Sonogashira Coupling of 2-Iodo-2-cycloalkenones: Synthesis of (+)- and (−)-Harveynone and (−)-Tricholomenyn A

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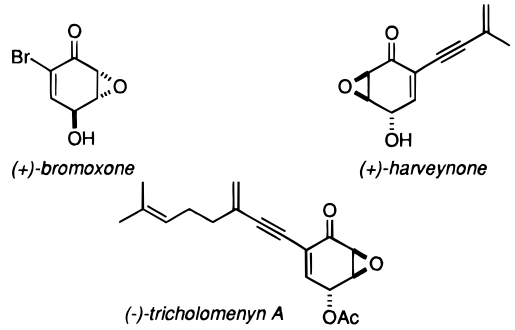
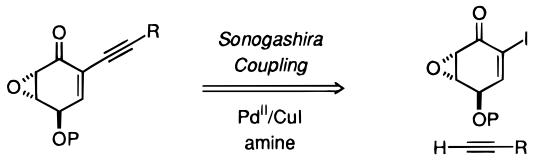
Our laboratory has been involved with the production of enantiopure, densely functionalized, bioactive targets.[2] Our strategy has involved the tandem use of biocatalysis as a method for the introduction of absolute stereochemistry[3] and transition metal catalysis as a tool for the elaboration of the enantiopure intermediates.[4] Recently, we initiated a program along these lines utilizing *p*-benzoquinone as a starting material and the bioactive, epoxyquinol natural products as targets. This preliminary study resulted in the first synthesis of enantiomerically pure (+)- and (−)-bromoxone (Chart 1).[5a] We have directed our attention toward the epoxyquinol natural products containing an acetylenic side chain at the 2-position, typified by (+)-harveynone and (−)-tricholomenyn A (Chart 1). (+)-Harveynone was isolated from *Pestalotiopsis theae* and was shown to be a phytotoxin.[6a] Its enantiomer, (−)-harveynone, was isolated from *Curvularia harveyi* and was found to possess antitumor activity (inhibitor of spindle formation).[6b,c] More recently, (−)-tricholomenyn A was isolated from *Tricholoma acerbum* and was reported to display antimitotic activity.[6d]

Near the completion of our studies, Kamikubo and Ogasawara described the synthesis of (−)-tricholomenyn A[7a] and Taylor and co-workers reported the synthesis of (±)-harveynone.[7b] In these studies, both Ogasawara[7a] and Taylor[7b] utilized a Stille coupling of a tin acetylide with a 2-iodo-2-cyclohexenone. Both reported that attempted Sonogashira coupling between the functionalized 2-iodo-2-cyclohexenone and the appropriate terminal acetylene failed to give the desired coupled product. In light of these reports, we describe below our entry into this class of epoxyquinol natural products utilizing as a key step a Sonogashira coupling of a 2-iodo-2-cycloalkenone with a terminal acetylene (Scheme 1).[8]

Chart 1



Scheme 1



Our first objective was to find optimal conditions for the Sonogashira coupling of a 2-iodo-2-cycloalkenone with a terminal acetylene.[9] The optimal conditions were found to be the presence of $PdCl_2(PPh_3)_2$, CuI, and diisopropylamine in THF at 0 °C (Table 1). The reaction was found to be complete within 25−45 min under these conditions. Five-, six-, and seven-membered ring 2-iodo-2-cycloalkenones gave good yields of the desired coupled product (74−97%). Oxygenated functionality did not affect the efficiency of the reaction (*i.e.*, **5**−**8**).

