HETEROYCLES, Vol. 54, No. 1, 2001, pp. 43 - 47, Received, 10th February, 2000

CASCADING SINGLE-STEP STEREOSELECTIVE CONSTRUCTION OF THE α-ALLOYOHIMBINE FRAMEWORK: A NEW SYNTHESIS OF (–)-NITRARAINE†

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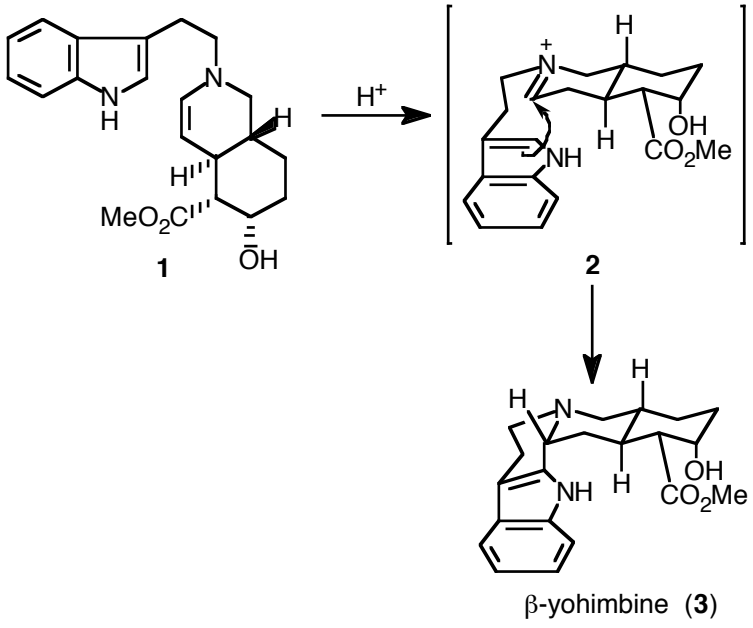
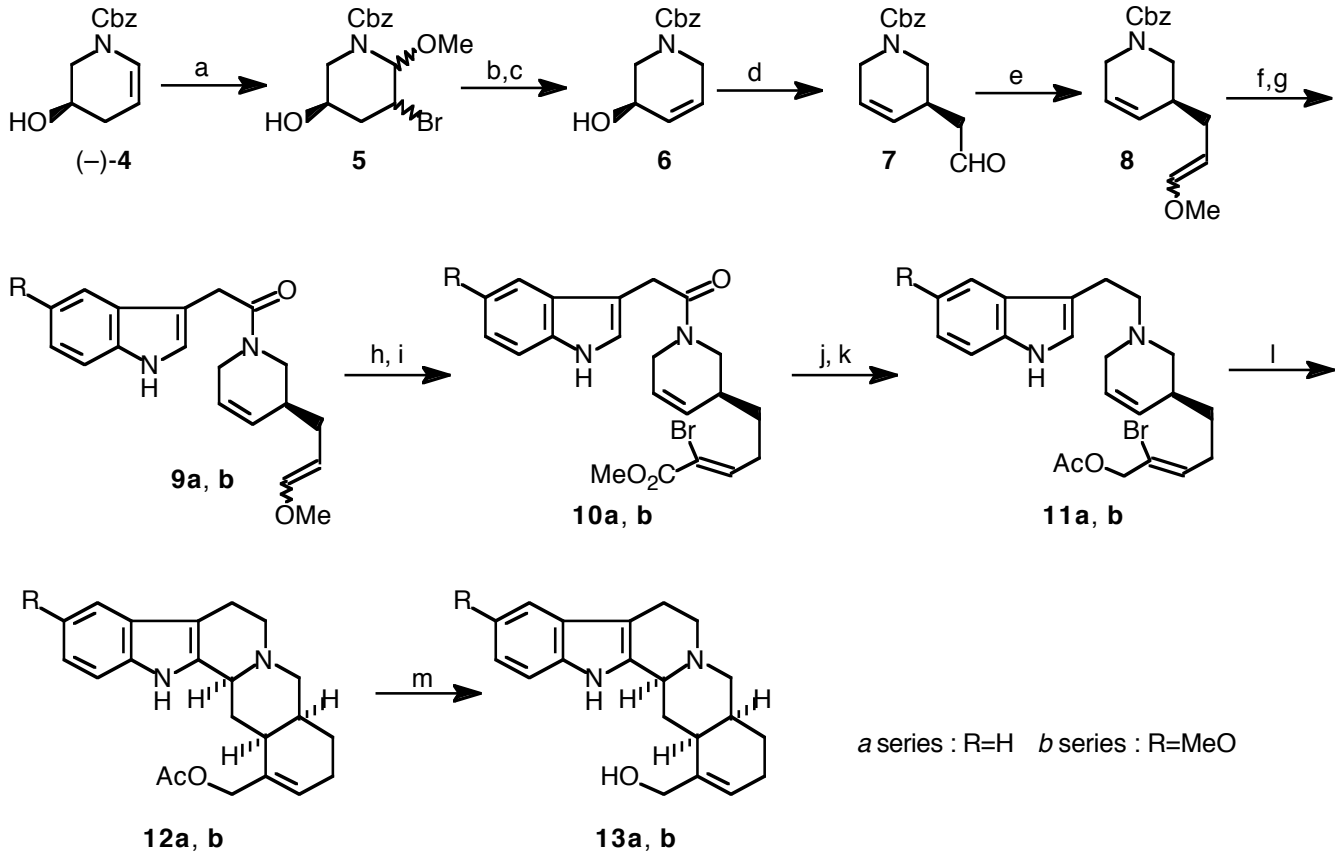
Abstract — (–)-Nitraraine and its 10-methoxy -analogue having an α-alloyohimbine framework have been constructed stereoselectively in a cascading single step sequence from chiral mono-substituted *N*-2-(3-indolyl)ethyltetrahydropyridine precursors under the Heck reaction conditions.

