Pergamon

Tetrahedron Letters 41 (2000) 10251–10255

TETRAHEDRON LETTERS

A new access to cyclopenta[*c*]pyridine ring system: syntheses of (−)-plectrodorine and (+)-oxerine

Masashi Ohba,* Rie Izuta and Emi Shimizu

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920-0934, Japan

Received 14 September 2000; revised 5 October 2000; accepted 12 October 2000

Abstract

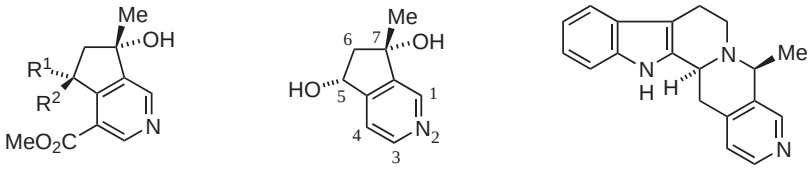
Total syntheses of (−)-plectrodorine [(−)-**1**] and (+)-oxerine [(+)-**3**] possessing the cyclopenta[*c*]pyridine ring system have been accomplished through a route starting from the chiral γ-butyrolactone **7** and exploiting the intramolecular oxazole–olefin Diels–Alder reaction. The sign of specific rotation for the synthetic (+)-**3** was in disagreement with that reported for natural oxerine, leaving the absolute configuration of this monoterpene alkaloid incomplete.

Keywords: Diels–Alder reactions; lactones; monoterpene alkaloids; oxazoles.

A number of monoterpene alkaloids containing the cyclopenta[*c*]pyridine ring system have been isolated and synthesized over the last several decades.[1] In 1989, Koch and co-workers[2] reported the isolation of two novel monoterpene alkaloids, plectrodorine (**1**) and isoplectrodorine (**2**), both as a racemate from the aerial parts of *Plectronia odorata* (Rubiaceae). The structures and relative stereochemistries of both alkaloids were determined by their spectral properties as well as chemical transformations. Thereafter, the French group[3] announced the isolation of (−)-oxerine [$[\alpha]_D^{20}$ −11° (*c* 0.20, MeOH)] from the aerial parts of *Oxera morieri* (Verbenaceae) and proposed its absolute stereochemistry to be (5*R*,7*S*)-**3** on the basis of the chemical correlation with harpagide, whose absolute configuration is known.[4] Racemic syntheses of oxerine have been accomplished by two research groups.[5] Recently, we have achieved the chiral synthesis of an indolopyridonaphthyridine alkaloid, normalindine (**4**), through a route featuring the assembly of the 2,7-naphthyridine skeleton attained by the intramolecular oxazole–olefin Diels–Alder reaction.[6] In the present study, the applicability of this strategy to an efficient construction of the cyclopenta[*c*]pyridine skeleton was tested in the chiral syntheses of plectrodorine and oxerine.

* Corresponding author. Fax: +81-76-234-1563; e-mail: ohba@dbs.p.kanazawa-u.ac.jp

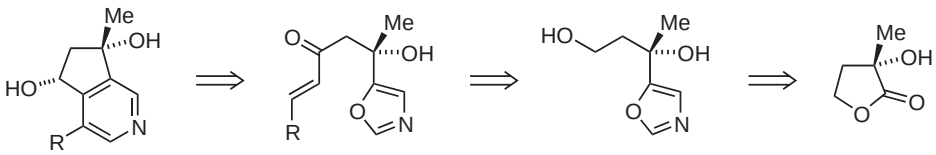
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01824-4



1: R^1 = OH, R^2 = H
2: R^1 = H, R^2 = OH

3 **4**

From the above retrosynthetic perspective, we envisioned the intermediacy of the oxazole–olefin **5** which would be obtained from **6** via the introduction of an appropriate dienophile (Scheme 1). The requisite oxazole alcohol **6**, in turn, would be secured by the addition of α-lithiated methyl isocyanide to the γ-butyrolactone **7**.

