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EFFICIENT SYNTHESIS OF FUNCTIONALIZED BENZAZEPINE DERIVATIVES UTILIZING INTRAMOLECULAR MITSUNOBU REACTION

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Abstract - The 5-hydroxy-2,3,4,5-tetrahydro-1*H*-benzazepine derivative (**2**), which is a typical metabolite of mozavaptan (**1**) having the 2,3,4,5-tetrahydro-1*H*-benzazepine skeleton, was synthesized by utilizing the intramolecular Mitsunobu reaction of the corresponding 2-(4-hydroxybutyl)aniline derivative. In the intramolecular Mitsunobu reaction, effect of the substituent group on nitrogen atom, influence of the functional group applying to synthesis of the other metabolites (**3, 4** and **5**) and utilization of synthesis of 2-substituent benzazepine derivatives were investigated.

INTRODUCTION

Benzazepines are important heterocyclic compounds that are used for a variety of applications with pharmaceuticals. The 2,3,4,5-tetrahydro-1*H*-benzazepine derivative has been applied to drugs as vasopressin V_2 receptor antagonists[1-3] (e. g., mozavaptan,[1] tolvaptan[2]) and an agonist[4] (OPC-51803). In metabolic studies of mozavaptan (**1**), we found the 5-hydroxy, 5-methylamino, 5-amino and 5-oxo metabolites (**2**, **3**, **4** and **5**)[5] which were produced by oxidation at the 5-position of the benzazepine ring (**Figure 1**). These metabolites having the 2,3,4,5-tetrahydro-1*H*-benzazepine ring showed potent vasopressin V_2 receptor antagonist activity.[3] Usually, the 1-substituted 2,3,4,5-tetrahydro-5-oxobenzazepine derivatives, which were available intermediates for synthesis of the 5-substituted benzazepine compounds, have been prepared by the Dieckmannn condensation of *N*-substituted ethyl

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This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of Tokyo University.

3-(2-methoxycarbonylphenylamino)butyrate with potassium *tert*-butoxide in toluene, followed by hydrolysis with acetic acid and hydrochloric acid.[6] However, this method involves a limitation for the introduction of substituent groups at the 3-, 4-, and 5-positions of the 2,3,4,5-tetrahydro-1*H*-benzazepine ring because of harsh conditions. On the other hand, the Mitsunobu reaction[7] has been widely utilized in organic synthesis and has been applied to esterification[8] and etherification,[9] the *N*-alkylation of the electron-deficient nitrogen atom[10] and heterocyclization[11] because it proceeds under the mild conditions. Here, we wish to report an efficient synthesis of 2,3,4,5-tetrahydro-1*H*- benzazepine derivatives utilizing the intramolecular Mitsunobu reaction.

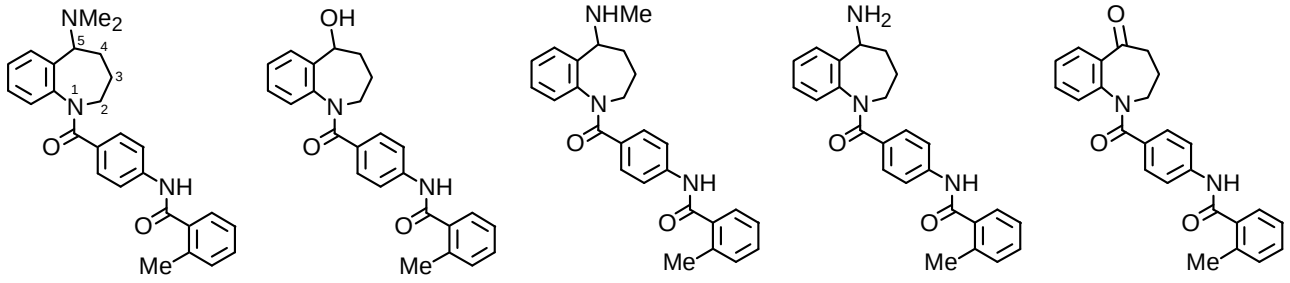
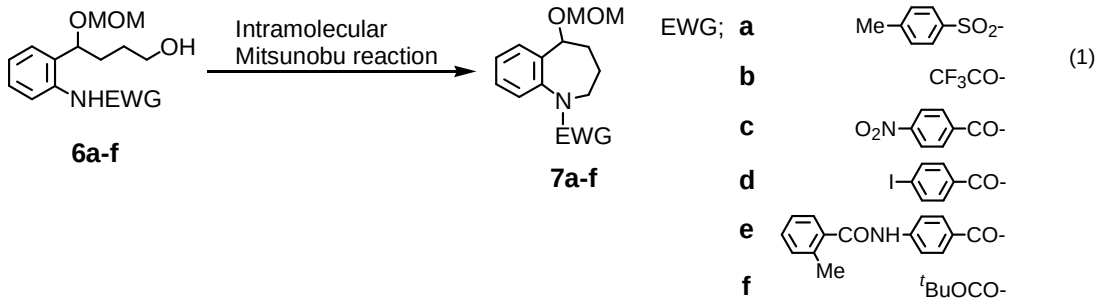


Figure 1

Synthesis

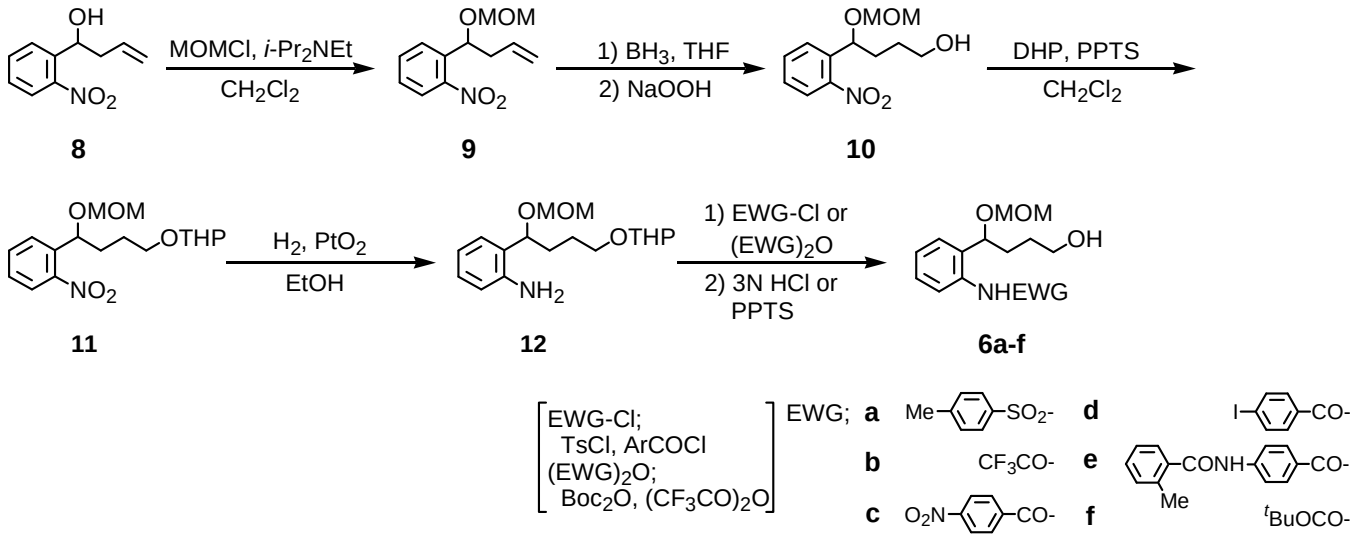
The Mitsunobu reaction is effected by a variety of nucleophiles,[12] which are the nitrogen atom substituted with electron withdrawing groups in our system. As the substituent groups on the nitrogen atom, we chose two types of electron-withdrawing groups. One is the general protecting groups (**6a**, **6b** and **6f**) and the other is the substituent groups (**6c**-**e**) which can be converted to the target compounds. Thus we first examined the effect of electron-withdrawing groups on the nitrogen atom of the 2-[4-hydroxy-1-methoxymethoxybutyl]- aniline derivatives (eq. 1).



The substrates (**6a-f**) were synthesized as shown in Scheme 1. The alcohol (**8**)[13] was treated with chloromethyl methyl ether (MOMCl) and *i*-Pr_2NEt to give the methoxymethyl (MOM) ether (**9**) in 90% yield. Hydroboration of **9** followed by treatment with alkaline hydrogen peroxide afforded the primary alcohol (**10**) in 85% yield. The alcohol (**10**) was allowed to react with 2,3-dihydropyran (DHP) and pyridinium *p*-toluenesulfonate (PPTS) quantitatively to obtain the tetrahydropyranyl (THP) compound (**11**).

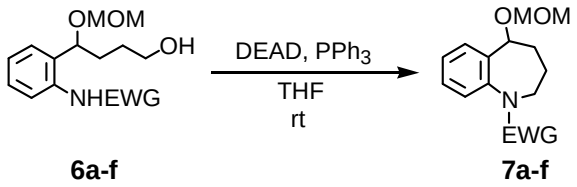
Hydrogenetion of **11** in the presence of PtO_2 gave the aniline (**12**) in 99% yield. Treatment of the aniline (**12**) with *p*-toluenesulfonyl chloride (TsCl), carboxylic acid chloride or acid anhydride followed by deprotection of the THP group, furnished the substrates (**6a-f**) in moderate yields.

Scheme 1



For the typical procedure of the intramolecular Mitsunobu reactions employing the substrates (**6a-f**), the primary alcohols (**6a-f**, 0.26 mmol) were treated with diethyl azodicarboxylate (1.2 eq.) and PPh_3 (1.2 eq.) in THF (3 mL) at room temperature. All results are summarized in Table 1.

