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Synthesis of (±)-Brazilin Using IBX

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Abstract

A short synthesis of (±)-brazilin is reported. This synthesis uses several interesting and underutilized transformations including a regioselective dirhodium-catalyzed aryl C–H insertion, a regioselective IBX phenol → *o*-quinone oxidation, a tautomerization of an *o*-quinone to a *p*-quinone methide, and an intramolecular aryl cyclization with a *p*-quinone methide.

The structurally related natural products (+)-brazilin (**1**) and (–)-haematoxylin (**2**)¹ and their reduced counterparts (+)-brazilane (**3**) and haematoxylane (**4**) have been known for some time.² Brazilide A (**5**) has been proposed as the newest constituent of this natural product family.³ Recent efforts culminated in the first enantioselective synthesis of a member of this family, a tris-methylated derivative of **1**.⁴ Compounds **1–5** (Figure 1) are all found in the alcoholic extracts of trees collectively referred to as Brazil wood located in the equator regions.⁵ These ethanolic tinctures were formally used in medicines, but have since found application in the production of dyes and inks. The origins of their pink color resides in the ability of these catechol products to oxidize to their *o*-quinone and tautomeric *p*-quinone methide counterparts. Beyond this redox chemistry, our interest in devising a general synthesis for this family emerged after reading a report on the ability of brazilin (**1**) to serve as a micromolar telomerase inhibitor⁶ and to nick DNA.⁷ These properties are fairly common among anticancer agents. Therefore, we devised a strategy that would enable an asymmetric preparation of **1** by desymmetrization. Herein, we report the successful conclusion of the initial phase of our plan, a racemic synthesis of brazilin (**1**) using *o*-iodoxybenzoic acid (IBX) for *o*-quinone formation followed by tautomerization and a desymmetrizing cyclization.

Our retrosynthetic plan for brazilin (**1**) is depicted in Scheme 1. The brazilin skeleton **6** would emerge from the symmetric *o*-quinone **7** by a tautomerization to the corresponding *p*-quinone methide and an intramolecular aryl cyclization. The *o*-quinone **7** would form upon the oxidation of the phenol **8** using a method developed by our group.⁸ The phenol **8** should appear upon addition of the metal species **10** to the indanone **9**, a ring system that seemed accessible from 3-hydroxy phenyl acetic acid **11** by homologation and aryl C–H insertion.

Some time ago, we revealed the first convenient method for regioselective formation of an *o*-quinone such as **7** from a phenol such as **8** and established the first step of this mechanism to be an intramolecular electrophilic aromatic substitution.⁸ Unlike the Fremy's salt procedure, our IBX procedure proves successful in oxidizing phenols to *o*-quinones even in the absence of a *para* substituent. Our disclosure of this transformation was followed by several publications from others. These included the development of a benzoic acid stabilized and supposedly nonexplosive IBX reagent,⁹ as well as the use of Dess-Martin periodane.¹⁰ In

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Supporting Information Available: Experimental procedures for the five-step sequence [*p*-hydroxyphenylacetic acid → **26** → **9** → **8** → **29** → **1**] (0.24% yield) and more efficient nine-step sequence [**11** → **21** → **24** → **25** → **28** → **8** → **29** → **7** → **6** → **1**] (8.5% yield) and key spectroscopic data for select compounds (**1**, **6–9**, **21–29**, **31–33**) and *o*-quinones. This material is available free of charge via the Internet at <http://pubs.acs.org>.

addition, our method found application in several syntheses.¹¹ We expect that it should enable improved synthetic access to a variety of biologically active catechols, such as those that inhibit protein tyrosine phosphatase 1B,¹² decrease anxiety,¹³ and serve as a 5-HT_{2C} receptor agonists.¹⁴ Given our considerable experience using this reagent for *o*-quinone formation, we were surprised by a recent article reporting low yields and poor selectivity when IBX was applied to the 2,3-dimethylphenol **12** and a tetralin system similar to **14** shown in Scheme 2.¹⁵ Because of our intended strategy for the synthesis of **1**, we paused to consider the cause of these potentially problematic findings. We began by evaluating literature examples of other electrophillic aromatic substitution reactions. As expected, trends in regioselective substitution have been known for some time. Among the most comprehensive and enlightening investigations are studies examining the regiochemistry for bromination¹⁶ and amino-methylation.¹⁷ An abbreviated excerpt from these studies is shown in Scheme 2 for 2,3-dimethyl phenol **12**, 2,3-dihydro-1*H*-inden-5-ol **13**, and 5,6,7,8-tetrahydro-naphthalen-2-ol **14**.

