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Novel Phosphorus Radical-Based Routes to Horsfiline

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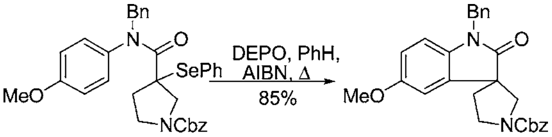
ABSTRACT



Radicals derived from the phosphorus reagents, ethylpiperidine hypophosphite (EPHP) and diethylphosphine oxide (DEPO), are used in two related approaches to synthesis of the alkaloid horsfiline (1). In particular, DEPO proves beneficial for effecting cyclizations at 80 °C that are difficult or impossible with Bu_3SnH.

Horsfiline **1** is a member of the spiropyrrolidinyloxindole family of alkaloids and was first isolated[1] by Bodo et al. from the roots of *Horsfieldia superba*, a small tree native to Malaysia. The spiropyrrolidinyloxindole molecules, and particularly horsfiline, have been popular targets for synthesis with quite a variety of approaches being recorded.[2]

These and related molecules are of interest in relation to cancer treatment. The findings[3] of Danishefsky et al. are particularly interesting in this regard; they tested compounds **3** and **4** (both diastereomers) (Figure 1) and reported significant activity against human breast cancer cells.

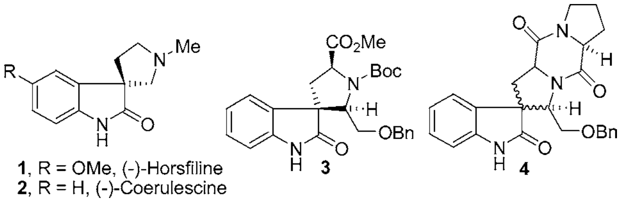


Figure 1. Natural and synthetic spiropyrrolidinoxindoles.

The two diastereoisomers **4**, differing in the configuration at the spiro-center, are equally active against the quoted cell line, suggesting either different mechanisms of action or an insensitivity to stereochemical configuration at this center. Compound **3** bears only the three basic rings of the spiropyrrolidinoindolones that are present in horsfiline (**1**) and coerulescine (**2**). Accordingly, new synthetic approaches to spiropyrrolidinoindolones are welcome.

In defining our new approach to horsfiline, we were attracted by the possibility of using a 1,5-hydrogen atom translocation (1,5-HAT) as the key step,[4] starting from **5** (X = I or Br) (Scheme 1).

Beckwith and Storey had already studied[5] the preparation of oxindoles, including **7** [R, R′ = $(CH_2)_n$, n = 2−5] by

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(1) Jossang, A.; Jossang, P.; Hadi, A.; Sevenet, T.; Bodo, B. *J. Org. Chem.* **1991**, *56*, 6527.

(2) (a) Jones, K.; Wilkinson, J. *J. Chem. Soc., Chem. Commun.* **1992**, 1767. (b) Pellegrini, C.; Strässler, C.; Weber, M.; Borschberg, H.-J. *Tetrahedron: Asymmetry* **1994**, *5*, 1979. (c) Bascop, S.-I.; Sapi, J.; Laronze, J.-Y.; Levy, J. *Heterocycles* **1994**, *38*, 725. (d) Palmisano, G.; Annunziata, R.; Papeo, G.; Sisti, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1. (e) Lakshmaiah, G.; Kawabata, T.; Shang, M.; Fuji, K. *J. Org. Chem.* **1999**, *64*, 1699. (f) Fischer, C.; Meyers, C.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 1175. (g) Kumar, U. K. S.; Ila, H.; Junjappa, H. *Org. Lett.* **2001**, *3*, 4193. (h) Lizos, D.; Tripoli, R.; Murphy, J. A. *Chem. Commun.* **2001**, 2732. (i) Selvakumar, N.; Azhagan, A. M.; Srinivas, D.; Krishna, G. G. *Tetrahedron Lett.* **2002**, *43*, 9175. (j) Lizos, D. E.; Murphy, J. A. *Org. Biomol. Chem.* **2003**, *1*, 117.

(3) Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147.

(4) Khan, T. A.; Tripoli, R.; Crawford, J. J.; Martin, C. G.; Murphy, J. A. *Org. Lett.* **2003**, *5*, 2971.