At this stage, we utilized technology we had developed in our bromoxone study (Scheme 2).[5a] The dibromide (+)-**9**, obtained in two steps from an enzymatically resolved diol, was converted into the allylic alcohol (+)-**10** in 81% yield (Zn/refluxing MeOH). The allylic alcohol (+)-**10** was oxidized (PCC) to the enone (+)-**11** in 82% yield. Iodination of the enone (+)-**11** (I_2/pyridine/CCl_4) furnished the iodoenone (+)-**12** in 77% yield.[10,11] Lastly, deprotection of the TBS ether (+)-**12** was accomplished utilizing DeShong's protocol (H_2SiF_6/CH_3CN)[12] which provided the alcohol (+)-iodoxone (**13**) in 86% yield ($[\alpha]_D$ +96.1 (*c* 0.95, acetone). In an analogous fashion, (-)-**9** was converted into (−)-iodoxone [(−)-**13**] ($[\alpha]_D$ −94.3 (*c* 0.70, acetone);[13] (+)- and (−)-iodoxone (**13**) were found to be ≥99% ee by chiral HPLC analysis.[14]

(1) Current address: Schering-Plough Research Institute, Kenilworth, NJ 07033.

(2) Johnson, C. R.; Adams, J. P.; Bis, S. J.; DeJong, R. L.; Golebiowski, A.; Medich, J. R.; Penning, T. D.; Senanayake, C. H.; Steensma, D. H.; Van Zandt, M. C. *Pure Appl. Chem.* **1992**, *64*, 1115.

(3) Enzymatic asymmetrization: Johnson, C. R.; Harikrishnan, L. S.; Golebiowski, A. *Tetrahedron Lett.* **1994**, *35*, 7735. Enzymatic resolution: Johnson, C. R.; Sakaguchi, H. *Synlett* **1992**, 813. Sundram, H.; Golebiowski, A.; Johnson, C. R. *Tetrahedron Lett.* **1994**, *35*, 6975.

(4) Suzuki coupling of a 2-iodo-2-cyclopentenone: (a) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* 1**993**, *115*, 11014. Stille coupling of 2-iodo-2-cycloalkenones: (b) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 919.

(5) (a) Johnson, C. R.; Miller, M. W. *J. Org. Chem.* **1995**, *60*, 6674. For a synthesis of (±)-bromoxone see: (b) Gautier, E. C. L.; Lewis, N. J.; McKillop, A.; Taylor, R. J. K. *Tetrahedron Lett.* **1994**, *35*, 8759.

(6) (a) Nagata, T.; Ando, Y.; Hirota, A. *Biosci. Biotech. Biochem.* **1992**, *56*, 8**10**. (b) Kawazi, K.; Kobayashi, A.; Oe, K. JP 03 41,075, 1991; *Chem. Abstr.* **1991**, *115*, 181517k. (c) Kobayashi, A.; Ooe, K.; Yata, S.; Kawazu, K. *Symposium of Papers*, the 31st Symposium on the Chemistry of Natural Products, Nagoya, October 1989, pp 388−395. (d) Garlaschelli, L.; Magistrali, E.; Vidari, G.; Zuffardi, O. *Tetrahedron Lett.* **1995**, *36*, 5633.

(7) (a) Kamikubo, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1996**, 1679. (b) Graham, A. E.; McKerrecher, D.; Huw Davies, D.; Taylor, R. J. K. *Tetrahedron Lett.* **1996**, *37*, 7445.

(8) Taylor[7b] examined a range of successful Sonagashira couplings with isomeric 3-iodo-2-cyclohexenones. The epoxyquinol products are very base sensitive, and in our hands it was found necessary to carefully remove all traces of amine promoters by extraction with cold aqueous 1 M HCl. Experimental details are not available in ref 7a,b; it is possible that their failures are attributable to workup conditions. The Sonogashira coupling reactions we examined proceeded faster with diisopropylamine than with triethylamine.

(9) For one example of a successful Sonogashira coupling between a 2-bromo-2-cycloalkenone (2-bromo-2-cyclopentenone/THF/60 °C) see: Buszek, K. R.; Jeong, Y. *Synth. Commun.* **1994**, *24*, 2461. For a recent review of the Sonogashira reaction see: Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proc.* **1995**, *27*, 129.

(10) Kamikubo and Ogasawara utilized the enantiomeric enones (−)-**11** and (−)-**12** in their synthesis of tricholomenyn A.[7a] Their synthesis of the enone (−)-**11** is quite different from ours.

