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A concise enantiocontrolled route to yohimbones using a bicyclo[3.2.1]octane chiral building block

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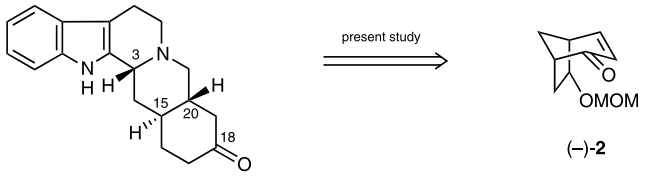
Abstract—A facile enantio- and diastereocontrolled construction of 18-keto-pseudoyohimbane from a bicyclo[3.2.1]octane chiral building block has been developed employing a tandem retro-aldol and Pictet–Spengler sequence. The epimerization of the resulting pseudoyohimbane into the corresponding yohimbane derivative has also been achieved.

We have recently developed an efficient preparation of the chiral building block **2** having a bicyclo[3.2.1]octane framework in both enantiomeric forms by a route involving either an enzymatic[1] or a chemical[2] resolution step. Because of its inherent stereochemical and chemical nature with a sterically biased structure, each of the enantiomers serves as a versatile chiral building block for diastereoselective modification. Its versatility has already been demonstrated in the efficient stereocontrolled syntheses of the antibiotic diterpene (+)-ferruginol,[1] the analgesic alkaloid (−)-morphine,[3] the anticancer sesquiterpene (+)-vernolepin,[4] the estrogenic steroid (+)-estrone[5] and the calcitriol A-ring[5] and C/D-ring precursors.[2] Highlighting its steric and chemical nature, we have now explored and extended its use as a chiral building block for the enantio- and diastereocontrolled construction of yohimbine- and corynanthe-type indole alkaloids,[6,7] which possess similar structures and have a wide range of interesting biological activities. We report here an efficient and concise enantio- and diastereocontrolled route leading to 18-keto-pseudoyohimbane (18-pseudoyohimbone) (+)-**1** and its epimerization into 18-keto-yohimbane (18-yohimbone) (−)-**14**, which may serve as common intermediates for the synthesis of both yohimbine- and corynanthe-type indole alkaloids, starting with the chiral building block (−)-**2** (Scheme 1).

By employing the previously established procedure,[1,2] the enone (−)-**2** was first transformed into the isomeric enone (+)-**3** in 71% overall yield via a three-step sequence involving alkaline epoxidation, Wharton rearrangement and manganese(IV) oxidation. Because of its sterically biased structure, the enone (−)-**3** exhibited convex-face selectivity to allow diastereoselective introduction of nitromethane to give the cyclohexanone **4**, $[\alpha]_D^{24}$ +78.7 (*c* 1.0, $CHCl_3$), as a single isomer. On ketalization using ethylene glycol bis-trimethylsilyl (TMS) ether under Noyori's conditions,[8] the ketone **4** afforded the ethylene ketal **5**, $[\alpha]_D^{27}$ −20.1 (*c* 1.0, $CHCl_3$), without affecting the MOM-protecting group in the molecule. Reduction of the nitro functionality of the ketal **5** was carried out with lithium aluminum hydride[9] to give the primary amine **6**. The amine **6** was condensed with indole-3-acetic acid in the presence of 1 - ethyl - 3 - (3 - dimethylaminopropyl)carbodiimide (WSC)[10] to give the secondary amide **7**, mp 65–67°C, $[\alpha]_D^{27}$ −20.1 (*c* 1.0, $CHCl_3$), which afforded the secondary amine **8**, $[\alpha]_D^{24}$ −22.0 (*c* 1.0, $CHCl_3$), on reduction with lithium aluminum hydride. The overall yield of the amine **8** from the chiral building block (−)-**2** was 27% in eight steps (Scheme 2).



(+)-18-keto-pseudoyohimbone **1** (−)-**2**

Scheme 1.

