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Synthesis of (±)-coerulescine and a formal synthesis of (±)-horsfiline

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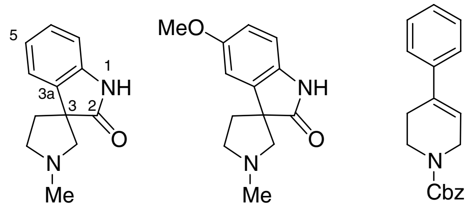
Abstract—A straightforward synthesis of (±)-coerulescine and (±)-horsfiline has been established from 3-formyl-3-phenylpyrrolidine employing 4-hydroxypiperidine as the starting material. There are two remarkable steps for the synthesis of (±)-coerulescine and (±)-horsfiline. One is the rapid access to produce 3-formyl-3-phenylpyrrolidine by Lewis acid-catalyzed rearrangement of 3,4-dihydroxy-4-phenylpiperidine. The other key step is an intramolecular electrophilic cyclization from 3-benzylcarbamoyl-3-phenylpyrrolidine to the 3,3-spirocyclic 2-oxindole ring skeleton.

1. Introduction

The derivatives of spiropyrrolidinyl-oxindole skeleton alkaloid are represented in nature such as spirotryprostatins A and B,[1] elacomine,[2] and strychnophylline.[3] Typically, they are biosynthesized from tryptamine or tryptophan derivatives and are characterized by a spiro-fused ring at the C-3 position.[4] The majority of these natural products have interesting biological activities and pharmacological properties. Among them, coerulescine (**1**) and horsfiline (**2**) represent the simplest prototype members of this subfamily. Recently, coerulescine (**1**) was isolated from the blue canary grass *Phalaris coerulescens*.[5a,b] Horsfiline (**2**) was first isolated in 1991 by Bodo and co-workers from Malaysian medical plant *Horsfildea superba* Warb. (Myristicaceae) and used as a source of intoxicating snuffs.[5]

The unique 3,3-spirocyclic oxindole structural features with the quaternary center and potential biological applications prompted the development of numerous strategies toward the synthesis of coerulescine (**1**) and horsfiline (**2**) from synthetic chemists.[6,7] Basically, the adopted strategies can be summarized in several oxidants promoted oxidative rearrangement (e.g., lead tetraacetate,[5b] sodium tungstate,[7j] *tert*-butylhypochlorite,[7h] and *N*-bromosuccinimide[7b]), Mannich reaction,[7c] ring-expansion reaction,[7f,i] 1,3-dipolar [3+2] cycloaddition,[7d,g,l] intramolecular radical cyclization,[7a,m–p] and asymmetric nitroolefination reaction.[7e] All of them find application on specific substrates for the construction of the 3,3-spirocyclic oxindole-derived alkaloids. Here, we report that a new synthetic study toward (±)-coerulescine (**1**) and (±)-horsfiline (**2**) from 1-benzyloxycarbonyl-4-phenyl-1,2,5,6-tetrahydropyridine (**3a**) as shown in Figure 1.



coerulescine (**1**) horsfiline (**2**) **3a**

Figure 1.

2. Results and discussion

The retrosynthetic analysis of (±)-coerulescine (**1**) and (±)-horsfiline (**2**) is shown in Scheme 1. A remarkable

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Keywords: Coerulescine; Horsfiline; 4-Hydroxypiperidine; Lewis acid catalyzed rearrangement; 3-Formyl-3-phenylpyrrolidine; 3,4-Dihydroxy-4-phenylpiperidine.

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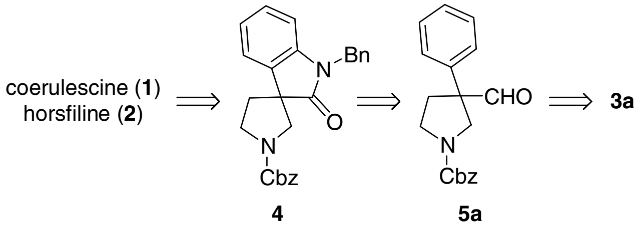


Scheme 1.

