TOTAL SYNTHESIS OF (-)-DIHYDROCORYNANTHEOL USING BICYCLO[3.2.1]OCTENONE CHIRAL BUILDING BLOCK†

Ayako Tosaka, Shinichiro Ito, Norio Miyazawa, Masatoshi Shibuya, Kunio Ogasawara,* and Yoshiharu Iwabuchi*

Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aobayama, Sendai 980-8578, Japan. E-mail: konol@mail.tains.tohoku.ac.jp
iwabuchi@mail.pharm.tohoku.ac.jp

Abstract – The diastereocontrolled synthesis of (-)-dihydrcorynantheol from a bicyclo[3.2.1]octane chiral building block has been achieved by employing a tandem retro-aldol-Pictet-Spengler reaction-C-3 epimerization sequence as the key step.

The topological placement of functional groups endows molecules with substantial reactivity. In endeavors aimed at developing versatile chiral building blocks, we have realized that certain bicyclo[3.n.1]alkanes harboring an aldol functionality straddled at the bridgehead are exclusively obliged, because of Bredt’s rule,1 to give rise to a retro-aldol reaction on acidic treatment2,3 (Scheme 1), and have been exploiting its use in organic synthesis.4,5 We previously reported a facile construction of 18-keto-pseudoyohimbane ketal (4) from the bicyclo[3.2.1]octene chiral building block (-)-(1) by employing a novel cascade sequence consisting of a Brønsted-acid-promoted retro-aldol reaction of 3 and the subsequent stereocontrolled Pictet-Spengler reaction.4c We also disclosed that 4 gradually isomerizes5 to the 18-keto-yohimbane ketal (5) on treatment with p-TsOH in boiling toluene,4c indicating its potential use as a common intermediate of both yohimbine- and corynanthe-type indole alkaloids,7 which are useful antiparasitic, antiviral, and analgesic agents.8 On the basis of these findings, we embarked on the total synthesis of (-)-dihydrcorynantheol (2), a representative of corynanthe-type indole alkaloids first isolated from the bark of Aspidosperma marcgravianum Woodson (Apocynaceae).9,10 We report here the stereocontrolled total synthesis of (-)-dihydrcorynantheol (2) from the chiral bicyclo[3.2.1]octene (1), featuring a tandem retro-aldol-Pictet-Spengler reaction-C-3 epimerization sequence to allow a facile construction of the 18-keto-yohimbane skeleton.
Scheme 1

In our initial effort employing 4 as the key intermediate, we encountered a serious problem: insufficient material throughput in the C-3 epimerization of 4 to 5. In light of the experimental result that 5 does not isomerize to 4 under an acidic condition causing the epimerization of 4 to 5,4c and calculations indicating that 4 is more stable than 5 by 6.8 kcal/mol,11 it was assumed that the incomplete epimerization is not due to maturation in equilibrium but to the protonation of the amine moiety giving the corresponding ammonium ion, in which a positive charge prevents the crucial protonation on the indole moiety that will trigger the subsequent epimerization. Our desire to improve the productivity of epimerization prompted us to explore an amide (8) as the substrate of the key reaction. By employing a previously established procedure, 8,12 mp 65–67 °C, [α]D27 −20.1° (c 1.0, CHCl3), was prepared in 62% overall yield from the bicyclo[3.2.1]octenone chiral building block (−)-(1)2,4c in a four-step sequence involving the regioselective and convex-face-selective introduction of a nitromethyl group, ketalization using ethylene glycol bis-trimethylsilyl ether under Noyori’s conditions,13 the reduction of the nitro group to a primary amino group, and condensation with indole-3-acetic acid.

Scheme 2
Scheme 3. Reagents and conditions: a) MeNO₂, DBU, MeCN (86%); b) (CH₂OTMS)₂, TMSOTf (cat.), CH₂Cl₂, -30 °C (77%); c) LiAlH₄, THF; d) indole-3-acetic acid, WSCD, THF, rt (94%, two steps).

Although 8 showed a slightly low reactivity in the Pictet-Spengler reaction, the resulting 18-keto-pseudoyohimbane ketal (12) was found to elicit an improved reactivity in the acid-promoted C-3 epimerization to give 16. Thus, on exposure to p-TsOH and ethylene glycol, in refluxing MeCN, which enables the stereoselective construction of pseudoyohimbane ketal (4) from 3 in 82% yield, 8 affored 12 and 16 in 21% and 22% yields, respectively. After considerable experimentation, we found effective conditions using methanesulfonic acid in boiling dioxane for 12 h that allowed us to obtain the desired 16, [α]D₂⁰ –44.5° (c 1.0, CHCl₃), in 52% yield together with pseudoyohimbane (12), [α]D₂⁰ +72.3° (c 1.0, CHCl₃), in 23% yield as a readily separable mixture.

