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ADVANCES IN SILOXANE-BASED COUPLING REACTIONS: APPLICATION OF PALLADIUM-MEDIATED ALLYL-ARYL COUPLING TO THE SYNTHESIS OF PANCRATISTATIN DERIVATIVES. THE FORMAL TOTAL SYNTHESIS OF (±)-7-DEOXYPANCRATISTATIN

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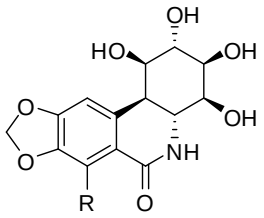
Abstract – Palladium-mediated coupling of an allylic carbonate and an aryl siloxane has been applied to the formal total synthesis of 7-deoxypancratistatin and pancratistatin analogues. The key coupling reaction involved the use of a novel palladium olefin complex resulting in regio- and stereoselective arylation yielding a tetracyclic A-C ring intermediate. The observed regioselectivity of the coupling reaction was consistent with a model in which an unsymmetrical π-allyl palladium complex was formed. Coupling of a variety of substituted phenyl siloxane derivatives was achieved using the new Pd(0) system to provide access to novel pancratistatin derivatives.

INTRODUCTION

The Amaryllidaceae alkaloids (+)-pancratistatin[1] (**1**) and (+)-7-deoxypancratistatin[2] (**2**) have attracted considerable attention in the synthetic community due to their potent antiviral and antitumor activity (Figure 1). Recently, Pandey and co-workers have shown that pancratistatin selectively induces apoptosis in various types of cancer cell lines (breast, colon, prostate, neuroblastoma, melanoma, and leukemia) at micromolar concentrations.[3] In spite of their interesting biological profiles, (+)-pancratistatin and (+)-7-deoxypancratistatin have found limited clinical applications because of their low natural abundance. Therefore, there is a need to design a practical and scalable route for the preparation of multigram quantities of these antitumor alkaloids.

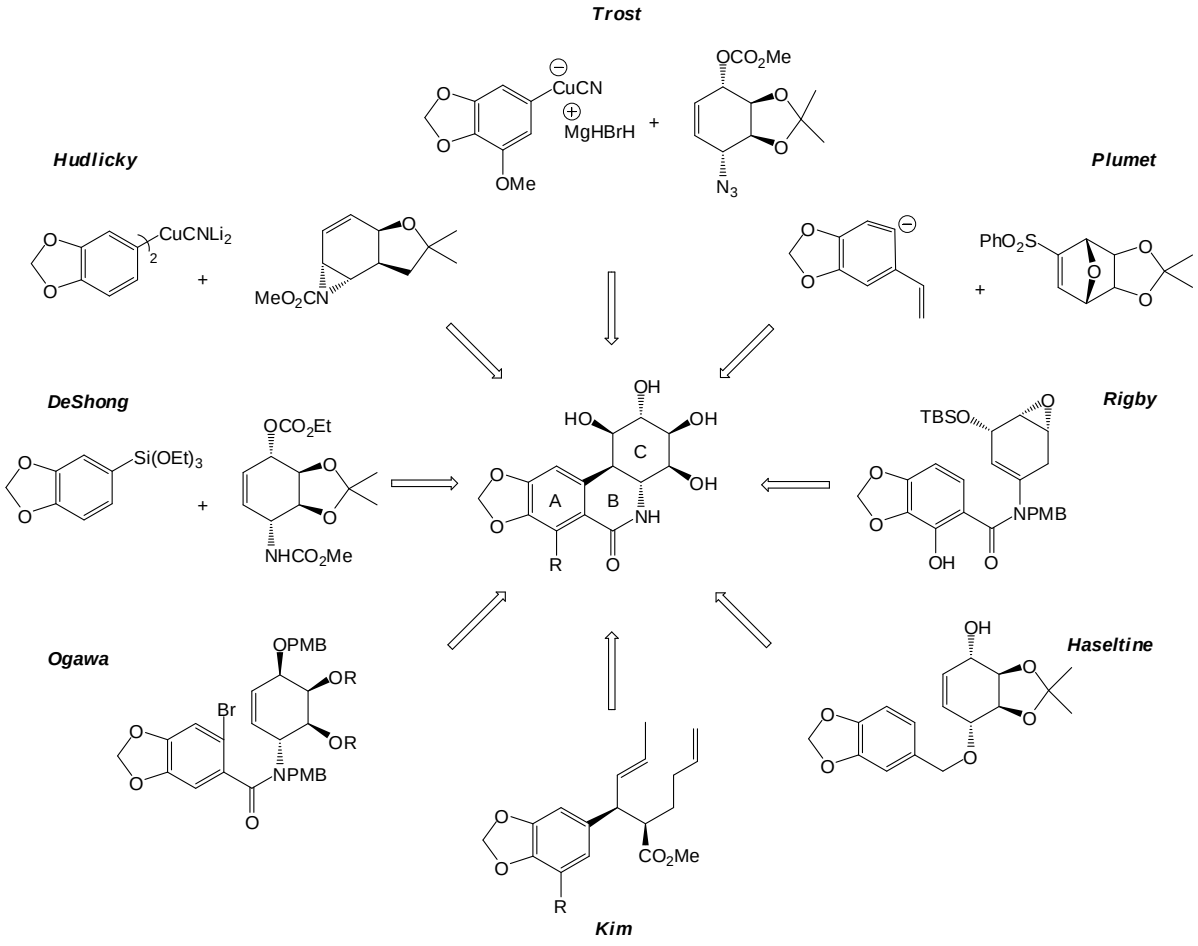
This paper is dedicated to Professor Ei-ichi Negishi for his 77 birthday