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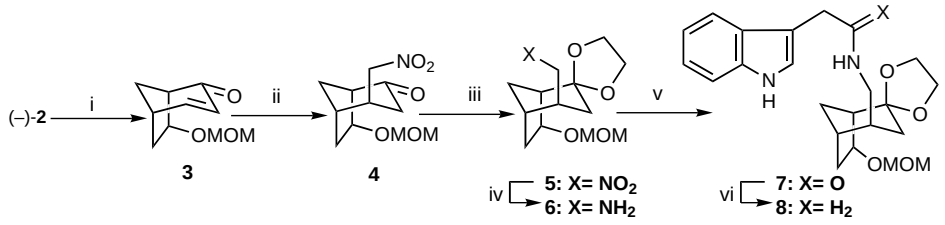
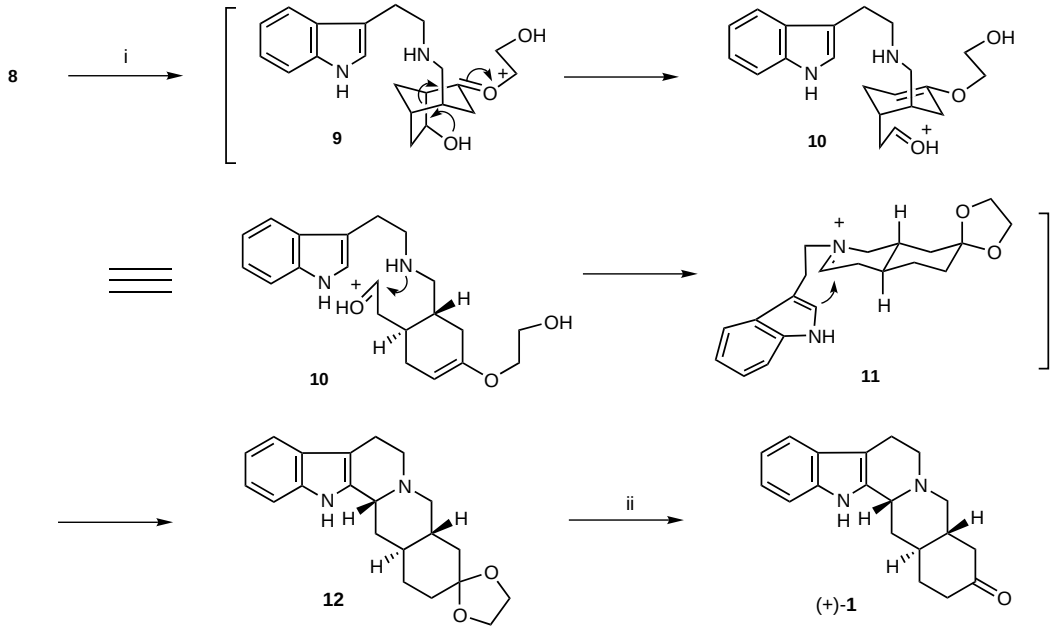


Scheme 2. *Reagents and conditions*: (i) (a) 30% H_2O_2, aq. NaOH, MeOH, 0°C (97%). (b) NH_2NH_2–H_2O, AcOH, MeOH (77%). (c) MnO_2, CH_2Cl_2, rt (95%). (ii) $MeNO_2$, DBU, MeCN (86%). (iii) $(CH_2OTMS)_2$, TMSOTf (cat.), CH_2Cl_2, −30°C (77%). (iv) $LiAlH_4$, THF (70%, two steps). (v) indole-3-acetic acid, WSC, THF, rt (94%, two steps). (vi) $LiAlH_4$, dioxane, reflux (86%).

In the hydrophenanthrene synthesis, that was used as the key step for the syntheses of (+)-ferruginol[1] and (−)-morphine[3] mentioned above, we found that ethylene glycol served as a good initiator for the tandem retro-aldolization and cyclization when it was refluxed with the masked-aldol substrates having a bicyclo[3.2.1]octane framework in benzene or toluene in the presence of *p*-toluenesulfonic acid. We therefore anticipated that the pseudoyohimbane **12** would be formed in one step when the amine **8** was subjected to the same conditions through a sequence involving a retro-aldolization step; namely, (i) the concomitant removal of the MOM-protecting group and the ketal-cleavage generating the activated aldol **9**, (ii) the retro-aldolization of **9** generating the activated aldehyde **10**, (iii) the subsequent intramolecular condensation of **10** with the internal secondary amine generating the iminium intermediate **11** and (iv) the final diastereoselective intramolecular Pictet–Spengler cyclization to generate the pseudoyohimbone ketal **12**. Although reaction of the amine **8** under the same conditions in benzene or toluene proceeded in a less satisfactory manner owing to the insolubility of the amine **8**, the expected reaction did occur to afford a minor amount of the desired pseudoyohimbone ketal **12**. After extensive experimentation, we found that the reaction occurred to give diastereoselectively the pseudoyohimbane **12**, mp 242–245°C, $[\alpha]_D^{27}$ +28.4 (*c* 1.0, $CHCl_3$), in 82% yield when the amine **8** was refluxed for 2 h with 3 equiv. of ethylene glycol in acetonitrile containing 1.5 equiv. of *p*-toluenesulfonic acid. It is well established that the exclusive generation of the pseudoyohimbane stereochemistry is due to the stereoelectronic effect[11] as shown (from **11** to **12**). On hydrolysis, the ketal **12** afforded 18-pseudoyohimbone (+)-**1**, mp 241–243°C, $[\alpha]_D^{27}$ +1.74 (*c* 0.8, $CHCl_3$), as colorless crystals (Scheme 3).

