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Synthesis of 3H-labeled Efomycine M

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Dedicated to Professor Ekkehard Winterfeldt on the occasion of his 75th birthday

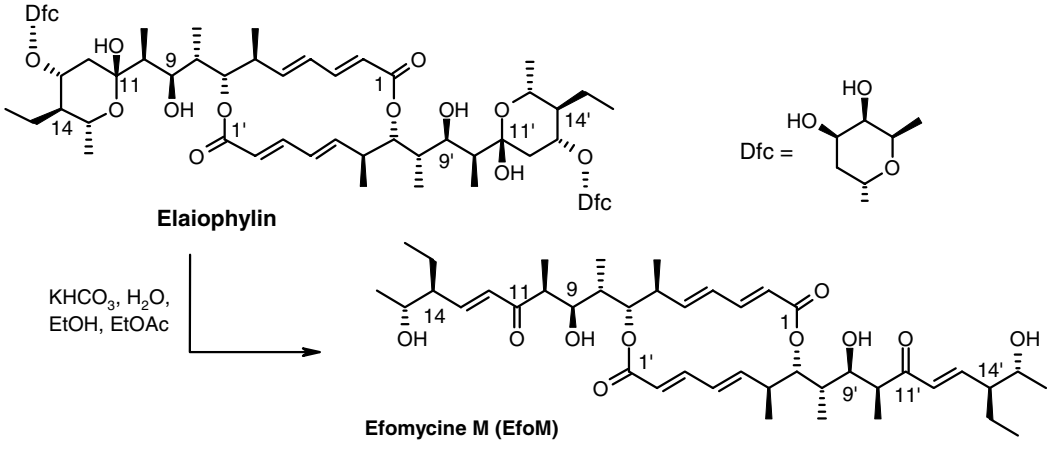
Abstract—For in-depth characterization as a putative pan-selectin antagonist 3H-labeled Efomycine M was synthesized starting from the natural product derived from Elaiophyline.

T-cells are the central effector cells in psoriasis as well as atopic and contact dermatitis.[1] The number of T-cells within the dermal and epidermal infiltrate correlates with the disease activity, which has been shown most elegantly in psoriasis.[2] Therefore, aiming to reduce the number of lesional T-cells within the skin appears to be a promising therapeutic approach in dermatology.

The first step for the transmigration of T-cells into the skin and finally to the site of inflammation is the interaction of E- and P-selectins, which are expressed by inflamed endothelial cells with their natural ligands such as sialyl Lewis^x (sLe^x) expressed by lymphocytes. A compound, which is able to block this interaction and therefore finally the transmigration of T-cells into the skin would be an attractive novel drug.

Experiments with E- and P-selectin double deficient mice demonstrate that a potent inhibitor must interfere with both E- and P-selectin binding.[3]

The natural compound Efomycine M (EfoM) was shown to inhibit E- and P-selectin binding in vitro and it is proposed that it is a dimeric sLe^x-analog. Further-



Scheme 1.

Keywords: Efomycine M; Selectin antagonist.
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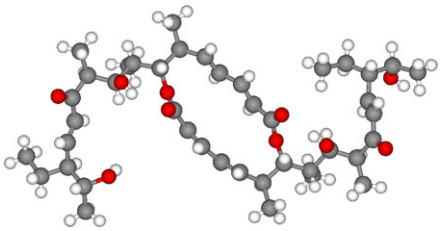
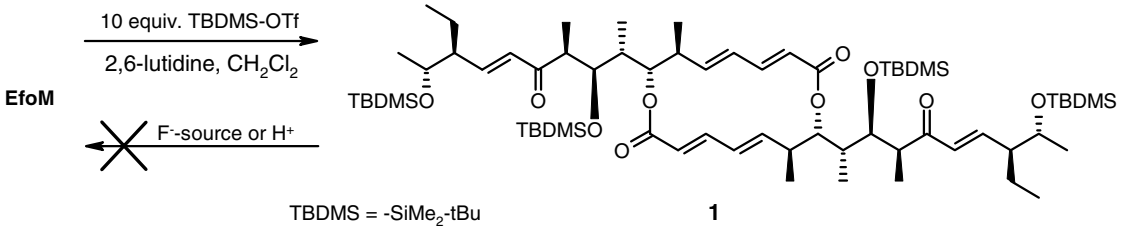


