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A Protecting Group Free Synthesis of (±)-Neostenine via the [5 + 2] Photocycloaddition of Maleimides

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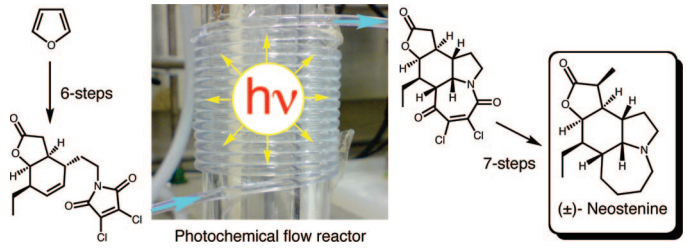

A concise, linear synthesis of the *Stemona* alkaloid (±)-neostenine is reported. Key features include an organocopper-mediated bislactone C_2-desymmetrization for the stereoselective construction of the cyclohexane−lactone C,D-rings. The assembly of the fused pyrrolo[1,2-*a*]azepine core was achieved by application of a [5 + 2] maleimide photocycloaddition. A custom FEP flow reactor was used to successfully overcome the scale limitations imposed by a classical immersion well batch reactor. The synthesis was completed in 14 steps from furan, in 9.5% overall yield, without the use of any protecting groups.

Introduction

The *Stemona* alkaloids are a diverse family of natural products isolated from Stemonaceae plant species. Nearly all members of this family contain the pyrrolo[1,2-*a*]azepine or perhydroazaazulene core. Unelaborated examples include stemoamide **1** and stemonine **2**; the latter contain a laterally fused butyrolactone ring that is prevalent throughout the *Stemona* alkaloids. The stenine group contains more intricate examples encompassing stenine **3** and pentacyclic member tuberostemonine **4**.[1] In 2003, neostenine **5** was isolated[2] from *Stemona tuberosa* and shown to be of the same stereogenicity as the previously characterized neotuberostemonine **6** and bisdehydroneotuberostemonine **7** (Figure 1).

For centuries, extracts of a variety of Stemonaceae plant species have been utilized in Chinese and Japanese traditional medicine as cough treatments for human diseases such as tuberculosis and bronchitis. The plants have also been used as antihelminthic agents in the treatment of parasitic infestation in humans and livestock. Subsequent pharmacological studies have demonstrated that **4** had an effect on the motility of three different species of helminthic worms.[3] Further studies on neuromuscular transmission in crayfish showed that **4** depressed glutamate-induced responses at levels similar to established inhibitors.[4] Significantly, Lin[2] reported that **5** and **6** possessed antitussive activity when tested against guinea pig models, thus identifying these as the likely active agents in Stemonaceae preparations used as cough suppressants. The stenine class of alkaloids has captured the attention of synthetic chemists over the last two decades, due in no small part to the intriguing and challenging array of seven contiguous stereocenters within a fused tetracyclic system. In 1990, Hart and Chen[5] published

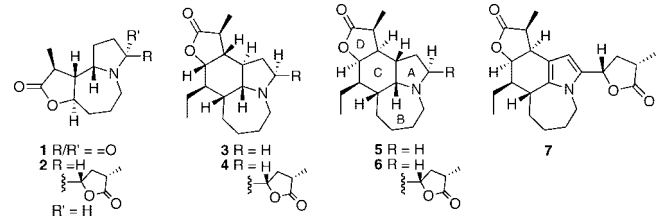

FIGURE 1. Representative examples of the *Stemona* alkaloids.

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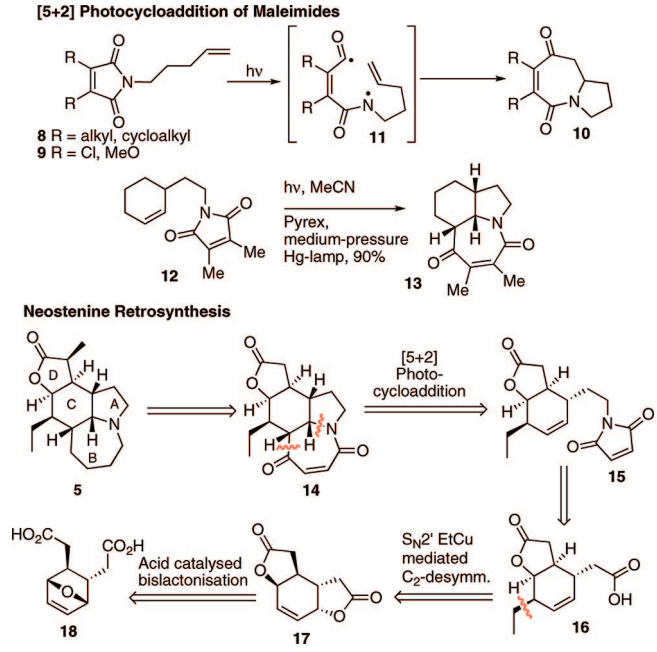
the first total synthesis of (±)-stenine which was followed by successful syntheses from Morimoto,[6] Padwa,[7] and Wipf.[8] In 2002, Wipf reported the total synthesis of (−)-tuberostemonine **4**, thus detailing the first successful approach to a pentacyclic member of the stenine family.[9] In 2005, Aubé reported an outstanding nine-step synthesis of (±)-stenine involving an elegant Diels−Alder/intramolecular Schmidt domino reaction strategy.[10] This group has very recently been able to modify their approach to deliver the first total synthesis of (±)-neostenine **5**.[11] In 2001, we embarked on a program to deliver neotuberostemonine **6** by a strategy that was to proceed via the use of an oxo derivative of neostenine **5** as an advanced intermediate.[12] At the time, **5** had not been identified, but following its isolation in 2003 it was evident that it would be within reach of our ongoing route to **6**.

For some time, we have had an interest in the application of organic photochemistry to the synthesis of natural products. While investigating a [2 + 2] photocycloaddition reaction of maleic anhydride derivatives,[13] we uncovered a powerful intramolecular [5 + 2] photocycloaddition of alkyl maleimides **8** which led directly to the pyrrolo[1,2-*a*]azepine **10** rather than the expected [2 + 2] adduct.[14,15] The reaction is general for a wide range of substrates, and use of chloro- or alkoxy-substituted maleimides **9** leads to further incorporation of useful functionality into the resulting azepines. Recent mechanistic studies of this process, using tunable UV lasers and time dependent-DFT, have led us to propose a singlet mechanism via cycloaddition of the diradical species **11**.[16] The ability of this reaction to deliver complex polycyclic fused azepine systems, exemplified in the cycloaddition of **12** to **13**, led us to investigate the application of it in alkaloid synthesis.[17] In particular, the all-cis stereochemistry observed for **13** made this photochemical strategy ideal as a key step in an approach to **5** and **6**. Our proposed retrosynthesis of neostenine involved an end game where the conjugated keto-amide functionality in the advanced tetracycle **14** would be reduced/deoxygenated and the lactone ring methylated to deliver **5**. Previously, we have described synthetic routes toward 7-desmethylasteriscanolide, pogostol, and kessane[18] which were devoid of standard protection/deprotection protocols, and so we were particularly keen that our stenine studies adhered to the same principles.[19]

SCHEME 1. Retrosynthetic Analysis of (±)-Neostenine 5



We proposed that construction of **14** would involve photocycloaddition of the maleimide−cyclohexene−lactone **15**, which in turn would be readily available from reduction of the acid **16** and Mitsunobu coupling of maleimide with its corresponding alcohol. Although a number of Diels−Alder/lactonization strategies were envisioned for the synthesis of **16**, it was considered that these would not improve upon existing methods used in previous total syntheses of related stenine congeners. Instead, we chose to attempt the preparation of **16** via a novel approach involving the anti-selective organocopper mediated S_N2' ring opening of C_2-symmetric bislactone **17**. A particularly appealing entry to **17** was conceived via acid-catalyzed bislactonization of the diacid **18** (Scheme 1).

