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General route to the total synthesis of sempervirine analogues containing modified E rings, potential cytostatics†

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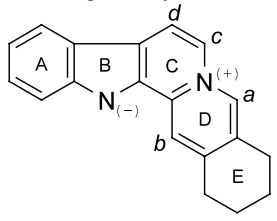
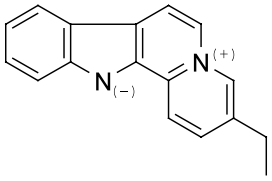
Abstract—Sempervirine analogues **13a–c** with different E rings have been obtained via inverse electron demand Diels–Alder reactions of 5-acetyl-3-(methylsulfanyl)-1,2,4-triazine with cyclic enamines (formation of D and E rings) followed by Fischer indole synthesis under microwave irradiation on solid support (formation of A and B rings) and subsequent annulation of indole derivatives **10a–c** via a directed metallation route (formation of C rings).

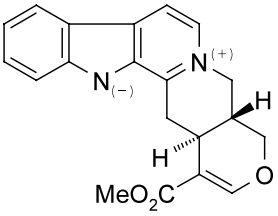
Sempervirine **1** is a representative of a family of indolo[2,3-*a*]quinolizine alkaloids represented by flavopereirine **2**, serpentine **3** and alstonine **4** which exhibit an interesting combination of biological activity. In addition to cytostatic effects they show anti-HIV,[1] immunostimulant, sedative and antipsychotic activities.[2] Sempervirine was first isolated in 1916 from *Gelsenium sempervirens*.[3] Since then several routes have been developed for its preparation.[4–7] Interestingly, there is no report on the synthesis and biological properties of sempervirine analogues containing a modified core system. As part of an ongoing medicinal chemistry program, we were interested in a convenient synthesis of sempervirine analogues **13a–c** which have a cyclopentene, cycloheptene or cyclooctene moiety in place of the original cyclohexene E ring.



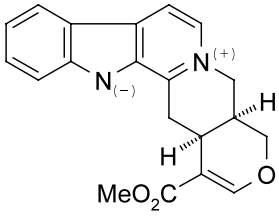
Sempervirine **1**



Flavopereirine **2**



Serpentine **3**



Alstonine **4**

We have recently reported the formation of substituted 3,4-cycloalkenopyridines via an inverse electron demand Diels–Alder reaction of 5-acyl-1,2,4-triazines.[8] This procedure was used for a model synthesis of 3-acetyl-1-(methylsulfanyl)-5,6,7,8-tetrahydroisoquinoline **8** ($n=2$) which was transformed (via the Fischer reaction) into 2-[3-(5,6,7,8-tetrahydroisoquinolinyl)]indole **10** ($n=2$),[9] a key intermediate in the total synthesis of sempervirine **1** described by Gribble.[6] In a later study, we have improved the final step of this synthesis by using microwave irradiation instead of conventional heating during the construction of the indole ring.[10] Based on these findings, we have been engaged in the total synthesis of sempervirine analogues **13a–c** with the goal of performing structure–activity relationship studies, in pursuit of potent cytostatics. Our total synthetic plan was based on the fact that these analogues could be accessed via the Diels–Alder reaction of readily available 5-acetyl-3-(methylsulfanyl)-1,2,4-triazine **5**[11] with cyclic enamines **6a–c**, followed by the Fischer indole synthesis of bicyclic intermediates **8a–c** and subsequent annulation of the appropriately protected indole derivatives **11a–c** via a directed metallation route (Scheme 1).

An intermolecular Diels–Alder reaction of **5** with an equimolar amount of 1-pyrrolidino-1-cyclopentene **6a**

Keywords: indolo[2,3-*a*]quinolizinium alkaloids; aza Diels–Alder reaction; solvent free microwave assisted synthesis.

