Natural Products Synthesis

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Enantioselective Synthesis of Oasomycin A, Part III: Fragment Assembly and Confirmation of Structure**

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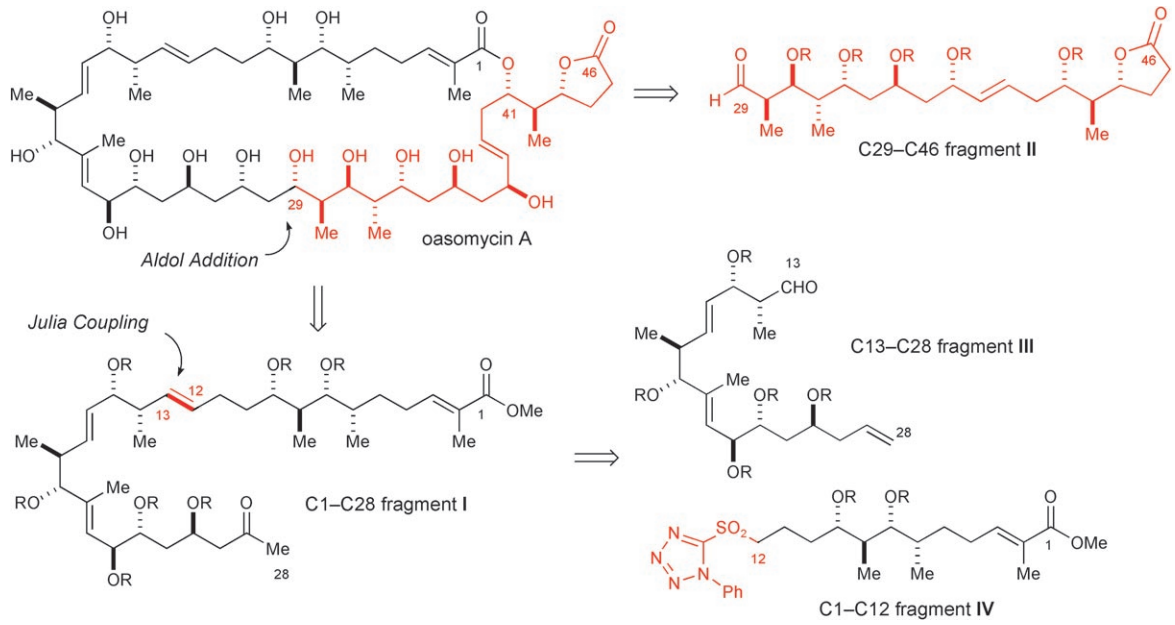
Dedicated to Professor Y. Kishi on the occasion of his 70th birthday.

Herein we address the total synthesis of the natural product oasomycin A by assembly of the C1–C12, C13–C28, and C29–C46 subunits, whose syntheses have been described in the preceding Communications.[1]

The synthesis plan (Scheme 1) incorporates a speculative late-stage macrolactonization of the linear seco acid precursor to form a 42-membered lactone that upon global deprotection would provide the natural product. Since oasomycin A is known to rearrange to the oasomycins D and E under basic conditions,[2] an acid-mediated global deprotection was obligatory. It was our intention to assemble the requisite seco acid by using an aldol addition of the C1–C28 ketone **I** to the C29–C46 aldehyde **II** with a concomitant installation of the C29 stereocenter, followed by a stereoselective reduction of the C27 ketone.

The assembly of ketone **I** through a Kocienski–Julia olefination[3] of the C13–C28 aldehyde **III** with C1–C12 fragment **IV** was undertaken first (Scheme 2). Sulfone **1** was selectively deprotonated with KHMDS and treated with aldehyde **2**[3] to afford the coupling product **3a** as a 7:1 mixture of *E*/*Z* isomers (57% yield). In addition, a significant amount of a by-product was consistently formed in 15–25% yield in this and related olefinations. This by-product with the general structure **3b** (Scheme 2) may be rationalized by a Brook rearrangement of the Julia intermediate followed by alkoxide attack on the sulfur center. All efforts to suppress this side reaction were unsuccessful.[4]



Scheme 1. Assembly of oasomycin A subunits.

