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Enantioselective synthesis of (*S*)-calycotomine employing catalytic asymmetric hydrogenation with an iridium(I)–(*R*)-BINAP–phthalimide complex[1]

Toshiaki Morimoto,* Naoaki Suzuki and Kazuo Achiwa

School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Shizuoka-shi 422, Japan

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Abstract

An optically active 1-hydroxymethyl-substituted tetrahydroisoquinoline alkaloid, (*S*)-calycotomine **1**, was conveniently synthesized by using catalytic asymmetric hydrogenation of 1-benzyloxymethyl-3,4-dihydro-6,7-dimethoxyisoquinoline **6** with 0.5 mol % of an iridium(I) complex of (*R*)-BINAP in the presence of 3,4,5,6-tetrafluorophthalimide.

Development of the methods for enantioselective or diastereoselective synthesis of optically active 1-substituted 1,2,3,4-tetrahydroisoquinolines has been an important subject in synthetic organic chemistry,[2] since most naturally occurring tetrahydroisoquinolines and their derivatives are optically active and have marked physiological activities[3] which are commonly different from those of their antipodes. Most of the traditional synthetic methods are based on the procedures employing a stoichiometric amount of chiral building blocks, auxiliaries, or reagents; for example, the Pictet–Spengler condensation,[4] nucleophilic or electrophilic introduction of carbon units into 1-position of dihydro- or tetrahydroisoquinolines,[5] and asymmetric (or diastereoselective) reduction of dihydroisoquinolines with chiral (or achiral) hydride reagents (Scheme 1).[6] Although catalytic asymmetric syntheses are much more efficient than stoichiometric ones for the preparation of optically active isoquinolines, very few methods using chiral catalysts have been developed. After the pioneering works by Kagan[7] and Achiwa,[8] Noyori and co-workers developed an efficient catalytic procedure for their preparation by reduction of cyclic enamides with Ru–BINAP complexes.[9] A more direct and efficient method for the preparation is the catalytic asymmetric hydrogenation of 1-substituted dihydroisoquinolines, and several new methods have recently been developed by ourselves, Buchwald, Noyori, and Kang employing BCPM or BINAP–Ir–phthalimide complexes,[10] a chiral titanocene complex,[11] chiral *N*-sulfonated diamine–Ru complexes (hydrogen source: formic acid),[12] and thiazazincolidine complexes (hydrogen source: BH_3),[13] respectively.

* Corresponding author. E-mail: morimtt@ys2.u-shizuoka-ken.ac.jp

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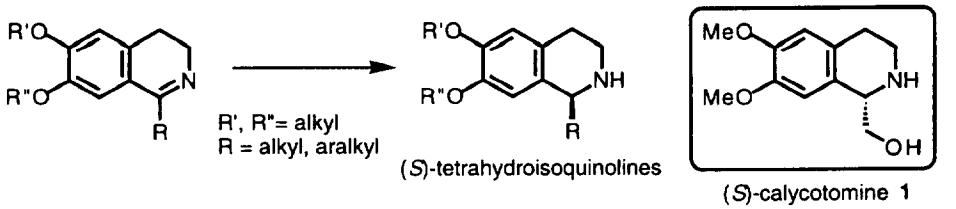
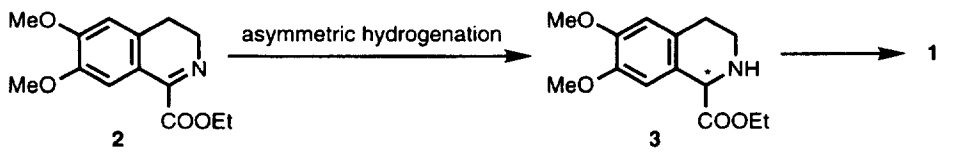


Scheme 1.

(*S*)-(+)-Calycotomine **1**, a 1,2,3,4-tetrahydroisoquinoline bearing a 1-hydroxymethyl group, whose absolute configuration is different from that of many other 1-substituted tetrahydroisoquinoline alkaloids, is a base constituent of *Calycotome spinosa* Link. and some other plants.[14] The absolute configuration of the naturally occurring calycotomine **1** was determined by its conversion to an (*R*)-salsolidine *N*-tosyl derivative which was correlated with the antipode (*S*-form) derived from the known (*S*)-salsolidine.[15] Enantioselective syntheses of (*R*)- or (*S*)-calycotomine **1** and its derivatives have been investigated by employing the Pictet–Spengler condensation of (*R*)-glyceraldehyde,[4d,16] or (2*R*)-*N*-glyoxyloylbornane-10,2-sultam[17] with dopamine hydrochloride and catalytic reduction of a chiral dihydroisoquinoline derived from D-ribonolactone.[18] However, to our knowledge, catalytic asymmetric synthesis of **1** has not been reported. We report herein an efficient enantioselective synthesis of (*S*)-calycotomine **1** using catalytic asymmetric hydrogenation with a catalyst system of a BINAP–Ir–phthalimide complex as a key step.

