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Synthetic Studies Toward the Taxane Class of Natural Products

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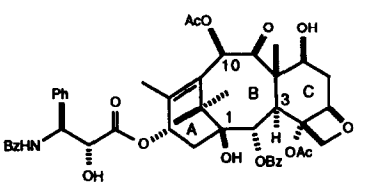
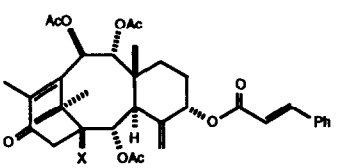
Abstract: The tricyclic enone **12**, containing the taxane ring system, has been synthesized, using an intramolecular Ni(II)/Cr(II)-mediated coupling of β-iodoenone aldehyde **11** as the key step.

Taxol (**1**), the most noted member of the taxane class of natural products, has received much attention due to its promising chemotherapeutic activity.[1] The molecular architecture of this class of natural products has intrigued synthetic chemists for over two decades.[2] In this communication, we would like to disclose portions of our work directed toward the synthesis of *O*-cinnamoyltaxicin I (**2**) and II (**3**).

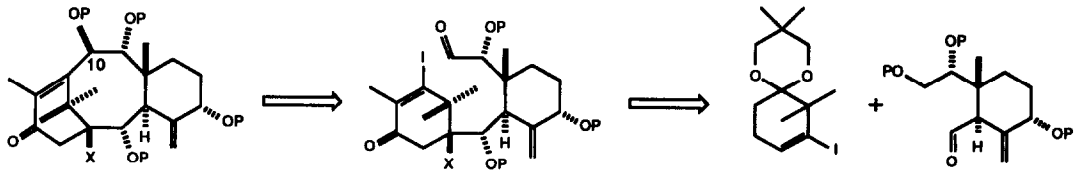


1: Taxol



2: *O*-Cinnamoyltaxicin-I Triacetate (X=OH)
3: *O*-Cinnamoyltaxicin-II Triacetate (X=H)

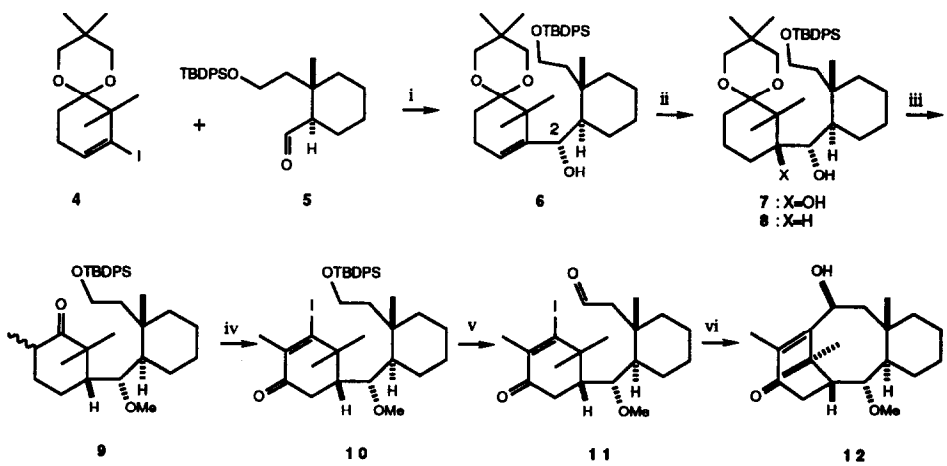
Studies from these and other laboratories have illustrated the utility of the Ni(II)/Cr(II)-mediated coupling of activated olefins with aldehydes.[3] In the total synthesis of ophiobolin C, we demonstrated that the intramolecular version of this coupling reaction was remarkably effective for 8-membered ring formation.[4] With this precedent, we were interested in the possibility of assembling the taxane ring system *via* the intramolecular cyclization of an appropriately functionalized iodoolefin aldehyde or its synthetic equivalent (Scheme 1). We were aware that such a cyclization would be accompanied by a substantial increase in steric congestion. However, we recognized three advantages of such an approach: (1) a high degree of convergence, (2) the mildness of the Ni(II)/Cr(II)-mediated coupling reaction would permit the use of advanced A- and C-ring precursors, and (3) analysis of molecular models suggested the major product formed would have the desired C.10 configuration.



