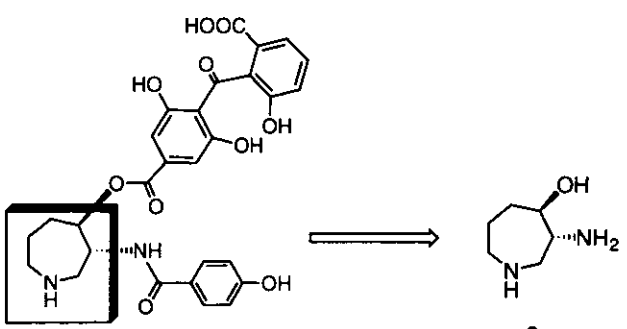
NEW APPROACH TO (3*R*, 4*R*)-3-AMINO-*N*-BENZYLOXYCARBONYL-4-HYDROXYHEXAHYDRO-1*H*-AZEPINE USING RING EXPANSION OF OPTICALLY ACTIVE PIPERIDINE DERIVATIVE

Toshiya Morie and Shiro Kato*

Discovery Research Laboratories I, Dainippon Pharmaceutical Co., Ltd., Enoki 33-94, Suita, Osaka 564, Japan

Abstract–New approach to (3*R*, 4*R*)-3-amino-*N*-benzyloxycarbonyl-4-hydroxyhexahydro-1*H*-azepine (**18**), which is the intermediate of the natural product balanol (**1**), is described. A key step in this method is ring expansion of the optically active piperidine derivative (**10**) to the corresponding hexahydro-1*H*-azepine (**12**) with retention of the configuration.

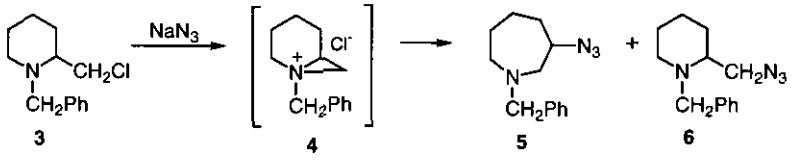
The (3*R*, 4*R*)-3-amino-4-hydroxyhexahydro-1*H*-azepine ring unit is a structural element found in the natural product balanol (**1**). Balanol (**1**) initially has been isolated as a metabolite produced by the fungus *Verticillium balanoides*[1] and more recently from species of *Fusarium mesismoides*[2] and markedly inhibits protein kinase C activity.[3] Due to its unique chemical structure, its biological activity, and its low availability from natural sources, the development of synthetic routes to balanol (**1**) or the derivatives of (3*R*, 4*R*)-3-amino-4-hydroxyhexahydro-1*H*-azepine (**2**) as logical precursors to **1** is of considerable interest. The optically active *N*-protected 3-amino-4-hydroxyhexahydro-1*H*-azepine has been prepared from D-serine,[4] D-isoascorbic acid,[5] (2*S*, 3*R*)-3-hydroxylysine,[6] or an acyclic chiral epoxy alcohol[7] obtained *via* Sharpless asymmetric epoxidation.[8] Moreover, syntheses of (±)-*trans*-3-amino-*N*-benzyl-4-hydroxyhexahydro-1*H*-azepine derivatives followed by the optical resolution of the racemate have been reported.[9]



1 2

We previously reported that 1-benzyl-2-(chloromethyl)piperidine (**3**) was treated with NaN_3 in MeCN at refluxing temperature to form the reactive intermediate, the aziridinium cation (**4**) in solution, which could undergo ring expansion by SN2-type attack of the azide anion at the methine carbon of the aziridinium ring to give 3-azido-1-benzylhexahydro-1*H*-azepine (**5**) along with the normal displacement product, the piperidine derivative (**6**), in good yield in 62 : 38 ratio (Scheme 1).[10] We expected that the reaction of

