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Towards a total synthesis of (−)-cephalotaxine: construction of the BCDE-tetracyclic core

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Abstract—The synthesis of the BCDE-tetracyclic core of (−)-cephalotaxine has been achieved in eight steps starting from *N*-Boc-L-proline methyl ester. An alkylidene carbene 1,5-CH insertion reaction was used as a key step in the stereocontrolled synthesis of the DE-spirocyclic fragment and an intramolecular Heck-type cyclisation was used to form the benzazepine ring, and hence complete the tetracycle formation. © 2002 Published by Elsevier Science Ltd.

The evergreen plum-yews of the genus *Cephalotaxus* produce a range of structurally related polycyclic alkaloids of which (−)-cephalotaxine **1** (Fig. 1) is the most abundant member.[1] Whilst **1** has little known biological activity, a considerable amount of interest has been paid to the potential therapeutic uses of a range of co-occurring cephalotaxine esters. In particular, homoharringtonine **2**[2] has attracted considerable attention due to its promising antileukaemic activity, and this material is currently undergoing advanced clinical trials.[3]

The combination of interesting chemical structure and profound biological activity have stimulated a large number of studies directed towards the total synthesis of these alkaloids. Cephalotaxine itself has attracted most of the synthetic interest and this has resulted in a number of rather elegant total syntheses.[4] Upon examination of this work, however, it is perhaps surprising to find that only three syntheses of enantiomerically pure (−)-cephalotaxine have been reported to date.[5]

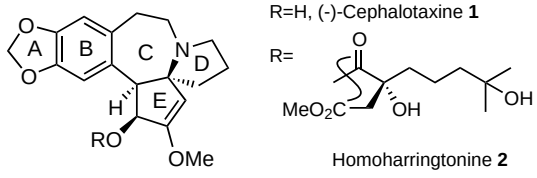
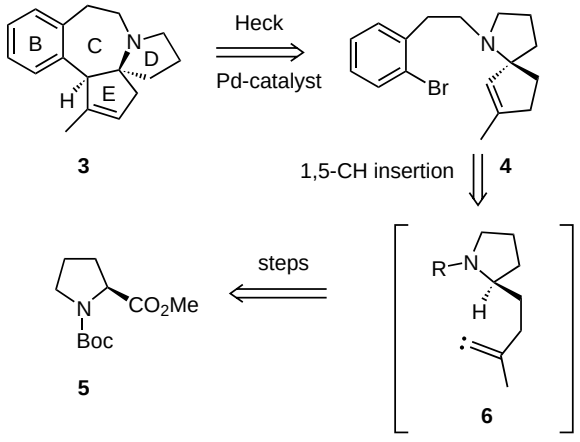


Figure 1.

Of the synthetic challenges presented by (−)-cephalotaxine **1**, the asymmetric construction of the quaternary stereocentre of the DE-spirocyclic fragment is perhaps the most demanding. We have an ongoing interest in the use of alkylidene carbenes for the asymmetric construction of nitrogen-bearing quaternary stereocentres,[6] and we wondered whether we could use a 1,5-CH insertion reaction for the formation of the key spirocyclic ring system. In order to test the suitability of this strategy for the synthesis of **1**, we first chose to examine the construction of a simpler model of the tetracyclic skeleton **3**. Our retrosynthetic analysis of the BCDE-tetracyclic core **3** is outlined in Scheme 1. Following good literature precedent[5a] we disconnected the C-ring using a retro-Heck reaction to reveal the spirocyclic tertiary amine **4** as an advanced intermediate. We were aware of the fact that a mixture of **3** and its exocyclic



Scheme 1. Retrosynthetic analysis of the BCDE core.

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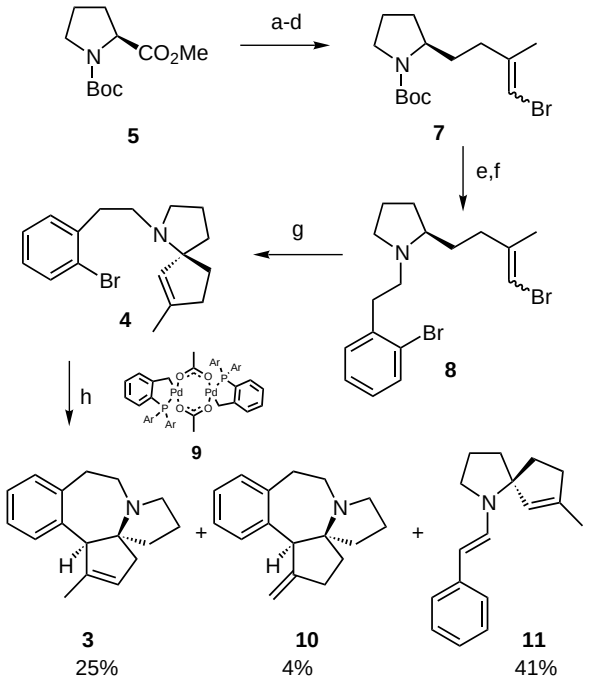
double bond isomer **10** were likely to be produced in the Heck reaction, but we felt that the fully functionalised cephalotaxine E-ring could be accessed from either of these materials using standard functional group interconversions, and this regiochemical issue did not concern us at this stage of the synthetic planning. Further disconnection of **4** via a retro-1,5-CH insertion reaction revealed the alkylidene carbene-substituted pyrrolidine **6** as a key reactive intermediate. We envisaged **6** as being accessed from readily available *N*-Boc proline methyl ester in only a few synthetic steps.

