Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 9379–9382

TETRAHEDRON

Novel total syntheses of (±)-oxerine by intramolecular Heck reaction

Jingrui Zhao,[a,b] Xiaoxia Yang,[a] Xueshun Jia,[b] Shengjun Luo[a] and Hongbin Zhai[a,*]

[a]*Laboratory of Modern Synthetic Organic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

[b]*Department of Chemistry, Shanghai University, Shanghai 200436, China*

Received 11 September 2003; revised 15 September 2003; accepted 19 September 2003

Abstract—Both a three-step and a five-step syntheses of monoterpene alkaloid (±)-oxerine from alcohol **6** have been accomplished. In the second approach, the synthetic efficiency was enhanced by implementing a one-pot protocol (deprotonation/silylation/ alkylation/desilylation). The construction of the cyclopenta[*c*]pyridine framework was realized by an intramolecular Heck reaction, which should be adaptable for the synthesis of other related monoterpene pyridine alkaloids.

1. Introduction

(−)-Oxerine[1] ((−)-**1**), (−)-actinidine[2] ((−)-**2**), aucubinine A[3a] (**3**) and aucubinine B[3] (**4**) are four representative monoterpene alkaloids possessing the cyclopenta[*c*]pyridine skeleton (Fig. 1). These natural products are usually of biological significance, as exemplified by (i) the abortive activities of the bark extract of *Oxera robsta* [a species related to *Oxera morieri*, from the aerial parts of which (−)-oxerine was isolated] and (ii) the cat-exciting effect[2] of (−)-actinidine. Hence the syntheses of cyclopenta[*c*]-pyridine monoterpene alkaloids have stimulated tremendous interests in the synthetic community since approximately a decade ago.[2,4] In the previous syntheses, two different approaches were adopted to construct the cyclopenta[*c*]-pyridine skeleton, either by a free radical cyclization[4a–c] or via an intramolecular oxazole–olefin Diels–Alder reaction.[4d] The former approach involves the use of a radical initiator such as tributyltin hydride or of SmI_2, while the latter requires the synthesis of a suitable oxazole precursor. We envisioned that the cyclopenta[*c*]pyridine framework of oxerine could be constructed effectively by an intramolecular Heck reaction from an appropriate precursor. The Heck reaction, first discovered by Mori and Heck groups in the early 1970s,[5] has become an indispensable tool for synthetic organic chemists.

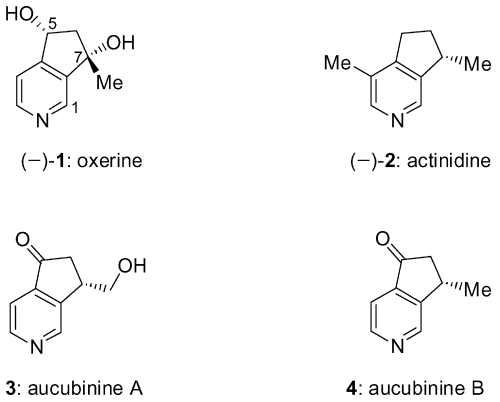


Figure 1.