Scheme 1

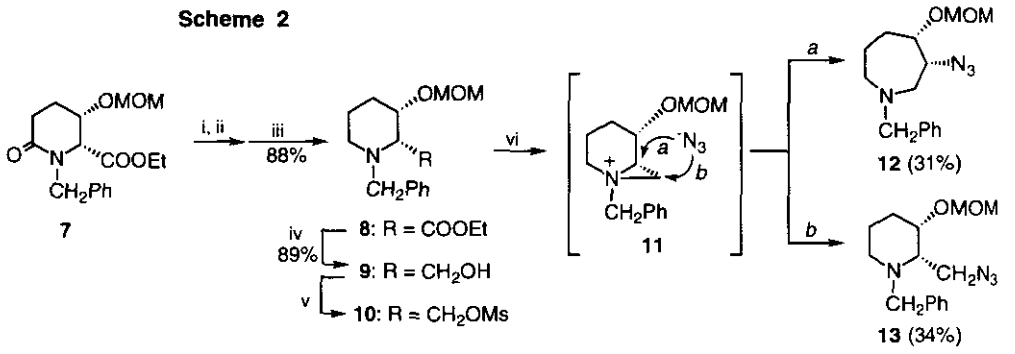


the chiral *N*-benzyl-2-(chloromethyl)-3-hydroxypiperidine with azide anion under the same conditions would afford the chiral 3-azido-*N*-benzyl-4-hydroxyhexahydro-1*H*-azepine as an expansion product, which is the important intermediate for the preparation of the (3*R*, 4*R*)-*N*-protected 3-amino-4-hydroxyhexahydro-1*H*-azepine. In this report, we describe a novel method for the preparation of (3*R*, 4*R*)-3-amino-*N*-benzyloxycarbonyl-4-hydroxyhexahydro-1*H*-azepine (**18**) based on ring expansion of the optically active 2-(methanesulfonyloxymethyl)piperidine derivative (**10**).

Our synthetic approach to **18** from the known compound (2*R*, 3*S*)-1-benzyl-3-methoxymethoxy-6-oxopiperidine-2-carboxylic acid ethyl ester[11] (**7**) is shown in Schemes 2 and 3. Reduction of the (2*R*, 3*S*)-6-oxopiperidine (**7**) with BH_3 in THF at room temperature followed by treatment with 1% aqueous HCl at refluxing temperature gave a mixture of the desired piperidine (**8**) and the deprotected product, 1-benzyl-3-hydroxypiperidine-2-carboxylic ester[12] in *ca.* 2 : 1 ratio. The mixture was treated with chloromethyl methyl ether in the presence of Hünig base in $CHCl_3$ to afford the 1-benzylpiperidine-2-carboxylic ester (**8**) in 88% overall yield. Reaction of the piperidine-2-carboxylic ester (**8**) with DIBAL-H in THF at 0 °C produced the 2-(hydroxymethyl)piperidine (**9**) in 89% yield. The ring expansion reaction was carried out according to our previously reported method.[10] Thus, **9** was treated with methanesulfonyl chloride in CH_2Cl_2 in the presence of Et_3N at 5 °C to give the corresponding mesylate (**10**), which without further purification was allowed to react with NaN_3 in MeCN at refluxing temperature for 2 h to afford a mixture of the desired ring expansion product, the 3-azidohexahydro-1*H*-azepine derivative (**12**) and the normal substituted piperidine (**13**) in 10 : 11 ratio.[13] The mixture was conveniently separated into the less polar hexahydro-1*H*-azepine **12** (31%) and the more polar piperidine **13** (34%) by medium-pressure column chromatography on silica gel. The structures of the diastereoisomerically pure compounds (**12**) and (**13**) were deduced using ^1H NMR, IR, and MS spectra.[14] In the reaction of the piperidines (**3**) and (**10**) with NaN_3, there was a clear difference in ratio of the hexahydro-1*H*-azepines (**5**) and (**12**) *vs* the piperidines (**6**) and (**13**). This may be due to the difference between the substituents at the 3-position of the starting piperidines. In the *cis*-aziridinium intermediate (**11**), in particular, the attack at the methylene carbon (path *b*) would be preferred over path *a*

owing to steric hindrance at the 3-MOM group. Attempts to convert the (3*S*)-hydroxy group of several intermediate piperidines into the corresponding *R* forms using Mitsunobu inversion[15] were unsuccessful (Scheme 2).[16]

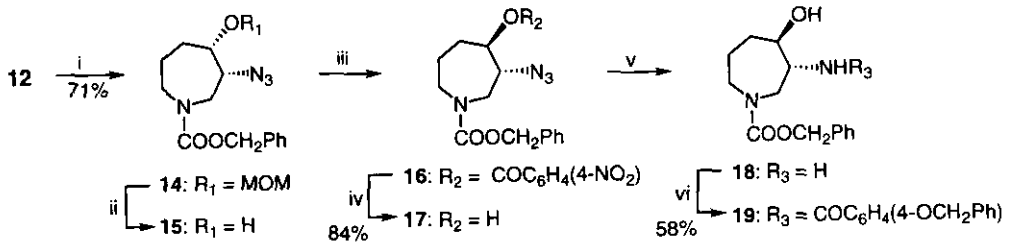
Scheme 2



Reagents and conditions: i: BH_3-THF, THF, room temperature; ii: 1% aq. HCl, reflux; iii: MOMCl, Hünig base, $CHCl_3$, reflux; iv: DIBAL-H, THF, 0 °C; v: MsCl, Et_3N, CH_2Cl_2, 5 °C; vi: NaN_3, MeCN, reflux.

