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Large scale synthesis of *N*-benzyl-4-formylpiperidine through partial reduction of esters using aluminum hydride reagents modified with pyrrolidine

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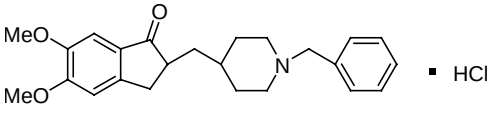
Abstract—The modification of sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) with pyrrolidine provided a highly selective reducing agent to transform *N*-benzyl-4-ethoxycarbonylpiperidine into *N*-benzyl-4-formylpiperidine **1** under mild conditions. However, this simple modification led to a significant amount of *N*-benzyl-4-(pyrrolidin-1-ylmethyl)piperidine **4** due to overreduction of an intermediate. Our extensive research revealed that an alkaline base such as potassium *tert*-butoxide could suppress the formation of the by-product to give the desired aldehyde, enabling us to establish a viable synthetic process for a key intermediate of donepezil hydrochloride. The potential applications of this reagent are also described.

Donepezil hydrochloride (Aricept®)[1–3] is a selective inhibitor of acetylcholinesterase (AChE) and is the first promising agent with this mode of action for the treatment of mild to moderate dementia of the Alzheimer's type. This new drug was approved first in the US in 1997 and later in 67 countries,[4] and has provided an effective remedy for this central nervous system dysfunction illness (Scheme 1).

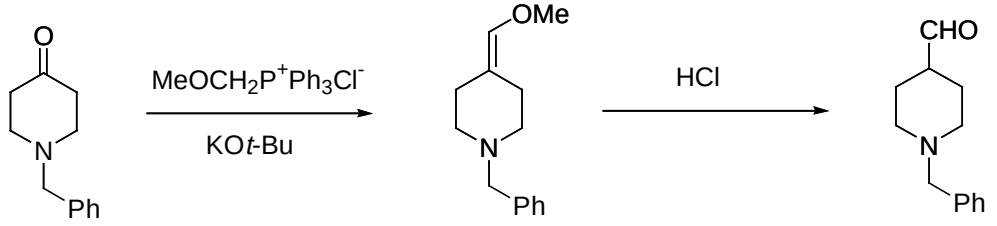


Aricept (Donepezil Hydrochloride)

Scheme 1.

Donepezil hydrochloride is synthesized through the Aldol condensation of 5,6-dimethoxy-1-indanone and *N*-benzyl-4-formylpiperidine (**1**), ensuing double bond reduction and hydrochlorination.[5] The aldehyde **1** was originally manufactured from *N*-benzylpiperidone via the Wittig reaction followed by acid hydrolysis of the enol ether, as shown in Scheme 2. However, the use of expensive (methoxymethyl)-triphenylphosphonium chloride raised the production cost, prompting us to seek a more economical process for **1**.

Our literature survey rendered us with three other methods[6–8] for the synthesis of **1**. Two of them were difficult to implement at the production scale because they require costly reagents and tedious procedures,[6,7] but one of the methods appeared to be quite promising. This method started with less expensive ethyl isonipecotate (INPE) which was



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Keywords: *N*-benzyl-4-formylpiperidine; partial ester reduction; sodium bis(2-methoxyethoxy)aluminum hydride.
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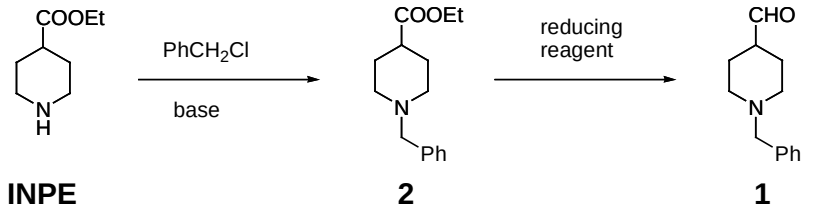


Scheme 3.

converted to *N*-benzylester (**2**), followed by partial reduction of the ester group with diisobutylaluminum hydride (DIBAL-H) to give the aldehyde **1** in 92% yield (Scheme 3).[8] However, the method required harsh cryogenic conditions, such as −78°C, which represented a problem for large scale production. Thus, we set out to find a more economical and milder reducing agent than DIBAL-H.

