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# Synthesis of the (9*S*,18*R*)-seco acid of the leukocyte adhesion inhibitor cyclamenol A

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**Abstract**

Cyclamenol A is a naturally occurring inhibitor of leukocyte adhesion to endothelial cells. The (9*S*,18*R*) diastereomer of cyclamenol A seco acid was synthesized by employing Sonogashira couplings and olefination reactions as the key steps. 

Adhesion of leukocytes to endothelial cells is an important event initiated by inflammation, tissue injury and infection.[1] It facilitates the transport of leukocytes to the site of injury and subsequent inflammation and immune responses. Over recruitment of these blood cells can be deleterious and various diseases and disorders ranging from chronic autoimmune diseases to acute inflammation may occur. Intervention of leukocyte recruitment by inhibiting their adhesion to endothelial cells is considered to be a new strategy for the development of anti-inflammatory agents, and it is expected that many acute symptoms such as reperfusion injury, stroke, asthma and arthritis may be treated with this approach. For this purpose the development of carbohydrate based inhibitors of the selectin/sialyl Lewis X interaction has attracted considerable interest.[2] However, non-carbohydrate natural products that inhibit leukocyte adhesion to endothelial cells have not been investigated so far.

Recently cyclamenol A **1** a macrocyclic polyene lactam with unknown absolute configuration was isolated from *Streptomyces spec.* MHW 846 by chemists of the Bayer corporation (Scheme 1).[3] This compound displays leukocyte adhesion inhibiting activity in an ex vivo model and it completely inhibits adhesion of leukocytes to arteriols in vivo (in hamsters). Given the high interest in the development of cell adhesion inhibitors we embarked on a program directed at the synthesis of cyclamenol A and cyclic and acyclic analogs of this polyene lactam. In this paper we report on a highly convergent synthesis of (9*S*,18*R*)-cyclamenol A seco acid **2** from four building blocks.

Retrosynthetic considerations: In developing a synthesis plan for the construction of cyclamenol A seco acid **2** particular attention was paid to the acid-sensitive polyene system present and the potential danger of formation of a fully conjugated system by dehydration under acidic conditions. Further

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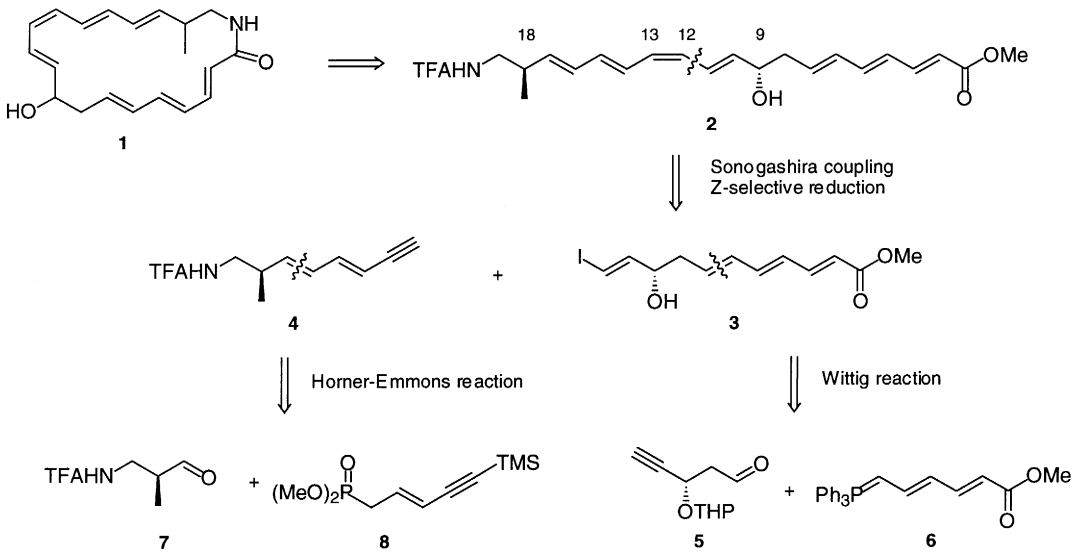


