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Synthesis of the A,G-spiroimine of pinnatoxins by a microwave-assisted tandem Claisen–Mislow–Evans rearrangement

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Abstract—The synthesis of the characteristic A,G-spiromine of pinnatoxins and pteriatoxins employing a microwave-assisted tandem Claisen–Mislow–Evans rearrangement is described. The study also features a highly efficient Suzuki–Miyaura cross-coupling reaction forming a tetrasubstituted vinyl ether as a part of the dihydropyran ring and a brief study of the hydrolytic stability of the spirocyclic imine.

Pinnatoxins belong to an expanding group of marine natural products characterized by the presence of unusual spirocyclic imines in their structure (Fig. 1).[1] Presently, this group also includes gymnodimine,[2] pteriatoxins,[1d,3] prorocentrolides,[4] and spirolides.[5] The structure of pinnatoxin A was established first by Uemura et al. in 1995.[1b] One of the particularly striking features of the natural products is the stability of the cyclic imine functional group toward hydrolysis.

A combination of intriguing molecular architecture and potent bioactivity makes these natural products compelling targets for total synthesis.[6] Recently, we developed the synthesis of the spirocyclic imine ring system common to pinnatoxins and pteriatoxins.[7] Our approach relies on a cascade sigmatropic process that integrates the Claisen and Mislow–Evans rearrangements to build the quaternary chiral center at the core of the A,G-spiroimine. Under the original conditions, the key cascade rearrangement requires heating the reaction mixture for 15 h at 150 °C (Scheme 1). In this letter, we describe an improved version of our original route. The most significant modifications include (a) a microwave-assisted tandem sigmatropic process that dramatically reduces the reaction time, and (b) an improved cross-coupling reaction en route to the substrate for the rearrangement (**1**). In addition, we report our observations regarding the hydrolytic stability of the A,G-spirocyclic imine fragment of pinnatoxins.

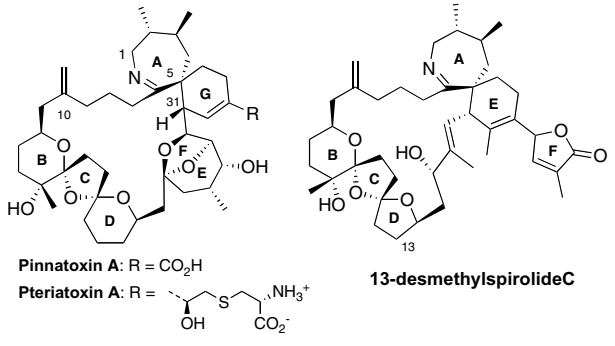
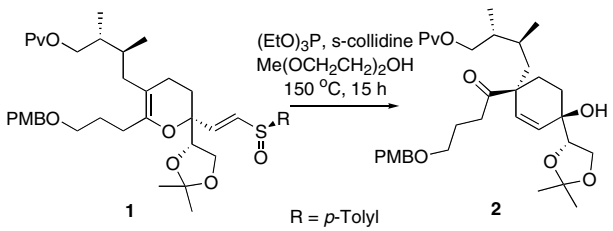


Figure 1.

Vinylic sulfoxide **1** has been prepared via triflate **3** derived from known ketone **4** in five straightforward steps (Scheme 2).[7] Perhaps the most challenging transformation in the synthetic sequence was the cross-coupling reaction with **3** resulting in a three-carbon chain extension. In our original approach, we employed the Negishi



Scheme 1.

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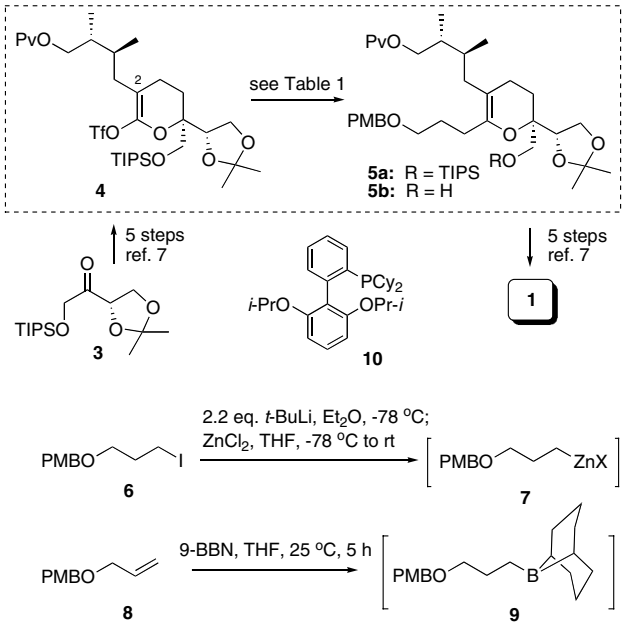


Scheme 2.

protocol to obtain dihydropyran **5**. Subsequently, compound **5** was advanced to sulfoxide **1** by a short series of reactions (Scheme 2).