Scheme 1. X = OP or H; P = a suitable protecting group, but all the Ps are not necessarily identical.

We chose the model system shown in Scheme 2 to demonstrate the feasibility of our approach. The ring A precursor **4** was prepared in 4 steps from 2,2-dimethyl-1,3-cyclohexadione[5] in 47% overall yield.[6] The ring C precursor **5** was readily synthesized in 8 steps from a 2-decalone in 13% overall yield.[7] With multigram quantities of both A and C ring precursors in hand, we first addressed the C.1-C.2 bond formation. Lithiation of iodoolefin **4** (1.5 equiv.) in degassed THF, followed by the addition of aldehyde **5**, afforded a separable 7:1 mixture of diastereomeric alcohols. Based on the Felkin transition state model[8], we anticipated the major diastereomer to have the desired C.2 stereochemistry, which was later confirmed by X-ray analysis.

We expected that the C.2 alcohol would direct functionalization of the C.1-C.14 olefin from the β-face. Indeed, MCPBA epoxidation, followed by LAH reduction, afforded the diol **7**, whose C.1 oxidation state and stereochemistry corresponded to that of taxol and taxicin I. Alternatively, hydrogenation in the presence of Rh on alumina[9] yielded the alcohol **8**, whose C.1 oxidation state and stereochemistry corresponded to that of taxicin II. In order to avoid reduction of the *tert*-butyldiphenylsilyl protecting group, transformation of **6** to **8** was carried out by a three step protocol (deprotection, reduction, and reprotection).



Scheme 2. i. *t*-BuLi, THF (65%). ii. For the transformation of **6** to **7**, a. MCPBA, CH_2Cl_2 (89%). b. LAH, Et_2O (90%). For the transformation of **6** to **8**, a. TBAF, THF (96%). b. Rh on Al_2O_3, H_2 (76%). c. TBDPSCl, imid., DMF (100%). iii. a. MeI, NaH, DMF (85%). b. *p*-TSA, acetone (94%). c. LDA, THF, MeI (90%). iv. a. KHMDS, THF, $PhNTf_2$ (73%). b. (*n*-Bu_3Sn)(*n*-Bu)$CuCNLi_2$, THF, then I_2 (89%). c. CrO_3-3,5-dimethylpyrazole, CH_2Cl_2 (62%). v. a. TBAF (pH 7), THF (91%). b. Swern oxid. (92%). vi. 1% $NiCl_2/CrCl_2$, DMSO (60%).

Protection of alcohol **8** as its methyl ether, followed by deketalization and installation of the C.18 methyl group provided ketone **9** as a 1:1 mixture of diastereomers. This mixture, although separable, was treated with KHMDS and the resultant enolate quenched with $PhNTf_2$, to afford the corresponding vinyl triflate. Addition of a THF solution of the vinyl triflate to $(n\text{-}Bu_3Sn)(n\text{-}Bu)CuCNLi_2$ in THF[10,11] gave a 1:1 mixture of alkene and vinyltin after work-up. However, when the cuprate reaction was quenched directly with an excess of iodine, the desired iodoolefin was cleanly formed in high yield. Finally, allylic oxidation of the iodoolefin gave the β-iodoenone **10**, without any detectable oxidation of the allylic C.18 methyl group.[12] This procedure reliably provided β-iodoenone **10** from **9** in 40% overall yield.