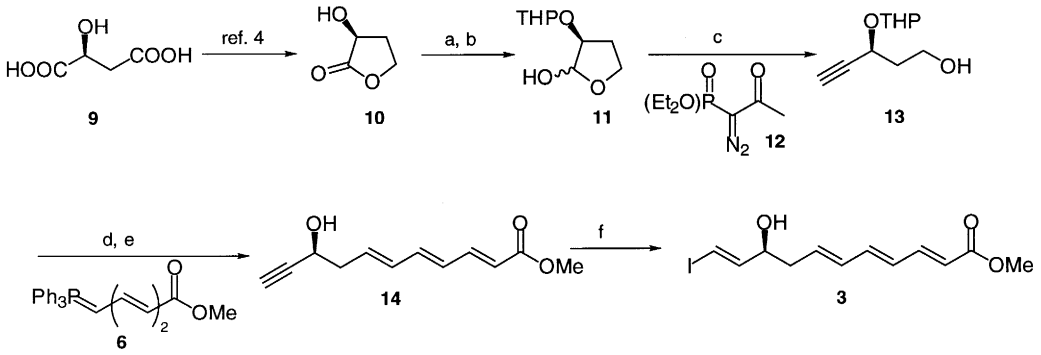

Scheme 1.

attention was focused on the fact that seco acid **2** embodies six *E*-double bonds and, in addition, one olefin with *Z*-configuration. Therefore, in a retrosynthetic sense **2** was divided into acetylene **4** and vinyl iodide **3** to be linked by a Sonogashira coupling. The *Z*-configuration of the C-12–C-13 double bond should be adjustable by *Z*-selective reduction of the acetylene present in the coupling product. We envisaged that vinyl iodide **3** might be accessible from aldehyde **5** and phosphorane **6** in a Wittig reaction. From the coupling product the desired vinyl iodide **3** should be accessible by hydrostannylation and subsequent treatment of the vinyl stannane with iodine. Similarly, we planned to synthesize the acetylenic C-12–C-19 fragment by a Horner olefination reaction employing aldehyde **7** and phosphonate **8**. This retrosynthetic disconnection leads to a highly convergent synthesis. In particular, the two stereocenters present in the target compound are relayed to starting materials readily accessible in both enantiomeric forms. This strategy should give access to all four possible diastereomers of seco acid **2**.

Synthesis of the C-1–C-11 fragment **3**: As starting material for the fragment **3** naturally occurring (*S*)-malic acid **9** was tentatively chosen. (*S*)-Malic acid **9** was transformed into the lactone **10** by a known procedure.[4] Protection of the hydroxy group and subsequent reduction with DIBAH afforded lactol **11**. Reaction of lactol **11** with phosphonate **12**[5] directly yielded alkynol **13**. Sequential one-pot Swern oxidation and Wittig reaction with phosphonium salt **6**[6] afforded, after deprotection of the THP–acetal, alcohol **14** without any elimination of the hydroxy group. The initial Wittig reaction proceeded only with poor stereoselectivity (*E*:*Z*=4:1). However due to the acidic deprotection conditions an acid-catalyzed isomerization may have occurred and no (*Z*)-isomer in the product could be detected by $^1$H NMR spectroscopy. Stereoselective palladium-catalyzed hydrostannation[7] and subsequent treatment with iodine afforded vinyl iodide **3** (Scheme 2).

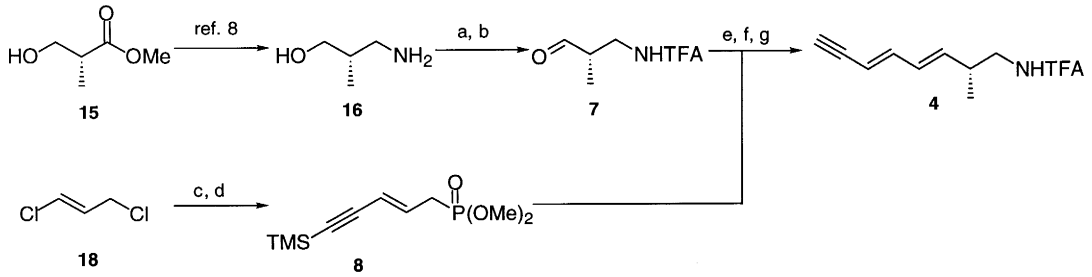
Synthesis of the C-12–C-19 fragment **4**: As starting material for the construction of the fragment **4** commercially available (*R*)-hydroxyisobutyric acid methyl ester **15** was tentatively chosen. Amino alcohol **16** was prepared from the building block according to a published procedure.[8] The free amino group was protected as a trifluoroacetamide and the alcohol was oxidized under Swern conditions to afford amino aldehyde **7**. Phosphonate **8** was efficiently obtained in a stereoselective manner starting form *E*-1,4-dichloro-1-butene **18** by Arbusov reaction and subsequent Sonogashira coupling.