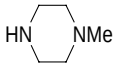
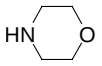
There have been only two reports on partial ester reduction other than DIBAL-H reduction. In the first method, sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) modified with *N*-methylpiperazine or morpholine was reported to transform methyl benzoate to benzaldehyde under mild conditions and in excellent yields.[9] Secondly, the modification of aluminum hydride with *N*-methylpiperazine was described as an expedient reductant for aliphatic and aromatic esters, carboxylic acids and amides to yield their corresponding aldehydes.[10–12] Of the two methods, the modified SMEAH reagent seemed to satisfy our needs, because it is commercially available, easy to handle even at the production scale, and the reaction temperature reported was mild (e.g. ice-cooling).

Following extensive screening of secondary amines, we found that SMEAH and pyrrolidine were the best combination, although a significant amount of by-products were formed. Our attempts to suppress the formation of the by-products led to a viable process for **1**, a key intermediate of donepezil hydrochloride. We wish to report here a new reducing agent named Red-ALP, effect of additional base on the reaction, the established synthetic process and the applicability of Red-ALP reduction to other substrates.

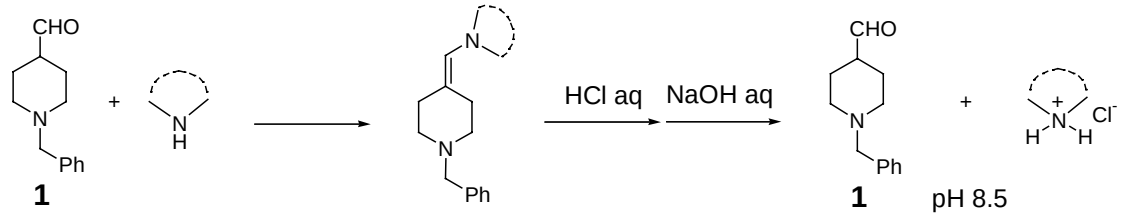
1. Results and discussion

INPE was alkylated with benzyl chloride at the *N*-position in the presence of $NaHCO_3$ to give the ethyl ester **2** in 93% yield. The ester **2** was then reduced with SMEAH modified with *N*-methylpiperazine or morpholine in THF at 10°C (entries 1 and 2, Table 1). As this reaction showed poor selectivity, several other secondary amines were examined. We noticed that when the reaction mixture was quenched with NaOH solution, the aldehyde **1** easily formed enamines with secondary amines in the extract. Thus, to determine

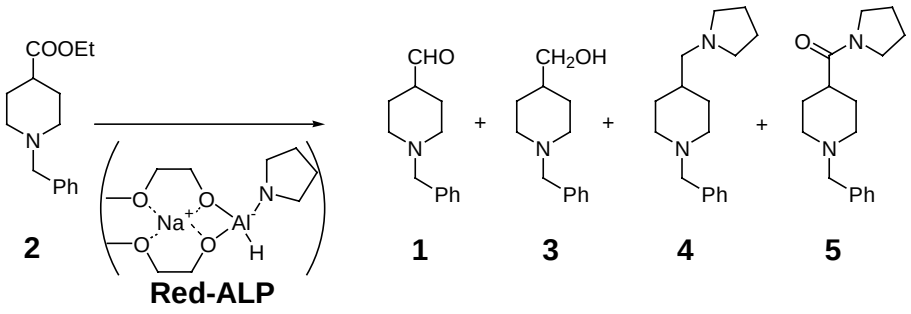
Table 1. Reduction of **2** with SMEAH modified with various secondary amines in THF

Entry	Amine	Product ratio[a,b] (%)			Selectivity
		Aldehyde **1**	Alcohol **3**	Others	Aldehyde/alcohol
1		66	25	4	2.6
2		58	35	6	1.7
3		69	21	9	3.3
4		63	28	8	2.3
5		71	3	26	23.7

Refer to Section 2 for reaction conditions.
[a] The crude product was obtained after the treatment described in Section 2.
[b] Product ratio was determined by GC.



Scheme 4.



Scheme 5.

