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



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

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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]

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 Me₄NBH(OAc)₃^[7] to afford a 1,3-anti diol (91:9 d.r.). Silvlation 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 wellprecedented three-step procedure consisting of reductive removal of the chiral auxiliary with LiBH₄, 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 silvlated (TESOTf, lutidine) and the resulting product was hydrogenated (H₂, 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) Me₄NBH(OAc)₃, MeCN/AcOH, -25 °C, (91:9 d.r.); c) TBSCl, imidazole, DMF, RT; d) DIBALH, toluene, $-90 \rightarrow -78 °C$, (77%, 3 steps); e) 1. **6**, Sn(OTf)₂, NEt₃, CH_2Cl_2 , $-20 \rightarrow -78 °C$; 2. **5**, CH_2Cl_2 , (95%, 95:5 d.r.); f) Me₄NBH(OAc)₃, MeCN/AcOH, -20 °C, (90:10 d.r.); g) TBSOTf, lutidine, CH_2Cl_2 , 0 °C, (75%, 2 steps); h) LiBH₄, THF, H₂O, 0 °C; i) PMPCH(OMe)₂, PPTS, CH_2Cl_2 ; j) Sc(OTf)₃ (0.1 equiv), BH₃·THF (5 equiv), CH_2Cl_2 , 0 °C, (80%, 3 steps); k) TESOTf, lutidine, THE 0 °C; i) PMO(DM) (C (0.1 equiv), L = toOAc; rm) DMP. Pt (C l (60%)

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, H₂, 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 silvlated^[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 (Et₂O/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 LiAlH₄, 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 (AlBr₃, 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, $-78 \rightarrow 20$ °C; b) PPh₃=CHCHO, CH₂Cl₂, (61 %, 2 steps); c) 1. 13, MgCl₂, TMSCl, NEt₃, EtOAc, 77 °C; 2. TFA, MeOH, (13:1 d.r.); d) Pd/C (10%), H₂, EtOAc, (88%, 2 steps); e) TESOTf, lutidine, CH₂Cl₂, 0°C, 90% f) EtSLi, THF, -20 °C; g) DIBALH, CH₂Cl₂, -90 °C; h) PPh₃=CHCO₂Et, CH₂Cl₂, (75%, 3 steps); i) HCl (0.05 N), MeOH; 90%; j) PMPCHO, KOtBu, Et₂O/toluene, -20 °C, 59%; k) LiAlH₄, Et₂O, 0 °C; l) 1-phenyl-1*H*-tetrazole-5-thiol, DEAD, PPh₃, THF; m) (NH₄)₆Mo₇O₂₄, H₂O₂, EtOH, (53%, 3 steps); n) AlBr₃, EtSH, CH₂Br₂/CH₂Cl₂; o) TMSCl, imidazole, CH₂Cl₂, (65%, 2 steps). DEAD=diethyl azodicarboxylate, TFA=tri-fluoroacetic acid.



Scheme 4. Assembly of C29–C46 subunit 25. Reagents and conditions: a) KHMDS, DME, $-48 \rightarrow 20$ °C, (>95:5 E/Z); b) PPTS, MeOH/CH₂Cl₂ (1:1), 0 °C, (71%, 2 steps); c) Rose Bengal, O₂, $h\nu$, (CH₂Cl₂, 90%; d) TMSCl, imidazole, CH₂Cl₂; e) PPTS, Py, MeOH/CH₂Cl₂ (1:2); f) DMP, Py, CH₂Cl₂, (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 singletoxygen 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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- D. A. Evans, P. Nagorny, K. J. McRae, D. J. Reynolds, L.-S. Sonntag, F. Vounatsos, R. Xu, *Angew. Chem.* 2007, 119, 543– 546; *Angew. Chem. Int. Ed.* 2007, 46, 537–540.
- [2] For the discussion of the synthesis plan, refer to the following Communication: D. A. Evans, P. Nagorny, K. J. McRae, L.-S. Sonntag, D. J. Reynolds, F. Vounatsos, *Angew. Chem.* 2007, 119, 551–554; *Angew. Chem. Int. Ed.* 2007, 46, 545–548.
- [3] For examples using 4,5-diphenyloxazole as a protecting group, see: a) H. H. Wasserman, R. J. Gambale, M. J. Pulwer, *Tetrahedron* **1981**, *37*, 4059–4067; b) H. H. Wasserman, R. J. Gambale, *Tetrahedron Lett.* **1981**, *22*, 4849–4852; c) H. H. Wasserman,

