ORGANIC LETTERS

2001
Vol. 3, No. 19
3005−3008

Formal Intramolecular [5 + 2] Photocycloaddition Reactions of Maleimides: A Novel Approach to the CDE Ring Skeleton of (−)-Cephalotaxine

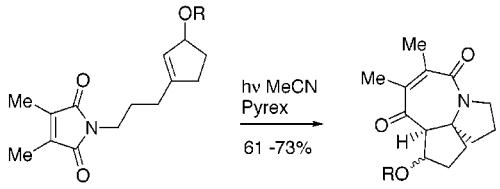
Kevin I. Booker-Milburn,*,† Leo F. Dudin,† Christopher E. Anson,‡ and Simon D. Guile§

School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, U.K., School of Chemical Sciences, University of East Anglia, Norwich, Norfolk NR4 7TJ, U.K., and AstraZeneca, R&D Charnwood, Bakewell Road, Loughborough LE11 5RH, U.K.

k.booker-milburn@bristol.ac.uk.

Received July 10, 2001

ABSTRACT



A concise approach to the cephalotaxine CDE ring skeleton based on the intramolecular formal [5 + 2] photocycloaddition of cyclopentenyl-substituted maleimides is described. An investigation of the diatereoselectivity afforded by various protected alkoxy groups demonstrated that the best selectivity (3.5:1) was afforded by the free hydroxyl group, strongly suggesting a hydrogen-bonded excited state.

(−)-Cephalotaxine (**1**, Scheme 1) is one of a number of alkaloids isolated from evergreen plum yews of the genus *Cephalotaxus*. Since its isolation[1] in 1963 and characterization[2] there have been a number of total syntheses of **1** reported, the most recent of these by Tietze et al. in 1999.[3] Current interest in **1** as a target for total synthesis is due to the fact that a number of derivatives, such as homoharringtonine **2**,[4] are in phase III clinical trials[5] as potential therapies for the treatment of chronic myelogenous leukaemia.

In this Letter we report an approach to the CDE skeleton of **1** that is based on a key step involving a formal [5 + 2] maleimide photocycloaddition sequence recently developed in our laboratories.[6] This particular reaction has so far proved to be highly efficient in the construction of complex fused azepines from simple *N*-alkenyl-substituted maleimides. Scheme 1 illustrates our synthetic strategy toward **1**. Disconnection leads to the tricyclic azepine **3** from which we believe we can access **1** via an arylation strategy.[7] The synthesis of **3** will be achieved by photocycloaddition of the maleimide **4**, which itself should be readily available via Mitsunobu coupling of the alkenol **5** with maleimide.[8] Depending on

† University of Bristol.
‡ University of East Anglia.
§ AstraZeneca.

(1) Paudler, W. M.; Kerley, G. I.; McKay, J. *J. Org. Chem.* **1963**, *28*, 2194−2197.

(2) Arora, S. K.; Bates, R. B.; Grady, R. A.; Germain, G.; Declercq, J. P.; Powell, R. G. *J. Org. Chem.* **1976**, *41*, 551−554 and references therein.

(3) For a recent total synthesis of (−)-cephalotaxine and reference to previous synthetic work in this area, see: Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264−10269.

(4) Keller, L.; Dumas, F.; d'Angelo, J. *Tetrahedron. Lett.* **2001**, *42*, 1911−1913 and references therein.

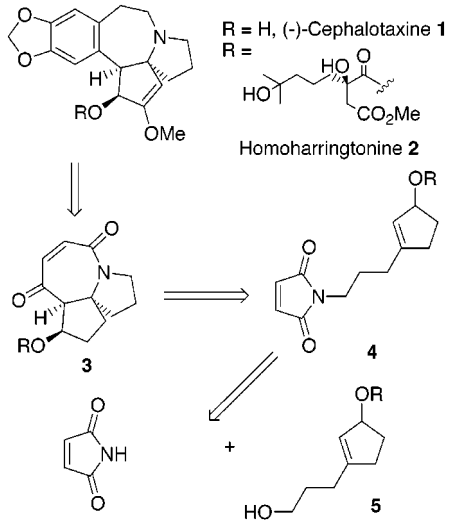
(5) O'Brien, S.; Kantarjian, H.; Koller. C.; Feldman, E.; Beran, M.; Andreeff, M.; Giralt, S.; Cheson, B.; Keating, M.; Freireich, E.; Rios, M. B.; Talpaz, M. *Blood* **1999**, *93*, 4149−4153.

