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An Efficient and Selective Synthesis of Nakienone A Involving a Novel Protocol for α-Alkenylation of Ketones via Palladium-Catalyzed Alkenyl-Alkenyl Coupling†

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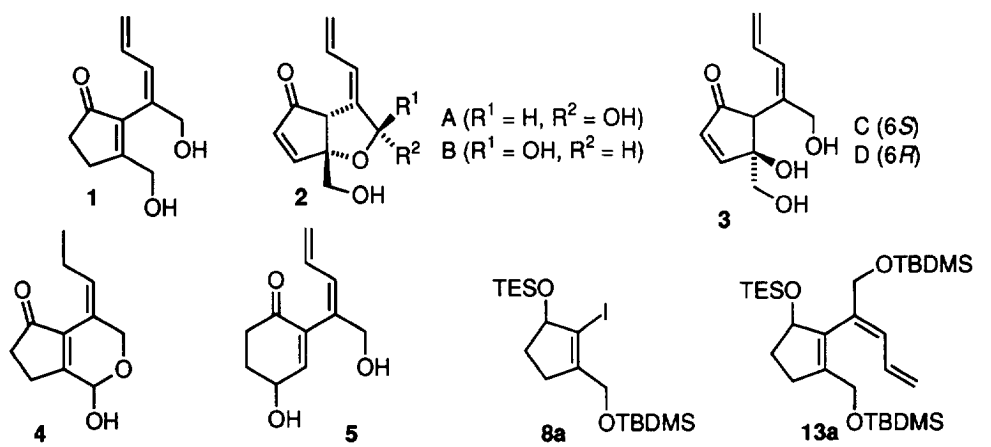
Abstract: Nakienone A was synthesized for the first time from 3-methoxy-2-cyclopentenone, dienyl iodide **7**, and $LiCH_2OMOM$ in 8 steps in 26% overall yield with full control of the alkene geometry using the Pd-catalyzed cross coupling reaction of a cyclopentenylzinc derivative **6a** with **7** as a key step.

Nakienone A (**1**)[1] and didemnenones A and B (**2**) as well as C and D (**3**)[2] are marine natural products characterized by the presence of densely functionalized cyclopentenones containing a common side chain, *i.e.*, (*E*)-2,4-pentadienyl group in an α position of the cyclopentenone moiety. These compounds, didemnenones in particular, display a variety of biological activities such as cytotoxicity, antibacterial, and antifungal activities. As might be expected from their structures, high sensitivity towards acids has been observed. For example, nakienone A is known to undergo a rearrangement to give **4** even under the conditions of NMR spectroscopy in $CDCl_3$ presumably via an acid-catalyzed process.[1] It thus appears to be essential to devise synthetic schemes avoiding acidic conditions. We recently devised such a protocol via Pd-catalyzed alkenyl-alkenyl coupling and applied it to the synthesis of nakienone B (**5**).[3]