Guided by our retrosynthetic analysis (Scheme 1), the desired alkylidene carbene cyclisation precursor **8** was synthesised in six steps from *N*-Boc proline methyl ester **5** in good overall yield (Scheme 2). Dibal-H reduction of **5** and homologation of the resulting aldehyde first produced the corresponding enone. Catalytic hydrogenation and a second olefination using bromomethyl triphenylphosphorane then provided the 1-bromo-1-alkene **7** as a 2.5:1 mixture of *E*:*Z* isomers. Acid-catalysed cleavage of the Boc-protecting group and reductive amination finally afforded the desired 1,5-CH insertion precursor **8.**

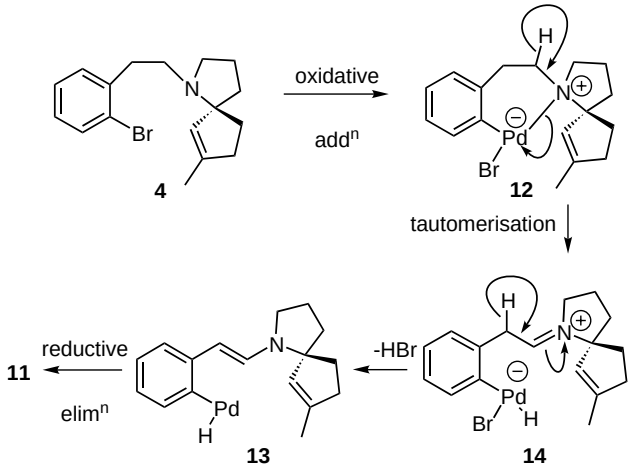
With the desired cyclisation precursor **8** in hand, we were now ready to examine the two remaining C–C bond formations necessary for tetracycle construction. Firstly, the alkylidene carbene 1,5-CH insertion reaction was examined. Thus, a diethyl ether solution of **8** was treated with an excess (2.0 equiv.) of KHMDS at room temperature,[7] and to our pleasure the desired spirocyclic product **4** was produced as the major product in good isolated yield (Scheme 2).[8] The success of this reaction meant that we were now in a position to effect the desired Heck-cyclisation reaction. After considering a number of alternatives, the palladacycle **9**[9] seemed like the most appropriate choice of catalyst for this transformation. Thus, after heating a solution of **4** (MeCN/DMF/H_2O (5:5:1))[5a] and **9** (10 mol%) at 120°C for 2 h, we were able to isolate the desired tetracyclic product **3** and its exocyclic double bond isomer **10** (6:1 ratio, respectively) in a combined yield of 25–30%. Although we were initially pleased with this result, we were a little concerned to find that the enamine **11** (41%) was formed as the major new product under the reaction conditions (Scheme 2).[10]



Scheme 2. *Reagents and conditions*: (a) Dibal-H, CH_2Cl_2, −78°C (72%); (b) $Ph_3PCHC(O)Me$, CH_2Cl_2, rt (80%); (c) H_2, Pd/C, EtOAc (92%); (d) KHMDS, $(Ph_3PCH_2Br)Br$, THF (70%); (e) TFA (30 equiv.), DCM, rt (100%); (f) *o*-Br-$PhCH_2CHO$, THF, HOAc, $NaBH(OAc)_3$ (70%); (g) KHMDS, Et_2O, rt (64%); (h) MeCN:DMF:H_2O (5:5:1), catalyst **9** (10 mol%), 120°C.