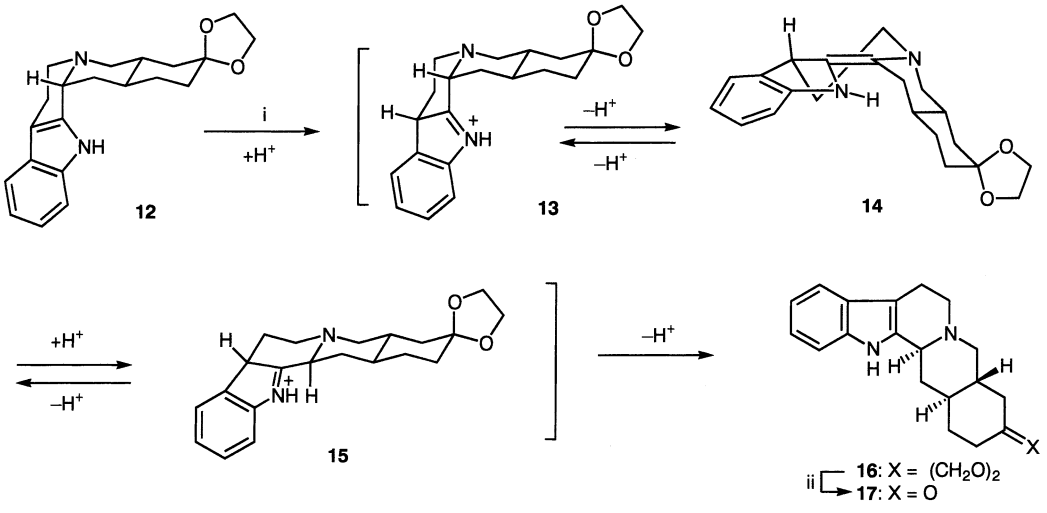


Scheme 3. *Reagents and conditions*: (i) *p*-TsOH, $(CH_2OH)_2$, MeCN, reflux, 2 h (82%). (ii) *p*-TsOH, 50% aq. acetone, reflux, 12 h (83%).

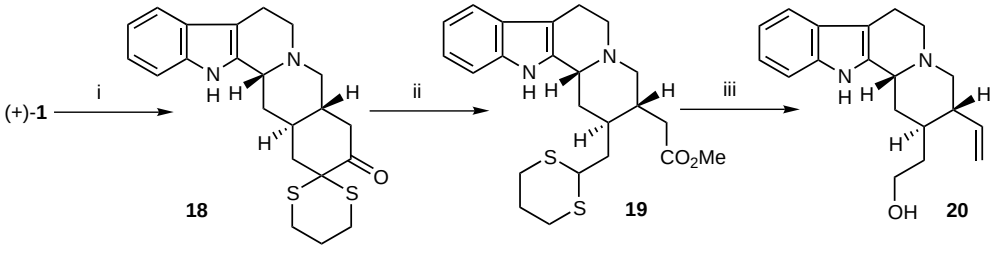
Although the reaction proceeded very slowly the pseudoyohimbane **12** was eventually transformed into the thermodynamically more stable yohimbane **13** on prolonged heating with ethylene glycol in acetonitrile in the presence of *p*-toluenesulfonic acid. Thus, **12** gave a readily separable mixture of the yohimbane **13** and the unchanged pseudoyohimbane **12** in a ratio of 3:7, quantitatively, after reflux with ethylene glycol for 12 h in acetonitrile in the presence of *p*-toluenesulfonic acid. Although the epimerization was slow, the yohimbane **13** obtained did not change under the same acidic conditions on prolonged heating thus indicating that no equilibrium exists between the yohimbane **16** and the pseudoyohimbane **12** by epimerization at C3 stereogenic center in which equilibrium between the two indolenium intermediates **13** and **15** via the 1,2-enediamine **14** exists. Under the same acid-catalyzed hydrolysis, the ketal **16** afforded 18-ketoyohimbone **17**, mp 199–202°C, $[\alpha]_D^{22}$ −109.7 (*c* 1.2, $CHCl_3$), as colorless crystals (Scheme 4).

