A Pd-Mediated Approach to the Synthesis of an Unusual β-Hydroxytryptophan Amino Acid Constituent of Cyclomarin A

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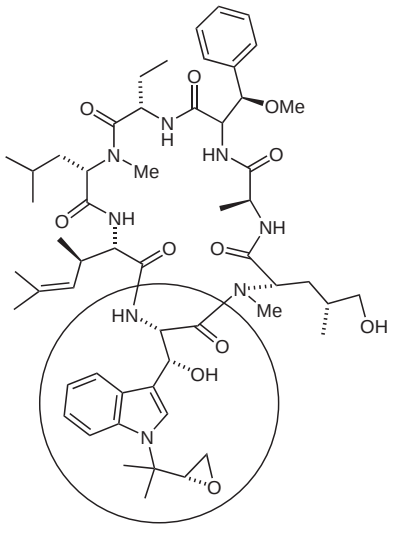
This work is dedicated to the memory of Prof. G. Sodano.

Abstract: A synthetic approach based on a palladium-mediated vinylation of indole derivatives was established for the preparation of **5**, a key intermediate in the synthesis of *N*-(*tert*-butoxycarbonyl)-L-1*H*-[(*R*)-1,1-dimethyl-2,3-epoxypropyl]-β-hydroxytryptophan ethyl ester (**6**). Unsatisfying yields were obtained using *N*-alkyl-3-haloderivatives. The best method proved to be the oxidative coupling on 3-unsubstituted indole derivative.

Key words: indoles, palladium, Heck reaction, marine natural product, Stille reaction

In 1999 Fenical and co-workers reported the isolation, structural elucidation and potent antiinflammatory activity of cyclomarin A (**1**, Figure 1), a compound produced by a marine bacterium (*Streptomyces sp.*).[1] Cyclomarin A is a cyclic heptapeptide which also shows antiviral[2] and antimycobacterial[3] activity and is currently under investigation for therapeutic application. This peptide incorporates three common and four unusual amino acids. One of these new amino acids **2** is a tryptophan derivative containing a reverse prenylated moiety.



cyclomarin A (**1**)

Figure 1

The interesting activities displayed by this peptide have stimulated synthetic studies[4–8] and recently two approaches for the synthesis of **2** have been reported, both starting from indoline (Scheme 1). In the approach of Sugijama et al.,[4] key steps of the synthesis are a Horner–Wadsworth–Emmons (HWE) reaction and Sharpless asymmetric aminohydroxylation (AAH). More recently, Hansen et al.[8] described another strategy based on a diastereoselective addition of an indole Grignard **7** to a chiral serine aldehyde equivalent **8**.

During our synthetic studies on *N*-isoprenylindole derivatives[9] we have planned the preparation of **2** using indole, instead of indoline, as starting material. To this purpose we have systematically evaluated the application of Pd-mediated coupling reactions to the construction of the required 3-functionalized indole and in this communication we describe our effort to develop this alternative synthetic strategy to **5**.

Bromo compound **9**, for the envisaged palladium-catalyzed coupling, was generated from **10** whose preparation followed a described strategy starting from indole.[10] Sharpless asymmetric dihydroxylation, using chiral ligand $(DHQD)_2PYR$, furnished diol **11** with a satisfying enantiomeric excess (76% ee). Finally, protection of diol **11** as acetonide completed the preparation of **9** (Scheme 2).

With the requisite bromo compound in hand we were able to prepare compound **12** using Heck coupling. However, the coupling reaction of **9** and ethyl acrylate proved to be somewhat difficult when typical procedures were considered. Due to the scarce reactivity of indole substrate, a large amount of Pd–phosphine complex was needed in order to obtain satisfying yields. In fact, increasing amounts, starting from 0.02 equivalent, were used and only using 0.3 equivalent of Pd–phosphine complex we succeeded to obtain reasonable yields (Scheme 3). The reaction afforded the expected coupling adduct together with large amounts of the debrominated indole derivative **13** as side product.