Using routine synthetic operations, we transformed **10** into the β-iodoenone aldehyde **11** in 84% overall yield. Treatment of a degassed DMSO solution of **11** with 1% $NiCl_2/CrCl_2$ at room temperature afforded a single diastereomer in 55-65% yield. The spectroscopic data (HR-MS, ^1H and ^{13}C NMR, and IR) of the product were consistent with the tricyclic structure **12**. As discussed, we anticipated the resultant C.10 configuration to be in the desired sense, which was supported by nOe experiments.[13] The definitive structure proof of **12** was provided by X-ray analysis. Thus, derivatization of the C.10 allylic alcohol as its *p*-bromobenzoate ester **13**, and recrystallization from a hexanes-methylene chloride bilayer resulted in a single crystal suitable for X-ray diffraction. The X-ray structure (Figure 1) clearly shows that **13** has not only the taxane skeleton, but also the desired configuration at the C.1, C.2, C.3, C.8 and C.10 positions.

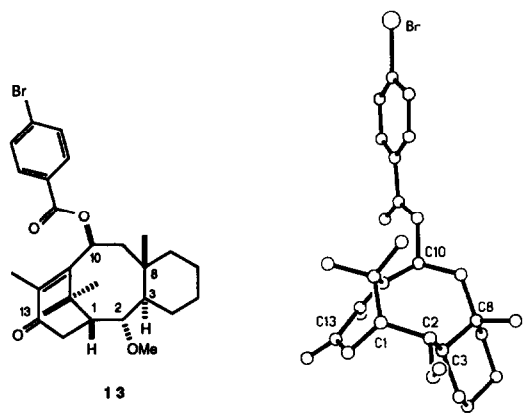


Figure 1. The X-ray structure of *p*-bromobenzoate ester **13** of the cyclization product **12.**

In conclusion, the intramolecular Ni(II)/Cr(II)-mediated coupling reaction has again demonstrated its versatility in the formation of highly functionalized, medium sized ring systems. Further studies will address the application of this coupling reaction to the synthesis of the taxane class of natural products.

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Service Award Training Grant: 5T32GM07598; 1991-1992), Natural Sciences and Engineering Research Council of Canada for a postdoctoral fellowship to R.R. (1991-1992), and Merck Sharp & Dohme for a Merck Postdoctoral Fellowship to R.R. (1990-1991). Michael J. Scott of Professor Holm's group, Harvard University, is gratefully acknowledged for providing the X-ray structure of compound **13**.

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6. The ring A precursor **4** was synthesized from 2,2-dimethyl-1,3-cyclohexanedione in 4 steps: 1. 2,2-dimethyl-1,3-propanediol/CH_2Cl_2/BF_3•Et_2O (74%); 2. 2,4,6-triisopropylsulfonhydrazide/THF/cat. conc. HCl (97%); 3. *n*-BuLi/THF-TMEDA/*n*-Bu_3SnCl (65%); 4. I_2/CH_2Cl_2 (100%).
7. The ring C precursor **5** was synthesized from 3,4,4a,5,6,7,8,8aβ-octahydro-4aα-methyl-2(1H)naphthalenone in 7 steps: 1. TMSI/HMDS (100%; 10:1, Δ^3:Δ^1 TMS enol ether selectivity); 2. O_3/CH_2Cl_2:MeOH/quench with $NaBH_4$/dil. HCl workup; 3. CH_2N_2/Et_2O; 4. TBDPSCl/imid./DMF (28% from TMS enol ether); 5. LAH/Et_2O (79%); 6. *n*-Bu_3P/*o*-$NO_2PhSeCN$/C_6H_6/then Et_3N/MCPBA/CH_2Cl_2 (72%); 7. O_3/CH_2Cl_2:MeOH/then DMS (91%).
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13. Difference nOe experiments were performed on the C.10 acetate in deuterated benzene. Irradiation of C.2 H showed the following enhancements: C.9 $H_{pro\text{-}S}$ (6%), C.1 H (6%), C.16 Me (8.5%), and C.19 Me (5%).

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