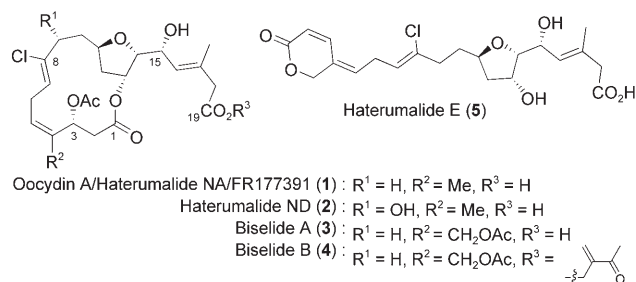


Total Synthesis of (+)-Oocydin A: Application of the Suzuki–Miyaura Cross-Coupling of 1,1-Dichloro-1-alkenes with 9-Alkyl 9-BBN**

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In 1999, the chlorinated macrolide (+)-oocydin A (**1**; Scheme 1) was extracted from the bacterium *Serratia marcescens*, which grows as an epiphyte on a Venezuelan aquatic

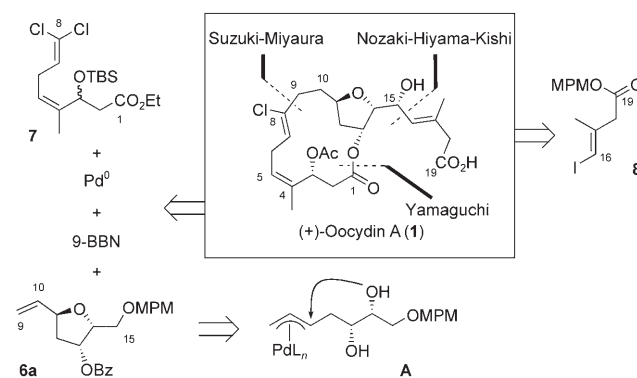


Scheme 1. The structures of (+)-oocydin A (**1**) and some related natural products.

plant.^[1] In the same year, (–)-haterumalide NA^[2a] was isolated from the sponge *Ircinia* sp. during the screening of extracts of marine organisms collected near Okinawa island and was presented as a diastereomer of **1**. The same substance was isolated from the soil bacterium *Serratia plymuthica* in 2001.^[2b] In 2005, Sato et al. isolated (+)-FR177391^[3] from *Serratia liquefaciens* and determined its structure unambiguously by X-ray crystallographic analysis of the corresponding propylamide. The ¹H and ¹³C NMR spectroscopic data of (+)-oocydin A (**1**), (–)-haterumalide NA, and FR177391 appear to be strictly identical, which indicates that they are one and the same compound despite their different optical rotations. (+)-Oocydin A (**1**) is a representative member of a unique class of structurally complex natural products with similar skeletons (Scheme 1, **2–5**). The substances that belong to the oocydin A family were extracted from various sources, such as bacteria, sponges, and ascidians^[4] (*Didemnidae* sp. and *Lissoclinum* sp.). It is intriguing that a structure as complex as **1** has been isolated from such a variety of sources, unless one

considers that symbiotic bacteria may biosynthesize this metabolite in sponges.

From a structural point of view, these molecules display a number of salient motifs in their complex framework, such as a tetrahydrofuran ring fused with a macrocyclic lactone and a Z chlorovinyl functionality. The latter functionality aroused our interest. We believed that it might be possible to synthesize (+)-oocydin A (**1**) through a palladium-mediated cross-coupling of a 9-alkyl 9-BBN reagent with a 1,1-dichloro-1-alkene to create the C8–C9 bond by the selective substitution of the most accessible *trans* chloride atom (Scheme 2).



Scheme 2. Retrosynthetic analysis of (+)-oocydin A (**1**). 9-BBN = 9-borabicyclo[3.3.1]nonane, Bz = benzoyl, MPM = 4-methoxyphenyl-methyl, TBS = *tert*-butyldimethylsilyl.

