermediate and be amenable to generation of the required *Z* double bond.

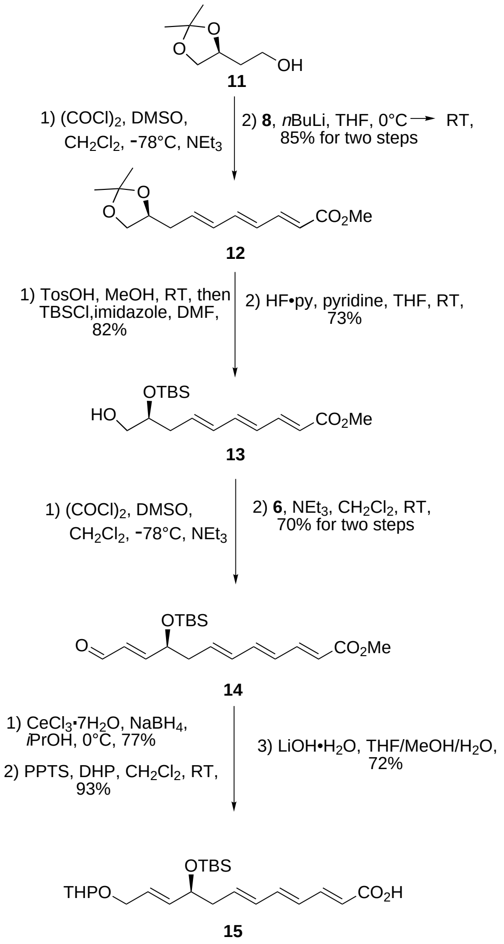
According to this plan the target compound was dissected between C12 and C13 and at the amide bond to yield aldehydes **2** and **3** as major intermediates (Scheme 1). Compound **2** was traced back to phosphonic acid ester **4** and protected amino alcohol **5**, which were to be coupled by means of a Horner olefination reaction after oxidation of **5**. Intermediate **3** was divided into building blocks **6**–**8** to be linked by Wittig olefination after subsequent oxidation of the primary alcohol functions of **7** to the respective aldehyde groups. Since the absolute configuration of cyclamenol A is not known the two stereocenters were abitrarily introduced in the (9*S*) and the (18*R*) configuration, which are accessible from (*S*)-malic acid and (*R*)-hydroxyisobutyric acid, respectively.[6]

The C13–C19 fragment **10** was built up in a short and efficient sequence from protected amino alcohol **5**[7] (Scheme 2). Swern oxidation of the primary alcohol and chain elongation with crotonoyl-phosphonate **4** yielded doubly unsaturated ester **9**, which was reduced to the allyl alcohol. Removal of the Boc group and extractive workup with K_2CO_3 solution gave amino alcohol **10** in high yield. It was used directly for the subsequent steps.

The C1–C12 fragment was synthesized from selectively protected butanetriol **11**[8] by two successive elongations of the carbon chain (Scheme 3). First the primary alcohol **11** was converted to the corresponding aldehyde by Swern oxidation; this was then treated with the ylide formed in situ from the phosphonium salt **8** (derived from sorbic acid) by deprotonation with butyllithium. The diol obtained after removal of the acetonide from **12** was rather unstable. Thus, it was immediately converted to the bis-silyl ether, and then the more labile *tert*-butyldimethylsilyl ether of the primary alcohol was cleaved selectively by treatment with a solution of pyridinium hydrofluoride in a mixture of pyridine and THF at room temperature. The selectively unmasked and highly unsaturated alcohol **13** was obtained in high overall yield. It was then subjected to a one-pot reaction sequence that included oxidation of the alcohol to the aldehyde and Wittig



Scheme 2. Synthesis of C13–C19 intermediate **10**. DIBAH = diisobutylaluminum hydride.



Scheme 3. Synthesis of C1–C12 intermediate **15**. Tos = *p*-toluenesulfonyl, PPTS = pyidinium *p*-toluene sulfonate, DHP = dihydropyran, THP = tetrahydropyranyl.