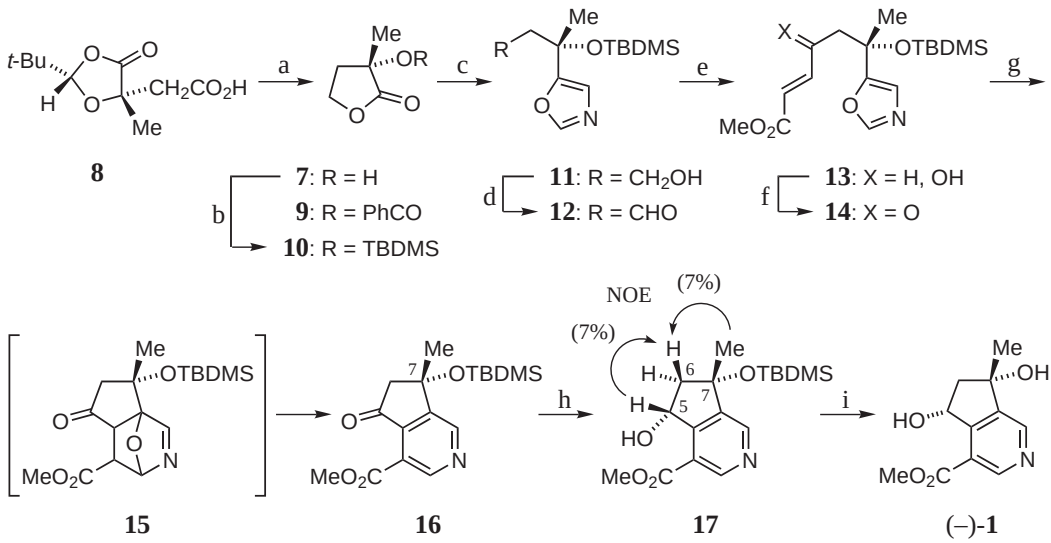


1: R = CO_2Me
3: R = H

5 **6** **7**

Scheme 1.

The synthetic route to plectrodorine (**1**) started with reduction of the dioxolanone **8**,[7,8] prepared from (*S*)-(−)-malic acid, with $BH_3{\cdot}Me_2S$ and subsequent alkaline hydrolysis followed by acid-promoted cyclization, giving the γ-butyrolactone **7** [$[\alpha]_D^{23}$ −36.3° (*c* 0.51, $CHCl_3$)] in 73% yield (Scheme 2). The absolute configuration of **7** was confirmed by its conversion to the



8

b: **7**: R = H; **9**: R = PhCO; **10**: R = TBDMS
d: **11**: R = CH_2OH; **12**: R = CHO
f: **13**: X = H, OH; **14**: X = O

NOE (7%) (7%)

15 **16** **17** (–)-**1**

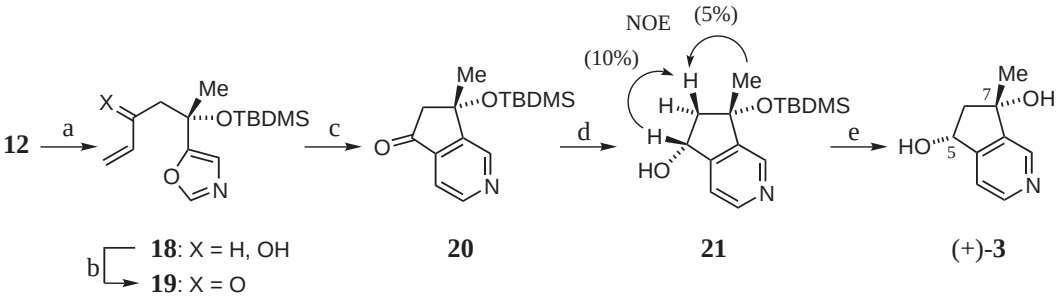
Scheme 2. *Reagents, conditions and yields:* (a) (1) $BH_3{\cdot}Me_2S$, THF, rt, 28 h; (2) 2N aq. NaOH, 0°C, 30 min; (3) aq. HCl, 73%; (b) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 2 h, 99%; (c) $LiCH_2NC$, THF, −78°C, 3 h, then AcOH, 66%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, −50°C, 30 min, then Et_3N, 85%; (e) methyl *trans*-3-iodoacrylate, $CrCl_2$, $NiCl_2$, DMSO, rt, 72 h, 61%; (f) Dess–Martin periodinane, CH_2Cl_2, rt, 45 min, 89%; (g) *o*-dichlorobenzene, 150°C, 48 h, 37%; (h) $NaBH_4$, MeOH, 0°C, 30 min, 75%; (i) Bu_4NF, THF, rt, 2 h, 73%

benzoate **9** and comparison of the specific rotation of **9** with that of the benzoate reported in the literature.[9] The tertiary hydroxy group of **7** was then protected in 99% yield as the corresponding *tert*-butyldimethylsilyl ether **10**. Jacobi et al.[10] have described that, in contrast to the Schöllkopf reaction of esters with α-lithiated methyl isocyanide,[11] similar reaction of lactones requires an addition of DMF and prolonged reaction time at room temperature to yield oxazole alcohols. However, the lactone **10** was found to be readily converted to the oxazole alcohol **11** under the conditions similar to those reported for esters. Thus, treatment of **10** with 2.5 equiv. of α-lithiated methyl isocyanide in THF at −78°C for 3 h, without the addition of DMF, followed by quenching with AcOH afforded **11** in 66% yield. Since the observation presented by Jacobi et al.[10] is based on bicyclic lactones, the difference between their and our results probably arises from the lactones employed.

