DOI: 10.1002/anie.200701065

Polyketides

Total Synthesis of Efomycine M**

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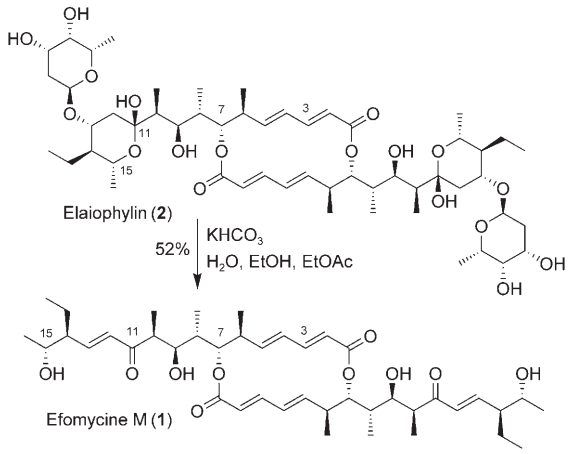
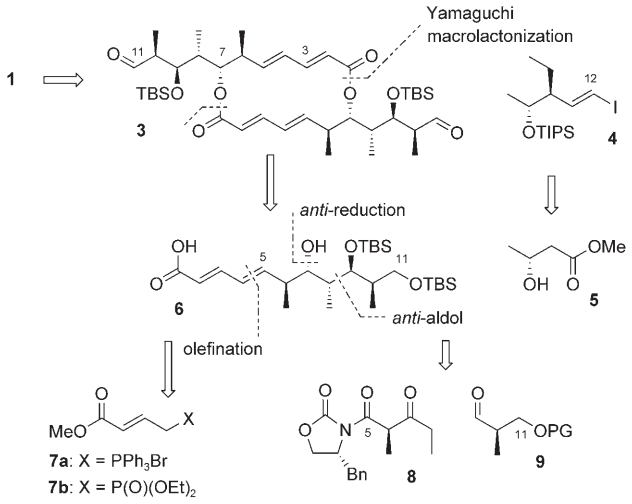
Dedicated to Professor Ekkehard Winterfeldt on the occasion of his 75th birthday

Characteristically, inflammatory skin diseases such as psoriasis and atopic dermatitis are accompanied by an expression of E- and P-selectins by endothelial cells. These selectins mediate T-cell rolling by their interaction with T-cell-expressed sialyl Lewis^x (sLe^x) epitopes.[1] Specific small-molecule inhibitors that structurally mimic the binding sites of selectin ligands reduce the number of skin-infiltrating T cells. The macrodiolide efomycine M (**1**) was reported to exhibit significant anti-inflammatory activity in two different mouse models of psoriasis by interfering with the binding of E- and P-selectins.[2] This result was hailed as a new therapeutic approach in the treatment of human inflammatory disorders,[3] until, quite recently, von Bonin et al., though confirming the anti-inflammatory profile of **1**, strongly doubted the reported mode of action.[4] In light of this controversy, detailed studies on the structure–activity relationships (SAR) appear appropriate for more insight into the biological profile of the compound.[5] In previous studies, **1** had been obtained semisynthetically from the natural product elaiophylin (azalomycin B, **2**) by base-catalyzed β elimination of the L-deoxyfucose moiety (Scheme 1).[6–8] Severe efforts to obtain suitable analogues from a chemical derivatization of **1** failed owing to the lability of the molecule.[5] Thus, we initiated a total synthesis of **1** which should be flexible enough to provide suitable derivatives for later SAR experiments.

Structurally, **1** features a 16-membered macrodiolide core, seven stereogenic centers and a labile α,β-enone moiety. Prompted by the C_2 symmetry of **1** we envisaged a two-directional approach (Scheme 2).[9] The C11–C12 bond was to be formed at a late stage by a double nucleophilic attack of an organometallic species obtained from vinyliodide **4** to dialdehyde **3**. The central stereopentad C5–C11 could be synthesized by an *anti*-aldol reaction followed by a diastereoselective ketone reduction. The dimerization of 2*E*,4*E*-*seco* acid **6** was to be achieved by Yamaguchi macrolactonization. Fragment C12–C16 could be synthesized from methyl



Scheme 1. Base-catalyzed formation of efomycine M (**1**) from elaiophylin (azalomycin B, **2**).[6]



Scheme 2. Retrosynthetic analysis of **1**. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl, Bn = benzyl, PG = protecting group.

