Natural Products Synthesis

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Enantioselective Synthesis of Oasomycin A, Part II: Synthesis of the C29–C46 Subunit**

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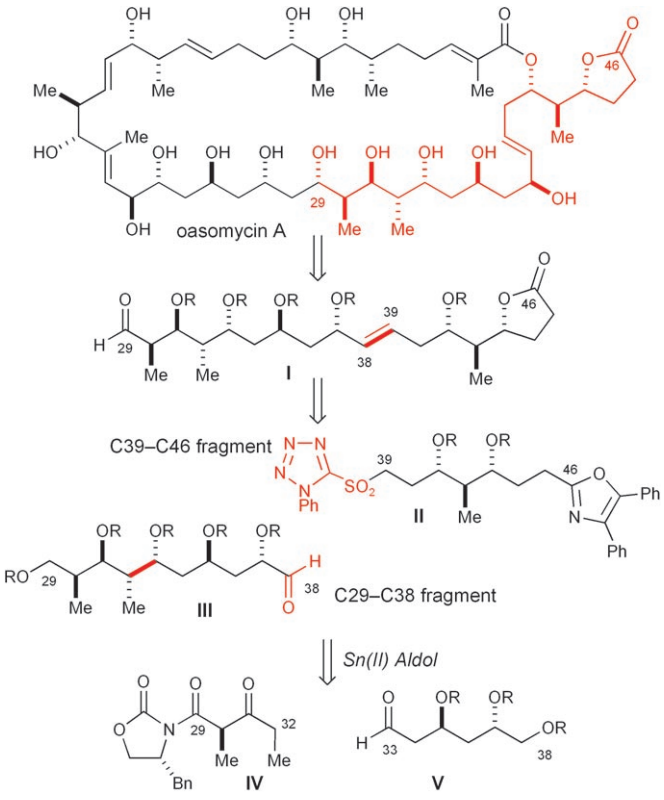
Dedicated to Professor Y. Kishi on the occasion of his 70th birthday.

Syntheses of the C1–C12 and C13–C28 oasomycin A subunits were described in the preceding Communication.[1] Herein we describe the synthesis and assemblage of the C29–C46 portion of this polyketide natural product. According to the synthesis plan,[2] the C29–C46 fragment targeted as aldehyde **I** is considered as one of the complex subgoals.

Julia disconnection of the Δ^{38} olefin in **I** affords fragments **II** and **III** of comparable complexity (Scheme 1). On the basis of the elegant studies of Wasserman et al., the decision was made to mask the C46 carboxy terminus in sulfone **II** as its derived 4,5-diphenyloxazole,[3] thus preserving its oxidation state. The singlet-oxygen-mediated liberation of this carboxy moiety could, in principle, be executed at numerous stages in the synthesis because of the compatibility of this transformation with the multitude of other oxygen-protecting groups in the assembled or partially assembled subunits. The C29–C38 fragment **III** (Scheme 1) is composed of both polyacetate and polypropionate subunits. The latter motif could be introduced by a Sn^{II}-mediated *syn*-selective aldol addition of dipropionyl synthon **IV** to aldehyde **V**—a reaction which was developed by us some years ago.[4]



Scheme 1. Retrosynthetic analysis of oasomycin A. Bn = benzyl.

