Pergamon

Tetrahedron Letters, Vol. 37, No. 41, pp. 7445-7448, 1996
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0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01607-3

Sonogashira Coupling Reactions of Highly Oxygenated Vinyl Halides: The First Synthesis of Harveynone and *epi*-Harveynone

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Abstract: Sonogashira coupling reactions of highly functionalised cyclohexenyl halides have been developed and utilised to prepare the naturally-occurring anti-cancer agent harveynone and its C-4 epimer.
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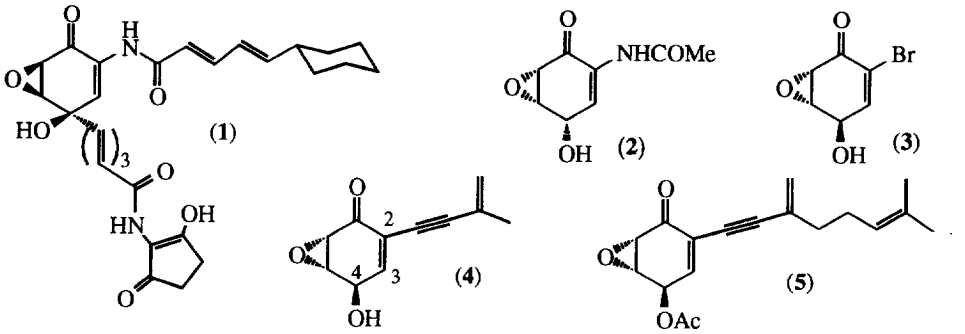
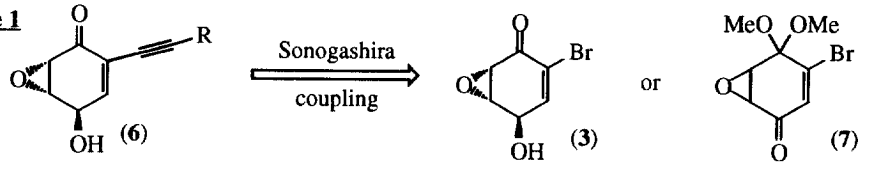
We have a continuing synthetic interest in highly oxygenated bioactive cyclohexanes.[1] Recent research has centred on epoxycyclohexenone natural products such as alisamycin (**1**),[2] LL-C10037α (**2**),[3] and bromoxone (**3**).[4] A number of naturally occurring epoxycyclohexenones are known which possess a carbon substituent at C-2 (*i.e.* α–to the carbonyl group).[5-8] Of particular interest were the newly discovered acetylenic derivatives harveynone (**4**)[6,7] and tricholomenyn A (**5**),[8] both of which have interesting anti-cancer properties.



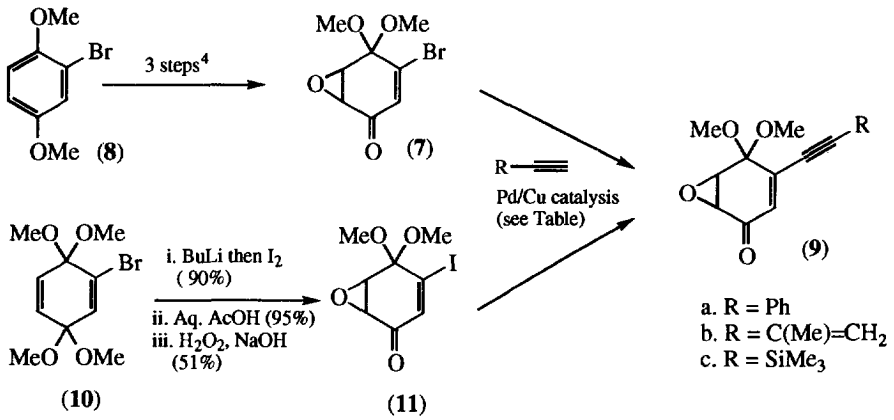
Harveynone was isolated from *Curvularia harveyi* and shown to possess anti-cancer properties[6] (as an inhibitor of spindle formation[7]). Detailed NMR data were obtained to establish the structure of harveynone although its relative stereochemistry was not determined. However, a compound reported to be the enantiomer of harveynone was later isolated from the tea gray blight fungus *Pestalotiopsis theae,* and the *trans*-relationship between the alcohol and epoxide assigned, primarily on the basis of NMR coupling constants ($J_{3,4}$ = 4.9 Hz).[7] Tricholomenyn A (**5**), which possesses anti-mitotic properties, also has the hydroxyl and epoxy units in a *trans*-orientation but has a geranyl acetylenic side chain in place of the C_5 side chain of harveynone.[8]