Table 1 Effect of Electron-withdrawing Group on Intramolecular Mitsunobu Reaction [a]



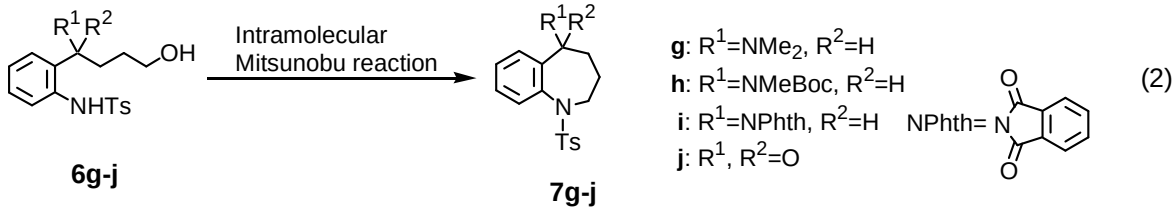
Entry	Substrate	EWG	Time	Product	Yield(%)
1	**6a**	Ts	2 h	**7a**	100
2	**6b**	CF_3CO	3 h	**7b**	85
3	**6c**	4-NO_2-C_6H_4CO	1 d	**7c**	88
4	**6d**	4-I-C_6H_4CO	1 d	**7d**	85
5	**6e**	4-(2-Me-C_6H_4)CONH-C_6H_4CO	1 d	**7e**	36
6	**6f**	Boc	1 d	**7f**	58
7 [b]	**6f**	Boc	1 d	**7f**	85

a. All reactions, except Entry 7, were carried out with stirring a mixture of substrate (0.26 mmoL), PPh_3 (1.2 eq.) and DEAD (1.2 eq.) in THF (3 mL) at rt. b. Reaction was carried out by stirring a mixture of substrate (0.26 mmoL), PPh_3 (2 eq.) and DEAD (2 eq.) in THF (3 mL) under refluxing conditions.

The reaction of the *p*-toluenesulfonyl anilides (**6a**) for 2 hours yielded benzazepine (**7a**) quantitatively (Entry 1). Although the *N*-acylbenzazepines (**7b**-**d**) were also obtained from the corresponding alcohols (**6b**-**d**) in good yields, their reaction times except for that of **6b** were longer than the case of **6a** (Entries 2-4).

Compound (**7e**) was obtained in a low yield (Entry 5) due to the production of unknown by-products. The yield of **7f** was also low (Entry 6), however, no by-product was observed in the reaction. Thus, this reaction was carried out under refluxing conditions for 1 day. As we expected, **7f** was obtained in better yield (Entry 7). It was found that the electron-withdrawing groups on the nitrogen atom affect the reaction time and the yield of the benzazepine products (**7a-f**) through these reactions.

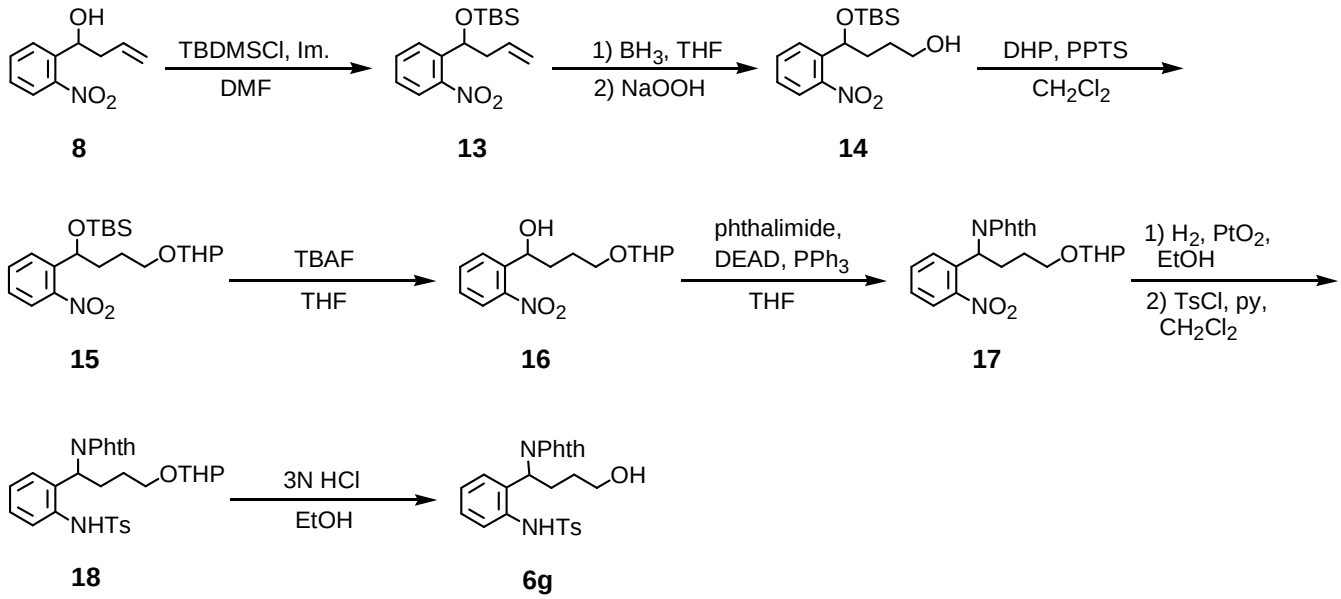
Next, in order to investigate the influence of the functional groups at the 1-position of the 4-hydroxybutyl groups in this reaction system, we selected suitable substrates (**6g-i**) (eq. 2).



6g-j **7g-j**

The substrate (**6g**) was synthesized as shown in Scheme 2. The alcohol (**8**) was treated with *tert*-butyldimethylsilyl chloride (TBDMSCl) and imidazole to give the *tert*-butyldimethylsilyl (TBS) ether (**13**) in 90% yield. Compounds (**14**) and (**15**) were synthesized by the same method as compounds (**9**) and (**10**) respectively. Desilylation of **15** with tetrabutylammonium fluoride (TBAF) gave compound (**16**) in 97% yield. Treatment of the resulting alcohol (**16**) with phthalimide, PPh_3, and DEAD afforded compound (**17**) in 72% yield. Hydrogenation of **17** followed by treatment with TsCl and pyridine gave **18** in 33% yield. Deprotection of the tetrahydropyranyl group of **18** was carried out by treatment with 3N hydrochloric acid (HCl) to give **6g** in quantitative yield.

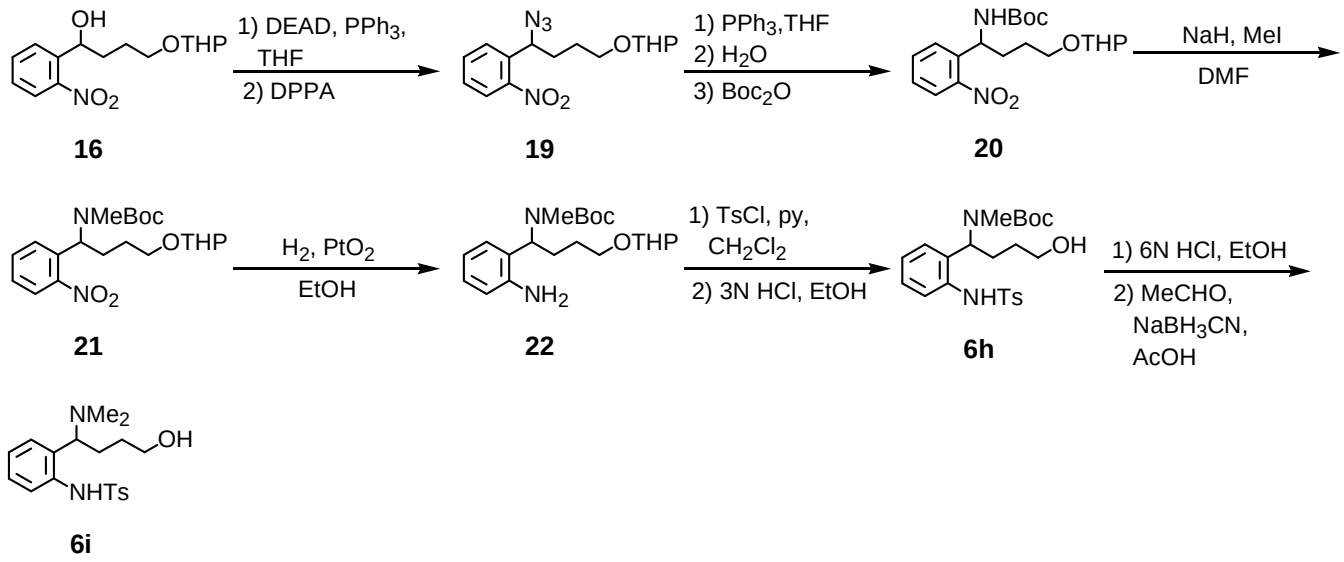
Scheme 2



The substrates (**6h** and **6i**) were synthesized as shown in Scheme 3. The reaction of **16** with DEAD and PPh_3 followed by treatment with diphenylphosphory azide (DPPA) gave **19** in 86% yield. The azide (**19**) was

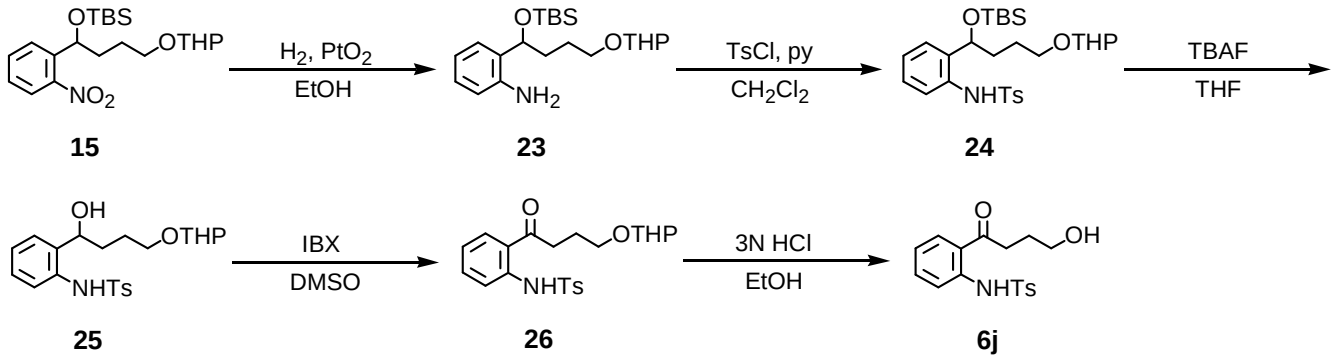
treated with PPh_3, hydrolyzed, and then subjected to protection of the resulting amino group with di-*tert*-butyl dicarbonate (Boc_2O) to give **20** in 92% yield. Methylation of the carbamate (**20**) with iodomethane in the presence of NaH afforded **21** (97% yield), which was hydrogenated on PtO_2 to give **22** in quantitative yield. The aniline (**22**) was treated with TsCl and pyridine followed by deprotection of the THP group furnished **6h** in 78% yield. Deprotection of the Boc group of **6h** with 6N HCl followed by reductive methylation using aqueous formaldehyde and sodium cyanoborohydride gave **6i** in 92% yield.