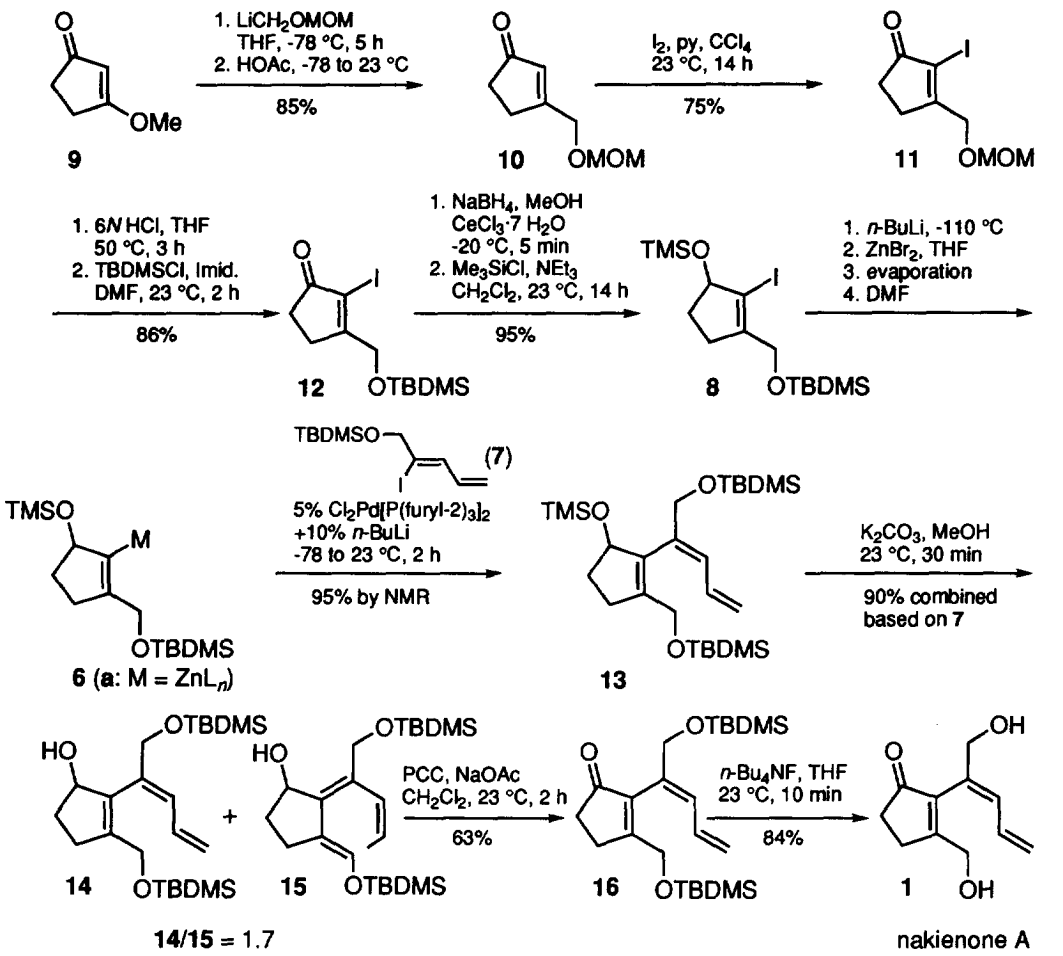


1 **2** **3** **4** **5** **8a** **13a**

We report herein the first synthesis of nakienone A through application of the above-mentioned Pd-catalyzed α-alkenylation protocol (Scheme 1), which not only confirms the structure of nakienone A[1] but provides a potentially general synthetic route to this and related groups of compounds.

†This paper is dedicated to Professor Shiro Ikegami of Teikyo University on the occasion of his 60th birthday.

Scheme 1



One crucial step of the synthesis summarized in Scheme 1 was the Pd-catalyzed cross coupling of a cyclopentenylmetal derivative **6** and a dienyl iodide **7**. The latter was prepared from propargyl alcohol in three steps in 43% overall yield as previously reported.[3] We have also reported that **7** must be used as the electrophilic component in the Pd-catalyzed cross coupling, as all attempts to metalate this iodide with *n*- or *t*-BuLi even at -110 °C led to its rapid decomposition to give vinylallene.[3] One of the critical questions was if the cyclopentenylmetal **6**, which not only is a tetrasubstituted alkene but contains a γ-oxy group poised to interact with the metal center through chelation, would satisfactorily couple with **7**. To examine this critical step the iodo derivative **8** corresponding to **6** was prepared from commercially available 3-methoxy-2-pentenone (**9**) in 4 steps in 52%. Treatment of *n*-Bu_3SnH with 1.05 equiv of $LiN(Pr\text{-}i)_2$ (LDA) in THF for 15 min at 0 °C followed by successive addition of $(CH_2O)_n$ provided *n*-Bu_3SnCH_2OH which was protected with MOMCl and *i*-Pr_2NEt in CH_2Cl_2 to give *n*-Bu_3SnCH_2OMOM[4] in 75% yield. Its treatment with 1 equiv