(11) For α-iodination of enones see: Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 917.

(12) Pilcher, A. S.; Hill, D. K.; Shimshock, S. J.; Waltermire, R. E.; DeShong, P. *J. Org. Chem.* **1992**, *57*, 2492.

(13) These are interesting analogues of the natural product (+)-bromoxone (ref 5). For a synthesis of (±)-**13** see ref 7b.

(14) Chiralcel OB: elution with *i*-PrOH/hexanes (15/85); 0.5 mL/min; 260 nm; 20 min (+)-**13**; 33 min (−)-**13**.

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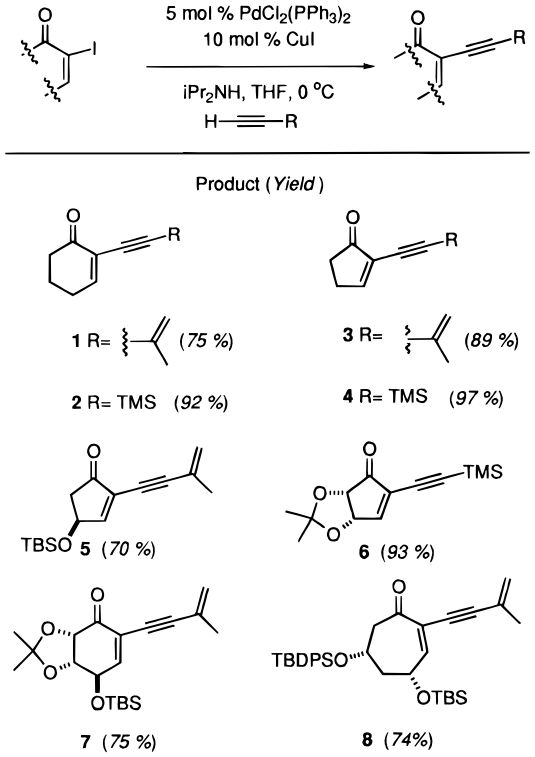
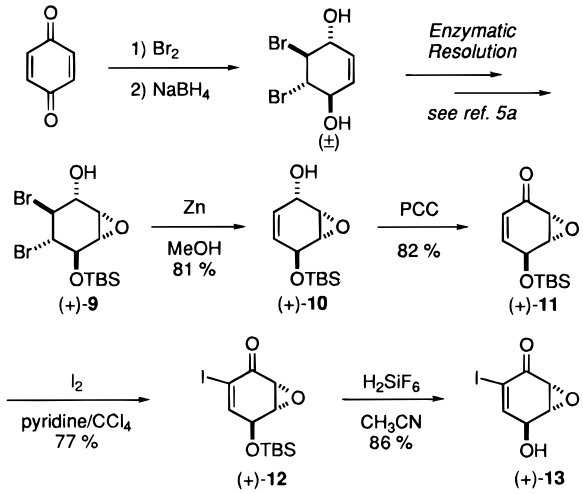
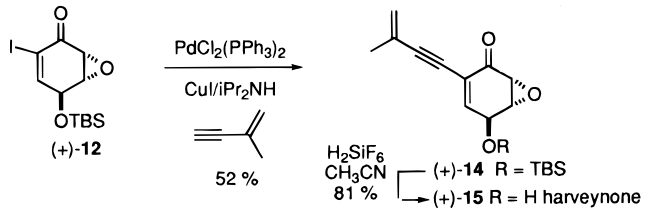
Table 1. Sonogashira Coupling with 2-Iodocycloalkenones