Results and Discussion

Multigram quantities (>50 g) of diol (±)-**19** were readily available following Paquette's[20] sequential procedure for the Diels−Alder cycloaddition between furan and fumaryl chloride followed by reduction with $LiAlH_4$. Reaction of **19** with 2 equiv of MsCl followed by displacement with KCN gave dinitrile **20**

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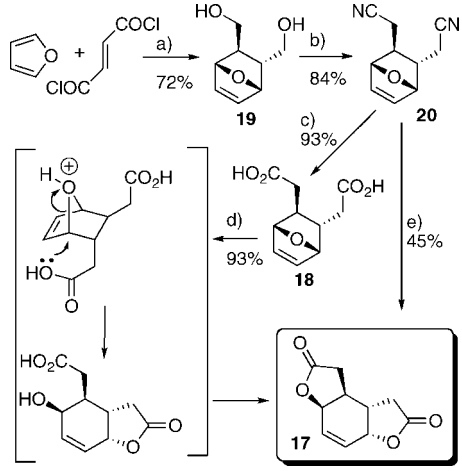
SCHEME 2. Synthesis of the C_2-Symmetric Bislactone 17[a]

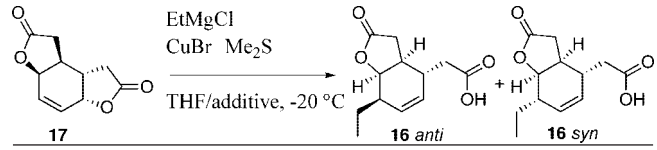


[a] Reagents and conditions: (a) THF, 0 °C, 2 h then $LiAlH_4$, 0 °C to rt, 48 h, 72% (ref 20); (b) (1) MsCl, Et_3N, THF, 25 °C, then KCN, DMSO, 100 °C, 84% overall; (c) KOH, H_2O, 100 °C, 93%; (d) *p*-TSA, PhMe, reflux, 93%; (e) H_2SO_4 (6 M), 100 °C, 2 h, 45%.

in 84% overall yield. Basic hydrolysis of **20** furnished key diacid **18** in good yield. We were then at the stage to examine the key acid-catalyzed bislactonization and were pleasantly surprised to see the clean formation of **17** on our first attempt with catalytic *p*-TSA on reflux in toluene. After optimization, the resulting highly crystalline bislactone could be consistently isolated in yields greater than 90%. The mechanism likely proceeds via protonation of the dihydrofuran oxygen followed by selective S_Ni cyclization of the *anti*-carboxylate and further lactonization of the resulting *syn*-hydroxy acid. It was also found that this could be achieved in one step from **20** by strong acid-promoted nitrile hydrolysis and concomitant cyclization of **18** in situ. Unfortunately, this attractive one-step procedure was not economic on scale-up (>3 mmol) as significant amounts of unidentified resinous material were formed from acid-catalyzed side reactions.

The subsequent step involved the attempted anti-selective organocopper-mediated S_N2' ring opening of **17** using conditions reported by Grieco,[21] Curran,[22] and Helmchen,[23] which typically employ 2−3 equiv of EtMgCl/CuBr·DMS and an unusual 2:1 solvent mixture of THF/DMS. The high crystallinity of **17** was a cause for concern, and even after it was ground into a fine powder it appeared to be completely insoluble in a range of solvents at room temperature. After a short optimization study, however, it was found that when a slurry of **17** was reacted with 10 equiv of EtMgCl/CuBr·DMS (1:1), the ring-opened and desymmetrized lactone−acid **16** was obtained as an 8.5:1 mixture of anti/syn isomers (Table 1, entry 1). Although these conditions were reproducible on a 2 mmol scale, we had great difficulty extending these to a larger scale, and >10 mmol resulted in incomplete reactions. DMPU (4 equiv) proved to be a useful substitute for DMS and gave good yields (81%) and a slightly improved anti/syn ratio (9.7:1; entry 6). Unfortunately, this variation also proved capricious on scale up, and complete removal of DMPU from product proved difficult. By reducing the amount of DMS cosolvent and equivalents of EtMgCl/CuBr·DMS an interesting trend was observed and a solution to scale up was achieved. Use of only 4 equiv of DMS gave a superior ratio of 12.2:1, which improved further to 14.2:1 when only 1 equiv was used (entries 2 and 4). Portionwise addition of solid **17** to a stirred solution of EtMgCl/CuBr·DMS (3 equiv) at −20 °C in the *absence* of DMS gave an isolated yield of **16** of 94% with an anti/syn ratio of 15.6:1 (entry 5). These latter conditions could be reliably applied to the reaction of **17** on scales of 30 mmol. This was a most surprising result in view of the apparent nonexistent solubility of **17** in pure THF at even room temperatures. On addition of solid **17** to the organocopper solution at −20 °C, the initially formed suspension is digested rapidly by reaction. Our experience with this reaction clearly demonstrates that the selectivity of the organocopper species resulting from EtMgCl/CuBr·DMS is significantly increased when the Me_2S cosolvent is omitted. It is possible that excess DMS (or DMPU) competes with the lactone rings in **17** for coordination to the Cu center, thus disrupting the anti mode of S_N2' ring opening.

TABLE 1. Optimization of Organocopper Ring-Opening of Bislactone 17



entry	EtMgCl (molar equiv)	CuBr·Me_2S (molar equi)	additive (molar equiv)	yield (%)	anti/syn
1	10	10	Me_2S (cosolvent)	89	8.5/1
2	3	3	Me_2S (4)	85	12.2/1
3	3	3	Me_2S (2)	84	13.8/1
4	3	3	Me_2S (1)	86	14.2/1
5	**3**	**3**	**none**	**94**	**15.6/1**
6	3	3	DMPU	81	9.7/1

Selective reduction of the carboxylic acid moiety of **16** in the presence of the lactone could be achieved by conversion to the mixed anhydride with ethyl chloroformate followed by reduction with $NaBH_4$.[24] In general, this sequence worked in consistently high yields, although prolonged reaction times with $NaBH_4$ led to decreased yields of **21** due to lactone ring opening. In preparation for the key [5 + 2] photocycloaddition, hydroxy lactone **21** was coupled to three different maleimides using Mitsunobu conditions (Scheme 3). This gave the three photosubstrates **22a−c** in moderate to good yield. Dimethyl substrate **22b** was chosen simply as a model, delivering a photoproduct that ought to be resistant to further photoreactions. The parent **22a** and the dichloro derivatives were the key subtrates for incorporation into the rest of the synthesis. Irradiation in a Pyrex immersion well photoreactor (125 W medium-pressure Hg lamp) with constant monitoring (TLC) of all three substrates led to the desired tetracyclic [5 + 2] photocycloaddition products **23a−c** in varying yields. Dimethyl adduct **23b** was formed in 75% yield as a single diastereomer, and X-ray crystallography confirmed that the relative stereochemistry was the same as that found in neostenine. The parent system **23a** was formed but in a meager yield (11%) with no recovery of starting material. This was not unexpected, as our previous experience with unsubstituted maleimides has shown that the [5 + 2] products are susceptible to further reactions including [2 + 2] dimerization and photodegradation. This unfortunately severely limits the use of the parent maleimides in synthesis and led us to investigate dichloromaleimides as alternatives. In our prior experience, the

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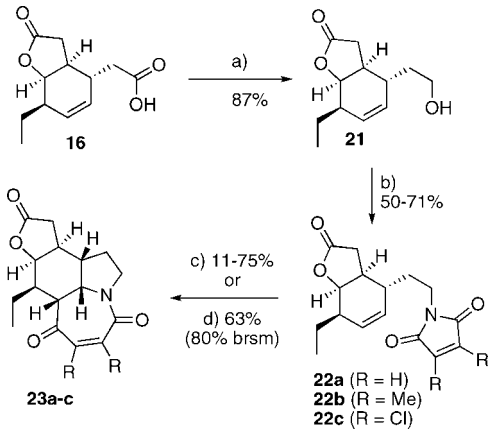
SCHEME 3. Synthesis of Cycloaddition Precursors 22a−c and Optimization of Key Photocycloaddition by a Custom FEP Flow Reactor[a]



[a] Reagents and conditions: (a) EtOCOCl, Et_3N, then $NaBH_4$; (b) maleimide/dimethylmaleimide/dichloromaleimide/Ph_3P, DEAD, THF, −78 °C to rt; (c) **22a−c**, *hν*, 125 W Hg lamp, Pyrex, CH_3CN; (d) **22c**, *hν*, 400 W Hg lamp, Pyrex 15-loop FEP flow reactor, CH_2Cl_2.

dichloro [5 + 2] adducts generally undergo slower photodegradation than their parent derivatives.

Initially, we were pleased to find that irradiation of **22c** gave 40−60% yields of the key cycloadduct **23c**, although all starting material had been consumed. These initial key test reactions were performed on a 50 mg scale in a 100 mL immersion well batch photoreactor using a 125 W medium-pressure Hg lamp. When scaled up to >100 mg batches, the yields of **23c** plummeted to below 20%, with total consumption of starting material. Attempts to carry out the reactions with larger but more dilute batches were met with equally disappointing results. This left us with the practical dilemma of proceeding with the synthesis of neostenine with a key reaction constrained to a 50 mg scale. This was clearly an untenable strategy as it would have involved multiple batch reactions and the loss of 40% of the photoprecursor **22c**.

During the evolution of this synthesis, we developed a novel flow reactor for continuous photochemical synthesis.[25] This reactor consisted of multiple loops of narrow bore fluorinated ethylene polymer (FEP) tubing wrapped tightly around a Pyrex water cooled immersion well containing a 125−400 W medium-pressure Hg lamp. This reactor proved capable of synthesizing maleimide/hex-1-yne [2 + 2] photoadducts on scales of >500 g per day using photolysates of up to 0.4 M. With this flow, reactor residence time (i.e., time of irradiation in reactor) could be controlled by flow rate and by reactor volume (length of FEP tubing in contact with UV lamp). We speculated that a custom flow reactor could be constructed which would allow the photolysis of **22c** to key intermediate **23c** on preparatively desirable scales. More specifically, it was felt that if a dilute solution of **22c** were to enter a low volume reactor at a high flow rate then the residence time would be kept very low, thus minimizing the degradation of product as it forms. If this were coupled with a high power UV source (400 W), then an acceptable balance of conversion vs degradation would be achieved that would be amenable to the scales required for a linear total synthesis.