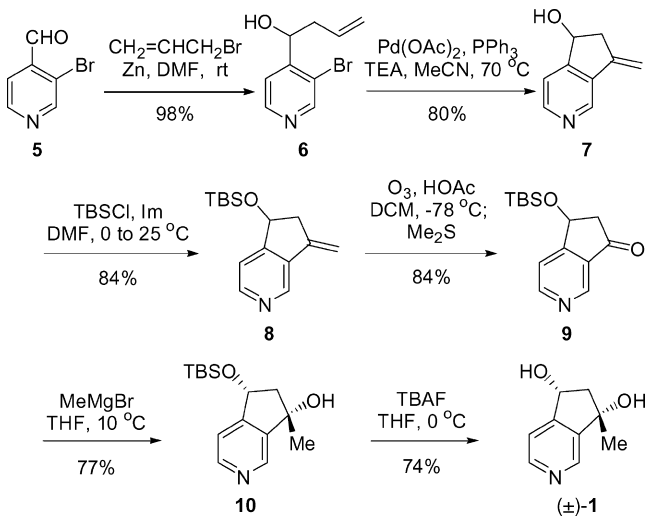
2. Results and discussion

We have been interested in the chemistry of pyridine-containing natural and unnatural products.[6] Herein we wish to report two novel concise total syntheses of (±)-**1**, which showcase the construction of cyclopenta[*c*]pyridine skeleton via an intramolecular Heck reaction. Our syntheses commenced from a known alcohol **6** (Scheme 1), which was reportedly[4b,c] prepared (73%) by a Barbier reaction of 3-bromo-4-pyridinecarboxaldehyde[7] **5** with allyl bromide and activated zinc in THF for 2 h. We discovered that allylation of aldehyde **5** with allyl bromide and unactivated zinc in DMF for 30 min smoothly afforded in 98% yield homoallylic alcohol **6** as a yellow oil, which set the stage for 5-*exo* cyclization via an intramolecular Heck reaction. Treatment[8] of **6** with $Pd(OAc)_2$ (0.05 equiv.), PPh_3 (0.1 equiv.) and Et_3N (2 equiv.) in CH_3CN at 70°C for 3.5 h led to the desired cyclopenta[*c*]pyridine intermediate **7**[4b,c] in 80% yield. In an attempt to stereoselectively set up

Keywords: intramolecular Heck reaction; monoterpene; oxerine; pyridine alkaloid; syntheses.

* Corresponding author. Tel.: +86-21-64163300; fax: +86-21-64166128; e-mail: zhaih@mail.sioc.ac.cn

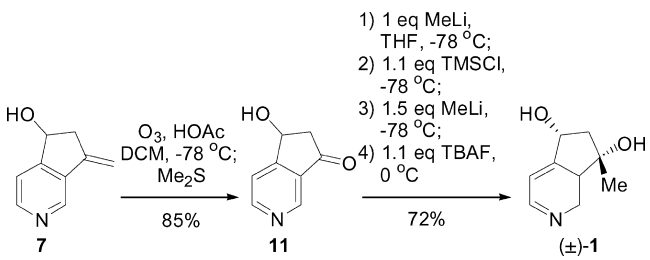
0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.09.079



Scheme 1.

the C-7 hydroxyl, alcohol **7** was subjected to the BuLi/CO_2[9] (or $ClCONH_2$)/I_2; however, no desired cyclic carbonate was formed. In addition, no cyclic diester was produced by the iodolactonization[10] (I_2/$NaHCO_3$/CH_3CN) of the monoester product obtained by reacting[11] **7** with succinic anhydride/pyridine/DMAP. Thus we resorted to a less direct but more practical strategy to address this problem. Hydroxyl protection[12] of **7** with TBSCl and imidazole in DMF furnished in 84% silyl ether **8**, ozonolysis[6a] of which in the presence of acetic acid (1 equiv.) led to the formation of ketone **9** in good yield (84%). Alkylation with methylmagnesium bromide in THF at 10°C provided tertiary alcohol **10** as a brownish solid (77%). The nucleophilic addition was in complete stereocontrol due to the steric factor. Upon desilylation with TBAF in THF at 0°C, (±)-**1** was obtained as a colorless solid (74%).

Next, a shorter synthetic route of (±)-**1** was developed, as delineated in Scheme 2. Upon ozonolysis of alcohol **7** by employing the same procedure for preparing **9**, a known aldol[4b,c] **11** was generated as a colorless solid (85%). Jones[4b,c] once reported that the direct methylation of **11** with excess methylmagnesium bromide (5 equiv.) in THF proved to be unsuccessful. We repeated this experiment and found that only a trace amount of (±)-**1** was produced while the starting material consumed away. To achieve a direct transformation of **11** to (±)-**1**, we designed a one-pot protocol, i.e. deprotonation/silylation/stereospecific alkylation/desilylation in sequence. Indeed, monoterpene alkaloid (±)-**1** could be produced from **11** in 72% yield in this manner. The material from this sequence gave ^1H NMR spectral data in accord with those reported.[1]



Scheme 2.