Our results for IBX oxidation of the three skeletons **12–14** are summarized in Scheme 3. Reactions were conducted in deuterated dimethylformamide (0.1 M, 0 °C) and monitored with ¹H NMR using a methylene chloride standard. Oxidation of the phenol **12** results in a 1.0:2.3 ratio of **15:16** in a 63% overall yield after 90 min. The indene skeleton **13** favors the regioisomer **18** over **17** with a 4.4:1.0 ratio and 70% overall yield after 75 min. Of some interest is the oxidation of the tetralin **14**, which favors the regioisomer **19** over **20** in a 3.5:1.0 ratio with a combined yield of 59% after 90 min. However, this reversal of selectivity was expected given the examples of electrophilic aromatic substitution shown in Scheme 2. It should be noted that when reactions were left unattended for lengthier periods of time without in situ reduction to the corresponding catechol, the *o*-quinone products began to decompose at different rates. As the yield decreases, the regiomer ratio can appear to improve or worsen.

With our worries concerning the oxidation of phenol **8** laid to rest, we began our synthesis of brazilin **1** in earnest. Sequential treatment of the 2-(3-hydroxyphenyl)acetic acid **11** (0.07 M in CH₂Cl₂/THF (10:1)) with oxalyl chloride (1.05 equiv), dimethylformamide (0.03 equiv), and diazomethane (2.2 equiv in ether) smoothly affords the phenolic diazoketone **21** in 68% yield. However, acid-promoted cyclization of the diazoketone **21** proved unsatisfactory; trifluoroacetic acid affords the 2,2,2-trifluoroacetate adduct **22** (90% yield) from **21** and a small amount of the 4-hydroxy-1*H*-inden-2(3*H*)-one **9**.¹⁸ On the other hand, addition of boron trifluoride etherate led to unidentified products and a 1:1 mixture of compounds **23** and **9** in a 40% overall yield. We were surprised to find that addition of rhodium acetate (0.02 equiv) to the diazoketone **21** (0.045 M in CH₂Cl₂) exclusively furnishes the more congested 4-hydroxy-1*H*-inden-2(3*H*)-one **23** in a 53% yield.¹⁹ Formation of product **23** suggests to us that the site of cyclization is governed by the unprotected phenol residue. This suspicion was confirmed by subjecting the 3-(methoxymethoxy)phenyl derivative **24**, prepared from **21**, to rhodium acetate for cyclization. The ensuing regioselective cyclization affords the 5-(methoxymethoxy)-1*H*-inden-2(3*H*)-one **25** in 74% yield. The desired indanone skeleton **9** was also prepared by treatment of the diazoketone **26**, derived from 4-hydroxyphenylacetic acid in 71% yield, with rhodium acetate. However, the resulting 28% yield implies that the cyclization suffers without the appropriately positioned and protected oxygen substituent.

Next, we examined nucleophiles in 1,2-addition reactions with the ketones **9** and **25**. The acidity of the methylene residues in the inden-2(3*H*)-ones **9** and **25** was an anticipated problem. Alkylation of the commercially available 3-(ben-zyloxy)phenol with (bromomethyl)-tributylstannane affords the stannane **27**.²⁰ After considerable experimentation, we found that adducts **8** (Scheme 4) and **28** are accessible in yields of 26% and 61%, respectively, by the addition of solid **9** (0.42 equiv) or solid **25** (0.83 equiv) directly to a solution of the lithium species (0.6 M in THF, precooled to -100 °C) derived from addition of *n*-butyllithium to the stannane **27**.