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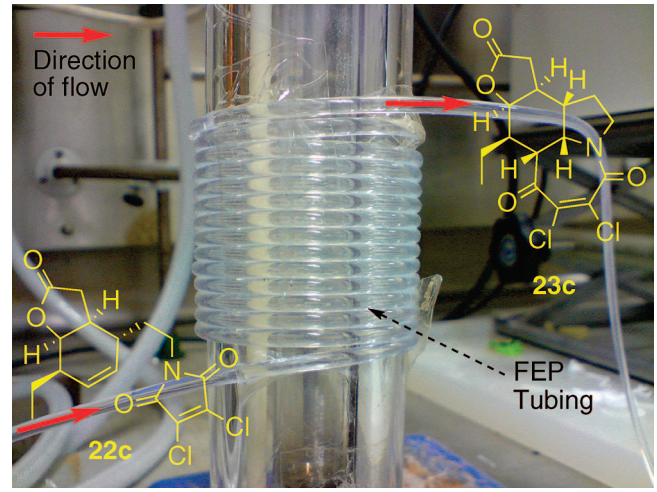
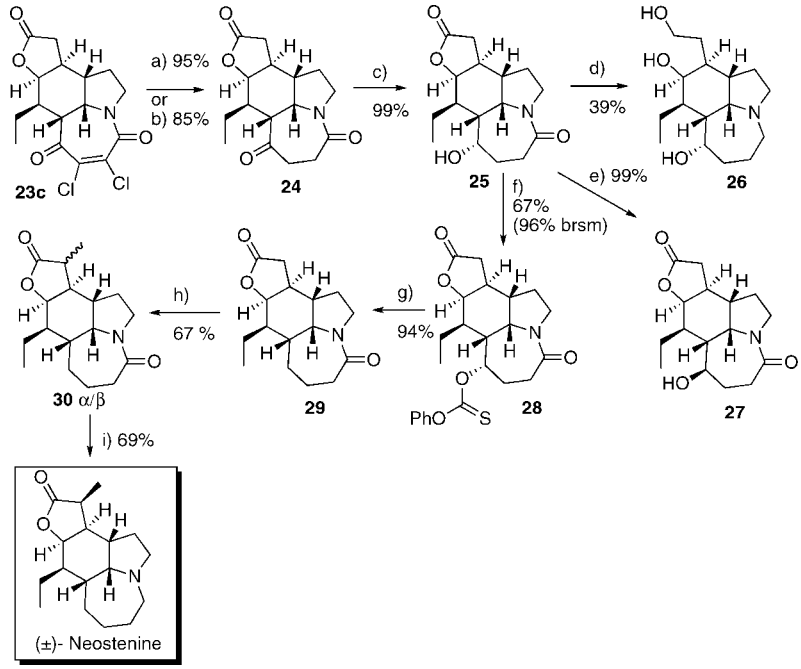


FIGURE 2. Custom high flow-rate/low volume continuous photochemical FEP reactor for the [5 + 2] photocycloaddition of maleimide **22c**.

After a great deal of experimentation, we found that construction of a reactor consisting of between 10 and 20 loops of FEP tubing wrapped around a custom water-cooled Pyrex immersion well gave promising results (Figure 2). After a number of optimization runs, we found that irradiation (400 W Hg lamp) of a 0.001 M solution of **22c** (2.1 g) in CH_2Cl_2 flowed through a 15-loop reactor (2 m FEP; 10 mL volume) at a flow rate of 11 mL min^{-1} allowed the isolation of 63% of **23c** and the recovery of 20% unreacted **22c**. This was a real breakthrough and enabled the synthesis of 1.3 g of the key [5 + 2] photoadduct in a single 9 h run. The importance of this cannot be overstated: to process 2.1 g of **22c** in batch at anywhere near this conversion would have required *42 successive* conventional immersion well irradiations, each on a maximum scale of 50 mg and with no recovery of starting material. We believe that high flow rate/low volume reactors configured in this way will prove generally useful for the scale up of sensitive photochemical reactions.

With a reliable, scale-tolerant route to **23c** now secured, we proceeded to the completion of neostenine, which involved selective reduction/deoxygenation of the B-ring functionality and stereoselective introduction of the methyl group in the lactone D-ring. Reduction of **23c** with either Pd/C/H_2 or Zn/AcOH[14] led to the reduced/dechlorinated product **24** in excellent yields. Hydrogenation was rather scale limited, as it required an excess of Pd/C to effect complete reduction. It was interesting to note that hydrogenation of **23c** with 10% Pd/C was slow and led to significant epimerization at the keto-stereocenter in **24**. More reproducible results were obtained with a Zn/AcOH reduction on various scales (0.5−0.8 g). The key to success with this latter reduction was to keep reaction times ≤1 h as prolonged reactions led to lower yields with the formation of unidentified high molecular weight compounds—perhaps through further acid-catalyzed aldol-type dimerization reactions of **24**. Considerable time was then spent investigating a variety of methods to reduce the ketone in **24** to the corresponding methylene, initially opting for a reduction/Barton−McCombie strategy. Preliminary attempts to selectively reduce the ketone in **24** with a variety of well-known metal hydride reagents were met with low yields and competing lactone reduction. Eventually, it was found that quantitative reduction to alcohol **25** could be achieved using $LiAl(O^tBu)_3H$.[26] Attempts were then made

SCHEME 4. Completion of the Total Synthesis of (±)-Neostenine 5[a]



[a] Reagents and conditions: (a) Zn, AcOH, 1 h; (b) $Pd/C/H_2$, K_2CO_3, MeOH, 1 atm; (c) $LiAl(O^tBu)_3H$, THF, 0 °C, 3 h; (d) (1) MsCl, Et_3N, THF; (2) $LiAlH_4$, THF, reflux; (e) 5% $InCl_3$, $ClPh_2SiH$, CH_2Cl_2, reflux, 16 h; (f) PhOCSCl, DMAP (1.5 equiv), CH_2Cl_2, reflux, 7 h; (g) Bu_3SnH, AIBN, C_6H_6, reflux, 30 min; (h) (1) LHMDS, MeI, THF, −78 °C (95%; $\alpha/\beta = 1/7$); (2) LHMDS, BHT, THF, −78 °C to rt (70%; $\alpha/\beta = 5/1$); (i) 5% $RhH(CO)(PPh_3)_3$, Ph_2SiH_2, THF, 30 min.

to convert **25** to suitable thiocarbonyl derivatives for Bu_3SnH-mediated deoxygenation using various reported reagent combinations and conditions. Unfortunately, all of these were met with failure, and only starting alcohol was recovered. It was clear that the hydroxyl group in **25** was very hindered, and a different reduction strategy was sought. Eventually, conditions were found where **25** could be converted to the corresponding mesylate; however, reduction with excess $LiAlH_4$ gave only triol amine **26** where the key alkoxy bond had remained intact. This was very likely a result of S−O cleavage due to shielding of the C−OMs bond by the concave environment of the ABC ring skeleton. It had been reported by Baba[27] that secondary alcohols could be reduced to alkanes by a $Ph_2SiHCl/InCl_3$ reductive protocol. To our surprise, the sole product isolated from this attempted reduction was inverted alcohol epimer **27** in quantitative yield. Clearly, reductive C−O cleavage had not taken place, and further investigations are ongoing to elucidate the mechanism and generality of this interesting inversion process. Investigations using a number of other techniques for the deoxygenation of **24** including Clemmensen, modified Shapiro, thioacetal formation then RaNi or Bu_3SnH, and enol triflate/phosphate then hydrogenation were unsuccessful, with many problems occurring during derivitization.

At this point, it was decided to return to the Barton−McCombie deoxygenation strategy and investigate more reactive conditions for thiocarbonate formation. Eventually, it was found that reaction of **25** with PhOCSCl with 1.5 equiv of DMAP[28] in refluxing CH_2Cl_2 led to the formation of the hindered thiocarbonate **28**. Unfortunately, **28** proved to be unstable to prolonged heating under the reaction conditions, and it was found that it was best to isolate this after 7 h (67%) and recover the unreacted starting material (29%) to recycle. Treatment of **28** under standard Bu_3SnH/AIBN conditions gave the long sought after deoxygenated lactone−amide **29** in excellent yield. Methylation of **29** with LHMDS/MeI gave methyl lactones **30** as a 7:1 mixture of epimers in favor of the unnatural β-epimer (95%). This was not unexpected, as simple molecular models of the enolate of **30** suggested that alkylation may proceed from the more accessible β-face (rear). We then investigated epimerization via an enolization/protonation sequence from the β-face. Pleasingly, treatment of the enolate of **30** with 10 equiv of 2,6-di-*tert*-butyl-4-methylphenol[29] (BHT) gave oxoneostenine **30** as a 5:1 mixture of α/β-epimers. Finally, reduction of purified (crystallization) **30**α to (±)-neostenine **5** was conveniently achieved, in one step, using a selective amide reduction with $RhH(CO)(PPh_3)_3/Ph_2SiH_2$ under conditions described by Ito.[30] These very selective conditions were particularly attractive as all previous Stenine alkaloid syntheses have adopted a two-step thionation/Ra−Ni reduction endgame to reduce the 7-membered amide. As such, this result highlights the usefulness of this catalyst/reagent combination for the reduction of amides in the presence of other metal hydride sensitive functionality (Scheme 4).

