Natural Product Synthesis

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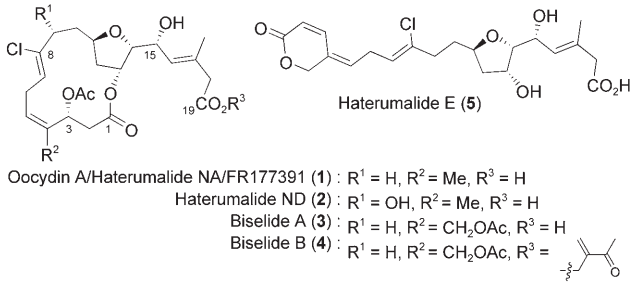
Total Synthesis of (+)-Oocydin A: Application of the Suzuki–Miyaura Cross-Coupling of 1,1-Dichloro-1-alkenes with 9-Alkyl 9-BBN**

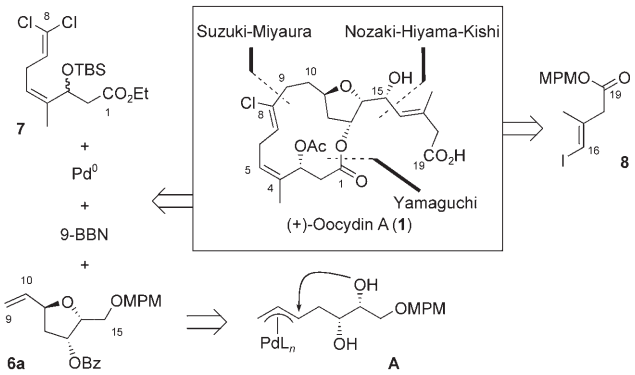
*Emmanuel Roulland**

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 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 ^{1}H and ^{13}C 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.



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

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-methoxyphenylmethyl, 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 Pd^{0}-catalyzed cross-

[*] Dr. E. Roulland
Institut de Chimie des Substances Naturelles, CNRS
Avenue de la Terrasse, 91198 Gif-sur-Yvette (France)
Fax: (+33) 1-6907-7247
E-mail: emmanuel.roulland@icsn.cnrs-gif.fr
Homepage: http://www.icsn.cnrs-gif.fr

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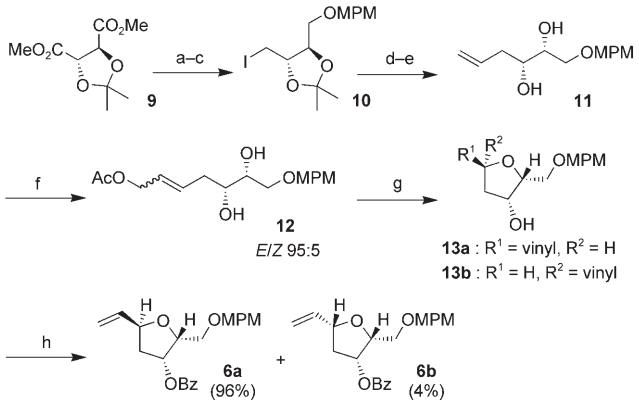
coupling reaction required the synthesis of the tetrahydrofuran derivative **6a** and the 1,1-dichloro-1-alkene subunit **7**. The tetrahydrofuran substructural motif of **6a** prompted us to explore a Pd^0-catalyzed cyclization through the postulated π-allyl palladium intermediate **A**. In this way, 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) $LiAlH_4$, Et_2O, 99%; b) MPMCl, NaOH, PhH, reflux, 73%; c) I_2, PPh_3, imidazole, toluene, reflux, 90%; d) vinylmagnesium chloride, CuI, THF, HMPA, −50°C, 85%; e) HCl, H_2O, EtOH, ethylene glycol, 0°C, 97%; f) second-generation Grubbs catalyst, allyl acetate, CH_2Cl_2, reflux, 77%; g) $[Pd_2(dba)_3]$, $P(p\text{-}OMeC_6H_4)_3$, 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 $[Pd_2(dba)_3]$ and PPh_3 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