This sequence for the preparation of the phosphonate **8** is significantly better than previously described



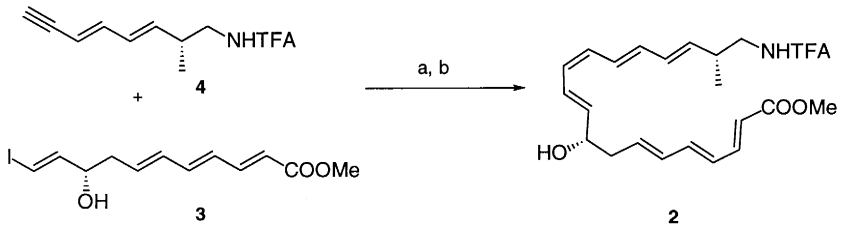

Scheme 2. Reagents and conditions. (a) DHP, PPTS, $CH_2Cl_2$; (b) DIBAH, $CH_2Cl_2$, −78°C, 83% for two steps; (c) $K_2CO_3$, **8**, MeOH, 80%; (d) $(COCl)_2$, DMSO, $NEt_3$, $CH_2Cl_2$, then **10**, 80%; (e) PPTS, MeOH, 45°C, 90%; (f) $Bu_3SnH$, $(Ph_3P)_4Pd$, $CH_2Cl_2$, then $I_2$, −20°C, 68%

procedures.[9] The crude aldehyde **7** was condensed with the phosphonate **8** to give the coupling product as a mixture of stereoisomers (*E*:*Z*=3:1). Although the construction did not proceed in a highly stereoselective manner, pure *E*-olefin could be obtained by treatment of the isomeric mixture with catalytic amounts of iodine and in daylight. The remaining *Z*-isomer could be easily separated from the equilibrated mixture (*E*:*Z*=10:1) by column-chromatography on silica gel. Finally, deprotection of the acetylenic terminus furnished C-12–C-19 fragment **4** (Scheme 3).




Scheme 3. Reagents and conditions. (a) TFAA, $NEt_3$, $CH_2Cl_2$, 90%; (b) $(COCl)_2$, DMSO, $NEt_3$; (c) $P(OMe)_3$, 110°C, 83%; (d) TMS–acetylene, piperidine, $(PhCN)_2PdCl_2$, CuI, THF, 70%; (e) LDA, THF, −78°C, **14**, 65% for two steps; (f) $I_2$(cat.) $CH_2Cl_2$, 80%; (g) $AgNO_3$, KCN, 90%

Final coupling and (*Z*)-selective reduction: Vinyl iodide **3** was stereoselectively coupled with alkyne **4** by means of a Sonogashira reaction[10] to yield the entire C-backbone of cyclamenol A **1**. Fortunately, this compound was quite stable and thus the stereoselective reduction of the acetylene was attempted. Upon treatment of the alkyne with activated zinc[11] the protected cyclamenol seco acid **2**[12] was obtained smoothly and with complete stereoselectivity (Scheme 4).




Scheme 4. Reagents and conditions. (a) Piperidine, $(PhCN)_2PdCl_2$, CuI, PhH, 87%; (b) Zn(Ag/Cu), MeOH, 55%

In conclusion, we have developed a highly convergent synthesis of the (9*S*,18*R*) diastereomer of cyclamenol A seco acid. This route makes the target compound accessible in multigram amounts (up to 2 g were prepared). By means of this modular building block strategy various cyclamenol A analogs should be readily accessible.[13]

## Acknowledgements

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13. Synthesis of (9*S*,18*R*)-cyclamenol A via a vanadium-mediated pinacol coupling as the key step: Nazaré, M.; Waldmann, H. *Angew. Chem*. **2000**, *112*, in press.