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# New Route to Azaspirocycles via the Organolithium-Mediated Conversion of β-Alkoxy Aziridines into Cyclopentenyl Amines

**Stephen P. Moore,[†] Susannah C. Coote,[†] Peter O'Brien,*[,†] and John Gilday[‡]**

*Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K., and Process R & D, AstraZeneca, Avlon Works, Severn Road, Hallen, Bristol BS10 7ZE, U.K.*

*paob1@york.ac.uk*

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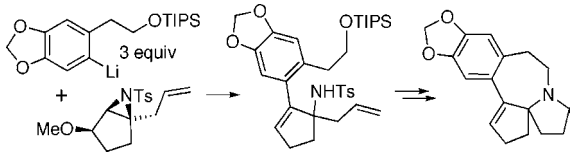
## ABSTRACT




**A new three-step route to azaspirocycles involving the organolithium-mediated conversion of β-alkoxy aziridines into substituted cyclopentenyl amines, hydroboration, and cyclization has been developed. The methodology is utilized in the construction of the pentacyclic ring system of cephalotaxine.**

The azaspirocyclic substructure is present in a number of naturally occurring alkaloids including the cylindricines, fasicularin, lepadiformine, halichlorine, histrionicotoxin, cephalotaxine, and the pinnaic acids. As a result of the biological activity associated with these natural products and their derivatives, they have attracted much recent synthetic activity.[1−4] In this paper, we describe a new route to cyclopentenyl azaspirocycles **1** ($n$ = 1, 2), which are potentially useful intermediates for the synthesis of cephalotaxine and halichlorine (Figure 1). The usefulness of our approach, which utilizes lithiated aziridines, is shown by the synthesis of a fully elaborated analogue of cephalotaxine.

Our group has an ongoing interest in the chemistry of lithiated aziridines[5,6] and we have previously reported the conversion of cyclic β-methoxy aziridines into substituted allylic sulfonamides.[7,8] As a typical example, the transforma-

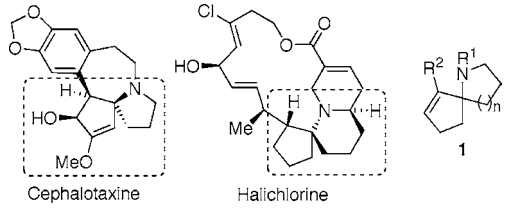



**Figure 1.**

[†] University of York.
[‡] AstraZeneca.

(1) El Bialy, S. A.; Braun, H.; Tietze, L. F. *Synthesis* **2004**, 2249.
(2) Dake, G. R. *Tetrahedron* **2006**, *62* 3467.
(3) Clive, D. L. J.; Yu, M.; Wang, J.; Yeh, V. S. C.; Kang, S. *Chem. Rev.* **2005**, *105*, 4483.
(4) Weinreb, S. M. *Chem. Rev.* **2006**, *106*, 2531.
(5) (a) O'Brien, P.; Rosser, C. M.; Caine, D. *Tetrahedron Lett.* **2003**, *44*, 6613. (b) O'Brien, P.; Rosser, C. M.; Caine, D. *Tetrahedron* **2003**, *59*, 9779. (c) Huang, J.; O'Brien, P. *Chem. Commun.* **2005**, 5696.
(6) For reviews containing information on the chemistry of lithiated aziridines, see: (a) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303. (b) Hodgson, D. M.; Bray, C. D.; Humphreys, P. G. *Synlett* **2006**, 1. (c) For a special issue on oxiranyl and aziridinyl anions, see: *Tetrahedron* **2003**, 9693−9847.
(7) Rosser, C. M.; Coote, S. C.; Kirby, J. P.; O'Brien, P.; Caine, D. *Org. Lett.* **2004**, *6*, 4817.
(8) For the conversion of β-methoxy epoxides into substituted allylic alcohols, see: (a) Dechoux, L.; Doris, E.; Mioskowski, C. *Chem. Commun.* **1996**, 549. (b) Doris, E.; Dechoux, L.; Mioskowski, C. *Synlett* **1998**, 337.