Scheme 3



The substrate (**6j**) was synthesized as shown in Scheme 4. Hydrogenation of **15** on PtO_2 afforded **23** (75% yield), which was treated with TsCl and pyridine to give **24** in 92% yield. Desilylation (96% yield) of **24** with TBAF followed by oxidation of the resulting alcohol (**25**) with *o*-iodoxybenzoic acid (IBX) afforded **26** in 66% yield. The ketone (**26**) was treated with 3N HCl to give **6j** in 78% yield.

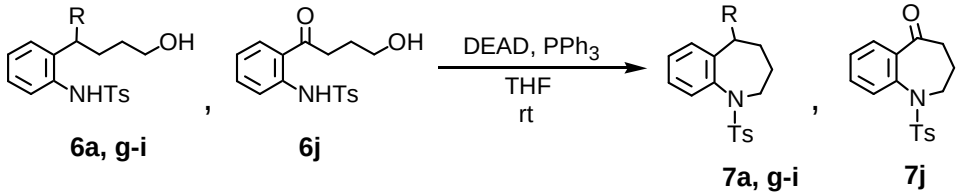
Scheme 4



The results of the intramolecular Mitsunobu reaction employing the substrates (**6a** and **6g-j**) bearing various 1-substituted 4-hydroxybutyl group are summarized in Table 2. In all the reactions, the substrates were converted to the desired products within 3 hours at rt. The reaction of **6g** and **6h** gave the

corresponding benzazepines (**7g**) and (**7h**) in good yields (Entries 2 and 3). However, the yield of **7j** was moderate (77%, Entry 5) and that of **7i** was low (36%, Entry 4), due to the formation of unknown products.

Table 2 Intramolecular Mitsunobu Reaction of the Compounds Bearing 1-Substituted 4-Hydroxybutyl Groups *

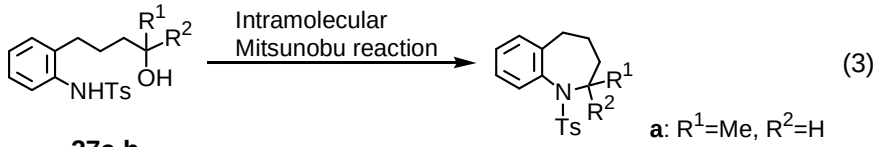


6a, g-i , **6j** , **7a, g-i** , **7j**

Entry	Substrate	R	Time	Product	Yield(%)
1	**6a**	OMOM	2 h	**7a**	100
2	**6g**	NPhth	3 h	**7g**	96
3	**6h**	NMeBoc	3 h	**7h**	100
4	**6i**	NMe_2	3 h	**7i**	36
5	**6j**	-	3 h	**7j**	77

* All reactions were carried out with stirring a mixture of substrate (0.26 mmol), PPh_3 (1.2 eq.) and DEAD (1.2 eq.) in THF (3 mL) at rt.

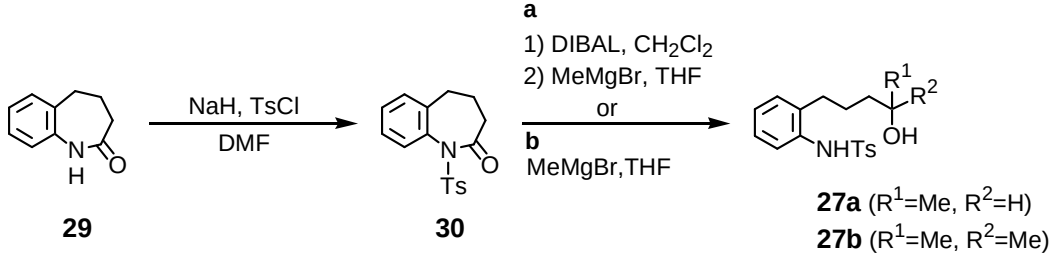
Finally, in order to apply this methodlogy to the synthesis of the 2-substituted benzazepine derivatives, we examined the cyclization reaction of the model substrates (**27a** and **27b**) bearing the secondary or tertiary hydroxyl group (eq. 3).



27a,b **28a,b** **a**: R^1=Me, R^2=H **b**: R^1=R^2=Me (3)

The substrates (**27a**) and (**27b**) were synthesized as shown in Scheme 5. The reaction of the lactam (**29**)[14] with NaH and TsCl afforded **30** in 83% yield. The secondary alcohol (**27a**) was prepared by the reduction of **30** with diisobutylalminium hydride (DIBAL) followed by treatment with methylmagnesium bromide in 58% yield. The tertiary alcohol (**27b**) was obtained by treatment of **30** with excess methylmagnesium bromide in 83% yield.

Scheme 5

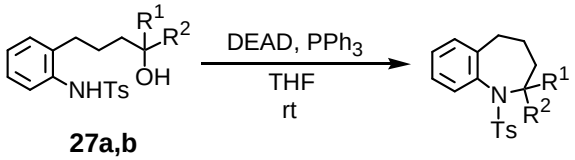


29 **30** **27a** (R^1=Me, R^2=H) **27b** (R^1=Me, R^2=Me)

The result of the intramolecular Mitsunobu reaction using compounds (**27a**) and (**27b**) are summarized in Table 3. The reaction of the secondary alcohol (**27a**) rapidly proceeded within 3 hours to give the

benzazepine (**28a**) in 92% yield (Entry 1), but the tertiary alcohol (**27b**) was not converted to the desirable cyclized product (**28b**) even after a day reaction (Entry 2).

Table 3 Intramolecular Mitsunobu Reaction of Secondary and Tertiary Alcohols *



27a,b **28a,b**

Entry	Substrate	R^1	R^2	Time	Product	Yield(%)
1	**27a**	Me	H	3 h	**28a**	92
2	**27b**	Me	Me	1 d	**28b**	0

*All reactions were carried out with stirring a mixture of substrate (0.26 mmol), PPh_3 (1.2 eq.) and DEAD (1.2 eq.) in THF (3 mL) at rt.

In conclusion, we have established the efficient synthesis of the benzazepine derivatives by the intramolecular Mitsunobu reaction. We also succeeded in the synthesis of the benzazepine derivatives bearing the functional groups at the 5-position as well as mozavaptan and its metabolites.

EXPERIMENTAL

All melting points were determined using a Yamato MP-21 apparatus and are uncorrected. The IR spectra were obtained using a Perkin-Elmer Spectrum 1000 FT-IR spectrophotometer. The ^{1}H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) spectra were recorded by a Bruker AVANCE DPX 250 spectrometer. Chemical shifts are given in δ values (ppm) using tetramethylsilane (TMS) as the internal standard. The HRMS spectra were recorded by a JEOL JMS-SX 102A mass spectrometer. Elementary combution analyses were performed using a Yamaco CHN CORDER MT-5. All reactions were monitored by TLC employing a 0.25 mm silica gel plate (Merck 5715; 60 F_{254}). Column chromatography was carried out on silica gel (Kanto Chemical Silicagel 60 (spherical); 63-210 μm) and NH-silica gel (Fuji Silysia Chemical Chromatorex NH-DM1020; 100 μm. All reagents were used as purchased.

2-(1-Methoxymethoxybut-3-enyl)nitrobenzene (9)

Chloromethyl methyl ether (1.2 mL, 0.15 mol) was added to a solution of **8** (5.7g, 30 mmol) and *i*-Pr_2NEt (30.8 mL, 0.18 mol) in CH_2Cl_2 (30 mL), and the mixture was refluxed for 2.5 h. The reaction mixture was cooled to 0 °C, poured into 2.4N HCl and then extracted with CH_2Cl_2. The extract was washed with a saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 11/1 - 9/1) to give **9** (6.5 g, 90%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.43-2.68 (2H, m), 3.31 (3H, s), 4.48 (1H, d, *J* = 6.8 Hz), 4.58 (1H, d, *J* = 6.8

Hz), 5.04-5.17 (2H, m), 5.29 (1H, dd, *J* = 4.3, 8.0 Hz), 5.92 (1H, tdd, *J* = 7.0, 10.0, 17.0 Hz), 7.36-7.46 (1H, m), 7.57-7.68 (1H, m), 7.76 (1H, dd, *J* = 1.5, 8.0 Hz), 7.93 (1H, dd, *J* = 1.3, 8.3 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 41.9, 55.8, 73.2, 95.2, 117.7, 124.3, 128.1, 128.5, 133.2, 134.1, 138.0, 148.3. IR (neat): 2951, 1527, 1347, 1155, 1099, 1023, 919 cm^{-1}. HRFAB-MS calcd for $C_{12}H_{15}NO_4Li$ $(M+Li)^+$: 244.1161, found: 244.1183.

2-(4-Hydroxy-1-methoxymethoxybutyl)nitrobenzene (10)

A solution of the borane-THF complex in THF (1 mol/L, 32 mL, 32 mmol) was added to a stirring solution of **9** (6.4 g, 27 mmol) in THF (65 mL) at –40 °C under a nitrogen atmosphere. The mixture was warmed to 0 °C and stirred for 7 h. Water (10 mL), 5N NaOH solution (23 mL) and 30% H_2O_2 (33 mL) were added in this order at 0–5 °C and the mixture was stirred at rt overnight. The reaction mixture was then poured into water and extracted with AcOEt. The extract was washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/CH_2Cl_2/AcOEt = 2/1/1 - 2/1/2) to give **11** (5.8 g, 85%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.53 (1H, t, *J* = 5.5 Hz), 1.69-2.03 (4H, m), 3.32 (3H, s), 3.65-3.77 (2H, m), 4.46 (1H, d, *J* = 6.8 Hz), 4.57 (1H, d, *J* = 6.8 Hz), 5.19-5.28 (1H, m), 7.36-7.46 (1H, m), 7.57-7.67 (1H, m), 7.75 (1H, dd, *J* = 1.5, 8.0 Hz), 7.93 (1H, dd, *J* = 1.3, 8.3 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 29.1, 34.2, 55.9, 62.3, 73.4, 95.3, 124.3, 128.1, 128.3, 133.3, 138.6, 148.3. IR (neat): 3413, 2950, 1526, 1345, 1150, 1098, 1030 cm^{-1}. HRFAB-MS calcd for $C_{12}H_{17}NO_5Li$ $(M+Li)^+$: 262.1267, found: 262.1259.