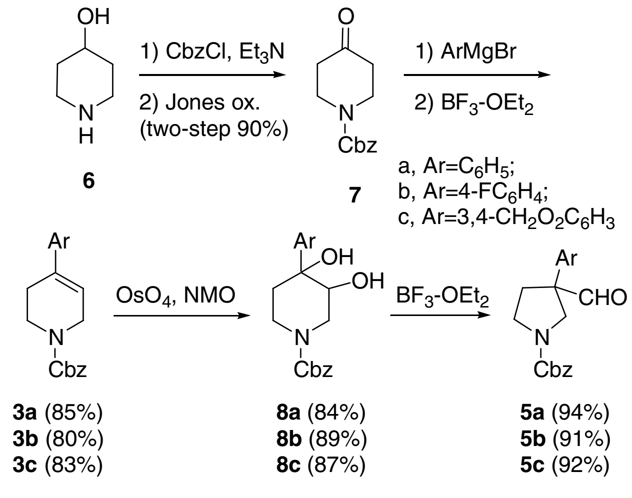
two-step transformation is described as follows. One is the rapid access to produce 3-formyl-3-phenylpyrrolidine **5a** by rearrangement of 3,4-dihydroxy-4-phenylpiperidine. The other step is an intramolecular electrophilic cyclization[8] from 3-benzylcarbamoyl-3-phenylpyrrolidine to the 3,3-spirocyclic 2-oxindole skeleton **4** (a Fuji's intermediate of horsfiline).[7e]

The synthesis began from compounds **5a**–**c** as shown in Scheme 2. Compounds **5a**–**c** were prepared by six-step standard protocol from the commercially available 4-hydroxypiperidine (**6**): (i) benzyloxycarbonylation of amine **6** with triethylamine and benzyloxycarbonyl chloride in tetrahydrofuran in ice bath for 1 h, (ii) oxidation of the resulting alcohol with Jones reagent in acetone in ice bath for 15 min, (iii) Grignard addition of ketone **7**[9a] with different Grignard reagents (a, Ar = C_6H_5; b, Ar = 4-FC_6H_4; c, Ar = 3,4-$CH_2O_2C_6H_3$) in tetrahydrofuran at −78 °C for 2 h, (iv) dehydration of the resulting tertiary alcohols with boron trifluoride etherate in dichloromethane in ice bath for 15 min, (v) dihydroxylation of olefins **3a**–**c**[9b] with *N*-methylmorpholine *N*-oxide and a catalytic amount of osmium tetroxide in the cosolvent of *tert*-butanol and water at reflux temperature for 2 h,[9c] and (vi) rearrangement of diols **8a**–**c** with boron trifluoride etherate in ice bath for 15 min. Thus, 3-aryl-3-formylpyrrolidines **5a**–**c** could be obtained in good yield. The total synthetic procedure was monitored by TLC until the reaction was completed. The overall procedure was achieved within one working day.

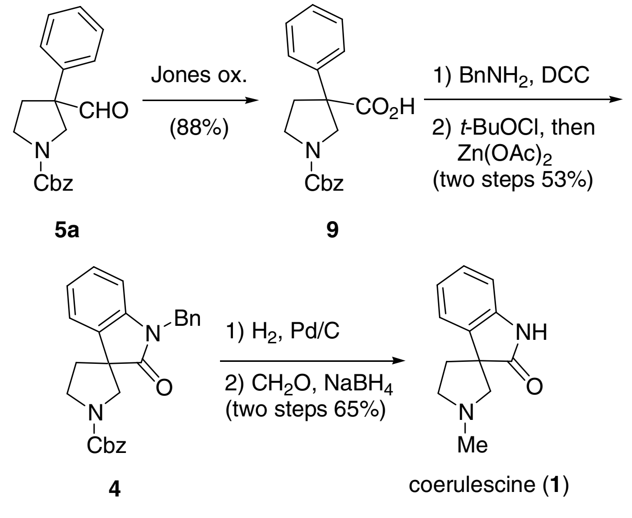
While searching the related literature of 3-substituted 3-formylpyrrolidine, we found that it was a useful building block in the synthesis of various potential biological compounds.[10,11] In view of the experimental simplicity, we chose compound **3a** as the model substrate to synthesize compound **5a** in a moderate scale (0.1 mol). The simple two-step procedure of dihydroxylation and Lewis acid-catalyzed rearrangement reaction also provided enough amounts of material **5a** in the synthesis of (±)-coerulescine (**1**) and (±)-horsfiline (**2**) in 73% yield.