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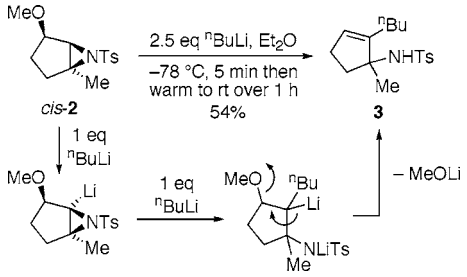
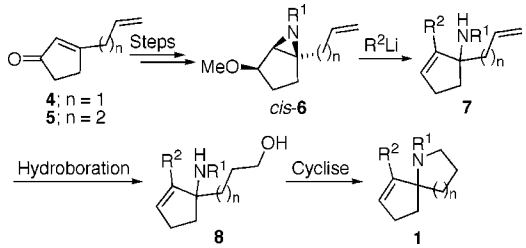
**Scheme 1**




tion of aziridine *cis*-**2** into allylic sulfonamide **3** (54% yield) was achieved using 2.5 equiv of *n*-BuLi and proceeded via aziridine α-lithiation, carbenoid insertion into the organolithium, and subsequent elimination of lithium methoxide (Scheme 1). In these reactions, aziridines derived from cyclopentenes gave higher yields of allylic sulfonamides compared with those of the corresponding cyclohexene-derived aziridines. Thus, our intitial efforts focused on developing a route to functionalized versions of cyclopentenyl sulfonamides **3** suitable for manipulation into halichlorine- and cephalotaxine-like azaspirocycles.

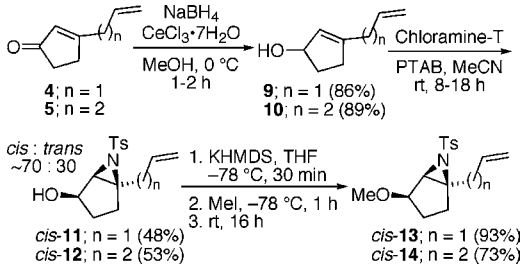
Our proposed strategy for the synthesis of the azaspirocyclic substructure present in cephalotaxine and halichlorine via lithiated aziridines is presented in Scheme 2. We anticipated preparing alkene-substituted aziridines *cis*-**6** (from cyclopentenones **4** and **5**) and then using excess organolithium reagents to convert them into allylic amines **7** using our established methodology.[7] Subsequent hydroboration of the less sterically hindered alkene to give **8** and then hydroxyl activation and cyclization would afford azaspirocycles **1**.

**Scheme 2**




To start with, known cyclopentenones **4**[9] and **5**[10] (see Supporting Information for their preparation) were reduced to allylic alcohols **9** and **10**, respectively, in good yield (Scheme 3). Then, aziridination[11] using Chloramine-T (TsNClNa) and phenyltrimethylammonium tribromide (PTAB) proceeded with good *cis*-selectivity (*cis* stereochemistry assigned by analogy with our earlier work[7,12]) providing

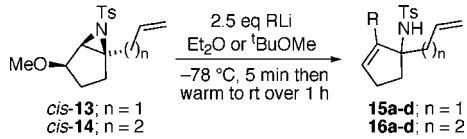
**Scheme 3**




satisfactory yields of aziridines *cis*-**11** (48%) and *cis*-**12** (53%) after chromatography (~70:30 *cis*:*trans* diastereoselectivity from the $^1$H NMR spectra of the crude reactions). Of note, these reactions also showed a high level of chemoselectivity as products from reaction of the terminal alkene in **9** and **10** were not detected. Low temperature (−78 °C) methylation using KHMDS and methyl iodide then completed the synthesis of the required β-methoxy aziridines *cis*-**13** and *cis*-**14** (Scheme 3).

The organolithium-mediated transformation of β-methoxy aziridines *cis*-**13** and *cis*-**14** into substituted allylic amines was next investigated (Table 1). These reactions were best carried out using 2.5 equiv of organolithium in $Et_2O$ or $^t$BuOMe (TBME) at −78 °C for 5 min before warming to room temperature. Pleasingly, the reactions proceeded

**Table 1.** Organolithium-Mediated Conversion of β-Methoxy Aziridines into Substituted Allylic Sulfonamides




| entry | SM | R | solvent | prod | % yield[a] |
|---|---|---|---|---|---|
| 1 | *cis*-**13** | $^n$Bu | $Et_2O$ | **15a** | 71 |
| 2 | *cis*-**13** | $^n$Bu | TBME | **15a** | 81 |
| 3 | *cis*-**13** | $Me_3SiCH_2$ | $Et_2O$ | **15b** | 63 |
| 4 | *cis*-**13** | $Me_3SiCH_2$ | TBME | **15b** | 77 |
| 5 | *cis*-**13** | Ph | $Et_2O$ | **15c** | 58 |
| 6 | *cis*-**13** | Ph | TBME | **15c** | 68 |
| 7 | *cis*-**13** | $^s$Bu | $Et_2O$ | **15d**[b] | 85 |
| 8 | *cis*-**13** | $^s$Bu | TBME | **15d**[b] | 82 |
| 9 | *cis*-**14** | $^n$Bu | $Et_2O$ | **16a** | 80 |
| 10 | *cis*-**14** | $Me_3SiCH_2$ | $Et_2O$ | **16b** | 82 |
| 11 | *cis*-**14** | Ph | $Et_2O$ | **16c** | 63 |

[a] Isolated yield after chromatography. [b] Obtained as a 1:1 mixture of diastereoisomers.