Scheme 2

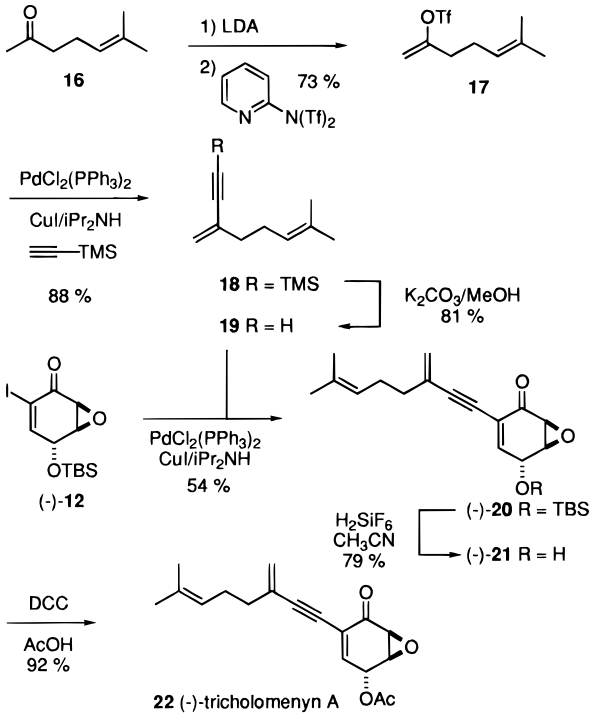


Scheme 3



The TBS ether (+)-**12** and 2-methyl-1-buten-3-yne were subjected to Sonogashira coupling ($PdCl_2(PPh_3)_2$/CuI/*i*-Pr_2NH) to provide enyne (+)-**14** in 52% yield (Scheme 3). The TBS ether (+)-**14** was deprotected (H_2SiF_6/CH_3CN), which furnished (+)-harveynone (**15**) in 81% yield. The data for synthetic (+)-**15** correspond well with those reported for natural (+)-**15**.[6a] In an analogous fashion, (−)-harveynone ($[\alpha]_D$ −208 (*c* 0.45, MeOH)) was prepared from (−)-**9**.[6b,c] Furthermore, (+) and (−)-harveynone were found to be ≥99% ee by chiral HPLC analysis.[15]

Scheme 4



For the synthesis of (−)-tricholomenyn A, the side chain **19** was assembled (Scheme 4).[7a] The commercially available ketone, 6-methyl-5-hepten-2-one (**16**), was converted into the vinyl triflate **17** using Comins' triflimide in 73% yield.[16] The vinyl triflate **17** was converted into the TMS enyne **18** in 88% yield (Sonogashira coupling). The TMS group in **18** was removed (K_2CO_3/MeOH), which gave the volatile enyne **19** in 81% yield. The iodo enone (−)-**12** and enyne **19** gave, after Sonogashira coupling ($PdCl_2(PPh_3)_2$/CuI/*i*-Pr_2NH), the functionalized enone (−)-**20** in 54% yield. The TBS ether was removed in (−)-**20** under the standard conditions (H_2SiF_6/CH_3CN) to furnish the allylic alcohol (−)-**21** in 79% yield. Lastly, conversion of the alcohol (−)-**21** into (−)-tricholomenyn A (**22**) proceeded in 92% yield (DCC/AcOH). The data for synthetic (−)-tricholomenyn A (**22**) agreed well with that reported for natural (−)-**22**.[6d] The synthetic (−)-tricholomenyn A was shown to be ≥99% ee by chiral HPLC analysis.[17] Thus, the synthesis of (−)-tricholomenyn A (**22**) and (+)- and (−)-harveynone (**15**) from intermediates of known, absolute stereochemistry have further corroborated their assignment.[6a,d,7a]

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Supporting Information Available: Experimental procedures, compound characterization data including chiral HPLC data, and ^1H and ^{13}C NMR spectra of compounds **1**−**8**, **10**−**15**, and **17**−**22** (51 pages).

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(15) Chiralcel OB: elution with *i*-PrOH/hexanes (5/95); 0.5 mL/min; 260 nm; 39 min (−)-**15** min; 47 min (+)-**15**.
(16) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.
(17) Chiralcel OB: elution with *i*-PrOH/hexanes (5/95); 0.5 mL/min; 260 nm; 23 min (−)-**22** min; 40 min (+)-**22**.