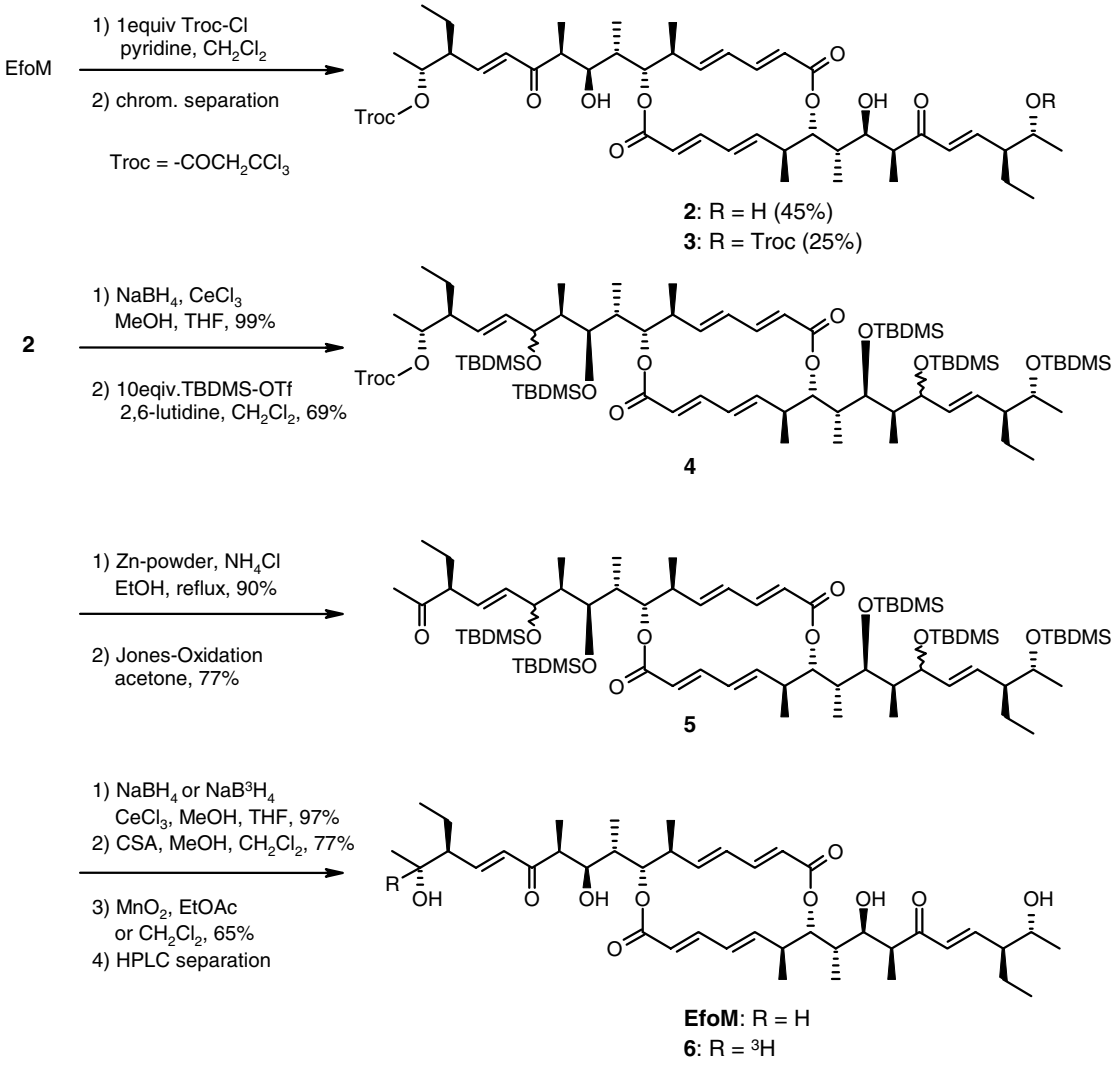
Figure 1. X-ray structure of EfoM.

more, the compound inhibits rolling of human T-cells on murine skin microvessels in vivo and is effective in a humanized psoriasis mouse model using SCID mice.[4]

EfoM has been first prepared by Hoechst AG[5] through a base catalyzed β-elimination of the deoxyfucose side chains from the natural product Elaiophyline, which itself is produced by *Streptomyces* sp. such as strain BS1261. A total synthesis of EfoM was accomplished by the group of Mulzer et al.[6]



Scheme 2.



Scheme 3.

For a more in-depth characterization of EfoM as pan-selectin antagonist we are interested in 3H-labeled EfoM. In this Letter we wish to present our synthetic efforts toward the synthesis of this compound.

Based on a known procedure we developed a fermentation process using *Streptomyces melanosporofaciens* DSM40318 that delivered kg amounts of Elaiophylin for the production of EfoM (Scheme 1) as starting material for structural modifications. During our synthesis program we were able to crystallize a small amount of EfoM getting the first X-ray structure of this compound (see Fig. 1).[7]

Within initial experiments of a protection–deprotection sequence we were not able to deprotect the tetra-silylated EfoM-derivative **1** to EfoM neither under fluoride nor under acidic conditions (Scheme 2).

In most of these experiments we saw a loss of the 9- and/or 9′-hydroxy group. Addressing this very labile β-hydroxy keto functionality we looked for an approach to overcome these synthetic difficulties.

In a straightforward manner one of the outer hydroxyl groups was protected as Troc ester yielding a mixture of **2** and **3** (Scheme 3). After chromatographic separation from diester **3** a borohydride reduction under Luche-conditions furnished a diastereomeric mixture of the corresponding pentaol. Using an excess of TBDMS triflate all hydroxyl groups were protected providing **4**. Selective removal of the Troc ester followed by Jones-oxidation led to **5**. In order to check if ketone **5** can be used as labeling precursor we reduced with sodium borohydride, followed by deprotection of all silylethers under acidic conditions. Finally, the two allylic alcohols in the obtained hexaol were oxidized with manganese dioxide followed by a separation of the epimeric mixture yielding pure EfoM.