As reactions between two coupling partners of this type had not been described in the literature, we investigated this approach and established conditions for their efficient cross-coupling, confirming for this reaction that the use of bisphosphines with a large bite angle as the palladium ligands is instrumental.^[5] We describe herein the first application of this methodology to total synthesis. The target, (+)-oocydin A (**1**), not only provides a synthetic challenge, but has intrinsic value as a compound with cytotoxic and phytopathogenic properties.^[1–3]

Several research groups strove to remove the ambiguities that remained in terms of the structure of **1** and finally demonstrated that (+)-oocydin A (**1**) and (–)-haterumalide NA were one and the same molecule. Only Hoye and Wang completed the total synthesis of **1**; however, they made no mention of the optical rotation of their product.^[6a] Both Kigoshi et al.^[6b] and Gu and Snider^[6c] described the synthesis of the methyl ester of *ent*-oocydin.

Our retrosynthetic analysis (Scheme 2) based on the formation of the C8–C9 bond by a Pd⁰-catalyzed cross-

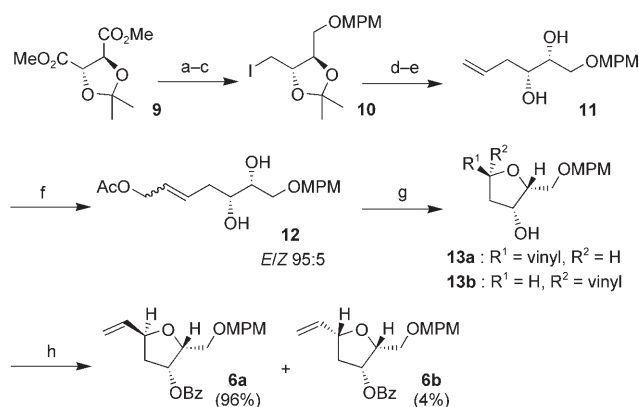
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coupling reaction required the synthesis of the tetrahydrofuran derivative **6a** and the 1,1-dichloro-1-alkene subunit **7**. The tetrahydrofuran substructural motif of **6a** prompted us to explore a Pd⁰-catalyzed cyclization through the postulated π -allyl palladium intermediate **A**. In this way, we expected to be able to install diastereoselectively the required vinyl functionality at C11. This vinyl group would then be hydroborated to give the desired 9-alkyl 9-BBN nucleophilic cross-coupling partner. The synthesis of the 1,1-dichloro-1-alkene subunit **7** was based on a challenging ring-closing metathesis (RCM) reaction to provide the α,β -unsaturated lactone **15** (Scheme 4). Thus, we would control the geometry of the C4–C5 double bond. We envisioned macrolactone ring closure under Yamaguchi conditions^[7] as described by Gu and Snider,^[6c] and planned to end our synthesis as reported by Kigoshi et al.^[6b] with the Nozaki–Hiyama–Kishi (NHK) coupling^[8] of fragment **8**.

Our straightforward synthesis of fragment **6a** started from the D-tartrate ester **9** (Scheme 3), which constitutes the sole



Scheme 3. Synthesis of subunit **6a**: a) LiAlH₄, Et₂O, 99%; b) MPMCl, NaOH, PhH, reflux, 73%; c) I₂, PPh₃, imidazole, toluene, reflux, 90%; d) vinylmagnesium chloride, CuI, THF, HMPA, –50 °C, 85%; e) HCl, H₂O, EtOH, ethylene glycol, 0 °C, 97%; f) second-generation Grubbs catalyst, allyl acetate, CH₂Cl₂, reflux, 77%; g) [Pd₂(dba)₃], P(*p*-OMeC₆H₄)₃, THF, 40 °C, 99%, **13a/13b** 96:4; h) PhCOCl, DMAP, pyridine. dba = dibenzylidene acetone, DMAP = 4-dimethylaminopyridine, HMPA = hexamethylphosphoramide.

source of chirality in our strategy. Thus, **9** was reduced to a diol and monoprotected as a 4-methoxybenzyl ether. After its transformation into the iodide derivative **10**, we performed a copper-catalyzed substitution with vinylmagnesium chloride and obtained, after deprotection, the allylic compound **11**. A cross-metathesis reaction^[9] catalyzed by the second-generation Grubbs catalyst^[10] between **11** and allyl acetate furnished compound **12** in good yield as an *E/Z* mixture (ca. 95:5).