Table 2. Effects of additional base on the reduction of **2**

Entry	Additive	Product ratio[a] (%)				
		1	**2**	**3**	**4**	**5**
1	–	65.6	1.8	1.6	30.3	0.3
2	$NaOC_2H_4OCH_3$	95.9	0.9	1.5	–	1.7
3	$NaOC(CH_3)_3$	93.5	–	3.1	–	1.5
4	$KOC(CH_3)_3$	95.2	0.2	3.2	–	1.2
5	PhONa	91.8	4.7	2.0	–	1.5
6	Et_3N	70.0	2.3	2.4	25.0	0.3

All reactions were carried out at 20°C and additive/SMEAH=0.14.
[a] Product ratio was determined by GC.

more precisely the selectivity, the products were treated with aqueous hydrochloric acid solution to hydrolyze the enamine, and then were re-extracted with organic solvent at pH 8.5, taking advantage of the difference in pK_a between **1** (pK_a≅10) and secondary amines (pK_a≅12) (Scheme 4).

The reduction of SMEAH modified with piperidine slightly improved the product ratio to 3.3 while a non-cyclic base, such as diethylamine, gave poor selectivity (2.3) (entries 3 and 4). Among the secondary amines, the five-membered base, pyrrolidine (entry 5) gave remarkable selectivity (23.7), although a large amount of other by-products were formed. This combination was named Red-ALP.

The structure of the major and minor by-products was identified as pyrrolidinylmethyl product (**4**) and amide (**5**), respectively, by ^{1}H NMR and mass spectroscopic analysis. A detailed scheme of Red-ALP reduction for the ester **2** is shown in Scheme 5.

1.1. Minimization of the pyrrolidinylmethyl product

Considering commercial scale production, the reaction solvent was changed from THF to *t*-butyl methyl ether (MTBE) (Table 2, entry 1). Under these conditions the aldehyde/alcohol selectivity slightly improved, although the pyrrolidinylmethyl by-product **4** increased to 30%. We also noticed that the yield of **4** varied from 30 to 3% from lot to lot of SMEAH. Therefore, we suspected that a key factor was present in the reagent itself.

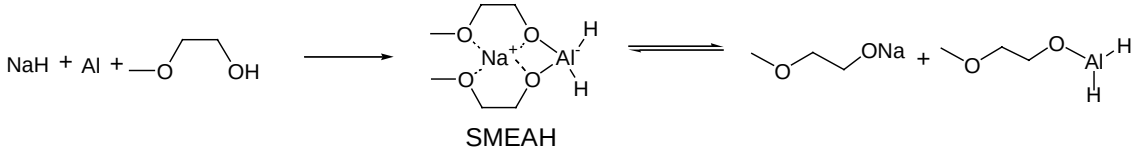
As shown in Scheme 6, SMEAH is manufactured from NaH, Al and 2-methoxyethanol, and has been reported to take a number of forms through equilibriums.[13] The equilibrium shown in the right hand appeared to be less plausible, but seemed to be worthy of consideration. We hypothesized that an excess or shortage of one of the components in the equilibrium may contribute to the differences in yield of by-product **4**.

To test this hypothesis, $NaOCH_2CH_2OCH_3$, one of the possible species in the reagent, was added to the reducing agent. This resulted in complete suppression of the formation of **4** (entry 2). Commercially available alkaline bases such as sodium *tert*-butoxide and potassium *tert*-butoxide (KTB) were examined and found to have the same effect (entries 3 and 4). Sodium phenoxide, a weaker base, showed also a similar effect (entry 5), whereas triethylamine could not suppress the formation of the by-product **4** (entry 6). Among the alkaline bases, KTB was chosen as the most suitable additive considering its availability, cost and solubility in organic solvents like THF.

1.2. Optimization of the reaction conditions

The reaction conditions such as reagent ratios, reaction temperature, and solvent were optimized. First, the amount of KTB was investigated. As shown in Table 3, the molar ratio of KTB against SMEAH was varied from 1 to 28% molar (entries 1–4). The formation of the by-product **4** at 1% molar was 3.5%, and from 7 to 14% molar was almost suppressed. On the other hand, when 28% molar KTB was used, the reaction did not reach completion. Seven percent molar was concluded to be the most suitable ratio.

Secondly, the addition sequence was examined. When Red-ALP was added to a mixture of **2** and KTB in MTBE, the



Scheme 6.