With both the C1–C28 and C29–C46 subunits in hand, we addressed the aldol coupling which would provide the oasomycin A skeleton. The logic behind the selection of an aldol addition to form the C28–C29 bond was based on the fact that the diastereoselectivity of this reaction should be reinforced by resident chirality in both reaction partners: the C25 stereocenter on the enolate [Eq. (1)],[5] and the C31 stereocenter on the aldehyde fragment [Eq. (2)].[6] Although

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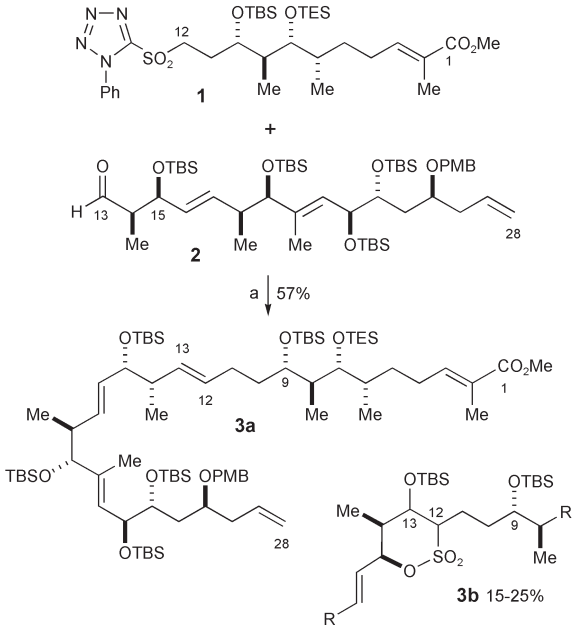
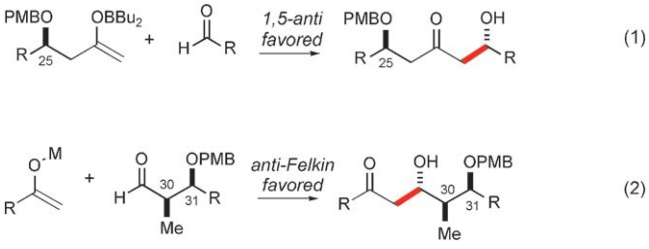
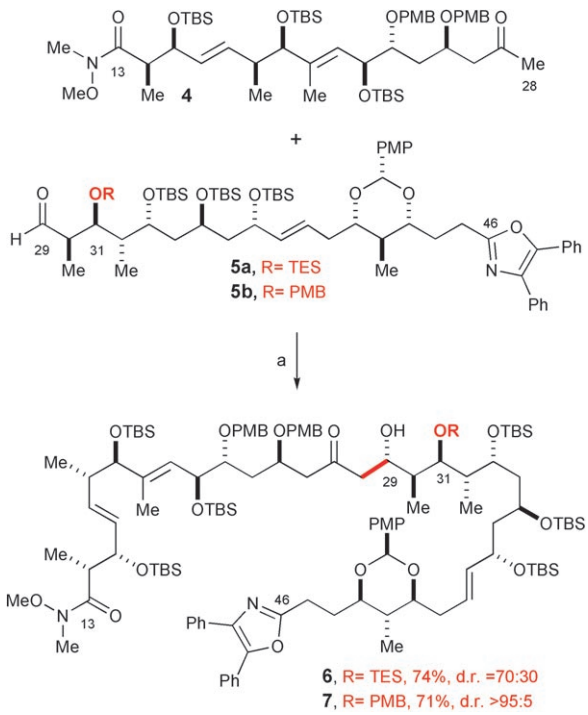


Scheme 2. Construction of the C1–C28 subunit **3a**. Reagents and conditions: a) 1. **1**, KHMDS, DME, −46 °C; 2. **2**, DME, −46 °C→RT, (57%, 7:1 *E*/*Z*). DME = 1,2-dimethoxyethane, HMDS = hexamethyldisilazide, PMB = 4-methoxybenzyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.



the selected aldol addition should proceed through the anti-Felkin pathway, the chosen control elements should be dominant in determining the reaction diastereoselectivity.[7] Indeed, during our preliminary studies,[8] the Bu_2BOTf-mediated aldol addition of ketone **4** to aldehydes **5a** and **5b**, proceeded in good yield and diastereoselectivity to afford the desired alcohol stereochemistry at C29 (Scheme 3).[9] From prior studies, it was known that benzylic protecting groups at C31 and C25 were required for good diastereoselectivity. The comparative reactions illustrated in Equations 1 and 2 reinforce this important point.