It has been shown[1] that the acid-catalyzed cyclization of the enamine (**1**) gave β-yohimbine (**3**) stereoselectively *via* the iminium intermediate (**2**) in agreement with the principle of stereoelectronic control[2] (**Scheme 1**). We are, therefore, interested in a stereocontrolled construction of the yohimbine alkaloids[3,4] *via* a formation of an enamine such as **1** by employing the intramolecular Heck reaction[5] of an appropriate chiral starting material. We wish to report here the first example leading to a stereoselective generation of the pentacyclic amines having an unexpected α-alloyohimbine framework from the chiral mono-substituted tetrahydropyridine precursors through a cascading double cyclization pathway under the Heck reaction conditions.



Scheme 1

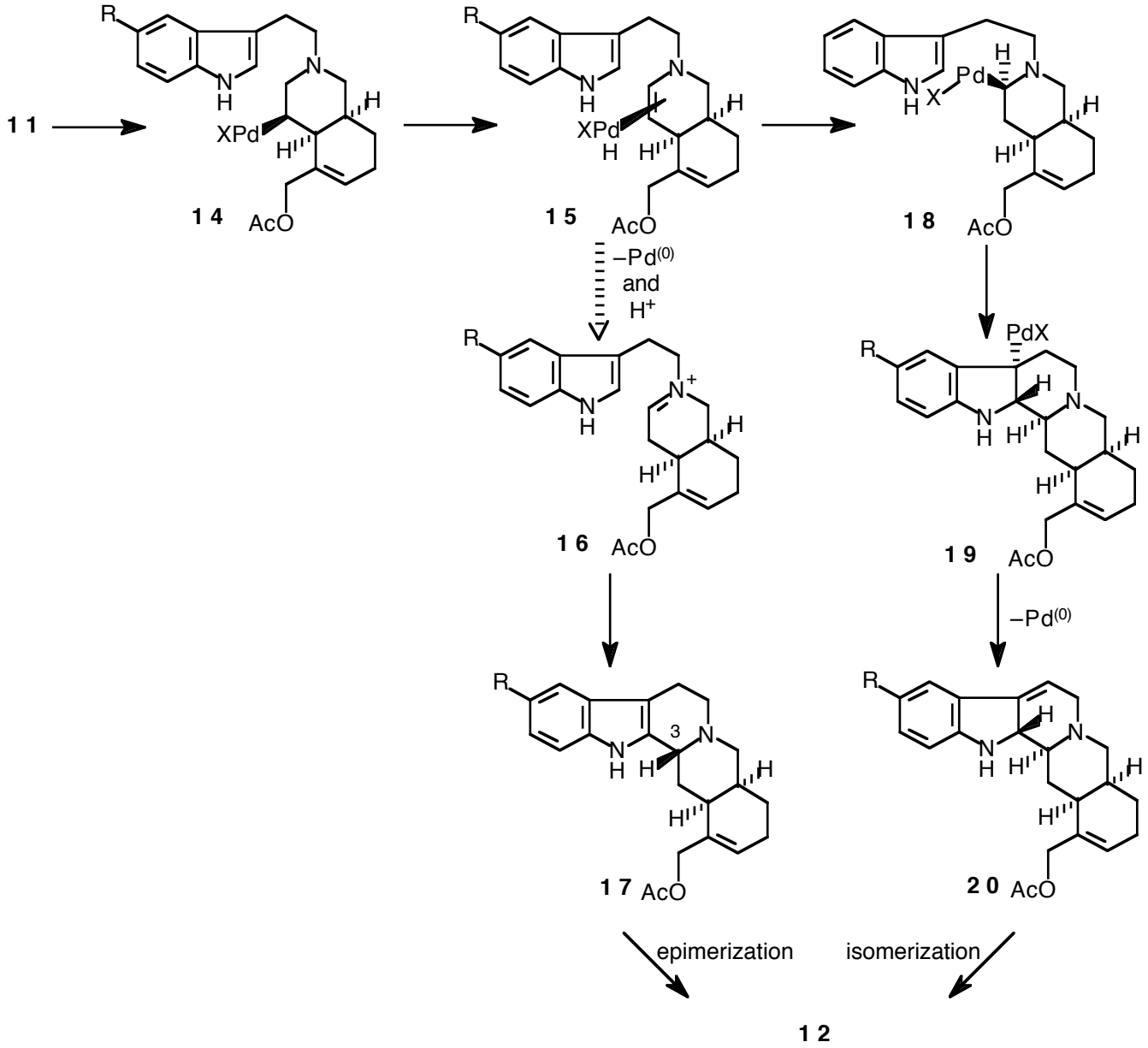
† Dedicated to Prof. Shô Itô on the occasion of his 77th birthday.