The synthesis of aldehyde **V** began with a chiral Lewis acid catalyzed aldol addition of the Chan diene[5] **1** to benzyloxy acetaldehyde **2** promoted by the Cu^{II} complex **3** (5 mol%) that was previously developed by our research group (Scheme 2).[6] The resultant ketoester **4** (95% *ee*) was reduced with $Me_4NBH(OAc)_3$[7] to afford a 1,3-*anti* diol (91:9 d.r.). Silylation of the diol (TBSCl, imidazole) followed by a reduction using DIBALH provided aldehyde **5** (77%, 3 steps). The dipropionyl synthon **IV** was next introduced by a Sn^{II}-mediated aldol addition of β-ketoimide **6** to aldehyde **5**[4] thus providing **7** as a 95:5 mixture of diastereomers. Immediate treatment of **7** with $Me_4NBH(OAc)_3$[7] afforded the anticipated *anti* diol **8a** (90:10 d.r.)[8] which was readily purified by flash chromatography. Selective protection (TBSOTf, lutidine) of the less sterically hindered C33 hydroxy group gave the TBS ether **8b** in 75% yield (2 steps). Since we were unable to directly protect the hindered C31 hydroxy group as the PMB ether, the well-precedented three-step procedure consisting of reductive removal of the chiral auxiliary with $LiBH_4$, protection of the diol as the *p*-methoxybenzylidene acetal, and selective reduction of the acetal with borane, catalyzed by $Sc(OTf)_3$,[9] was then accomplished (80%, 3 steps). Interestingly, when the aforementioned acetal reduction was attempted with DIBALH, none of the desired product was obtained and the reaction resulted in loss of the TBS group at C37. Alcohol **9** was then silylated (TESOTf, lutidine) and the resulting product was hydrogenated (H_2, dry $Pd(OH)_2$/C, EtOAc) to give the alcohol at C38 that was then oxidized with Dess–Martin reagent[10] to afford the desired C29–C38 subunit **10**.

The construction of sulfone **II** (Scheme 1) began with the preparation of α,β-unsaturated aldehyde **12** from the known 4,5-diphenyloxazole **11** (Scheme 3).[11] The aldol addition of oxazolidinone **13** to aldehyde **12** catalyzed by magnesium chloride[12] afforded the corresponding *anti* aldol adduct that

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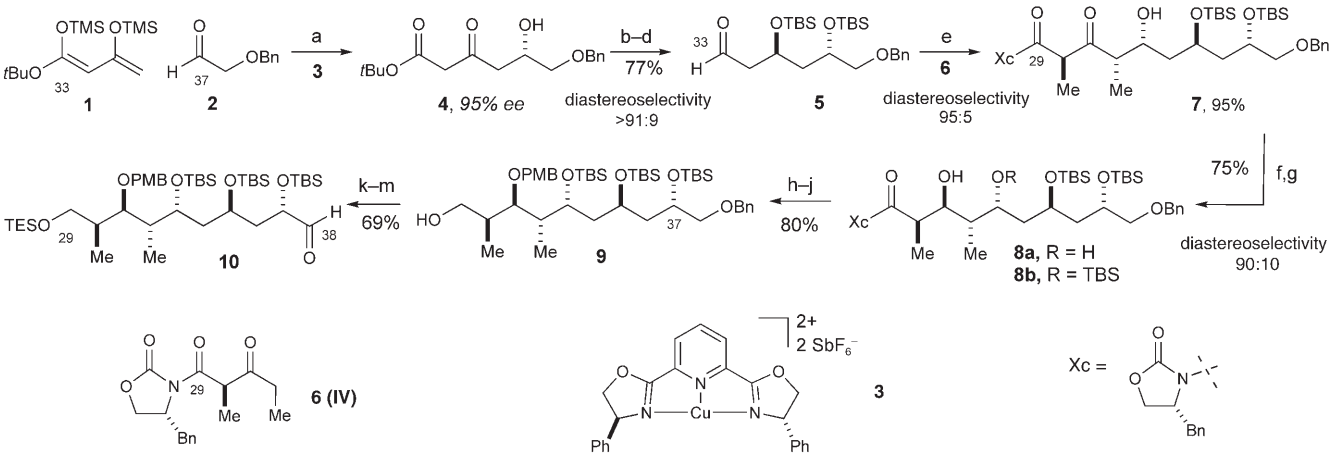
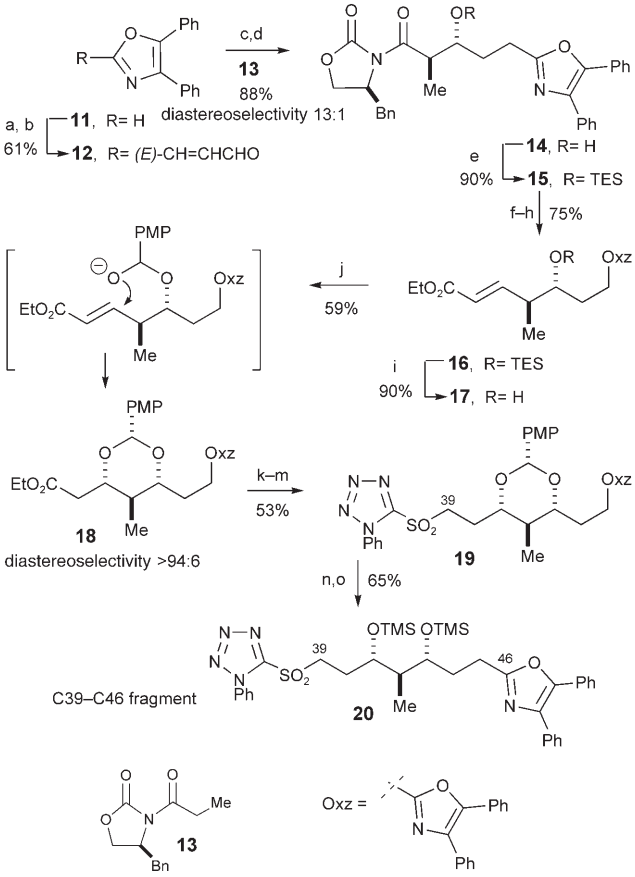