With compound **12** in hand, we investigated the formation of the tetrahydrofuran ring (Table 1). In a first trial, we treated the acetate **12** with a catalytic amount of [Pd₂(dba)₃] and PPh₃ in THF at 20 °C. Good diastereoselectivity was observed in favor of the expected product (**13a/13b** 90:10),^[11] albeit with a poor combined yield of 54% (Table 1, entry 1). This diastereoselectivity was unexpected, as only a few cases of the synthesis of substituted tetrahydrofurans by this

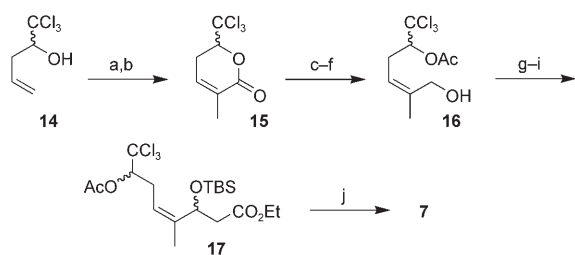
Table 1: Optimization of the synthesis of **13a** from **12** (cf. Scheme 2).^[a]

Entry	Phosphine ^[b]	<i>t</i> [h]	<i>T</i> [°C]	Yield [%]	13a/13b
1	PPh ₃	48	20	54 ^[c]	90:10
2	PPh ₃	3.75	40	98	88:12
3	PPh ₃	0.67	66	100	87:13
4	P(<i>o</i> -Tol) ₃	18	66	n.r. ^[c]	
5	P(<i>o</i> -Tol)Ph ₂	2.5	50	100	92:8
6	P(2-furyl) ₃	0.5	40	93	83:17
7	AsPh ₃	20	40	90 ^[d]	90:10
8	P(<i>p</i> -CF ₃ C ₆ H ₄) ₃	24	50	n.r. ^[d]	
9	<i>S,S</i> ligand ^[e]	20	55	60 ^[c]	91:6
10	<i>R,R</i> ligand ^[e]	0.67	45	100	40:60
11 ^[f]	P(<i>p</i> -OMePh) ₃	4	40	99	96:4

[a] Reactions were carried out in THF. [b] Palladium source: [Pd₂(dba)₃] (2.5 mol %); added monophosphine: 10 mol % or bisphosphine: 5 mol %. [c] Unchanged compound **12** was recovered. [d] Partial degradation was observed. [e] Trost ligand: 1,2-diaminocyclohexane-*N,N'*-bis(2'-diphenylphosphanylbenzoyl). [f] Results of a trial reaction on an 11-mmol scale with [Pd₂(dba)₃] (1 mol %).

method have been reported.^[12] It must be added that the occurrence of acetate **12** as an *E/Z* mixture has no consequence for the diastereomeric outcome of the reaction. In acetonitrile, the rate of the reaction remained slow at 20 °C, and palladium black was formed. In THF, higher temperatures led to much quicker reactions with **13a,b** formed in quantitative yield but with lower diastereoselectivity (Table 1, entries 3 and 5). The presence of chloride anions is known to accelerate the rate of the inversion of configuration of the π -allyl palladium intermediate.^[13] However, in our case, there was no improvement in the **13a/13b** ratio upon the addition of Bu₄NCl; we only observed faster palladium-black formation. The encumbered phosphine P(*o*-Tol)₃ or electron-deficient P(*p*-CF₃C₆H₄)₃ did not promote any reaction even in THF at reflux (Table 1, entries 4 and 8). Moreover, neither trifurylphosphane nor AsPh₃ led to any improvement in the diastereomeric ratio of the product (Table 1, entries 6 and 7). Assays with the Trost chiral bidentate phosphines were more interesting, as we observed mismatching effects: The *S,S* ligand gave good diastereoselectivity for the desired product **13a**, albeit with a very low reaction rate and incomplete conversion (Table 1, entry 9), whereas the use of the *R,R* ligand led to a fast and complete reaction with the opposite diastereoselectivity (Table 1, entry 10). Finally, we discovered that P(*p*-OMeC₆H₄)₃ with [Pd₂(dba)₃] in THF at 40 °C gave the product with the best diastereomeric ratio and in quantitative yield (Table 1, entry 11). The two diastereomers **13a** and **13b** were not readily separable even by preparative HPLC; however, the corresponding benzoyl esters **6a** and **6b** were separated by simple flash chromatography. Thus, the targeted tetrahydrofuran **6a** was obtained through a method that compares favorably with those used by other research groups for the total synthesis of **1**.

