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INVESTIGATIONS OF Pd-CATALYZED ARYL SUBSTITUTION REACTIONS. A CASE STUDY TOWARDS ZOANTHENOL†

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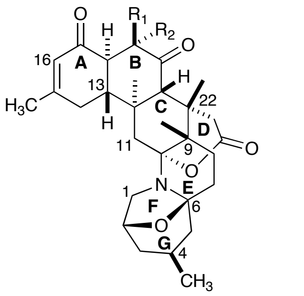
Abstract – Synthesis studies feature results for variations of Heck reaction strategies utilized for aryl substitution processes toward construction of the fully functionalized AB ring system of zoanthenol. A novel intramolecular Michael reaction is described, and the deployment of sensitive allylation reactions are reported.

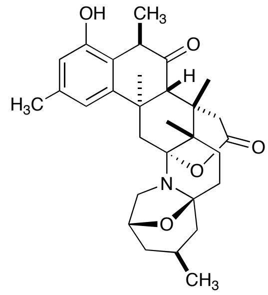
Studies of the chemical constituents of colonial species of the genus *Zoanthus* have led to the discovery of a new class of marine alkaloids. Zoanthamine (**1**) is a typical representative of this family,[1] and zoanthenol (**2**) is a singular example possessing an aromatic A-ring.[2] The polycyclic zoanthamine alkaloids elicit a spectrum of biological activity, including anti-inflammatory properties, analgesic effects, antitumor activity, inhibition of platelet aggregation and anti-osteoporetic effects.[3,4] Miyashita and coworkers have communicated the first synthesis of norzoanthamine (**3**).[5] Early investigations have also described a general strategy for construction of the enamine-aminal heterocyclic core,[6] and several studies have reported a pathway for synthesis of the AB and ABC ring systems of **1** (or **3**).[7] Hirama and coworkers have illustrated an interesting approach toward zoanthenol (**2**).[8] Herein we report exploratory findings of aryl substitution processes specifically directed towards construction of a functionalized AB system of zoanthenol.

Our preliminary investigations have examined a number of Heck cross-coupling opportunities[9] using substituted aryl triflates to address the substitution pattern of zoanthenol. Early efforts are summarized by the reactions of **4** and **6** efficiently providing dihydrobenzofurans (**5** and **7**). While formation of these

† *Dedicated to Professor Steven M. Weinreb in celebration of his 65th birthday.*

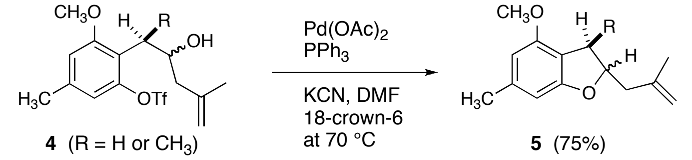


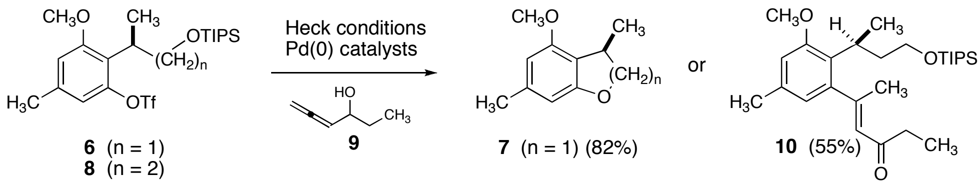
1 Zoanthamine $R_1 = CH_3$, $R_2 = H$
3 Norzoanthamine $R_1 = H$, $R_2 = H$

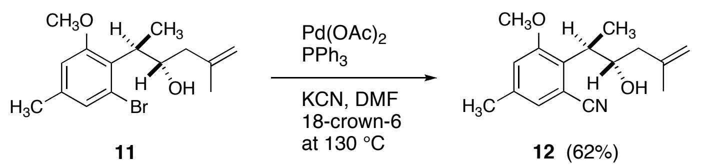


2 Zoanthenol

five-membered furanyl systems was not unanticipated based on our previous studies of amphidinolide K,[10] the inclusion of excessive amounts of potassium cyanide in the case of **4** or TIPS protection in **6** did not impede the intramolecular cyclization. In contrast, the homologous silyl ether (**8**) afforded Heck reactions that included use of the allenic alcohol (**9**), conveniently yielding the *E*-α,β-unsaturated ketone (**10**) [$Pd(dba)_2$, dppb, Me_2NAc, KOAc, Bu_4NCl, (55%)] in a single step.[11] In these cases, no evidence of pyran ring formation was observed.

