Formal Synthesis of (±)-Pancracine Using Stereoselective Radical Cyclization of *N*-(2-Cyclohexenyl)-α-aryl-α-(phenylthio)acetamide

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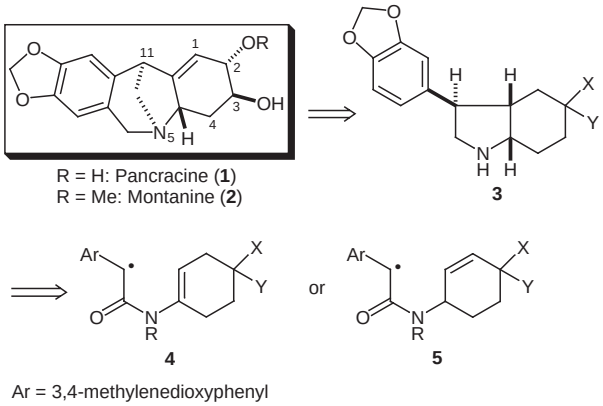
Abstract: $(Me_3Si)_3SiH$-mediated 5-*exo-trig* radical cyclization of *N*-(2-cyclohexenyl)-α-aryl-α-(phenylthio)acetamide **19** proceeded in a stereoselective manner to give (3*R**,3a*S**,7a*S**)-3-aryloctahydroindol-2-one **20**. The product was transformed into the key intermediate **25** for the synthesis of (±)-pancracine (**1**), a montanine-type *Amaryllidaceae* alkaloid.

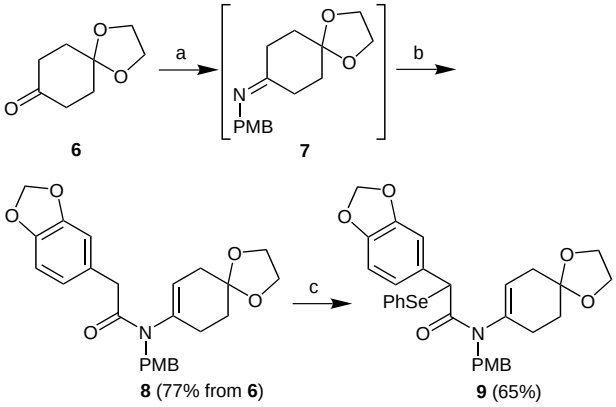
The 5,11-methanomorphanthridine skeleton is a basic structural element of montanine-type *Amaryllidaceae* alkaloids such as pancracine (**1**) and montanine (**2**).[1] The first total synthesis of this class of alkaloids were reported concurrently by Overman [for (±)-pancracine][2] and Hoshino [for (±)-pancracine and (±)-montanine][3] in 1991, and subsequently many works have been reported for the synthesis of optically active and racemic methanomorphanthridine family of *Amaryllidaceae* alkaloids.[4] In continuation of our studies directed towards the synthesis of natural products using radical cyclizations as the key step,[5] we were interested in the synthesis of 3-aryloctahydroindole **3** through 5-*endo-trig*[6] or 5-*exo-trig*[7] cyclization of the *N*-(1- or 2-cyclohexenyl)carbamoylmethyl radical **4** or **5**. The Pictet-Spengler cyclization of the compounds having the same stereochemistry as **3** is known to provide the methanomorphanthridines.[2] We found that the 5-*exo-trig* cyclization of *N*-(2-cyclohexenyl)-α-aryl-α-(phenylthio)acetamide **19** proceeded in a stereoselective manner to give (3*R**,3a*S**,7a*S**)-3-aryloctahydroindol-2-one **20**. The present paper describes an application of the method to the formal synthesis of (±)-pancracine.



Scheme 1

We initiated our investigation by examining the 5-*endo-trig* cyclization of the carbamoylmethyl radical **4**. The synthesis of the radical precursor **9** was begun by condensation of 1,4-cyclohexanedione monoethylene acetal **6** with *p*-methoxybenzylamine to give imine **7**. Acylation of **7** with (3,4-methylenedioxyphenyl)acetic pivalic anhydride gave enamide **8** (an oil), which was then treated successively with LDA and phenylselenenyl chloride to give **9** (an oil).