We then focused our efforts on the synthesis of the C1–C8 fragment **7** (Scheme 4). As Hoyer and Wang^[6c] had demonstrated previously that the configuration at C3 can be established readily by the reduction of the ketone **21** (Scheme 5), we chose to perform a non-asymmetric synthesis of **7**. We started from alcohol **14**,^[14] which was synthesized in

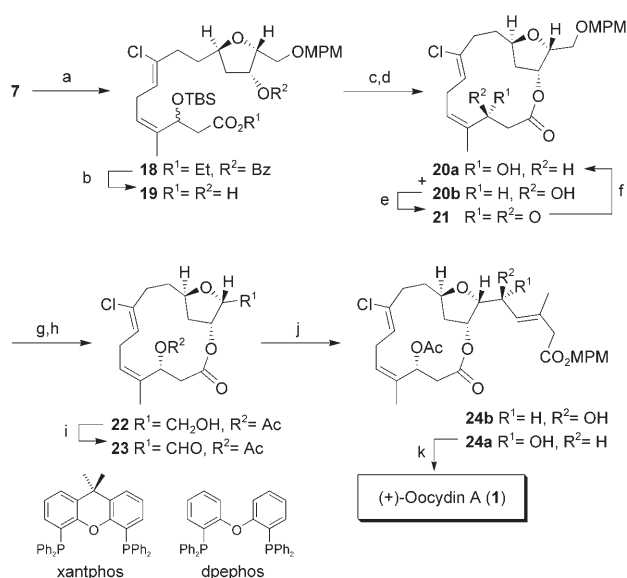


Scheme 4. Synthesis of subunit **7**: a) Methacryloyl chloride, $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , $-78^\circ\text{C} \rightarrow \text{RT}$, 99%; b) second-generation Grubbs catalyst, CH_2Cl_2 , reflux under Ar, $c = 0.01 \text{ M}$, 84%; c) NaBH_4 , CeCl_3 , MeOH ; d) TBSCl , imidazole, DMF ; e) Ac_2O , pyridine, 94% (3 steps); f) PPTS, MeOH , reflux, 96%; g) Swern oxidation; h) EtOAc , LDA , THF , 93% (2 steps); i) TBSCl , imidazole, DMF , 100%; j) SmI_2 , THF , 97%. $\text{DMF} = N,N$ -dimethylformamide, $\text{LDA} = \text{lithium diisopropylamide}$, PPTS = pyridinium 4-toluenesulfonate.

high yield by the treatment of a preformed allyllindium reagent with chloral hydrate in DMF . We prepared the methacrylic ester of alcohol **14** in good yield by coupling it with methacryloyl chloride at low temperature. RCM then gave the lactone **15**. The RCM reaction has to be conducted in a dilute medium (0.01 M) in freshly distilled CH_2Cl_2 (distilled over CaH_2 under argon) to avoid dimerization of the starting material. Toluene has been reported to be a better solvent for the RCM of substrates that bear an electron-poor and/or hindered double bond;^[15] however, no improvement was noticed in our case. Inspired by a recent article,^[16] we also attempted a direct synthesis of lactone **15** by condensing chloral with tigloyl chloride through a hetero-Diels–Alder process, but lactone **15** was obtained in poor yield. We reduced the lactone **15** to a diol to provide alcohol **16** after a selective protection–deprotection sequence. Alcohol **16** was then oxidized to an aldehyde under Swern conditions,^[17] and the product was submitted directly to an aldol condensation with EtOAc to give compound **17** in good yield after TBS protection. Finally, the 1,1-dichloro-1-alkene functionality was generated by the treatment of **17** with SmI_2 (2 equiv) in THF ^[18] to afford the targeted subunit **7**.