Scheme 2. Synthesis of the C29–C38 fragment **10**. Reagents and conditions: a) 1. **3** (0.05 equiv), CH_2Cl_2, −95 °C; 2. PPTS, MeOH, (95 % *ee*); b) $Me_4NBH(OAc)_3$, MeCN/AcOH, −25 °C, (91:9 d.r.); c) TBSCl, imidazole, DMF, RT; d) DIBALH, toluene, −90→−78 °C, (77 %, 3 steps); e) 1. **6**, $Sn(OTf)_2$, NEt_3, CH_2Cl_2, −20→−78 °C; 2. **5**, CH_2Cl_2, (95 %, 95:5 d.r.); f) $Me_4NBH(OAc)_3$, MeCN/AcOH, −20 °C, (90:10 d.r.); g) TBSOTf, lutidine, CH_2Cl_2, 0 °C, (75 %, 2 steps); h) $LiBH_4$, THF, H_2O, 0 °C; i) $PMPCH(OMe)_2$, PPTS, CH_2Cl_2; j) $Sc(OTf)_3$ (0.1 equiv), BH_3·THF (5 equiv), CH_2Cl_2, 0 °C, (80 %, 3 steps); k) TESOTf, lutidine, THF, 0 °C; l) $Pd(OH)_2$/C (0.1 equiv), H_2, EtOAc; m) DMP, Py, CH_2Cl_2, (69 %, 3 steps). DIBALH = diisobutylaluminum hydride, DMF = dimethylformamide, DMP = Dess–Martin Periodinane, PMB = 4-methoxybenzyl, PMP = 4-methoxyphenyl, PPTS = pyridinium *p*-toluenesulfonate, Py = pyridine, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.