In the course of our experiments it became apparent that dihydropyranyl triflate **4** is a challenging substrate for palladium-catalyzed cross-coupling reactions. Thus, a reaction of **4** with alkylzinc reagent **7**, generated in situ from iodide **6**, in the presence of 7 mol % of Pd(dppf)Cl_2 in THF/NMP at 50 °C for 15 h yielded only 14% of coupling product **5** along with 72% of recovered starting material (Table 1, entry 1). Because cross-coupling reactions with similar substrates lacking a substituent at the C2 position are well-documented,[8] and because our model cross-coupling reactions with 4-iodotoluene were very facile, we postulated that the reason for poor reactivity of **4** is due to steric shielding provided by the alkyl group at C2, which impedes either the oxidative addition or, less likely, the reductive elimination step in the catalytic cycle. As an alternative, we turned to a more electron-rich Pd[*t*-Bu_3P]$_2$ catalyst.[9] This resulted in a dramatically faster reaction, giving the expected product in 75–80% yield after 30 min at 30 °C (Table 1, entry 2). However, a significant disadvantage of the reaction was its poor reproducibility. In many instances, the reaction halted at 25–30% conversion requiring resubmission of the mixture of products to the cross-coupling protocol. In this manner, the reaction could be driven to completion after several cycles. High cost of the palladium catalyst coupled with its extremely low stability made this procedure quite exasperating and compelled us to continue the search for a more practical alternative. Attempted generation of the catalyst in situ from Pd_2dba_3 (0.05 equiv, dba = dibenzylideneacetone) and *t*-Bu_3P (0.2 equiv) resulted in no reaction (Table 1, entry 3). The palladium complex generated from Buchwald's ligand **10** also failed to promote the cross-coupling reaction (Table 1, entry **4**).[10]

The Suzuki–Miyaura cross-coupling was investigated next.[11] The requisite reagent, borane **9**, could be expediently accessed in situ from allyl *p*-methoxybenzyl ether and 9-borabicyclo[3.3.1]nonane. Intriguingly, while Pd[PPh_3]$_4$ proved to be an excellent catalyst in the cross-coupling reaction, Pd(dppf)Cl_2 was ineffective. As expected, sodium hydroxide was superior to potassium phosphate as the base additive in ethereal solvents (Table 1, entry 5). The use of excess sodium hydroxide was detrimental and resulted in a rapid decomposition of the starting material (Table 1, entry 6). With excess borane **9** with respect to sodium hydroxide, the cross-coupling reaction occurred smoothly to give the desired product. Thus, under optimized conditions, the reaction of triflate **4** with 4 equiv of alkylborane **9** in the presence of sodium hydroxide (3 equiv) and Pd[Ph_3P]$_4$ (0.05 equiv) at 60 °C for 3 h afforded the coupling product **5** in 91% yield (Table 1, entry 8).[12,13] Importantly, the reaction was highly reproducible even with commercial Pd[Ph_3P]$_4$ (Aldrich).

Having found an efficient cross-coupling procedure, a substantial amount of key vinylsulfoxide **1** for further study was expediently prepared. Previously, the next step involved a thermal cascade sigmatropic rearrangement of **1** to **2** (Scheme 1).

The benefits of microwave synthesis, most important of which are cleaner reactions and significantly reduced reaction times, for slower reactions with high activation energy are well recognized.[14] We were attracted by the possibility of the application of microwave technology for the cascade sigmatropic rearrangement of **1**. After a series of preliminary optimization experiments, we found that the tandem rearrangement can indeed be carried out using microwave conditions at 50 W, 172 °C, in 20 min and in only a slightly diminished yield (Scheme 3). As before, the presence of *s*-collidine as a buffer was advantageous and ensured more consistent results.[15] The microwave-assisted reaction allows for an improved material throughput as several runs can be performed in the course of a few hours delivering gram quantities of the rearrangement product.