2-[1-Methoxymethoxy-4-(tetrahydropyran-2-yloxy)butyl]nitrobenzene (11)

A solution of **10** (3.7 g, 14 mmol), 3,4-dihydro-2*H*-pyrane (2.0 mL, 22 mmol) and pyridinium *p*-toluene-sulfonate (728 mg, 2.9 mmol) in CH_2Cl_2 (37 mL) was stirred at rt for 15 h. The reaction mixture was poured into a saturated $NaHCO_3$ solution and then extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 3/1) to give **11** (4.9 g, quantitative) as a yellow oil. ^{1}H NMR($CDCl_3$) δ (ppm): 1.43-2.01 (10H, m), 3.31 (3H, s), 3.37-3.55 (2H, m), 3.72-3.91 (2H, m), 4.43-4.50 (1H, m), 4.53-4.62 (2H, m), 5.18-5.27 (1H, m), 7.36-7.45 (1H, m), 7.57-7.67 (1H, m), 7.71-7.78 (1H, m), 7.87-7.94 (1H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.5, 19.6, 25.4, 26.2, 26.3, 30.7, 34.5, 34.8, 55.8, 62.2, 62.3, 66.9, 67.3, 73.3, 73.5, 95.2, 95.3, 98.79, 98.84, 124.2, 128.0, 128.4, 133.1, 138.6, 148.4. IR (neat): 2944, 1527, 1352, 1076, 1033 cm^{-1}. HRFAB-MS calcd for $C_{17}H_{25}NO_6Li$ $(M+Li)^+$: 346.1842, found: 346.1816.

2-[1-Methoxymethoxy-4-(tetrahydropyran-2-yloxy)butyl]aniline (12)

A mixture of **11** (3.0 g, 8.8 mmol) and PtO_2 (300 mg) in EtOH (30 mL) was stirred at rt for 2 h under a hydrogen atmosphere. The mixture was filtered and the residue was washed with EtOH. The filtrate was

then concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 4/1 - 2/1) to give **12** (2.7 g, 99%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ (ppm) 1.4: 0-2.15 (10H, m), 3.32-3.54 (5H, m, including 3.39, s), 3.70-3.92 (2H, m), 4.17 (2H, br. s), 4.50-4.70 (4H, m), 6.59-6.73 (2H, m), 6.98-7.11 (2H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.6, 25.4, 26.5, 30.67, 30.77, 30.81, 55.7, 62.2, 67.20, 67.23, 77.9, 78.0, 93.91, 93.93, 98.8, 116.6, 118.1, 124.7, 128.5, 129.2, 144.58, 144.61. IR (neat): 3369, 2944, 1617, 1496, 1456, 1120, 1032, 751 cm^{-1}. HRFAB-MS calcd for $C_{17}H_{27}NO_4$ M^+: 309.1940, found: 309.1919.

***N*-[2-(4-Hydroxy-1-methoxymethoxybutyl)phenyl]-*p*-toluenesufonamide (6a)**

p-Toluenesulfonyl chloride (616 mg, 3.2 mmol) was added to a solution of **12** (500 mg, 1.6 mmol) and pyridine (0.8 mL, 0.01 mol) in CH_2Cl_2 (5 mL) and the mixture was refluxed for 3 h. The reaction mixture was poured into water and then extracted with CH_2Cl_2. The extract was washed with 2.4N HCl, a saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (NH-silica gel; eluent, hexane/AcOEt = 2/1 - 1/1) to give the *N*-tosylated product as a colorless oil. 3N HCl (3.5 mL) was added to a solution of the above-mentioned product in MeOH (7 mL) and the resulting mixture was stirred at rt for 1 h. The mixture was poured into water and then extracted with AcOEt. The extract was washed with a saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 1/1) to give **6a** (556 mg, 91%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.22-1.82 (5H, m), 2.83 (3H, s), 3.35 (3H, s), 3.48-3.62 (2H, m), 4.38 (1H, d, *J* = 6.8 Hz), 4.50 (1H, d, *J* = 6.8 Hz), 4.53 (1H, dd, *J* = 5.5, 8.3 Hz), 7.00-7.12 (2H, m), 7.18-7.29 (3H, m), 7.54-7.61 (1H, m), 7.66-7.75 (2H, m), 8.33 (1H, br s). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.4, 28.7, 32.1, 55.9, 62.2, 94.3, 121.8, 124.6, 127.0, 128.5, 128.6, 129.6, 131.1, 135.3, 137.0, 143.8. IR (neat): 3268, 2949, 1599, 1495, 1335, 1161, 1092, 1030, 923, 815, 761, 662 cm^{-1}. HRFAB-MS calcd for $C_{19}H_{25}NO_5LiS$ $(M+Li)^+$: 386.1613, found: 386.1588.

***N*-[2-(4-Hydroxy-1-methoxymethoxybutyl)phenyl]-trifluoroacetamide (6b)**

Trifluoroacetic anhydride was added to a solution of **12** (500 mg, 1.6 mmol) in pyridine (5 mL) and the mixture was stirred overnight at rt. The reaction mixture was poured into 1N HCl and then extracted with AcOEt. The extract was washed with a saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 6/1 - 4/1) to give the *N*-trifluoroacetyl product as a pale yellow oil. 3N HCl (3 mL) was added to a solution of the above-mentioned product in MeOH (6 mL) and the rusulting mixture was stirred at rt for 1 h. The reaction mixture was poured into water and then extracted with AcOEt. The extract was washed with a saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue

was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 2/1 - 1/1) to give **6b** (439 mg, 85%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.36-1.92 (4H, m, including 1.40, t, *J* = 5.0 Hz), 1.95-2.12(1H, m), 3.39 (3H, s), 3.60-3.72 (2H, m), 4.62 (1H, d, *J* = 6.8 Hz), 4.65 (1H, d, *J* = 6.8 Hz), 4.74 (1H, dd, *J* = 6.8, 7.8 Hz), 7.15-7.21 (2H, m), 7.30-7.42 (1H, m), 8.19 (1H, d, *J* = 8.0 Hz), 10.11 (1H, br s). IR (neat): 3301, 2950, 1732, 1594, 1546, 1454, 1283, 1156, 1027, 908, 762, 723 cm^{-1}. HRFAB-MS calcd for $C_{14}H_{18}NO_4F_3Li$ $(M+Li)^+$: 328.1348, found: 328.1359.

***N*-[2-(4-Hydroxy-1-methoxymethoxybutyl)phenyl]-4-nitrobenzamide (6c)**

As a yellow oil, **6c** (975 mg, 89%) was obtained by the same treatment of **12** (900 mg, 2.9 mmol) with 4-nitrobenzoyl chloride (810 mg, 4.4 mmol) as the case of **6b**. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.32-1.99 (4H, m), 2.02-2.20 (1H, m), 3.41 (3H, s), 5.54-5.73 (2H, m), 4.68 (1H, d, *J* = 6.8 Hz), 4.71 (1H, d, *J* = 6.8 Hz), 4.77 (1H, t, *J* = 7.3 Hz), 7.09-7.24 (2H, m), 7.33-7.45 (1H, m), 8.04-8.18 (2H, m), 8.30-8.46 (3H, m), 9.93 (1H, br s). ^{13}C NMR ($CDCl_3$) δ (ppm): 29.1, 31.7, 56.1, 62.1, 79.1, 94.6, 122.7, 124.0, 124.9, 128.2, 128.9, 129.0, 129.6, 136.0, 140.3, 149.6, 162.9. IR (neat): 3344, 2948, 1678, 1604, 1590, 1526, 1450, 1348, 1313, 1027, 853, 761, 714 cm^{-1}. HRFAB-MS calcd for $C_{19}H_{23}N_2O_6$ $(M+H)^+$: 375.1556, found: 375.1579.

***N*-[2-(4-Hydroxy-1-methoxymethoxybutyl)phenyl]-4-iodobenzamide (6d)**

As a white powder, **6d** (643 mg, 87%) was obtained by the same treatment of **12** (500 mg, 1.6 mmol) with 4-iodobenzoyl chloride (646 mg, 2.4 mmol) as the case of **6b**. mp 96-99 °C (Et_2O-hexane). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.33-1.97 (4H, m, including 1.37, t, *J* = 5.3 Hz), 1.99-2.18 (1H, m), 3.40 (3H, s), 3.54-3.68 (2H, m), 4.66 (1H, d, *J* = 6.8 Hz), 4.69 (1H, d, *J* = 6.8 Hz), 4.74 (1H, t, *J* = 7.3 Hz), 7.05-7.21 (2H, m), 7.30-7.42 (1H, m), 7.61-7.72 (2H, m), 7.81-7.93 (2H, m), 8.37 (1H, d, *J* = 8.0 Hz), 9.75 (1H, br s). ^{13}C NMR ($CDCl_3$) δ (ppm): 29.2, 31.5, 56.1, 62.2, 79.3, 94.5, 98.9, 122.6, 124.4, 128.6, 128.9, 129.0, 129.2, 134.2, 136.5, 138.0, 164.3. IR (KBr): 3417, 3227, 2943, 1645, 1536, 1494, 1322, 1098, 1062, 1036, 966, 761 cm^{-1}. HRFAB-MS calcd for $C_{19}H_{23}NO_4I$ $(M+H)^+$: 456.0672, found: 456.0657.

***N*-[2-(4-Hydroxy-1-methoxymethoxybutyl)phenyl]-4-(*o*-toluoylamino)benzamide (6e)**

As a colorless amorphous solid, **6e** (535 mg, 72%) was obtained by the same treatment of **12** (500 mg, 1.6 mmol) with 4-(*o*-toluoylamino)benzoyl chloride (663 mg, 2.4 mmol) as the case of **6b**. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.40-1.98 (4H, m), 2.00-2.19 (1H, m), 2.52 (3H, s), 3.42 (3H, s), 3.53-3.67 (2H, m), 4.67 (1H, d, *J* = 6.8 Hz), 4.70 (1H, d, *J* = 6.8 Hz), 4.76 (1H, t, *J* = 7.3 Hz), 7.04-7.21 (2H, m), 7.22-7.45 (4H, m), 7.51 (1H, d, *J* = 7.8 Hz), 7.72-7.86 (3H, m), 7.89-8.00 (2H, m), 8.37 (1H, d, *J* = 8.0 Hz), 9.77 (1H, br s). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.8, 29.2, 31.5, 56.0, 62.1, 79.1, 94.4, 119.6, 122.8, 124.3, 125.8, 126.7, 128.1, 128.7, 129.0, 129.6, 130.1, 130.5, 131.2, 135.9, 136.5, 136.6, 141.4, 164.6, 168.5. IR (KBr): 3294, 2946, 1659,

1592, 1514, 1447, 1317, 1263, 1024, 763 cm^{-1}. HRFAB-MS calcd for $C_{27}H_{31}N_2O_5$ $(M+H)^+$: 463.2233, found: 463.2231.