Although the former sequence precludes protection and deprotection, we chose the latter. Compound **28** undergoes quantitative deprotection to phenol **8** (MeOH, concentrated HCl). Oxidation of the phenol **8** (0.03 M in DMF, room temperature) with IBX (1.05 equiv) affords the *o*-quinone **7** in 67% yield as determined by ¹H NMR. Inspection of the crude ¹H NMR spectrum reveals an 84% yield of a 4:1 ratio of **7** and what we tentatively assign as the regiomer *o*-quinone. However, over 1–2 h the undesired material succumbs to selective destruction most likely through polymerization. After 2 h, in situ reduction of the crude reaction mixture with sodium hydrosulfite (3 equiv) affords the benzylated catechol **29** in 58% isolated yield without contamination by the corresponding regiomer catechol. After chromatography, the *o*-quinone **7** can be reformulated by oxidation (0.03 M in THF) with bis-trifluoroacetate-phenyliodine (PIFA, 1.00 equiv)²¹ or by oxidation (0.03 M in DMSO) with silver oxide (5 equiv). Without further purification, the *o*-quinone **7** (0.03 M in THF) is readily trapped through a 1,6-conjugate addition with phenyl thiol (1.05 equiv) to produce the isolable catechol (±)-**31** in 91% yield from **29**, thereby confirming the identity of the transitory intermediate.

The *o*-quinone **7** (0.03 M in THF) suffers tautomerization upon the addition of Hünig's base (1.0 equiv) to afford the thermodynamically more stable *p*-quinone methide (±)-**30**.²² The existence of (±)-**30** was substantiated by ¹H NMR and by isolation of its thioether adduct (±)-**32**, which emerges as a single diastereomer in 81% from **29**. In the absence of a thiol or other nucleophile, the *p*-quinone methide (±)-**30** undergoes cyclization to produce the tetracycle (±)-**6** in 41% overall yield from **29** (70% BORSM **29**). Lithium iodide appears to catalyze the cyclization processes. Subsequent hydrogenolysis of the benzyl ether **6** (0.01 M in EtOAc), 1 atm H₂, Pd/C affords synthetic (±)-brazilin (**1**), identical in every respect with the known natural product. We were surprised to find that (±)-brazilin (**1**) also forms in an 8% yield when the catechol **29** is subjected to hydrogenolysis (0.01 M in EtOAc/EtOH (1:1), 1 atm H₂, Pd/C). This transformation most likely proceeds through similar quinone intermediates. As yet, we are unable to improve the yield of brazilin (**1**) in this one-pot oxidation-tautomerization-cyclization-hydrogenolysis process.

In conclusion, we have disclosed a unique route to a useful class of compounds. During this endeavor, we have employed several unusual and underutilized methods for constructing catechols, *o*-quinones, and *p*-quinone methides. While most syntheses of brazilin (**1**) have stopped at the corresponding tris-methylated derivative, ours does not and so it appears well positioned to address the entire family of natural products in their unprotected form. With access to sizable amounts of these compounds and their analogues, it should be possible to determine the process by which this family inhibits telomerase activity, as well as the mechanism by which compound **1** nicks the telomeric region of DNA. These insights should enable the development of a second series of more potent compounds. Last, it should be noted that during the tautomerization process, the achiral compound **7** becomes the *chiral* compound (±)-**30**. This transformation seems irreversible, which suggests a process for the enantioselective synthesis of brazilin (**1**) and its derivatives through desymmetrization. Our findings in these studies and their application toward (±)-brazilide (**5**) will be reported in due course.