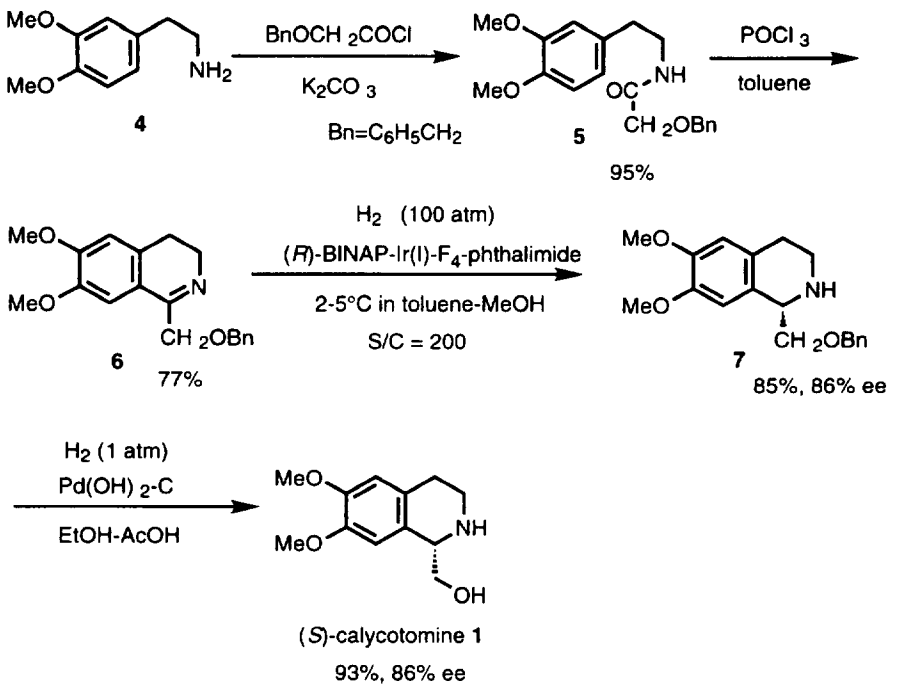
As mentioned above, we reported a convenient method for the enantioselective synthesis of several naturally occurring tetrahydroisoquinolines by catalytic asymmetric hydrogenation with Ir complexes of (2*S*,4*S*)-BCPM and (*S*)-BINAP in the presence of phthalimides.[10] Since (2*S*,4*S*)-BCPM and (*S*)-BINAP were found to show (1*S*)-enantioselectivity in the hydrogenation of 1-alkyl (or aralkyl)-substituted dihydroisoquinolines, we employed the antipode, (*R*)-BINAP to gain (*S*)-calycotomine **1** whose absolute configuration corresponds to that of the other (1*R*)-alkyl (or aralkyl) derivatives. Initially, asymmetric hydrogenation of ethyl 3,4-dihydro-6,7-dimethoxyisoquinoline-1-carboxylate **2** was carried out with a BINAP (or BCPM)–Ir–phthalimide complex catalyst under 100 atm of hydrogen, but unfortunately, the reaction proceeded only slowly to give an almost racemic hydrogenation product **3** (Scheme 2). Asymmetric hydrosilylation of **2** with diphenylsilane and several chiral Rh-complex catalysts gave unsatisfactory results also.



Scheme 2.

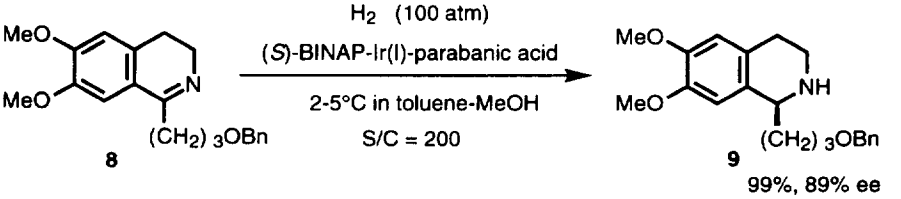
Therefore, we employed a 1-benzyloxymethyl-substituted dihydroisoquinoline **6** as a substrate. The synthetic route of **1** *via* **6** is described in Scheme 3. 3,4-Dimethoxyphenethylamine **4** was acylated with benzyloxyacetyl chloride in the presence of K_2CO_3 in a two phase system of ether and water, affording the corresponding amide **5** (95%). The Bischer–Napieralski reaction of the amide **5** by heating with $POCl_3$ in toluene gave 1-benzyloxymethyl-3,4-dihydro-6,7-dimethoxyisoquinoline **6** in 77% isolated yield. Asymmetric hydrogenation of the dihydroisoquinoline **6** was carried out in a mixed solvent of MeOH–toluene with 0.5 mol% of an (*R*)-BINAP–Ir(I) complex in the presence of a phthalimide (1 mol%) under 100 atm of hydrogen.[19] A better enantioselectivity was obtained with 3,4,5,6-tetrafluorophthalimide (86% ee) in comparison with phthalimide (75% ee). The hydrogenation