Having obtained **11** as the azadiene partner required for the intramolecular oxazole–olefin Diels–Alder reaction,[12] we next investigated the introduction of an olefinic dienophile into **11**. After Swern oxidation[13] of **11**, coupling of the resulting aldehyde **12** (85% yield) with methyl *trans*-3-iodoacrylate[14] was effected by using $CrCl_2$ and a catalytic amount of $NiCl_2$ in DMSO according to Kishi's modification[15] of the Nozaki conditions,[16] giving the allylic alcohol **13** as a 2:1 diastereoisomeric mixture in 61% yield. Oxidation of **13** with the Dess–Martin periodinane[17] resulted in the formation of the desired oxazole–olefin substrate **14** in 89% yield.

When a 0.05 M solution of **14** in *o*-dichlorobenzene was heated at 150°C under argon for 48 h, the ester **16** [$[\alpha]_D^{22}$ +105.7° (*c* 0.50, $CHCl_3$)] possessing the cyclopenta[*c*]pyridine skeleton was obtained in 37% yield (48% on the basis of the recovered starting material) probably via the adduct **15**. Reduction of **16** with $NaBH_4$ in MeOH at 0°C occurred predominantly from an orientation opposite to the bulky *tert*-butyldimethylsilyloxy group at the 7-position, providing the alcohol **17** in 75% yield together with its C(5)-epimer (10% yield). The stereochemical assignment of **17** was secured from 7% NOE enhancements observed for the same proton [C(6)-Hβ] signal on separate irradiations of C(5)-H and C(7)-Me signals. The first target compound [(−)-**1**] [$[\alpha]_D^{24}$ −78.4° (*c* 0.40, MeOH)] was obtained in 73% yield by deprotection of **17** with tetrabutylammonium fluoride. The UV (MeOH), ^{1}H NMR ($CDCl_3$) and mass spectra of the synthetic (−)-**1** were virtually superimposable on those recorded for natural plectrodorine [$[\alpha]_D^{20}$ 0° (*c* 1, MeOH)].[2]

Our effort was then focused on the synthesis of oxerine (**3**). Grignard reaction of the aldehyde **12** with vinylmagnesium bromide was performed in THF at −10°C to furnish the allylic alcohol **18** as a 1:1 diastereoisomeric mixture in 82% yield (Scheme 3). On oxidation with the



Scheme 3. *Reagents, conditions and yields:* (a) vinylmagnesium bromide, THF, −10°C, 30 min, 82%; (b) Dess–Martin periodinane, CH_2Cl_2, rt, 80 min, 93%; (c) *o*-dichlorobenzene, 150°C, 9 h, 23%; (d) $NaBH_4$, EtOH, 0°C, 30 min, 84%; (e) Bu_4NF, THF, rt, 2 h, 91%

Dess–Martin periodinane,[17] **18** was converted into the oxazole–olefin **19** (93% yield), which was then subjected to the intramolecular Diels–Alder reaction under the conditions similar, except for the reaction time, to those for **14**. After 9 h, the desired pyridine **20** [$[\alpha]_D^{28}$ +84.8° (*c* 0.50, $CHCl_3$)] was obtained in 23% yield with the disappearance of the starting oxazole–olefin **19**. Stereoselective reduction of **20** was carried out with $NaBH_4$ in EtOH at 0°C to generate the alcohol **21** (84% yield), whose stereochemistry was also determined by the NOE experiments. Finally, deprotection of **21** with tetrabutylammonium fluoride provided the second target compound [(+)-**3**] [$[\alpha]_D^{23}$ +10.6° (*c* 0.21, MeOH); CD (MeOH) λ_{ext} 267 nm ($\Delta\varepsilon$ +2.54), 264 (+2.00), 261 (+2.15), 244 (−1.04), 231 (−0.39), 214 (−2.17)] in 91% yield. Although the UV (MeOH), ^1H NMR (CD_3OD) and mass spectra of the synthetic (+)-**3** were virtually identical with those of natural oxerine, to our surprise, the signs of specific rotation for the two samples were opposite. Unfortunately, since no sample of the alkaloid, to which the absolute stereochemistry (5*R*,7*S*)-**3** was assigned,[3] was available for detailed and direct chiroptical comparison with the synthetic (+)-**3**, the absolute configuration of oxerine is not yet fully understood.

In conclusion, a new access to the cyclopenta[*c*]pyridine ring system has now become possible through the intramolecular oxazole–olefin Diels–Alder reaction as exemplified by the syntheses of (−)-plectrodorine [(−)-**1**] and (+)-oxerine [(+)-**3**] from the chiral γ-butyrolactone **7**. It is hoped that the knowledge obtained on the synthetic (+)-**3** will be of great help toward unambiguous determination of the absolute configuration of oxerine after further isolation of this alkaloid from natural sources.

Acknowledgements

We are grateful to Professor Michel Koch (Université René Descartes) for providing us with spectral copies of natural plectrodorine and oxerine.

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