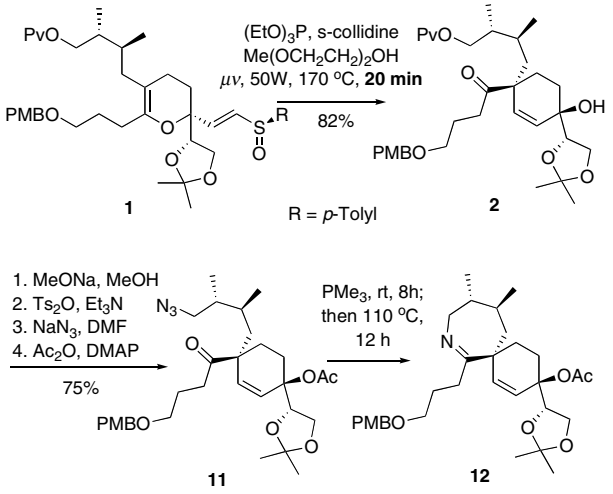
With cylcohexenol **2** in hand, we set out to prepare the A,G-spiroimine ring system of pinnatoxins. Removal of the pivaloate with sodium methoxide, tosylation of the primary alcohol, displacement of the tosylate with azide, and acetylation of the tertiary allylic alcohol delivered azide **11** in good overall yield.[7] The azepine ring closure was achieved by Staudinger reduction of the azide and aza-Wittig cyclization of the intermediate iminophosphorane affording cyclic imine **12** in quantitative yield.[7]

The stability of the cyclic imine is one of the most intriguing attributes of pinnatoxins and related natural products. The precise structural features imparting this resistance to acidic or basic hydrolysis are not established. It has been proposed that the proximity of a quaternary carbon center at the core of the spiroimine ring system at least partially contributes to the imine stability.[16] In spirolides, the relationship between the ring A

Table 1. Reaction conditions for conversion of **4** to **5** shown in Scheme 2

Entry	Reagent (equiv)	Catalyst (mol %)	Reaction conditions	Yield (%)
1	**7** (3)	$Pd(dppf)Cl_2$ (7)	THF, NMP, 0 °C, 10 min, 50 °C, 15 h	14
2	**7** (3)	$Pd[t\text{-}Bu_3P]_2$ (5)	THF, NMP, 0 °C, 10 min, 30 °C, 30 min	75[b]
3	**7** (3)	Pd_2dba_3 (5), $t\text{-}Bu_3P$ (20)	THF, NMP, 0 °C, 10 min, 30 °C, 3 h	0 (starting material recovered)
4	**7** (3)	Pd_2dba_3 (2.5), **10** (10)	THF, NMP, 0 °C, 10 min, 65 °C, 3 h	0 (starting material recovered)
5	**9** (3)	$Pd[Ph_3P]_4$ (5)	K_3PO_4 (3 equiv), dioxane, 60 °C, 24 h	<5 (starting material recovered)
6	**9** (3)	$Pd[Ph_3P]_4$ (5)	NaOH (10 equiv), dioxane, 25 °C, 24 h	0[a]
7	**9** (2)	$Pd[Ph_3P]_4$ (5)	NaOH (3 equiv), dioxane, 25 °C, 24 h	30
8	**9** (4)	$Pd[Ph_3P]_4$ (5)	NaOH (3 equiv), dioxane, 60 °C, 3 h	91[c]
9	**9** (4)	$Pd(dppf)Cl_2$ (5)	NaOH (3 equiv), dioxane, 60 °C, 3 h	0 (starting material recovered)

[a] Decomposition.
[b] Low reproducibility.
[c] Overall after two steps involving the cross-coupling and removal of the primary TIPS protecting group.[12,13]



Scheme 3.

stability and bioactivity has been demonstrated.[5a] It has been shown that spirolides that contain the vicinal dimethyl group in the imine ring are stable to aqueous hydrolysis, while those that do not are readily hydrolyzed. Because of this unusual behavior of the imine group and to gain further insight into properties of the marine natural products we investigated the hydrolytic stability of imine **12**.

We found that imine **12** is stable in solution in anhydrous toluene or deuterochloroform, but decomposes rapidly upon exposure to water. Rather than clean hydrolytic cleavage to the amino ketone, we observed a complex, intractable mixture of products (500 MHz NMR). Our results indicate that the presence of a quaternary chiral center at the core of the spiroimine ring system *and* the vicinal dimethyl group are not sufficient for the hydrolytic stability of pinnatoxins and, probably, spirolides. It is likely that the correct position of the double bond in the cyclohexene ring and a side-chain at C31 are at least the minimum requirements. Further studies in that direction are underway in our laboratory.

In conclusion, we achieved a significant improvement in the cross-coupling reaction of hindered dihydropyranyl triflate **4** using the Suzuki–Miyaura protocol affording **5** in high yield. The microwave-assisted version of the key tandem Claisen–Mislow–Evans rearrangement was developed and was found to be a viable alternative significantly reducing reaction times. Finally, the hydrolytic stability of the A,G-spiroimine fragment of pinnatoxins and pteriatoxins was explored. The results indicate that the imine stability in the natural products is due to a combination of structural features, rather than to one single structural element imparting the stability to the pharmacophore.