Table 3. Optimization of reduction conditions

Entry	Pyrrolidine/SMEAH	SMEAH/**2**	Temp. (°C)	$KOC(CH_3)_3$/SMEAH (mol%)	Product ratio[a] (%)				
					1	**2**	**3**	**4**	**5**
1	1.05	1.4	20	1	92.5	–	2.7	3.5	1.2
2	1.05	1.4	20	7	94.4	–	4.2	–	1.6
3	1.05	1.4	20	14	90.0	1.5	3.3	0.2	1.8
4	1.05	1.4	20	28	72.5	21.5	3.3	–	2.3
5[b]	1.05	1.4	20	14	77.0	2.3	14.0	–	1.3
6[c]	1.05	1.4	10	14	52.3	0.5	6.5	17.2	1.3
7	1.15	1.7	20	7	96.3	0.8	1.0	–	1.3
8	1.25	2.0	20	7	95.0	0.6	1.4	–	2.9
9	1.50	2.8	20	7	95.4	–	1.2	–	3.1
10	1.25	2.0	10	7	97.7	–	1.0	0.4	1.3
11	1.25	2.0	0	7	97.2	–	1.1	–	1.3
12[d]	1.15	1.5	10	7	97.5	–	0.9	–	1.4
13[e]	1.05	1.4	10	7	88.5	0.6	3.4	3.3	1.7
14[f]	1.05	1.4	10	7	95.5	0.2	0.9	0.5	1.9

[a] Product ratio was determined by GC.
[b] KTB was added to a solution of **2** in MTBE.
[c] Addition order was reversed.
[d] Total amount of the reaction was reduced by 1/3 (to 3.6 volume of **2** from 11.4 volume).
[e] Toluene was used as solvent.
[f] THF was used as solvent.

production of **4** was suppressed to zero while the aldehyde/alcohol selectivity decreased to 5.5 (entry 5). When the order of addition was reversed, a higher ratio of **4** was produced (entry 6). These results indicated that KTB interacts with SMEAH to prevent the formation of the by-product.

Next, we investigated the ratio between pyrrolidine and SMEAH (entries 2, 7–9). As the ratio of pyrrolidine was increased, alcohol **3** slightly declined, amide **5** slightly increased, and more SMEAH was needed to complete the reaction. From the practical viewpoint, the use of an excess of pyrrolidine was thought to be more advantageous because it gave a clear solution while Red-ALP at the ratio of 1.05 gave a cloudy suspension. We thus concluded that 1.15–1.25 was the most adequate ratio.

To optimize the reaction temperature, the reaction was carried out at 20, 10, 0°C (entries 8, 10 and 11). At 20°C, slightly more alcohol (**3**) was produced than under the other conditions. The most adequate temperature was determined to be 10°C. Further efforts to minimize the amount of reaction solvent led us to the optimal reaction conditions (entry 12).

