Natural Products Synthesis

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Enantioselective Synthesis of Oasomycin A, Part I: Synthesis of the C1–C12 and C13–C28 Subunits**

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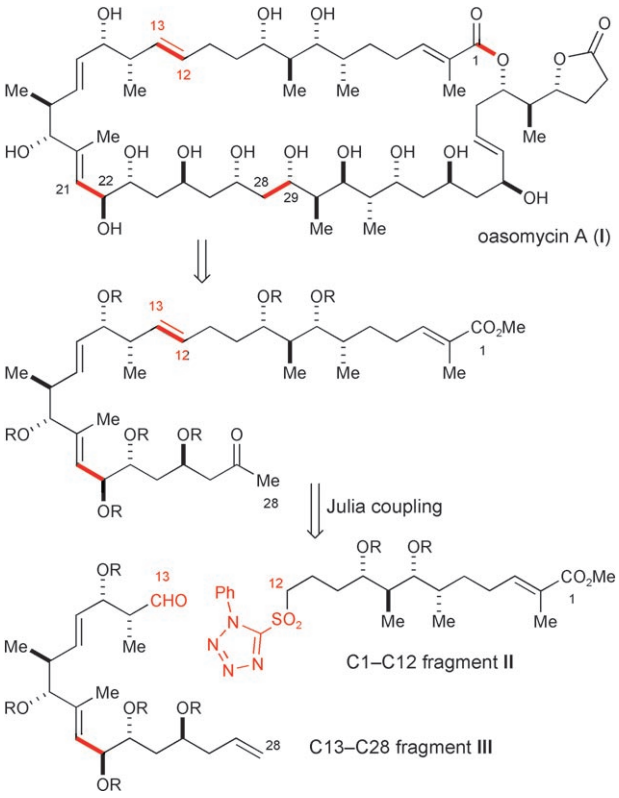
Dedicated to Professor Y. Kishi on the occasion of his 70th birthday.

Oasomycin A (**I**) is a member of the desertomycin family of macrolide natural products and was isolated in 1993 by Thiericke and co-workers during the screening of secondary metabolites of *Streptoverticillium baldacii*.[1] The overall structure of oasomycin A was established through extensive NMR spectroscopic studies and by direct comparison to other members of the desertomycin family.[1a] In 2001, Kishi and co-workers issued a proposal for the relative and absolute stereochemistry of oasomycin A through the use of their "universal NMR database" (Scheme 1).[2] To validate the structural assignment of oasomycin A, we decided to pursue the synthesis of the reported structure, **I**.

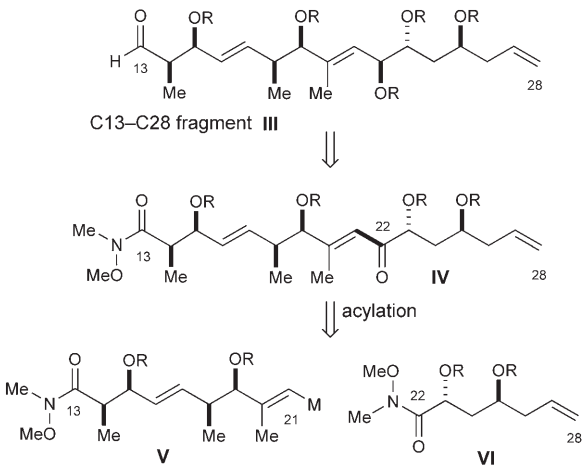
Herein, and in the following Communications,[23] we describe our efforts which culminated in the synthesis of oasomycin A (**I**) and confirm the stereochemical assignment by Kishi and co-workers. First, we describe the synthesis of the C1–C12 and C13–C28 subunits **II** and **III**, respectively, which will be united by using the Julia coupling reaction (Scheme 1).