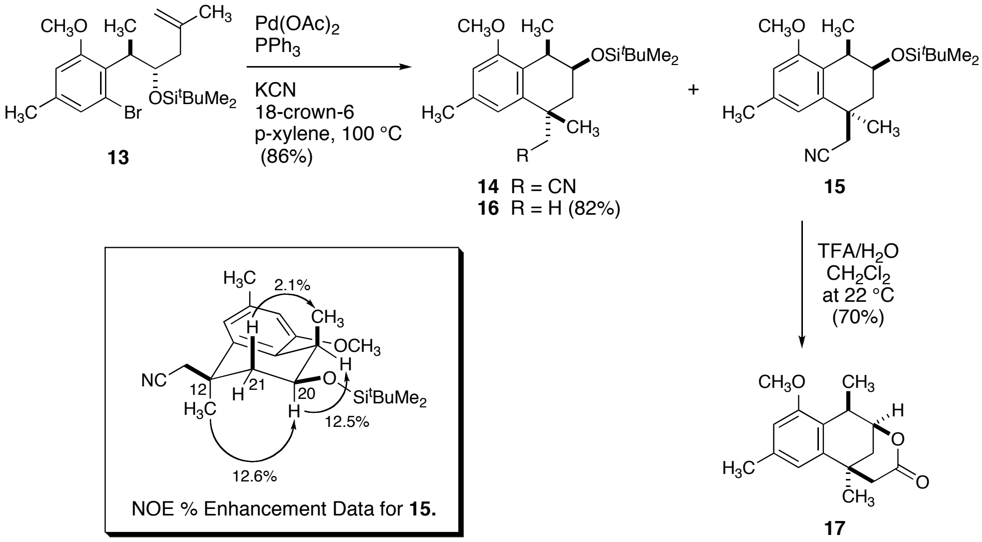




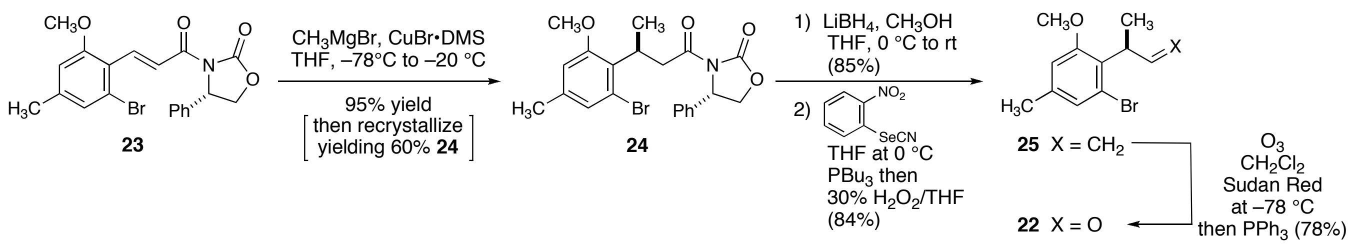


In addition, the corresponding aryl bromide (**11**) featured distinct reactivity leading solely to the nitrile (**12**) without cyclization to the benzofuran. The increased nucleophilicity of potassium cyanide in polar media was assumed to lead to rapid substitution of bromide in the palladium intermediate prior to reductive elimination.[12] Internal coordination of the free hydroxyl group in **11** was believed to inhibit palladium insertion with the neighboring olefin. In the event of silation [^{t}BuMe$_2$SiOTf, collidine, CH_2Cl_2 at –78 °C, (92%)], the TBS ether (**13**) provided for the intramolecular Heck cyclization to give diastereomeric **14** and **15** (dr 1:1.5) in 86% isolated yield (Scheme 1). After separation by silica gel chromatography, these isomers were fully characterized, and the relative stereochemistry of the major nitrile product (**15**) was established via a nuclear Overhauser (nOe) difference experiment as summarized by the % enhancements shown. Additionally, treatment of **15** with aqueous trifluoroacetic acid gave the bridged lactone (**17**), confirming these assignments.