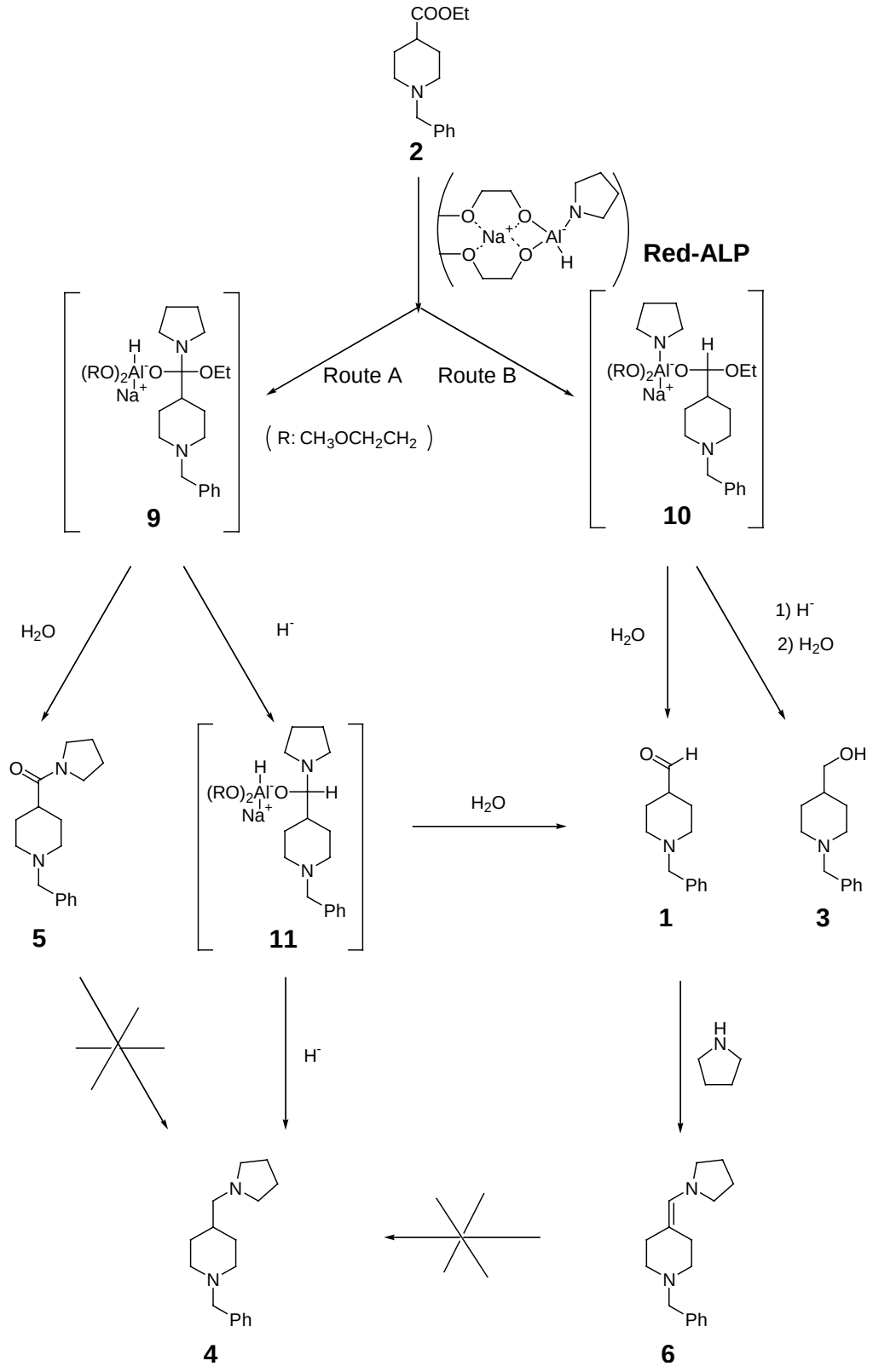
Concerning the reaction solvent, toluene did not deter the formation of **4** and seemed to increase the formation of alcohol **3**, as KTB was insoluble (entry 13). THF gave results similar to those of MTBE, however, a larger amount of solvent like MTBE was necessary to extract the products (entry 14). We could not find any merits for THF, and concluded that MTBE was the best solvent for the reaction.

Overall, we optimized the reaction conditions and manufactured the key intermediate aldehyde **1** up to a 250 kg scale.

1.3. Effect of alkaline bases on Red-ALP reduction

To elucidate the role of KTB, we draw the most plausible mechanism for Red-ALP reduction in Scheme 7. As Mukaiyama[10] described for the mechanism of aluminum hydride-*N*-methylpiperazine reduction system, the reaction between Red-ALP and the ester **2** could proceed in two different ways to provide intermediates (**9**) and (**10**). In route A, Red-ALP would simply act as a Lewis acid toward the ester **2** to form the adduct **9**. The hydrolysis of the intermediate **9** would give the amide **5**, and the reduction of **9** with intra- or intermolecular hydride would give rise to another intermediate (**11**), which could be hydrolyzed into the aldehyde **1**. In route B, Red-ALP would act as a reducing agent by passing its hydride to the ester **2** to form the intermediate **10**. The hydrolysis of **10** would give the aldehyde **1** and the alcohol **3**. The enamine (**6**) could be formed from **1** and pyrrolidine as already mentioned. This scheme suggests three candidates which could yield **4**: the amide **5**, the enamine **6**, and the intermediate **11**. To identify the real intermediate, the candidates were reduced with Red-ALP. The reduction of the amide **5** with Red-ALP gave the amine **4** and **1**, however, since only trace amounts of the amide **5** were detected in the Red-ALP reaction, we concluded that the amide **5** was less likely to be the intermediate. The reduction of the enamine **6** with Red-ALP did not give **4**, thus eliminating this as a possible route. Although it was difficult to obtain direct evidence, the overreduction of **11** appeared to be the most likely mechanism for the formation of **4**.