Scheme 1



We decided to extend the bromoxone methodology[4] in order to develop a general synthetic route for the preparation of harveynone, tricholomenyn A and related compounds; Sonogashira acetylenic coupling[9] seemed to be the ideal procedure for introducing the alkyne substituent (Scheme 1). A literature review indicated that bromoxone (**3**) was unlikely to be a suitable Sonogashira substrate[10] and so intermediates from the bromoxone synthesis were considered. Bromide (**7**)[4] was chosen for further study as the β–bromoenone structure seemed likely to facilitate Sonogashira displacement. Preliminary results are shown in Scheme 2.[11]

Scheme 2



The commercially available 1-bromo-2,5-dimethoxybenzene (**8**) was converted into epoxide (**7**) using the published procedure.[4,12] However, Sonogashira coupling reactions of (**7**) using commercially available phenylacetylene and 2-methyl-1-buten-3-yne were extremely slow and proceeded in disappointing yields (Table). Using standard conditions[9] with bis(triphenylphosphine)palladium(II) chloride or palladium(II) acetate/ triphenylphosphine as catalyst, triethylamine or diisopropylamine (DIPA) as base, and DMF or THF as solvent, the maximum yield of (**9**) was 41%. We therefore prepared the corresponding iodide (**11**) from (**10**),[13] using the sequence shown in Scheme 2, and investigated its coupling reactions (Table).

Table[a]

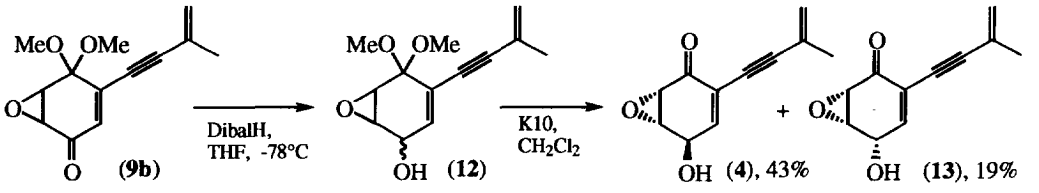
Substrate	Acetylene	Base	Catalyst	Solvent	Time(h)	Yield (%)
7	PhC≡CH	Et_3N	$PdCl_2(PPh_3)_2$	THF	48	**9a**, 35
7	PhC≡CH	DIPA	$PdCl_2(PPh_3)_2$	THF	24	**9a**, 31
7	CH_2=C(Me)C≡CH	DIPA	$PdCl_2(PPh_3)_2$	THF	18	**9b**, 38
7	CH_2=C(Me)C≡CH	DIPA	$PdCl_2(PPh_3)_2$	DMF	12	**9b**, 41
7	CH_2=C(Me)C≡CH	DIPA	$Pd(OAc)_2$/2 PPh_3	THF	18	**9b**, 41
11	Me_3SiC≡CH	Et_3N	$Pd(OAc)_2$[b]	MeCN[b]	1.5	**9c**, 68
11	CH_2=C(Me)C≡CH	Et_3N	$Pd(OAc)_2$[b]	MeCN[b]	3	**9b**, 62

[a]0.3 - 3.0 mmol of substrate, 5 mol % each of CuI and Pd salt, room temperature (RT).
[b]Similar yields were obtained using THF as solvent with or without the addition of PPh_3.

Reaction of iodide (**11**), under similar conditions to those described previously, proceeded more efficiently, and much more quickly, to give adducts (**9b**) and (**9c**) in reasonable yields. The use of iodide (**11**) rather than bromide (**7**) in the Sonogashira coupling reactions is therefore preferred. A further benefit of this approach is that iodide (**11**) is a stable crystalline compound which can be stored for several months without noticeable decomposition.