Reaction of the hexahydro-1*H*-azepine (**12**) thus prepared with benzyl chloroformate in toluene at room temperature proceeded smoothly to produce the carbamate (**14**) in 71% yield. After deprotection of the MOM group of **14** with 10% aqueous HCl, conversion of the resulting *cis* isomer (**15**) into the *trans* isomer (**17**) was carried out using Mitsunobu reaction; treatment of **15** with 4-nitrobenzoic acid, triphenylphosphine, and diisopropyl azodicarboxylate, followed by hydrolysis of the *trans* 4-nitrobenzoate derivative (**16**) by 2N NaOH gave the (3*R*, 4*R*)-3-azido-4-hydroxyhexahydro-1*H*-azepine (**17**) in 84% overall yield. Reduction of the azide group of the *trans* azido alcohol (**17**) with triphenylphosphine in aqueous THF at room temperature[17] gave the 3-amino-4-hydroxyhexahydro-1*H*-azepine (**18**), which was subsequently treated with 4-(benzyloxy)benzoyl chloride in CH_2Cl_2 in the

Scheme 3



Reagents and conditions: i: $ClCOOCH_2Ph$, toluene, room temperature; ii: 10% aq. HCl, THF, reflux; iii: DIAD, Ph_3P, 4-$NO_2C_6H_4COOH$, THF, 0 °C to room temperature; iv: 2N aq. NaOH, MeOH—1,4-dioxane, room temperature; v: Ph_3P, aq. THF, room temperature; vi: $ClCOC_6H_4(4\text{-}OCH_2Ph)$, Et_3N, CH_2Cl_2, room temperature.

presence of Et_3N at room temperature to afford the optically active 4-benzyloxy-*N*-(1-benzyloxycarbonyl-4-hydroxyhexahydro-1*H*-azepin-3-yl)benzamide (**19**) in 58% yield in 2 steps.[18] Spectroscopic data of **19** were identical with those prepared by different route[4a] (Scheme 3).

In conclusion, we have shown that the optically active 2-(methanesulfonyloxymethyl)piperidine (**10**) undergoes ring expansion with azide anion as a nucleophile to give the hexahydro-1*H*-azepine derivative (**12**) *via* the aziridinium cation (**11**). This ring expansion reaction was applied for the preparation of (3*R*, 4*R*)-3-amino-4-hydroxyhexahydro-1*H*-azepine derivative (**18**), which is the intermediate of balanol (**1**).

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12. In the ^1H NMR (200 MHz, $CDCl_3$) spectrum, the signal for the hydroxy group at the 3-position appeared as a doublet centered at δ 2.83 with coupling constant of 7 Hz.
13. The ratio of **12** and **13** in the reaction mixture was determined by ^1H NMR spectrum.
14. **12**; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.52—2.21 (m, 4H), 2.52—2.83 (m, 4H), 3.42 (s, 3H, OCH_3), 3.61 (m, 1H, 3-H), 3.65 and 3.73 (each d, each 1H, J = 14 Hz, CH_2Ph), 4.00 (ddd, 1H, $J_{4\text{-H-5-H}}$ = 8, 3 Hz, $J_{4\text{-H-3-H}}$ = 3 Hz, 4-H), 4.68 and 4.73 (each d, each 1H, J = 5 Hz, OCH_2O), 7.20—7.38 (m, 5H); MS m/z: 290 (M^+), 248 (M^+–N_3); IR: 2095 (N_3) cm^{-1}. **13**; ^1H NMR (200 MHz, $CDCl_3$) δ:

1.41—1.85 (m, 4H), 2.37—2.61 (m, 2H), 3.10 (ddd, 1H, $J_{2\text{-H-CH2}}$ = 7, 4 Hz, $J_{2\text{-H-3-H}}$ = 4 Hz, 2-H), 3.38 (s, 3H, OCH_3), 3.52 (dd, 1H, $J_{CH2\text{-}2\text{-H}}$ = 4 Hz, $J_{CH2\text{-}CH2}$ = 12 Hz, CH_2N_3), 3.65 (dd, 1H, $J_{CH2\text{-}2\text{-H}}$ = 4 Hz, $J_{CH2\text{-}CH2}$ = 12 Hz, CH_2N_3), 3.80 (s, 2H, CH_2Ph), 3.89 (ddd, 1H, $J_{3\text{-H-4-H}}$ = 4, 9 Hz, $J_{3\text{-H-2-H}}$ = 4 Hz, 3-H), 4.66 and 4.71 (each d, each 1H, J = 5 Hz, OCH_2O), 7.20—7.40 (m, 5H); MS m/z: 290 (M^+), 234 (M^+–CH_2N_3); IR: 2095 (N_3) cm^{-1}.