To demonstrate its potential as a precursor for the construction of corynanthe-type indole alkaloids, the 18-yohimbone (+)-**1** obtained was first treated with pyrrolidine to form an enamine which was immediately treated with trimethylene dithiotosylate[12,13] to generate regioselectively, the 17,18-diketone mono-17-thioketal **18**, mp 170–173°C, $[\alpha]_D^{22}$ −140.0 (*c* 1.0, $CHCl_3$). Upon exposure to potassium hydroxide in *tert*-butyl alcohol, the α-diketone monothioketal **18** was easily cleaved[14,15] to give the *seco*-acid thioketal having the corynanthe framework which was isolated as the methyl ester **19**, mp 196–197°C, $[\alpha]_D^{22}$ +20.8 (*c* 0.8, $CHCl_3$), after treatment with diazomethane. The overall yield of the tetracyclic ester **19** was 69% in two steps. The structure of the ester **19** was confirmed by transformation into the corynanthe-type indole alkaloid, (−)-isocorynantheol **20**, isolated from *Cinchona ledgeriana*[16] and synthesized previously by our laboratory employing a different procedure[17] (Scheme 5).

In conclusion, a concise enantio- and diastereocontrolled synthesis of (+)-18-pseudoyohimbone has been accomplished employing a novel tandem sequence involving a retro-aldolization and an intramolecular Pictet–Spengler cyclization. We have also achieved the epimerization of the pseudoyohimbone ketal into the yohimbone ketal leading to (−)-18-yohimbone. Conversion of these yohimbone derivatives into yohimbine- and corynanthe-type indole alkaloids to extend the versatility of the bicyclo[3.2.1]octane chiral building block and to develop new routes to these alkaloids is presently under investigation.



Scheme 4. *Reagents and conditions*: (i) *p*-TsOH, $(CH_2OH)_2$, MeCN, reflux, 12 h (30% with 70% recovery of **12**). (ii) *p*-TsOH, 50% aq. acetone, reflux, 12 h (73%).



Scheme 5. *Reagents and conditions*: (i) pyrrolidine, benzene, reflux, then trimethylene dithiotosylate. (ii) KOH, *tert*-BuOH, reflux, acid workup, then diazomethane (69% overall). (iii) steps based on Ref. 17.

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References

1. Nagata, H.; Miyazawa, N.; Ogasawara, K. *Org. Lett.* **2001**, *3*, 1737.
2. Hanada, K.; Miyazawa, N; Nagata, H.; Ogasawara, K. *Synlett* **2002**, 125.
3. Nagata, H.; Miyazawa, N.; Ogasawara, K. *Chem. Commun.* **2001**, 1094.
4. Miyazawa, N.; Ogasawara, K. *Synlett*, in press.
5. To be published.
6. For pertinent reviews, see: (a) Szantay, C.; Blasko, G.; Honty, K.; Dörnyei, G. In *The Alkaloids: Corynantheine, Yohimbine, and Related Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, 1986; Vol. 27, pp. 131–268; (b) Baxter, E. W.; Mariano, P. S. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Springer Verlag: New York, 1992; Vol. 8, pp. 197–319; (c) Aube, J.; Ghosh, S. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI Press: Greenwich, 1996; Vol. 3, pp. 99–150.
7. For a recent chiral approach to yohimbane, see: Bergmeier, S. C.; Seth, P. P. *J. Org. Chem.* **1999**, *64*, 3237.
8. Tsunoda, T.; Suzuki, R.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.
9. Nystrom, R. D.; Brown, W. G. *J. Am. Chem. Soc.* **1948**, *70*, 3738.
10. Sheehan, J. C.; Preston, J.; Cruickshank, P. A. *J. Am. Chem. Soc.* **1965**, *87*, 2492.
11. Deslongchamps, P. In *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; pp. 209–290.
12. Woodward, R. B.; Pachter, I. J.; Scheinbaum, M. L. *Org. Synth. Coll.* **1988**, *6*, 1014.
13. Takano, S.; Hiroya, K.; Ogasawara, K. *Chem. Lett.* **1983**, 255.
14. Marshall, J. A.; Seitz, D. E. *J. Org. Chem.* **1974**, *39*, 1985.
15. Takano, S.; Ogasawara, K. *J. Synth. Org. Chem. Jpn.* **1977**, *35*, 795.
16. Keene, A. T.; Phillipson, J. D.; Warhurst, D. C.; Koch, M.; Seguin, E. *Planta Med.* **1987**, 201.
17. Kawamura, M.; Ogasawara, K. *Tetrahedron Lett.* **1995**, *36*, 3369.