Our plan for the synthesis of the C13–C28 fragment **III** is outlined in Scheme 2. Aldehyde **III** could be derived from a chelate-controlled reduction of the α,β-unsaturated ketone **IV**, which in turn can be disconnected at the C21−C22 bond to afford fragments **V** and **VI**. We predict successful union of these two fragments because of the greater reactivity of the Weinreb amide **VI**, which is required to avoid self-condensation of **V** (M = Li, MgX). This prediction is based on the supposition that the inductive effect of the α-alkoxy substituent should elevate the amide reactivity of **VI** above that of its reaction partner **V**.

Synthesis of subunit **II** commenced with the aldol addition of known β-ketoimide **1**[3] to aldehyde **2**,[4] which afforded the desired *anti*,*anti* aldol adduct[5] as an 84:16 mixture of



Scheme 1. Retrosynthetic analysis of oasomycin A (**I**).



Scheme 2. Retrosynthesis of the C13–C28 subunit **III**.

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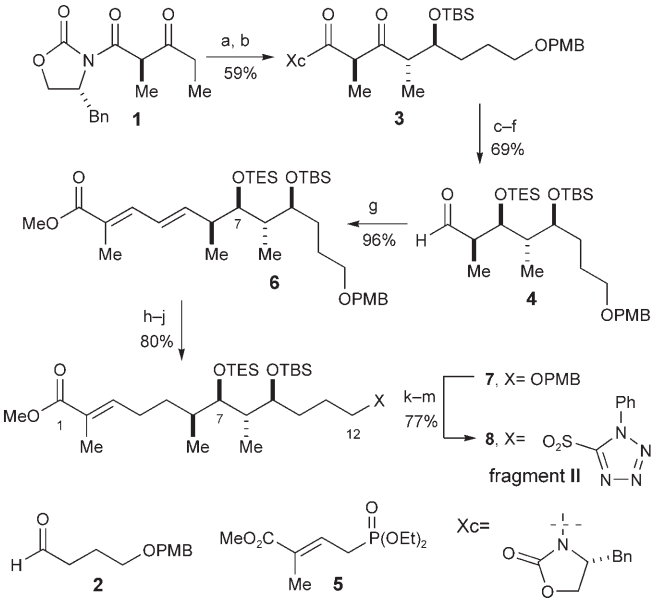
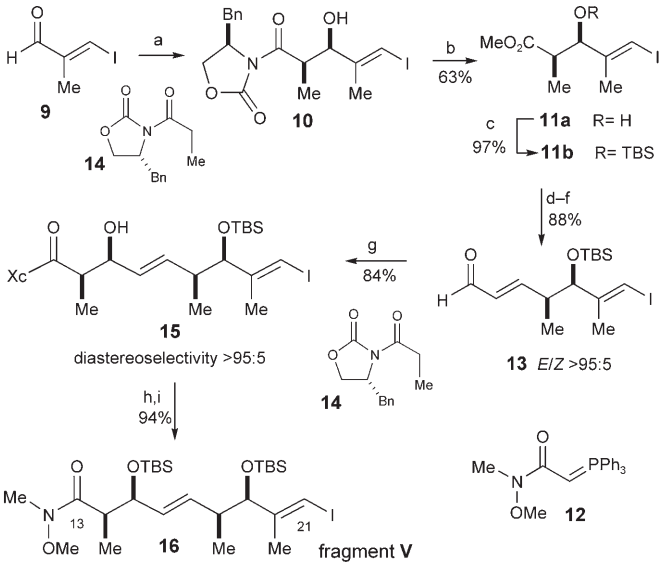