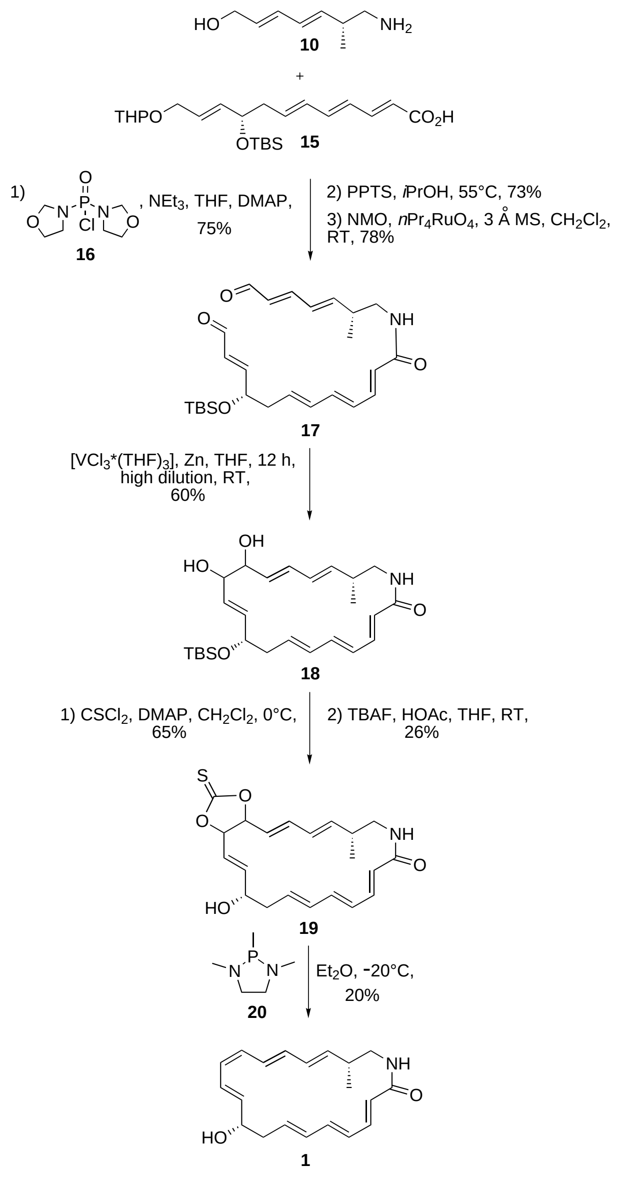
reaction with formylmethylenetriphenylphosphonium chloride **6** in the presence of NEt_3. In this way the isolation of the very unstable α-alkoxyaldehyde intermediate was circumvented. The significantly more stable α,β-unsaturated aldehyde **14** could be isolated in high yield.

For the amide linkage of the C1–C12 and C13–C19 fragments, the aldehyde group in **14** had to be reduced and the resulting allyl alcohol was masked as a THP ether which is orthogonally stable to the TBS ether and the methyl ester in **14**. This protection proved to be necessary since the unmasked primary alcohol interfered with the subsequent formation of the amide bond. After sponification of the methyl ester the resulting carboxylic acid was preactivated by treatment with BOP-Cl (BOP = 1-benzotriazolyloxytris(dimethylamino)-phosphonium hexafluorophosphate). The activated intermediate reacted chemoselectively with amino alcohol **10** to yield the desired amide in high yield. Strong preactivation with BOP-Cl was necessary to achieve a high yield in this step since the tetraene carboxylic acid **15** is only moderately reactive. Other activation methods gave markedly lower yields. Next the THP ether was removed and the bis-allyl alcohol was oxidized to the moderately stable dialdehyde intermediate **17** (Scheme 4).

The formation of the carbon–carbon bond to generate the twenty-membered ring system turned out to be very difficult. Neither titanium- or samarium-mediated pinacol formation[9] nor McMurry reaction employing various titanium reagents[10] were successful. After substantial experimentation finally the use of the vanadium reagent $[V_2Cl_3\cdot(THF)_6][Zn_2Cl_6]$[11] (prepared in situ) in THF as solvent and under high dilution conditions turned out to be the method of choice. It afforded the cyclic pinacol **18** in 60% yield.