Conclusion

A unique total synthesis of (±)-neostenine **5** has been achieved in 14 linear steps from furan, in a strategy devoid of standard protection/deprotection protocols. Key findings include a novel approach to C_2-symmetric bislactones via the acid-

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catalyzed bislactonization of bridged bicyclic dihydrofuran acids. The C_2-symmetric bislactones have been shown to be useful substrates for the anti-selective EtMgCl/CuBr·DMS-mediated S_N2' ring opening to the neostenine C,D-ring system. Contrary to literature conditions, this organocopper ring opening gave the best selectivities in the absence of any additives such as DMS or DMPU. The key to this synthesis was the application of our [5 + 2] photocycloaddition maleimide reaction. This allowed the construction of the perhydroazaazulene A,B-rings and furnished the tetracyclic neostenine ring system in a single step. Crucial to the success of this, however, has been the novel application of our continuous FEP photochemical flow reactor technology. Adopting a high flow rate/low volume reactor topology coupled with a high power UV source has allowed the scale up of a key photochemical reaction that was severely limited in batch and thus unsustainable in our original route. We believe that our findings may stimulate others to adopt flow reactors for similarly sensitive or scale-compromised photoreactions. Present studies are concerned with adaptation of our current chemistry to provide concise routes to neotuberostemonine **5** and bisdehydroneotuberostemonine **6**.

Experimental Section

(±)-(1*R*,2*S*,3*S*,4*S*)-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-diyldimethanol (19).[20] Fumaryl chloride (95%, 80.48 g, 500 mmol) was added dropwise to furan (34.03 g, 500 mmol) over a period of 30 min at 0 °C. The mixture was stirred for a further 1 h, at which point the reaction mixture had solidified. THF (500 mL) was added, and the resulting solution was added dropwise to a solution of $LiAlH_4$ (438 mL, 2.4 M in THF, 1050 mmol) in THF (750 mL) at 0 °C, allowed to warm to rt, and stirred for 48 h. The reaction mixture was carefully quenched by addition of NaOH (2 M, 200 mL) at 0 °C, stirred for 4 h, allowed to warm to rt, filtered through Celite, and washed with THF (8 × 600 mL) and then THF/MeOH (4:1, 4 × 400 mL). The combined organic extracts were concentrated in vacuo and subjected to column chromatography (10% MeOH in EtOAc) to yield **19** (56.2 g, 72%) as a yellow oil: IR (film) 3338, 2926, 1318, 1083, 1029, 981 cm^{-1}; ^1H (400 MHz; $CDCl_3$) δ 1.43−1.47 (1H, m), 2.09−2.14 (1H, m), 2.51 (2H, s), 3.26 (1H, dd, J = 9.5 and 9.0 Hz), 3.52 (1H, dd, J = 10.0 and 6.5 Hz), 3.64 (1H, dd, J = 10.0 and 8.0 Hz), 3.79 (1H, dd, J = 10.0 and 6.5 Hz), 4.74 (1H, s), 4.95 (1H, d, J = 4.0 Hz), 6.31 (1H, dd, J = 6.0 and 1.0 Hz), 6.47 (1H, dd, J = 6.0 and 2.0 Hz); ^{13}C (101 MHz; $CDCl_3$) δ 45.4 (CH_2), 46.4 (CH_2), 64.4 (CH), 65.0 (CH), 79.7 (CH), 80.6 (CH), 133.3 (CH), 136.8 (CH); *m/z* (E.I.) 155 (5, M^+) 138 (20), 120 (26), 84 (65), 68 (100).

(±)-2,2′-((1*R*,2*R*,3*R*,4*S*)-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-diyl)diacetonitrile (20). To a solution of **19** (19.2 g, 123 mmol) and Et_3N (51.4 mL, 369 mmol) in THF (500 mL) at 0 °C was added methanesulfonyl chloride (20.2 mL 27 mmol) dropwise over 20 min, and then the mixture was allowed to warm to rt and stirred for a further 2.5 h. Solvent was removed in vacuo and the residue partitioned between CH_2Cl_2 (500 mL) and water (300 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL), and the organic layers were combined, washed with brine (150 mL), dried over $MgSO_4$, and concentrated in vacuo to yield the bis-mesylate (38.1 g, 99%) as a labile, pale yellow oil which was used immediately in the proceeding step: IR (film) 1330, 1166, 954, 812 cm^{-1}; ^1H (270 MHz; $CDCl_3$) δ 1.63−1.70 (2H, m), 3.01 (3H, s), 3.03 (3H, s), 3.88 (1H, dd, J = 9.9 and 9.6 Hz), 4.11 (1H, dd, J = 10.2 and 6.9 Hz), 4.20−4.33 (2 H, m), 4.81 (1H, s), 5.01 (1H, d, J = 4.0), 6.40 (1H, dd, J = 5.9 and 1.7 Hz), 6.50 (1H, dd, J = 5.9 and 1.7 Hz); ^{13}C (101 MHz; $CDCl_3$) δ 37.6 (2 × CH_3), 42.7 (CH), 43.0 (CH), 70.2 (CH_2), 71.2 (CH_2), 79.5 (CH), 79.9 (CH), 133.8 (CH), 136.8 (CH); *m/z* (C.I.) 313 (22, $[M + H]^+$) 217 (27), 149 (65), 121 (100), 93 (46); HRMS found $[M + H]^+$, 313.0419, $C_{10}H_{17}O_7S_2$ requires 313.0416.

Potassium cyanide (3.1 g, 48.0 mmol) was added in one portion to a solution of the freshly prepared bis-mesylate (5.0 g, 16.0 mmol) in DMSO (128 mL) and heated to 100 °C for 4 h. After being cooled to rt, the reaction mixture was extracted with Et_2O/THF (1:1), (3 × 100 mL), the organic layers were combined concentrated in vacuo and partitioned between Et_2O (150 mL) and water (150 mL), and the aqueous layer was extracted with further Et_2O (3 × 100 mL). The organic layers were combined, dried over $MgSO_4$, concentrated in vacuo, and subjected to column chromatography (10% MeCN in CH_2Cl_2) to yield **20** (2.3 g, 84%) as a pale yellow oil: IR (film) 2248, 1424, 1353, 1326, 1173, 1002, 885 cm^{-1}; ^1H (400 MHz; $CDCl_3$) δ 1.58 (1H, dt, J = 7.6 and 3.5 Hz), 2.06−2.12 (1H, m), 2.18 (1H, dd, J = 16.6 and 8.3 Hz), 2.34 (1H, dd, J = 16.6 and 7.3 Hz), 2.53 (1H, dd, J = 16.6 and 8.3 Hz), 2.60 (1H, dd, J = 16.6 and 7.3 Hz), 4.73 (1H, s), 5.01 (1H, d, J = 4.4 Hz), 6.40 (1H, dd, J = 6.0 and 1.6 Hz), 6.56 (1H, dd, J = 5.9 and 1.7 Hz); ^{13}C (101 MHz; $CDCl_3$) δ 19.9 (CH_2), 21.7 (CH_2), 41.8 (CH), 42.0 (CH), 80.6 (CH), 82.5 (CH), 118.0 (CH), 118.6 (CH), 133.3 (CH), 137.6 (CH); *m/z* (C.I.) 175 (31, $[M + H]^+$) 148 (97), 134 (48), 121 (20), 107 (100), 80 (94); HRMS found $[M + H]^+$, 175.0865, $C_{10}H_{11}N_2O$ requires 175.0871.

(±)-2,2′-((1*R*,2*R*,3*R*,4*S*)-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-diyl)diacetic Acid (18). The dinitrile **20** (9.7 g, 55.7 mmol) was heated to reflux for 4 h in aqueous potassium hydroxide solution (1.27 M). After completion, the reaction was allowed to cool, acidified to pH 1 with HCl (2 M), and extracted with EtOAc (3 × 300 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated in vacuo to yield **18** (11.0 g, 93%) as a colorless powder: mp 124−126 °C; IR (film) 3012, 1707, 1409 and 891 cm^{-1}; ^1H (270 MHz; CD_3OD) δ 1.49−1.56 (1H, m), 1.98−2.16 (2H, m), 2.31−2.49 (2H, m), 2.63 (1H, dd, J = 16.5 and 6.6 Hz), 4.60 (1H, s), 4.94 (1H, d, J = 4.0 Hz), 6.34 (1H, dd, J = 5.9 and 1.3 Hz), 6.50 (1H, dd, J = 5.9 and 1.7 Hz); ^{13}C (101 MHz; CD_3OD) δ 39.0 (CH_2), 40.3 (CH_2), 43.1 (CH), 43.7 (CH), 83.2 (CH), 85.1 (CH), 135.5 (CH), 138.7 (CH), 177.1 (CH), 177.5 (CH); *m/z* (C.I.) 213 (43, $[M + H]^+$) 195 (47), 149 (60), 121 (36), 99 (92), 81 (44); HRMS found $[M + H]^+$, 213.0765, $C_{10}H_{13}O_5$ requires 213.0763. Anal. Calcd for $C_{10}H_{13}O_5$: C, 56.76; H, 5.75. Found: C, 56.60; H, 5.70.