1: pancratistatin, R = OH
2: 7-deoxypancratistatin, R = H

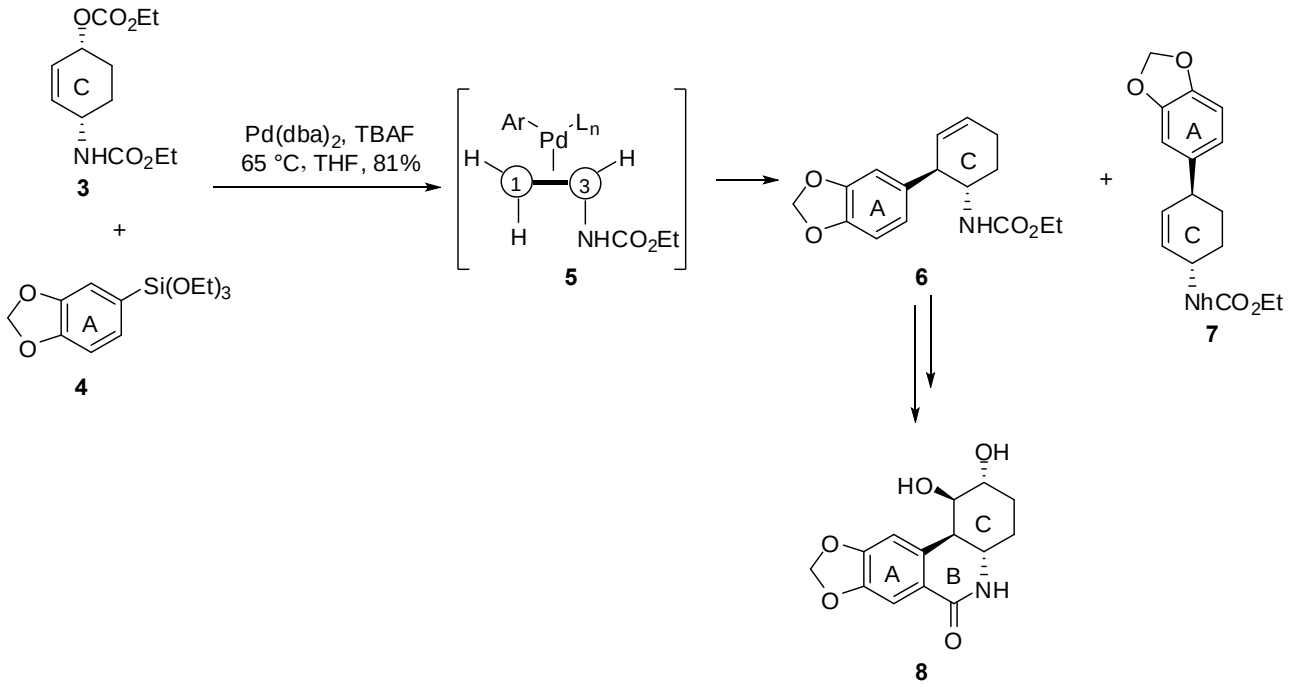
Figure 1. Structures of (+)-Pancratistatin and (+)-7-Deoxypancratistatin

An obvious approach for the synthesis of pancratistatin (**1**) and 7-deoxypancratistatin (**2**) involves the formation of a bond between the aromatic ring (A ring) and a functionalized cyclohexane (C ring) (Scheme 1).[4-13] The majority of the synthetic routes that have been reported to date employ the A-C coupling strategy; however, they are either too lengthy or low yielding for practical preparations of the natural products. The purpose of this study was to develop an efficient synthetic route to antitumor alkaloids pancratistatin (**1**) and 7-deoxypancratistatin (**2**) utilizing palladium-catalyzed allylic-aryl coupling methodology developed in our group,[14] thus providing multigram quantities of these compounds for clinical evaluation. Denmark has reported the alternative allylic-aryl coupling reaction in which an aryl bromide is coupled to an allylic silonate.[15]



Scheme 1. Summary of Synthetic Strategies for Pancratistatin Derivatives

In order to establish the viability of the siloxane coupling methodology, diol **8**, an analogue of 7-deoxypancratistatin was synthesized (Scheme 2). As previously reported, the key reaction in the synthesis of diol **8** was stereoselective construction of a carbon-carbon bond between the A and C rings *via* coupling of aryl siloxane **4** with allylic carbonate **3**.[16] The regio- and stereoselectivity of the coupling reaction was consistent with the formation of an aryl-π-allyl intermediate **5** that underwent reductive elimination to produce a mixture of urethanes **6** and **7** (**6**:**7** = 1:1.6). We proposed that the poor regioselectivity of this coupling occurred due to formation of a "symmetrical" π-allyl palladium complex **5**. In this instance, reductive elimination from complex **5** is equally probable onto either carbon 1 or 3, resulting in the formation of two regioisomers, **6** and **7** as outlined in Scheme 2. However, we anticipated that the coupling reaction of the allylic carbonate to provide the actual natural products, pancratistatin and 7-deoxypancratistatin, would show excellent regioselectivity due to the additional oxygen substituents (*vide infra)*.