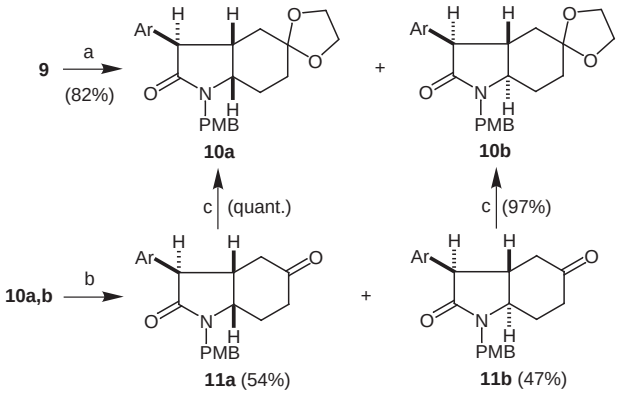
When a boiling solution of **9** in benzene was treated slowly with a benzene solution of 1.1 equiv. of tributyltin hydride and a catalytic quantity of azobis(isobutyronitrile) (AIBN), an inseparable mixture of two cyclization products **10a** and **10b** (*ca*. 1:1 by ^{1}H NMR spectroscopy) was obtained in 82% combined yield. The structures of **10a** and **10b** were confirmed by the following chemical evidence. Hydrolysis of the mixture of ethylene acetals **10a,b** gave ketones **11a** and **11b** in 54 and 47% isolated yields, respectively, and each of the ketones **11a** and **11b** was again protected with ethylene glycol to give acetals **10a** (mp 148-150 °C) and **10b** (an oil) as single stereoisomers, respectively. Compounds **10a** and **10b** were then heated independently with EtONa in boiling EtOH or with *tert*-BuOK in boiling *tert*-BuOH to result in the recovery of the starting material in both cases. These results indicate that two hydrogen atoms between 3- and 3a-positions of both **10a** and **10b** have the *trans* relationship.[8] The *cis*-stereochemistry of the ring struncture of **10a** was established by transforming the same compound prepared by an alternate method to the known compound **25** (*vide infra*), and hence the stereochemistry of the ring structure of **10b** was deduced to be *trans*.



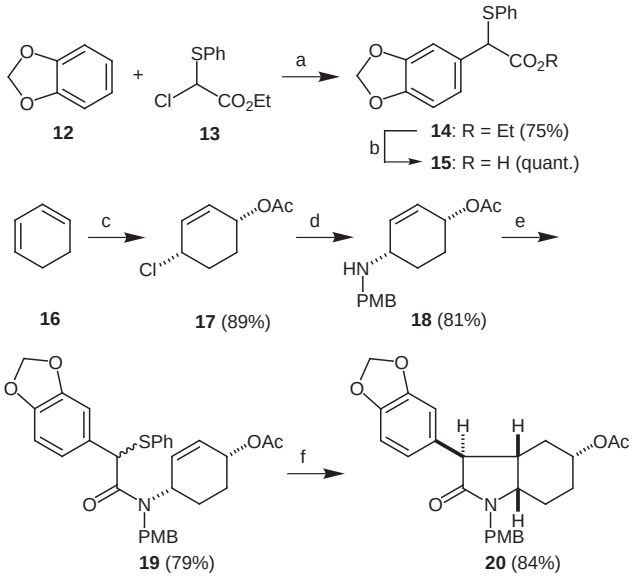
Scheme 2. (a) *p*-methoxybenzylamine, benzene, reflux; (b) (3,4-methylenedioxyphenyl)acetic pivalic anhydride, pyridine, benzene, 30-40 °C; (c) LDA, HMPA, THF, -78 °C then PhSeCl.

Thus, the 5-*endo-trig* cyclization of the carbamoylmethyl radical **4** resulted in the formation of a considerable amount of the undesired isomer **10b**. Therefore, our attention was next turned to the 5-*exo-trig* cyclization of the carbamoylmethyl radical **5** leading to 3-aryloctahydroindol-2-ones.