It is well known that *N*-sulfonyl-3-bromoindole and *N*-acyl-3-bromoindole derivatives are in general poor substrates in Heck coupling, probably due to the high electron density of the halogenated carbon leading to a slower oxidative addition to Pd(0)[11,12] and this can explain the disappointing yields obtained with the more electron-rich *N*-alkyl-3-bromo derivatives. In view of this fact, we

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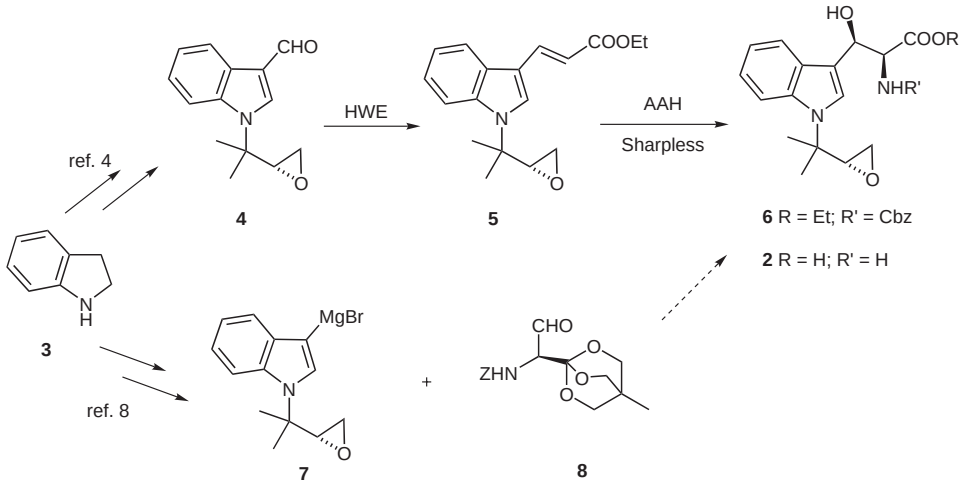
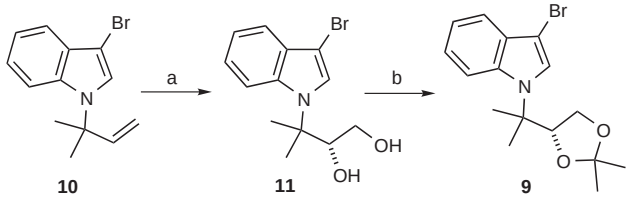
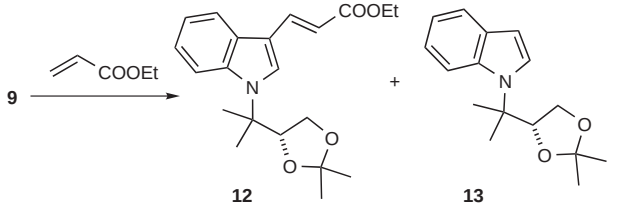


Scheme 1 Reported approaches to **2** starting from indoline.



Scheme 2 *Reagents and conditions*: a) OsO_4, $K_3Fe(CN)_6$, $(DHQD)_2PYR$, K_2CO_3, H_2O–*t*-BuOH 1:1, 16 h, 0 °C, 76% ee; b) $Me_2C(OMe)_2$, *p*-TsOH, r.t., 1.5 h, 85%, two steps.



$Pd(OAc)_2$, $P(o\text{-tol})_3$, TEA, 80 °C, 24 h, DMF	56%	41%	
$Pd_2(dba)_3$, $P(o\text{-tol})_3$, TEA, 80 °C, 18 h, CH_3CN	46%	18%	(+ 32% of **9**)

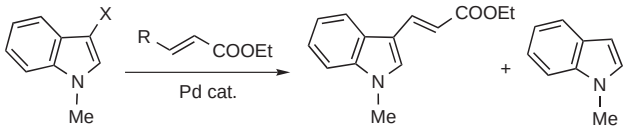
Scheme 3

thought that the employment of the more reactive iodo derivative could have reduced the amount of **13** and improve yield of **12**. No data in literature were found on Heck coupling of *N*-alkyl-3-haloindoles, so we decided to compare the reactivity of the model compounds **14** and **15** (Table 1).