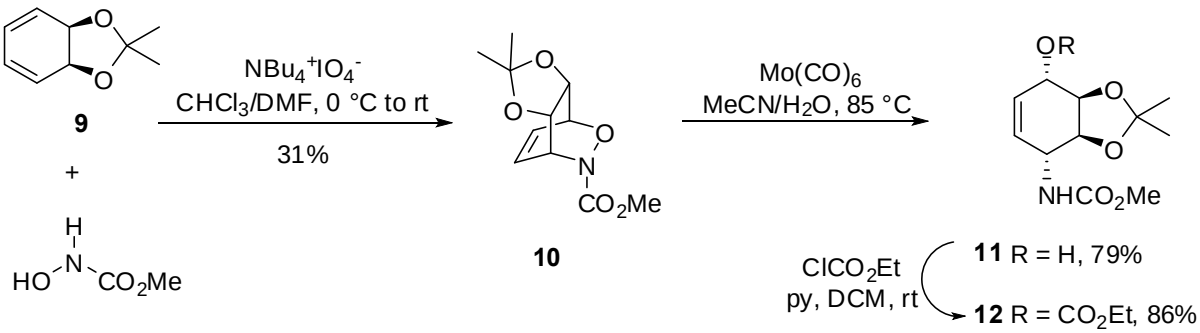


Scheme 2. Synthesis of (±)-7-Deoxypancratistatin Analogue **8**

RESULTS AND DISCUSSION

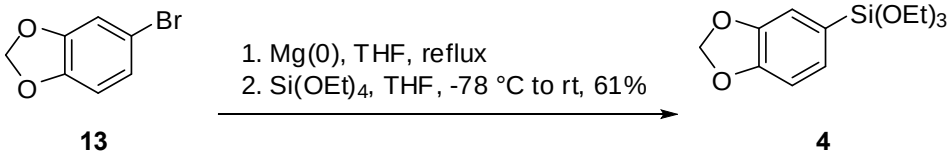
Precursors for the coupling reaction in the (±)-7-deoxypancratistatin system were prepared as outlined in Schemes 3 and 4. Allylic carbonate **12** was synthesized from diene **9**[17] through the cycloaddition of a nitroso dienophile (Scheme 3). This synthetic strategy is similar to the methodology employed by Martin,[18] Hudlicky[19] and Yan[20] in the syntheses of narciclasine alkaloids. We utilized racemic diene **9** in this study, due to the ability to prepare it in large quantities. Hudlicky has previously reported the synthesis of

(+)-enantiomer analogue of diene **9**.[21,22] The Diels-Alder reaction of diene **9** with the acyl nitroso moiety generated *in situ*, provided racemic hydroxamate **10**.[23] Reduction of the N-O bond generated allylic alcohol **11**,[24] and subsequent esterification of the alcohol with ethylchloroformate provided allylic carbonate **12**.



Scheme 3. Synthesis of Allylic Carbonate **12**

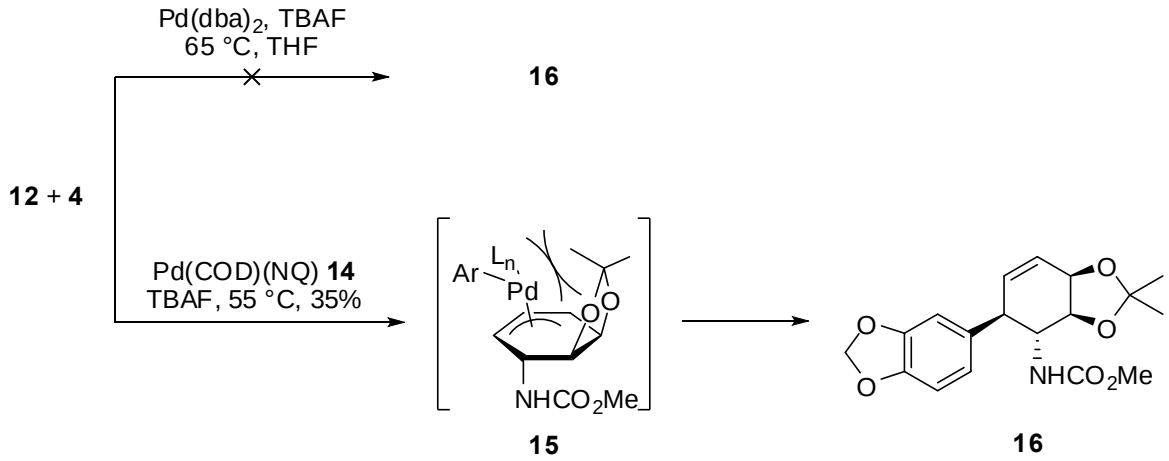
Aryl siloxane **4** was synthesized from commercially available aryl bromide **13** according to a procedure previously reported by Manoso and DeShong (Scheme 4).[25] Aryl bromide **13** was converted to the Grignard reagent, which was quenched with tetraethylorthosilicate to form aryl siloxane **4**. This procedure is general for the preparation of aryl siloxane derivatives, and has been employed to synthesize aryl siloxanes with a variety of substituents.[26]



Scheme 4. Synthesis of Aryl Siloxane **4**

While the siloxane methodology was successfully applied to the synthesis of a (±)-7-deoxypancratistatin analogue **8** (Scheme 2), attempts to couple carbonate **12** and siloxane **4** under analogous conditions for the synthesis of (±)-7-deoxypancratistatin (**2**) failed to produce the desired adduct **16** (Scheme 5). To understand the causes of the failure of the coupling reaction, a detailed mechanistic study was undertaken.[27] This mechanistic study of the siloxane coupling reaction indicated that the best Pd(0) system for the allyl-aryl cross-coupling reaction would have palladium bonded to sterically demanding, but weakly σ-bonding ligands. This set of ligand requirements is not found in the typical Pd(0) complexes employed for the coupling of aryl derivatives, since Pd(0) is typically stabilized by strong σ-donating ligand systems (phosphines). However, there are few Pd(0) complexes containing alkenes as the only ligands that possess these characteristics (Figure 2).[28-39] The catalytic activity of this family of Pd(0)-olefin complexes has not

been widely investigated. A few of these Pd(0)-olefin complexes have been employed as catalysts in Suzuki-Miyaura and Mizoroki-Heck coupling reactions.[40-42] Also, Fairlamb has recently reported the use of ion-tagged π-acidic alkene ligands in the presence of palladium precatalyst to catalyze allyl-aryl cross coupling reactions in an ionic liquid.[43] Accordingly, we surveyed a series of Pd(0)-olefin complexes for the allyl-aryl coupling reaction and found that tri-olefin Pd-complex **14**[31,32] was effective for this particular coupling reaction. The coupling of allylic carbonate **12** and aryl siloxane **4** in the presence of 50 mol% **14** produced the desired coupling product **16** in 35% yield (Scheme 5). Also, rearranged allyl alcohol, generated from rearrangement and hydrolysis of allylic carbonate **12**, was isolated (18-32%) under various reaction conditions. The decomposition of Pd-complex **14** to palladium black may also have contributed to lower product yield.