Scheme 3. Synthesis of the C1–C12 fragment **II.** Reagents and conditions: a) Cy_2BCl, Me_2NEt, Et_2O, −78 °C; then **2**, Et_2O, −78 °C, (84:16 d.r.); b) TBSOTf, lutidine, CH_2Cl_2, −78 °C, (59 %, 2 steps); c) $Zn(BH_4)_2$, CH_2Cl_2, −78 → −25 °C, (10:1 d.r.); d) TESOTf, lutidine, CH_2Cl_2, −78 °C; e) EtSLi, THF, −20 °C; f) DIBALH, CH_2Cl_2, −90 °C, (69 %, 4 steps); g) **5**, *n*BuLi, THF, −78 °C; then **4**, 96 %; h) CSA, $MeOH/CH_2Cl_2$ 1:1; i) Crabtree cat. (10 mol %), CH_2Cl_2, RT; j) TESOTf, lutidine, CH_2Cl_2, −78 °C, (80 %, 3 steps); k) DDQ, CH_2Cl_2/H_2O 12:1; l) 1-phenyl-1*H*-tetrazole-5-thiol, DEAD, PPh_3, THF; m) $(NH_4)_6Mo_7O_{24}$, H_2O_2, EtOH, (77 %, 3 steps). Bn = benzyl, cod = cycloocta-1,5-diene, CSA = camphorsulfonic acid, Cy = cyclohexyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DEAD = diethyl azodicarboxylate, DIBALH = diisobutylaluminum hydride, PMB = 4-methoxybenzyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, Tf = trifluoromethanesulfonyl.

diastereomers (Scheme 3). This mixture was immediately silylated (TBSOTf, lutidine) to provide **3** as a single diastereomer after flash chromatography. Successive chelate-controlled reduction of **3** with $Zn(BH_4)_2$ (10:1 d.r.),[6,7] alcohol protection (TESOTf, lutidine), removal of the oxazolidinone auxiliary (EtSH, *n*BuLi THF, −20 °C), and reduction of the derived thioester with DIBALH afforded aldehyde **4** (69 %, 4 steps). Aldehyde **4** was condensed with the known phosphonate **5**[8] under standard Horner–Wadsworth–Emmons conditions to afford diene **6** (96 %, *E*/*Z* 10:1).

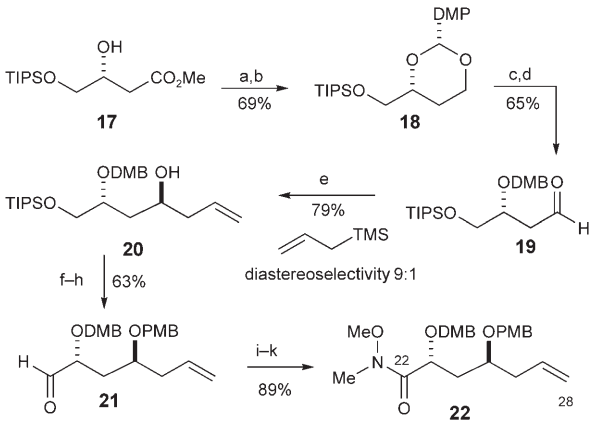
The selective hydrogenation of the *trans* Δ^4 olefin in **6** was complicated by the generation of inseparable side products that resulted from overreduction.[9] This problem was overcome by resorting to a hydroxy-directed hydrogenation. Selective deprotection of the C7 hydroxy group in **6** (CSA, CH_2Cl_2/MeOH 1:1) and hydrogenation of the derived homoallylic alcohol with the Crabtree catalyst $[Ir(cod)py(PCy_3)]PF_6$[10] afforded a now-separable 11:1 mixture of the desired olefin and the fully hydrogenated by-product.[11] The C7 hydroxy group was then reprotected using TESOTf, thus affording **7** (80 %, 3 steps). Methyl ester **7** was next transformed into sulfone **8** (synthon **II**, Scheme 1) by removal of the C12 PMB group (DDQ, CH_2Cl_2/H_2O 12:1), Mitsunobu reaction of the resulting primary alcohol with 1-phenyl-1*H*-tetrazole-5-thiol, and oxidation (H_2O_2, $(NH_4)_6Mo_7O_{24}$, EtOH)[12,13] of the resulting sulfide.