(5) (a) Beckwith, A. L. J.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1995**, 977. (b) For recent work on the mechanism of the final rearomatization step, see: Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 95.

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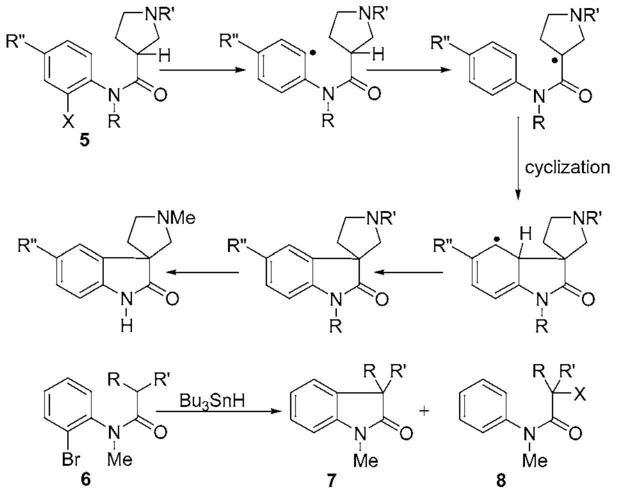
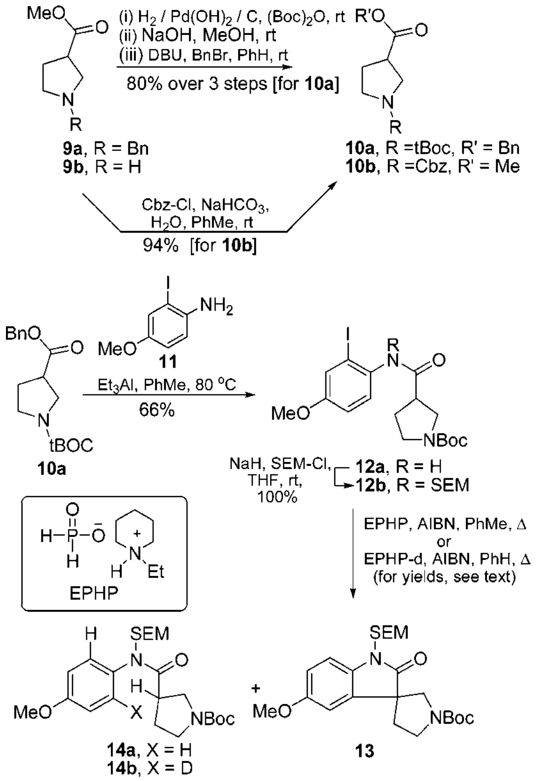
Scheme 1. Radical Translocation Approach to Horsfiline



Scheme 2. Route to Horsfiline Skeleton Using EPHP



hydrogen atom abstraction, using tributyltin hydride. At 80 °C in benzene and using AIBN as initiator, significant amounts of uncyclized, reduced compounds **8** (X = H) had been formed. However, reaction at 160 °C with *t*-Bu_2O_2 as initiator was much more successful. The formation of the desired cyclized product was, therefore, favored by the increase of temperature.

Recently, as part of the general drive to develop alternatives to toxic organotin reagents, we have explored the chemistry of modern phosphorus-based radical precursors. The chosen reagents, ethylpiperidine hypophosphite (EPHP)[6] and diethylphosphine oxide (DEPO),[4] provide easy isolation of products as the phosphorus byproducts can be washed into water.[7] The phosphorus-based reagents appear to have relatively strong P−H bonds, facilitating cyclizations where Bu_3SnH might, in contrast, encourage premature reduction of radicals.[6,7] They are thus poorer chain-transfer reagents, but low cost and easy reaction workup make the reagents attractive.

Our initial cyclizations in this study featured ethylpiperidine hypophosphite (EPHP) (Scheme 2).

Pyrrolidine ester **10a** was prepared from the pyrrolidine **9a**[8] in 80% overall yield. This pyrrolidine was then coupled[9a] with 2-iodo-4-methoxybenzenamine **11**,[2h,10] and the amide **12a** was then protected to give the desired precursor **12b** (R = SEM) for the cyclization.[2a] The best conditions for the radical cyclization were found to use EPHP and AIBN in refluxing toluene. However, this gave the desired cyclized product **13** in a disappointing yield (33%) along with reduced compound **14a** as a dominant side product (51%) (Scheme 2).