(*R*)-3-hydroxybutyric acid (**5**) by a Fráter–Seebach alkylation and C_1 homologation.

Our synthesis started with the selective formation of the *E* enolate of β-ketoimide **8** using Cy_2BCl/Me_2NEt (Scheme 3). Subsequent reaction with aldehydes **9a**[10] or **9b**[11] gave β-hydroxyketones **10a** (62%, d.r. 91:9) and **10b** (80%, d.r. 95:5), respectively, in high yield. The excellent diastereoselectivity of the addition can be explained in terms of matched double stereodifferentiation, as aldehyde **9** regularly prefers the Felkin–Anh mode.[12] The use of TBDPS as a protecting group at C11 gave higher yields and better

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[**] R.B. gratefully acknowledges financial support from the Austrian Academy of Sciences (DOC fellowship). We thank Dr. B. Buchmann, Schering AG, for helpful discussions and an authentic sample of efomycine M. We also thank Dr. H. Kählig and S. Felsinger for NMR spectra and M. Zinke for HPLC analysis.

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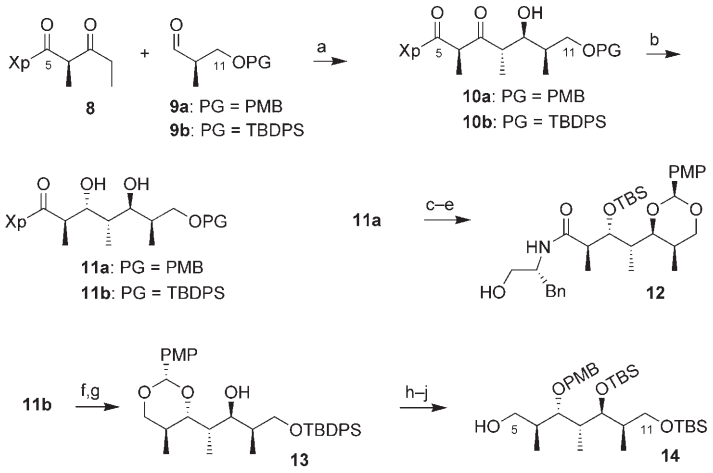


Scheme 3. Preparation of stereopentad **14**. Reagents and conditions: a) Cy_2BCl, Me_2NEt, Et_2O, −78 °C→0 °C (**10a**: 62%, d.r. 91:9; **10b**: 80%, d.r. 95:5); b) $NaBH(OAc)_3$, AcOH, MeCN, −40 °C (**11a**: 72%, d.r. 94:6; **11b**: 79%, d.r. 96:4); c) DDQ, MS 4 Å, CH_2Cl_2, 0 °C (33%); d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (99%); e) $LiBH_4$, H_2O, Et_2O, 0 °C (69%); f) $LiBH_4$, H_2O, Et_2O, 0 °C (87%); g) $PMPCH(OMe)_2$, (±)-CSA, CH_2Cl_2, RT; h) TBAF, THF, RT (99% over two steps); i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (91%); j) DIBAL, CH_2Cl_2, −30 °C (69%). Xp = (4*R*)-methylphenyloxazolidin-2-one-3-yl, PMB = *para*-methoxybenzyl, TBDPS = *tert*-butyldiphenylsilyl, PMP = *para*-methoxyphenyl, Cy = cyclohexyl, DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone, MS = molecular sieves, TBS = *tert*-butydimethylsilyl, OTf = triflouromethanesulfonate, PMB-$(OMe)_2$ = *para*-methoxybenzaldehyde dimethylacetal, CSA = camphorsulfonic acid, TBAF = tetrabutylammonium fluoride, DIBAL = diisobutylaluminum hydride.

diastereoselectivity than the PMB ether. A stereoselective *anti* reduction with $NaBH(OAc)_3$ completed the synthesis of the stereopentads **11a** (72%, d.r. 94:6) and **11b** (79%, d.r. 96:4, Scheme 3).[13]