_N_-[2-(4-Hydroxy-1-methoxymethoxybutyl)phenyl]-*tert*-butylcarbamate (6f)

A solution of **12** (500 mg, 1.6 mmol) and *tert*-butyl dicarbonate (0.74 mL, 3.2 mmol) in THF (5 mL) was refluxed for 1 d. The reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 9/1 - 4/1) to give the *N*-*tert*-butyloxycarbonyl compound as a colorless amorphous solid. Pyridinium *p*-toluenesulfonate (72 mg, 0.29 mmol) was added to a solution of the above-mentioned product in EtOH (6mL) and the resulting mixture was stirred at 40 °C for 7 h. The reaction mixture was poured into water and then extracted with AcOEt. The extract was washed with a saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 2/1) to give **6f** (416 mg, 79%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.39-1.94 (13H, m, including 1.52, s), 1.95-2.13 (1H, m), 3.39 (3H, s), 3.65 (2H, t, *J* = 6.5 Hz), 4.57 (1H, d, *J* = 6.8 Hz), 4.61 (1H, d, *J* = 6.8 Hz), 4.67 (1H, dd, *J* = 6.5, 7.5 Hz), 6.99 (1H, dt, *J* = 1.3, 7.5 Hz), 7.11 (1H, dd, *J* = 1.8, 7.5 Hz), 7.22-7.32 (1H, m), 7.85 (1H, br s), 7.90-7.99 (1H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 28.4, 29.2, 31.3, 55.9, 62.4, 78.5, 80.2, 94.2, 121.6, 123.0, 128.6, 128.8, 128.9, 136.9, 153.3. IR (neat): 3378, 2936, 1729, 1590, 1523, 1448, 1236, 1158, 1024, 756 cm^{-1}. HRFAB-MS calcd for $C_{17}H_{27}NO_5$ M^+: 325.1889, found: 325.1903.

2-(1-*tert*-Butyldimethylsiloxybut-3-enyl)nitrobenzene (13)

tert-Butyldimethylsilyl chloride (19.6 g, 0.13 mol) was added to a solution of **8** (20.9 g, 0.11 mmoL) and imidazole (26.6 g, 0.39 mol) in DMF (100 mL) and the mixture was stirred at rt for 12 h. The reaction mixture was poured into water and then extracted with AcOEt. The extract was washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 32/1) to give **13** (30.0 g, 90%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ (ppm): -0.16 (3H, s), 0.02 (3H, s), 0.87 (9H, s), 2.31-2.46 (1H, m), 2.47-2.60 (1H, m), 4.97-5.09 (2H, m), 5.37 (1H, dd, *J* = 4.0, 7.3 Hz), 5.75-5.95 (1H, m), 7.34-7.43 (1H, m), 7.57-7.66 (1H, m), 7.83 (1H, dd, *J* = 1.5, 8.0 Hz), 7.89 (1H, dd, *J* = 1.3, 8.3 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): -5.02, -4.97, 18.1, 25.7, 44.4, 69.6, 117.8, 123.9, 127.7, 128.8, 133.0, 134.3, 140.7, 147.1. IR (neat): 3078, 2956, 2930, 2858, 1610, 1529, 1346, 1258, 1091, 915, 836, 778, 745 cm^{-1}. HRFAB-MS calcd for $C_{16}H_{24}NO_3Si$ $(M-H)^+$: 306.1526, found: 306.1534.

2-(1-*tert*-Butyldimethylsiloxy-4-hydroxybutyl)nitrobenzene (14)

As a yellow oil, **14** (21.5 g, 87%) was obtained by the same treatment of **13** (23.3 g, 76 mmol) as that of **10**. ^{1}H NMR ($CDCl_3$) δ (ppm): -0.19 (3H, s), 0.04 (3H, s), 0.88 (9H, s), 1.40-1.97 (5H, m), 3.60-3.74 (2H, m), 5.29-5.40 (1H, m), 7.34-7.43 (1H, m), 7.57-7.66 (1H, m), 7.83 (1H, dd, *J* = 1.5, 8.0 Hz), 7.89 (1H, dd, *J* =

1.3, 8.3 Hz). ^{13}C NMR (ppm): -5.1, -4.9, 18.1, 25.7, 28.8, 36.3, 62.6, 69.4, 124.0, 127.7, 128.7, 133.1, 141.1, 147.0. IR (neat): 3332, 2930, 1526, 1343, 1252, 1060, 835, 775 cm^{-1}. HRFAB-MS calcd for $C_{16}H_{27}NO_4Si$ M^+: 325.1709, found: 325.1702.

2-[1-*tert*-Butyldimethylsiloxy-4-(tetrahydropyran-2-yloxy)butyl]nitrobenzene (15)

As a yellow oil, **15** (25.6 g, 95%) was obtained by the same treatment of **14** (21.4 g, 66 mmol) as that of **11**. ^{1}H NMR ($CDCl_3$) δ (ppm): -0.18 (3H, s), 0.04 (3H, s), 0.88 (9H, s), 1.43-1.92 (10H, m), 3.34-3.53 (2H, m), 3.68-3.91 (2H, m), 4.51-4.59 (1H, m), 5.30-5.39 (1H, m), 7.32-7.41 (1H, m), 7.54-7.64 (1H, m), 7.78-7.89 (2H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): -5.1, -5.0, 18.1, 19.58, 19.60, 25.5, 25.7, 25.8, 25.9, 30.7, 36.6, 36.8, 62.2, 62.3, 67.1, 67.4, 69.4, 69.5, 98.8, 123.9, 127.6, 128.8, 132.9, 141.2, 141.3, 147.2. IR (neat): 2953, 2858, 1528, 1472, 1349, 1259, 1077, 1035, 837, 778 cm^{-1}. HRFAB-MS calcd for $C_{21}H_{35}NO_5LiSi$ $(M+Li)^+$: 416.2445, found: 416.2448.

2-[1-Hydroxy-4-(tetrahydropyran-2-yloxy)butyl]nitrobenzene (16)

A solution of **15** (3.0 g, 7.3 mmol) and tetra-*n*-butylammonium fluoride (1 mol/L in THF, 15 mL, 15 mmol) in THF (15 mL) was stirred at rt for 6 h. The reaction mixture was concentrated *in vacuo*. The residue was added to water and then extracted with AcOEt. The extract was washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 4/1 - 2/1) to give **16** (2.1 g, 97%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.45-2.12 (10H, m), 3.41-3.62 (3H, m), 3.79-3.95 (2H, m), 4.59-4.67 (1H, m), 5.25-5.35 (1H, m), 7.35-7.45 (1H, m), 7.58-7.67 (1H, m), 7.82-7.93 (2H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.4, 19.6, 25.3, 26.5, 26.6, 30.46, 30.54, 36.1, 36.3, 62.3, 62.5, 67.3, 67.7, 69.0, 69.1, 98.9, 99.1, 124.2, 127.7, 128.0, 128.1, 133.3, 140.38, 140.41, 147.7. IR (neat): 3419, 2945, 1526, 1350, 1120, 1023, 856, 745 cm^{-1}. HRFAB-MS calcd for $C_{15}H_{21}NO_5Li$ $(M+Li)^+$: 302.1580, found: 302.1566.

2-[1-*N*-Phthalimidoyl-4-(tetrahydropyran-2-yloxy)butyl]nitrobenzene (17)

Diethyl azodicarboxylate (1.2 mL, 7.6 mmol) was added to a solution of **16** (2.1 g, 7.1 mmoL), phthalimide (1.1 g, 7.5 mmol) and PPh_3 (2.0 g, 7.6 mmol) in THF (30 mL) and the mixture was stirred at rt for 1.5 h under a nitrogen atmosphere. The reaction mixture was concentrated *in vacuo* and then the residue was purified by column chromatography (NH-silica gel; eluent, hexane/AcOEt = 9/1 - 8/2) to give **17** (2.2 g, 72%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.38-1.92 (8H, m), 2.26-2.48 (1H, m), 2.65-2.87 (1H, m), 3.39-3.54 (2H, m), 3.72-3.91 (2H, m), 4.53-4.62 (1H, m), 5.89-6.02 (1H, m), 7.36-7.46 (1H, m), 7.53-7.63 (1H, m), 7.65-7.75 (2H, m), 7.76-7.86 (3H, m), 7.96-8.05 (1H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.5, 25.4, 27.0, 27.1, 28.5, 28.8, 30.6, 49.8, 50.0, 62.3, 66.4, 66.8, 98.9, 123.3, 124.1, 128.6, 130.1, 131.47, 131.49,

132.8, 134.1, 134.2, 134.3, 149.4, 168.3. IR (neat): 2943, 2870, 1774, 1714, 1530, 1353, 1120, 1076, 1033, 726 cm^{-1}. HRFAB-MS calcd for $C_{23}H_{24}N_2O_6Li$ $(M+Li)^+$: 431.1794, found: 431.1796.

***N*-[2-[1-(*N*-Phthalimidoyl)-4-(tetrahydropyran-2-yloxy)butyl]phenyl]-*p*-toluenesufonamide (18)**

A mixture of **17** (1.0 g, 2.4 mmol) and PtO_2 (100 mg) in AcOEt (10 mL) was stirred at rt for 3 h under a hydrogen atmosphere. The mixture was filtered and the residue was washed with AcOEt. The filtrate was concentrated *in vacuo* to give a crude product as a yellow oil. *p*-Toluenesulfonyl chloride (900 mg, 4.7 mmol) was added to a solution of the above-mentioned product and pyridine (1.2 mL, 15 mmol) in CH_2Cl_2 (10 mL) and the resulting mixture was refluxed for 3 h. The reaction mixture was poured into 0.6N HCl and then extracted with CH_2Cl_2. The extract was washed with 0.1N HCl, a saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (NH-silica gel; eluent, hexane/AcOEt = 4/1 - 1/1 and then silica gel; eluent, hexane/CH_2Cl_2/AcOEt = 4/2/1 - 2/1/1) to give **18** (429 mg, 33%) as a colorless amorphous solid. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.03-1.31 (2H, m), 1.42-1.89 (7H, m), 2.37 (3H, s), 2.52-2.76 (1H, m), 3.16-3.30 (1H, m), 3.42-3.67 (2H, m), 3.75-3.89 (1H, m), 4.46-4.54 (1H, m), 4.80-4.91 (1H, m), 7.15-7.33 (4H, m), 7.55-7.62 (1H, m), 7.63-7.82 (7H, m), 8.14-8.22 (1H, m). IR (KBr): 3239, 2942, 2869, 1768, 1713, 1494, 1386, 1335, 1165, 1092, 1033, 815, 722, 666 cm^{-1}. Anal. Calcd for $C_{30}H_{32}N_2O_6S$: C, 65.67; H, 5.88; N, 5.11. Found: C, 65.59; H, 5.89; N, 4.76.