The assembly of oasomycin A began with the Wacker oxidation of terminal olefin **3a** to methyl ketone **8** (Scheme 4). Since **3a** has low solubility in polar solvents, a stoichiometric amount of $PdCl_2$ in aqueous THF buffered with $Cu(OAc)_2$ was used for this oxidation.[10] The resulting methyl ketone **8** was transformed into its derived boron enolate and added to the C29–C46 aldehyde **9** to afford the oasomycin A seco acid derivative **10** (78%, >10:1 d.r.).[11] Chelate-controlled reduction of **10** ($Zn(BH_4)_2$, CH_2Cl_2/Et_2O, −25 °C) provided the corresponding boronic acid diester

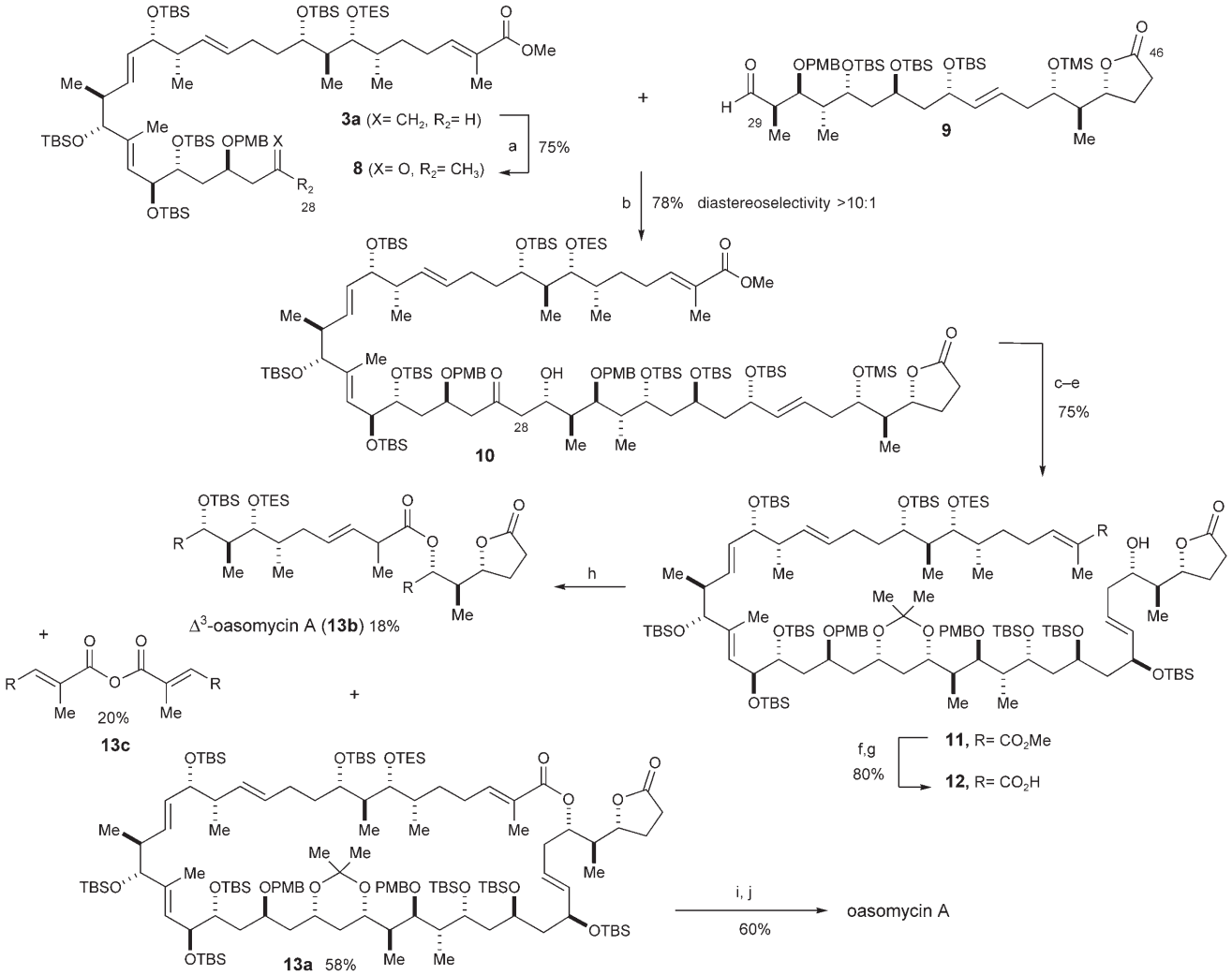


Scheme 3. Model studies for the aldol addition. Reagents and conditions: a) 1. **4**, Bu_2BOTf, iPr_2NEt, Et_2O, −78 °C; 2. **5**, Et_2O, −78 °C. PMP = 4-methoxyphenyl, Tf = trifluoromethanesulfonyl.

