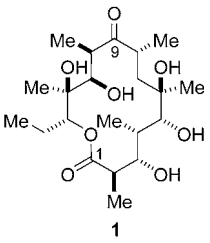
Natural Product Synthesis

Total Synthesis of Erythronolide A by Mg^{II}-Mediated Cycloadditions of Nitrile Oxides**

*Dieter Muri, Nina Lohse-Fraefel, and Erick M. Carreira**

Since its discovery in 1952,[1] erythromycin A has captured the imagination of research groups all over the world. The total syntheses of erythromycin A and its related derivatives (erythronolide A, erythromycin B, erythronolide B, (9*S*)-dihydroerythronolide A, 6-deoxyerythronolide B, 9,12-anhydroerythronolide A) have become benchmarks for the study of new methodologies in polyketide synthesis.[2–4] We have recently reported a general approach for the synthesis of polyketide building blocks by means of Kanemasa's Mg^{II}-mediated cycloadditions of nitrile oxides to allylic alcohols.[5] The nature of this approach allows the modular preparation of the entire spectrum of functionality and stereochemical permutations found in polyketide-derived structures. In this communication, we demonstrate the power and generality of this cycloaddition in the context of the total synthesis of erythronolide A (**1**). Erythronolide A was completed in 21 linear steps from the readily available oxime **2**.[5a] Of additional importance, we demonstrate the potential of the strategy to provide access to nonnatural analogues (ketolides) of this important agent.



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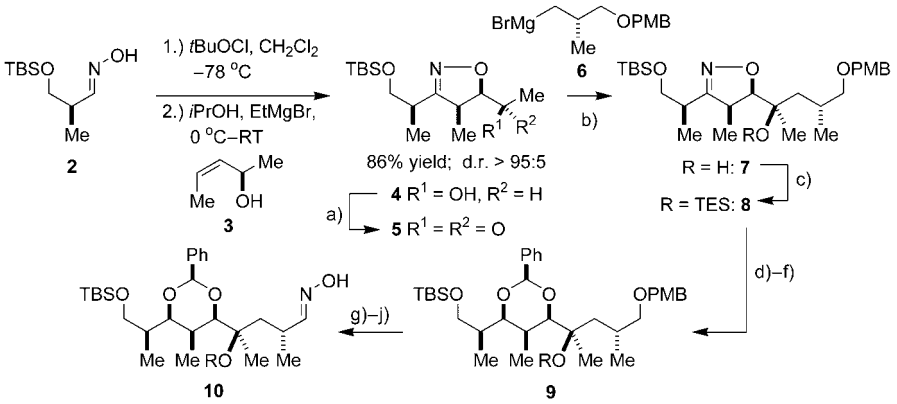
The synthesis commences with the cycloaddition of oxime **2** to allylic alcohol **3**; the former is available in three steps from (*S*)-methyl-3-hydroxyisobutyrate (Roche ester)[6] and the latter in two steps by Noyori reduction of propargylic ketone and semihydrogenation over the Lindlar catalyst.[7] Oxime **2** was treated with *t*BuOCl (−78 °C), which, after addition to a solution of *i*PrOH, EtMgBr, and **3**, provided isoxazoline **4** in 86 % yield on a 35-mmol scale and with a diastereomeric ratio of >95:5 as determined by ^{1}H NMR spectroscopy (Scheme 1). Oxidation of the secondary hydroxy group in **4** under conditions described by Ley et al. [8] and treatment with Grignard reagent **6**[9] afforded tertiary alcohol **7** in 64 % yield



Scheme 1. Conditions: a) TPAP, NMO, CH_2Cl_2, RT, 1.5 h, 82 %; b) **6**, THF, −78 °C, 1 h, 64 %, (d.r. > 98:2); c) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 93 %; d) Raney Ni (W2), $B(OH)_3$, H_2, $MeOH/H_2O$, RT, 2 h, 89 %; e) $Zn(BH_4)_2$, CH_2Cl_2, −30 °C, 2.5 h, 60 % (d.r. > 95:5); f) $PhCH(OMe)_2$, CSA (10 mol %), toluene, 50 mbar, RT, 1.5 h, 87 %; g) DDQ, pH 7 buffer, CH_2Cl_2, 0 °C, 2 h, 85 %; h) TEMPO (15 mol %), NaOCl, KBr (10 mol %), pH 8.6 buffer, CH_2Cl_2, 0 °C, 10 min; j) $H_2NOH{\cdot}HCl$, pyridine, EtOH, RT, 20 min, 85 % (over 2 steps). CSA = camphorsulfonic acid, DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone, NMO = *N*-methylmorpholine *N*-oxide, PMB = *para*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxyl, TESOTf = triethylsilyl trifluoromethanesulfonate, TPAP = tetrapropylammonium perruthenate.