Both Heck and Stille coupling reactions were assayed. 3-Iodo-*N*-methylindole (**15**), although not a particularly efficient substrate, was more reactive than 3-bromo-*N*-methylindole (**14**) in the Heck reaction (shorter reaction time, better yield of **16**, minor amount of dehalogenated product **17**). Under Stille coupling conditions,[13,14] the yields were lower.

However, these results encouraged us to use iodoindole derivative as coupling reagent. The trend in reactivity of haloindoles was confirmed because 3-iodoindole **18**, obtained as depicted in Scheme 4, reacted in the Heck

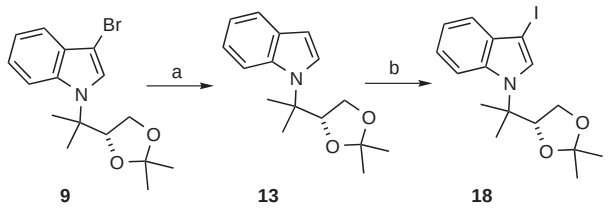
Table 1 Heck and Stille Coupling on *N*-Methyl-3-haloindoles **14** and **15**



14: X = Br
15: X = I

	X	R	Conditions	Yield of **16** (%)	Yield of **17** (%)
1	Br	H	$Pd(OAc)_2$ (0.2 equiv), $P(o\text{-tol})_3$, Et_3N, 100 °C, 24 h	36	41
2	I	H	$Pd(OAc)_2$ (0.1 equiv), $P(o\text{-tol})_3$, Et_3N, 100 °C, 2 h	48	19
3	I	Bu_3Sn	$Pd(PPh_3)_4$ (0.1 equiv), LiCl, 65 °C, 18 h	41	traces
4	I	Bu_3Sn	$Pd_2(dba)_3$ (0.2 equiv), PPh_3, CuI, LiCl, 100 °C, 4 h	35	traces
5	Br	Bu_3Sn	$PdCl_2(PPh_3)_2$ (0.1 equiv), Et_4NCl, 80 °C, 44 h	–	–

coupling with ethyl acrylate in shorter time with higher yield (68% yield) and minor amount of dehalogenated indole **13** (23%, Table 2, entry 1). As is the case of *N*-methyl derivative, Stille coupling protocols (Table 2, entries 2, 3) showed low efficiency.



Scheme 4 *Reagents and conditions*: a) 1. *t*-BuLi, Et_2O, –100 °C; 2. H_2O, 92%; b) I_2, KOH, DMF, r.t., 77%.

Finally, we decided to investigate the use of the Pd-catalyzed oxidative coupling between indole **13** and ethyl acrylate as an alternative protocol, to avoid the use of halogenated substrates. An oxidative palladium(II)-mediated process in the coupling of arenes with olefins was first described by Fujiwara et al. in 1967.[15] In this reaction the coupling of arenes with olefins is promoted by the cleavage of aromatic C–H bonds in the presence of Pd compounds.[16] The application of this methodology to indole was reported in 1999[17] and two recent papers described conditions for the C-2 and C-3 alkenylation of indole.[18,19] These recent results prompted us to apply this procedure to our substrate. Compound **13** was subjected to coupling under $Pd(OAc)_2$ catalysis at 80 °C, employing $Cu(OAc)_2$ as the oxidant (Table 2, entry 4).[20] Indoleacrylic ester (**12**)[21] was obtained with a good yield (70%). This reaction afforded also considerable amounts of self-coupling product **19**[22] (23%, Figure 2).