The radical precursor **19** was prepared as follows. The Friedel-Crafts reaction of chlorosulfide **13**[9] with 1,2-(methylenedioxy)benzene (**12**) in the presence of $TiCl_4$ gave ester **14** (75%), which was hydrolyzed to give carboxylic acid **15** (quant.). On the other hand, according to the procedure reported by Bäckvall,[10] *cis*-1-acetoxy-4-chloro-2-cyclohexene **17**, prepared from 1,3-cyclohexadiene (**16**),[11] was treated with *p*-methoxybenzylamine in the presence of bis(dibenzylideneacetone)palladium (0) [$Pd(dba)_2$] to give amine **18** in 81% yield. Compound **18** was acylated with carboxylic acid **15** in the presence of DCC to give **19** (an oil) in 79% yield.



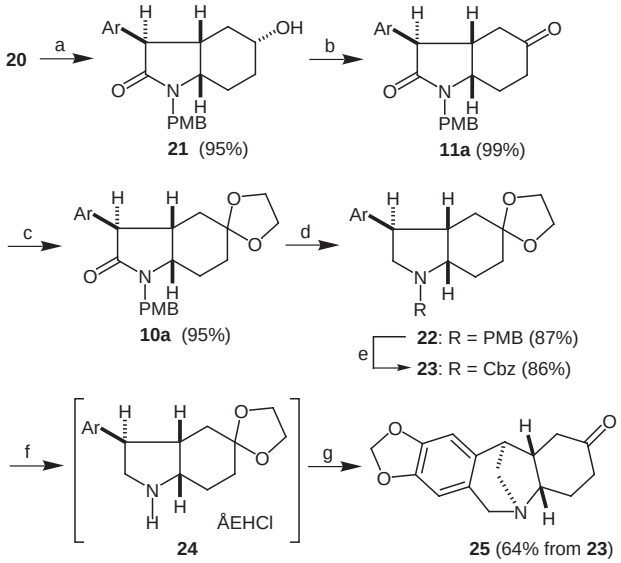
Scheme 3. (a) Bu_3SnH, AIBN, benzene, reflux; (b) 5% HCl, acetone, reflux; (c) ethylene glycol, TsOH, benzene, reflux.



Scheme 4. (a) $TiCl_4$, $CHCl_3$, 0 °C to r.t.; (b) (i) KOH, H_2O-EtOH, reflux, (ii) HCl; (c) $Pd(OAc)_2$, LiCl, LiOAc-$2H_2O$, *p*-benzoquinone, AcOH, r.t.; (d) *p*-methoxybenzylamine, $Pd(dba)_2$, PPh_3, NEt_3, THF, r.t.; (e) **15**, DCC, DMAP, CH_2Cl_2 , r.t.; (f) $(Me_3Si)_3SiH$, AIBN, benzene, reflux.

When a boiling solution of **19** in benzene was treated slowly with a mixture of 4 equiv. of tris(trimethylsilyl)silane and a catalytic quantity of AIBN, (3*R**,3a*S**,7a*S**)-3-aryloctahydroindol-2-one **20** (mp 149-150 °C) was obtained in high yield (84%) as a single stereoisomer.

The stereochemistry of **20** was confirmed by transforming it to the key intermediate **25** for the synthesis of (±)-pancracine. Thus, hydrolysis of the acetoxy group of **20** with LiOH followed by Swern oxidation of the resulting alcohol **21** gave keto-lactam **11a**, which was identical to that obtained by hydrolysis of **10a**, one of the radical cyclization products from **9**. Protection of ketone **11a** with ethylene glycol followed by reduction of the resulting lactam **10a** with alane gave amine **22** (87%). Treatment of **22** with benzyloxycarbonyl chloride gave carbamate **23** (an oil) (86%), whose hydrogenolysis in the presence of hydrochloric acid gave the amine hydrochloride **24**. Compound **24** was then subjected to the Pictet-Spengler cyclization to give, with concomitant deprotection of the ethylene acetal, 5,11-methanomorphanthridine **25** in 64% yield from **23**. The melting point (125-126 °C, lit.[4c] 125 °C) and ^1H NMR spectrum of **25** herein obtained was identical with those of an authentic sample.[12] Since compound **25** has already been converted to (±)-pancracine (**1**),[4c] the present sequence of the reactions means in a formal sense a total synthesis of (±)-pancracine.