When 3-benzyloxy-1-benzyloxycarbonyl-4-hydroxy-4-phenyl piperidine (**8d**) (prepared from monobenzylation of diol **8a**) was treated with boron trifluoride etherate, the sole 3-formyl-3-phenylpyrrolidine **5a** was still isolated in quantitative yield. The conversion of **8a**–**d** to **5a**–**c** is pinacol to pinacolone rearrangement. For providing aldehyde **5a**, the similar reaction had been investigated on *N*-substituted 4-aryl-3,4-epoxypiperidines.[10] According to the report,[10a] different *N*-substitutents (methyl or carbamate functional group) can affect the distribution of products.

With compound **5a** in hand, aldehyde **5a** was transformed into acid **9** by Jones oxidation as shown in Scheme 3. Treatment of acid **9** with dicyclohexylcarbodiimide and benzylamine gave a benzyl amide product. Intramolecular electrophilic cyclization[8] of the benzyl amide with *tert*-butylhypochlorite followed by zinc acetate gave the compound **4**. The known approach had been investigated by Kikugawa and co-workers.[8] Compound **4** was a known intermediate of horsfiline (**2**) in Fuji's report.[7e] According to this report, compound **4** could be transformed to horsfiline (**2**) via regioselective oxidation with lead tetrakis(trifluoroacetate) at the C-5 position and O-methylation of the resulting phenolic compound. This constitutes a formal synthesis of (±)-horsfiline (**2**). Finally, (±)-coerulescine (**1**) was achieved by hydrogenation of compound **4** with hydrogen in the presence of a catalytic amount of 10% palladium on carbon followed by N-methylation with sodium borohydride and formaldehyde. The ^1H NMR spectral data of compounds **1** and **4** were in accordance with those reported in the literature.[7e,1]



Scheme 2.



Scheme 3.

3. Conclusion

We explored a Lewis acid catalyzed rearrangement reaction of 4-aryl-*N*-benzyloxycarbonyl-3,4-dihydroxypiperidine to form 3-aryl-3-formylpyrrolidine skeleton. This strategy of intramolecular electrophilic cyclization is synthetically useful for constructing (±)-coerulescine (**1**) and (±)-horsfiline (**2**) with 3,3-spirocyclic oxindole alkaloids. We are currently studying the scope of this process as well as additional applications of the methodology to the synthesis of piperidines, indolizidines, quinolizidines, and indoles.

Supplementary data

Experimental procedures and photocopies of ^{1}H NMR ($CDCl_3$) spectral data for **1**, **3a–c**, **4**, **5a–c**, **7**, **8a–d**, and **9** were supported. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.015.