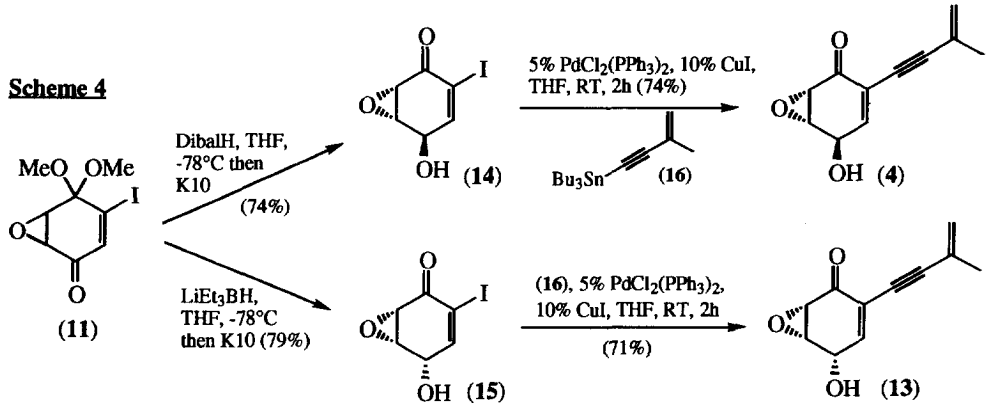
With alkyne (**9b**) in hand we were able to complete the first synthesis of (±)-harveynone (**4**) (Scheme 3). Thus, DibalH reduction followed by acetal removal from (**12**) using Montmorillonite K10[14] produced a mixture of (**4**) and its C-4 epimer (**13**) which were separable by silica chromatography. This sequence produced harveynone in 43% overall yield with the epimer in 19%. The selectivity in favour of the *trans*-isomer (**4**) using DibalH was expected by analogy to earlier studies.[4] Comparison of ^{1}H NMR and ^{13}C NMR data[15] with published values[6,7] confirmed that the major product was harveynone (**4**). In addition, comparison of the ^{1}H NMR spectra of (**4**) and (**13**) with related examples in the literature[3-8] provided unambiguous confirmation of the *trans*-orientation of substituents in harveynone; the coupling constants of H-3 are diagnostic showing a doublet of doublets for (**4**) (*J* 5.1, 2.4 Hz) but an apparent triplet for (**13**) (*J* 2.7 Hz).

Scheme 3



With this success we returned to the original idea of producing harveynone by coupling to a fully elaborated nucleus. This approach is attractive for the preparation of novel analogues. As direct coupling to bromoxone seemed potentially problematic[10] we decided to investigate coupling reactions of the corresponding iodide (Scheme 4). Reduction of iodoenone (**11**) using sodium borohydride in methanol, followed by acetal removal, gave a 1:1 mixture of epimeric alcohols (**14**) and (**15**). As expected,[4] it proved possible to control the stereoselectivity by judicious choice of reducing agent: DibalH in THF gave, after acetal removal, the *trans*-alcohol (**14**) with little, if any, of the epimer (**15**) present, according to high field NMR spectroscopy, whereas superhydride gave the opposite stereoselectivity.

Scheme 4



Thus, with iodide (**11**), complete stereoselectivity for the *trans*- or *cis*-hydroxy epoxides is possible simply by changing the reductant. This contrasts to the reduction of bromide (**7**)[4] and alkyne (**9b**). Compound (**14**), a stable crystalline solid, is the iodo analogue of the natural product bromoxone (**3**). Sonogashira coupling between (**14**) and 2-methyl-1-buten-3-yne under a range of conditions again failed to give the required adduct. We therefore turned to the Stille alkynylstannane modification[16] which has been used with great success by Johnson's group.[17] Palladium/copper catalysed coupling of (**14**) with stannylated alkyne (**16**), under extremely mild conditions, gave (±)-harveynone (**4**) in 74% isolated yield as shown in Scheme 4. In a similar manner, the epimeric alcohol (**15**) gave (±)-4-*epi*-harveynone (**13**) in 71% yield.

We are currently applying this methodology to the synthesis of novel harveynone analogues and tricholomenyn A.[18]

Acknowledgements

We are grateful to the EPSRC for the award of a Postdoctoral Research Assistantship (AEG) and a CASE studentship (DMcK). We also thank Zeneca Pharmaceuticals (Alderley Park, UK) for their contributions to the CASE studentship.