R. J. Gambale, M. J. Pulwer, *Tetrahedron Lett.* 1981, 22, 1737–1740; d) H. H. Wasserman, R. J. Gambale, *J. Am. Chem. Soc.* 1985, *107*, 1423–1424; e) H. H. Wasserman, R. W. DeSimone, W. B. Ho, K. E. McCarthy, K. Spencer Prowse, A. P. Spada, *Tetrahedron Lett.* 1992, *33*, 7207–7210.

- [4] D. A. Evans, J. S. Clark, R. Metternich, V. J. Novack, G. S. Sheppard, J. Am. Chem. Soc. 1990, 112, 866–868.
- [5] G. A. Molander, O. K. Cameron, J. Am. Chem. Soc. 1993, 115, 830–846.
- [6] a) D. A. Evans, M. C. Kozlowski, J. A. Murray, C. S. Burgey, K. R. Campos, B. T. Connell, R. J. Staples, *J. Am. Chem. Soc.* **1999**, *121*, 669–685; for a recent review on catalytic, enantioselective, vinylogous aldol reactions, see: b) S. E. Denmark, J. R. Heemstra, Jr., G. L. Beutner, *Angew. Chem.* **2005**, *117*, 4760– 4777; *Angew. Chem. Int. Ed.* **2005**, *44*, 4682–4698.
- [7] The reduction of 4 is described in Ref. [6]. For the original procedure for Me₄NBH(OAc)₃ reduction, see: D. A. Evans, K. T. Chapman, E. M. Carreira, J. Am. Chem. Soc. 1988, 110, 3560-3578.
- [8] The diol was lactonized to **26** and its configuration was determined by NOESY experiments.



- [9] C. C. Wang, S. Y. Luo, C. R. Shie, S. C. Hung, Org. Lett. 2002, 4, 847–849.
- [10] D. B. Dess, J. C. Martin, J. Am. Chem. Soc. 1983, 105, 4155– 4156.
- [11] W. W. Pei, S. H. Li, X. P. Nie, Y. W. Li, J. Pei, B. Z. Chen, J. Wu, X. L. Ye, *Synthesis* **1998**, 1298–1304.
- [12] a) D. A. Evans, J. S. Tedrow, J. T. Shaw, C. W. Downey, J. Am. Chem. Soc. 2002, 124, 392–393; for a review of recent studies with chiral imides, see: b) D. A. Evans, J. T. Shaw, Actual. Chim. 2003, 4–5, 35–38.
- [13] The stereochemistry of **14** was proven by X-ray crystallography of its derivative **27**:
- [14] Protection as the silvl ether simplified the purification of 15 from the minor diastereomer giving > 18:1 d.r. after flash chromatography.



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- [15] D. A. Evans, J. A. Gauchet-Prunet, J. Org. Chem. 1993, 58, 2446–2453.
- [16] The stereochemistry of acetal **18** was proven by 1D NOE experiments.
- [17] H. S. Schultz, H. B. Freyermuth, S. R. Buc, J. Org. Chem. 1963, 28, 1140-1142.
- [18] For the use of this reagent combination in the deprotection of benzyl ethers, see: D. A. Evans, J. L. Katz, G. S. Peterson, T. Hintermann, J. Am. Chem. Soc. 2001, 123, 12411-12413.
- [19] a) P. J. Kocienski, A. Bell, P. R. Blakemore, *Synlett* 2000, 365–366; for a recent review on this topic, see: b) P. R. Blakemore, *J. Chem. Soc. Perkin Trans.* 1 2002, 2563–2585.
- [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.