(±)-(3a*R*,5a*R*,8a*S*,8b*S*)-1,8,8a,8b-Tetrahydrobenzofuro[5,4-*b*]furan-2,7-(3a*H*,5a*H*)-dione (17). (a) A solution of **18** (11.0 g, 51.8 mmol) and *p*-TSA (2.5 g, 13.0 mmol) in toluene (300 mL) was heated to reflux for 3 h. After the solution was allowed to cool, it concentrated in vacuo and triturated using CH_2Cl_2 (150 mL) to yield **17** (9.4 g, 93%) as a colorless solid: 210 °C dec; IR (film) 1755, 1421, 1317, 1187, 1175, 1003, 984 cm^{-1}; ^1H (270 MHz; CD_3OD) δ 2.44 (2H, dd, J = 17.5 and 8.6 Hz), 2.69 (2H, dd, J = 17.5 and 8.3 Hz), 2.87−2.98 (2H, m), 5.08 (2H, dd, J = 5.9 and 1.3 Hz), 6.10 (2H, d, J = 1.7 Hz); ^{13}C (101 MHz; $CDCl_3$) δ 32.8 (CH_2), 34.6 (CH), 72.6 (CH), 127.5 (CH), 177.5 (CH); *m/z* (C.I.) 195 (70, $[M + H]^+$) 177 (17), 149 (100), 135 (57), 121 (43); HRMS found $[M + H]^+$, 195.0667, $C_{10}H_{11}O_4$ requires 195.0657. Anal. Calcd for $C_{10}H_{11}O_4$: C, 61.85; H, 5.19. Found: C, 62.10; H, 5.38.

(b) Compound **20** (420 mg, 2.4 mmol) was heated at reflux in 6 M sulfuric acid (7 mL) for 30 min. Water (20 mL) was added to the cooled reaction mixture extracted with CH_2Cl_2 (4 × 30 mL). The organic layers were combined, washed with brine (30 mL), dried over $MgSO_4$, concentrated in vacuo, and subjected to column chromatography (EtOAc/CH_2Cl_2 1:2) to yield 17 (210 mg, 45%) as a colorless solid. The material was found to be identical in all aspects to that prepared in (a).

(±)-2-((3a*S*,4*R*,7*R*,7a*R*)-7-Ethyl-2-oxo-2,3,3a,4,7,7a-hexahydrobenzofuran-4-yl)acetic Acid (16). Copper bromide−dimethyl sulfide complex (18.51 g, 90 mmol) was placed in a 250 mL RBF equipped with a large magnetic stirring bar and covered with anhydrous THF (60 mL). Ethylmagnesium chloride (45 mL, 2 M in THF, 90 mmol) was added dropwise via syringe at −20 °C. After 30 min of stirring, **17** (5.82 g, 30 mmol) was added portionwise as a solid (best done out of a vial) over 5 min and stirring continued for a further 1 h

while the reaction mixture was allowed to warm to 0 °C. HCl (2M, 50 mL) was then carefully added dropwise (gas formation). The organic solvent was then removed in vacuo and the residue diluted with HCl (2 M, 50 mL) and water (100 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and dry-loaded onto SiO_2 (20 g). Purification by flash column chromatography (SiO_2 100 g, hexane/EtOAc 1:1 and 1% AcOH) yielded a small amount of *syn*-**16** as a colorless solid (0.4 g, 6%). Further elution gave *anti*-**16** as a colorless solid (5.9 g, 88%): mp 106−109 °C; IR (film) 3109, 1770, 1731, 1705, 1416, 1158, 988, 726 cm^{-1}; ^1H (400 MHz; $CDCl_3$) δ 0.98 (3H, t, J = 7.3 Hz), 1.44−1.66 (2H, m), 2.20−2.26 (1H, m), 2.31−2.35 (1H, m), 2.36−2.45 (4H, m), 2.75 (1H, dd, J = 17.2 and 7.2 Hz), 4.66 (1H, t, J = 4.4 Hz), 5.58 (1H, d, J = 10.3 Hz), 5.7s3 (1H, dt, J = 10.3 and 2.7 Hz), 11.54 (1H, s); ^{13}C (101 MHz; $CDCl_3$) δ 11.8 (CH_3), 24.5 (CH_2), 34.4 (CH_2), 37.8 (CH), 38.4 (CH_2), 38.5 (CH), 38.9 (CH), 80.7 (CH), 127.9 (CH), 128.9 (CH), 177.3 (CH), 177.5 (CH); *m*/*z* (C.I.) 225 (56, $[M + H]^+$), 207 (78), 179 (66), 165 (66), 133 (76), 119 (100); HRMS found $[M + H]^+$, 225.1126, $C_{12}H_{17}O_4$ requires 225.1127. Anal. Calcd for $C_{12}H_{17}O_4$: C, 64.27; H, 7.19. Found: C, 64.49; H, 7.41.

(±)-(3a*S*,4*R*,7*R*,7a*R*)-7-Ethyl-4-(2-hydroxyethyl)-3a,4,7,7a-tetrahydrobenzofuran-2(3*H*)-one (21). Ethyl chloroformate (3.0 mL, 31.7 mmol) was added dropwise to a solution of **16** (4.7 g, 21.1 mmol) and Et_3N (8.9 mL, 63.4 mmol) in THF (200 mL) at −20 °C and stirred for 30 min. A solution of sodium borohydride (8.0 g, 211.3 mmol) in water (105 mL) was cautiously added at −20 °C and the mixture allowed to warm to rt over 20 min with stirring. The reaction mixture was extracted with CH_2Cl_2 (3 × 200 mL), and the combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and subjected to column chromatography (EtOAc/hexane 1:1) to yield **21** (3.9 g, 87%) as a pale yellow oil: IR (film) 3420, 1760, 1156, 1056, 907, 705 cm^{-1}; ^1H (270 MHz; $CDCl_3$) δ 1.02 (3H, t, J = 7.4 Hz), 1.41−1.73 (5H, m), 2.03−2.13 (1 H, m), 2.20−2.43 (3 H, m), 2.74 (1H, dd, J = 17.2 and 7.3 Hz), 3.72 (2H, t, J = 6.4 Hz), 4.66 (1H, t, J = 4.5 Hz), 5.58 (1H, d, J = 10.2), 5.70 (1H, dt, J = 10.2 and 3.0 Hz); ^{13}C (101 MHz; $CDCl_3$) δ 11.9 (CH_3), 24.6 (CH_2), 34.5 (CH), 37.4 (CH_2), 38.1 (CH), 38.7 (CH_2), 38.9 (CH), 60.4 (CH_2), 80.8 (CH), 128.1 (CH), 129.0 (CH), 177.2 (C); *m*/*z* (C.I.) 211 (44, $[M + H]^+$), 193 (88), 181 (40), 165 (46), 151 (68), 147 (76), 133 (100), 119 (42); HRMS found $[M + H]^+$, 211.1325, $C_{12}H_{19}O_3$ requires 211.1334.

(±)-3,4-Dichloro-1-(2-((3a*S*,4*R*,7*R*,7a*R*)-7-ethyl-2-oxo-2,3,3a,4,7,7a-hexahydrobenzofuran-4-yl)ethyl)-1*H*-pyrrole-2,5-dione (22c). Diisopropyl azodicarboxylate (2.6 mL, 13.0 mmol) was added to a cooled solution of triphenylphosphine (3.6 g, 13.6 mmol) in THF (120 mL) at −78 °C and stirred for 2 h, after which a pale yellow precipitate formed. A solution of **21** (3.0 g, 14.2 mmol) in THF (3 mL) was added dropwise and stirred for 15 min after which dichloromaleimide (1.6 g, 13.0 mmol) was added in one portion. The resulting yellow solution was stirred for 10 min and allowed to warm to rt over 16 h. The reaction mixture was concentrated in vacuo and subjected to column chromatography (Et_2O/hexane 4:1) to yield **22c** (3.3 g, 71%) as pale yellow oil: IR (film) 1768, 1720, 1397, 1156, 877, 728 cm^{-1}; UV−vis (ν_{max}) 285 nm; ^1H (400 MHz; $CDCl_3$) δ 1.01 (3H, t, 7.3 Hz), 1.48−1.69 (3H, m), 1.79−1.86 (1H, m), 1.90−1.97 (1H, m), 2.19−2.26 (1H, m), 2.30 (1H, d, 17.2 Hz), 2.35−2.40 (1H, m), 2.76 (1H, dd, 16.8 and 7.3 Hz), 3.57−3.69 (2H, m), 4.67 (1H, t, 4.8 Hz), 5.61 (1H, d, 10.3 Hz), 5.70 (1H, dt, 10.3 and 2.9 Hz); ^{13}C (75 MHz; $CDCl_3$) δ 11.7 (CH_3), 24.4 (CH_2), 32.3 (CH_2), 35.3 (CH), 36.7 (CH_2), 37.9 (CH), 38.0 (CH), 38.4 (CH_2), 80.4 (CH), 127.5 (CH), 129.2 (CH), 133.4 (C), 162.9 (C), 176.5 (C); *m*/*z* CI 358 (8, $[M + H]^+$), 342 (58), 340 (73), 314 (25) 312 (36), 300 (33), 298 (48), 193 (27), 175 (16), 147 (93), 133 (100), 119 (16), 108 (38), 95 (15), 79 (12); HRMS found $[M + H]^+$, 358.0608, $C_{16}H_{18}NO_4Cl_2$ requires 358.0613.