(9) Piers, E.; Banville, J.; Lau, C. K.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 2965.

(10) Wolff, S.; Agosta, W. C. *J. Org. Chem.* **1981**, *46*, 4821.

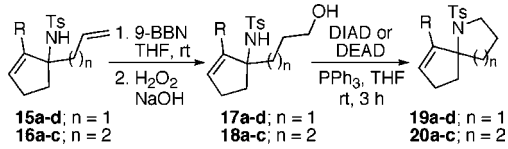
(11) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844.

(12) We have identified some useful, diagnostic trends in the $^1$H NMR spectra of aziridines **11** and **12** that enable assignment of their relative stereochemistry. For the CHN proton: $\delta_H$ 3.45 (d, $J$ = 2.5 Hz) for *cis*-**11** and $\delta_H$ 3.35 (s) for *trans*-**11**; $\delta_H$ 3.42 (d, $J$ = 2.5 Hz) for *cis*-**12** and $\delta_H$ 3.31 (s) for *trans*-**12**. Thus, for the *cis* aziridines, the CHN proton appears more downfield and is a doublet ($J$ = 2.5 Hz) compared to the *trans* aziridines.

smoothly and allylic sulfonamides **15a**−**d** and **16a**−**c** were generated in 58−85% yield. For aziridine *cis*-**13**, TBME was the preferred solvent as it generally gave a ∼10% improvement in yield (Table 1, compare entries 1/2, 3/4, and 5/6). In general, reactions using PhLi gave lower yields compared with those using primary and secondary alkyllithium reagents (Table 1, compare entries 1/3/5/7 and 9−11). In all of the examples shown in Table 1, we saw no evidence in the $^1$H NMR spectra of the crude products of intramolecular cyclopropanation of the aziridines, even though such a process is well established for certain lithiated epoxides and aziridines equipped with a pendent alkene.[13]

With allylic sulfonamides **15a**−**d** and **16a**−**c** in hand, we were ready to investigate a two-step conversion into the desired azaspirocycles. First of all, chemo- and regioselective hydroboration of the terminal alkene was achieved using 9-BBN[14] to give alcohols **17a**−**d** and **18a**−**c** in 35−86% yield (Table 2). Then, cyclization under Mitsunobu conditions[15] using DEAD or DIAD and $PPh_3$ gave azaspirocycles **19a**−**d** and **20a**−**c** in 61−87% yield (Table 2). Thus, a simple, three-step route from $\beta$-methoxy aziridines *cis*-**13** and *cis*-**14** to azaspirocycles **19a**−**d** and **20a**−**c** has been established. Azaspirocycles **20a**−**c** correspond to the spirocyclic substucture of halichlorine, and $Me_3SiCH_2$-substituted allylic sulfonamide **20b** could be elaborated toward this natural product.

**Table 2.** Hydroboration−Mitsunobu Cyclization of Allylic Sulfonamides **15** and **16**

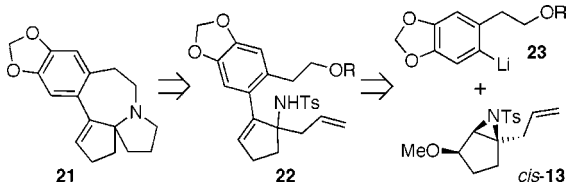



| entry | SM | R | prod, % yield[a] | prod, % yield[a] |
|---|---|---|---|---|
| 1 | **15a** | $^n$Bu | **17a**, 35 | **19a**, 65 |
| 2 | **15b** | $Me_3SiCH_2$ | **17b**, 86 | **19b**, 76 |
| 3 | **15c** | Ph | **17c**, 79 | **19c**, 61 |
| 4 | **15d** | $^s$Bu | **17d**, 60[b] | **19d**, 71[b] |
| 5 | **16a** | $^n$Bu | **18a**, 64 | **20a**, 79 |
| 6 | **16b** | $Me_3SiCH_2$ | **18b**, 71 | **20b**, 87 |
| 7 | **16c** | Ph | **18c**, 69 | **20c**, 76 |

[a] Isolated yield after chromatography. [b] Obtained as a 1:1 mixture of diastereoisomers.