Scheme 1.

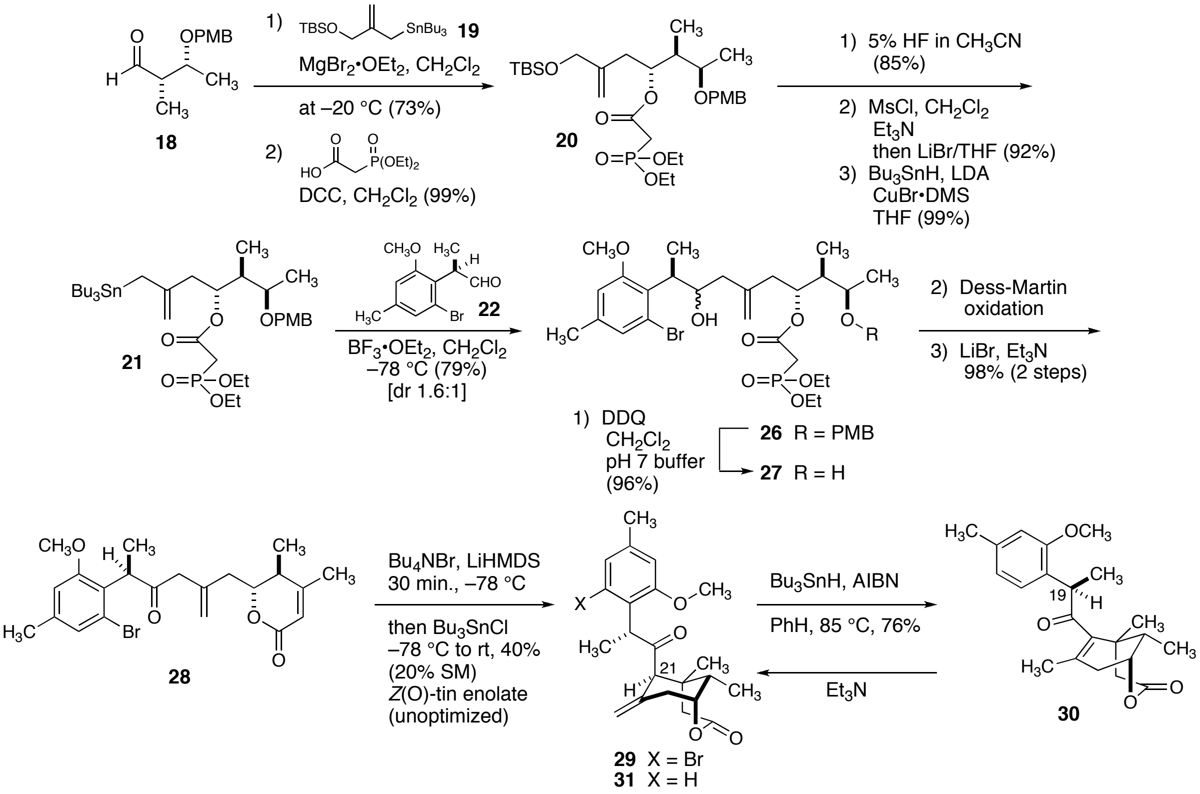


Our successful palladium-catalyzed cyclization of the A/B ring system of zoanthenol illustrated formation of a quaternary stereogenic carbon with cyanation.[13] However, cyclization of TBS ether (**13**) proved equally effective using sodium formate as a hydrogen donor leading to the gem-dimethyl substitution of **16** [$Pd(OAc)_2$, PPh_3, NaO_2CH, *n*-Bu_4NBr in DMF at 135 °C].[14] Based on this body of results, the synthesis of a key aryl bromide precursor toward zoanthenol was devised (Scheme 2). Optically active aldehyde (**18**) was prepared via the known Evans aldol procedure[15] and allylation conditions of β-chelation control[16] using magnesium bromide precomplexation smoothly provided a homoallylic alcohol in 73% yield (dr 9:1). Esterification of the pure alcohol with diethylphosphonoacetic acid gave **20**, which permitted convenient introduction of the allylic stannane in **21**. Chiral, nonracemic aldehyde (**22**) was prepared using asymmetric conjugate addition methodology beginning with enone (**23**).[17] Although yields of methylcopper addition to **23** were consistently high, diastereomeric selectivity ranged from 5:1 to 17:1 depending on temperature variations and reaction scale. In all cases, recrystallization of these mixtures afforded **24** as a white solid (dr > 18:1). Reductive removal of the chiral auxiliary and mild oxidative elimination gave the terminal olefin (**25**), which was stored for ozonolysis to **22** immediately prior to use.