(98:2 d.r., ^{1}H NMR). The tertiary hydroxy group was protected as triethylsilyl ether (93 % yield). Reductive cleavage of the N–O bond (Raney Ni, $B(OH)_3$, 93 % yield),[10] *syn* reduction of the ensuing hydroxy ketone ($Zn(BH_4)_2$, 60 % yield),[11] and protection of the isolated 1,3-diol provided **9** (87 % yield) as a single diastereomer (^{1}H NMR). Adduct **9** was converted to oxime **10** by a short three-step sequence of reactions in 72 % overall yield.

With oxime **10** in hand, we were ready for the second cycloaddition of a nitrile oxide. We were pleased to observe that this highly functionalized nitrile oxide smoothly underwent Mg^{II}-mediated 1,3-dipolar cycloaddition with allylic alcohol **3** under our standard reaction conditions (Scheme 2).[6] Isoxazoline **11** was obtained in excellent yield (86 %) as a single diastereomer as determined by ^{1}H NMR spectroscopy. The nitrile oxide derived from **10** represents one of the most complex substrates used in dipolar cycloaddition reactions and attests to the versatility of the cycloaddition strategy for the synthesis of polyketides.

Oxidation of the secondary hydroxy group in **11** with TEMPO/NaOCl provided the corresponding ketone in 93 % yield, which was subjected to Wittig olefination[12] ($PrPPh_3Br$ and *t*BuLi) to give a trisubstituted olefin in 78 % yield and 33:1 *Z*/*E* ratio. Dihydroxylation of this olefin with $(DHQD)_2PHAL/K_2OsO_4{\cdot}2H_2O$ (4 mol %) furnished the 1,2-diol **12** in 81 % yield and 96:4 d.r.[13,14] Selective deprotection of the primary *tert*-butyldimethylsilyl ether over the tertiary triethylsilyl ether could be accomplished with HF·pyridine/pyridine (1:3).[15] Chemoselective two-step oxi-

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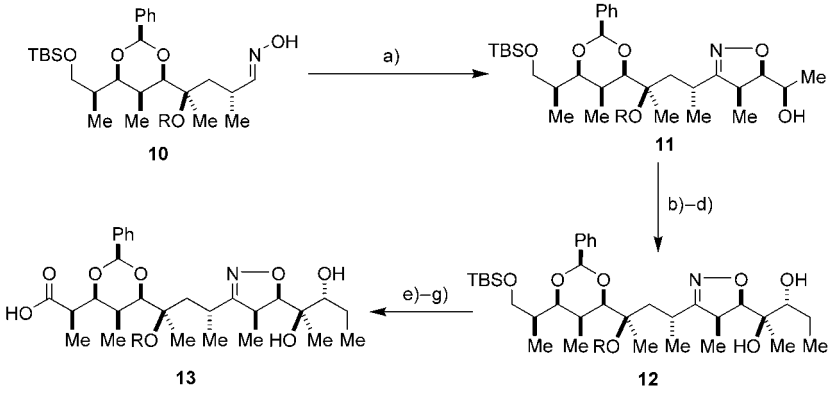
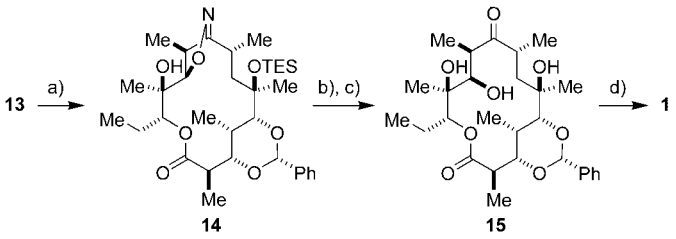


Scheme 2. Conditions: a) i) *t*BuOCl, CH_2Cl_2, −78 °C, 1.5 h, ii) *i*PrOH, EtMgBr, **3**, CH_2Cl_2, 0 °C→RT, 86%, (d.r. > 99:1); b) TEMPO (15 mol%), NaOCl, KBr (10 mol%), pH 8.6 buffer, CH_2Cl_2, 0 °C, 1 h, 93%; c) $PrPPh_3Br$, *t*BuLi, THF, −78 °C→RT, 15 h, 78%, (*Z*:*E* 33:1); d) $(DHQD)_2PHAL$ (20 mol%), $K_3[Fe(CN)_6]$, $MeSO_3NH_2$, K_2CO_3, $K_2OsO_4{\cdot}2H_2O$, *t*BuOH/H_2O, 0 °C, 2.5 h, 81% (d.r. 96:4); e) HF·py:py (1:3), 0 °C, 3 h, 80%; f) TEMPO (15 mol%), NaOCl, KBr (10 mol%), pH 8.6 buffer, CH_2Cl_2, 0 °C, 30 min; g) $NaClO_2$, 2-methyl-2-butene, pH 3.8 buffer, *t*BuOH, 0 °C, 30 min, 83% (over 2 steps). py = pyridine, $(DHQD)_2PHAL$ = dihydroquinidine phthalazine ligand. R = TES.

dation (TEMPO/NaOCl, $NaClO_2$, 83% yield) completed the synthesis of erythronolide A seco acid **13**.