(>10:1 d.r.), which was hydrolyzed (PPTS, CH_2Cl_2/MeOH) with concurrent deprotection of the C43 TMS ether followed by protection of the formed diol to afford acetonide **11** (75%, 3 steps).[12] The hydrolysis of **11** mediated by LiOH effected cleavage of both the C1 methyl ester and C46 lactone moieties, and the resultant diacid was relactonized in acidified chloroform to afford the seco acid **12**.

Macrolactonization of **12** posed a problem as the standard Yamaguchi procedure[13] provided only minor amounts of macrolactone **13a** accompanied by its Δ^3-olefin isomer **13b** along with the symmetric anhydride **13c** as the predominant product. In addition, investigation of the various lactonization conditions reported by the research groups of Yonemitsu, Shiina, and Keck[14] did not result in any improvement in the yield of **13a**. After considerable effort, modified lactonization conditions were developed to deliver the desired lactone **13a** in 58% yield. It was found that an excess of 2,4,6-trichlorobenzoyl chloride (17 equiv) and Hünig base (43 equiv) followed by addition of the mixed anhydride to DMAP (91 equiv) in toluene (25 °C) over two hours was required to suppress the isomerization of the mixed anhydride to **13c** and minimize the deconjugation to **13b**.[15]

Having prepared lactone **13a**, the deprotection of the resident protecting groups was addressed. Oxidative removal of the PMB groups (DDQ, CH_2Cl_2, pH 7 buffer, 0 °C) was followed by treatment of the derived diol with hydrofluoric acid (CH_2Cl_2, CH_3CN, H_2O, 7 °C, 4 d) to afford synthetic oasomycin A (60%, 2 steps).[16] At this point we do not have clear evidence of the Δ^3 oasomycin A that would result from the by-product **13b**. The spectroscopic data of the synthetic



Scheme 4. Final assembly. Reagents and conditions: a) $PdCl_2$, $Cu(OAc)_2$, THF/H_2O, 75%; b) 1. **8**, Bu_2BOTf, iPr_2NEt, Et_2O, −78 °C; 2. **9**, Et_2O, −78 °C, 78%; c) $Zn(BH_4)_2$, CH_2Cl_2/Et_2O, −25 °C; d) PPTS, CH_2Cl_2/MeOH (1:1), 0 °C; e) PPTS, 2,2-dimethoxypropane, (75%, 3 steps); f) LiOH, $THF/MeOH/H_2O$; g) TFA (0.5 mol.%), $CHCl_3$, (80%, 2 steps); h) 1. 2,4,6-trichlorobenzoyl chloride (17 equiv), iPr_2NEt (43 equiv), THF; 2. DMAP (91 equiv), toluene, 2 h addition, 25 °C, 58%; i) DDQ, CH_2Cl_2/pH 7 buffer, 0 °C; j) 1. HF, $CH_2Cl_2/CH_3CN/H_2O$, 0→7 °C; 2. TMSOMe, 7→20 °C, (60%, 2 steps). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = 4-dimethylaminopyridine, PPTS = pyridinium *p*-toluenesulfonate, TFA = trifluoroacetic acid, TMS = trimethylsilyl.

material were consistent with those for the natural oasomycin A,[17] as evident from the ^1H and ^{13}C NMR spectra, HPLC-MS/UV traces, and optical rotation ($[\alpha]^D = -8.8$, $c = 1.5$ versus the reported $[\alpha]^D = -13.1$, $c = 0.122$).[18]

Herein and in the preceding Communications,[1] we have reported the asymmetric synthesis of oasomycin A based on the structural assignment made by Kishi and co-workers.[19] On the basis of the spectroscopic data of the synthetic and natural samples, we conclude that the stereochemical assignment for oasomycin A is correct. As a final note in passing, the 42-membered macrolactonization reported in this synthesis is among the largest carboxy-activated ring closure yet reported in the literature.[20] An unrelated macrocyclization that has extended the precedent for achieving such ring closures may be found in the synthesis of swinholide A (44-membered lactone) reported by Paterson et al.[21] However, one should be cautious of concluding that such chemical events are now routine.

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[15] For further details, see the Supporting Information.
[16] We found the optimal concentration of HF for the deprotection was 1–2 M, at 7 °C as more concentrated solutions of HF or higher temperatures decompose oasomycin A. Minor amounts of mono-TBS-protected oasomycin A (ca. 10–20%) were also recovered after workup and then recycled. The yield reported was calculated after one such recycling.
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