Continuous Flow Photochemical Reactor. Flow reactors were constructed according to the literature method using between 15 and 20 loops of FEP tubing (2.7 mm inner diameter) wrapped around a water-cooled Pyrex immersion well.[24] The system was flushed with clean solvent before use. The substrate was dissolved in the stated solvent, and nitrogen was bubbled through the mixture for 5 min to remove dissolved oxygen. A 400 W medium-pressure mercury lamp was inserted into the well and switched on 5 min before commencing flow of the substrate solutions. Using a Masterflex peristaltic pump, the solution was pumped at the specified flow rate through the reactor system. After complete uptake of the substrate solution, a volume of clean solvent 2× the internal volume of the reactor was passed through the system and collected with the product solution before the lamp was turned off. The resulting mixtures were concentrated in vacuo and typically purified by column chromatography and/or recrystallization. Alternatively, the outflow tubing of the reactor can be connected to a rotary evaporator and the photosylate continuously evaporated as it exits the reactor.

(±)-(3^1*S*,7a*R*,8*R*,8a*S*,11a*S*,11b*S*)-5,6-Dichloro-8-ethyl-1,2,8,8a,11,11a-hexahydroazepino[3,2,1-*hi*]furo[3,2-e]indole-4,7,10(3^1*H*,7a*H*,11b*H*)-trione (23c). A solution of **22c** (2.1 g, 5.8 mmol) was dissolved in CH_2Cl_2 (5.8 L) and passed through a 15-loop FEP flow reactor (2 m of FEP tubing; 10 mL reactor volume) at 11 mL min^{-1} (8 h 50 min) after which a further portion of CH_2Cl_2 (50 mL) was passed through the reactor. The combined photosylates were concentrated in vacuo and subjected to column chromatography (20% EtOAc in hexane) to yield recovered **22c** as a pale yellow oil (0.4 g, 20%). Further elution gave **23c** (1.3 g, 63%) as a colorless solid: 198 °C dec; IR (film) 1776, 1635, 1418, 1195, 1157, 906, 733 cm^{-1}; ^1H (400 MHz; CD_3Cl) δ 0.99 (3H, t, J = 7.3 Hz), 1.27−1.39 (1H, m), 1.55−1.67 (1H, m), 1.79−1.84 (1H, m), 1.96−2.12 (2H, m), 2.20−2.25 (1H, m), 2.27−2.32 (1H, m), 2.43 (1H, d, J = 17.3 Hz), 2.89 (1H, dd, J = 17.1 and 7.3 Hz), 3.27 (1H, dd, J = 12.5 and 3.2 Hz), 3.76−3.92 (2H, m), 4.11 (1H, dd, J = 4.6 and 3.4 Hz), 4.68 (1H, dd, J = 4.9 and 2.9 Hz); ^{13}C (101 MHz; CD_3Cl) δ 11.0 (CH_3), 22.6 (CH_2), 28.0 (CH_2), 34.4 (CH), 36.3 (CH), 37.9 (CH_2), 42.5 (CH), 48.9 (CH_2), 49.7 (CH), 55.6 (CH), 78.0 (CH), 138.7 (C), 140.4 (C), 157.9 (C), 175.0 (C), 189.7 (C); *m*/*z* (C.I.) 358 (100, $[M + H]^+$) 322 (70), 288 (30), 262 (12), 147 (18), 133 (24); HRMS found $[M + H]^+$, 358.0616, $C_{16}H_{18}NO_4Cl_2$ requires 358.0613.

(±)-(3^1*S*,7a*R*,8*R*,8a*S*,11a*S*,11b*S*)-8-Ethyloctahydroazepino[3,2,1-*hi*]furo[3,2-*e*]indole-4,7,10-(3^1*H*,7a*H*,11b*H*)-trione (24). Zinc powder (2.9 g, 44.8 mmol) was activated by stirring with glacial acetic acid (40 mL) for 20 min at rt. A solution of **23c** (0.8 g, 2.2 mmol) in glacial acetic acid (28 mL) was added and stirred at rt for 1 h. The reaction mixture was then filtered through Celite, washed with EtOAc (3 × 50 mL), concentrated in vacuo, and subjected to column chromatography (10% MeOH in EtOAc) to yield **24** (0.6 g, 95%) as a colorless solid: IR (film) 1771, 1702, 1631, 1423, 1178, 906 cm^{-1}; ^1H (400 MHz; CD_2Cl_2) δ 1.03 (3H, t, J = 7.2 Hz), 1.15−1.32 (3H, m), 1.63 (1H, dd, J = 12.8 and 6.0 Hz), 1.90−2.00 (1H, m), 2.25 (1H, d, J = 16.5 Hz), 2.46−2.55 (3H, m), 2.58−2.68 (2H, m), 2.78−2.88 (2H, m), 2.94−3.04 (1H, m), 3.17 (1H, dt, J = 11.9 and 6.0 Hz), 3.99 (1H, dd, J = 11.8 and 7.1 Hz), 4.07 (1H, d, J = 8.2 Hz), 4.94 (1H, dd, J = 8.4 and 6.8 Hz); ^{13}C (101 MHz; CD_2Cl_2) δ 15.7 (CH_3), 20.7 (CH_2), 28.6 (CH_2), 32.7 (CH_2), 35.0 (CH_2), 35.6 (CH), 35.7 (CH_2), 41.5 (CH), 42.9 (CH), 45.3 (CH_2), 58.3 (CH), 79.5 (CH), 80.3 (CH), 172.0 (C), 178.0 (C), 207.3 (C); *m*/*z* (C.I.) 292 (100, $[M + H]^+$) 274 (9), 246 (7), 232 (31), 147 (8), 133 (7); HRMS found $[M + H]^+$, 292.1548, $C_{16}H_{22}NO_4$ requires 292.1549.

(±)-(3^1*S*,7*S*,7a*R*,8*R*,8a*S*,11a*S*,11b*S*)-8-Ethyl-7-hydroxydecahydroazepino[3,2,1-*hi*]furo[3,2-*e*]indole-4,10(3^1*H*,11b*H*)-dione (25). To a solution of **24** (71 mg, 0.24 mmol) in THF (25 mL) was added 1.0 M $LiAl(O^tBu)_3H$ solution in THF (0.24 mL, 0.24 mmol) dropwise at 0 °C and the mixture allowed to stir at rt for 3 h. The reaction mixture was quenched by the dropwise addition of H_2O (0.3 mL) and allowed to stir for 30 min. The mixture was filtered through Celite, and the filter cake was washed with THF (5 × 15 mL). The solution was concentrated in vacuo onto silica gel and

subjected to column chromatography (10% MeOH in CH_2Cl_2) to yield **25** (71 mg, 99%) as a colorless crystalline solid: IR (film) 3378, 1759, 1627, 906 cm^{-1}; ^1H (400 MHz; CD_2Cl_2) δ 0.94 (3H, t, J = 7.5 Hz), 1.43−1.54 (1H, m), 1.60 (1H, ddt, J = 12.5, 6.8 and 2.2 Hz), 1.73−1.94 (4H, m), 2.02 (1H, ddd, J = 14.2, 7.5 and 4.0 Hz), 2.06−2.17 (2H, m), 2.19−2.26 (1H, m), 2.31 (1H, dd, J = 17.3 and 1.5 Hz), 2.39 (1H, ddd, J = 15.6, 11.4 and 4.5 Hz), 2.63 (1H, ddd, J = 15.5, 6.1 and 3.7 Hz), 2.83 (1H, dd, J = 17.2 and 7.7 Hz), 3.36−3.46 (1H, m), 3.72−3.76 (1H, m), 3.79 (1H, dd, J = 5.4 and 2.7 Hz), 3.93 (1H, dt, J = 10.4 and 2.9 Hz), 4.75 (1H, dd, J = 5.4 and 2.4 Hz); ^{13}C (101 MHz; CD_2Cl_2) δ 11.5 (CH_3), 21.5 (CH_2), 26.6 (CH_2), 28.8 (CH_2), 34.7 (CH), 35.6 (CH_2), 36.5 (CH), 38.4 (CH_2), 40.1 (CH), 43.5 (CH), 47.4 (CH_2), 59.7 (CH), 76.6 (CH), 80.0 (CH), 173.7 (C), 176.3 (C); *m*/*z* (C.I.) 294 (100, $[M + H]^+$) 276 (30), 265 (4), 234 (4), 216 (4), 192 (3); HRMS found $[M + H]^+$, 294.1704, $C_{16}H_{24}NO_4$ requires 294.1705.

