Natural-Product Synthesis

A Rapid Stereocontrolled Entry to the ABCD Tetracyclic Core of Neotuberostemonine**

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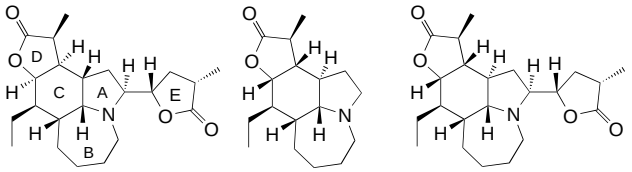
Neotuberostemonine (**1**), stenine (**2**), and tuberostemonine (**3**) are three of a number of complex polycyclic alkaloids isolated from the roots of stemonaceous plants. Extracts of these plants have long been used in China and Japan as



1 **2** **3**

human cough remedies and antihelminthics in domestic animals.[1] X-ray crystallography and 2D NMR spectroscopic studies have confirmed that neotuberostemonine differs from **2** and **3** at three of the contiguous stereocentres on the ACD ring junctures.[2] A number of syntheses of **2** have now been reported reported since the first successful total synthesis by Hart and Chen,[3] and include contributions from the groups of Wipf,[4] Morimoto,[5] and Padwa.[6] Morimoto et al.[7] have described a full account of their total synthesis of **2**, from which they aim to develop a strategy towards **3**. Very recently, Wipf et al.[8] described the first total synthesis of **3**. To date no synthesis of **1** has been reported.

Previously we demonstrated that *N*-alkenyl maleimide derivatives undergo a very powerful [5+2] photocycloaddition reaction to yield the hexahydroazaazulene ring system common to all the *Stemona* alkaloids. For example, irradiation of the maleimide **4** gave the tricyclic azepine **6** in excellent yield. The reaction is thought to proceed through the fragmentation of the zwitterionic [2+2] cycloadduct **5** formed initially (Scheme 1 a).[9] Recently, we showed that this reaction can be used to construct the tricyclic core of the

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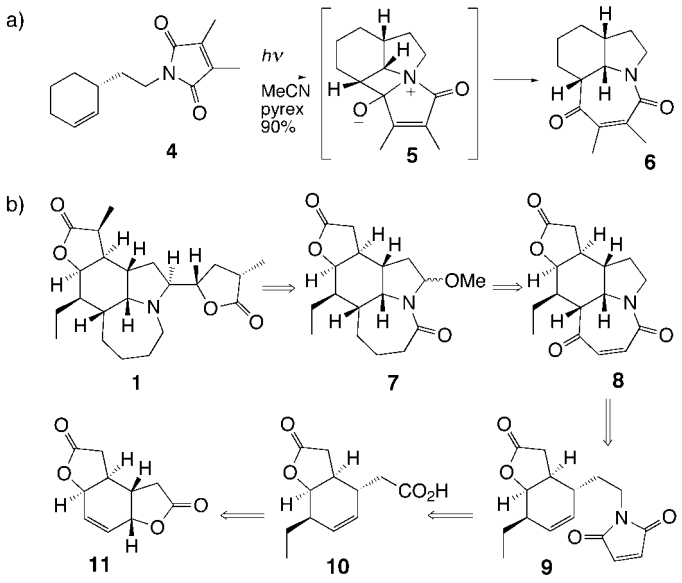
[**] This work was supported by a grant (GR/R02382/01) from the Engineering and Physical Sciences Research Council (EPSRC).

Supporting information for this article (NMR data and experimental details) is available on the WWW under http://www.angewandte.org or from the author.

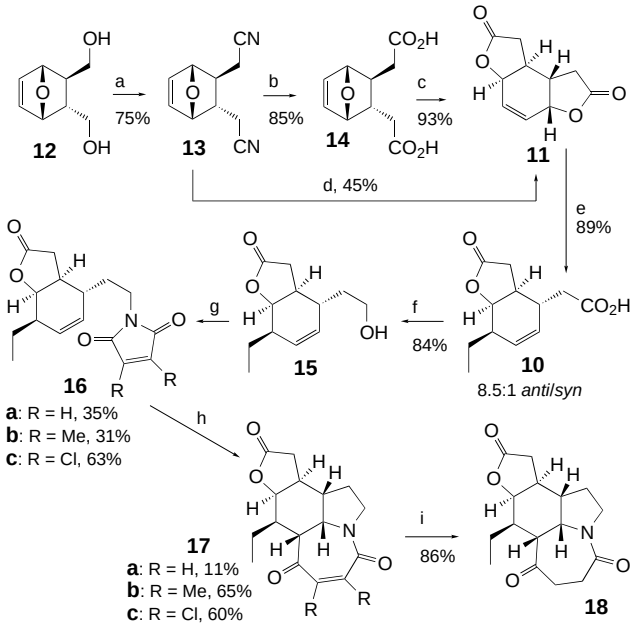
  DOI: 10.1002/ange.200250507



Scheme 1. a) The formation of the tricyclic azepine **6** in excellent yield by irradiation of maleimide **4** is thought to proceed via zwitterionic cycloadduct **5**. b) Retrosynthetic analysis of neotuberostemonine (**1**).