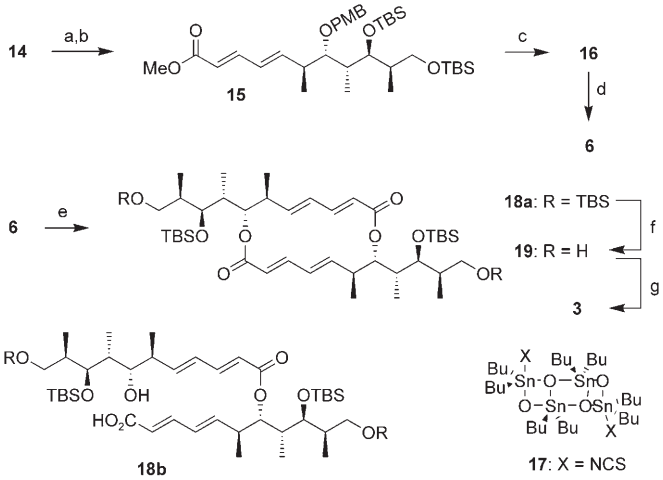
Next we had to differentiate between the two secondary hydroxy groups. In our initial approach we used the primary PMB group of **11a** to protect the neighboring free hydroxy group as a PMP acetal.[14] However, the protection of the remaining hydroxy group and reductive removal of the auxiliary proved to be problematic because of a reductive opening of the isoxazolidinone ring to give **12** (Scheme 3).

A satisfactory solution was finally achieved by reductive removal of the auxiliary of **11b** followed by regioselective protection of the terminal 1,3-diol as a PMP acetal by treatment with $PMPCH(OMe)_2$ to give **13**. At a later stage, the differentiation of the C9 and C11 OH functions was envisaged. This was deemed easier by introducing two TBS groups. Regioselective reductive opening of the acetal with DIBAL[15] furnished stereopentad **14** in gram quantities.

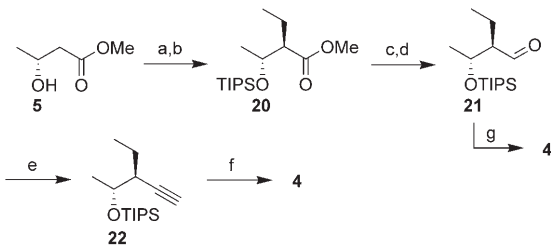
We next planned to construct the diene ester moiety of **1** in a single olefination reaction (Scheme 4). Oxidation of the primary alcohol was best achieved with Dess–Martin periodinane; Swern oxidation resulted in partial epimerization at C6. Wittig reaction using phosphonium salt **7a**[16] gave moderate yields only (46%), and the phosphine oxide was difficult to remove by chromatography. In contrast, the Horner–Wadsworth–Emmons olefination with phosphonate **7b** and LDA[17] delivered 2*E*,4*E* dienoate **15** as a single stereoisomer in excellent yield (up to 96%, 4*E*:4*Z* > 50:1). *seco* Acid **6** was obtained after cleavage of the PMB protecting group and base-induced hydrolysis of the methyl ester.

Dimerization of the *seco* methyl ester **16** with distannoxane catalyst **17** as reported by Panek et al. failed and gave *seco* acid **6** only.[18] Therefore, **6** was dimerised by means of the modified Yamaguchi macrolactonization protocol (Yonemitsu conditions)[19] to give the crystalline dimer **18a** (59%) along with minor amounts of the uncyclized dimer **18b**. The primary TBS group was easily removed in the presence of the secondary one with a dilute solution of HF·pyridine in THF (Scheme 4), and the resulting dialcohol **19** was oxidized to give dialdehyde **3**.

The synthesis of fragment C12–C16 started with the diastereoselective alkylation of methyl (*R*)-3-hydroxybutyric acid (**5**) (Scheme 5).[20] Protection of the hydroxy group as a TIPS ether followed by DIBAL reduction and oxidation gave aldehyde **21** in 97% overall yield. The TIPS protecting group



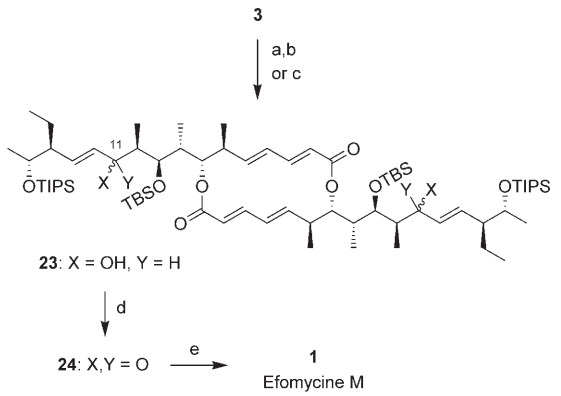
Scheme 4. Horner–Wadsworth–Emmons olefination and Yamaguchi dimerization. Reagents and conditions: a) Dess–Martin periodinane, CH_2Cl_2, 0 °C→RT; b) **7b**, LDA, THF, −78 °C (89% over two steps, *E*:*Z* > 50:1); c) DDQ, phosphate buffer pH 7, CH_2Cl_2, 0 °C→RT (98%); d) LiOH, H_2O, THF, RT (91%); e) 2,4,6-$Cl_3C_6H_2C(O)Cl$, NEt_3, toluene, RT, then DMAP (**18a**: 59%); f) 7% HF·pyridine, THF, RT (86%); g) Dess–Martin periodinane, CH_2Cl_2, 0 °C (94%). LDA = lithium diisopropylamide, DMAP = 4-dimethylaminopyridine.