(6) (a) Booker-Milburn, K. I.; Costin, N. J.; Dainty, R. F.; Patel, D.; Sharpe, A. *Tetrahedron. Lett.* **1998**, *39*, 7423. (b) Booker-Milburn, K. I.; Anson, C. E.; Clissold, C.; Costin, N. J.; Dainty, R. F.; Murray, M.; Patel, D.; Sharpe, A. *Eur. J. Org. Chem.* **2001**, 1473−1482.

(7) Chan, T. H.; Brownbridge, P. *J. Am. Chem. Soc.* **1980**, *102*, 3534.

10.1021/ol016411h CCC: $20.00
Published on Web 08/24/2001

Scheme 1

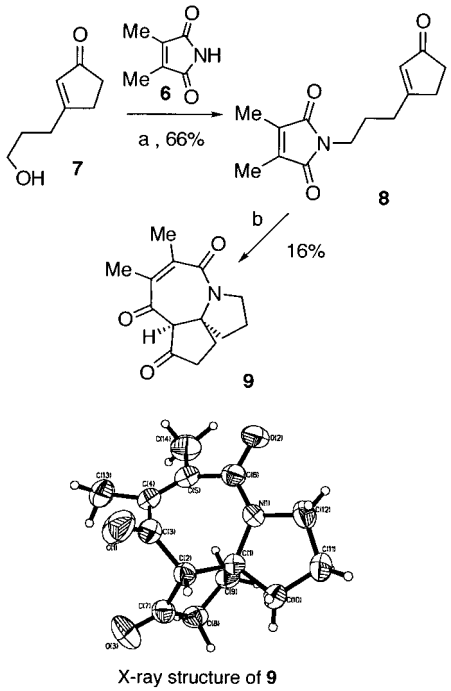


the nature of R, it is envisioned that the single stereogenic center in **4** would have an influence on the cycloaddition, either by steric repulsion or hydrogen bonding, and thus allow an asymmetric synthesis toward (−)-cephalotaxine to be realized.

Initial model studies were carried out using dimethyl maleimide **6**, as our previous studies showed that photocycloaddition of simple maleimide derivatives leads to side products resulting from dimerization.[6] Mitsunobu coupling of **6** with the known[9] cyclopentenone-alcohol **7** gave the photocycloaddition precursor **8** in 66% yield. Irradiation of this in acetonitrile for 29 h gave a 16% yield of the tricyclic azepine **9** along with 30% recovered starting material. Confirmation of the structure and proof that the relative stereochemistry of **9** was the same as **1** was confirmed by X-ray crystallographic analysis (Scheme 2).[10] The low yield and uncharacteristically long irradiation time for this system was attributed to the presence of the cyclopentenone unit. It was postulated that the enone unit was effectively quenching the excited state of the maleimide by intersystem crossing, thus preventing efficient turnover of the substrate. Attempts to avoid this problem by reduction of the enone carbonyl, and thus removal of the competing chromaphore, were fruitless. It was found that whatever the reducing agent employed, we were unable to reduce **8** effectively, as reduction of the maleimide carbonyls was always an attendant problem.

To overcome these problems an alternative synthesis of cyclopentenol-substituted ethers was developed. 3-Bromo-2-cyclopentene-1-ol **10** was readily available, in multigram quantities, from cyclopentane-1,3-dione.[11] Protection of **10**

Scheme 2[a]



[a] Reaction conditions: (a) DEAD, Ph_3P, THF, rt; (b) *hν*, MeCN, Pyrex, 29 h.

using standard protocols gave the ethers **11a**−**c** in moderate to excellent yields. Metal halogen exchange with *t*-BuLi and reaction of the resulting vinyllithiums with oxetane under BF_3•Et_2O catalysis[12] gave the alkenols **12a**−**c**. Mitsunobu coupling of these with dimethyl maleimide as before gave the photocycloaddition precursors **13a**−**c** in good yield. Irradiation of these gave the [5 + 2] products **14a**−**c** as mixtures of diastereoisomers. The fact that the yields were higher and irradiation times much shorter confirmed that the cyclopentenone chromophore in **8** was indeed responsible for the very limited lack of success with this system. However, it was disappointing to note the poor levels of diastereoselection obtained with the three alkoxy groups studied. Even with very bulky silyl groups such as TIPS (**14b**) the highest de observed was only 17%. This would clearly suggest that any alkoxy group has a very minor influence over which face of the cyclopentene the photoexcited maleimide unit adds to (Scheme 3).