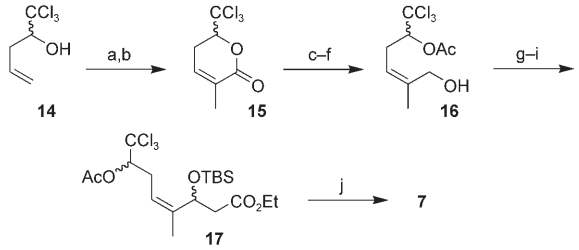
Table 1: Optimization of the synthesis of **13a** from **12** (cf. Scheme 2).[a]

Entry	Phosphine[b]	*t* [h]	*T* [°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	$P(o\text{-Tol})_3$	18	66	n.r.[c]	
5	$P(o\text{-Tol})Ph_2$	2.5	50	100	92:8
6	$P(2\text{-furyl})_3$	0.5	40	93	83:17
7	$AsPh_3$	20	40	90[d]	90:10
8	$P(p\text{-}CF_3C_6H_4)_3$	24	50	n.r.[d]	
9	*S,S* ligand[e]	20	55	60[c]	91:6
10	*R,R* ligand[e]	0.67	45	100	40:60
11[f]	$P(p\text{-OMePh})_3$	4	40	99	96:4

[a] Reactions were carried out in THF. [b] Palladium source: $[Pd_2(dba)_3]$ (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 $[Pd_2(dba)_3]$ (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 Bu_4NCl; we only observed faster palladium-black formation. The encumbered phosphine $P(o\text{-Tol})_3$ or electron-deficient $P(p\text{-}CF_3C_6H_4)_3$ did not promote any reaction even in THF at reflux (Table 1, entries 4 and 8). Moreover, neither trifurylphosphane nor $AsPh_3$ 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 $P(p\text{-}OMeC_6H_4)_3$ with $[Pd_2(dba)_3]$ 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 Hoye 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

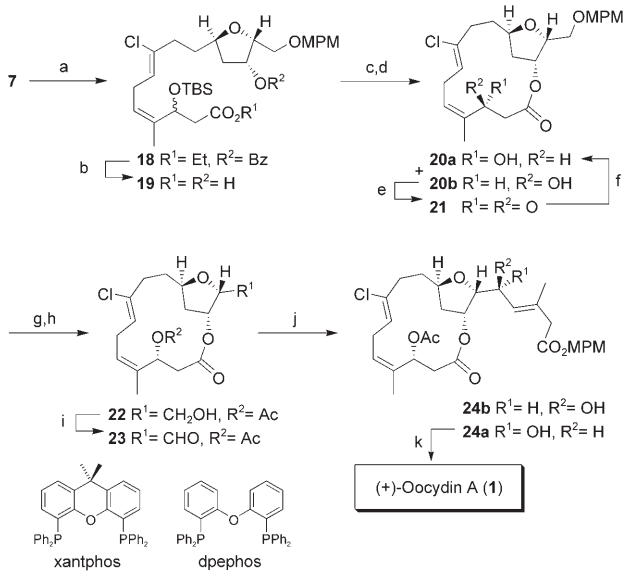


Scheme 4. Synthesis of subunit **7**: a) Methacryloyl chloride, iPr$_2$NEt, CH_2Cl_2, −78 °C→RT, 99%; b) second-generation Grubbs catalyst, CH_2Cl_2, reflux under Ar, c = 0.01 M, 84%; c) $NaBH_4$, $CeCl_3$, MeOH; d) TBSCl, imidazole, DMF; e) Ac_2O, pyridine, 94% (3 steps); f) PPTS, MeOH, reflux, 96%;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

high yield by the treatment of a preformed allylindium 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] ([$Pd_2(dba)_3$], 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 [$Pd_2(dba)_3$] (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, j) **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, DMSO = dimethyl sulfoxide, TBAF = tetrabutylammonium fluoride, TFA = 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 ($[\alpha]_D^{23} = +11.8$ deg cm^3 g^{-1} dm^{-1} (c=0.79 g/100 cm^3, MeOH); lit.:[1] $[\alpha]_D^{23} = +18.2$ deg cm^3 g^{-1} 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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