Scheme 5. Synthesis of Hudlicky's Intermediate **16**

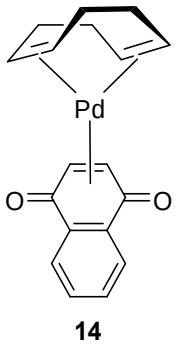
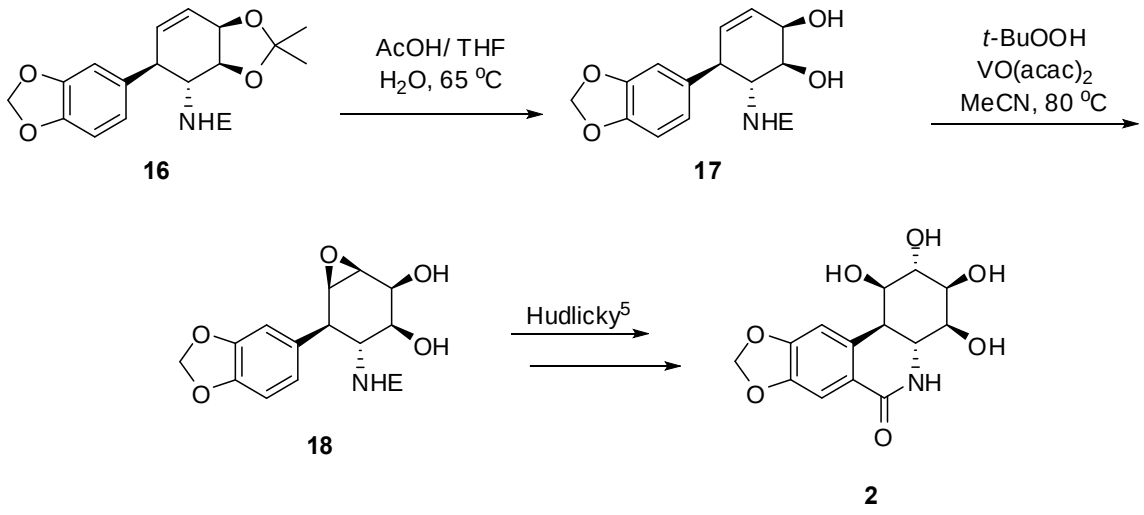


Figure 2. Structure of Pd(COD)(NQ), COD = 1,5-cyclooctadiene, NQ = 1,4-naphthoquinone

As anticipated utilizing the model developed previously, the Pd(COD)(NQ) **14** mediated coupling reaction of allylic carbonate **12** exclusively produced regioisomer **16**. Due to steric bulk arising from the acetonide

moiety, an "unsymmetrical" π-allyl palladium complex **15** is formed, where palladium resides further from the acetonide group (Scheme 5).[44] The regiochemistry of carbamate **16** was established using ^{1}H-^{1}H COSY analysis (see Supporting Information). The formation of the carbamate **16** *via* palladium-mediated allylic-arylation constituted the formal total synthesis of natural product (±)-7-deoxypancratistatin (**2**). The spectra of carbamate **16** were identical to those reported by Hudlicky in his synthesis of (+)-7-deoxypancratistatin.[5]

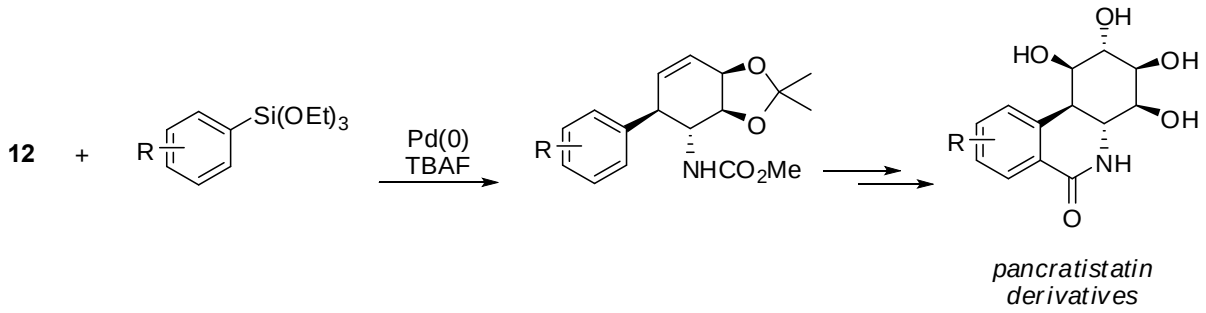
According to Hudlicky's synthesis of (+)-7-deoxypancratistatin, the key steps after the formation of carbamate **16** include the installation of a *trans*-diol in allylic-alcohol **17** *via* directed epoxidation, and a Friedel-Crafts acylation to generate the B ring (Scheme 6). Following Hudlicky's procedure, the carbamate **16** was deprotected to generate allylic alcohol **17**. Epoxidation of allylic alcohol **17** was performed in benzene as reported by Hudlicky.[5] However, the poor solubility of diol **17** in benzene led to longer reaction times and extensive decomposition of the diol. Using acetonitrile as the solvent improved solubility of diol **17**, and NMR analysis of the crude product indicated the formation of a diastereomeric mixture of epoxides **18** in which the β-epoxide predominated (traces of α-epoxide observed by ^{1}H NMR). This result was analogous to the results reported by Hudlicky who had reported the conversion β-epoxide to 7-deoxypancratistatin.[5] Accordingly, at this point the formal total synthesis of 7-deoxypancratistatin was complete, and the focus of our remaining efforts were to demonstrate that this coupling strategy could be utilized for the preparation of pancratistatin-related compounds for potential biological evaluation.