Acknowledgements

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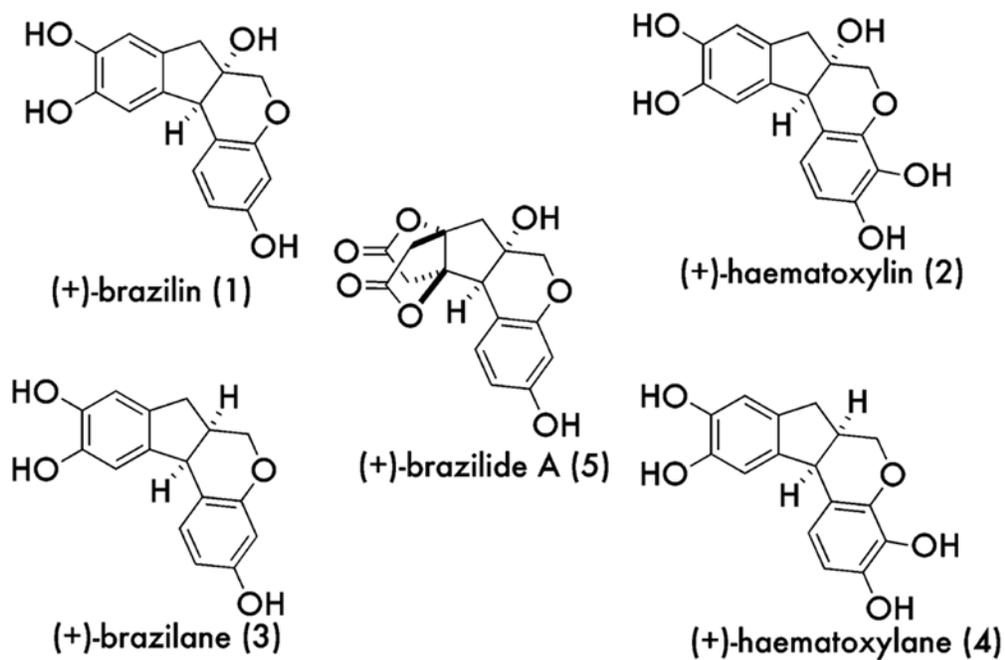
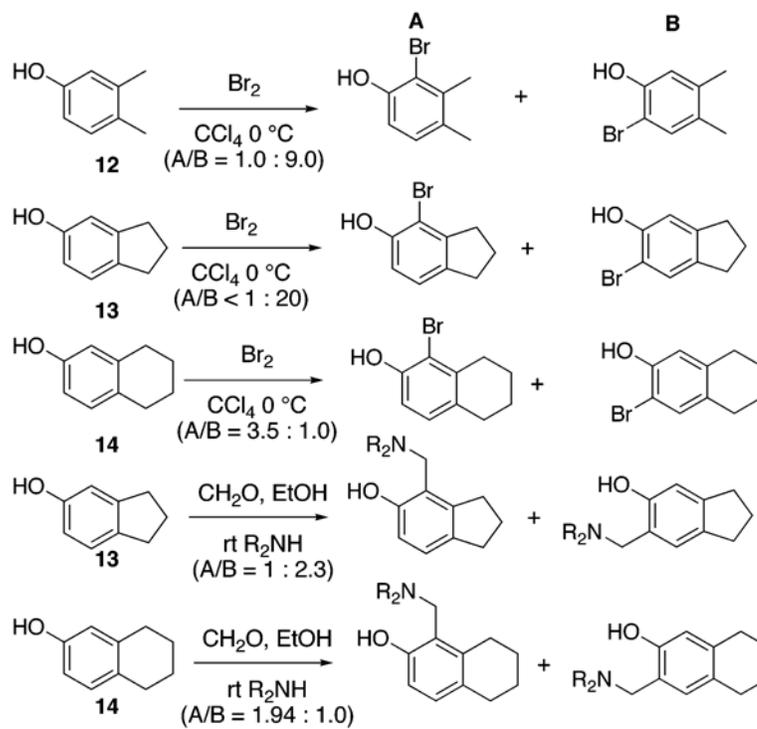
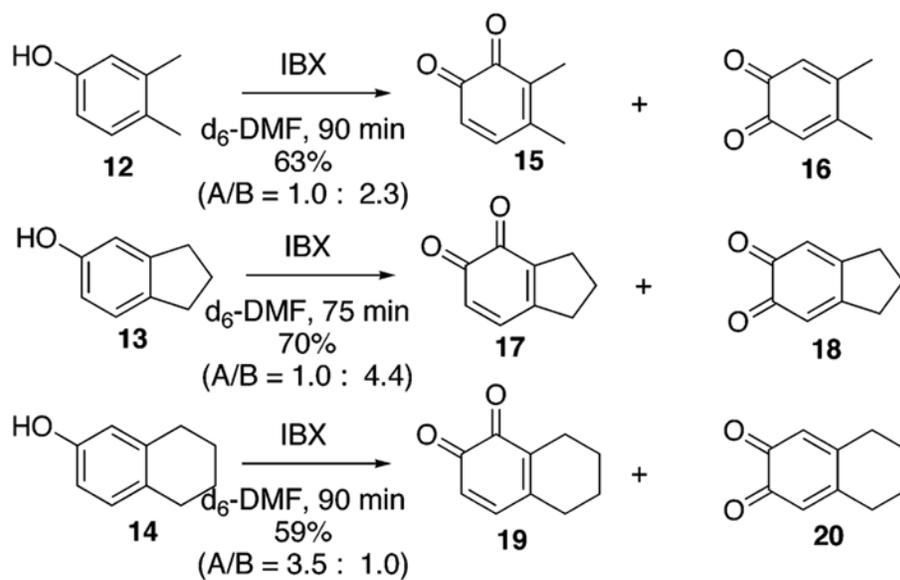