antileukemia alkaloid cephalotaxine.[10] As the azepine **6** contains three of the five rings of neotuberostemonine (**1**) we undertook a total synthesis program with the aim of synthesizing **1**, using our [5+2] photocycloaddition as the key step. The retrosynthetic analysis outlined in Scheme 1b illustrates our overall strategy. It was envisaged that the E ring could be installed in **7** by using elements of the elegant iminium ion chemistry developed both by Martin et al.[11] and by Morimoto et al.[12] in their independent studies on the synthesis of *Stemona* alkaloids. It is anticipated that the pyrrolidine ring of reduced derivatives of **8** will undergo selective alkoxylation by use of the Mn^{III} salen chemistry developed by Katsuki and Punniyamurthy.[13] The tetracycle **8** could, in turn, be assembled in a key step from the maleimide lactone **9** by using our [5+2] photocycloaddition. It was envisaged that the key cycloaddition precursor could be derived from the lactone acid **10** after chemoselective reduction and Mitsunobu coupling with maleimide. In one of a number of strategies it was conceived that **10** could derived from the C_2-symmetric bislactone **11** by way of an appealing cuprate-mediated S_N2' ring-opening desymmetrization sequence. *Anti*-selective ring-opening reactions of a monolactone related to **11** were recently reported by Helmchen and Bergner.[14]

Multigram quantities of the racemic diol **12** were easily prepared from furan and fumaryl chloride according to the Diels–Alder/reduction sequence described by Paquette et al.[15] Mesylation of **12** followed by treatment of the labile bismesylate with KCN gave the dinitrile **13** in 75% overall yield (Scheme 2). Compound **13** was easily converted into the diacid **14** by hydrolysis under basic conditions. Diacid **14** was then cyclized to the C_2-symmetric bislactone **11** by an acid-catalyzed tandem furan-ring-opening–lactonization sequence. This same sequence was also possible in a single hydrolytic step from **13**, albeit at the expense of overall yield. To our knowledge this acid-catalyzed bislactonization procedure is novel and may well prove to have application in the synthesis of other C_2-symmetric bislactones. Helmchen and Bergner described the successful S_N2' ring-opening of cyclohexene-fused lactones using an organocopper species derived from Grignard reagents and $CuBr{\cdot}Me_2S$.[14] Unfortunately, the bislactone **11** proved to be remarkably insoluble in most organic solvents and as a result the initial cuprate-mediated S_N2' ring-opening experiments based on the literature conditions met with failure. Eventually it was found that the use of *10 equivalents* of the organocopper reagent derived from $EtMgBr–CuBr{\cdot}Me_2S$ in a THF/Me_2S solvent mixture (2:1) led to the ring-opened lactone acid **10** in 89% yield as a separable mixture of isomers (*anti*/*syn* = 8.5:1). Use of less organocopper reagent led to very slow and incomplete conversion into product. Interestingly, ring opening of **11** with the less stereochemically demanding MeMgBr led to better *anti*/*syn* ratios (11:1). Selective reduction of the acid with the $NaBH_4$/mixed anhydride technique described by Zoutani et al.[16] gave the alcohol **15** in good yield. Mitsunobu coupling with maleimide, dimethylmaleimide, and dichloromaleimide then gave three photocyclization precursors **16** in low to moderate yields. Very pleasingly, irradiation of the dimethyl derivative **16b** was found to proceed without event and gave the key tetracycle **17b**[17] in 65% yield as a single diastereoomer (Scheme 2). The correct relative stereochemistry of **17b** was confirmed by X-ray crystallographic analysis (Figure 1). In



Scheme 2. Synthesis of the ABCD core of **1**: a) MsCl, Et_3N, Et_2O, 2 h, then KCN, DMSO, 100 °C, 5 h; b) KOH, EtOH, H_2O; c) *p*TSA, toluene, reflux; d) H_2SO_4 (6 M), heat, 2 h; e) EtMgBr (10 equiv), $CuBr{\cdot}Me_2S$ (10 equiv), THF/Me_2S (2:1), −20 °C; f) EtOCOCl, Et_3N, then $NaBH_4$; g) maleimide/dimethylmaleimide/dichloromaleimide, DIAD, PPh_3, THF, −78 °C→RT, 24 h; h) *hν*, pyrex, MeCN, 30–120 min; i) Zn, AcOH, room temperature, 1.5 h. Ms = methanesulfonyl, DMSO = dimethyl sulfoxide, *p*TSA = *para*-toluenesulfonic acid, DIAD = diisopropylazodicarboxylate.