3. Conclusion

In conclusion, both a three-step and a five-step syntheses of monoterpene alkaloid (±)-oxerine from alcohol **6** have been accomplished. In the second approach, the synthetic efficiency was enhanced by implementing a one-pot protocol. The construction of the cyclopenta[*c*]pyridine framework was realized by an intramolecular Heck reaction, which should be adaptable for the synthesis of other related monoterpene pyridine alkaloids.

4. Experimental

4.1. General

Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$, DMSO-d_6 or CD_3OD (^1H at 300 MHz and ^{13}C at 75.47 MHz), using TMS as the internal standard when appropriate. Column chromatography was performed on silica gel. DCM, DMF, CH_3CN, and TEA were distilled over calcium hydride under N_2. Ether and THF were distilled over sodium benzophenone ketyl under N_2.

4.1.1. 3-Bromo-4-(1′-hydroxy-3′-butenyl)pyridine (6). Zn powder (2.88 g, 44.1 mmol) was added to a solution of **5** (1.64 g, 8.82 mmol) and allyl bromide (1.2 mL, 14 mmol) in DMF (10 mL) at room temperature (rt) under N_2. An exothermic reaction started within 10 min and ceased in 30 min. After evaporation of DMF under reduced pressure, saturated aqueous $NaHCO_3$ solution and EtOAc were added. The two layers were separated and the aqueous layer was further extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a residue, which was chromatographed (SiO_2, EtOAc/hexanes, 1:10) to afford **6**[4c] (1.98 g, 98%) as a yellow oil: ^1H NMR ($CDCl_3$) δ 2.30–2.35 (m, 1H), 2.59–2.62 (m, 1H), 4.07 (br s, 1H), 5.03 (dd, J=8.0, 3.6 Hz, 1H), 5.14–5.20 (m, 2H), 5.77–5.96 (m, 1H), 7.53 (d, J=5.1 Hz, 1H), 8.41 (d, J=5.1 Hz, 1H), 8.54 (s, 1H).

4.1.2. 1-Hydroxy-4-methylenocyclopentano[2,3-*c*]pyridine (7). To a solution of **6** (110 mg, 0.48 mmol) in CH_3CN (5 mL) were added Et_3N (0.13 mL, 0.93 mmol), $Pd(OAc)_2$ (5.4 mg, 0.02 mmol) and PPh_3 (12.6 mg, 0.05 mmol). The resultant mixture was heated at 70°C for 3.5 h. After evaporation of the volatile organics under reduced pressure, saturated aqueous $NaHCO_3$ solution and EtOAc were added. The two layers were separated and the aqueous layer was further extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a residue, which was purified by flash chromatography (SiO_2, EtOAc/hexanes, 1:1) to afford **7**[4c] (57 mg, 80%) as a colorless solid: mp 97–99°C; ^1H NMR ($CDCl_3$) δ 2.34–2.35 (br, 1H), 2.64–2.73 (m, 1H), 3.17–3.27 (m, 1H), 5.21 (t, J=2.1 Hz, 1H), 5.28–5.32 (m, 1H), 5.65 (t, J=2.1 Hz, 1H), 7.41 (d, J=5.1 Hz, 1H), 8.51 (d, J=5.1 Hz, 1H), 8.80 (s, 1H).

4.1.3. 1-((*t*-Butyldimethylsilyl)oxy)-4-methylenocyclopentano[2,3-*c*]pyridine (8). To a solution of **7** (226 mg, 1.54 mmol) in DMF (1.5 mL) at 0°C was added imidazole (221 mg, 3.25 mmol) and TBSCl (333 mg, 2.21 mmol). The

reaction mixture was allowed to warm to 25°C, stirred at that temperature for 11 h, diluted with water (15 mL), and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a residue, which was chromatographed (SiO_2, EtOAc/hexanes, 1:3–1:1) to afford **8** (337 mg, 84%) as a colorless solid: mp 43–45°C; ^{1}H NMR ($CDCl_3$) δ 0.17 (s, 3H), 0.20 (s, 3H), 0.96 (s, 9H), 2.65–2.72 (m, 1H), 3.09–3.11 (m, 1H), 5.14–5.20 (m, 1H), 5.28 (t, J=6.6 Hz, 1H), 5.60 (dd, J=3.3, 1.8 Hz, 1H), 7.28–7.31 (m, 1H), 8.51 (d, J=5.1 Hz, 1H), 8.79 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −4.7, −4.5, 18.2, 25.8, 43.0, 73.3, 105.6, 119.6, 135.4, 143.2, 143.9, 149.0, 155.4. Anal. calcd for $C_{15}H_{23}NOSi$: C, 68.91; H, 8.87; N, 5.36. Found: C, 69.07; H, 8.96; N, 5.10.