A remarkable yield improvement to 86%, however, was assessed with $PdCl_2$ as catalyst at 40 °C (Table 2, entry 5).[23] No traces of **19** were observed when employing $PdCl_2$.

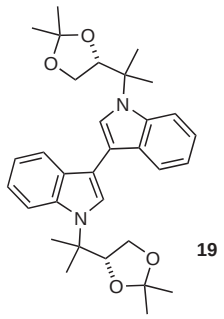
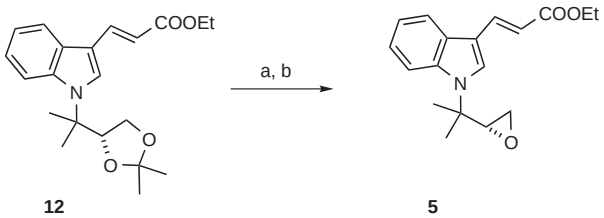


Figure 2

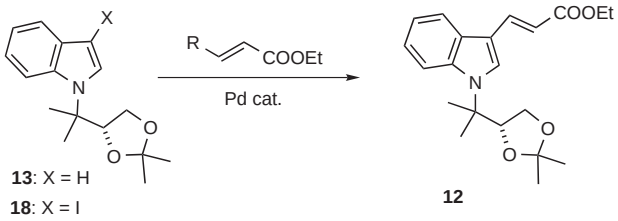
The formal synthesis was completed by deprotection of acetonide **12** by acetic acid and transformation of the resulting diol into epoxide (**5**) by the internal displacement of the corresponding monotosylate (Scheme 5).



Scheme 5 *Reagents and conditions*: a) AcOH 90%, THF, r.t., 7 d; b) 1) TsCl, Et_3N, CH_2Cl_2, 0 °C, 15 h; 2) K_2CO_3, EtOH, r.t., 48 h, 60%, three steps.

In conclusion, synthesis of compound **5** was accomplished using a strategy centred on a Pd coupling reaction. In our study we have shown that the best method for C-3 palladium-mediated vinylation of the indole moiety is the oxidative Heck coupling. Since this advanced intermediate has been converted into **6**,[4] this synthesis constitutes a formal synthesis of the unusual 3-hydroxytryptophan amino acid **2**.

Table 2 Coupling Reaction on Indole Derivatives **13** and **18**



	X	R	Conditions	Yield of **12** (%)	Yield of **13** (%)
1	I	H	$Pd(OAc)_2$ (0.2 equiv), P(*o*-tol)$_3$, TEA, 80 °C, 5 h	68	23
2	I	Bu_3Sn	$Pd(PPh_3)_4$ (0.1 equiv), LiCl, 65 °C, 5 h	36	2
3	I	Bu_3Sn	$Pd_2(dba)_3$ (0.2 equiv), PPh_3, CuI, LiCl, 100 °C, 6 h	39	15
4	H	H	$Pd(OAc)_2$ (0.4 equiv), $Cu(OAc)_2$, 80 °C, 5 h	70	–
5	H	H	$PdCl_2$ (0.3 equiv), $Cu(OAc)_2$, 40 °C, 5 h	86	–

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(20) **Procedure for $Pd(OAc)_2$-Catalyzed Oxidative Heck Coupling (Table 2, Entry 4).**
A mixture of indole **13** (90 mg, 0.35 mmol), $Pd(OAc)_2$ (36 mg, 0.16 mmol), $Cu(OAc)_2$ (0.318 g, 1.75 mmol) and ethyl acrylate (0.11 mL, 1.0 mmol) in dry DMF–DMSO 9:1 (10 mL) was deoxygenated and heated at 80 °C in a capped Schlenk tube. After 24 h, the reaction vessel was cooled to r.t. and CH_2Cl_2 (20 mL) was added. The organic phase was washed with H_2O (3 × 30 mL) and the resulting aqueous phases were again extracted with CH_2Cl_2 (20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography (gradient elution with PE–Et_2O mixtures from 100:0 to 1:1) afforded product **12** (87 mg, 70% yield) as a yellow oil and an additional product **19** (21 mg, 23% yield).