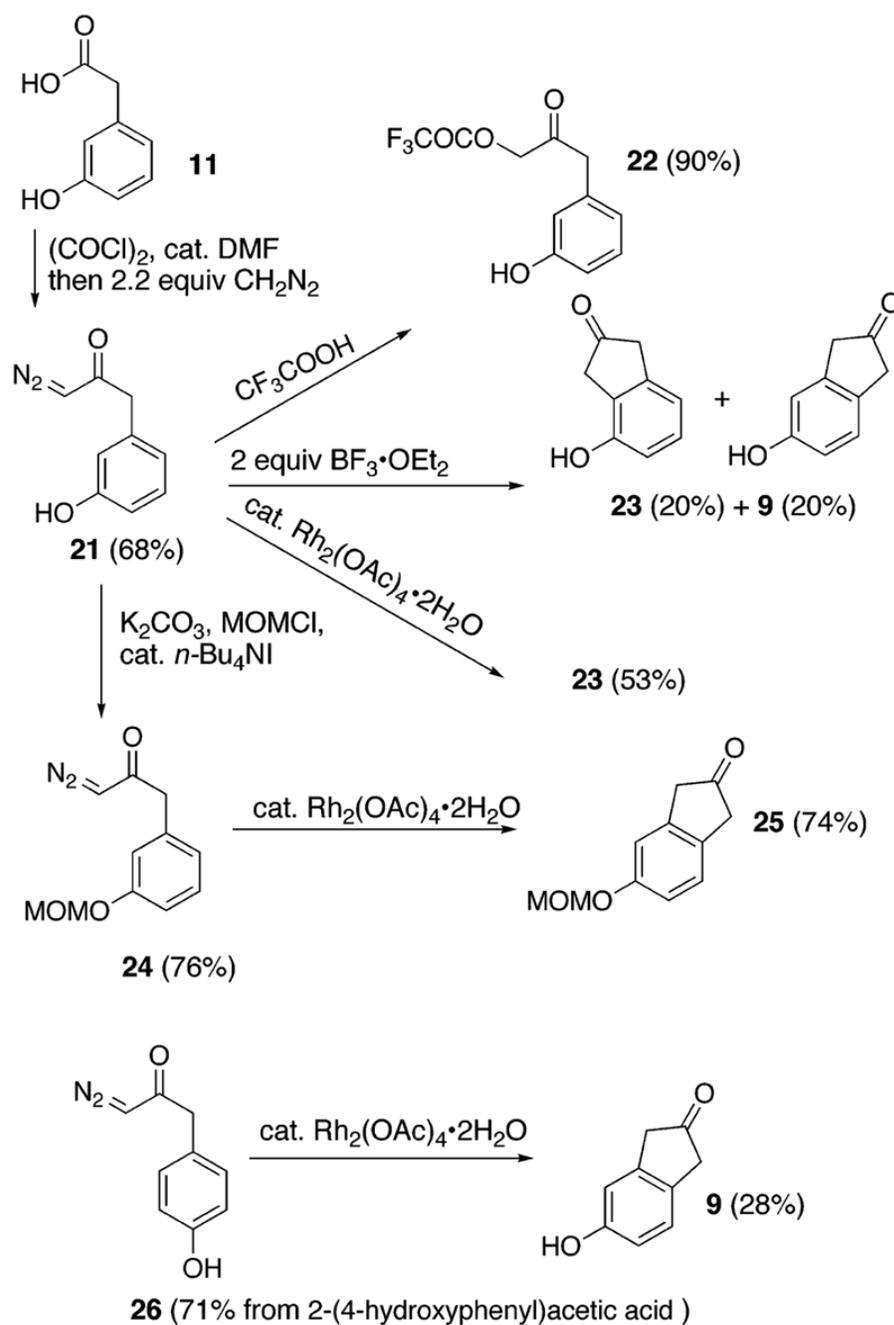
Figure 1.
Brazilin family of natural products.