Acknowledgements

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12. A solution of 9-BBN (0.5 M in THF, 30 mL, 15.0 mmol) was added dropwise to a solution of *p*-methoxybenzyl allyl ether (2.67 g, 15.0 mmol) in dry THF (7.0 mL) under argon at room temperature. The solution was stirred for 5 h at rt. The solvent was removed under vacuum at 0 °C and was replaced with dry 1,4-dioxane (35 mL). In a separate flask was placed triflate **4** (2.64 g, 3.76 mmol), $Pd(PPh_3)_4$ (Aldrich, 0.22 g, 0.19 mmol), and NaOH (0.45 g, 11.3 mmol) under argon followed by dioxane (20 mL). This solution was stirred for <1 min at 0 °C, and then the borane was transferred via cannula. This solution was then stirred at 60 °C for 3 h, cooled to rt and the reaction mixture quenched with saturated aqueous ammonium chloride. The organic phase was washed with water (3×30 mL), the combined aqueous layers were extracted with EtOAc and the combined organic layers washed with brine, dried with anhydrous sodium sulfate, and concentrated under reduced pressure and dried under vacuum. The crude product was then submitted to the next step without further purification. Data for purified a sample: $[\alpha]_D^{20}$ −8.9 (*c* 1.0 CH_2Cl_2). IR (film, cm^{-1}): 3442, 2956, 2924, 2874, 1614, 1514, 1462, 1380, 1372, 1248, 1210, 1174, 1154, 1070, 1036, 1014. ^1H NMR (500 MHz, C_6D_6); δ (ppm): 7.26 (d, $J = 8.5$ Hz, 2H); 6.83 (d, $J = 8.5$ Hz, 2H); 4.62 (dd, $J_1 = J_2 = 7.5$ Hz, 1H); 4.37 (s, 2H); 4.26 (dd, $J_1 = J_2 = 8.5$ Hz, 1H); 4.12 (dd, $J_1 = 8.0$ Hz, $J_2 = 7.0$ Hz, 1H); 4.03 (dd, $J_1 = 11.0$ Hz, $J_2 = 7.0$ Hz, 1H); 3.97 (dd, $J_1 = 11.0$ Hz, $J_2 = 6.5$ Hz, 1H); 3.83 (d, $J = 10.5$ Hz, 1H); 3.76 (d, $J = 10.5$ Hz, 1H); 3.45 (t, $J = 6.0$ Hz, 2H); 3.33 (s, 3H); 2.45 (ddd, $J_1 = 16.0$ Hz, $J_2 = J_3 = 8.0$ Hz, 1H); 4.37 (ddd, $J_1 = 16.0$ Hz, $J_2 = J_3 = 8.0$ Hz, 1H); 2.11 (dd, $J_1 = 13.0$ Hz, $J_2 = 6.5$ Hz, 1H); 2.04–1.94 (m, 4H); 1.91–1.87 (m, 1H); 1.84–1.76 (m, 4H); 1.50 (s, 3H); 1.38 (s, 3H); 1.21 (s, 9H); 1.12–1.09 (m, 21H); 0.76–0.75 (m, 6H). ^{13}C NMR (75 MHz, C_6D_6); δ (ppm): 177.6, 159.6, 147.4, 131.5, 129.2, 114.0, 109.0, 103.9, 77.7, 76.5, 72.7, 69.7,67.9, 65.0, 64.1, 54.7, 38.8, 37.5, 35.7, 32.4, 28.5, 27.6, 27.4, 26.7, 25.4, 23.7, 22.2, 18.2, 14.6, 12.3, 11.6. HRMS (ESI) calcd for $C_{42}H_{72}O_8SiNa$ [M+Na] 755.48941, found 755.49282.
13. Tetra-*n*-butylammonium fluoride trihydrate (3.57 g, 11.3 mmol) was added to a solution of the crude **5a** in THF (50 mL) and the mixture was stirred at room temperature for 0.5 h. Saturated aqueous ammonium chloride was added, and the mixture was extracted with EtOAc, washed with water and brine, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The resultant oil was purified by column chromatography (silica, 40% ethyl acetate–hexanes containing 1.5% triethylamine) to give 1.97 g (3.41 mmol, 91%) of primary alcohol **5b**. $[\alpha]_D^{20}$ +13.6 (*c* 1.0 CH_2Cl_2). IR (film, cm^{-1}): 3444, 2960, 2934, 1728, 1680, 1614, 1514, 1480, 1396, 1284, 1098, 1038. ^1H NMR (300 MHz, C_6D_6); δ (ppm): 7.24 (d, $J = 8.4$ Hz, 2H); 6.82 (d, $J = 8.4$ Hz, 2H); 4.41 (t, $J = 6.6$ Hz, 1H); 4.32 (s, 2H); 4.10–3.85 (m, 4H); 3.70–3.60 (br m, 2H); 3.33 (s, 3H); 3.39–3.29 (m, 2H); 2.45 (br s, 1H); 2.28 (t, $J = 7.2$ Hz, 2H); 2.00–1.68 (m, 10H); 1.41 (s, 3H); 1.27 (s, 3H); 1.20 (s, 9H); 0.73 (d, $J = 6.6$ Hz, 3H); 0.69 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6); δ (ppm): 177.9, 159.7, 146.9, 131.1, 129.5, 114.2, 114.0, 109.2, 104.4, 78.7, 76.2, 72.8, 69.7, 68.1, 65.0, 63.2, 54.8, 38.9, 37.3, 35.8, 32.4, 28.2, 27.7, 27.4, 26.4, 25.1, 22.5, 21.8, 14.7, 11.8.
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15. To a flame dried 10 mL microwave reactor vial were added vinylsulfoxide **1** (77 mg, 0.108 mmol), $(EtO)_3P$ (74 μL, 0.433 mmol), *s*-collidine (57 μL, 0.433 mmol), and $MeOCH_2CH_2OCH_2CH_2OH$ (1.2 mL). The vial was sealed with a septum and purged with argon for 10 min. The septum was removed and replaced by a reusable cap (CEM part # 908140) and the vial placed in a microwave reactor (CEM Discover). The reaction was carried out with the following parameters: temperature 172 °C; maximum pressure 15 psi; max power 50 W; ramp time 5 min; reaction time 20 min. After a brief cool down period, the solution was diluted with EtOAc and washed with saturated aqueous ammonium chloride, with water three times, and the combined aqueous layers were extracted with ethyl acetate. The combined organic layers were washed with brine, dried with anhydrous sodium sulfate and concentrated. The residue was subjected to column chromatography (silica, 40% ethyl acetate–hexanes) to yield 52 mg (0.087 mmol, 81%) of **2**. $[\alpha]_D^{20}$ −25.4 (*c* 0.5 CH_2Cl_2). IR (film, cm^{-1}): 2928, 2934, 1726, 1706, 1612, 1514, 1458, 1370, 1284, 1068, 672. ^1H NMR (500 MHz, C_6D_6); δ (ppm): 7.23 (d, $J = 8.5$ Hz, 2H); 6.83 (d, $J = 8.5$ Hz, 2H); 5.93 (d, $J = 10.0$ Hz, 1H); 5.54 (d, $J = 10.0$ Hz, 1H); 4.30 (s, 2H); 3.97–3.92 (m, 2H); 3.88 (dd, $J_1 = J_2 = 8.0$ Hz, 1H); 3.84 (dd, $J_1 = 11.5$ Hz, $J_2 = 6.5$ Hz, 1H); 3.79 (dd, $J_1 = 8.0$ Hz, $J_2 = 7.0$ Hz,