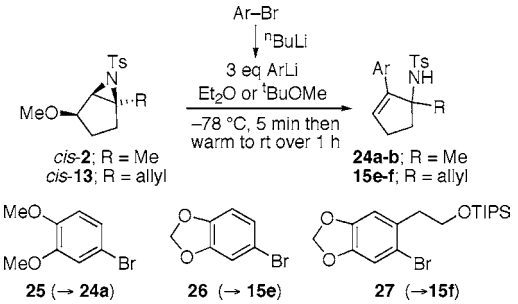
Our next aim was to utilize this azaspirocycle synthetic methodology for the preparation of azaspirocycle **21**, a potential intermediate for cephalotaxine synthesis. Naturally ocurring esters derived from cephalotaxine (e.g., deoxyharringtonine) show pronounced antileukemic activity and have thus been the subject of several recent synthetic studies.[1,16] As outlined in Scheme 4, we envisaged that azaspirocycle **21** could be obtained from allylic sulfonamide **22** by two cyclization processes (including *N*-Ts deprotection). To prepare allylic sulfonamide **22**, reaction of aziridine *cis*-**13** with excess functionalized aryllithium **23** (obtained by lithium-bromine exchange) was to be explored.

**Scheme 4**




To investigate the viability of using functionalized aryllithium reagents in combination with $\beta$-methoxy aziridines, reactions between the aryllithiums derived from either bromobenzene or bromides **25**−**27**[17] and aziridines *cis*-**2**[7] and *cis*-**13** were studied (Table 3). Lithium-bromine exchange[18] of bromobenzene or **24** was accomplished using *n*-BuLi, and

**Table 3.** Transformation of $\beta$-Methoxy Aziridines into Substituted Allylic Sulfonamides Using Functionalized Aryllithium Reagents




| entry | SM | ArBr | solvent | product | % yield[a] |
|---|---|---|---|---|---|
| 1 | *cis*-**2** | PhBr | $Et_2O$ | **24a**[b] | 46[c] |
| 2 | *cis*-**2** | 25 | $Et_2O$ | **24b**[b] | 46 |
| 3 | *cis*-**13** | 26 | $Et_2O$ | **15e** | 64 |
| 4 | *cis*-**13** | 26 | TBME | **15e** | 54 |
| 5 | *cis*-**13** | 26 | $Et_2O$ | **15e** | 44[d] |
| 6 | *cis*-**13** | 27 | $Et_2O$ | **15f** | 43 |
| 7 | *cis*-**13** | 27 | TBME | **15f** | 37 |

[a] Isolated yield after chromatography. [b] Reaction carried out using 2.5 equiv of ArLi. [c] 69% yield of **24a** using a commercial solution of PhLi in $^n$Bu$_2$O. [d] Reaction carried out using 1.5 equiv of **26** and 3 equiv of $^n$BuLi.

(13) (a) Dechoux, L.; Agami, C.; Doris, E.; Mioskowski, C. *Tetrahedron* **2003**, *59*, 9701. (b) Hodgson, D. M.; Chung, Y. K.; Paris, J.-M. *J. Am. Chem. Soc.* **2004**, *126*, 8664. (c) Hodgson, D. M.; Humphreys, P. G.; Ward, J. G. *Org. Lett.* **2006**, *8*, 995.

(14) Riber, D.; Hazell, R.; Skrydstrup, T. *J. Org. Chem.* **2000**, *65*, 5382.

(15) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Davis Harris, G.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709.

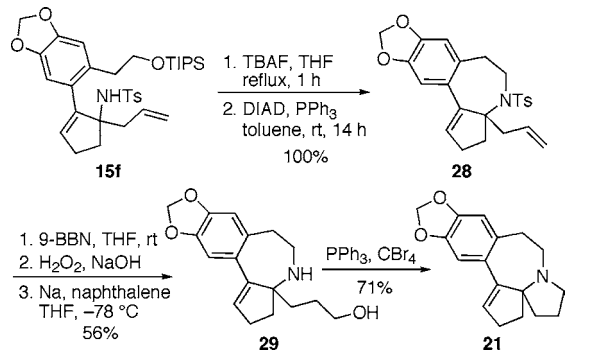
(16) For selected recent examples, see: (a) Eckelbarger, J. D.; Wilmot, J. T.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 10370. (b) Zhao, Z.; Mariano, P. S. *Tetrahedron* **2006**, *62*, 7266. (c) Li, W.-D. Z.; Ma, B.-C. *J. Org. Chem.* **2005**, *70*, 3277. (d) Planas, L.; Perard-Viret, J.; Royer, J. *J. Org. Chem.* **2004**, *69*, 3087. (e) Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264.

the resulting aryllithiums were then reacted with model aziridine *cis*-**2** to give allylic sulfonamides **24a** and **24b** in 46% yield for each reaction (Table 3, entries 1/2). By way of comparison, the equivalent reaction with a commercially available solution of PhLi delivered allylic sulfonamide **24a** in 69% yield.