In light of this we then elected to study if a free hydroxy group could influence the stereochemical outcome of the photocycloaddition by formation of a hydrogen-bonded intermediate. Initial attempts to desilylate **13c** were frustrated by the apparent instability of the alcohol **15** to the standard TBAF reaction conditions. It was found, however, that **15** could be isolated in high yield if the TBAF-mediated desilylation was effected in the presence of AcOH.[13] Irradia-

(8) In reality a protected maleimide will be used to avoid potential problems with photodimerization (ref 6).

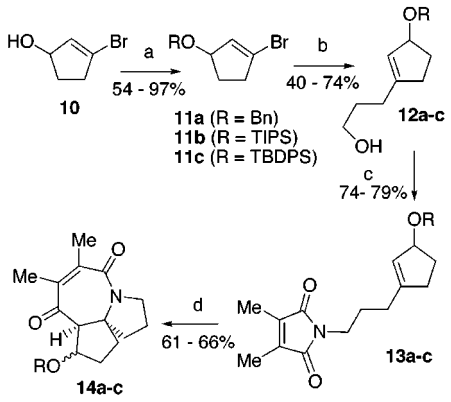
(9) Molander, G. A.; Hiersemann, M. *Tetrahedron Lett*. **1997**, *38*, 4347.

(10) Data deposited at Cambridge Crystallographic Data Centre (CCDC 158520).

(11) (a) Ito, S. I.; Kasai, M.; Ziffer, H. Silverton, J. V. *Can. J. Chem*. **1987**, *65*, 574−582. (b) Piers, E.; Grierson, J. R.; Lau, C. K.; Nagakura, I. *Can. J. Chem*. **1982**, *60*, 210−223.

(12) (a) Eis, M. J.; Wrobel, J. E.; Ganem, B.; Bach, T.; Bergmann, H. *J. Am. Chem. Soc*. **1984**, *106*, 3693−3694. (b) Yamaguchi, M.; Shibato, K.; Hirao, I. *Tetrahedron Lett*. **1984**, *25*, 1159−1162. (c) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc*. **1988**, *110*, 2248−2256.

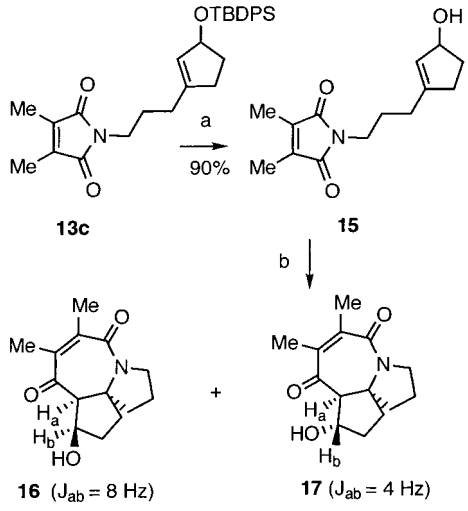
Scheme 3[a]



[a] Reaction conditions: (a) (R = Bn) NaH, BnBr, TBAI, THF, rt; (R = TIPS) TIPSCl, imidazole, CH_2Cl_2; (R = TBDPS) TBDPSCl, DMAP, imidazole, CH_2Cl_2; (b) *t*BuLi (2 equiv), THF, −78 °C then oxetane, $BF_3{\cdot}Et_2O$, −78 °C; (c) dimethyl maleimide, DEAD, Ph_3P, THF, rt; (d) *hν*, MeCN, Pyrex, 4 h.

tion of **15** in MeCN gave the diastereomeric photocycloadducts **16** and **17** in a much improved ratio of 2.5:1. Experimentation with less polar solvent systems such as toluene and 30% toluene/hexane gave a further improvement in the ratio to 3.5:1 in favor of **16** (Scheme 4). Unfortunately

Scheme 4[a]



Solvent	Yield	16:17
MeCN	65%	2.5:1
Toluene	73%	3.5:1
30% Toluene/ hexane	54%	3.5:1

[a] Reaction conditions: (a) TBAF, AcOH, THF; (b) *hν*, solvent, Pyrex, 4−9 h.

it was not possible to assess the reaction in a pure hexane solution, as **15** proved to be insoluble. Stereochemical assignments were based on the coupling constants between H_a and H_b. Molecular models of **16** and **17** suggest H_a-H_b dihedral angles of approximately 30° and 120°, respectively. The observed coupling constants for **16** (J_{ab} = 8 Hz) and **17** (J_{ab} = 4 Hz) are entirely consistent with these models (Scheme 4).