When the cyclization experiment was carried out with substrate **12b** using EPHP-*d* and AIBN in refluxing benzene, a much improved yield (60%) of cyclized product **13**, along with 36% reduced product **14b**, was isolated. This compound showed three aromatic protons in the ^1H NMR spectrum and a single deuterium resonance at 7.16 ppm in the ^2H NMR spectrum.

The completion of the synthesis consisted in removal of the protecting groups from **13** and N-methylation in situ using formaldehyde and $NaCNBH_3$ in CH_2Cl_2 to afford horsfiline (**1**) (47% in first step; 89% yield over the last two steps) (Scheme 3) with spectroscopic data identical to an authentic sample.[2f]

The results obtained from EPHP-*d* in this case were welcome since the cyclization proceeded in much higher yield and also because no HAT was identified from the SEM protecting group or from undesired positions on the pyrrolidine to the aryl radical. However, the position of the

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(6) (a) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1992**, *33*, 5709. (b) Calderon, J. M. B.; Chicharro, G. J.; Fiandhorn, R. J.; Huss, S.; Ward, R. A. EP2284 970506, 1997. (c) McCague, R.; Pritchard, R. G.; Stoodley, R. J.; Williamson, D. S. *Chem. Commun.* 1998, 2691. (d) Graham, S. R.; Murphy, J. A.; Coates, D. *Tetrahedron Lett.* **1999**, *40*, 2415. (e) Graham, S. R.; Murphy, J. A.; Kennedy, A. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3071. (f) Kita, Y.; Nambu, H.; Ramesh, N. G.; Anilkumar, G.; Matsugi, M. *Org. Lett.* **2001**, *3*, 1157. (g) Roy, S. C.; Guin, C.; Kumar, K. K.; Maiti, G. *Tetrahedron* **2002**, *58*, 2435. (h) Jang, D. O.; Cho, D. H. *Tetrahedron Lett.* **2002**, *43*, 5921. (i) Thomson, D. W.; Commeureuc, A. G. J.; Berlin, S.; Murphy, J. A. *Synth. Commun.* **2003**, *33*, 3631. (j) Caddick, S.; Hamza, D.; Judd, D. B.; Reich, M. T.; Wadman, S. N.; Wilden, J. D. *Tetrahedron Lett.* **2004**, *45*, 2363. (k) Cho, D. Y.; Jang, D. O. *Synlett* **2005**, 59. For a complete list of references, see ref 4.

(7) For other phosphorus reagents under development, see: (a)Jessop C. M.; Parsons, A. F.; Routledge, A.; Irvine, D. *Tetrahedron Lett.* **2004**, *45*, 5095. (b) Jessop C. M.; Parsons, A. F.; Routledge, A.; Irvine, D. *Tetrahedron Lett.* **2003**, *44*, 479.

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(9) (a) Cossy, J.; Cases, M.; Pardo, D. G. *Tetrahedron Lett.* **1998**, *39*, 2331. (b) A. G. Wright and J. A. Murphy, unpublished results.

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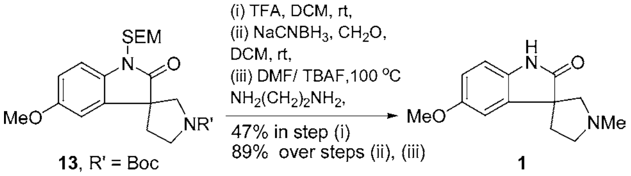
deuterium label in the reduced byproduct **14b** was surprising. The outcome contrasted with results reported by Beckwith et al. in a cyclization reaction on a simpler substrate [**6**, R, R′ = $(CH_2)_2$] using tributyltin deuteride.[5] In that case, the entire isotope found in the reduced product **8** resided in the side chain at C-1 in the cyclopropane ring [**8**, R, R′ = $(CH_2)_2$, X = D] (Scheme 1). That result indicated that the radical translocation step was much faster than the deuterium atom transfer from Bu_3SnD to the aryl radical.[5] In turn, that meant that the later cyclization step was the less efficient of the two key steps since it suffered competition by radical reduction.