Next, reactions between aziridine *cis*-**13** and the aryllithiums obtained from bromides **26** and **27** were investigated (Table 3, entries 3−7). The desired allylic sulfonamides **15e** and **15f** were generated in 37−64% yield, and $Et_2O$ was preferred to TBME as solvent in these cases (Table 3, compare entries 3/4 and 6/7). Allylic sulfonamide **15f** has been further elaborated toward cephalotaxine (vide infra), and it was best generated (43% yield) using 3 equiv of the aryllithium derived from bromide **27** in $Et_2O$ (Table 3, entry 6). We also briefly attempted to reduce the quantity of aryl bromide **26** required in the reaction. Thus, 3 equiv of *n*-BuLi was combined with only 1.5 equiv of aryl bromide **26** before reaction with aziridine *cis*-**13**. It was anticipated that the excess *n*-BuLi would carry out the required aziridine lithiation and then the resulting lithium carbenoid would insert into the aryllithium to produce **15e**. Indeed, this turned out to be the case as allylic sulfonamide **15e** was produced in 44% yield (Table 3, entry 5) accompanied by small amounts of **15a** (not isolated).[19]

Having demonstrated that functionalized aryllithium reagents could be used in lithiation-carbenoid insertion processes with aziridines, we set about constructing the pentacyclic ring structure present in cephalotaxine (Scheme 5). Thus, the tri-isopropylsilyl group in allylic sulfonamide **15f** was deprotected using TBAF, and the resulting alcohol was cyclized under Mitsunobu conditions to give sulfonamide **28** in quantitative yield. Next, hydroboration followed by *N*-Ts deprotection using Na/naphthalene[20] gave amino alcohol **29** (56% yield over two steps). Finally, **29** was cyclized

**Scheme 5**




to pentacycle **21** using $PPh_3/CBr_4$[21] (71% yield), thus completing a connective approach to the cephalotaxine core.[22]

In summary, a three-step route to azaspirocycles via the organolithium-mediated conversion of $\beta$-alkoxy aziridines into substituted cyclopentenyl amines, hydroboration, and Mitsunobu cyclization has been developed. In a useful extension of our lithiated aziridine methodology, functionalized aryllithium reagents have been successfully employed, and this enabled a concise and connective approach to the pentacyclic ring system of cephalotaxine (nine steps from cyclopentenone **4**) to be developed.

**Acknowledgment.** We thank the EPSRC and AstraZeneca for a CASE award (to S.P.M.) and the EPSRC for a DTA award (to S.C.C.).

**Supporting Information Available:** Full experimental procedures, characterisation data, and copies of $^1H$ NMR and $^{13}C$ NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Bromides **25** and **26** are commercially available. Bromide **27** was prepared by silylation of the alcohol (see Supporting Information). For synthesis of the alcohol, see: Tietze, L. F.; Schirok, H.; Wöhrmann, M.; Schrader, K. *Eur. J. Org. Chem.* **2000**, 2433.

(18) (a) Bailey, W. F.; Luderer, M. R.; Jordan, K. P. *J. Org. Chem.* **2006**, *71*, 2825. (b) Lin, X.; Kavash, R. W.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 7335.

(19) For an example of the use of mixtures of two organolithium reagents in a related reaction of an epoxide, see: Hodgson, D. M.; Paruch, E. *Tetrahedron* **2004**, *60*, 5185.

(20) Williams, J. T.; Bahia, P. S.; Kariuki, B. M.; Spencer, N.; Philp, D.; Snaith, J. S. *J. Org. Chem.* **2006**, *71*, 2460.

(21) For a related cyclisation, see: Kavash, R. W.; Mariano, P. S. *Tetrahedron Lett.* **1989**, *30*, 5709.

(22) For a different route to a similar intermediate for cephalotaxine synthesis, see: Sha, C.-K.; Young, J.-J.; Yeh, C.-P.; Chang, S.-C.; Wang, S.-L. *J. Org. Chem.* **1991**, *56*, 2694.