We believe that the formation of **11** can be explained by invoking an intramolecular palladium-catalysed redox process (Scheme 3). The process begins with an initial oxidative addition to produce the expected organometallic species, but instead of undergoing the usual carbo-palladation of the adjacent olefin, the oxidised palladium species forms a chelate **12** with the basic nitrogen atom of the spirocycle. A tautomerisation of this complex results in the production of an iminium ion **14**, which can lose HBr to form **13**. A final reductive elimination affords the observed enamine **11** and regenerates the palladium catalyst, thus completing the catalytic cycle.[11] A number of other palladium catalysts (e.g. $Pd(P^tBu_3)_2$/$MeNCy_2$,[12a] $Pd(OAc)_2$/dppp/K_2CO_3)[12b] were tested for their ability to perform the desired Heck reaction, but in general these were found to result in lower conversions and the enamine **11** was produced as the major new compound in all cases.

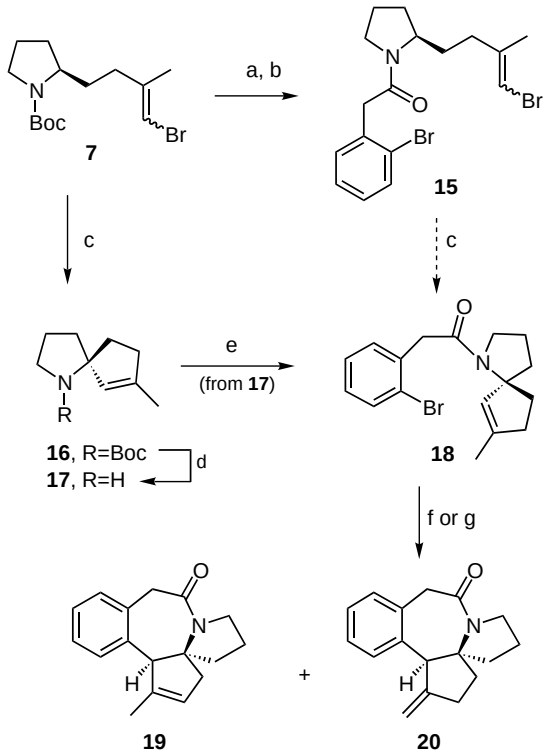
From these results, it became clear that we needed to modify our synthetic plan to take into account these new findings. The most obvious way of preventing the formation of the enamine **11** would be to use an amide **18**, rather than an amine-derived cyclisation precursor, and the synthesis of this material became our next goal.



Scheme 3.

We first tried to access **18** from the amide **15** via a 1,5-CH insertion reaction, and although **15** proved relatively easy to prepare, we were unable to effect the desired KHMDS-mediated cyclisation reaction.[13] A successful synthesis of **18** was however completed from **7** via the three-step sequence shown in Scheme 4. Firstly, KHMDS induced 1,5-CH insertion of **7** produced the spirocycle **16** (>93% e.e.) and deprotection of the Boc group afforded the corresponding secondary amine product **17**. Purification of this material proved difficult and it was used in crude form in subsequent reactions. Finally, the synthesis of **18** was completed, albeit in modest overall yield, using standard amide forming conditions.[14] Pleasingly, cyclisation of **18** mediated by 10 mol% of the catalyst **9** afforded the desired tetracyclic amides **19** and **20** as the major products of the reaction as a 3:1 mixture in 54% yield. The isolated yield of tetracyclic product could be increased to 62% if $Pd(P^tBu_3)_2$ was used as catalyst in the presence of $MeNCy_2$, but in this case only the endocyclic olefin isomer **19** was observed.

In summary, we have shown that the tetracyclic core of the cephalotaxus alkaloids can be accessed from proline using an alkylidene carbene 1,5-CH insertion to construct the DE spirocyclic ring system. We have also shown that a Heck-type cyclisation of an amide-derived precursor **18** leads to the formation of the desired BCDE-tetracyclic core structure **19** in 62% yield. In addition, we have shown that a related tertiary amine-derived Heck reaction precursor **4** leads to the formation of the BCDE-tetracyclic core as a mixture of regioisomers (**3** and **10**) in only modest yield. During this reaction the enamine **11** was formed as the major reaction product via an interesting palladium-catalysed pathway. From this initial proof of concept study, we can see that our proposed route to (–)-cephalotaxine **1** should be feasible from an amide-derived substrate similar to **18**, although some optimisation of its synthesis will be necessary. These and further studies in this area will be published in due course.



Scheme 4. *Reagents and conditions*: (a) MeOH, AcCl, rt; (b) *o*-Br-$PhCH_2CO_2H$, EDCI, HOBt, NMM, DCM (80%, two steps); (c) KHMDS, Et_2O, rt (60–65%); (d) MeOH, AcCl, rt or TFA, CH_2Cl_2; (e) *o*-Br-$PhCH_2CO_2H$, EDCI, HOBt, NMM, DCM (29%, two steps); (f) MeCN:DMF:H_2O (5:5:1), catalyst **9** (10 mol%), 120°C (41% **19** and 13% **20**); (g) $Pd(P^tBu_3)_2$, $NMeCy_2$, dioxane, 100°C (62% **19** only).