(±)-(3^1*S*,7*S*,7a*R*,8*R*,8a*S*,11a*S*,11b*S*)-8-Ethyl-4,10-dioxotetradecahydroazepino[3,2,1-*hi*]furo[3,2-*e*]indol-7-yl Methanesulfonate. To a solution of **25** (70 mg, 0.24 mmol) and Et_3N (166 μL, 1.2 mol) in THF (20 mL) was added methanesulfonyl chloride (74 μL, 0.96 mmol) dropwise at 0 °C and the mixture allowed to stir at rt for 5 min. The reaction mixture was concentrated in vacuo onto silica gel and subjected to column chromatography (5% MeOH in CH_2Cl_2) to give the mesylate **25a** (89 mg, 99%) as a colorless crystalline solid: IR (film) 1773, 1628, 1461, 1350, 1170 cm^{-1}; ^1H (400 MHz; DMSO-d_6) δ 0.96 (3H, t, J = 7.3 Hz), 1.31−1.41 (1H, m), 1.54−1.58 (1H, m), 1.73−1.85 (3H, m), 1.93−2.06 (1H, m), 2.11−2.16 (3H, m), 2.33 (1H, d, J = 17.2 Hz), 2.44−2.54 (2H, m), 2.64 (1H, ddd, J = 15.5, 6.3 and 3.0 Hz), 2.91 (1H, dd, J = 17.2 and 7.6 Hz), 3.03 (3H, s), 3.40 (1H, m), 3.64 (1H, dd, J = 8.9 and 7.6 Hz), 3.92 (1H, dd, J = 4.5 and 2.5 Hz), 4.78 (1H, dd, J = 4.3 and 2.0 Hz), 4.88 (1H, dt, J = 10.8 and 3.2 Hz); ^{13}C (101 MHz; DMSO-d_6) δ 11.6 (CH_3), 21.8 (CH_2), 24.9 (CH_2), 28.7 (CH_2), 32.1 (CH_2), 33.7 (CH), 34.9 (CH_2), 36.1 (CH), 38.2 (CH_2), 38.4 (CH), 43.3 (CH_3), 47.5 (CH_2), 58.7 (CH), 79.5 (CH), 85.5 (CH), 172.3 (C), 176.9 (C); *m*/*z* (C.I.) 371 (3, $[M + H]^+$) 323 (35), 322 (56), 292 (28), 290 (44), 276 (70) 178 (48), 102 (73), 97 (100), 86 (52), 65 (52); HRMS found $[M + Na]^+$, 394.1308, $C_{17}H_{25}NaNO_6S$ requires 394.1295.

(±)-(3^1*S*,7*S*,7a*R*,8*R*,9*S*,10*S*,10a*S*)-8-Ethyl-10-(2-hydroxyethyl)-dodecahydroazepino[3,2,1-*hi*]indole-7,9-diol (26). To a slurry of $LiAlH_4$ (100 mg, 2.6 mmol) in THF (10 mL) was added **25a** (125 mg, 0.34 mmol) at 0 °C and then heated at reflux for 1 h. The reaction mixture was quenched with water (0.1 mL), 15% NaOH (0.1 mL), and additional water (0.3 mL). After 1 h, the mixture was filtered through Celite, and the filter cake was washed with THF (5 × 10 mL), concentrated in vacuo onto silica gel, and subjected to column chromatography (CH_2Cl_2/MeOH/NH_3 200:8:1) to give **26** (39 mg, 39%) as a colorless oil: IR (film) 3364, 1119 and 972 cm^{-1}; ^1H (400 MHz; D_3OD) δ 0.94 (3H, t, J = 7.3 Hz), 1.33−1.43 (2H, m), 1.52−1.80 (7H, m), 1.84−2.00 (4H, m), 2.10−2.17 (1H, m), 2.43−2.50 (2H, m), 2.70−2.75 (1H, m), 2.89 (1H, dt, J = 12.2 and 4.3 Hz), 3.10 (1H, dt, J = 10.5 and 7.2 Hz), 3.56−3.73 (2H, m), 3.93 (1H, t, J = 1.8 Hz), 4.09 (1H, dt, J = 8.6 and 3.1 Hz); ^{13}C (101 MHz; D_3OD) δ 10.7 (CH_3), 21.7 (CH_2), 22.9 (CH_2), 27.8 (CH_2), 30.3 (CH_2), 32.9 (CH_2), 39.5 (CH), 41.0 (CH), 41.5 (CH), 42.7 (CH), 55.4 (CH_2), 59.2 (CH_2), 66.5 (CH), 68.8 (CH), 70.5 (CH); *m*/*z* (C.I.) 284 (9, $[M + H]^+$) 266 (16), 115 (30), 79 (100); HRMS found $[M + H]^+$, 284.2216, $C_{16}H_{30}NO_3$ requires 284.2226.

(±)-(3^1*S*,7*R*,7a*R*,8*R*,8a*S*,11a*S*,11b*S*)-8-Ethyl-7-hydroxydecahydroazepino[3,2,1-*hi*]furo[3,2-*e*]indole-4,10(3^1*H*,11b*H*)-dione (27). To a solution of **25** (10 mg, 0.03 mmol) and chloro(diphenyl)silane (16 μL, 0.07 mmol) in CH_2Cl_2 (1 mL) was added $InCl_3$ (0.4 mg, 5 mol%) stirred at reflux for 16 h. The reaction mixture was allowed to cool to rt at which point a precipitate was observed. The reaction mixture was filtered and the solid washed with CH_2Cl_2 (3 × 2 mL). The solid was dissolved in acetone (15 mL) and filtered, and the filtrate was then concentrated in vacuo to give **27** (10 mg, 99%) as a colorless crystalline solid: IR (film) 3087, 1755, 1686, 1249, 1155, 913 cm^{-1}; ^1H (400 MHz; $CD_3C(O)$) δ 1.05 (3H, t, J = 7.3 Hz), 1.49−1.59 (1H, m), 1.91−1.99 (1H, m), 2.15−2.24 (2H, m), 2.34−2.54 (7H, m), 2.46 (1H, d, J = 16.9 Hz), 2.68−2.78 (1H, m), 2.98 (1H, dd, J = 16.9 and 6.4 Hz), 3.77−3.92 (2H, m), 4.43−4.49 (1H, m), 4.86 (1H, dd, J = 3.7 and 3.4 Hz), 5.06 (1H, ddd, J = 10.3, 6.1, and 2.9 Hz); ^{13}C (101 MHz; $CD_3C(O)$) δ 10.6 (CH_3), 21.5 (CH_2), 25.8 (CH_2), 28.1 (CH_2), 29.9 (CH_2), 34.4 (CH), 35.5 (CH), 36.5 (CH), 37.4 (CH_2), 40.2 (CH), 45.5 (CH_2), 59.6 (CH), 78.0 (CH), 78.8 (CH), 175.0 (C), 175.6 (C); *m*/*z* (C.I.) 294 (100, $[M + H]^+$) 276 (48), 250 (6), 232 (9), 216 (8), 115 (75), 99 (5), 95 (13), 79 (46), 59 (90); HRMS found $[M + H]^+$, 294.1692, $C_{16}H_{24}NO_4$ requires 294.1705.

(±)-*O*-(3^1*S*,7*S*,7a*R*,8*R*,8a*S*,11a*S*,11b*S*)-8-Ethyl-4,10-dioxotetradecahydroazepino[3,2,1-*hi*]furo[3,2-*e*]indol-7-yl *O*-Phenyl Carbonothioate (28). To a solution of **25** (175 mg, 0.6 mmol) and DMAP (112 mg, 0.9 mmol) in CH_2Cl_2 (20 mL) was added *o*-phenyl chlorothionoformate (98 μL, 0.7 mmol) dropwise and the mixture allowed to stir at reflux for 7 h 15 min. The reaction mixture was concentrated in vacuo onto silica gel and subjected to column chromatography (2% MeOH in CH_2Cl_2) to yield **28** (172 mg, 67%) as a colorless crystalline solid (mp 209−210 °C) and recovered **25** (51 mg, 29%): IR (film) 1776, 1623, 1576, 1403, 1294, 1194 cm^{-1}; ^1H (400 MHz; $CDCl_3$) δ 0.98 (3H, t, J = 7.3 Hz), 1.46−1.56 (1H, m), 1.63 (1H, dd, J = 12.5, and 6.4 Hz), 1.78−1.97 (3H, m), 2.07−2.21 (4H, m), 2.38 (1H, d, J = 17.1 Hz), 2.48−2.56 (1H, m), 2.57−2.65 (1H, m), 2.79−2.90 (2H, m), 3.49 (1H, dt, J = 11.9 and 6.4 Hz), 3.86−3.91 (2H, m), 4.73 (1H, dd, J = 3.9 and 2.2), 5.49 (1H, dt, J = 7.0 and 3.2 Hz), 7.11 (2H, dd, J = 8.4 and 1.1 Hz), 7.27−7.33 (1H, m), 7.39−7.46 (2H, m); ^{13}C (101 MHz; $CDCl_3$) δ 11.4 (CH_3), 21.3 (CH_2), 23.3 (CH_2), 28.5 (CH_2), 34.1 (CH_2), 35.5 (CH), 36.7 (CH), 37.6 (CH), 38.4 (CH_2), 43.7 (CH), 47.7 (CH_2), 59.7 (CH), 79.6 (CH), 87.8 (CH), 122.0 (CH), 126.8 (CH), 129.7 (CH), 153.3 (C), 172.9 (C), 176.0 (C), 193.8 (C); HRMS found $[M + Na]^+$ 452.1495, $C_{23}H_{28}NaNO_5S$ requires 452.1502.