Synthesis of the C13–C21 fragment **V** (Scheme 2) began with the aldol addition of the (*Z*)-dibutylboron enolate of imide **14** to known aldehyde **9**[14] to afford the expected aldol adduct **10** (Scheme 4). The chiral auxiliary was removed with sodium methoxide in methanol (63 %, 2 steps) to afford the known ester **11a**.[14] This ester **11a** was successively silylated to the known TBS ether **11b**[14] (TBSOTf, lutidine) and then transformed into the unstable α,β-unsaturated aldehyde **13** by a reduction/Wittig olefination/reduction sequence in 88 % yield over the three steps. Reaction of the (*Z*)-dibutylboron enolate of chiral imide **14** with aldehyde **13** proceeded smoothly to give aldol adduct **15** (84 %, > 95:5 d.r.). The chiral auxiliary was then removed ((MeO)MeNH·HCl, $AlMe_3$), and the resulting alcohol protected as the TBS ether (TBSOTf, lutidine, 94 %, 2 steps) to complete the synthesis of the C13–C21 fragment **16**.

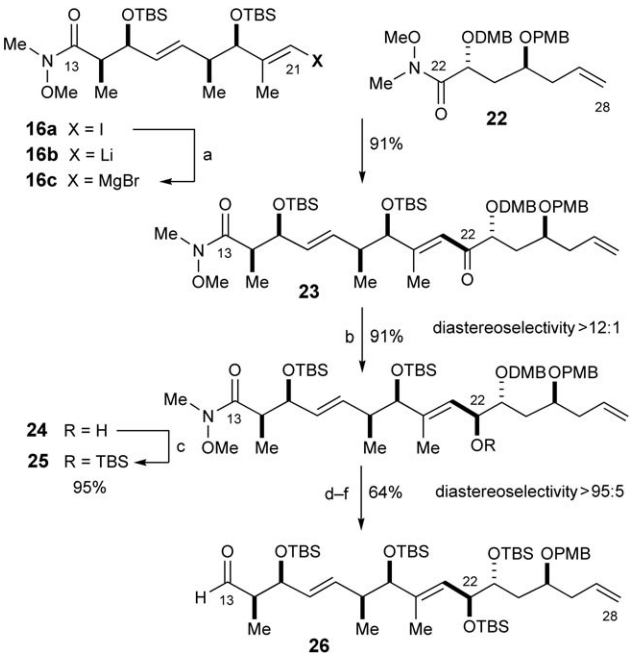


Scheme 4. Synthesis of the C13–C21 fragment **V**. Reagents and conditions: a) **14**, Bu_2BOTf, NEt_3, CH_2Cl_2, −78 → 0 °C; then **9**, CH_2Cl_2, −78 °C; b) NaOMe, $MeOH/CH_2Cl_2$, −25 °C, (63 %, 2 steps); c) TBSOTf, lutidine, CH_2Cl_2, −10 °C, 97 %; d) DIBALH, toluene, −90 → −80 °C; e) **12**, CH_2Cl_2; f) DIBALH, CH_2Cl_2, −90 °C, (88 %, 3 steps); g) **14**, Bu_2BOTf, NEt_3, CH_2Cl_2, −10 → 0 °C; then **13**, CH_2Cl_2, −78 °C, 84 % h) $AlMe_3$, Me(MeO)NH·HCl, THF, 0 °C; i) TBSOTf, lutidine, CH_2Cl_2, −10 °C; (94 %, 2 steps).

The synthesis of the C22–C28 fragment (Scheme 5) began with $LiAlH_4$ reduction of the D-malic acid derivative **17**,[15] followed by diol protection to form the 3,4-dimethoxybenzylidene acetal **18** (69 %, 2 steps). The regioselective reduction of **18** was accomplished with DIBALH, and the primary alcohol was then oxidized under Parikh–Doering conditions[16] to provide aldehyde **19** (65 %, 2 steps). Allylation of **19** under chelate-controlled conditions ($AlMe_2Cl$, allyltrimethylsilane) afforded **20** as a 9:1 mixture of diastereomeric alcohols that were separable by medium pressure liquid chromatography.[17] Protection of **20** as its PMB ether (PMBBr, NaHMDS), removal of the TIPS group with