***N*-[2-[4-Hydroxy-1-(*N*-phthalimidoyl)butyl]phenyl]-*p*-toluenesufonamide (6g)**

3N HCl (3.5 mL) was added to a solution of **18** (612mg, 1.1 mmol) in MeOH (8 mL) and the mixture was stirred at rt for 1 h. The reaction mixture was poured into water and then extracted with AcOEt. The extract was washed with a saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 7/3 and then CH_2Cl_2/MeOH = 40/1) to give **6g** (526 mg, quantitative) as a colorless amorphous solid. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.04-1.33 (3H, m, including 1.27, t, J = 5.3 Hz), 1.53-1.72 (1H, m), 2.38 (3H, s), 2.58-2.77 (1H, m), 3.46-3.59 (2H, m), 4.92 (1H, dd, J = 6.0, 10.0 Hz), 7.15-7.33 (3H, m), 7.54 (1H, dd, J = 1.5, 8.0 Hz), 7.64-7.83 (8H, m), 8.17 (1H, br s). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.4, 26.7, 29.8, 49.7, 61.9, 123.5, 126.3, 126.6, 127.1, 128.9, 129.1, 129.6, 131.3, 132.6, 134.3, 134.4, 137.0, 143.7, 169.0. IR (KBr): 3535, 3234, 2932, 1769, 1704, 1494, 1387, 1333, 1163, 1092, 722, 665 cm^{-1}. HRFAB-MS calcd for $C_{25}H_{25}N_2O_5S$ $(M+H)^+$: 465.1484, found: 465.1512.

2-[1-Azido-4-(tetrahydropyran-2-yloxy)butyl]nitrobenzene (19)

A solution of diethyl azodicarboxylate (2.4 mL, 15 mmol) in THF (5 mL) and then a solution of diphenylphosphryl azide (3.2 mL, 15 mmol) in THF (5 mL) were successively added in this order to a solution of **16** (4.0 g, 14 mmol) and PPh_3 (3.9 g, 15 mmol) in THF (40 mL) at 0 °C under a nitrogen

atmosphere, and the resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was poured into a saturated $NaHCO_3$ solution and then extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (NH-silica gel; eluent, hexane/AcOEt = 32/1 - 16/1) to give **19** (3.9 g, 86%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.38-2.06 (10H, m), 3.36-3.56 (2H, m), 3.71-3.91 (2H, m), 4.53-4.62 (1H, m), 5.23-5.34 (1H, m), 7.39-7.54 (1H, m), 7.62-7.73 (2H, m), 7.90-7.98 (1H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.5, 19.6, 25.4, 26.4, 30.61, 30.62, 33.7, 34.0, 60.8, 60.9, 62.27, 62.32, 66.6, 66.8, 98.8, 98.9, 124.60, 124.61, 128.5, 128.7, 133.6, 133.7, 135.67, 135.70, 148.2. IR (neat): 2943, 2098, 1527, 1351, 1121, 1075, 1033, 787, 744 cm^{-1}. HRFAB-MS calcd for $C_{15}H_{21}N_4O_4$ $(M+H)^+$: 321.1563, found: 321.1580.

2-[1-*tert*-Butoxycarbonylamino-4-(tetrahydropyran-2-yloxy)butyl]nitrobenzene (20)

A solution of **19** (3.8 g, 12 mmol) and PPh_3 (3.8 g, 14 mmol) in THF (40 mL) was stirred at rt for 13 h. After the addition of water, the mixture was stirred at 60 °C for 3.5h. Di-*tert*-butyl dicarboxylate (4.1 mL) was added to the stirring mixture cooled down to rt and then the mixture was stirred at rt for 2.5 h. The reaction mixture was poured into 0.2N HCl and then extracted with AcOEt. The extract was washed with a saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 3/1) to give **20** (4.2 g, 92%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.95-2.09 (19H, m), 3.34-3.60 (2H, m), 3.68-3.99 (2H, m), 4.50-4.64 (1H, m), 4.85-5.68 (2H, m), 7.32-7.44 (1H, m), 7.47-7.65 (2H, m), 7.81-7.97 (1H, m). IR (neat): 3338, 2943, 1704, 1527, 1366, 1167, 1023, 856, 786 cm^{-1}. HRFAB-MS calcd for $C_{20}H_{31}N_2O_6$ $(M+H)^+$: 395.2182, found: 395.2164.

2-[1-(*N*-Methyl-*tert*-butoxycarbonylamino)-4-(tetrahydropyran-2-yloxy)butyl]nitrobenzene (21)

A 60% dispersion of NaH in oil (183 mg, 4.6 mmol) was added to a solution of **20** (1.5 g, 3.8 mmol) and MeI (0.40 mL, 6.4 mmol) in THF (15 mL) at 0 °C. The mixture was stirred at 0°C for 1 h and then at rt for 5 h. The reaction mixture was poured into water and then extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (NH-silica gel; eluent, hexane/AcOEt = 6/1) to give **21** (1.5 g, 97%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.33-2.13 (19H, m, including 1.41, s), 2.66-2.80 (3H, m), 3.40-3.57 (2H, m), 3.75-3.94 (2H, m), 4.54-4.63 (1H, m), 5.62-5.75 (1H, m), 7.35-7.44 (1H, m), 7.45-7.59 (2H, m), 7.67-7.76 (1H, m). IR (neat): 2944, 2872, 1694, 1531, 1455, 1392, 1367, 1258, 1141, 1076, 1034, 869, 783 cm^{-1}. HRFAB-MS calcd for $C_{21}H_{33}N_2O_6$ $(M+H)^+$: 409.2339, found: 409.2334.

2-[1-(*N*-Methyl-*tert*-butoxycarbonylamino)-4-(tetrahydropyran-2-yloxy)butyl]aniline (22)

As a yellow oil, **22** (1.3 g, quantitative) was synthesized from **21** (1.4 g, 3.4 mmol) by the same method as that for **12**. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.37-2.19 (19H, m, including 1.48, s), 2.52 (3H, s), 3.41-3.58 (2H,

m), 3.75-3.95 (2H, m), 4.03-4.69 (3H, m, including 4.38, br s), 5.06-5.45 (1H, m), 6.59-6.76 (2H, m), 7.01-7.19 (2H, m). IR (neat): 3456, 3370, 3252, 2942, 1670, 1458, 1392, 1366, 1329, 1139, 1033, 870, 749 cm^{-1}. HRFAB-MS calcd for $C_{21}H_{35}N_2O_4$ $(M+H)^+$: 379.2597, found: 379.2608.

***N*-[2-[4-Hydroxy-1-(*N*-methyl-*tert*-butoxycarbonylamino)butyl]phenyl]-*p*-toluenesufonamide (6h)**

p-Toluenesulfonyl chloride (1.2 g, 6.3 mmol) was added to a solution of **21** (1.2 mg, 3.2 mmol) and pyridine (1.5 mL, 19 mol) in CH_2Cl_2 (12 mL), and then the mixture was refluxed for 1.5 h. The reaction mixture was poured into water and then extracted with CH_2Cl_2. The extract was washed with water, 0.5N HCl, a saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (NH-silica gel; eluent, hexane/AcOEt = 6/1 - 2/1) to give the *N*-tosylated product as a pale yellow amorphous solid. Pyridinium *p*-toluenesulfonate (130 mg, 0.52 mmol) was added to a solution of the above-mentioned product in EtOH (14 mL) and the rusulting mixture was stirred at 40 °C for 7 h. The reaction mixture was poured into water and then extracted with AcOEt. The extract was washed with a saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2/MeOH = 50/1 - 45/1) to give **6h** (1.1 g, 78%) as a colorless amorphous solid. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.02-1.68 (13H, m, including 1.33, t, *J* = 5.0 Hz, 1.50, s), 1.80-2.01 (1H, m), 2.36 (3H, s), 2.49 (3H, s), 3.44-3.70 (2H, m), 4.87 (1H, dd, *J* = 5.5, 9.8 Hz), 7.03-7.32 (5H, m), 8.69-9.89 (3H, m), 9.35 (1H, br s). IR (KBr): 3454, 3178, 2936, 2866, 1621, 1494, 1455, 1397, 1338, 1162, 1092, 934, 814, 766, 688, 666 cm^{-1}. Anal. Calcd for $C_{23}H_{32}N_2O_5S$: C, 61.58; H, 7.19; N, 6.24. Found: C, 61.46; H, 7.02; N, 6.07.

***N*-[2-[4-Hydroxy-1-(*N*,*N*-dimethylamino)butyl]phenyl]-*p*-toluenesufonamide (6i)**

6N HCl (3 mL) was added to a solution of **6h** (580 mg, 1.3 mmol) in MeOH (12 mL) and the mixture was stirred at rt for 2h and then at 60 °C for 0.5 h. The reaction mixture was poured into 0.5N NaOH solution, saturated with NaCl and then extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, concentrated *in vacuo* to afford the crude product as a white powder. An aqueous solution of formaldehyde (0.6 mL), $NaBH_3CN$ (132 mg, 2.1 mmol) and AcOH (0.4 mL) were added in this order to a solution of the above-mentioned product in MeOH (10 mL) at 0 °C. The mixture was stirred at rt for 2.5 h. 5N NaOH (2 mL) and then brine was added to the mixture. It was then extracted with CH_2Cl_2 and the extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2/MeOH = 100/0 - 100/1) to give **6i** (432 mg, 92%) as a colorless amorphous solid. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.79-0.99 (1H, m), 1.07-1.29 (1H, m), 1.46 (1H, dtd, *J* = 5.0, 10.8, 13.0 Hz), 1.79-1.99 (1H, m), 2.23 (6H, s), 2.37 (3H, m), 2.95 (1H, dd, *J* = 4.3, 10.8 Hz), 3.33 (1H, quint., *J* = 6.3 Hz), 3.37 (1H, quint., 6.3 Hz), 6.87-6.97 (2H, m), 7.11-7.28 (3H, m), 7.46-7.56 (1H, m),

7.72-7.82 (2H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.4, 26.3, 30.2, 43.0, 62.3, 71.7, 119.0, 122.8, 126.9, 128.0, 128.9, 129.5, 129.9, 137.1, 137.8, 143.3. IR (KBr): 3369, 3056, 2964, 1594, 1485, 1448, 1271, 1229, 1123, 1084, 1051, 1031, 970, 813, 752, 658 cm^{-1}. Anal. Calcd for $C_{19}H_{26}N_2O_3S$: C, 62.96; H, 7.23; N, 7.73. Found: C, 62.79; H, 7.12; N, 7.49.