With this procedure in hand ketone **5** was reduced with tritiated reducing reagent yielding at the end of the known sequence 3H-EfoM derivative **6**.

Compound **6** was produced with a radiochemical purity >98%, a total activity of 37 MBq, and a specific activity of 266 GBq/mmol (365 MBq/mg). With this compound in hands we aimed to analyze its binding characteristics. To our surprise, we could not detect specific binding of 3H-EfoM to P- and L-selectin. Nevertheless, the compound is active in skin inflammation models. Based on more extended in house pharmacological experiments[4e] the question arised, how EfoM inhibited inflammatory processes in the skin. Potential explanations could be (a) indirect modification of the selectin structure and function as observed for integrins following the binding of chemokines to chemokine receptors or (b) interference with intracellular signaling of EfoM upon binding of selectin ligands to selectins. Future work may, hopefully, give the answer to the mode of action of EfoM.

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References and notes

1. (a) Herz, U.; Bunikowski, R.; Renz, H. *Int. Arch. Allergy Immunol.* **1998**, *115*, 179; (b) Kalish, R.; Askenase, P. *J. Allergy Clin. Immunol.* **1999**, *103*, 192; (c) Asadullah, K.; Volk, H.-D.; Sterry, W. *Trends Immunol.* **2002**, *23*, 47.
2. Krueger, J. G.; Wolfe, J. T.; Nabeya, R. T.; Vallat, V. P.; Gilleaudeau, P.; Heftler, N. S.; Austin, L. M.; Gottlieb, A. B. *J. Exp. Med.* **1995**, *182*, 2057.
3. (a) Staite, N. D.; Justen, J. M.; Sly, L. M.; Beaudet, A. L.; Bullard, D. C. *Blood* **1996**, *88*, 2973; (b) Homeister, J. W.; Zhang, M.; Frenette, P. S.; Hynes, R. O.; Wagner, D. D.; Lowe, J. B.; Marks, R. M. *Blood* **1998**, *92*, 2345; (c) Catalina, M. D.; Estess, P.; Siegelman, M. H. *Blood* **1999**, *93*, 580.
4. (a) Schoen, M. P.; Krahn, T.; Schoen, M.; Rodriguez, M.-L.; Antonicek, H.; Schultz, J. E.; Ludwig, R. J.; Zollner, T. M.; Bischoff, E.; Bremm, K.-D.; Schramm, M.; Henninger, K.; Kaufmann, R.; Gollnick, H. P. M.; Parker, C. M.; Boehncke, W.-H. *Nat. Med.* **2002**, *8*, 366; (b) Schoen, M. P.; Krahn, T.; Schoen, M.; Rodriguez, M.-L.; Antonicek, H.; Schultz, J. E.; Ludwig, R. J.; Zollner, T. M.; Bischoff, E.; Bremm, K.-D.; Schramm, M.; Henninger, K.; Kaufmann, R.; Gollnick, H. P. M.; Parker, C. M.; Boehncke, W.-H. *Nat. Med.* **2002**, *8*, 639, [Erratum]; (c) Schoen, M. P.; Boehncke, W.-H. *BIOspektrum* **2003**, *9*, 164; (d) Wienrich, B. G.; Krahn, T.; Schoen, M.; Rodriguez, M. L.; Kramer, B.; Busemann, M.; Boehncke, W.-H.; Schoen, M. P. *J. Invest. Dermatol.* **2006**, *126*, 882; (e) von Bonin, A.; Buchmann, B.; Bader, B.; Rausch, A.; Venstrom, K.; Schaefer, M.; Gruendemann, S.; Guenther, J.; Zorn, L.; Nubbemeyer, R.; Asadullah, K.; Zollner, T. M. *Nat. Med.* **2006**, *12*, 873; (f) Wienrich, B. G.; Oostingh, G. J.; Ludwig, R. J.; Enders, S.; Harms, G.; Tauber, R.; Krahn, T.; Kramer, B.; Boehncke, W.-H.; Schoen, M. P. *Nat. Med.* **2006**, *12*, 873; (g) Oostingh, G. J.; Ludwig, R. J.; Enders, S.; Gruener, S.; Harms, G.; Boehncke, W.-H.; Nieswandt, B.; Tauber, R.; Schoen, M. P. *J. Invest. Dermatol.* **2007**, *127*, 90.
5. (a) Hoechst AG, Patent DE 3831695 A1 **1998**; (b) Hamann, P.; Kretzschmar, G. *Z. Naturforsch.* **1990**, *45B*, 515.
6. Personal communication.
7. Schaefer, M.; Baesler, S.; Buchmann, B.; Neumann, G. *Acta Crystallogr., Sect. E*, submitted for publication.