Scheme 2

Reagents and conditions: a) NBS, MeOH, 0 °C (90%). b) DBU, toluene, reflux. c) $NaBH_3CN$, $BF_3{\cdot}OEt_2$, THF, 0 °C (61%, 2 steps). d) ethyl vinyl ether, $Hg(OAc)_2$ (cat.), sealed tube (84%). e) $Ph_3P^+CH_2OMeCl^-$, $NaCH_2SOCMe$, THF, 0 °C (74%). f) 50% KOH, EtOH, reflux. g) indole-3-acetic acid, DCC, DMAP (cat.) (87% for **9a** and 89% for **9b**, 2 steps). h) Amberlyst-15, acetone-H_2O (9:1). i) $Ph_3P{=}C(Br)CO_2Me$, CH_2Cl_2, rt. (70% for **10a** and 52% for **10b**, 2 steps). j) DIBAL, CH_2Cl_2, –78 °C. k) Ac_2O, pyridine (58% for **11a** and 73% for **11b**, 2 steps). l) $Pd(OAc)_2$ (10 mol %), $P(o\text{-Tol})_3$ (40mol %), *i*-Pr_2NEt (3 equiv.), DMF, 90 °C (8% for **12a** : 21% for **12b**). m) K_2CO_3, MeOH (89% for **13a**: 81% for **13b**).

Since we have established[6] an efficient synthesis of enantiopure *N*-carbobenzoxy-3-hydroxy-1,2,3,4-tetrahydropyridine (**4**) in both enantiomeric forms from 3-hydroxypyridine, we used (–)-**4** as a starting material for the present investigation. Thus, (–)-**4**, $[\alpha]_D^{29}$ –7.14° (*c* 0.91, $CHCl_3$) (> 99% ee by HPLC using a column with a chiral stationary phase: CHIRALCEL OD, elution with 2% *i*-PrOH-hexane), was treated with *N*-bromosuccinimide (NBS) in methanol to give the bromo ether (**5**) as a mixture of the diastereomers. The mixture was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene at refluxing temperature and the product, after removal of the solvent, was reduced with sodium cyano borohydride in THF at 0 °C in the presence of boron trifluoride to give 3-hydroxy-1,2,3,6-tetrahydropyridine (**6**), $[\alpha]_D^{27}$ –68.7° (*c* 1.02, $CHCl_3$) (> 99% ee by HPLC using a column with a chiral stationary phase: CHIRALCEL OD, elution with 10% Pr^iOH-hexane). On Claisen rearrangement using an excess ethyl vinyl ether in a sealed tube in the presence of mercury(II) acetate at 200 °C, **6** furnished the γ,δ-unsaturated aldehyde (**7**), $[\alpha]_D^{29}$ +72.3° (*c* 1.09, $CHCl_3$). This was elongated by Wittig reaction[7] to give the enol ether (**8**) as an E/Z-mixture.