After this crucial step had been accomplished attention was focussed on finding proper and gentle reaction conditions for generating the sensitive polyene system and for the deprotection of the secondary alcohol. In particular, the order in which these steps had to be carried out was crucial to the success of the synthesis. Thus, in a first approach, the final C12–C13 double bond was generated and then we attempted to cleave the silyl ether protecting group. However, once the heptaene is established protected cyclamenol A becomes very sensitive to both acid and base, and numerous attempts to cleave the silyl ether only led to decomposition. This final problem could, however, be solved by reversing the order of the synthetic transformations, that is the silyl ether was removed first and the sensitive polyene was generated in the final step. To this end, pinacol **18** was converted to the corresponding thionocarbonate by reaction with thiophosgene, and then the TBS ether was cleaved to give the deprotected alcohol in moderate yield. Finally, the thionocarbonate **19** was fragmented by treatment with trimethyldiazaphospholidine **20**[12] to yield (9*S*,18*R*)-cyclamenol A.

Comparison of the spectroscopic data recorded for the synthetic sample with the data obtained for the natural product[3, 13] clearly proved that the desired cyclic polyene system had been formed. However, whereas naturally occurring cyclamenol A[14] displayed a specific rotation of $[\alpha]_D^{20} = +1000^\circ$ ($c = 0.01$ in DMF), we measured a value of $[\alpha]_D^{20} = +60^\circ$ ($c = 0.01$ in DMF) for the synthetic compound. Thus the natural product does not have the (9*S*,18*R*)-configuration. We stress, however, that the enantiomers of chiral building blocks **5** and **7** are readily available, implying that the other diastereomers of the natural product are also accessible by the route detailed above.



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Scheme 4. Coupling of fragments **10** and **15** and completion of the synthesis. NMO = *N*-methylmorpholine-*N*-oxide, DMAP = 4-dimethylaminopyridine, TBAF = tetrabutylammonium fluoride.

We have developed a synthesis of the (9*S*,18*R*)-diastereomer of the leukocyte adhesion inhibitor cyclamenol A. The synthesis is highly convergent and proceeds with high efficiency, that is the longest linear sequence consists of ten steps and relays the stereogenic centers of the polyene macrolactam to two building blocks from the chiral pool that are readily available in both enantiomeric forms. The flexibility and convergent character of the synthetic route will give access to all diasteromers of the natural product as well as to various analogues with improved stability and altered biological properties. This synthesis now provides the opportunity to develop a new class of non-carbohydrate and non-peptidic inhibitors of leukocyte adhesion to endothelial cells.