of *n*-BuLi at -78 °C followed by successive addition of **9** (-78 °C, 4-5 h) and HOAc (3 equiv) provided **10** in 85% yield. Its iodination with 1.5 equiv of I_2 and pyridine in CCl_4[5] for 14 h at 23 °C produced **11** in 75% yield. Hydrolysis of **11** with 6*N* HCl in THF at 50 °C for 3 h followed by OH protection with 3 equiv *t*-$BuMe_2SiCl$ (TBDMSCl), and imidazole in DMF at 23 °C for 2 h gave **12** in 86% yield. Introduction of the $TBDMSOCH_2$ group via the indirect route described above was mandated by the fact that treatment of *n*-$Bu_3SnCH_2OTBDMS$ with *n*-BuLi even at −110 °C induced *O*-to-*C* migration of the silyl group via Brook rearrangement.[6] As discussed in our previous report,[3] **12** can, in principle, be acetalized and then metalated for cross coupling with **7**. However, undesirable acetal-to-ketone conversion under acidic conditions would be required. We therefore reduced **12** with 1.1 equiv of $NaBH_4$ and 0.4*M* $CeCl_3 \cdot 7H_2O$[7] at -20 °C for 5 min, and the OH group was protected with 1.2 equiv of Me_3SiCl and NEt_3 (1.5 equiv) in CH_2Cl_2 (23 °C, 14 h) to give **8** in 95% yield. A Et_3Si-protected analogue **8a** was also prepared in comparable yield using Et_3SiCl in place of Me_3SiCl.

To our disappointment lithiation of **8a**, with *n*-BuLi at -110 °C in a 4:1:1 mixture of THF, H_2O, and pentane for 20 min, zincation with dry $ZnBr_2$ (0.5 equiv) at -78 to 23 °C, and cross coupling with **7** in the presence of 5 mol % of $Pd(PPh_3)_4$ in DMF at 23 °C for 12 h followed by heating at 70 °C for 48 h gave the Et_3Si analogue of **13**, *i.e.*, **13a**, only in 16% NMR yield. At no time during the entire reaction period did the yield exceed this figure. Analysis of the worked-up reaction mixture indicated that 76% of **7** was remaining unreacted along with the deiodinated cyclopentene reagent (70%). It should be pointed out that the same reaction conditions were quite satisfactory for the synthesis of nakienone B.[3] We then made three changes in the hope of maximizing the yield of cross coupling. We initially used a Et_3Si protecting group to prevent homo-Brook rearrangement.[6] However, its large steric requirements might have hindered the desired cross coupling. It was then found that the homo-Brook rearrangement would not be a problem even with a Me_3Si group. We also replaced $Pd(PPh_3)_4$ with Farina's[8] $Cl_2Pd[P(furyl\text{-}2)_3]_2$ which was *in situ* reduced with 2 equiv of *n*-BuLi, as Farina's catalyst has been shown to be superior in some difficult cases of cross coupling.[9] Since the presence of nonpolar solvents, such as pentane, has been shown to have some detrimental effects,[9] the solvents used to generate the alkenylzinc reagent **6a** were evaporated and replaced with DMF, which has been shown to be one of the most desirable solvents for Pd-catalyzed cross coupling.[9] With these modifications the yield of **13** was 95% by NMR spectroscopy,[10] even though it was not clear which of the three changes was most critical. Although no attempts were made to use cyclopentenylmetal derivatives containing Sn (**6b**) and B (**6c**), previous observations by us[3] and others[8] have indicated that cycloalkenylstannanes in general do not readily undergo Pd-catalyzed cross coupling under currently known conditions. We have also experienced difficulties in cleanly converting cycloalkenyl iodides into the corresponding cycloalkenylboron derivatives via Li–I exchange followed by treatment with $B(OPr\text{-}i)_3$.[11]