With compounds **6a** and **7** in hand, the setting for studying the key step of this synthesis was established (Scheme 5). Unfortunately, the use of our previously described optimal conditions^[5] ($[\text{Pd}_2(\text{dba})_3]$, xantphos, KF , and K_3PO_4 in THF at reflux) led to compound **18** in only 34% yield along with degradation of the starting material. We therefore reinvestigated our methodology and eventually found that the use of dpephos (another large-bite-angle bisphosphine) in place of xantphos in the absence of KF led to an effective cross-coupling of **6a** and **7** to give **18** in a much improved yield of 87%. At that stage our strategy had been fully validated, and we were able to complete the synthesis of (+)-oocydin A (**1**).

The diester **18** was saponified to give the seco acid **19**, which underwent macrolactonization under Yamaguchi conditions in acceptable yield. We also tried the Shiina macrolactonization method,^[19] but the yield was not improved. The removal of the TBS protecting group produced alcohols **20a** and **20b**, which were separated readily.^[6c] The unwanted isomer **20b** was recycled into **20a** through an oxidation–



Scheme 5. Completion of the total synthesis of **1**: a) **6a**, 9-BBN, THF , then $[\text{Pd}_2(\text{dba})_3]$ (6 mol %), dpephos (13 mol %), K_3PO_4 , THF , reflux, 44 h, 87%; b) KOH , THF , MeOH , H_2O , 84%; c) trichlorobenzoyl chloride, Et_3N , THF , then DMAP, toluene, 55%; d) TBAF, THF , **20a**: 34%, **20b**: 54%; e) DMP, CH_2Cl_2 , 100%; f) NaBH_4 , CeCl_3 , MeOH , 99%; g) Ac_2O , pyridine, 95%; h) DDQ, H_2O , CH_2Cl_2 , 95%; i) DMP, CH_2Cl_2 , **8**, CrCl_2 , NiCl_2 , DMSO , **24a**: 43%, **24b**: 4% (2 steps); k) Et_3SiH , TFA , CH_2Cl_2 , 0°C , 71%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMP = Dess–Martin periodinane, $\text{DMSO} = \text{dimethyl sulfoxide}$, TBAF = tetrabutylammonium fluoride, $\text{TFA} = \text{trifluoroacetic acid}$.

reduction sequence during which the corresponding ketone **21** was reduced stereoselectively into **20a** under Luche conditions in EtOH . The acetylation of alcohol **20a** and removal of the 4-methoxybenzyl protecting group led to the primary alcohol **22**, which was oxidized to the fragile aldehyde **23**. Fragment **8**^[6c] was synthesized in three steps from homopropargylic alcohol by a zirconium-catalyzed carboalumination reaction.^[20]

The condensation of fragment **8** with aldehyde **23** under the NHK conditions furnished alcohol **24a** (43% yield from alcohol **22**) along with a trace amount of **24b**. Nevertheless, a special workup with sodium serinate to sequester the chromium cations was necessary to obtain **24a** in acceptable yield.^[21] To improve this step, we investigated a catalytic version of the NHK coupling;^[22] however, the expected alcohol **24** was not formed under these conditions. In a final step, deprotection of the masked carboxylic acid^[23] in **24a** supplied the target compound (+)-oocydin A (**1**), the chemical data of which were similar to those of the naturally occurring compound ($[\alpha]_D^{23} = +11.8 \text{ deg cm}^3 \text{ g}^{-1} \text{ dm}^{-1}$ ($c = 0.79 \text{ g/100 cm}^3$, MeOH); lit.:^[1] $[\alpha]_D^{23} = +18.2 \text{ deg cm}^3 \text{ g}^{-1} \text{ dm}^{-1}$).

In conclusion, we have completed the total synthesis of (+)-oocydin A (**1**) in 18 steps from alcohol **14** and in 6.1% overall yield. The subunit **6a** was synthesized in eight steps in 39% overall yield by an efficient and stereoselective Pd^0 -catalyzed cyclization to form the tetrahydrofuran ring. The subunit **7** was obtained in 68% yield over 10 steps. The key

step of this total synthesis, a new application of the Suzuki–Miyaura cross-coupling, constitutes the first implementation of methodology that we had described previously.^[5] This mild reaction enabled the cross-coupling of the sensitive fragments **6a** and **7** in 87 % yield on a 4.9-mmol scale.

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