Acknowledgements

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References

1. (a) Wall, M. E. *J. Am. Pharm. Assoc.* **1954**, *43*, 505; (b) Paudler, W. W.; Kerley, G. I.; McKay, J. *J. Org. Chem.* **1963**, *28*, 2194; (c) Powell, R. G.; Weisleder, D.; Smith, C. R., Jr.; Wolff, I. A. *Tetrahedron Lett.* **1969**, *9*, 4081; (d) Abraham, D. J.; Rosenstein, R. D.; McGandy, E. L. *Tetrahedron Lett.* **1969**, *9*, 4081; (e) Paudler, W. W.; McKay, J. *J. Org. Chem.* **1973**, *38*, 2110.
2. Powell, R. G.; Weisleder, D.; Smith, C. R., Jr.; Rohwedder, W. K. *Tetrahedron Lett.* **1970**, *10*, 815.
3. O'Brien, S.; Kantarjian, H.; Koller, C.; Feldman, E.; Beran, M.; Andreeff, M.; Giralt, S.; Cheson, B.; Keating, M.; Freireich, E.; Rios, M. B.; Talpaz, M. *Blood* **1999**, *93*, 4149–4153.
4. (a) Ikeda, M.; El Bialy, S. A. A.; Hirose, K.; Kotake, M.; Sato, T.; Bayomi, S. M. M.; Shehata, I. A.; Abdelal, A. M.; Gad, L. M.; Yakura, T. *Chem. Pharm. Bull.* **1999**, *47*, 983; (b) Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett.* **2002**, *4*, 885; (c) Ikeda, M.; Hirose, K.-I.; El Bialy, S. A. A.; Sato, T.; Yakura, T.; Bayomi, S. M. M. *Chem. Pharm. Bull.* **1998**, *46*, 1084; (d) For an excellent review, see: Miah, M. A. J.; Hudlicky, T.; Reed, J. W. *The Alkaloids* **1998**, *51*, 199.
5. (a) Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264; (b) Nagasaka, T.; Sato, H.; Saeki, S.-I. *Tetrahedron: Asymmetry* **1997**, *8*, 191; (c) Isono, N.; Mori, M. *J. Org. Chem.* **1995**, *60*, 115.
6. (a) Gabaitsekgosi, R.; Hayes, C. J. *Tetrahedron Lett.* **1999**, *40*, 7713; (b) Green, M. P.; Prodger, J. C.; Sherlock, A. E.; Hayes, C. J. *Org. Lett.* **2001**, *3*, 3377.
7. (a) Taber, D. F.; Christos, T. E.; Neubert, T. D.; Batra, D. *J. Org. Chem.* **1999**, *64*, 9673; (b) Taber, D. F.; Neubert, T. D. *J. Org. Chem.* **2001**, *66*, 143; (c) Taber, D. F.; Meagley, R. P.; Doren, D. J. *J. Org. Chem.* **1996**, *61*, 5723.

8. The spirocyclic amine **4** has an $[\alpha]_D = -29$ (*c* 1.06, $CHCl_3$) but we have been unable to find a suitable assay to determine the % enantiomeric excess. Previous studies from our research group, however, have shown that alkylidene carbene 1,5-CH insertions of this type proceed with retention of stereochemistry (see Ref. 6).
9. Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844.
10. Tietze et al. showed that a similar precursor to **4** could be cyclised with Herrmann's catalyst to produce a tetracyclic product in 81% yield (see Ref. 5a). We believe that steric interaction between the palladium catalyst and the methyl substituent on the olefin in **4** facilitates preferential coordination to the tertiary amine rather than the trisubstituted olefin.
11. β-Hydride elimination of palladium–amine complexes is a known process. See: Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348 and references cited therein.
12. (a) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989; (b) Vallain, K. S. A.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2001**, *66*, 4340.
13. Compound **15** contains a particularly acidic methylene moiety, and we believe that initial deprotonation at this site by KHMDS results in the subsequent 1,1-elimination reaction being retarded.
14. We believe that the modest overall yield observed for the formation of **18** from **16** is due to decomposition of the intermediate spirocyclic secondary amine **17** under the acidic deprotection conditions. Control experiments show that samples of the ammonium salt of **17** decompose over time, even at −20°C. We are currently examining the use of different protecting groups for the secondary amine that can be removed under neutral or basic conditions.