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# Towards schizozygine: synthesis of 15α-hydroxystrempeliopine

Tomáš Pilarčík,[a] Jaroslav Havlíček[b] and Josef Hájíček[a,*]

[a]*Zentiva Research Institute of Pharmacy and Biochemistry, U Kabelovny 130, 10201, Prague 10, Czech Republic*
[b]*Zentiva, U Kabelovny 130, 10237 Prague 10, Czech Republic*

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**Abstract**—15α-Hydroxystrempeliopine (**6**), a model hexacyclic base for our planned total synthesis of schizozygine (**2**), has been synthesized using a Zn-mediated reductive rearrangement of indolenine **14** as the key step. The structure and relative stereochemistry of **6** were assigned by a combination of COSY, NOESY, HSQC and HMBC correlations.
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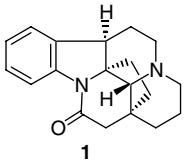
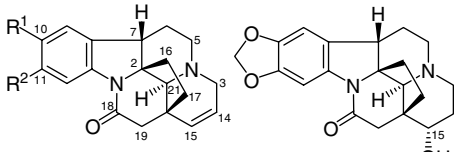
Schizozyganes constitute a small group of post-secodine hexacyclic alkaloids, which have been known for more than 40 years.[1–3] With the exception of (−)-strempeliopine (**1**) (Fig. 1), an alkaloid of the Cuban species *Strempeliopsis strempelioides* K. Schum.,[4] all have been isolated from the East-African monotypic shrub *Schizozygia coffaeoides* (Boj.) Baill.[5] This plant has been used as a traditional medicine for skin diseases;[6] leaf extracts show high antifungal and antimicrobial activity.[7] (+)-Schizozygine (**2**) is the major alkaloid accompanied among others, by the minor bases **3**–**5** (Fig. 2).[8]

Schizozygane alkaloids are attractive synthetic targets due to their interesting skeleton and pharmaceutical properties. While the synthesis of *seco*-schizozygane/vallesamidine bases has been described repeatedly,[9–14] only one synthesis of the parent base of the group, (−)-strempeliopine (**1**), has been reported[15] to date. This is based on a reductive rearrangement of an indolenine.[9,10]



**1**

**Figure 1.** (−)-Strempeliopine.



**2** $R^1$, $R^2$=$OCH_2O$
**3** $R^1$=$R^2$=OMe
**4** $R^1$=H, $R^2$=OMe
**5**

**Figure 2.** Selected alkaloids from *Schizozygia coffaeoides* (Boj.) Baill.

Recently, a synthesis of the biogenetically related alkaloid isoschizogamine was also described.[16]

Renner has proposed[2] that the 14,15-unsaturation in bases **2**–**4** might be derived from the corresponding 15-ketone. However, the implementation of such a strategy in the synthesis of schizozygine (**2**) would require proof of compatibility of the carbonyl group with the anticipated reaction conditions. We now report on the successful realization of such an approach and describe a synthesis of 15α-hydroxystrempeliopine (**6**).[17]

Thus, it was expected that the base **6** might be synthesized by reductive rearrangement of an indolenine with suitable functionalization at C-18. An allyl group at C-20 has already proved to be an effective precursor for the lactam by ozonolytic oxidative cleavage.[15,18] The introduction of oxygen at C-15 would result in intermediate **7**, which could be derived from β-anilinoacrylate **8** (Scheme 1). This should be accessible by application of Kuehne's efficient protocol[19] starting from indoloazepine **9**.[20] 1-Chloro-2-allyl-1,4-pentadienone (**10**) was designed as the second building block for the preparation of **8**.

*Keywords*: Indole alkaloids; Schizozygane alkaloids; Strempeliopine; Alkaloid synthesis; Indolenine; Reductive rearrangement.
* Corresponding author. Tel.: +420 267 243 707; fax: +420 267 243 741; e-mail: josef.hajicek@zentiva.cz

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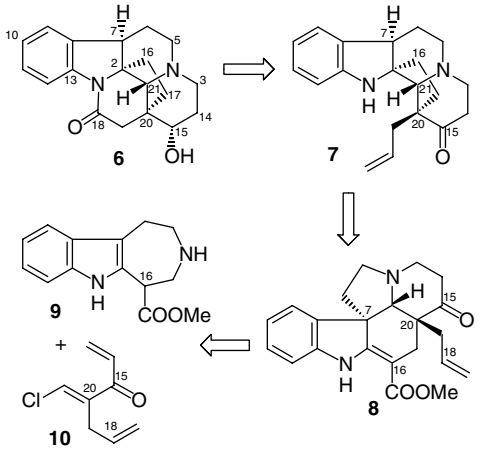
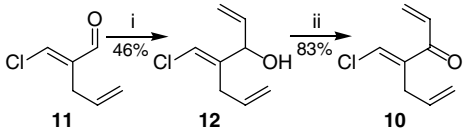


