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



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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Scheme 1. a) The formation of the tricyclic azepine **6** in excellent yield by irradiation of maleimide **4** is thought to proceed via zwitterionic cycload-duct **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 acidcatalyzed 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·Me₂S.^[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·Me₂S in a THF/Me₂S 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 NaBH₄/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 deriv-

ative **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, Et₃N, Et₂O, 2 h, then KCN, DMSO, 100 °C, 5 h; b) KOH, EtOH, H₂O; c) *p*TSA, toluene, reflux; d) H₂SO₄ (6 M), heat, 2 h; e) EtMgBr (10 equiv), CuBr·Me₂S (10 equiv), THF/Me₂S (2:1), -20 °C; f) EtOCOCl, Et₃N, then NaBH₄; g) maleimide/dimethylmaleimide/dichloromaleimide, DIAD, PPh₃, THF, -78 °C \rightarrow RT, 24 h; h) *hv*, 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.

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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.

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- [17] Crystal dimensions: $0.75 \times 0.60 \times 0.10$ mm³, orthorhombic, space group *Pbca*, a = 11.7444(16), b = 7.6959(10), c = 34.758(6) Å, $V = 3141.5(8) \text{ Å}^3$, $\rho_{\text{calcd}} = 1.342$, $2\theta_{max} = 55.0^\circ$, $Mo_{K\alpha}$ 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 $1.5 \times$ (methyl) or $1.2 \times$ (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 CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ ccdc.cam.ac.uk).