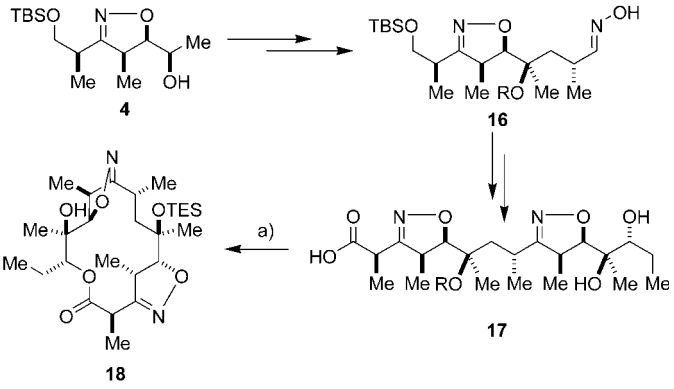
At the outset of this project, it was far from certain whether the cyclization could be successfully executed with the isoxazoline carboxylic acid **13**. The classic work of Woodward on the total synthesis of erythromycin A underscores the sensitivity of related macrolactonizations of carboxylic acids to the constellation of protecting groups.[16] On the basis of modeling, we hypothesized that an isoxazoline bridging C9–C11 would lead to a favorable conformation of **13** and facilitate macrolactonization. Indeed, following a modified Yamaguchi protocol,[17] the desired macrolactone was isolated in 78% yield without detection of any other cyclization by-products (Scheme 3). Deprotection of the triethylsilyl ether and subsequent N–O bond cleavage (Raney-Ni, AcOH) provided **15** in 93% yield, thus completing the formal total synthesis of erythronolide A. Treatment of **15** with $Pd(OAc)_2$ for 6 h under an atmosphere of H_2 produced erythronolide A. Its ^1H and ^{13}C NMR spectra as well as melting point and optical rotation are identical with those of naturally derived erythronolide A.[18]

An important aspect of this cycloaddition strategy would be the ability to access nonnatural polyketides. This approach



Scheme 3. Conditions: a) i)2,4,6-$Cl_3C_6H_2COCl$, NEt_3, THF, 0 °C, 30 min; ii) DMAP, toluene, 50 °C, 4 h, 78%; b) HF·NEt_3, NEt_3, CH_3CN, RT, 64 h, > 99%; c) Raney-Ni (W2), AcOH, H_2, EtOH, RT, 20 min, 93%; d) $Pd(OAc)_2$, MeOH, H_2, RT, 6 h, 40%. DMAP = 4-*N*,*N*-dimethylaminopyridine.

would extend the methodology beyond an aldol-equivalent strategy to one that could provide unusual analogues not directly accessible either through genetic engineering or traditional synthetic methods. A number of erythromycin analogues investigated in the pharmaceutical industry are heterocyclic derivatives (bridging C9–C11, for example) prepared from the natural product.[19] We thus became interested in the generation of nonnatural analogues such as **18** (Scheme 4). In a similar reaction sequence as described above, isoxazoline **4** could easily be converted to oxime **16** and subsequently to carboxylic acid **17**. Under modified Yamaguchi conditions, we obtained macrolactone **18** in 60% yield. Since the nitrile oxide and allylic alcohol partners can be varied readily, this strategy enables an approach to a plethora of



Scheme 4. Conditions: a) i) 2,4,6-$Cl_3C_6H_2COCl$, NEt_3, THF, 0 °C, 30 min; ii) DMAP, toluene, 50 °C, 4 h, 60%.

derivatives that may exhibit useful properties and allow the development of new antibiotics against multiresistant bacterial strains.

In summary, we have reported a stereoselective total synthesis of erythronolide A, whose focal points are two Mg^{II}-mediated cycloadditions of nitrile oxides, making this the shortest synthesis of erythronolide A to date: 21 linear steps, 4% overall yield. These accomplishments establish this methodology as a powerful tool for the synthesis of polyketide natural products. The isoxazoline serves as a robust protecting group for β-hydroxyketones that can be cleaved at a late stage of the synthesis within a densely functionalized structure. Moreover, the isoxazoline proved suitable for the delicate macrolactonization of erythronolide A seco acid **13**. Of broader significance, the strategy, beyond its use as an aldol equivalent process, opens up new possibilities for the preparation of nonnatural analogues.

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