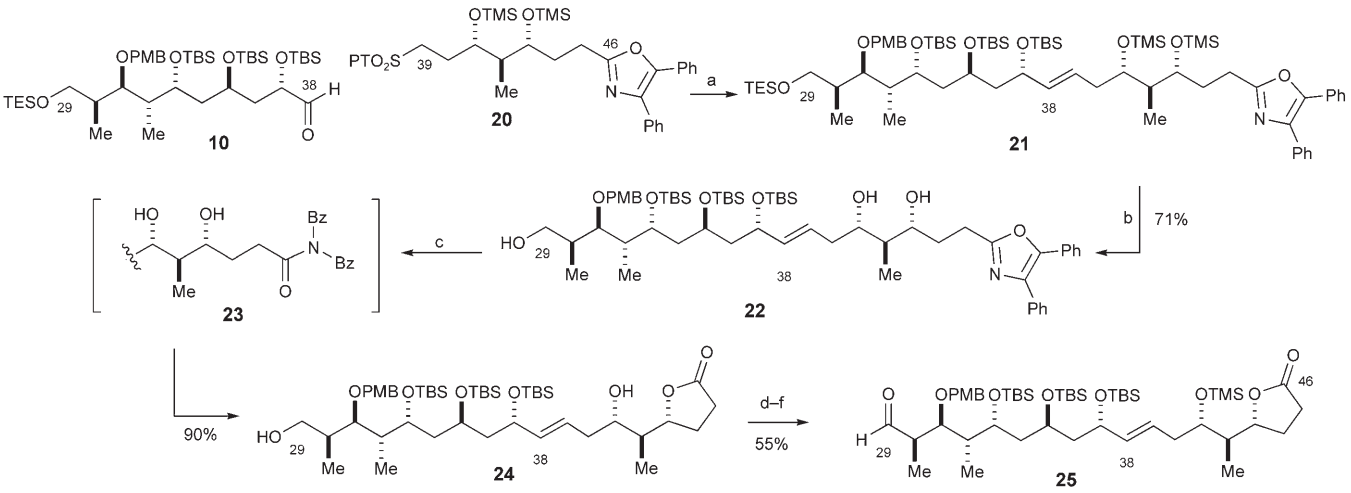
was then hydrogenated (Pd/C, H_2, EtOAc) to give alcohol **14**[13] (88 %, 2 steps). Remarkably, the diastereoselectivity of the aldol addition was counterintuitively temperature dependent. Thus, when the reaction temperature was raised from −10 to 77 °C, the diastereoselectivity for the *anti* product increased from 1:1 to 13:1. The *anti* aldol adduct **14** obtained was then silylated[14] (TESOTf, lutidine) and the chiral auxiliary was removed by a two-step procedure to provide the corresponding aldehyde, which was treated with ethyl (triphenylphosphoranylidene)acetate to give the α,β-unsaturated ester **16**. Cleavage of the TES group (HCl, MeOH) followed by an intramolecular heteroconjugate addition[15] of the hemiacetal *p*-anisaldehyde adduct of **17** (Scheme 3) resulted in the formation of acetal **18** (59 %, 94:6 d.r.), in accord with our previous findings.[16] We found that a nonpolar solvent system (Et_2O/PhMe) was required for this reaction to proceed with significant conversion.

Incorporation of the phenyltetrazole sulfone moiety at the C38 terminus of **18** was then executed by a three-step procedure: 1) reduction of the ester with $LiAlH_4$, 2) Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol, and 3) oxidation of the derived sulfide[17] to give **19** in 53 % yield over the three steps. The *p*-methoxybenzylidene acetal was removed ($AlBr_3$, EtSH)[18] and silylation of the resultant unstable diol (TMSCl, imidazole) afforded the fully elaborated C39–C46 fragment **20** in good yield (65 %, 2 steps).

With fragments **10** and **20** in hand, their coupling was then addressed (Scheme 4). Kocienski–Julia olefination proved to be optimal under Barbier conditions and proceeded with excellent stereoselectivity (>95:5 *E*/*Z*).[19] However, this transformation was highly dependent on the nature of the