Scheme 3

Removal of the carbamate functionality of **8** was carried out on reflux with 50% ethanolic potassium hydroxide to give the secondary amine which was condensed with indole-3-acetic acid[8] in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) to give the amide (**9a**). On the same reaction with 5-methoxyindole-3-acetic acid,[8] **8** gave the 5-methoxy-analogue (**9b**) in a comparable yield. The amides (**9a**,**b**) were treated with Amberlyst-15 in aqueous acetone solution (10% v/v) to give the aldehydes which on Wittig reaction[9] afforded the corresponding (Z)-α-bromo-α,β-unsaturated esters (**10a**,**b**) without difficulty. Since neither the Heck reaction of **10a**,**b** nor chemoselective reduction of the amide functionality of **10a**,**b** proceeded well, **10a**,**b** were transformed into the allyl acetates (**11a**,**b**) by reduction of the amide and the ester functionalities in the molecules with diisobutylaluminum hydride (DIBAL) followed by acetylation.

Upon treatment[10,11] with palladium(II) acetate (10 mol %), tri(*o*-tolyl)phosphine (40 mol %) and Hünig base (3 equiv.) in DMF at 90 °C, **11a**, $[\alpha]_D^{29}$ +25.1° (*c* 0.78, $CHCl_3$), furnished the pentacyclic acetate (**12a**), diastereoselectively, in one step though only in 8% yield as the sole isolable product.[12] Alkaline methanolysis of **12a** afforded (–)-nitraraine[12] (**13a**), mp 112-114 °C, $[\alpha]_D^{20}$ –172.6° (*c* 0.11, $CHCl_3$) [lit.,[13]: mp 114-116 °C, $[\alpha]_D^{23}$ –175.9° (*c* 0.75, $CHCl_3$)], having an α-alloyohimbine framework but not an expected β-alloyohimbine framework. On the same treatment, the methoxy-analogue (**11b**) afforded the pentacyclic acetate (**12b**), diastereoselectively, in 21% yield as the sole isolable product[12] which was further transformed into 10-methoxynitraine (**13b**), $[\alpha]_D^{29}$ –165.6° (*c* 0.10, $CHCl_3$). It was presumed that **13b** has an α-alloyohimbine stereochemistry on the basis of the spectroscopic comparison[14] with (–)-nitraraine (**13a**) (**Scheme 2**).

Although the yields of (–)-nitraine (**13a**) and its 10-methoxy-analogue (**13b**) were far less than satisfactory, the observed single step generation of these compounds from the bromides (**11a**,**b**) under the Heck conditions was extremely of interest in two points. Namely, the first is the formation of the cyclization products without acid catalyst and the second is the stereospecific formation of the products having an α-alloyohimbine stereochemisty, but not a β-yohimbine stereochemistry. If the iminium intermediate such as **16** was generated from the first Heck cyclization intermediate (**14**) *via* the enamine complex (**15**), it should first give the pentacyclic amine (**17**) having a β-alloyohimbine stereochemistry, by following the principle of stereoelectronic control,[2] which required a concurrent epimerization of the C3 stereogenic center to give the α-alloyohimbine products (**12**) under the conditions. These seem very improbable under weak basic conditions employed in the present Heck reaction. We, therefore, propose an alternative explanation neither involving the iminium intermediate (**16**) nor the β-alloyohimbine intermediate (**17**). Thus, the enamine π-complex (**15**) first isomerizes to give the σ-complex (**18**), stereoselectively, which undergoes the second Heck reaction to generate the pentacyclic σ-complex (**19**) followed by the styrylamine (**20**), stereoselectively, which finally isomerized to afford the observed indolic products (**12**) having an α-alloyohimbine chromophore (**Scheme 3**).

In short, we have demonstrated that the construction of the α-alloyohimbine framework in a cascading single step sequence from a mono-substituted *N*-2-(3-indolyl)ethyltetrahydropyridine for the first time by employing the intramolecular Heck reaction.