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[13] **1**: $R_f = 0.40$ (CHCl$_3$/MeOH 9:1); $R_f = 0.14$ (Et$_2$O); ^{1}H NMR (CDCl$_3$, 500 MHz): $\delta = 7.20$ (dd, $^3J = 15$, $^3J = 10$ Hz, 1H), 6.88 (dd, $^3J = 15$, $^3J = 10$ Hz, 1H), 6.52 (dd, $^3J = 15$, $^3J = 10$ Hz, 1H), 6.20 (m, 5H), 6.06 (m, 1H), 6.02 (m, 1H), 5.80 (m, 2H), 5.52 (dd, $^3J = 15$, $^3J = 6$ Hz, 1H), 5.41 (d, $^3J = 15$ Hz, 1H), 4.20 (m, 1H), 3.31 (m, 1H), 2.96 (m, 1H), 2.40 (m, 1H), 2.32 (m, 1H), 2.24 (m, 1H), 1.02 (d, $^3J = 7$ Hz, 3H); MS (ESI, positive mode, MeOH/CHCl$_3$ 2:1): 312 [M^++H]; MS (ESI, negative mode, MeOH/CHCl$_3$ 2:1): 345 [M^-+Cl], 310 [M^- − H]. To further support the good agreement of the NMR data recorded for the olefin region of (9*S*,18*R*)-**1** with the values measured for the natural stereoisomer of cyclamenol A, we have calculated the differences in total energy and total steric energy for the 12,13-*cis* and the 12,13-*trans* isomers of (9*S*,18*R*)-cyclamenol. The calculations were performed with the PM3 and the MM+ programs implemented in HyperChem 5.02. The semiempirical calculations at the PM3 level revealed a difference in total energy of $\Delta H_{\text{total}}(12,13\text{-}cis) - \Delta H_{\text{total}}(12,13\text{-}trans) = -37.2\ \text{kJ mol}^{-1}$ and the force field calculations at the MM+ – level yielded a difference in total steric energy of $\Delta H_{\text{total}}(12,13\text{-}cis) - \Delta H_{\text{total}}(12,13\text{-}trans) = -49.7\ \text{kJ mol}^{-1}$. Thus, the 12,13-*cis* isomer is energetically much more favored than the corresponding *trans* isomer, and the formation of the *trans* isomer can be ruled out for energetic reasons. In addition, for related tetraene and polyene systems it is known that the energetically less favorable isomers spontaneously isomerize to the more stable analogues: a) K. C. Nicolaou, S. E. Webber, J. Ramphal, Y. Abe, *Angew. Chem.* **1987**, *99*, 1077–1079; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1019–1021; b) M. B. Andrus, S. D. Lepore, *J. Am. Chem. Soc.* **1997**, *119*, 2327–2328; c) B. Crousse, M. Alami, G. Linstrumenelle, *Tetrahedron Lett.* **1995**, *36*, 4245–4248. In addition, the ^{1}H NMR spectrum of the *O*-silylated thionocarbonate obtained from diol **18** displays a coupling constant of 7 Hz for the two CH(OCS) signals of the five-membered ring. This indicates that the two hydrogen atoms are *cis*-oriented (in related compounds coupling constants of 6.5–7.8 Hz are found: d) P. S. Manchand, P. S. Belica, M. J. Holman, T. Huang, H. Maehr, S. Y.-K. Tam, R. T. Yang, *J. Org. Chem.* **1992**, *57*, 3473–3478; e) I. Maeba, N. Morishita, P. Francom, M. J. Robins, *J. Org. Chem.* **1998**, *63*, 7539–7541; f) De Angelis, M. Marzi, P. Minetti, D. Misiti, S. Muck, *J. Org. Chem.* **1997**, *62*, 4159–4161; g) M. G. Lester, G. M. P. Giblin, G. G. A. Inglis, P. A. Procopiou, B. C. Ross, N. S. Watson, *Tetrahedron Lett.* **1993**, *34*, 4357–4360. Since the elimination of thionocarbonates to olefins is known to be a stereospecific *syn*-elimination the *cis*-olefin must have been formed.

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Crossed Condensation of Two Different Hydrosulfido-Bridged Dinuclear Complexes: Structures and Reactivities of TiRu$_3$S$_4$ Cubane-Type Sulfido Clusters[**]

Shin-ichiro Kabashima, Shigeki Kuwata, Keiji Ueno, Motoo Shiro, and Masanobu Hidai[*]

Rational construction of sulfido clusters has been a major objective in synthetic inorganic chemistry because these clusters have possible relevance to metalloenzymes and

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[*] Prof. Dr. M. Hidai, S. Kabashima, Dr. S. Kuwata
Department of Chemistry and Biotechnology
Graduate School of Engineering
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-8656 (Japan)
Fax: (+81) 3-5841-7265
E-mail: hidai@chembio.t.u-tokyo.ac.jp

Dr. K. Ueno
Department of Chemistry
Graduate School of Science
Tohoku University
Aoba-ku, Sendai 980-8578 (Japan)

Dr. M. Shiro
Rigaku Corporation X-ray Research Laboratory
Matsubara-cho, Akishima-shi, Tokyo 196-8666 (Japan)

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