(21) Compound **12**: $[\alpha]_D^{22}$ +12.3 (*c* 1.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (1 H, m, indole H-4 or H-7), 7.90 (1 H, d, *J* = 16.0 Hz, β-acrylic C*H*), 7.70 (1 H, m, indole H-4 or H-7), 7.62 (1 H, s, indole H-2), 7.20–7.24 (2 H overlapped, m, indole H-5, H-6), 6.41 (1 H, d, *J* = 16.0 Hz, α-acrylic C*H*), 4.84 (1 H, dd, *J* = 7.0, 6.1 Hz, acetonide C*H*), 4.27 (2 H, q, *J* = 7.1 Hz, acrylate CH_2), 3.86 (1 H, dd, *J* = 8.9, 7.0 Hz, acetonide CH_2), 3.60 (1 H, dd, *J* = 8.9, 6.1 Hz, acetonide CH_2), 1.79 (3 H, s, CH_3), 1.72 (3 H, s, CH_3), 1.41 (3 H, m, acetonide CH_3), 1.35 (3 H, t, *J* = 7.1 Hz, acrylate CH_3), 1.34 (3 H, m, acetonide CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 138.0, 136.6, 130.8, 127.7, 122.3, 121.1, 120.7, 114.2, 112.7, 111.6, 110.3, 79.1, 65.3, 61.0, 60.0, 25.9, 24.7, 24.2, 23.5, 14.4. MS (EI, 70 eV, 250 °C): *m/z* = 357 [M^+], 256. Anal. Calcd for $C_{21}H_{27}NO_4$ (%): C, 70.56; H, 7.61; N, 3.92. Found: C, 70.27; H, 7.43; N, 3.92.

(22) Compound **19**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (1 H, m, indole H-4 or H-7), 7.76 (1 H, m, indole H-4 or H-7), 7.53 (1 H, s, indole H-2), 7.21 (1 H, m, indole H-5 or H-6), 7.13 (1 H, m, indole H-5 or H-6), 4.95 (1 H, dd, *J* = 7.0, 6.0 Hz, acetonide C*H*), 3.83 (1 H, dd, *J* = 8.9, 7.0 Hz, acetonide CH_2), 3.69 (1 H, dd, *J* = 8.9, 6.0 Hz, acetonide CH_2), 1.87 (3 H, s, CH_3), 1.79 (3 H, s, CH_3), 1.45 (3 H, m, acetonide CH_3), 1.37 (3 H, m, acetonide CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 135.7, 129.1, 123.6, 121.3, 120.5, 119.2, 113.6, 110.1, 109.0, 79.5, 65.4, 60.3, 26.0, 25.1, 24.8, 23.2. MS (ES): *m/z* = 517 [M + H]$^+$. Anal. Calcd for $C_{32}H_{40}N_2O_4$ (%): C, 74.39; H, 7.80; N, 5.42. Found: C, 74.37; H, 7.77; N, 5.39.

(23) **Procedure for $PdCl_2$-Catalyzed Oxidative Heck Coupling (Table 2, Entry 5).**
A mixture of indole **13** (78 mg, 0.30 mmol), $PdCl_2$ (15 mg, 0.085 mmol), $Cu(OAc)_2$ (0.168 g, 0.92 mmol) and ethyl acrylate (0.10 mL, 0.92 mmol) in dry MeCN (3.5 mL) was deoxygenated and heated at 40 °C in a capped Schlenk tube. After 24 h, the reaction vessel was cooled to r.t. Brine was added (25 mL) and the mixture was extracted with EtOAc (3 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography (gradient elution with PE–Et_2O mixtures from 8:2 to 4:6) afforded product **12** (92 mg, 86% yield).