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Application of Palladium-Catalyzed Allylic Arylation to the Synthesis of a (±)-7-Deoxypancratistatin Analogue

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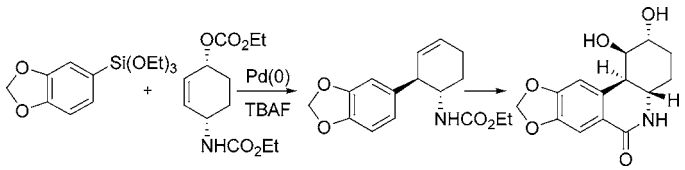
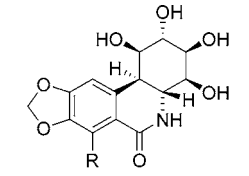
ABSTRACT



Palladium-catalyzed coupling of an aryl siloxane and an allylic carbonate proceeded in good yield to give an adduct that was converted to an analogue of (±)-7-deoxypancratistatin.

The natural products pancratistatin (**1**), 7-deoxypancratistatin (**2**), and their analogues have been shown to possess antiviral and antitumor activity under high dosage conditions (Figure 1).[1] The biological activity of these compounds and their stereochemical complexity have made them challenging synthetic targets. Controlling the stereochemistry of the dense array of oxygenated functionality on ring C and the *trans*-fused BC-ring junction have proven to be the key elements in the previous syntheses of this family of lycorane derivatives.[1d,2]



R = OH (**1**, pancratistatin)
R = H (**2**, 7-deoxypancratistatin)

Figure 1. Structures of pancratistatin and 7-deoxypancratistatin.

We have previously reported the coupling of silicate anions with allylic esters in the presence of a palladium(0) catalyst to provide homostyrene derivatives.[3] These couplings are stereospecific, occurring with inversion of configuration and

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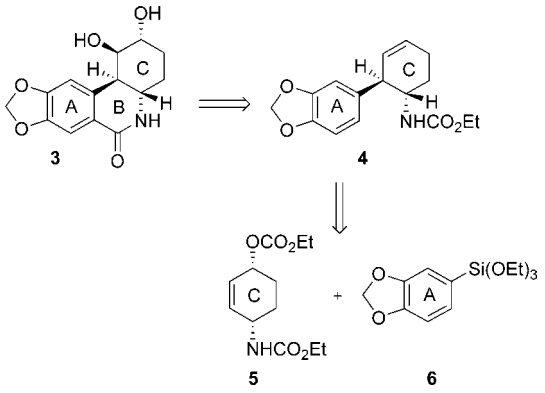
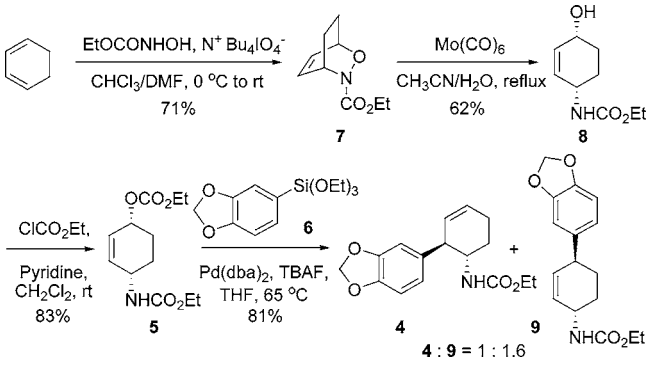
are highly regioselective; a model has been proposed to explain the high regioselectivity observed in the coupling. We were interested to determine the scope and limitation of this coupling strategy by synthesizing diol **3**, an analogue of 7-deoxypancratistatin. Based on precedent, coupling of allylic carbonate **5** with aryl siloxane **6** would occur with inversion of configuration to join the A and C rings and establish the requisite *trans*-BC ring juncture. Ring B would be constructed by a Bischler−Napieralski cyclization (Scheme 1).

Scheme 1. Retrosynthesis



Allylic carbonate **5** was prepared as shown in Scheme 2.