Scheme 6. Formal Synthesis of (±)-7-deoxypancratistatin following Hudlicky's Procedure

The palladium-mediated allylic-arylation approach reported above involved coupling of allylic carbonate **12** with aryl siloxane **4** (Scheme 5). Furthermore, the coupling reaction can be performed at ambient

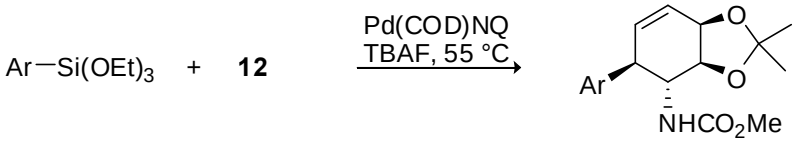
temperature without affecting the yield. Though the yield for the key reaction was modest, the ability to couple using readily available precursors is a distinct advantage over the allylic-arylation methodology reported by Trost[4] and Hudlicky[5] (Scheme 1). Also, due to the ease of preparation of coupling partners, the siloxane coupling methodology is particularly well suited for the commercial synthesis of these natural products and subsequent derivatives as outlined in the Scheme 7. Aryl siloxane coupling with allylic carbonate **12** produced the coupling products (**20**, **22**, **24**, and **26**), as summarized in the Table 1. These coupling products can be converted to a variety of pancratistatin derivatives (Scheme 7).[5]

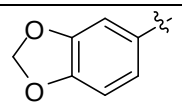
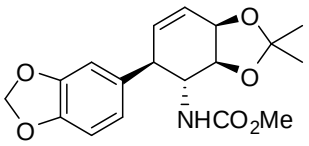
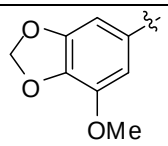
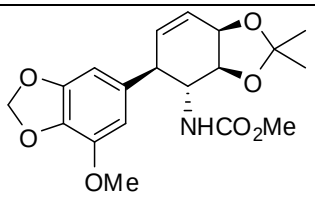
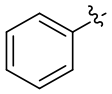
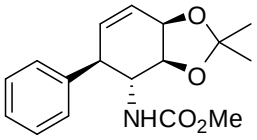
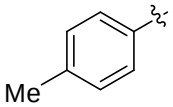
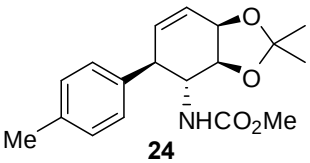
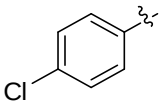
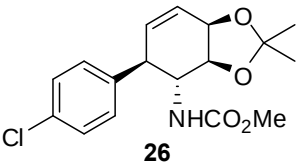


Scheme 7. Synthesis of Pancratistatin Derivatives

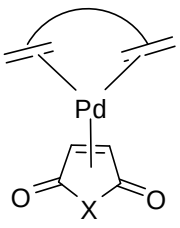
This study demonstrated that novel tri-olefin Pd-complex **14** (Figure 2) could be employed in the synthesis of (±)-7-deoxypancratistatin (**2**). Extensive optimization studies were performed to identify the appropriate palladium-olefin complex. During these studies, we noticed differences in the reactivity as well as stability of metal-olefin complexes when the electronics and sterics of the olefin ligand of complex **14** were altered. Subtle changes, such as inclusion of an aromatic ring, modification of the electronic nature of the diene, as well as type of electron withdrawing olefin, strongly affected yields of the allyl-aryl coupling reaction. While the yield of the coupled product obtained under these conditions was modest, this is a marked improvement over the coupling reactions employing traditional Pd(0) catalysts such as Pd-dba and Pd-phosphine complexes in which minimal (< 5%) coupling was observed. Future studies shall focus on the development of novel Pd-olefin complexes **27** (Figure 3) and application of these complexes in a variety of coupling reactions. Pd(0) complexes such as **14** and its congeners were reported in 1983,[31] however, the utilization of these complexes in Pd(0)-mediated allyl-aryl couplings has not been reported previously. In our systems, complex **14** has been shown to be the only Pd(0) complex capable of actuating the allylic-aryl coupling. Accordingly, these complexes, such as **14** and **27,** may prove to be valuable additions to the arsenal of coupling methodology for systems in which the more traditional Pd(0) catalysts such as $Pd_x(dba)_y$ are ineffective. We shall report on the use of complexes **27** in coupling reactions in due course.

Table 1. Aryl Siloxane Couplings with Allylic Carbonate **12**



Ar	Coupling Product	Yield (%)[a]
 **4**	 **16**	35
 **19**	 **20**	30
 **21**	 **22**	38
 **23**	 **24**	16
 **25**	 **26**	38

[a] Yield was determined by column chromatography and is an average of at least two runs.