1H); 3.36–3.29 (m, 2H); 3.32 (s, 3H); 2.61 (ddd, $J_1 = 18.5$ Hz, $J_2 = J_3 = 7.0$ Hz, 1H); 2.48 (ddd, $J_1 = 18.5$ Hz, $J_2 = J_3 = 7.0$ Hz, 1H); 2.26 (ddd, $J_1 = 13.5$ Hz, $J_2 = 9.5$ Hz, $J_3 = 4.0$ Hz, 1H); 2.04 (br s, 1H); 1.97–1.92 (m, 2H); 1.78–1.62 (m, 5H); 1.40–1.35 (m, 1H); 1.35 (s, 3H); 1.29 (dd, $J_1 = 14.0$ Hz, $J_2 = 7.0$ Hz, 1H); 1.27 (s, 3H); 1.21 (s, 9H); 0.68 (d, $J = 7.0$ Hz, 3H); 0.65 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6); δ (ppm): 210.7, 177.7, 159.7, 135.0, 131.2, 130.1, 129.4, 114.0, 109.4, 80.7, 72.6, 69.3, 69.0, 67.4, 65.2, 54.7, 52.8, 42.7, 38.8, 37.6, 35.6, 30.4, 29.9, 27.4, 26.4, 25.3, 24.5, 15.9, 11.2. HRMS (ESI) calcd for $C_{34}H_{52}O_8SNa$ [M+Na] 611.3559, found 611.3531.

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