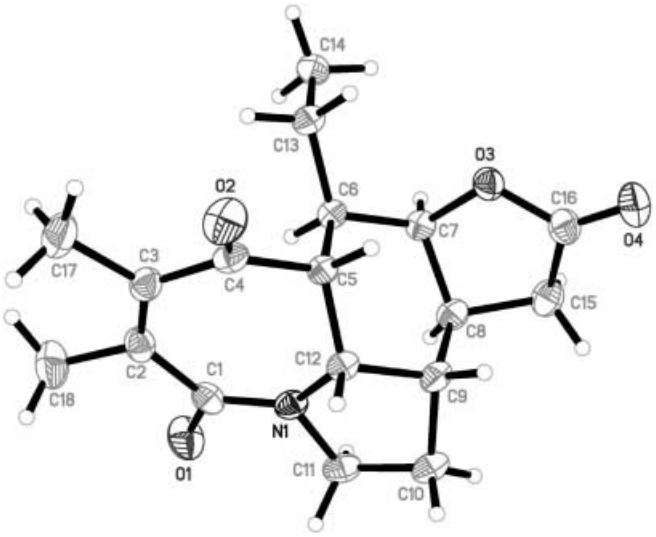


Figure 1. Molecular structure of the tetracyclic [5+2] photocycloadduct **17b** (R = Me). Ellipsoids set at the 50% probability level.

light of our previous experience with substrates derived from the parent maleimide, [9] it was perhaps not too surprising to find that **16a** (R = H) gave only a low yield (11%) of the corresponding photoadduct **17a**; the majority of the product underwent further photoreactions as it was formed. Fortunately the dichloro derivative **16c** underwent photolysis to give the [5+2] cycloadduct **17c** in 60% yield. Finally, reduction of the alkene, with concomitant dehalogenation, yielded the ketoamide **18** in excellent yield upon treatment of **17c** with zinc in acetic acid under our previously developed conditions.[9] This ketoamide has all the functionality necessary for completion of the synthesis of **1**. After reduction of the ketone and deoxygenation, we will investigate the installation of the methyl group of the lactone either by direct methylation or by a methylenation–hydrogenation sequence. Alkoxylation and lactone formation will be attempted as described in Scheme 1, after which thioamide formation and reduction with Raney nickel[3] should complete the synthesis of **1**.

In summary, an original route to the tetracyclic core of neotuberostemonine (**1**) has been described which highlights the application of the maleimide [5+2] photocycloaddition in natural-product synthesis. This linear route is notable for its brevity, partly a result of the fact that *no protecting groups* are used anywhere in the sequence—six steps to **17** from **12** by the shortest sequence. Also of note is a novel cuprate-mediated ring-opening desymmetrization of a C_2-symmetric bislactone, which may prove useful for the synthesis of other highly functionalized cyclohexene-fused butyrolactones. Present work is concerned with exploring the reactivity of **18** and ultimate implementation of this as an advanced intermediate for the total synthesis of **1**.

Received: November 8, 2002 [Z50507]

Keywords: asymmetric synthesis · cuprates · lactones · natural products · photocyclization · total synthesis

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[17] Crystal dimensions: $0.75 \times 0.60 \times 0.10$ mm^3, orthorhombic, space group *Pbca*, $a = 11.7444(16)$, $b = 7.6959(10)$, $c = 34.758(6)$ Å, $V = 3141.5(8)$ Å^3, $\rho_{calcd} = 1.342$, $2\theta_{max} = 55.0°$, $Mo_{K\alpha}$ radiation (0.71073 Å). Data were collected at 100 K as a series of frames, each covering 0.3° in ω, and integrated software (SAINT, Bruker 2001) to give a Lorentz polarization corrected data set of 18721 measured and 3579 independent reflections. An absorption correction (SADABS, Sheldrick 2001) was applied ($\mu = 0.094$, $T_{min} = 0.772$, $T_{max} = 1.000$). Solution and refinement (SHELXTL, Bruker-AXS 2001) against $|F^2|$ used 211 parameters with all hydrogen atoms constrained to ideal geometries and refined with isotropic displacement parameters equal to 1.5× (methyl) or 1.2× (all other hydrogen atoms) the equivalent isotropic displacement parameter of their parent atom. Final residuals: R_1 [2715 data with $I > 2\sigma(I)$] = 4.4%, wR_2 (all data) = 12.5%. Max/min residual electron density: +0.310, −0.265 e Å^{-3}. CCDC 196931 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).