27

Figure 3. Pd-olefin complex

In conclusion, palladium-mediated allylic-arylation has been applied to the formal total synthesis of (±)-7-deoxypancratistatin (**2**) *via* Hudlicky's intermediate **16** (Schemes 5 and 6). The key reaction of this approach was the coupling of an allylic carbonate **12** and an aryl siloxane **4** in the presence of a novel Pd(0) olefin complex, Pd(COD)(NQ) **14**, which resulted in stereoselective arylation to form a single constitutional isomer. This coupling approach provided yields that were comparable to the allyl-aryl coupling methodology reported by Trost[4] and Hudlicky[5]; however, this protocol is an improvement on the previously reported methods due to the ease of preparation as well as stability of the coupling precursors **12** and **4**. Additionally, this coupling strategy can be utilized to prepare a variety of pancratistatin derivatives. Future goals are to further develop olefin based palladium complexes to optimize the key reaction.

EXPERIMENTAL

All reactions were run under an atmosphere of argon unless otherwise noted. Glassware used in the reactions was dried for a minimum of 12 h in an oven at 120 °C. Tetrahydrofuran was distilled from sodium/benzophenone ketyl, while methylene chloride, pyridine and dimethylformamide were distilled from calcium hydride. Infrared spectra were recorded on a Nicolet 560 FT-IR spectrophotometer. Samples used for obtaining infrared spectra were either dissolved in carbon tetrachloride or taken neat. IR band positions are reported in reciprocal centimeters (cm^{-1}) and relative intensities are listed as br (broad), s (strong), m (medium), or w (weak). Nuclear magnetic resonance (^1H, ^{13}C NMR) spectra were recorded on a 400 or 500 MHz spectrometer. Chemical shifts are reported in parts per million (δ) and coupling (*J* values) are reported in hertz (Hz). Spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad singlet) and br d (broad doublet). Low resolution mass spectrometry (LRMS) and high resolution mass spectrometry (HRMS) were obtained on a JEOL SX-02A instrument.

2,2-Dimethyl-3a,7a-dihydrobenzo[*d*][1,3]dioxole **9**[17] and Pd(COD)(NQ) **14**[31,32] were prepared by previously reported procedures. Triethoxy(phenyl)silane **21** was purchased from Sigma-Aldrich. Benzo[*d*][1,3]dioxol-5-yltriethoxysilane **4**,[16] (4-methylphenyl)triethoxysilane **23**[26] and (4-chlorophenyl)triethoxysilane **25**[25] were prepared from commercially available 5-bromo-1,3-benzodioxole, *p*-bromotoluene and *p*-chloroiodobenzene respectively according to the procedure reported by the DeShong group.

Hydroxamate (10): To 32.8 g (75.9 mmol, 1.40 equiv.) of $NBu_4^+IO_4^-$ (tetrabutylammonium periodate) under argon was added chloroform (110 mL) and DMF (55.0 mL). The reaction mixture was cooled to 0 °C and then 8.25 g (54.2 mmol, 1.00 equiv.) of diene **9** was added. Finally, 4.93 g (54.2 mmol, 1.00 equiv.) of hydroxamic acid ($HONHCO_2Me$) dissolved in chloroform (55.0 mL) and DMF (18.0 mL) was added *via* addition funnel. The reaction mixture was stirred at 0 °C to room temperature for 3 days. The

product was extracted with Et_2O (5 × 100 mL), washed with H_2O (100 mL), dried over $MgSO_4$, concentrated *in vacuo* to give the crude hydroxamate **10** as an orange oil. Flash column chromatography on silica gel (30% EtOAc/70% hexane, R_f = 0.11) gave 4.06 g (31%) of hydroxamate **10** as a light yellow solid; mp 146-148 °C; IR (CCl_4) 3087 (w), 2999 (m), 2985 (m), 2935 (m), 1719 (s), 1440 (s), 1379 (s), 1336 (s), 1250 (s), 1215 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.45-6.35 (m, 2H), 5.03-5.00 (m, 1H), 4.87-4.84 (m, 1H), 4.53-4.46 (m, 2H), 3.70 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 130.6, 129.4, 110.9, 73.0, 72.5, 71.3, 53.6, 52.8, 25.5, 25.3; HRMS (ESI) calcd for $C_{11}H_{16}O_5N$ $(M+H)^+$ 242.1029, found 242.1016.

Methyl 7-hydroxy-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-ylcarbamate (11): To 3.77 g (15.6 mmol, 1.00 equiv.) of the hydroxamate **10** dissolved in 160 mL acetonitrile and 8.00 mL distilled water was added 4.96 g (18.8 mmol, 1.20 equiv.) of molybdenum hexacarbonyl ($Mo(CO)_6$). The reaction mixture was refluxed at 85 °C for 48 h. The black-brown reaction mixture was vacuum filtered through celite and the filtrate was concentrated *in vacuo* to give crude alcohol-carbamate **11** as brown solid. Flash column chromatography on silica gel (75% EtOAc/25% hexane, R_f = 0.49) gave 2.98 g (79%) of allylic alcohol **11** as a white solid; mp 86-88 °C; IR (CCl_4) 3617 (m), 3449 (m), 3414 (w), 3049 (w), 2995 (m), 2942 (m), 2909 (m), 1730 (s), 1551 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.91-5.88 (m, 1H), 5.78-5.74 (m, 1H), 5.4 (br d, *J* = 8 Hz, 1H), 4.21-4.18 (m, 3H), 4.08-4.06 (m, 1H), 3.7 (s, 3H), 3.1 (br s, 1H), 1.4 (s, 3H), 1.3 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 131.1, 129.7, 109.1, 79.2, 76.8, 68.9, 52.2, 51.1, 26.9, 24.6; HRMS (ESI) calcd for $C_{11}H_{18}O_5N$ $(M+H)^+$ 244.1185, found 244.1180. ^1H NMR spectrum was identical to the data previously reported.[19]