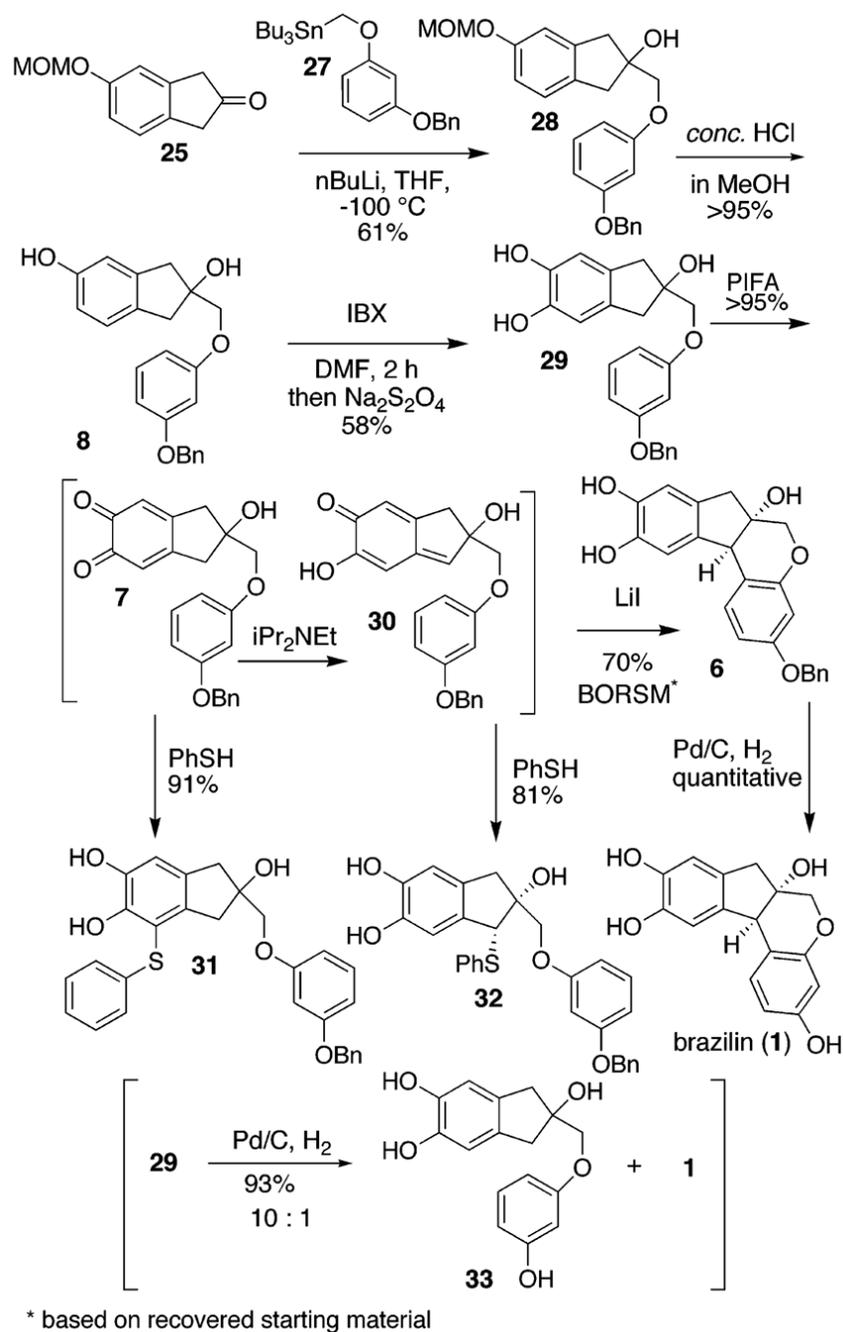
Scheme 2.
Some Literature Examples of Regioselective Electrophilic Aromatic Substitutions



Scheme 3.
Regioselective Oxidations of **12–14** with IBX



Scheme 4.
 Synthesis of Indenones and Unusual Proximity Effects of Phenols; Comparison of H^+ - and Rh^{2+} -Promoted Cyclizations



Scheme 5.
o-Quinone Formation, Reduction, Tautomerization, 1,4-Conjugate Addition, and Cyclization