However, our observation of no deuterium incorporation at the aliphatic carbon atom in **14** and the high yield of **13** implies that, under our conditions and with our substrate, the radical generated after 1,5-hydrogen atom abstraction in a reaction of **12b** does not abstract deuterium from EPHP-*d* but cyclizes with total efficiency (Scheme 2).

This surprising observation persuaded us to investigate an alternative and more direct route to the indolones, avoiding HAT and featuring, instead, direct radical generation in the alkyl side chain, followed by cyclization. The most direct route to a formal total synthesis of horsfiline would be by synthesis of **19**, an advanced precursor in the Fuji synthesis[2e] of horsfiline. Accordingly, we prepared precursor **17** for horsfiline synthesis, as illustrated in Scheme 4.

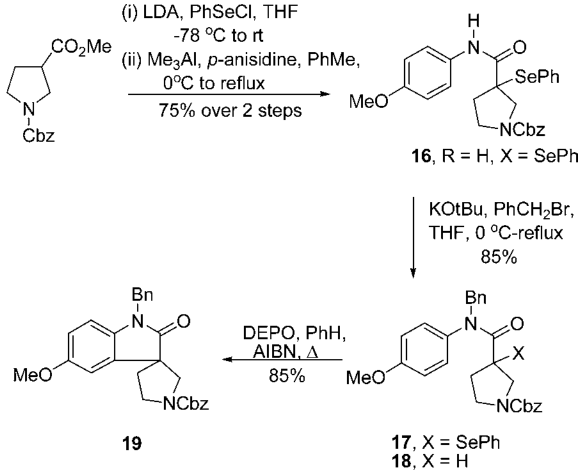
Scheme 3. Completion of EPHP Route to Horsfiline



Ester **10b** was prepared easily from pyrrolidine **9b**[11] (Scheme 2), and the phenylseleno group was introduced to give selenide **15**. This was directly reacted with *p*-anisidine in the presence of trimethylaluminum[9] to give amide **16**. The amide nitrogen of **16** was protected to produce the desired precursor **17** in 85% yield (Scheme 4). This was then treated with EPHP and AIBN in refluxing toluene, but only reduced product **18** was obtained.[12]

We have recently established that DEPO[4] has all of the advantages of EPHP, but that it is significantly slower to quench carbon radicals.[13] Hence, it was tried in this reaction. When precursor **17** was treated with DEPO and AIBN in refluxing dry benzene, the substrate underwent smooth radical cyclization and the only product obtained was the desired cyclized product **19** in 85% isolated yield (Scheme 4).[14] [This is also in complete contrast to the findings of Beckwith and Storey[5] for a related bromide **8** (R = R′ = Me, X = Br), which under Bu_3SnH conditions at 80 °C underwent 98% reduction and only 2% cyclization to indolone.]

Scheme 4. Concise Route to Horsfiline Using DEPO



As mentioned, **19** is an advanced precursor in the Fuji synthesis[2e] of horsfiline (**1**). We thus completed a formal synthesis of the horsfiline (**1**) using the newly developed phosphorus radical precursor, diethylphosphine oxide (DEPO). In particular, this work shows the advantages of DEPO in synthesis, compared to either tributyltin hydride or EPHP.

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Supporting Information Available: Experimental methods and spectroscopic data for selected compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) This may result from generation of PhSeH from attack by nucleophiles on small amounts of PhSeP(O)H(O)$^-$ formed from radical reaction in situ. Protonation of the leaving PhSe$^-$ would generate PhSeH. The excellent radical quenching ability of PhSeH has been established. See: (a) Newcomb, M.; Manek, M. B.; Glenn, A. G. *J. Am. Chem. Soc.* **1991**, *113*, 949. (b) Crich, D.; Yao, Q. W. *J. Org. Chem.* **1995**, *60*, 84.

(13) Although the kinetics of hydrogen atom abstraction for DEPO and EPHP appear not to have been studied quantitatively, kinetic data for hydrogen abstraction from other H−P bonds (e.g., dialkyl phosphites) show them to be relatively poor hydrogen donors. See: Chatgilialoglu, C.; Timokhin, V. I.; Ballestri, M. *J. Org. Chem.* **1998**, *63*, 1327.

(14) A blank experiment was conducted in which DEPO was not added. This led solely to recovery of starting material **17**; no cyclization was observed.