Methyl 7-(ethoxycarbonyloxy)-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-ylcarbamate (12): To 2.95 g (12.1 mmol, 1.00 equiv.) of allylic alcohol **11** in 40.0 mL anhydrous CH_2Cl_2 and 1.47 mL (18.2 mmol, 1.50 equiv.) anhydrous pyridine was added 1.80 mL (18.2 mmol, 1.50 equiv.) of ethyl chloroformate dropwise *via* syringe under argon. The reaction was allowed to stir at room temperature for 7 days. Additional 1.50 equiv. of pyridine and 1.50 equiv. of ethyl chloroformate were added and reaction mixture was stirred for 24 h. The reaction mixture was extracted with CH_2Cl_2 (5 × 50 mL), washed with H_2O (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography on silica gel (30% EtOAc/70% hexane, R_f = 0.33) afforded 3.27 g (86%) of the allylic carbonate **12** as a off-white solid; mp 63-65 °C; IR (CCl_4) 3442 (m), 2992 (m), 2956 (m), 2906 (m), 1751 (s), 1733 (s), 1554 (m), 1508 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.86-5.80 (m, 2H), 5.2 (br s, 1H), 5.1 (s, 1H), 4.30-4.27 (m, 1H), 4.19-4.14 (q, *J* = 8 Hz, 4H), 3.6 (s, 3H), 1.4 (s, 3H), 1.28-1.24 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 154.2, 131.3, 127.0, 109.2, 75.9, 75.8, 73.9, 64.3, 52.1, 50.3, 26.8, 24.7, 14.1; HRMS (ESI) calcd for $C_{14}H_{22}O_7N$ $(M+H)^+$ 316.1396, found 316.1383.

Triethoxy(7-methoxybenzo[*d*][1,3]dioxol-5-yl)silane (19): Aryl siloxane **19** was prepared from the

corresponding aryl bromide, which was prepared according to the procedure of Magnus and Sehbat.[6] A solution of 1.5 g (6.5 mmol) of aryl bromide,[6] 0.24 g (9.8 mmol) of fresh magnesium turnings and one crystal of iodine in 15 mL of dry THF was refluxed under an argon atmosphere for 2 h. The reaction mixture was cooled to 25 °C and then added dropwise *via* cannula to a solution of tetraethyl orthosilicate (4.1 g, 20 mmmol) in 5.0 mL of THF. The reaction mixture was stirred for 1 h at 25 °C, then quenched by the addition of 5.0 mL of ethanol and concentrated *in vacuo*. The crude reaction mixture was then partitioned between 50 mL of water and 4 × 50 mL of Et_2O, and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by flash chromatography (5% EtOAc/95% hexane, R_f = 0.25) gave 1.0 g (50%) of siloxane **19** as a colorless oil; IR (CCl_4) 2975 (m), 2926 (m), 2885 (m), 1622 (m), 1504 (m), 1412 (m), 1114 (s) 1082 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.8 (s, 1H), 6.0 (s, 2H), 3.9 (s, 3H), 3.8 (q, *J* = 7 Hz, 6H), 1.2 (t, *J* = 7 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 143.9, 137.3, 124.4, 114.1, 108.0, 101.3, 58.7, 56.5, 18.2; LRMS (FAB) 315 ((M+1), 47), 314 ((M^+), 100), 313 (44), 269 (39), 165 (20); HRMS (FAB) calcd for $C_{14}H_{22}O_6Si$ (M^+) 314.1186, found 314.1198.

Methyl 2,2-dimethyl-3a,4,5,7a-tetrahydro-5,5'-bibenzo[*d*][1,3]dioxol-4-ylcarbamate (16): To 462 mg (1.63 mmol, 2.00 equiv.) of aryl siloxane **4** and 256 mg (0.813 mmol, 1.00 equiv.) of allylic carbonate **12** dissolved in 15.0 mL anhydrous THF was added 1.63 mL (1.63 mmol, 2.00 equiv.) TBAF under argon. This was followed by addition of 152 mg (0.407 mmol, 0.500 equiv.) Pd(COD)(NQ). The reaction mixture was heated at 55 °C for 24 h. The reaction was then quenched by addition of 30.0 mL H_2O. The product was extracted with 3 × 50 mL CH_2Cl_2 and washed with H_2O. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give brown oil. Flash column chromatography on silica gel (30% EtOAc/70% hexane, R_f = 0.17) gave 98 mg (35%) of carbamate **16** (racemic) as off-white solid, mp 177-179 °C (hexane-EtOAc); IR (CCl_4) 3467 (w), 3442 (w), 3042 (w), 2995 (w), 2881 (w), 1730 (s), 1504 (s), 1486 (s), 1250 (s) cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2CO$) δ 6.8 (d, *J* = 8 Hz, 1H), 6.68-6.65 (m, 2H), 6.2 (br d, *J* = 8 Hz, 1H), 5.97-5.93 (m, 3H), 5.9 (d, *J* = 10 Hz, 1H), 4.7 (t, *J* = 5 Hz, 1H), 4.25-4.22 (m, 1H), 3.6 (q, *J* = 10 Hz, 1H), 3.5 (br d, *J* = 10 Hz, 1H), 3.4 (s, 3H), 1.5 (s, 3H), 1.3 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 157.4, 148.6, 147.4, 136.9, 136.6, 124.8, 122.5, 109.9, 109.4, 108.8, 101.9, 77.9, 73.3, 56.9, 51.6, 47.1, 28.7, 26.6; HRMS (ESI) calcd for $C_{18}H_{22}O_6N$ $(M+H)^+$ 348.1447, found 348.1440. ^1H and ^{13}C NMR spectra of carbamate **16** in $CDCl_3$ are identical with that reported by Hudlicky.[5] The regiochemistry of carbamate **16** was established using ^1H-^1H COSY (500 MHz, $(CD_3)_2CO$) (see Supporting Information).