Facile allylation utilizing **21** (Scheme 2) in the presence of BF_3 etherate gave a 1.6:1 ratio of diastereomeric alcohols (**26**) without evidence of epimerization at C_{19}. Furthermore, oxidative deprotection afforded diol (**27**) for Dess-Martin oxidation [18] and subsequent intramolecular Horner-Wadsworth-Emmons cyclization to yield the six- membered lactone (**28**) (98% for 2 steps). It is

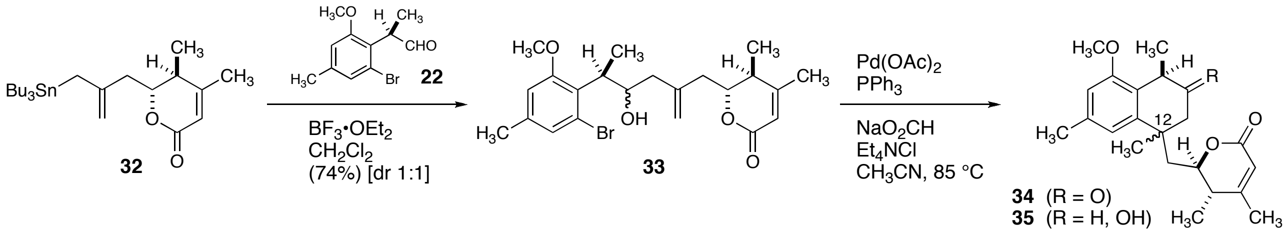
Scheme 2.



noteworthy that this sequence provided the sensitive **28** as a pure stereoisomer without epimerization or conjugation of the β,γ-alkene.

Finally, our hypothesis for intramolecular conjugate addition leading to an appropriately functionalized C-ring precursor of zoanthenol was successfully demonstrated via addition of stoichiometric base to **28** at –78 °C with formation of *Z*(O)-tin enolate and warming to 22 °C.[19] Bicyclic lactone (**29**) was isolated in 40% yield in addition to the recovery of 20–25% of starting **28**. The undesired *R*-configuration at C_{21} is favored owing to allylic strain considerations.[20] However, conjugated **30** was obtained via initial generation of the aryl radical and internal H-abstraction at C_{21}. Ketone (**30**) was not stable and readily isomerized to **31** (with partial isomerization at C_{19}). Unfortunately, all attempts for Heck cyclizations of **29** with palladium catalysis in the presence of sodium formate led solely to the reduced arene identified as **31**.

An alternative route has been explored via the allylation of **22** with stannane (**32**), which is prepared in an analogous fashion as described in Scheme 2. Condensation has provided diastereomeric alcohols (**33**) (74% yield, dr 1:1), and these efforts have led to a successful intramolecular reductive Heck cyclization, which is accompanied by oxidation to the C_{20} ketone (**34**) (dr 1.4:1 at C_{12}). Interestingly, these unoptimized reactions also produce small amounts (8–14% yields) of alcohol (**35**), which is obtained as a single hydroxy epimer. Substantial quantities of starting **33** have been recovered (47%) suggesting opportunities for further development.



In conclusion, our exploratory studies toward zoanthenol have uncovered significant aspects of reactivity for palladium-catalyzed aryl substitution processes leading to cyclizations of functionalized six-membered rings. Labile precursors are efficiently prepared via sensitive allylation reactions, and a novel intramolecular Michael reaction has established a bridged [3.3.1]bicyclic lactone. Further studies toward zoanthenol are underway.

ACKNOWLEDGEMENTS

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20. Application of MMX force field in PCModel 8.0 indicates that **29** is 9 Kcal/mol more stable than the corresponding equatorial (C-21) isomer. A transition state argument leading to ketone (**29**) describes an antiperiplanar arrangement of enolate and C=C bonds.