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References and notes

1. (a) Cui, C. B.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *52*, 12651; (b) Cui, C. B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 832.
2. James, M. N. G.; Williams, G. J. B. *Can. J. Chem.* **1972**, *50*, 2407.
3. (a) Leclercq, J.; De Pauw-Gillet, M. C.; Bassleer, R.; Angenot, L. *J. Ethnopharmacol.* **1986**, *15*, 305; (b) Dupont, P. L.; Lamotte-Brasseur, J.; Dideberg, O.; Campsteyn, H.; Vermeire, M.; Angenot, L. *Acta Crystallogr. Sect. B* **1977**, *33*, 1801.
4. (a) Finch, N.; Taylor, W. I. *J. Am. Chem. Soc.* **1962**, *84*, 1318; (b) Finch, N.; Taylor, W. I. *J. Am. Chem. Soc.* **1962**, *84*, 3871; (c) Shavel, J.; Zinnes, H. *J. Am. Chem. Soc.* **1962**, *84*, 1320.
5. (a) Anderton, N.; Cockrum, P. A.; Colegate, S. M.; Edgar, J. A.; Flower, K.; Vit, I.; Willing, R. I. *Phytochemistry* **1998**, *48*, 437; (b) Colegate, S. M.; Anderton, N.; Edgar, J.; Bourke, C. A.; Oram, R. N. *Aust. Vet. J.* **1999**, *77*, 537; (c) Jossang, A.; Jossang, P.; Hadi, H. A.; Sévenet, T.; Bodo, B. *J. Org. Chem.* **1991**, *56*, 6527.
6. For a review: Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209.
7. (a) Jones, K.; Wilkinson, J. *J. Chem. Soc., Chem. Commun.* **1992**, 1767; (b) Pellegrini, C.; Strässler, C.; Weber, M.; Borschberg, H.-J. *Tetrahedron: Asymmetry* **1994**, *5*, 1979; (c) Bascop, S.-I.; Sapi, J.; Laronze, J.-Y.; Lévy, J. *Heterocycles* **1994**, *38*, 725; (d) Palmisano, G.; Annunziata, R.; Papeo, G.; Sisti, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1; (e) Lakshmaiah, G.; Kawabata, T.; Shang, M.; Fuji, K. *J. Org. Chem.* **1999**, *64*, 1699; (f) Fischer, C.; Meyers, C.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 1175; (g) Cravotto, G.; Giovenzana, G. B.; Pilati, T.; Sisti, M.; Palmisano, G. *J. Org. Chem.* **2001**, *66*, 8447; (h) Kuehne, M. E.; Roland, D. M.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3705; (i) Syam Kumar, U. K.; Ila, H.; Junjappa, H. *Org. Lett.* **2001**, *3*, 4193; (j) Somei, M.; Noguchi, K.; Yamagami, R.; Kawada, Y.; Yamada, K.; Yamada, F. *Heterocycles* **2000**, *53*, 7; (k) Bell, S. E. V.; Brown, R. F. C.; Eastwood, F. W.; Horvath, J. M. *Aust. J. Chem.* **2000**, *53*, 183; (l) Selvakumar, N.; Azhagan, A. M.; Srinivas, D.; Krishna, G. G. *Tetrahedron Lett.* **2002**, *43*, 9175; (m) Lizos, D. E.; Murphy, J. A. *Org. Biomol. Chem.* **2003**, *1*, 117; (n) Cossy, J.; Cases, M.; Pardo, D. G. *Tetrahedron Lett.* **1998**, *39*, 2331; (o) Lizos, D.; Tripoli, R.; Murphy, J. A. *Chem. Commun.* **2001**, 2732; (p) Murphy, J. A.; Tripoli, R.; Khan, T. A.; Mali, U. M. *Org. Lett.* **2005**, *7*, 3287; (q) Kornet, T.; Thio, A. P. *J. Med. Chem.* **1976**, *19*, 892.
8. (a) Prata, J. V.; Clemente, D. T. S.; Prabhakar, S.; Lobo, A. M.; Mourato, I.; Branco, P. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 513; (b) Fleming, I.; Moses, R. C.; Tercel, M.; Ziv, J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 617; (c) Kikugawa, Y.; Kawase, M. *J. Am. Chem. Soc.* **1984**, *106*, 5728; (d) Kawase, M.; Kitamura, T.; Kikugawa, Y. *J. Org. Chem.* **1989**, *54*, 3394.
9. (a) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2000**, *56*, 8433; (b) Eastwood, P. R. *Tetrahedron Lett.* **2000**, *41*, 3705; (c) Bursavich, M. G.; West, C. W.; Rich, D. H. *Org. Lett.* **2001**, *3*, 2317; (d) Harriman, G. C. B.; Shao, J.; Luly, J. R. *Tetrahedron Lett.* **2000**, *41*, 8853.
10. (a) Nagai, Y.; Hino, K.; Uno, H.; Minami, S. *Chem. Pharm. Bull.* **1980**, *28*, 1387; (b) Lyle, R. E.; Krueger, W. E. *J. Org. Chem.* **1965**, *30*, 394; (c) Hershenson, F. M.; Christensen, L. *Synth. Commun.* **1981**, *11*, 615.
11. (a) Lyles-Eggleston, M.; Altundas, R.; Xia, J.; Sikazwe, D. M. N.; Pan, P.; Yang, Q.; Li, S.; Zhang, W.; Zhu, X.; Schmidt, A. W.; Vanase-Frawley, M.; Shrihkande, A.; Villalobos, A.; Borne, R. F.; Ablordeppey, S. Y. *J. Med. Chem.* **2004**, *47*, 497; (b) Xue, C.-B.; Chen, X.-T.; He, X.; Roderick, J.; Corbett, R. L.; Ghavimi, B.; Liu, R.-Q.; Covington, M. B.; Qian, M.; Ribadeneira, M. D.; Vaddi, K.; Trzaskos, J. M.; Newton, R. C.; Duan, J. J. W.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4453; (c) Hagen, S. E.; Domagala, J. M.; Heifetz, C. L.; Sanchez, J. P.; Solomon, M. *J. Med. Chem* **1990**, *33*, 849; (d) Jenkins, S. M.; Wadsworth, H. J.; Bromidge, S.; Orlek, B. S.; Wyman, P. A.; Riley, G. J.; Hawkins, J. *J. Med. Chem.* **1992**, *35*, 2392.