Methyl 7'-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-5,5'-bibenzo[*d*][1,3]dioxol-4-ylcarbamate (20): Carbamate **20** was prepared from allylic carbonate **12** as described for the preparation of carbamate **16** except aryl siloxane **19** was used in place of aryl siloxane **4**; white solid (30% yield); mp 164-165 °C

(pentane-EtOAc); IR (Neat) 3292 (w), 2995 (w), 2949 (w), 2906 (w), 1697 (s), 1558 (s), 1508 (m), 1079 (s), 1043 (s) cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2CO$) δ 6.5 (d, *J* = 2 Hz, 1H), 6.4 (d, *J* = 2 Hz, 1H), 6.2 (br d, *J* = 8 Hz, 1H), 5.9 (m, 3H), 5.88 (d, *J* = 10 Hz, 1H), 4.7 (br s, 1H), 4.25-4.24 (m, 1H), 3.84 (s, 3H), 3.6 (q, *J* = 10 Hz, 1H), 3.47-3.44 (m, 4H), 1.5 (s, 3H), 1.3 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 157.5, 149.9, 144.5, 137.3, 136.8, 135.0, 124.8, 109.9, 109.2, 103.0, 102.1, 77.9, 73.4, 57.0, 56.7, 51.7, 47.3, 28.7, 26.5; HRMS (ESI) calcd for $C_{19}H_{24}O_7N$ $(M+H)^+$ 378.1553, found 378.1550.

Methyl 2,2-dimethyl-5-phenyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-ylcarbamate (22): Carbamate **22** was prepared from allylic carbonate **12** as described for the preparation of carbamate **16** except aryl siloxane **21** was used in place of aryl siloxane **4**; off-white solid (38% yield); mp 148-150 °C (hexane-EtOAc); IR (CCl_4) 3469 (w), 3448 (w), 2987 (w), 1730 (s), 1507 (s), 1246 (s), 1221 (s) cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 7.30-7.27 (m, 2H), 7.22-7.18 (m, 3H), 6.2 (br d, *J* = 8 Hz, 1H), 5.99-5.95 (m, 1H), 5.9 (d, *J* = 10 Hz, 1H), 4.7 (t, *J* = 5 Hz, 1H), 4.3 (m, 1H), 3.7 (q, *J* = 10 Hz, 1H), 3.5 (br d, *J* = 10 Hz, 1H), 3.4 (s, 3H), 1.5 (s, 3H), 1.3 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 157.3, 142.7, 136.8, 129.3, 129.1, 127.5, 124.8, 109.8, 77.9, 73.3, 56.7, 51.6, 47.4, 28.7, 26.5; HRMS (ESI) calcd for $C_{17}H_{22}O_4N$ $(M+H)^+$ 304.1549, found 304.1563.

Methyl 2,2-dimethyl-5-*p*-tolyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-ylcarbamate (24): Carbamate **24** was prepared from allylic carbonate **12** as described for the preparation of carbamate **16** except aryl siloxane **23** was used in place of aryl siloxane **4**; white solid (16% yield); mp 164-166 °C (hexane-EtOAc); IR (CCl_4) 3467 (w), 3446 (w), 2991 (w), 2957 (w), 2930 (w), 2868 (w), 1730 (s), 1516 (s), 1380 (w), 1370 (w), 1241 (s), 1217 (s) cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 7.09, 7.06 (ABq, J_{AB} = 8 Hz, 4H), 6.2 (br d, *J* = 8 Hz, 1H), 6.0 (d, *J* = 10 Hz, 1H), 5.8 (d, *J* = 10 Hz, 1H), 4.68-4.67 (m, 1H), 4.27-4.23 (m, 1H), 3.7 (q, *J* = 10 Hz, 1H), 3.50-3.47 (m, 1H), 3.4 (s, 3H), 2.3 (s, 3H), 1.5 (s, 3H), 1.3 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 157.4, 139.7, 137.1, 136.9, 129.8, 129.2, 124.7, 109.9, 78.0, 73.4, 56.8, 51.6, 47.0, 28.7, 26.6, 21.1; HRMS (ESI) calcd for $C_{18}H_{24}O_4N$ $(M+H)^+$ 318.1705, found 318.1711.

Methyl 5-(4-chlorophenyl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-ylcarbamate (26): Carbamate **26** was prepared from allylic carbonate **12** as described for the preparation of carbamate **16** except aryl siloxane **25** was used in place of aryl siloxane **4**; white solid (38% yield); mp 202-204 °C (pentane-Et_2O); IR (Neat) 3281 (w), 3099 (w), 3027 (w), 2985 (w), 1694 (s), 1558 (s), 1254 (s), 1211 (s), 1079 (s), 1047 (s) cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 7.3 (d, *J* = 8 Hz, 1H), 7.2 (d, *J* = 8 Hz, 1H), 6.3 (br d, *J* = 8 Hz, 1H), 6.02-5.98 (m, 1H), 5.9 (d, *J* = 10 Hz, 1H), 4.7 (t, *J* = 5 Hz, 1H), 4.27-4.23 (m, 1H), 3.7 (q, *J* = 10 Hz, 1H), 3.55-3.53 (m, 1H), 3.4 (s, 3H), 1.4 (s, 3H), 1.3 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 157.4, 141.8, 136.1, 132.9, 131.1, 129.2, 125.4, 110.0, 77.7, 73.3, 56.8, 51.7, 47.0, 28.7, 26.5; HRMS (ESI) calcd for $C_{17}H_{21}O_4NCl$ $(M+H)^+$ 338.1159, found 338.1140.

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