Scheme 5. (a) LiOH-H_2O, H_2O-MeOH, reflux; (b) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, -60 °C; (c) ethylene glycol, TsOH, benzene, reflux; (d) AlH_3 ($LiAlH_4$-$AlCl_3$), THF-Et_2O, r.t.; (e) CbzCl, benzene, reflux; (f) H_2, Pd-C, conc. HCl, MeOH, r.t.; (g) (i) 36% formalin, NEt_3, MeOH, r.t., (ii) 6 N HCl, MeOH, 30 °C.

Thus, we revealed that the 5-*exo*-*trig* radical cyclization of *N*-(2-cyclohexenyl)-α-aryl-α-(phenylthio)acetamides provided a new stereoselective synthesis of (3*R**,3a*S**,7a*S**)-3-arylhydroindoles, which are useful intermediates for the synthesis of 5,11-methanomorphanthridine alkaloids.

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References and Notes

(1) For comprehensive reviews of *Amaryllidaceae* alkaloids, see: Martin, S.F. In *The Alkaloids;* Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, pp 251-376. Hoshino, O. In *The Alkaloids;* Cordell, G.A., Ed.; Academic Press: New York, 1998; Vol. 51, pp 323-424.

(2) Overman, L.E.; Shim, J. *J. Org. Chem.* **1991**, *56*, 5005.

(3) Ishizaki, M.; Hoshino, O.; Iitaka, Y. *Tetrahedron Lett.* **1991**, *32*, 7079.

(4) (a) Overman, L.E.; Shim, J. *J. Org. Chem.* **1993**, *58*, 4662. (b) Ishizaki, M.; Hoshino, O.; Iitaka, Y. *J. Org. Chem.* **1992**, *57*, 7285. (c) Ishizaki, M.; Kurihara, K.; Tanazawa, E.; Hoshino, O. *J. Chem. Soc., Perkin Trans. 1* **1993**, 101. (d) Jin, J.; Weinreb, S.M. *J. Am. Chem. Soc.* **1997**, *119*, 2050.

(5) For recent references, see (a) Ishibashi, H.; Kameoka, C.; Kodama, K.; Kawanami, H.; Hamada, M.; Ikeda, M. *Tetrahedron* **1997**, *53*, 9611. (b) Ishibashi, H.; Kawanami, H.; Ikeda, M. *J.*

Chem. Soc., Perkin Trans. 1 **1997**, 817. (c) Ishibashi, H.; Kawanami, H.; Nakagawa, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2291. (d) Ikeda, M.; Kugo, Y.; Yamazaki, T.; Sato, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3339. (e) Ishibashi, H.; Higuchi, M.; Ohba, M.; Ikeda, M. *Tetrahedron Lett.* **1998**, *39*, 75. (f) Ikeda, M.; Teranishi, H.; Nozaki, K.; Ishibashi, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1691.

(6) Sato, T.; Nakamura, N.; Ikeda, K.; Okada, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2399.

(7) Ishibashi, H.; So, T.S.; Okochi, K.; Sato, T.; Nakamura, N.; Nakatani, H.; Ikeda, M. *J. Org. Chem.* **1991**, *56*, 95. (b) Curran, D.P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746. (c) Ishibashi, H.; Uemura, N.; Nakatani, H.; Okazaki, M.; Sato, T.; Nakamura, N.; Ikeda, M. *J. Org. Chem.* **1993**, *58*, 2360.

(8) It is known that 3-phenyloctahydroindol-2-one having *cis*-stereochemistry of two hydrogen atoms between 3- and 3a-positions, on treatment with EtONa in boiling EtOH, isomerizes to the thermodynamically more stable corresponding *trans*-isomer. See: ref 6.

(9) Ishibashi, H.; Ikeda, M.; Choi, H.D.; Nakagawa, H.; Ueda, Y.; Tamura, Y. *Chem. Pharm. Bull.* **1985**, *33*, 5310 and references cited therein.

(10) Gatti, R.G.P.; Larsson, A.L.E.; Bäckvall, J.-E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 577.

(11) Bäckvall, J.-E.; Nyström, J.-E.; Nordberg, R.E. *J. Am. Chem. Soc.* **1985**, *107*, 3676.

(12) The authors thank Professor Hoshino, Science University of Tokyo, for providing ^{1}H NMR spectrum of **25**.