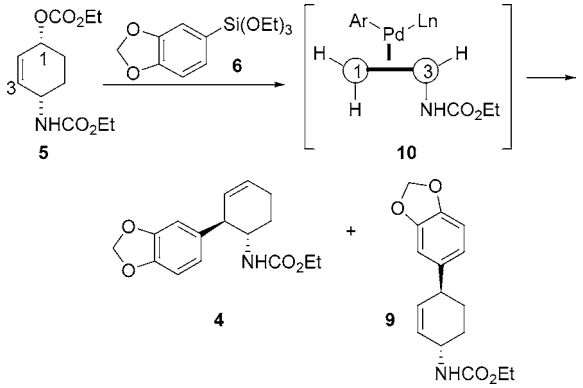
Scheme 2. Synthesis of Carbamate **4**



Diels−Alder reaction of cyclohexadiene with the acyl nitroso dienophile (generated in situ) gave hydroxamate **7**.[4] The hydroxamate underwent reductive N−O bond cleavage with molybdenum hexacarbonyl to form allylic alcohol−carbamate **8**,[5] followed by acylation with ethyl chloroformate to give carbonate−carbamate **5**. Coupling of carbonate **5** with electron-rich aryl siloxane **6**[6] in the presence of TBAF and a Pd(0) catalyst gave the allylic arylated coupling products **4** and **9**, respectively, in 81% yield as a 1:1.6 mixture of regioisomers. In this instance, the allylic coupling had occurred with complete inversion of stereochemistry as expected but had not displayed regioselectivity for the desired isomer.

On the basis of previous investigations of regioselectivity in cyclohexenyl systems, formation of a mixture of regioisomeric coupling products **4** and **9** was anticipated.[7] Using the model developed in our laboratory, the π-allyl Pd complex derived from allylic carbonate **5** formed on the face opposite from the departing carbonate group (Scheme 3).

Scheme 3. Explanation for Observed Regioselectivity of Coupling Products **4** and **9**



The resulting "symmetrical" Pd complex **10** does not have substituents on the face of the π-complex which has Pd attached. Accordingly, subsequent reductive elimination of the aryl group from silicon would occur with equal proclivity at the 1 and 3 positions. Under these circumstances, modest regioselectivity was anticipated. The role of electronic factors on the regioselectivity of the coupling reaction was unknown, but results from Szabó[8] indicated that the coupling reaction would favor carbamate **9**, as was ultimately observed in the experiment. Surprisingly, when the benzyl carbamate (Cbz) analogue of **5** was used as coupling partner with the siloxane **6**, the yield of coupled products (Cbz analogues of **4**/**9**) dramatically decreased.

The mixture of regioisomeric carbamates **4** and **9** was subjected to Bischler−Napieralski cyclization using P_2O_5 and $POCl_3/Me_3SiOSiMe_3$ (1:1), and only regioisomer **4** underwent cyclization to provide lactam **11** (Scheme 4).[9] The Friedel−Crafts cyclization was completely regioselective, giving only the desired tricycle. None of the regioisomeric tricycle was observed, in analogy with the results of Magnus.[10]

Previous syntheses of pancratistatin and its analogues had shown that C-ring alkenes were significantly less reactive

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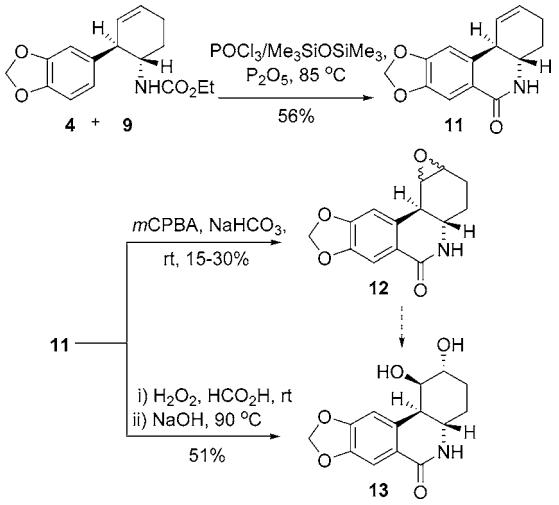
Scheme 4. Cyclization and Installation of *trans*-Diol



than normal, so we were not surprised when epoxidation of the double bond achieved using *m*-CPBA[11] gave a mixture of diastereomeric epoxides **12** in low yield (15−30%). Attempts to improve the yield of epoxides using more reactive epoxidation reagents led to extensive decomposition of the alkene. In principle, the stereoselectivity in the epoxidation reaction was of no consequence since the diaxial opening of each epoxide should be regiospecific and give only *trans*-diol **13**.