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16. The corresponding tetrahydropyridine derivatives were isolated instead of the desired *trans* products.
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18. ^{1}H NMR (200 MHz, $CDCl_3$), MS, and IR (neat) spectral data of some selected compounds: Compound (**8**): δ 1.30 (t, 3H, J = 7 Hz, CH_2CH_3), 1.40—1.64 (m, 2H), 1.65—1.87 (m, 2H), 1.95 (m, 1H), 2.39 (td, 1H, J = 5, 7 Hz), 2.91 (dt, 1H, J = 4, 10 Hz), 3.35 (s, 3H, OCH_3), 3.61 (d, 1H, J = 14 Hz, CH_2Ph), 3.70 (d, 1H, J = 14 Hz, CH_2Ph), 3.94 (ddd, 1H, J = 5, 10, 10 Hz, 3-H), 4.21 (q, 2H, J = 7 Hz, CH_2CH_3), 4.62 (d, 1H, J = 7 Hz, OCH_2O), 4.68 (d, 1H, J = 7 Hz, OCH_2O), 7.18—7.34 (m, 5H); MS m/z: 308 (MH^+); IR: 1728 (CO) cm^{-1}; Compound (**9**): δ 1.55—1.80 (m, 4H), 2.34 (td, 1H, J = 5, 13 Hz), 2.68 (ddd, 1H, J = 5, 10, 10 Hz), 2.90 (ddd, 1H, J = 5, 7, 10 Hz), 3.39 (s, 3H, OCH_3), 3.74 (d, 1H, J = 13 Hz, CH_2Ph), 3.88 (d, 2H, J = 7 Hz, CH_2OH), 3.89 (d, 1H, J = 13 Hz, CH_2Ph), 4.01 (m, 1H, 3-H), 4.65 (d, 1H, J = 7 Hz, OCH_2O), 4.70 (d, 1H, J = 7 Hz, OCH_2O), 7.20—7.36 (m, 5H); MS m/z: 266 (MH^+); IR: 3449 (OH) cm^{-1}; Compound (**14**): δ 1.46—2.15 (m, 4H), 3.19 (m, 1H), 3.36 (dd, 1H, J = 8, 14 Hz), 3.42 (d, 3H, J = 2 Hz, OCH_3), 3.62—3.98 (m, 4H), 4.67 (d, 1H, J = 7 Hz, OCH_2O), 4.72 (d, 1H, J = 7 Hz, OCH_2O), 5.13 (d, 1H, J = 7 Hz, CH_2Ph), 5.14 (d, 1H, J = 7 Hz, CH_2Ph), 7.28—7.43 (m, 5H); MS m/z: 335 (MH^+); IR: 2101 (N_3), 1701 (CO) cm^{-1}; Compound (**16**): δ 1.60—2.13 (m, 3H), 2.99—3.35 (m, 2H), 3.50 (m, 1H), 3.67—4.18 (m, 4H), 5.18 (d, 1H, J = 4 Hz, CH_2Ph), 5.19 (d, 1H, J = 4 Hz, CH_2Ph), 7.30—7.42 (m, 4H), 8.15—8.43 (m, 5H); MS m/z: 440 (MH^+); IR: 2108 (N_3), 1716 (CO), 1528, 1350 (NO_2) cm^{-1}; Compound (**17**): δ 1.47—1.74 (m, 2H), 1.75—2.07 (m, 2H), 2.13 (dd, 1H, J = 3, 7 Hz), 3.00 (dd, 1H, J = 7, 14 Hz), 3.15—3.55 (m, 3H), 3.70 (m, 1H), 3.96 (ddd, 1H, J = 3, 14, 24 Hz), 5.16 (d, 1H, J = 7 Hz, CH_2Ph), 5.21 (d, 1H, J = 7 Hz, CH_2Ph), 7.30—7.45 (m, 5H); MS m/z: 291 (MH^+); IR: 3420 (OH), 2108 (N_3), 1682 (CO) cm^{-1}.

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