2-[1-*tert*-Butyldimethylsiloxy-4-(tetrahydropyran-2-yloxy)butyl]aniline (23)

As a yellow oil, **23** (2.1 g, 75%) was synthesized from **15** (3.0 g, 7.3 mmol) by the same method as that of **12**. ^{1}H NMR ($CDCl_3$) δ (ppm): -0.11 (3H, s), 0.06 (3H, s), 0.87 (9H, m), 1.38-2.11 (10H, m), 3.30-3.55 (2H, m), 3.65-3.94 (2H, m), 4.29 (2H, br s), 4.50-4.59 (1H, m), 4.64 (1H, dd, *J* = 6.0, 7.8 Hz), 6.54-6.70 (2H, m), 6.92 (1H, dd, *J* = 1.5, 7.5 Hz), 7.03 (1H, dt, *J* = 1.5, 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): -5.2, -4.9, 18.1, 19.57, 19.63, 25.5, 25.6, 25.8, 26.6, 30,7, 33.0, 33.1, 62.2, 62.3, 67.36, 67.41, 98.8, 98.9, 116.7, 117.8, 127.9, 128.1, 144.5. IR (neat): 3459, 3369, 2951, 2857, 1616, 1497, 1462, 1257, 1137, 1121, 1034, 836, 778, 748 cm^{-1}. HRFAB-MS calcd for $C_{21}H_{37}NO_3Si$ M^+: 379.2543, found: 379.2532.

***N*-[2-[1-*tert*-Butyldimethylsiloxy-4-(tetrahydropyran-2-yloxy)butyl]phenyl]-*p*-toluenesufonamide (24)**

p-Toluenesulfonyl chloride (1.0 g, 5.2 mmol) was added to a solution of **23** (1.0 g, 2.6 mmol) and pyridine (1.3 mL, 16 mol) in CH_2Cl_2 (10 mL) and the mixture was refluxed for 3 h. The reaction mixture was poured into 0.4N HCl and then extracted with CH_2Cl_2. The extract was washed with 0.1N HCl, saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 9/1 - 4/1) to give **24** (1.3 g, 92%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ (ppm): -0.08 (3H, s), 0.09 (3H, s), 0.91 (9H, s), 1.08-1.92 (10H, m), 2.37 (3H, s), 3.06-3.24 (1H, m), 3.41-3.60 (2H, m), 3.74-3.91 (1H, m), 4.44-4.53 (1H, m), 4.54-4.65 (1H, m), 6.86-6.99 (2H, m), 7.13-7.28 (3H, m), 7.55-7.64 (1H, m), 7.70-7.79 (2H, m), 8.85 (1H, br s). ^{13}C NMR ($CDCl_3$) δ (ppm): -5.2, -5.1, 18.1, 19.7, 21.4, 25.4, 25.7, 26.3, 30.7, 34.59, 34.65, 62.4, 66.9, 67.0, 77.6, 98.87, 98.94, 119.9, 120.0, 123.2, 123.3, 127.0, 128.1, 128.2, 129.5, 131.5, 131.6, 136.1, 137.5, 143.49, 143.53. IR (neat): 3249, 2952, 2859, 1586, 1495, 1342, 1165, 1035, 839, 780 cm^{-1}. Anal. Calcd for $C_{28}H_{43}NO_5SSi$: C, 63.00; H, 8.12; N, 2.62. Found: C, 62.74; H, 7.87; N, 2.31.

***N*-[2-[1-Hydroxy-4-(tetrahydropyran-2-yl)oxybutyl]phenyl]-*p*-toluenesufonamide (25)**

As a pale yellow amorphous solid, **25** (3.1 g, 96%) was synthesized from **24** (4.1 g, 7.7 mmol) by the same method as that of **16**. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.46-1.94 (10H, m), 2.37 (3H, s), 3.28-3.63 (2H, m), 3.69-3.97 (3H, m), 4.58-4.74 (2H, m), 6.95-7.06 (2H, m), 7.12-7.29 (3H, m), 7.44-7.54 (1H, m), 7.67-7.76 (2H, m), 8.73-8.92 (1H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.59, 19.64, 21.4, 25.19, 25.24, 26.6, 26.7, 30.49,

30.54, 34.8, 35.0, 62.6, 62.7, 67.4, 67.7, 74.6, 74.7, 99.2, 99.3, 121.3, 124.1, 127.1, 127.7, 128.2, 129.5, 132.8, 135.9, 137.2, 143.49, 143.53. IR (neat): 3237, 2946, 1586, 1495, 1337, 1161, 1092, 1022, 813, 759, 662 cm^{-1}. HRFAB-MS calcd for $C_{22}H_{29}NO_5S$ M^+: 419.1766, found: 419.1796.

***N*-[2-[1-Oxo-4-(tetrahydropyran-2-yloxy)butyl]phenyl]-*p*-toluenesufonamide (26)**

A solution of **25** (1.2 g, 2.9 mmol) and *o*-iodoxybenzoic acid (1.0 g, 3.6 mmol) was stirred at rt for 14 h. A solution of 25% $Na_2S_2O_4$ saturated with $NaHCO_3$ was added to the stirring mixture and the mixture was stirred at rt for 1 h. The reaction mixture was poured into water and then extracted with AcOEt. The extract was washed with a saturated $NaHCO_3$ solution, water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 2/1) to give **26** (810 mg, 66%) as a pale yellow amorphous solid. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.43-2.02 (8H, m), 2.36 (3H, s), 2.96-3.07 (2H, m), 3.38-3.56 (2H, m), 3.72-3.90 (2H, m), 4.50-4.59 (1H, m), 7.00-7.10 (1H, m), 7.16-7.25 (2H, m), 7.39-7.49 (1H, m), 7.65-7.77 (3H, m), 7.85 (1H, dd, *J* = 1.5, 8.0 Hz), 11.43 (1H, br s). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.7, 21.4, 24.5, 25.4, 30.7, 36.3, 62.6, 66.3, 99.1, 119.4, 122.4, 122.6, 127.2, 129.6, 131.0, 134.5, 136.6, 139.9, 143.8, 204.1. IR (KBr): 2943, 1651, 1602, 1577, 1494, 1452, 1342, 1161, 1091, 1033, 922, 814, 756, 662 cm^{-1}. HRFAB-MS calcd for $C_{22}H_{27}NO_5LiS$ $(M+Li)^+$: 424.1770, found: 424.1772.

***N*-[2-[4-Hydroxy-1-oxobutyl]phenyl]-*p*-toluenesufonamide (6j)**

As colorless needles, **6j** (457 mg, 78%) was synthesized from **26** (743 mg, 1.8 mmol) by the same method as that of **6g**, mp 114-117 °C (AcOEt - hexane). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.49 (1H, t, *J* = 5.3 Hz), 1.84-2.00 (2H, m), 2.36 (3H, s), 3.04 (2H, t, *J* = 7.0 Hz), 3.70 (2H, q, *J* = 5.3 Hz), 7.00-7.11 (1H, m), 7.17-7.25 (2H, m), 7.39-7.50 (1H, m), 7.64-7.77 (3H, m), 7.85 (1H, dd, *J* = 1.3, 8.0 Hz), 11.37 (1H, br s). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.5, 26.9, 36.1, 61.8, 119.3, 122.3, 122.7, 127.2, 129.6, 131.0, 134.7, 136.5, 139.9, 143.9, 204.4. IR (KBr): 3301, 3051, 2955, 1660, 1495, 1340, 1186, 1172, 1160, 1092, 915, 760, 706 cm^{-1}. Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20. Found: C, 61.08; H, 5.63; N, 3.81.

1-(*p*-Toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (30)

A 60% dispersion of NaH in oil (500 mg, 13 mmol) was added to a solution of 2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (**29**) (2.0 g, 12 mmol) in THF (30 mL) , and the mixture was stirred at rt for 30 mim. *p*-Toluenesulfonyl chloride (2.4 g, 13 mmol) was added to the mixture at 0 °C. The mixture was stirred at rt for 2 h. The reaction mixture was poured into an aqueous citric acid solution and then extracted with AcOEt. The extract was washed with a saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 6/1 - 3/1) to give **30** (3.2 g, 83%) as a colorless amorphous solid. ^{1}H NMR ($CDCl_3$) δ

(ppm): 1.66-1.97 (1H, m), 2.00-2.29 (3H, m), 2.41-2.61 (5H, m, including 2.45, s), 7.18-7.26 (1H, m), 7.29-7.22 (4H, m), 7.48-7.58 (1H, m), 7.87-7.96 (2H, m). IR (KBr): 2917, 1708, 1488, 1365, 1168, 1138, 1087, 765, 686, 654 cm^{-1}. Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44. Found: C, 64.34; H, 5.41; N, 4.19.

***N*-[2-(4-Hydroxypentyl)phenyl]-*p*-toluenesufonamide (27a)**

A solution of DIBAL in toluene (1 mol/L, 2.5 mL, 2.5 mmol) was added to a solution of **30** (750 mg, 2.4 mmol) in THF (15 mL) under a nitrogen atmosphere at –78 °C, and the mixture was stirred at the same temperature for 1 d. The reaction mixture was quenched with MeOH, then poured into an aqueous NH_4Cl solution and extracted with AcOEt. The extract was washed with a saturated NH_4Cl solution, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/CH_2Cl_2/AcOEt = 8/3/1 - 4/2/1) to give the reduced product as a colorless amorphous solid. A solution of MeMgBr in THF (0.93 mol/L, 4.1 mL, 3.8 mmol) was added to a solution of the above-mentioned product in THF (10 mL) under a nitrogen atmosphere at 0 °C, and the mixture was stirred at the same temperature for 2 d. The reaction mixture was poured into a saturated NH_4Cl solution and then extracted with AcOEt. The extract was washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/CH_2Cl_2/AcOEt = 4/2/1 - 2/1/1) to give **27a** (465 mg, 58%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.13-1.64 (7H, m, including 1.23, d, *J* = 6.3 Hz), 1.85 (1H, br s), 2.25-2.50 (5H, m, including 2.37, s), 3.87-4.03 (1H, m), 7.02-7.24 (5H, m), 7.36-7.44 (1H, m), 7.57-7.67 (2H, m), 7.73 (1H, br s). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.5, 24.1, 27.0, 30.2, 36.4, 68.3, 123.6, 125.6, 126.8, 127.1, 129.5, 129.8, 134.6, 135.2, 136.8, 143.5. IR (neat): 3503, 3278, 2966, 2927, 1599, 1493, 1329, 1159, 1092, 923, 815, 757, 663 cm^{-1}. HRFAB-MS calcd for $C_{18}H_{23}NO_3S$ M^+: 333.1399, found: 333.1421.