(±)-(3^1*R*,7a*R*,8*R*,8a*R*,11a*S*,11b*S*)-8-Ethyldecahydroazepino[3,2,1-*hi*]furo[3,2-*e*]indole-4,10(3^1*H*,11b*H*)-dione (29). A solution of **28** (143 mg, 0.33 mmol), AIBN (16 mg, 0.11 mmol), and tributyltin hydride (181 μL, 0.66 mmol) in benzene (12 mL) was heated at reflux for 30 min. The cooled reaction mixture was concentrated in vacuo onto silica gel and subjected to column chromatography (1% MeOH in CH_2Cl_2) to give **29** (87 mg, 94%) as a colorless crystalline solid after recrystallization from EtOAc (mp 172−173 °C): IR (film) 1765, 1617, 1430, 1263, 1008 cm^{-1}; ^1H (300 MHz; $CDCl_3$) δ 0.97 (3H, t, J = 7.3 Hz), 1.27−1.43 (1H, m) 1.44−1.73 (6H, m), 1.76−1.91 (1H, m), 2.02−2.20 (4H, m), 2.33 (1H, d, J = 16.9 Hz), 2.26−2.39 (1H, m), 2.64−2.74 (1H, m), 2.81 (1H, dd, J = 16.9 and 6.9 Hz), 3.40 (1H, dt, J = 11.9 and 6.2 Hz), 3.77 (1H, dd, J = 4.8 and 2.0 Hz), 3.90 (1H, dd, J = 12.3 and 8.4 Hz), 4.65 (1H, dd, J = 4.5 and 2.4 Hz); ^{13}C (101 MHz; CD_3CO) δ 11.2 (CH_3), 17.8 (CH_2), 20.9 (CH_2), 28.4 (CH_2), 31.0 (CH_2), 33.4 (CH), 33.7 (CH), 37.1 (CH), 38.7 (CH_2), 39.7 (CH_2), 43.5 (CH), 47.5 (CH_2), 61.8 (CH), 80.1 (CH), 175.2 (C), 176.4 (C); *m*/*z* (C.I.) 278 (100, $[M + H]^+$), 233 (4), and 218 (3); HRMS found $[M + H]^+$, 278.1753, $C_{16}H_{24}NO_3$ requires 278.1756.

(±)-(3^1*R*,7a*R*,8*R*,8a*R*,11*R*,11a*R*,11b*S*)-8-Ethyl-11-methyldecahydroazepino[3,2,1-*hi*]furo[3,2-*e*]indole-4,10(3^1*H*,11b*H*)-dione (30*β*). To a solution of **29** (112 mg, 0.41 mmol) in THF (20 mL) at −78 °C was added LiHMDS (0.43 mL, 0.43 mmol) dropwise and the mixture allowed to stir at −78 °C for 1 h. Iodomethane (76 μL, 1.2 mmol) was added dropwise at −78 °C and the mixture allowed to stir for 2 h. The reaction mixture was quenched with IPA (2 mL) and allowed to warm to rt over 30 min. The reaction mixture was concentrated in vacuo onto silica gel and subjected to column chromatography using (1% MeOH in CH_2Cl_2) to give **30** (112 mg, 95%) as a colorless crystalline solid as a 1:7 mixture of α/*β*-epimers. Major isomer: ^1H (400 MHz; $CDCl_3$) δ 0.95 (3H, t, J = 7.2 Hz), 1.28−1.38 (1H, m), 1.32 (3H, d, J = 7.6 Hz), 1.46−1.62 (6H, m),

1.78−1.89 (2H, m), 1.92−2.04 (2H, m), 2.08−2.16 (1H, m), 2.33 (1 H, ddd, J = 15.0, 10.9 and 3.9 Hz), 2.43 (1H, dq, J = 7.6 and 2.0 Hz), 2.59−2.67 (1H, m), 3.37 (1H, ddd, J = 12.2, 10.4 and 6.7 Hz), 3.75−3.85 (2H, m), 4.76 (1H, dd, J = 5.5 and 2.6 Hz); ^{13}C (101 MHz; $CDCl_3$) δ 11.0 (CH_3), 15.3 (CH_3), 17.6 (CH_2), 20.6 (CH_2), 28.5 (CH_2), 30.2 (CH_2), 33.4 (CH), 33.9 (CH), 38.8 (CH_2), 42.9 (CH), 43.6 (CH), 44.6 (CH), 46.9 (CH_2), 60.8 (CH), 77.3 (CH), 174.5 (C), 179.2 (C).

(±)-(3^1*R*,7a*R*,8*R*,8a*R*,11*S*,11a*R*,11b*S*)-8-Ethyl-11-methyldecahydroazepino[3,2,1-*hi*]furo[3,2-*e*]indole-4,10(3^1*H*,11b*H*)-dione (30α). LiHMDS (0.42 mL, 0.42 mmol) was added dropwise to a stirred solution of **30α/β** (1:7) (112 mg, 0.38 mmol) in THF (30 mL) at −78 °C. After 10 min, the reaction mixture was allowed to warm to rt for 15 min and then cooled back down to −78 °C. A 1 M solution of BHT (3.8 mL, 3.8 mmol) was added dropwise at −78 °C and the mixture allowed to stir for 2 h. The reaction mixture was warmed to rt, then concentrated in vacuo onto silica gel, and subjected to column chromatography (1% MeOH in CH_2Cl_2) to give a mixture of **30α/β** (5:1) (78 mg, 70%) (mp 167−169 °C). This was then recrystallized from EtOAc to give pure **30α** as a colorless crystalline solid: IR (film) 1769, 1630, 1423, 1168, 978 cm^{-1}; ^{1}H (400 MHz; $CDCl_3$) δ 0.99 (3H, t, J = 7.3 Hz), 1.29 (3H, d, J = 7.3 Hz), 1.31−1.74 (7H, m), 1.80−1.93 (1H, m), 2.06−2.22 (4H, m), 2.30−2.38 (1H, m), 2.73 (1H, dd, J = 16.4 and 6.8 Hz), 2.95 (1H, quin, J = 6.6 Hz), 3.41 (1H, dt, J = 12.2 and 6.1 Hz), 3.79 (1H, dd, J = 4.4 and 1.95 Hz), 3.94 (1H, dd, J = 12.3 and 8.4 Hz), 4.58 (1H, t, J = 3.1 Hz); ^{13}C (101 MHz; $CDCl_3$) 9.6 (CH_3), 11.2 (CH_3), 17.8 (CH_2), 20.7 (CH_2), 29.3 (CH_2), 31.2 (CH_2), 33.4 (CH), 33.5 (CH), 38.5 (CH), 39.9 (CH_2), 40.7 (CH), 42.2 (CH), 47.4 (CH_2), 62.1 (CH), 78.4 (CH), 175.3 (C), 178.8 (C); *m*/*z* (C.I.) 292 (100, $[M + H]^+$), 278 (2), 247 (4), 218 (9); HRMS found $[M + H]^+$, 292.1909, $C_{17}H_{26}NO_3$ requires 292.1913.

(±)-Neostenine (5). $RhH(CO)(PPh_3)_3$ (6 mg, 5 mol %) was added in a single portion to a solution of **30α** (35 mg, 0.1 mmol) and diphenylsilane (44 μL, 0.23 mmol) in THF (4 mL) and the mixture allowed to stir for 30 min. The reaction mixture was loaded directly onto an IST CBA cartridge (1 g, 0.7 mmol) and washed with MeCN (2 × 5 mL). Then cartridge was then eluted with 2 × 5 mL volumes of a Et_3N/MeCN solution (1/3 v/v). The eluent was concentrated in vacuo to give (±)-neostenine **5** (23 mg, 70%) as a colorless crystalline solid which was recrystallized from EtOAc: mp 122−123 °C (lit.[2] mp 90−92 °C; lit.[11] 126−128 °C); IR (film) 1765, 1171, 953 cm^{-1}; ^{1}H (400 MHz; CD_3Cl) δ 0.99 (3H, t, J = 7.5 Hz), 1.21 (3H, d, J = 7.5 Hz), 1.36−1.48 (2H, m), 1.57−1.91 (10H, m), 1.92−2.04 (1H, m), 2.23−2.48 (4H, m), 2.81−2.90 (2H, m), 3.17−3.25 (1H, m), 4.51 (1H, dd, J = 4.0 and 2.5 Hz); ^{13}C (101 MHz; CD_3Cl) δ 10.1 (CH_3), 11.3 (CH_3), 21.1 (CH_2), 21.2 (CH_2), 28.1 (CH_2), 28.4 (CH_2), 30.2 (CH_2), 34.3 (CH), 37.3 (CH), 37.4 (CH), 42.5 (CH), 42.9 (CH), 55.6 (CH_2), 55.9 (CH_2), 70.9 (CH), 79.3 (CH), 179.6 (C); *m*/*z* (C.I.) 278 (100, $[M + H]^+$), 233 (8), 204 (10), 191 (7); HRMS found $[M + H]^+$, 278.2116, $C_{17}H_{28}NO_2$ requires 278.2120.

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Supporting Information Available: Copies of ^{1}H/^{13}C spectra of all new compounds and the X-ray crystallographic files (CIF) for **23b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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