It is possible to attribute this highly significant increase in stereoselectivity to the hydrogen-bonded model depicted in Figure 1. We have previously argued that the photocy-

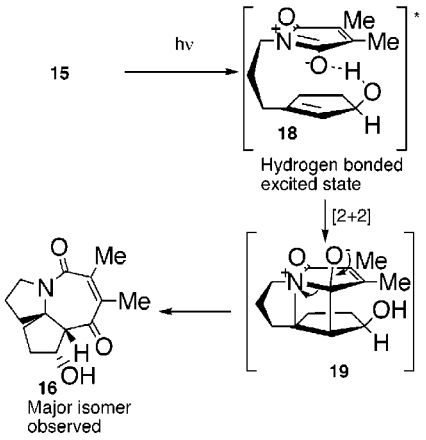


Figure 1. Proposed hydrogen-bonded excited state.

cloaddition of these maleimides proceeds by a mechanism suggested by Mazzocchi et al. for related reactions observed with phthalimide.[14] Thus, it is reasonable to postulate that irradiation[15] of **15** leads to an excited state **18** in which the facial selectivity of the subsequent [2 + 2] photocycloaddition can be controlled by hydrogen bonding[16] between the hydroxyl group and the imide oxygen. Dreiding models were in good agreement with this, as was the observed stereochemistry of the product. After cycloaddition the zwitterionic intermediate **19** then undergoes spontaneous fragmentation to the product **16**.

In conclusion, we have demonstrated that the formal intramolecular [5 + 2] photocycloaddition of maleimides can be used as an efficient key step in a concise approach to the cephalotaxine skeleton. Particularly noteworthy is the unusual level of diastereoselection observed when the unprotected alcohol **15** is used as the cyclization precursor. This

(13) Allsop, A.; Brooks, G.; Edwards, P. D.; Kaura, A. C.; Southgate, R. *J. Antibiot*. **1996**, *49*, 921−928.

(14) (a) Mazzocchi, P. H.; Bowen, M.; Narain, N. *J. Am. Chem. Soc.* **1977**, *99*, 7063. (b) Mazzocchi, P. H.; Minamikana, S.; Wilson, P. *J. Org. Chem.* **1979**, *44*, 1186. (c) Mazzocchi, P. H.; Minamikana, S.; Wilson, P.; Bowen, M.; Narain, N. *J. Org. Chem.* **1981**, *46*, 4846. (d) Mazzocchi, P. H.; Khachik, F.; Wilson, P. *J. Am. Chem. Soc.* **1981**, *103*, 6498. (e) Mazzocchi, P. H.; Wilson, P.; Khachik, F.; Klingler, L.; Minamikana, S. *J. Org. Chem.* **1983**, *48*, 2981.

(15) Pyrex-filtered UV light from a 125-W medium-pressure Hg lamp was used throughout this study (see ref 6 for full details). The maleimides used in this and previous studies all have characteristic UV absorptions at 210−240 nm (strong) and 290−310 nm (weak). As a Pyrex-filtered UV source is used (>290 nm) it is likely that photocycloaddition arises from absorption in the 290−310 nm region.

selectivity is attributed to a hydrogen-bonded excited state. Present work is concerned with the application of this methodology to the total synthesis of cephalotaxine and other hexahydroazaazulene-based alkaloids.

(16) For previous examples of photocycloadditions controlled by H-bonding, see: (a) Bach, T.; Bergmann, H. *J. Am. Chem. Soc.* **2000**, *122*, 11525. (b) Bach, T.; Bergmann, H.; Harms, K. *J. Am. Chem. Soc.* **1999**, *121*, 10650.

Acknowledgment. We thank the EPSRC (postdoctoral grant GR/M14258) and AstraZeneca (CASE award to L.F.D.) for generous funding of this work.

Supporting Information Available: Experimental procedures and characterization of **8**, **9**, **11c**, **12c**, **13c**, **14c**, and **15**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016411H