4.1.4. 1-((*t*-Butyldimethylsilyl)oxy)-4-oxocyclopentano-[2,3-*c*]pyridine (9). A solution of **8** (337 mg, 1.29 mmol) and acetic acid (74 μL, 1.3 mmol) in CH_2Cl_2 (15 mL) was stirred at −78°C as ozone was passed through the solution (until the solution turned blue), which was purged with oxygen for 15 min. Me_2S (0.6 mL, 8 mmol) was added at −78°C and the solution was allowed to warm to rt. Saturated aqueous $NaHCO_3$ solution was added and the two layers were separated. The aqueous layer was further extracted with CH_2Cl_2/2-propanol (3:1). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to give a residue, which was purified by chromatography (SiO_2, EtOAc/hexanes, 1:1–3:1) to afford **9** (287 mg, 84%) as a colorless solid: mp 67–69°C; ^{1}H NMR ($CDCl_3$) δ 0.20 (s, 3H), 0.24 (s, 3H), 0.96 (s, 9H), 2.63 (dd, J=18.3, 3.9 Hz, 1H), 3.08 (dd, J=18.6, 6.6 Hz, 1H), 5.37 (dd, J=6.6, 3.9 Hz, 1H), 7.57 (d, J=5.1 Hz, 1H), 8.83 (d, J=5.1 Hz, 1H), 9.02 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −4.8, −4.5, 18.0, 25.6, 47.6, 68.5, 120.7, 131.4, 145.8, 154.3, 163.1, 201.4. Anal. calcd for $C_{14}H_{21}NO_2Si$: C, 63.84; H, 8.04; N, 5.32. Found: C, 63.76; H, 8.04; N, 5.15.

4.1.5. (1*R* *,4*S* *)-1-((*t*-Butyldimethylsilyl)oxy)-4-hydroxy-4-methylcyclopentano[2,3-*c*]pyridine (10). To a dry solution of **9** (400 mg, 1.52 mmol) in THF (25 mL) was added dropwise a solution of MeMgBr (2.4 M, 0.9 mL, 2.2 mmol) in ether diluted with THF (3 mL) at 10°C. The reaction mixture was stirred at 10°C for 3 h, allowed to warm to 30°C over 0.5 h, quenched with saturated aqueous NH_4Cl solution (5 mL), evaporated, and extracted with CH_2Cl_2/2-propanol (3:1). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a residue, which was chromatographed (SiO_2, MeOH/CH_2Cl_2, 1:20–1:10) to afford **10** (325 mg, 77%) as a brownish solid: mp 99–100°C; ^{1}H NMR ($CDCl_3$) δ 0.16 (s, 3H), 0.18 (s, 3H), 0.92 (s, 9H), 1.54 (s, 3H), 2.14 (dd, J=13.0, 5.8 Hz, 1H), 2.56 (dd, J=12.9, 6.3 Hz, 1H), 5.04 (t, J=6.3 Hz, 1H), 7.21 (d, J=4.8 Hz, 1H), 8.46 (d, J=5.1 Hz, 1H), 8.58 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −4.7, −4.5, 18.0, 25.7, 27.7, 53.4, 72.4, 77.5, 119.0, 143.3, 145.0, 148.9, 152.4. Anal. calcd for $C_{15}H_{25}NO_2Si$: C, 64.47; H, 9.02; N, 5.01. Found: C, 64.42; H, 8.85; N, 4.79.