**Scheme 1.** Retrosynthetic analysis.

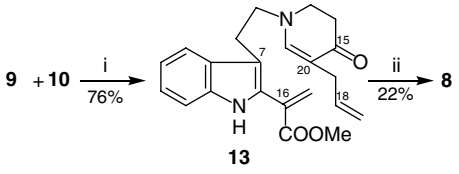
Dienone **10** was prepared from 2-allyl-3-chloroacrolein[21] **11** by Grignard reaction with vinylmagnesium bromide at 0 °C in THF and subsequent oxidation of the resulting sensitive alcohol **12** by Dess–Martin periodinane (Scheme 2).

Condensation of the dienone **10** with indoloazepine **9** in methanol at room temperature for 20 min afforded an unstable (rapid dimerization) secodine derivative **13** (76% yield), which was immediately subjected to a [4+2] cycloaddition reaction in boiling toluene (Scheme 3). The desired 18-methylene-15-oxovincadifformine (**8**) was thus obtained in a 22% yield.

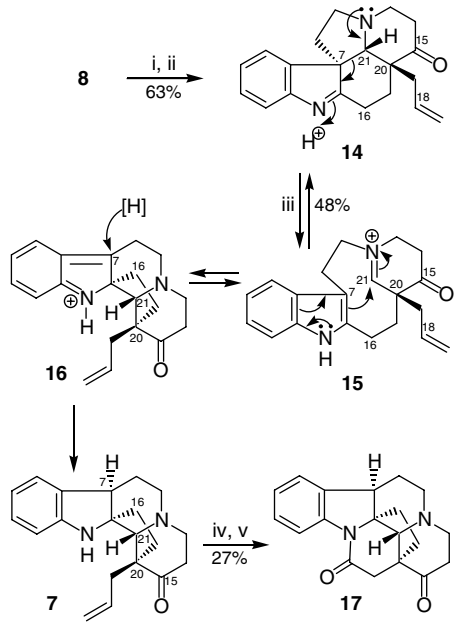
Alkaline hydrolysis of ester **8** followed by decarboxylation of the acid in boiling benzene gave the indolenine **14** in 63% yield (Scheme 4). Zinc-mediated reductive rearrangement of **14** in the presence of catalytic $CuSO_4{\cdot}5H_2O$ in hot acetic acid[10,15] proceeded presumably via the intermediary iminium ions **15** and **16**,[22] and led to the formation, in 48% yield, of the 2,2,3-trisubstituted indoline **7**, which was formylated by the mixed-anhydride method.[23]



**Scheme 2.** Synthesis of dienone **10**. Reagents and conditions: (i) vinylmagnesium bromide, THF, 0 °C; (ii) Dess–Martin periodinane, dichloromethane, 4 °C to rt.



**Scheme 3.** Synthesis of 18-methylene-15-oxovincadifformine (**8**). Reagents and conditions: (i) MeOH, rt, 20 min, rapid isolation of **13** under cooling; (ii) toluene, reflux, 20 h.



**Scheme 4.** Synthesis of 15-oxostrempeliopine (**17**). Reagents and conditions: (i) KOH, EtOH, reflux, 4 h; (ii) benzene, reflux, 3 h; (iii) Zn, $CuSO_4{\cdot}5H_2O$ (cat.), AcOH, 105 °C, 5 h; (iv) HCOOH, $Ac_2O$, rt, overnight; (v) $O_3$, MeOH, 1 M $H_2SO_4$, 0 °C then 30% $H_2O_2$, 18 h.

Synthesis of 15-oxostrempeliopine (**17**) was completed (27%) by gentle ozonolysis in a mixture of 1 M sulfuric acid/methanol at 0 °C followed by treatment with hydrogen peroxide. Finally, smooth reduction of ketone **17** proved to be highly diastereoselective even with