A more direct method of introducing the *trans*-diol functionality was successful: one-pot *trans*-dihydroxylation with hydrogen peroxide in formic acid (presumably via the epoxide) gave diol **13** in 51% yield.[12] The initial product of the reaction is a mixture of alcohol−formates (from opening of the expoxide) which is hydrolyzed immediately to give the desired diol. Purification of diol **13** by a variety of normal or reverse-phase methods led to extensive loss of product. The most efficient purification method ultimately involved an extraction−precipitation regime.

The relative stereochemistry of diol **13** was confirmed by COSY experiments and correlation to published ^{1}H NMR data of the benzoate of the 7-deoxypancratistatin derivative (**14**).[13] For example, the coupling constant $J_{1,10b}$ for tricycle **13** is 2 Hz (Figure 2). The small coupling constant is

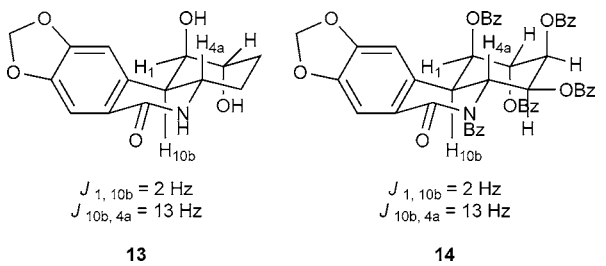
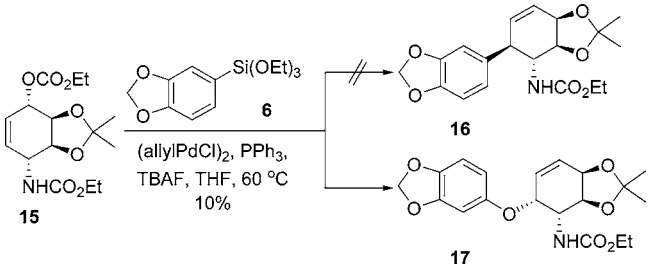


Figure 2. Relative stereochemistry was confirmed from correlation with ^{1}H NMR coupling constants.

diagnostic of a syn relationship between the two protons. Protons H_{10b} and H_{4a} of **13** exhibit a 13 Hz coupling constant which is indicative of a trans diaxial relationship. These coupling constant values are in accord with the coupling observed (2 Hz) for protons H_1 and H_{10b} and (13 Hz) for protons H_{10b} and H_{4a} respectively in **14**.

To synthesize pancratistatin (**1**) or 7-deoxypancratistatin (**2**) by this approach, it would be necessary to couple carbonate **15** with arylsiloxane **6** in analogy with the reactions described above (Scheme 5). Unlike the model system with

Scheme 5. Preliminary Studies Related to Couplings of Pancratistatin and 7-Deoxypancratistatin



allylic carbonate **5** that gave no regioselectivity in the coupling (Schemes 2 and 3), fully functionalized carbonate **15** was expected to couple with high regioselectivity based on the model developed in our previous studies and shown in Scheme 3. However, repeated attempts to effect coupling between carbonate **15** and siloxane **6** were unsuccessful; no traces of the desired adduct **16** were detected. Generally, the allylic carbonate was recovered unchanged from the reaction indicating that π-allyl complex formation had not occurred. Under forcing conditions using allyl palladium chloride dimer as the catalyst, aryl ether **17** was isolated in 10% yield. The structure of ether **17** was confirmed by X-ray crystallographic analysis. Formation of aryl ethers in these coupling reactions is unprecedented and a logical mechanistic rationale for the formation of the ether product is under investigation.

Failure of carbonate **15** to undergo the allylic arylation reaction can be attributed to steric congestion of the β face of the alkene, the face on which the transition metal must reside, by the methyl group of the isopropylidene protecting group on the diol moiety. Carbonate **15** is conformationally rigid and adopts a clamshell like conformation that places this methyl group almost directly over the alkene, thus blocking π-allyl formation. Presumably, replacement of the diol protecting with groups that allow conformational mobility (i.e., MOM, etc.) should result in efficient allylic arylations. These studies will be reported in due course.

Acknowledgment. The generous financial support of the National Institutes of Health, National Cancer Institute is

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Supporting Information Available: Synthetic procedures and spectroscopic data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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