Surprisingly, removal of the Me_3Si group by treatment of **13** with 20 mol % of K_2CO_3 in MeOH at 23 °C for 30 min led to a 1.7/1 mixture of the desired **14** and its isomer **15**, which presumably was formed via a concerted sigmatropic rearrangement. Furthermore, attempts to separate the two led to further isomerization, and **14** and **15** appeared to be in equilibrium. We therefore isolated them as a 1.7/1 mixture in 90% overall yield based on **7** and subjected the mixture to oxidation with 3 equiv each of PCC and NaOAc in CH_2Cl_2 at 23 °C for 2 h. The enone **16** was formed in about 80% NMR yield and isolated in 63% yield. Significantly, it was ≥98% stereoisomerically pure. Consequently, if the sigmatropic rearrangement is indeed reversible, it must be stereospecific. Removal of the TBDMS groups with 2.4 equiv of *n*-Bu_4NF in THF at 23 °C for 10 min cleanly produced an 84% yield of essentially pure nakienone A (**1**), the NMR and IR spectral

data of which were in excellent agreement with those reported in the literature.[1] Thus, nakienone A was synthesized with full control of the alkene geometry in 8 steps in 26% overall yield from **7**, **9**, and $LiCH_2OMOM$.

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10. The Pd-catalyzed cross coupling of **7** and **8** was performed as follows. To **8** (1.30 g, 3.05 mmol) in THF-Et_2O-pentane (4:1:1.6) at -110 °C were added successively *n*-BuLi in hexanes (2.5 *M*, 1.29 mL, 3.23 mmol, 20 min) and dry $ZnBr_2$ (0.48 g, 2.13 mmol) in THF, and the mixture was warmed to 23 °C. To a suspension of $Cl_2Pd[P(2\text{-furyl})_3]_2$ (75 mg, 0.12 mmol) in THF (1 mL) placed in another flask were added successively at -78 °C *n*-BuLi (2.5 M, 0.1 mL, 1 h) and **7** (0.76 g, 2.34 mmol) in DMF (3 mL), and the mixture was warmed to 23 °C. To the resultant mixture was added at 23 °C the alkenylzinc prepared above. After stirring for 2 h at 23 °C, the usual extractive workup involving treatment with Et_2O and H_2O drying over Na_2SO_4, and evaporation *in vacuo* provided a crude product. Its analysis by NMR indicated the formation of **13** in 95% yield. The crude product was treated with K_2CO_3 (65 mg, 0.47 mmol) in MeOH (10 mL) at 23 °C for 1 h and worked up as above to give 0.896 g (90% overall based on **7**) of a 1.7/1 mixture was **14** and **15**, 850 mg (2 mmol) of which was oxidized with PCC (1.29 g, 6 mmol) and NaOAc (0.49 g, 6 mmol) at 23 °C for 2 h. Filtration through a short column of neutral alumina, concentration *in vacuo*, and chromatography on silica gel (15/85 Et_2O-hexane) provided a 63% yield of **16**: ^1H NMR (200 MHz, $CDCl_3$ δ 0.04 (s, 6H), 0.06 (s, 6H), 0.88 (s, 9H), 0.90 (s, 9H), 2.4-2.5 (m, 2H), 2.7-2.8 (m, 2H), 4.23 (s, 2H), 4.41 (s, 2H), 5.09 (dd, *J* = 10.1 and 1.2 Hz, 1H), 5.26 (dd, *J* = 16.7 and 1.3 Hz, 1H), 5.9-6.15 (m, 1H), 6.35 (bd, *J* = 11.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ -5.62 (2C), -5.52 (2C), 18.11, 18.20, 25.66 (3C), 25.77 (3C), 27.16, 34.36, 61.39, 64.82, 118.45, 128.56, 132.84, 134.07, 136.33, 176.03, 207.58; IR (neat) 2956 (s), 1708 (s), 1472 (m) cm^{-1}.
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