Scheme 3. Synthesis of the C39–C46 fragment **20**. Reagents and conditions: a) 1. *n*BuLi, THF, −78 °C; 2. DMF, −78→20 °C; b) PPh_3=CHCHO, CH_2Cl_2, (61 %, 2 steps); c) 1. **13**, $MgCl_2$, TMSCl, NEt_3, EtOAc, 77 °C; 2. TFA, MeOH, (13:1 d.r.); d) Pd/C (10 %), H_2, EtOAc, (88 %, 2 steps); e) TESOTf, lutidine, CH_2Cl_2, 0 °C, 90 % f) EtSLi, THF, −20 °C; g) DIBALH, CH_2Cl_2, −90 °C; h) PPh_3=$CHCO_2Et$, CH_2Cl_2, (75 %, 3 steps); i) HCl (0.05 N), MeOH; 90 %; j) PMPCHO, KO*t*Bu, Et_2O/toluene, −20 °C, 59 %; k) $LiAlH_4$, Et_2O, 0 °C; l) 1-phenyl-1*H*-tetrazole-5-thiol, DEAD, PPh_3, THF; m) $(NH_4)_6Mo_7O_{24}$, H_2O_2, EtOH, (53 %, 3 steps); n) $AlBr_3$, EtSH, CH_2Br_2/CH_2Cl_2; o) TMSCl, imidazole, CH_2Cl_2, (65 %, 2 steps). DEAD = diethyl azodicarboxylate, TFA = trifluoroacetic acid.



Scheme 4. Assembly of C29–C46 subunit **25**. Reagents and conditions: a) KHMDS, DME, −48→20 °C, (>95:5 *E*/*Z*); b) PPTS, MeOH/CH_2Cl_2 (1:1), 0 °C, (71 %, 2 steps); c) Rose Bengal, O_2, *hv*, $(CH_2Cl)_2$, 90 %; d) TMSCl, imidazole, CH_2Cl_2; e) PPTS, Py, MeOH/CH_2Cl_2 (1:2); f) DMP, Py, CH_2Cl_2, (55 %, 3 steps). Bz = benzoyl, DME = 1,2-dimethoxyethane, HMDS = hexamethyldisilazide, PT = 5-phenyltetrazole.

protecting groups on the sulfone fragment **20**, with TMS groups affording the optimal yield.[20] The unpurified product was then treated with PPTS to remove the primary TES group and the two TMS groups to provide triol **22** in 71 % yield (2 steps). This successful cross-coupling reaction confirmed our prediction that the CH kinetic acidity conferred on **20** by the sulfone moiety would be greater than the acidity contributed by the oxazole synthon. The subsequent singlet-oxygen oxidation of the 4,5-diphenyloxazole moiety in **22** proceeded with concomitant lactonization via **23** to provide lactone **24** in 90 % yield. The hydroxy groups at C29 and C41 of compound **24** were then protected as TMS ethers (TMSCl, imidazole) and the product subjected to PPTS buffered with pyridine to selectively remove the primary TMS group at C29.[21] The product was then oxidized to afford the targeted C29–C46 subunit of oasomycin A (55 %, 3 steps).

The study described above provided an efficient route to the C29–C46 portion of oasomycin A, and led to the culmination of the total synthesis of oasomycin A that is addressed in the following Communication.

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Keywords: aldol reaction · Kocienski–Julia olefination · macrolactonization · natural products · total synthesis

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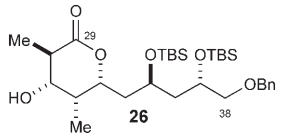
[8] The diol was lactonized to **26** and its configuration was determined by NOESY experiments.



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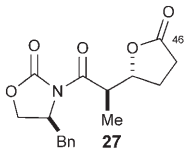
[13] The stereochemistry of **14** was proven by X-ray crystallography of its derivative **27**:



[14] Protection as the silyl ether simplified the purification of **15** from the minor diastereomer giving >18:1 d.r. after flash chromatography.

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[20] A similar coupling reaction with the TES-protected versions of **20** proceeded in 35% yield whereas the corresponding cyclopentylidene ketal afforded the Julia coupling product in 65% yield.
[21] The diol **24** resulting from deprotection of both TMS ethers was also recovered in 10–25% yield, and recycled. The yield was calculated after one such recycling of **24**.