product, (*S*)-1-benzyloxymethyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline **7** was isolated in 85% yield by silica gel chromatography. Hydrogenolysis of the *O*-benzyl group was difficult with Pd on carbon (1 atm H_2) in EtOH, but could be accomplished with a $Pd(OH)_2$ catalyst in a mixed solvent system of EtOH:AcOH (10:1), yielding natural (*S*)-calycotomine **1** (86% ee) in high yield;[20,21] without AcOH, partial racemization occurred. Recrystallization from toluene increased the enantiomeric purity to 96% ee. Palladium black using HCOOH as a hydrogen source was less active, affording a lower yield of the product than the $Pd(OH)_2$ catalyst (H_2).



Scheme 3.

Asymmetric hydrogenation of 1-[3-(benzyloxy)propyl]-3,4-dihydro-6,7-dimethoxyisoquinoline **8** was also performed under similar conditions using (*S*)-BINAP and parabanic acid (as an additive), leading to the corresponding tetrahydroisoquinoline **9** with 89% ee (estimated to be *S*) in a quantitative yield (Scheme 4).



Scheme 4.

Thus we developed a convenient method for the enantioselective synthesis of (*S*)-calycotomine employing asymmetric hydrogenation with an (*R*)-BINAP–Ir–tetrafluorophthalimide complex as a key reaction. Since optically active calycotomine or its derivative is known to be a useful synthetic intermediate of other isoquinoline alkaloids,[4d,16] further application of this procedure to asymmetric synthesis of naturally occurring compounds is in progress.

Acknowledgements

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19. *Catalytic asymmetric hydrogenation of* **6**: A solution of (*R*)-BINAP (1.8×10^{-2} mmol, 11.2 mg) and chloro(1,5-cyclooctadiene)iridium(I) dimer, $[Ir(COD)Cl]_2$ (7.5×10^{-3} mmol, 5.0 mg) in a mixed solvent (18 ml) of toluene and MeOH (1:1) was stirred at rt for 15 min under argon. The catalyst solution was added to a mixture of dihydroisoquinoline **6** (3 mmol, 934 mg) and tetrafluorophthalimide (3×10^{-2} mmol, 6.6 mg) in a glass tube. The glass tube was placed in an autoclave, pressurized with hydrogen to 100 atm after several exchange with hydrogen, and the mixture was stirred at 2–5°C for 3 days. The reaction solution was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography using a mixed solvent of EtOH, AcOEt, and Et_2NH (1:1:0.001). (*S*)-1-Benzyloxymethyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline **7** was isolated as a syrup in 85% yield; $[\alpha]_D^{25}$ +19.3 (*c* 1.23, EtOH). After conversion of a small portion of the product to its *N*-acetyl derivative, the enantiomeric excess was determined to be 86% ee (*S*) by HPLC with a chiral column (Chiralpak AS); solvent: 2-propanol:hexane=5:1, 0.7 ml/min; detection: 235 nm light; t_R=45.8 min, t_S=84.1 min.
20. *(S)-Calycotomine* **1**: A mixture of (*S*)-1-benzyloxymethyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline **7** (0.7 mmol, 220 mg) and 20% $Pd(OH)_2$ on carbon (70 mg) in a mixed solvent of EtOH (5 ml) and AcOH (0.5 ml) was stirred at rt for 15 h under an atmospheric pressure of hydrogen. After filtration of the catalyst through Celite, the filtrate was concentrated

in vacuo. The residue was treated with 20% KOH (4 ml) and extracted with $CHCl_3$ (4×10 ml). The combined extracts were dried over K_2CO_3 and concentrated *in vacuo* to give (*S*)-calycotomine **1** (145 mg, 93%) as a solid; $[\alpha]_D^{25}$ +30.1 (*c* 1.06, H_2O) [lit.[21] $[\alpha]_D$ +36 (*c* 1, H_2O)]. The enantiomeric excess of the product was determined to be 86% ee by HPLC (Chiralpak AS) analysis of its *N*-BOC derivative. Recrystallization from toluene gave pure **1** as prisms (66%, 96% ee), $[\alpha]_D^{29}$ +33.7 (*c* 1.05, H_2O).

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