**Table 1.** $^1H$ and $^{13}C$ NMR data of **6** in $CDCl_3$ at 300 K[a]

| | $\delta_H$ | $\delta_C$ | HMBC ($^1H$) |
|---|---|---|---|
| 2 | | 71.9 | 6β, 7α, 16, 17α |
| 3α | 2.90 (1H, ddd, 11.6, 4.0, 2.7) | 52.7 | 5β, 14, 21β |
| 3β | 2.17 (1H, btd, 11.7, 3.3) | | |
| 5α | 2.97 (1H, ddd, 11.3, 7.9, 5.9) | 49.7 | 3α, 6, 7α, 21β |
| 5β | 2.23 (1H, dt, 11.4, 6.0) | | |
| 6α | 2.11 (1H, bdq, 14.2, 6.2) | 26.2 | 7α, 5β, 5α |
| 6β | 1.97 (1H, dtd, 14.2, 7.9, 5.9) | | |
| 7α | 3.25 (1H, bt, 7.1) | 41.6 | 5, 6α, 21α |
| 8 | | 132.8 | 12, 10, 6, 7α |
| 9 | 7.17 (1H, d, 7.4) | 123.6 | 7α |
| 10 | 7.07 (1H, t, 7.4) | 124.0 | 12 |
| 11 | 7.23 (1H, t, 7.7) | 128.1 | 9, 7α |
| 12 | 8.06 (1H, d, 8.0) | 115.9 | 10 |
| 13 | | 142.0 | 12, 11, 7α |
| 14α | 1.89 (1H, m) | 31.0 | 3 |
| 14β | 1.83 (1H, m) | | |
| 15β | 3.67 (1H, dd, 10.6, 5.4) | 74.5 | 3β, 19 |
| 16a | 2.33 (1H, m) | 37.8 | 7α, 17β, 21β |
| 16b | 2.31 (1H, m) | | |
| 17a | 2.29 (1H, m) | 27.8 | 15β, 16, 19, 21β |
| 17b | 1.63 (1H, m) | | |
| 18 | | 168.9 | 19 |
| 19α | 2.95 (1H, d, 18.2) | 48.2 | 15β |
| 19β | 2.56 (1H, dd, 18.2, 2.4) | | |
| 20 | | 48.5 | 17, 19 |
| 21β | 2.09 (1H, s) | 68.9 | 3α, 5β, 7α, 16, 19 |

[a] Data from Bruker Avance, measured at 500.13 MHz and 125.77 MHz, respectively; for atom numbering, see structure **6**, Scheme 1.

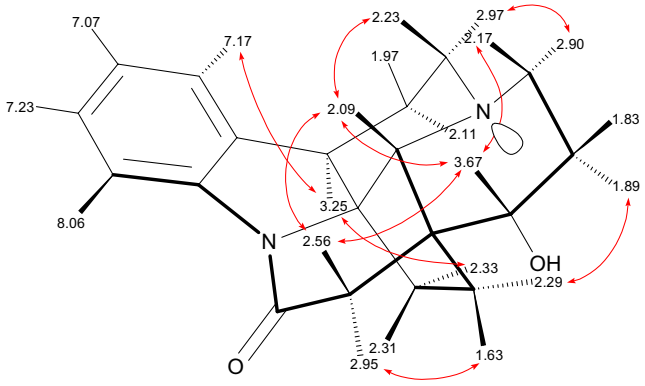



**Figure 3.** Observed non-trivial NOE interactions in base **6**.

sodium borohydride in ethanol and provided a 90% yield of the desired base **6**.

The base **6** showed a pseudomolecular ion peak at $m/z$ 310 ($M^+$), which corresponded to the molecular formula $C_{19}H_{22}N_2O_2$. The structure and stereochemistry was assigned on the basis of both 1D and 2D $^1H$ and $^{13}C$ NMR experiments (Table 1 and Fig. 3).

The $^1H$ NMR spectrum displayed characteristic proton signals at $\delta$ 3.25 ppm (H-7) and 2.09 ppm for H-21, and the $^1H$–$^1H$ COSY spectrum showed a diagnostic long-range coupling (W) between H-19 at $\delta$ 2.56 ppm and H-17a at $\delta$ 2.29 ppm ($J = 2.4$ Hz). The relative configuration at C-15 stems from the fact the signal at $\delta$ 3.67 ppm showed as a cross peak in the NOESY spectrum with H-3β at $\delta$ 2.17 ppm as well as with H-21. Moreover, H-15 appears as a doublet of doublets ($J = 10.6$ and 5.4 Hz), while the H-15 signal in the $^1H$ NMR spectrum of epimeric natural (+)-α-schizozygol (**5**) appears as a triplet with $J \sim 3.0$ Hz.[24] The base is thus 15α-hydroxystrempeliopine (**6**) with an equatorial hydroxy group. Not surprisingly, alcohol **6** failed to afford any olefine on attempted dehydration through tosylation.

The application of this strategy to a total synthesis of schizozygine (**1**) is underway. The results will be published in due course.

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23. Formylation both changes polarity and thus facilitates separation of related minor impurities, and protects indoline nitrogen in the subsequent step.[15c]
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