Scheme 5. Synthesis of the C22–C28 fragment **22**. Reagents and conditions: a) $LiAlH_4$, Et_2O, 0 °C; b) $DMPCH(OMe)_2$, CSA, CH_2Cl_2, (69 %, 2 steps); c) DIBALH, CH_2Cl_2, −78 → −10 °C; d) SO_3·Py, NEt_3, $DMSO/CH_2Cl_2$ 1:1, −10 °C, (65 %, 2 steps); e) $AlMe_2Cl$ (2 equiv), $CH_2{=}CHCH_2TMS$, CH_2Cl_2, −93 °C, (9:1 d.r., 79 % yield); f) PMBBr, NaHMDS, TBAI, DMF/THF 1:2, −15 °C; g) TBAF, THF, 0 °C; h) SO_3·Py, NEt_3, $DMSO/CH_2Cl_2$ 1:1, −10 °C, (63 %, 3 steps); i) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, *t*BuOH/H_2O 3:2; j) $TMSCHN_2$, MeOH/PhH 10:1; k) Me(MeO)NH·HCl, *i*PrMgCl, THF, −10 °C, (89 %, 3 steps). DMB = 3,4-dimethoxybenzyl, DMP = 3,4-dimethoxyphenyl, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, Py = pyridine, TBA = *tert*-butylammonium, TIPS = triisopropylsilyl, TMS = trimethylsilyl.



Scheme 6. Synthesis of the C13–C28 fragment **26**. Reagents and conditions: a) 1. **16** (1.00 equiv), *n*BuLi (1.09 equiv), Et_2O, −78 °C; 2. $MgBr_2{\cdot}Et_2O$ (1.31 equiv), Et_2O/THF −78 → −20 °C; 3. **22** (0.965 equiv), Et_2O/THF, −20 → 0 °C, 91 %; b) $Zn(BH_4)_2$, Et_2O/CH_2Cl_2, −30 °C, 91 %; c) TBSOTf, lutidine, THF, 0 °C, 95 %; d) DDQ, H_2O/CH_2Cl_2 1:10, −3 °C; e) TBSOTf, lutidine, CH_2Cl_2, 0 °C; f) DIBALH, toluene, −78 °C, (64 %, 3 steps).

TBAF, followed by Parikh–Doering oxidation afforded aldehyde **21** (63 %, 3 steps). Aldehyde **21** could then be converted into the Weinreb amide **22** by a three-step sequence involving Kraus–Pinnick oxidation,[18] methylation ($TMSCHN_2$, MeOH/PhH), and amidation by using the Merck procedure (89 %, 3 steps).[19]

The coupling of the C13–C21 and C22–C28 fragments gave us the opportunity to test the relative reactivities of Weinreb amides **16** and **22** (Scheme 6). Metalation of vinyl iodide **16a** afforded vinyllithium **16b**. We predicted that this intermediate would react with **22** rather than with itself based on the observation that α-alkoxycarbonyl compounds are usually more reactive electrophiles than the corresponding α-alkylcarbonyl derivatives.[20] The desired chemoselectivity was indeed achieved; however, transmetalation of **16b** to the corresponding alkenylmagnesium **16c** was required to attenuate the reactivity of the nucleophile. Thus, under the aforementioned conditions, the coupling of **16** and **22** afforded the coupled C13–C28 product **23**[21] in 91 % yield. Ketone **23** was then reduced under chelate-controlled conditions ($Zn(BH_4)_2$) to give alcohol **24** in 91 % yield (12:1 d.r.).[7] Protection of **24** as its derived TBS ether (TBSOTf, lutidine) afforded **25** (95 % yield), which was then elaborated to aldehyde **26** by a three-step sequence: selective deprotection (DDQ, CH_2Cl_2/H_2O) of the 3,4-dimethoxybenzyl ether at C23,[22] protection of the resulting alcohol with TBSOTf, and reduction of the Weinreb amide with DIBALH (64 %, 3 steps).

Thus we have described the stereoselective synthesis of the C1–C12 and C13–C28 fragments of oasomycin A, a sequence that allowed us to prepare significant quantities of these materials. The following Communications[23] describe the synthesis of the C29–C46 fragment and the assembly of the fragments to afford oasomycin A.

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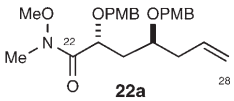

22a

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