REFERENCES AND NOTES

1 G. Stork and R. N. Guthikonda, *J. Am. Chem. Soc*., 1972, **94**, 5109.

2 P. Deslongchamps, " Stereoelectronic Effects in Organic Chemistry" , Pergamon, Oxford, 1983, pp. 209-290.

3 A pertinent review, see: C. Szantay, G. Blasko, K. Honty, and G. Dornyei, *The Alkaloids*, 1986, **27**, 131.

4 J. Leonard, *Nat. Prod. Rep*., 1999, **16**, 319 and former reports.

5 A most recent example, see: M. E. Fox, C. Li, J. P. Marino, Jr., and L. E. Overman, *J. Am. Chem. Soc*., 1999, **121**, 5467 and references cited therein.

6 (a) H. Sakagami, T. Kamikubo, and K. Ogasawara, *Chem. Commun.*, 1996, 1433. (b) H. Sakagami, T. Kamikubo, and K. Ogasawara, *Synlett,* 1997, 221. (c) H. Sakagami and K. Ogasawara, *Synthesis*, in press.

7 (a) G. Wittig and M. Schlosser, *Chem. Ber.*, 1961, **94**, 1373. (b) E. J. Corey and S. Nozoe, *J. Am. Chem. Soc.*, 1965, **87**, 5728.

8 K. Samizu and K. Ogasawara, *Synlett,* 1994, 499.

9 D. B. Denney and S. T. Ross, *J. Org. Chem.*, 1962, **27**, 998.

10 L. Shi, C. K. Narula, K. T. Mak, L. Kao, Y. Xu, and R. F. Heck, *J. Org. Chem.*, 1983, **48**, 3894.

11 Y. Sato, S. Watanabe, and M. Shibasaki, *Tetrahedron Lett.*, 1992, **33**, 2589; G. C. Nwokogu, *Tetrahedronn Lett.*, 1984, **25**, 3263.

12 Neither other isolable compound nor the starting material was obtained.

13 S. Takano, K. Samizu, T. Sugihara, and K. Ogasawara, *Chem. Lett.*, 1989, 1777. Spectroscopic data of (–)-nitraine (**13a**) obtained in the present study were identical with those of the authentic material.

14 Spectroscopic data: (–)-nitraraine (**13a**) — IR ($CHCl_3$): ν = 3400, 3000~2770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ =7.93 (1H, brs), 7.46 (1H, d, *J* =7.7 Hz), 7.30 (1H, d, *J* =7.4 Hz), 7.13 (1H, td, *J* =7.7, 1.0 Hz), 7.07 (1H, td, *J* =7.4, 1.0 Hz), 5.71 (1H, s), 4.20 (1H, d, *J* =12.6 Hz), 4.07 (1H, d, *J* =12.6 Hz), 3.26-3.17 (1H, m), 3.01-2.86 (3H, m), 2.76-2.62 (2H, m), 2.56-2.36 (2H, m), 2.32-2.20 (1H, m), 2.20-1.90 (4H, m), 1.90-1.74 (1H, m), 1.65-1.48 (2H, m); ^{13}C NMR (75 Hz, $CDCl_3$): δ =140.7 136.2, 127.6, 125.3, 121.3, 119.5, 118.2, 111.0, 108.3, 66.0, 61.5, 60.3, 53.6, 35.5, 34.4, 32.3, 25.8, 23.4, 21.7; H RMS (m/z): calcd $C_{20}H_{24}N_2O$: 308.1888. Found: 308.1884. (–)-10-methoxynitraine (**13b**) — IR (film): ν =3298, 3000~2770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ =7.71 (1H, brs), 7.19 (1H, d, *J* =8.8 Hz), 6.92 (1H, d, *J* =2.2 Hz), 6.78 (1H, dd, *J* =8.8, 2.2 Hz), 5.70 (1H, s), 4.19 (1H, d, *J* =12.1 Hz), 4.07 (1H, d, *J* =12.1 Hz), 3.85 (3H, s), 3.25-3.13 (1H, m), 3.05-2.87 (3H, m), 2.73-2.60 (2H, m), 2.60-2.38 (2H, m), 2.30-2.18 (1H, m), 2.18-1.95 (4H, m), 1.88-1.48 (3H, m); H RMS (m/z): Calcd $C_{21}H_{26}N_2O_2$ 338.1994. Found: 338.1992.