4.1.6. (±)-Oxerine (1). *Method A* (*Prepared from* **10**). A solution of TBAF in THF (1 M, 0.6 mL, 0.6 mmol) was added to a solution of **10** (64.2 mg, 0.23 mmol) in THF (7 mL) at 0°C under N_2. The mixture was stirred at 0°C for 45 min and then at 25°C for 3 h, quenched with water (5 mL), evaporated, and extracted with CH_2Cl_2/2-propanol (3:1). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to give a residue, which was purified by chromatography (SiO_2, MeOH/CH_2Cl_2, 1:10–1:5) to afford **1** (28 mg, 74%) as a colorless solid: mp 187°C dec.; ^{1}H NMR (CD_3OD) δ 1.47 (s, 3H), 2.09 (dd, J=12.8, 8.2 Hz, 1H), 2.68 (dd, J=12.4, 7.5 Hz, 1H), 5.06 (t, J=7.5 Hz, 1H), 7.45 (d, J=4.8 Hz, 1H), 8.46 (d, J=5.1 Hz, 1H), 8.55 (s, 1H); ^{13}C NMR (CD_3OD) δ 29.3, 53.9, 72.2, 77.8, 120.8, 145.4, 145.9, 149.3, 155.0. Anal. calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.25; H, 6.75; N, 8.57.

Method B (*Prepared directly from* **11**). A solution of MeLi (1.51 M, 0.16 mL, 0.24 mmol) in ether was added to a stirred solution of **11** (35 mg, 0.23 mmol) in THF (10 mL) at −78°C. After 30 min, a solution of TMSCl (32 μL, 0.25 mmol) in THF (5 mL) was added at −78°C over 5 min. The reaction mixture was stirred at −78°C for 50 min before a solution of MeLi (1.51 M, 0.23 mL, 0.35 mmol) in ether was added. The mixture was stirred at −78°C for 1 h, allowed to warm to 10°C, and stirred at that temperature for 1.5 h. Finally, a solution of TBAF (1 M, 0.26 mL, 0.26 mmol) in THF was added at 0°C. The mixture was stirred at 0°C for 30 min, allowed to warm to rt overnight, quenched with saturated aqueous $NaHCO_3$ solution, evaporated, and extracted with CH_2Cl_2/2-propanol (3:1). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to give a residue, which was purified by chromatography (SiO_2, MeOH/CH_2Cl_2, 1:10–1:5) to furnish **1** (28 mg, 72%) as a colorless solid.

4.1.7. 1-Hydroxy-4-oxocyclopentano[2,3-*c*]pyridine (11). A solution of **7** (61 mg, 0.41 mmol) and acetic acid (30 μL, 0.52 mmol) in CH_2Cl_2 (4 mL) was stirred at −78°C as ozone was passed through the solution (until the solution turned blue), which was purged with oxygen for 15 min. Me_2S (0.24 mL, 3.2 mmol) was added at −78°C and the solution was allowed to warm to rt. Saturated aqueous $NaHCO_3$ solution was added and the two layers were separated. The aqueous layer was further extracted with CH_2Cl_2/2-propanol (3:1). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to give a residue, which was purified by chromatography (SiO_2, EtOAc/hexanes, 1:1–3:1) to afford **11**[4c] (52.5 mg, 85%) as a colorless solid: mp 104°C dec.; ^{1}H NMR (acetone-d_6) δ2.52 (dd, J=18.8, 3.6 Hz, 1H); 3.08 (dd, J=18.9, 5.4 Hz, 1H); 5.46 (dd, J=3.6, 3.3 Hz, 1H); 7.77 (d, J=4.8 Hz, 1H); 8.81 (d, J=5.1 Hz, 1H); 8.85 (s, 1H). ^{1}H NMR (DMSO-d_6) δ 2.39–2.52 (m, 1H), 2.97–3.08 (m, 1H), 5.25 (br, 1H), 5.97 (dd, J=9.0, 6.6 Hz, 1H), 7.73–7.75 (m, 1H), 8.81 (dd, J=5.1, 2.4 Hz, 1H), 8.85 (s, 1H).

Acknowledgements

We thank the following agencies for financial support: Chinese Academy of Sciences ('Hundreds of Talent' Program); Science and Technology Commission of Shanghai Municipality ('Venus' Program); National Natural Science Foundation of China; The Bureau of Tobacco, PRC.

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