Scheme 4. Reagents and conditions: a) MsOH, (CH₂OH)₂, 1,4-dioxane, Dean-Stark, reflux, 12 h, 52% of 16 with 23% of 12; b) MsOH, (CH₂OH)₂, 1,4-dioxane, reflux, 6 h, 59% of 16 with 29% of 12.
The prolongation of the reaction time led to the complete consumption of 12, as determined by TLC; however, it also diminished the yield of 16 to 40% because of concomitant decompositions. We therefore separated these isomers and the recovered 12 was again subjected to the above-mentioned acidic conditions to obtain 16 in 59% yield and unreacted 12 in 29% yield.\(^{14}\) As a result of this sequence, 16 was obtained in 66% yield from 8. Note that 16 did not afford 12 under the same acidic conditions and that 12 isomerized to 16, indicating that no equilibrium exists between 16 and 12 by epimerization at the C3 stereogenic center in which two indolenium intermediates (13 and 15) via 1,2-diamine (14) exist, as in the case of the amine substrate (5).\(^{4c}\)

Having established an acceptable method for obtaining 16, we next examined the conversion of 16 into (−)-dihydrocorynantheol (2). Thus, to realize the transformation of the E-ring moiety to the seco form as expressed in 2, ketal was deprotected and the resulting ketone was treated with pyrrolidine to form an enamine, which was immediately treated with trimethylene dithiosylate\(^{16,17}\) to generate 17,18-diketone mono-17-thioketal (17), mp 198 °C, \([\alpha]_D^{24} -139.1^\circ\) (c 1.0, DMSO), as brown needles. Upon exposure to potassium hydroxide in boiling tert-butyl alcohol, the dithioketone moiety was cleaved to obtain seco-acid thioketal having a corynanthe framework, which was isolated as a methyl ester (18), \([\alpha]_D^{27} +24.3^\circ\) (c 1.0, CHCl\(_3\)), as brown amorphous powder, after esterification using TMSCl in MeOH.\(^{18}\)

![Scheme 5](image)

**Scheme 5.** Reagents and conditions: a) \(p\)-TsOH, aq. acetone (98%); b) (i) pyrrolidine, benzene, Dean-Stark; (ii) TsS(CH\(_2\)_2)STs, Et\(_3\)N, MeCN (85%, two steps); c) (i) KOH, \(t\)-BuOH, reflux; (ii) TMSCl, MeOH (58%); d) MeI, aq. MeCN; e) NaBH\(_4\), MeOH (79%, two steps); f) TBSCI, DMAP, imidazole (cat.), DMF (72%); g) LiAlH\(_4\), THF, 0 °C (94%); h) MsCl, imidazole, CH\(_2\)Cl\(_2\); i) LiAlH\(_4\), dioxane, reflux (65%, two steps).
The treatment of 18 with iodomethane in aqueous acetonitrile followed by the reduction of the resulting aldehyde with sodium borohydride yielded 19, \( \alpha \)D\( ^{29} \) –20.0° (c 1.01, CHCl\(_3\)), as yellow amorphous powder. The primary alcohol (19) was first protected as TBS ether, which was then treated with lithium aluminum hydride in THF to convert the ester functionality into a primary hydroxy group. After mesylation, the resulting mesylate (20) was subjected to reduction using lithium aluminum hydride in boiling dioxane to furnish, with the concomitant reduction of the amide functionality to amine as well as the deprotection of the TBS group, (−)-dihydrocorycopine (2), mp 176–179 °C, \( \alpha \)D\( ^{24} \) –16.3° (c 0.3, pyridine),\( ^{19} \) [lit.,\( ^{9d} \) mp 178–180 °C, \( \alpha \)D\( ^{24} \) –30±2° (c 0.68, pyridine).

In conclusion, we have accomplished the total synthesis of (−)-dihydrocorycopine starting from the bicyclo[3.2.1]octenone chiral building block we developed by exploiting a practical method that enables the relay of the tandem retro-aldol-Pictet-Spengler reaction giving 18-keto-pseudoyohimbane with its epimerization at C-3 to give the 18-keto-yohimbane skeleton and have extended the versatility of such a chiral building block.

REFERENCES (AND NOTES)
† This paper is dedicated to Professor Steven M. Weinreb on the occasion of his 65th birthday.


11. Calculations were performed on Chem 3D (Cambridge Soft) using the MM2 force field.

12. All new compounds were fully characterized by spectroscopic means [\(^1H\)-NMR (400 MHz in CDCl\(_3\)), \(^13C\)-NMR (100 MHz in CDCl\(_3\)), IR] and gave satisfactory HREIMS. Yields referred to homogeneous samples obtained by chromatographic purification on silica gel.


14. Calculations indicated that 16 is more stable than 12 by 3.5 kcal/mol.\(^{11}\)

15. On treatment with MsOD and (CH\(_2\)OD)\(_2\) in boiling 1,4-dioxane, 12 afforded C3-deuterated 16, supporting the validity of the mechanism shown in Scheme 4.


17. (a) S. Takano, K. Hiroya, and K. Ogasawara, *Chem. Lett.*, 1983, 255; (b) M. Kawamura and K.


19. $^1$H-NMR (400 MHz in CDCl$_3$), $^{13}$C-NMR (100 MHz in CDCl$_3$), and IR data of synthetic (−)-dihydrocorynantheol (2) were in good agreement with those reported for the natural product. We unexpectedly observed the yellowing of 2 during the measurement of specific rotation in pyridine. The TLC results indicate the partial decomposition of 2, which we attribute the decrease in the absolute value of the specific rotation.