References and Notes

1. McKillop, A.; McLaren, L.; Watson, R. J.; Taylor, R. J. K.; Lewis, N. *Tetrahedron Lett.* **1993**, *34*, 5519; Montana, J. G.; Phillipson, N.; Taylor, R. J. K. *Chem. Commun.* **1994**, 2289; Guo, Z. X.; Haines, A. H.; Taylor, R. J. K. *Synlett.* **1993**, 607; Guo, Z. X.; Haines, A. H.; Pyke, S. M.; Pyke, S. G.; Taylor, R. J. K. *Carbohydrate Research* **1994**, *264*, 147.
2. Alcaraz, L.; Macdonald, G. J.; Kapfer, I.; Lewis, N.; Taylor, R. J. K. *Tetrahedron Lett.* In press.
3. Kapfer, I.; Lewis, N. J.; Macdonald, G.; Taylor, R. J. K. *Tetrahedron Lett.* **1996**, *37*, 2101.
4. Gautier, E. C. L.; Lewis, N. J.; McKillop, A.; Taylor, R. J. K. *Tetrahedron Lett.* **1994**, *35*, 8759.
5. Kamikubo, T.; Hiroya, K.; Ogasawara, K. *Tetrahedron Lett.* **1996**, *37*, 499 and references therein.
6. Kawazu, K.; Kobayashi, A.; Oe, K. *JP* **1991**, 03 41, 075 (*Chem. Abstr.* **1991**, *115*, 181517k).
7. Nagata, T.; Ando, Y.; Hirrota, A. *Biosci. Biotech. Biochem.* **1992**, *56*, 810.
8. Garlaschelli, L.; Magistrali, E.; Vidari, G.; Zuffardi, O. *Tetrahedron Lett.* **1995**, *36*, 5633.
9. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467; For recent reviews see Campbell, I. B., Ch. 10 in *Organocopper Reagents; A Practical Approach*, Ed. Taylor, R. J. K., Oxford University Press, Oxford, 1994; Sonogashira, K., Ch. 2.4 in *Comprehensive Organic Synthesis*, Vol. 3, Eds. Trost, B. M., Fleming, I., Pergamon, Oxford, 1991.
10. Comins, D. L.; Joseph, S. P.; Chen, X. *Tetrahedron Lett.* **1995**, *36*, 9141 and references therein.
11. All new compounds were fully characterised by high field ^{1}H- and ^{13}C-NMR spectroscopy and by elemental analysis or high resolution mass spectrometry.
12. The first two steps of the published procedure[4] could be carried out on 50-100 g quantities but the final epoxidation gave disappointing yields on a larger scale (2 g, 46%; 10 g, 27%).
13. Preparation of (**10**): Manning, M. J.; Raynolds, P. W.; Swenton, J. S. *J. Amer. Chem. Soc.* **1976**, *98*, 5008 (see also Gautier, E. C. L.; Lewis, N. J.; McKillop, A.; Taylor, R. J. K. *Synth. Commun.* **1994**, *24*, 2989. Lithiation of (**10**): Chenard, B. L.; Manning, M. J.; Raynolds, P. W.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 378.
14. *Encyclopedia of Reagents for Organic Synthesis* (p. 3667), Ed. Paquette, L. A., Wiley, Chichester, 1995. The use of this reagent for acetal deprotection has apparently not been described; we are currently investigating this process: Graham, A. E.; McKerrecher, D.; Taylor, R. J. K., Unpublished results.
15. δ_H ($CDCl_3$) 1.93 (3H, br s, Me), 2.56 (1H, d, *J* 8.7, OH), 3.59 (1H, dd, *J* 1.0, 3.6, H-6), 3.82 (1H, ddd, *J* 1.2, 2.4, 3.6, H-5), 4.74 (1H, m, H-4), 5.34 and 5.42 (each 1H, br d, *J* 1.7, $=CH_2$), 6.84 (1H, dd, *J* 2.4, 4.9, H-3); δ_C (C_6D_6) 23.0, 53.6, 57.5, 63.2, 82.6, 95.9, 122.85, 123.8, 126.6, 146.0, 190.4; literature[6] 23.0, 53.4, 57.3, 63.1, 82.6, 95.9, 123.0, 123.7, 126.6, 145.4, 189.8.
16. Stille, J. K.; Simpson, J. H. *J. Amer. Chem. Soc.* **1987**, *109*, 2138.
17. Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 919; see also Johnson, C. R.; Adams, J. P.; Collins, M. A. *J. Chem. Soc., Perkin Trans. I* **1993**, 1 and Bosse, F.; Tunoori, A. R.; Niestroj, A. J.; Gronwald, O.; Maier, M. E. *Tetrahedron* **1996**, *52*, 9485.
18. After the completion of this manuscript the total synthesis of trichlolomenyn A was published using similar chemistry to that described above: Kamikubo, T.; Ogasawara, K. *Chem. Commun.* **1996**, 1679.

(*Received in UK* 26 *July* 1996; *revised* 9 *August* 1996; *accepted* 15 *August* 1996)