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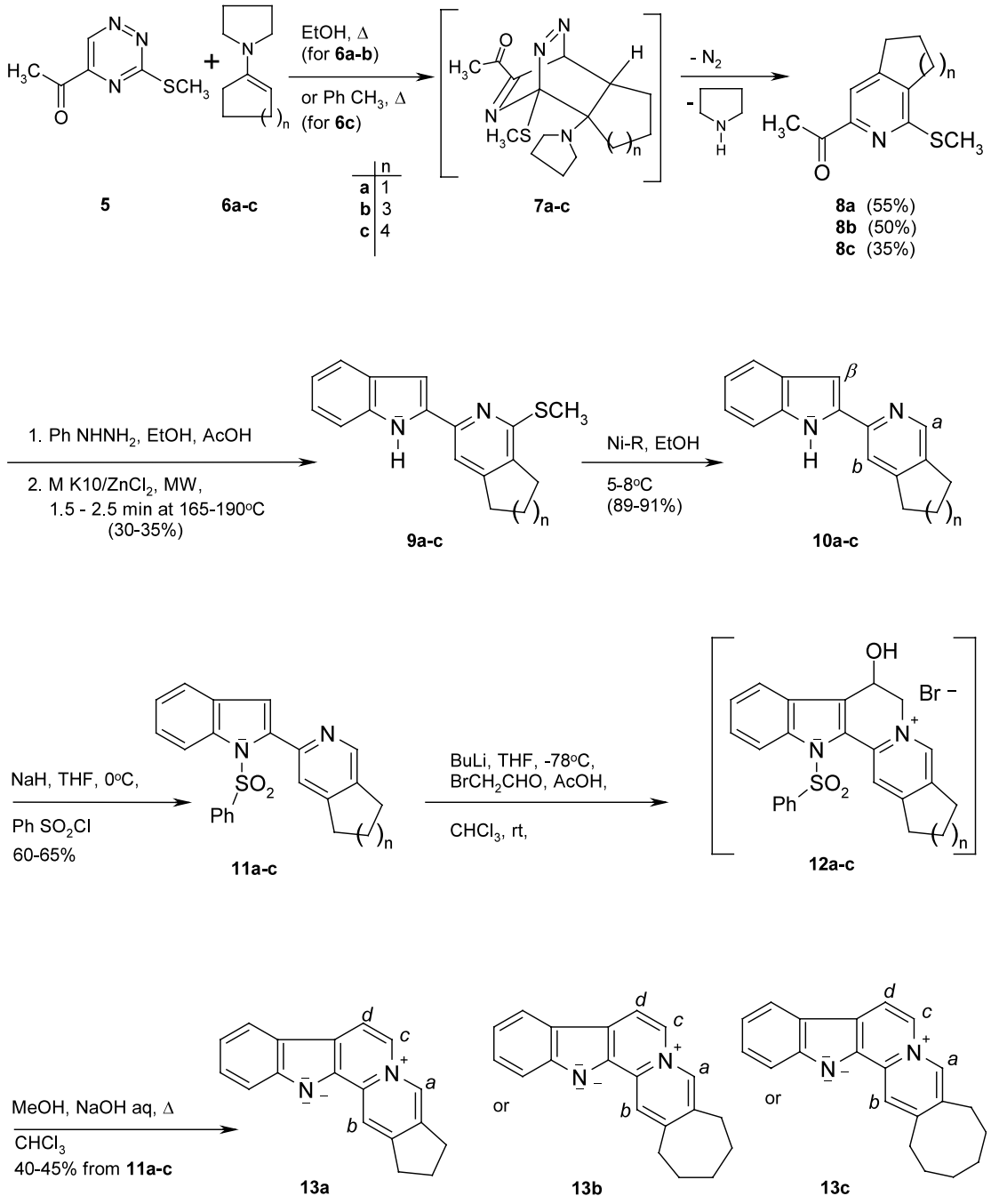
in refluxing ethanol for 4 h followed by loss of nitrogen from bicyclic intermediate **7a** gave 2,3-cyclopentenopyridine **8a** in 55% yield. The utility of this reaction was further demonstrated by the one-step synthesis of cyclohepteno- and cyclooctenopyridines **8b** (50%) and **8c** (35%), respectively. However, the reaction conditions for the latter were very severe (up to 25 h in boiling toluene) in comparison to those used for **8a** and **8b**. Treatment of compounds **8a–c** with phenylhydrazine in boiling ethanol in the presence of a catalytic amount of acetic acid gave the corresponding phenylhydrazones quantitatively, which were immediately converted into indoles **9a–c**. Compounds **9a–c** were obtained in reasonable yields under solvent free conditions with montmorillonite K10 modified with zinc chloride under microwave irradiation.[12] Conversion of **9a–c** to **10a–c** was effected with Raney nickel in ethanol at low temperature affording the desired products in 88–91% yields. Compounds **10a–c** served as excellent intermediates for the synthesis of sempervirine analogues **13a–c** by the previously reported method.[6] Thus, treatment of the protected derivatives **11a–c** with *n*-butyllithium at −78°C followed by quenching with anhydrous bromoacetaldehyde and subsequent alkaline hydrolysis of the *N*-phenylsulfonyl protecting groups in **12a–c** and dehydration afforded the desired analogs **13a–c** in 40–



Scheme 1.

Table 1. ^{1}H NHR chemical shifts and coupling constants for diagnostic protons in the final products **13a–c** (in CD_3OD) and their precursors **10a–c** (in CD_3Cl), as well as sempervirine **1** (in CD_3OD)

Compound number	δ H_a (s)	δ H_b (s)	δ H_c (d)	δ H_d (d)	δ H_β (m)
			$J_{c-d}=6.8$ Hz		
1	9.05	8.51	8.72	8.53	–
13a	9.10	8.61	8.70	8.53	–
13b	9.06	8.54	8.75	8.57	–
13c	9.10	8.58	8.75	8.54	–
10a	8.42	7.70	–	–	6.99
10b	8.34	7.58	–	–	6.97
10c	8.27	7.49	–	–	6.96

45% yields. The structures of all products[13] were elucidated by spectroscopic methods (UV, IR, ^{1}H NMR, MS, HRMS) and microanalysis. Table 1 shows the chemical shifts and coupling constants of the diagnostic protons in compounds **10a–c**, **13a–c** and **1**.

In conclusion, we have achieved the total synthesis of sempervirine analogs **13a–c** requiring six steps from the readily accessible 5-acetyl-3-(methylsulfanyl)-1,2,4-triazine **5**. Pharmacological properties of these derivatives are under investigation.

Acknowledgements

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12. Montmorillonite K10 (Aldrich) was modified using zinc chloride (0.36 mmol $ZnCl_2$ on 1 g of support) according to the procedure described in Ref. 10. The Prolabo microwave synthesizer SYNTHEWAVE 402 was used with feedback temperature control (IR detector).
13. Melting points for new compounds in °C: **8a**: 66–67, **8b**: 49–50, **8c**: 98–99, **9a**: 102–103, **9b**; 114–115, **9c**: 144–145, **10a**: 167–168, **10b**: 141–142, **10c**: 173–174, **11a**: 139–140, **11b**: 135–137, **11c**: 140–141, **13a–c**; amorphous, decomposition above 250°C.