***N*-[2-(4-Hydroxy-4-methylpentyl)phenyl]-*p*-toluenesufonamide (27b)**

A solution of MeMgBr in THF (0.93 mol/L, 4.1 mL, 3.7 mmol) was added to a solution of **30** (400 mg, 1.3 mmol) in THF (5 mL) under an argon atmosphere at rt. The mixture was then refluxed for 2 h. The reaction mixture was cooled to 0 °C, then poured into a saturated NH_4Cl solution and extracted with AcOEt. The extract was washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane/AcOEt = 2/1) to give **27b** (365 mg, 83%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.24 (6H, s), 1.34-1.46 (2H, m), 1.47-1.63 (2H, m), 1.78 (1H, br s), 2.31-2.44 (5H, m, including 2.37, s), 7.01-7.25 (5H, m), 7.36-7.45 (1H, m), 7.57-7.66 (2H, m), 7.79 (1H, br s). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.5, 25.2, 29.8, 30.9, 40.9, 71.7, 123.7, 125.7, 126.7, 127.1, 129.4, 129.8, 134.6, 135.3, 136.8, 143.4. IR (neat): 3510, 3279, 2969, 1599, 1493, 1330, 1160, 1092, 911, 814,

758, 662 cm^{-1}. HRFAB-MS calcd for $C_{19}H_{25}NO_3S$ M^+: 347.1555, found: 347.1552.

General procedure of intramolecular Mitsunobu reaction with substrate (6a-j) and (27a,b)

Diethyl azodicarboxylate (50 μL, 0.32 mmol) was added to a solution of the substrate (**6a-j** and **27a**,**b**, 0.26 mmoL) and PPh_3 (84 mg, 0.32 mmol) in THF (3 mL) under a nitrogen atmosphere at 0 °C and the resulting mixture was stirred at rt within 1d. After removal of the THF, the residue was purified by column chromatography (NH-silica gel; eluent, hexane/AcOEt = 9/1 – 7/3) to obtain the benzazepin **7a-j** and **28a**. These yields are listed in Tables 1-3 and their spectrum data are listed below.

5-Methoxymethoxy-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (7a)

As a white powder, mp 67-70 °C (CH_2Cl_2 - hexane). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.43-2.04 (4H, m), 2.41 (3H, s), 3.05-3.42 (4H, m, including 3.29, s), 3.90-4.19 (1H, m), 4.23-4.40 (2H, m, including 4.33, d, *J* = 6.5 Hz), 4.53 (1H, d, *J* = 6.5 Hz), 7.18-7.37 (5H, m), 7.38-7.46 (1H, m), 7.60-7.69 (2H, m). IR (KBr): 2941, 1596, 1495, 1445, 1327, 1157, 1104, 1090, 1028, 814, 773, 710 cm^{-1}. Anal. Calcd for $C_{19}H_{23}NO_4S$: C, 63.13; H, 6.41; N, 3.88. Found: C, 63.16; H, 6.30; N, 3.64.

5-Methoxymethoxy-1-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine (7b)

As a colorless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.52-1.88 (2H, m), 2.02-2.33 (1.4H, m), 2.44-2.68 (0.6H, m), 2.71-2.95 (1H, m), 3.34 (1.8H, s), 3.38 (1.2H, s), 4.40 (0.6H, d, *J* = 7.0 Hz), 4.43 (0.6H, d, *J* = 7.0 Hz), 4.52-4.71 (1.4H, m, including 4.63, d, *J* = 6.8 Hz), 4.73-4.86 (1.4H, m, including 4.78, d, *J* = 6.8 Hz), 7.15-7.39 (3.2H, m), 7.40-7.48 (0.4H, m), 7.56-7.65 (0.4H, m). IR (neat): 2936, 1697, 1496, 1426, 1201, 1149, 1034, 919, 757 cm^{-1}. Anal. Calcd for $C_{14}H_{16}NO_3F_3$: C, 55.44; H, 5.32; N, 4.62. Found: C, 55.46; H, 5.40; N, 4.37.

5-Methoxymethoxy-1-(4-nitrobenzoyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (7c)

As a pale yellow amorphous solid. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.18-1.30 (2H, m), 1.60-1.91 (2H, m), 2.75-3.06 (1H, m), 3.40 (1.5H, s), 3.45 (1.5H, s), 4.54-4.79 (2H, m), 4.80-4.94 (1H, m), 4.97-5.18 (1H, m), 6.52-6.68 (1H, m), 6.89-7.05 (1H, m), 7.05-7.19 (0.5H, m), 7.19-7.30 (1H, m), 7.31-7.46 (1H, m), 7.51-7.65 (1.5H, m), 7.91-8.12 (2H, m). IR (KBr): 2921, 1641, 1529, 1409, 1352, 1313, 1144, 1098, 1023, 850 cm^{-1}. Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 63.81; H, 5.72; N, 7.65.

5-Methoxymethoxy-1-(4-iodobenzoyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (7d)

As a colorless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.59-1.87 (2H, m), 1.93-2.56 (2H, m), 2.70-3.00 (1H, m), 3.37 (1.2H, s), 3.42 (1.8H, s), 4.58-4.78 (2H, m), 4.79-4.91 (1H, m), 4.96-5.14 (1H, m), 6.54-6.70 (1H, m), 6.86-7.06 (2H, m), 7.06-7.31 (2.6H, m), 7.40-7.61 (2.4H, m). IR (neat): 2938, 1644, 1583, 1489, 1397,

1312, 1145, 1029, 1008, 918, 835, 750 cm^{-1}. HRFAB-MS calcd for $C_{19}H_{21}NO_3I$ $(M+H)^+$: 438.0566, found: 438.0567.

5-Methoxymethoxy-1-[4-(*o*-toluoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (7e)

As a colorless amorphous solid. ^1H NMR ($CDCl_3$) δ (ppm): 1.59-1.90 (2H, m), 1.94-2.52 (5H, m, including 2.46, s), 2.67-3.05 (1H, m), 3.30-3.49 (3H, m, including 3.39, s, 3.44, s), 4.50-4.96 (3H, m), 4.96-5.24 (1H, m), 6.55-6.79 (1H, m), 6.93-7.69 (12H, m). IR (KBr): 3289, 3256, 2946, 1678, 1625, 1595, 1525, 1395, 1322, 1026, 846, 761 cm^{-1}. Anal. Calcd for $C_{27}H_{28}N_2O_4$: C, 72.95; H, 6.35; N, 6.30. Found: C, 72.96; H, 6.35; N, 6.02.

5-Methoxymethoxy-1-*tert*-butoxycarbony-2,3,4,5-tetrahydro-1*H*-1-benzazepine (7f)

As a colorless oil. ^1H NMR ($CDCl_3$) δ (ppm): 1.08-4.97 (21H, m, including 1.34, s, 1.51, s, 3.35, br. s), 6.88-7.67 (4H, m). IR (neat): 2930, 1702, 1391, 1365, 1314, 1165, 1035, 926, 834, 760 cm^{-1}. HRFAB-MS calcd for $C_{17}H_{26}NO_4$ $(M+H)^+$: 308.1862, found: 308.1854.

5-(*N*-Phthalimidoyl)-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (7g)

As colorless needles, mp 216-218 °C (CH_2Cl_2 - hexane). ^1H NMR ($CDCl_3$) δ (ppm): 1.70-2.07 (3H, m), 2.40-2.60 (4H, m, including 2.46, s), 3.07 (1H, ddd, *J* = 3.3, 11.3, 14.5 Hz), 4.44 (td, *J* = 3.8, 14.5 Hz), 5.35 (1H, dd, *J* = 1.8, 11.3 Hz), 6.84-6.95 (1H, m), 7.09-7.25 (2H, m), 7.29-7.45 (3H, m), 7.70-7.82 (4H, m), 7.83-7.94 (2H, m). IR (KBr): 2924, 1779, 1714, 1390, 1372, 1336, 1155, 1091, 886, 723, 711, 690, 650 cm^{-1}. Anal. Calcd for $C_{25}H_{22}N_2O_4S$: C, 67.25; H, 4.97; N, 6.27. Found: C, 67.28; H, 5.02; N, 6.12.

5-(*N*-Methyl-*tert*-butoxycarbonylamino)-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (7h)

As a colorless amorphous solid. ^1H NMR ($CDCl_3$) δ (ppm): 1.43 (9H, br s), 1.65-2.24 (4H, m), 2.43 (3H, s), 2.60-3.39 (4H, m, including 2.83, br s), 3.93-4.40 (1H, m), 4.53-5.40 (1H, m), 6.93-7.38 (6H, m), 7.63-7.83 (2H, m). IR (KBr): 2937, 1689, 1344, 1156, 1094, 858, 776, 710, 698 cm^{-1}. Anal. Calcd for $C_{23}H_{30}N_2O_4S$: C, 64.16; H, 7.02; N, 6.51. Found: C, 63.95; H, 6.87; N, 6.30.

2-Methyl-1-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (28a)

As colorless granular, mp 90-92 °C (CH_2Cl_2 - hexane). ^1H NMR ($CDCl_3$) δ (ppm): 0.94 (3H, d, *J* = 7.0 Hz), 1.31-1.71 (3H, m), 1.82-2.01 (1H, m), 2.20-2.48 (5H, m, including 2.41, s), 4.56-4.74 (1H, m), 7.03-7.78 (6H, m), 7.54-7.67 (2H, m). IR (KBr): 2931, 1494, 1455, 1335, 1164, 1135, 1092, 1034, 932, 824, 769, 687, 659 cm^{-1}. Anal. Calcd for $C_{18}H_{21}NO_2S$: C, 68.54; H, 6.71; N, 4.44. Found: C, 68.43; H, 6.54; N, 4.14.

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