Scheme 5. Synthesis of vinyliodide **4**. Reagents and conditions: a) **5**, LDA, THF, −40 °C, then EtI, −78 °C→RT (76%, d.r. 97:3); b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; c) DIBAL, toluene, −78 °C (99% over two steps); d) Dess–Martin periodinane, CH_2Cl_2, RT (99%); e) $TMSCHN_2$, *n*BuLi, Et_2O, −78 °C, then **21**, 0 °C (58%); f) $[Cp_2Zr(H)Cl]$, THF, RT, then I_2 (66%, *E*:*Z* > 50:1); g) $CrCl_2$, CHI_3, THF, 0 °C (18%, *E*:*Z* > 40:1). Cp = cyclopentadienyl.

proved to be the most compatible one in this sequence among a variety of alternatives such as TBS, PMB, and MOM. We first tried to synthesize vinyliodide **4** by Takai iodoolefination.[21] However, all attempts gave **4** in low yields only (18%) although with a high E:Z ratio (>40:1). In a more convenient approach, aldehyde **21** was converted into the alkyne **22** by a Colvin rearrangement using $TMSCHN_2$/nBuLi.[22] The more popular Corey–Fuchs homologation[23] turned out to be very sluggish and required repeated chromatographic purification. Finally, **22** was hydrozirconated with the Schwartz reagent according to a protocol devised by Negishi et al.[24] The organozirconium intermediate was quenched with iodine to give E vinyliodide **4** (66%, E:Z > 50:1).

For the coupling of C11 and C12 (Scheme 6) we first attempted a $CrCl_2$/$NiCl_2$-mediated Nozaki–Hiyama–Kishi reaction,[25] which gave diallylic alcohol **23** in a disappointingly low yield of 34%. Hydrozirconation of alkyne **22** followed by transmetalation with Et_2Zn[26] and addition to **3** failed (<5%). Finally, lithiation of vinyliodide **4** with tBuLi and subsequent addition of **3** gave **23** in excellent yield (89%) as a statistical 2:1:1 mixture of stereoisomers. The macrolactone carbonyl functions were completely unreactive even in the presence of excess vinyllithium reagent. Oxidation of the diastereomeric mixture to give enone **24** followed by desilylation with 70% HF·pyridine in MeCN/THF gave **1** in 57% yield over two steps. The use of TBAF resulted in elimination to give the 10E,12E dienone, whereas AcOH-buffered TBAF gave no reaction at all. The ^{1}H and ^{13}C NMR, IR, and mass spectra and the optical rotation of our synthetic sample of **1** were in complete agreement with those obtained from authentic material.[27]



Scheme 6. The final C11–C12 bond connection. Reagents and conditions: a) **4**, $CrCl_2$, $NiCl_2$, THF, DMF, RT (34%); b) **22**, [$Cp_2Zr(H)Cl$], THF, RT, then Et_2Zn, −78°C, toluene, then **3**, RT (<5%); c) **4**, tBuLi, Et_2O, −78°C, then **3**, −78°C→0°C (89%); d) Dess–Martin periodinane, CH_2Cl_2, 0°C→RT (82%); e) 70% HF·pyridine, THF, MeCN, RT (70%). DMF = *N*,*N*-dimethylformamide.

In conclusion, we have completed the first total synthesis of efomycine M (**1**) by a convergent approach in 17 steps over the longest linear sequence in 7% overall yield. Currently we are extending our stereo- and regiocontrolled synthesis for the preparation of simplified analogues for biological screening. In this connection, stereochemical variations as well as modifications of the C12–C16 side chain will be examined.

Received: March 10, 2007
Published online: June 26, 2007

Keywords: aldol reaction · asymmetric synthesis · macrolides · polyketides · total synthesis

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