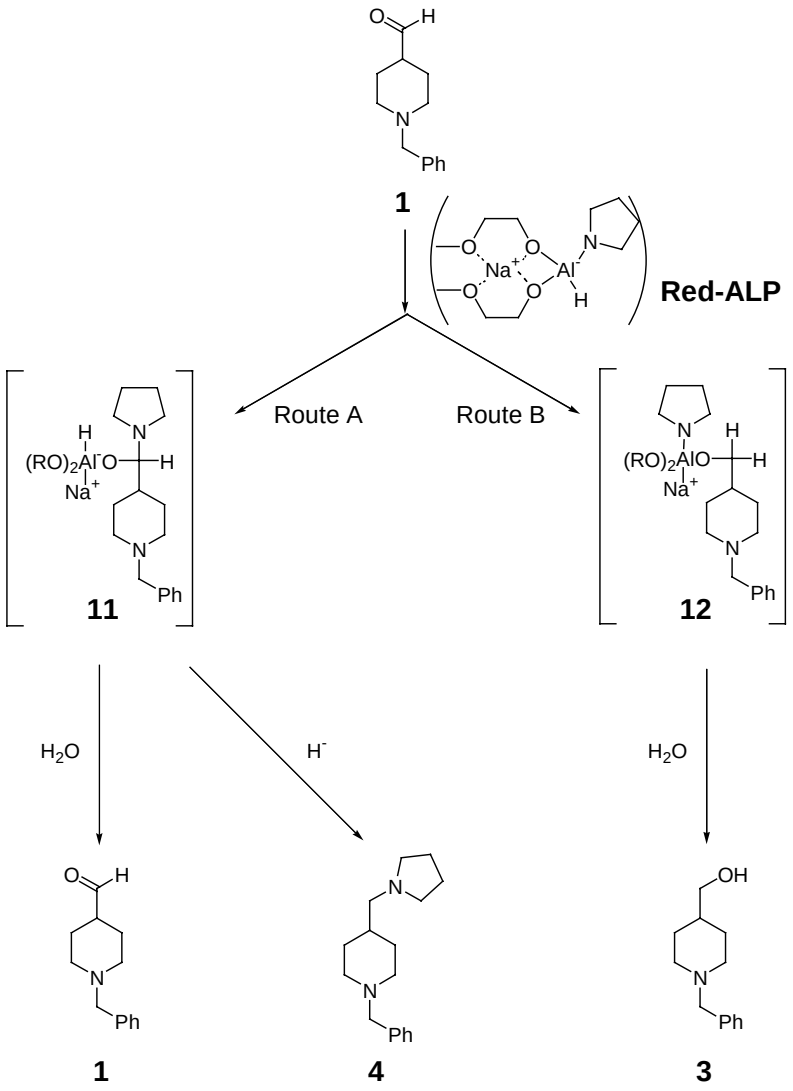
In order to confirm this hypothesis, the aldehyde **1** was reacted with Red-ALP. Scheme 8 illustrates a possible scheme for the reaction. The reaction between **1** and Red-ALP would probably give two intermediates, **11** and **12**. From the intermediate **11**, the aldehyde **1** and by-product **4** could be obtained. On the other hand, intermediate **12** would give the alcohol **3**. GC analysis of the reaction mixture showed a 48:26:25 mixture of **1**, **3**, **4** as expected (Table 4, entry 1). When additional 0.5 equiv. of Red-ALP was added to the reaction mixture of entry 1, the amount of alcohol **3** did not change and the amount of **4** increased,



Scheme 7.

whereas **1** decreased (entry 2). This indicated that the extra amount of Red-ALP reduced the intermediate **11** exclusively to give **4**. Thus, the overreduction of **11** by Red-ALP is the more plausible route for the formation of the pyrrolidinylmethyl by-product **4**.

However, the above mechanism is not enough to explain the effect of alkaline bases. Considering the components of SMEAH, we postulated that two kinds of active species might be present in SMEAH. One is aluminum trialkoxide, which could be formed if sodium is deficient in SMEAH and



Scheme 8.

Table 4. Reduction of **2** with Red-ALP

Entry	Red-ALP (equiv.)	Product ratio[a] (%)		
		1	**3**	**4**
1	1.0	48	26	25
2	Entry 1+0.5	29	24	47

[a] Product ratio was determined by GC.

would work as a Lewis acid in the reaction. The other is trivalent aluminum hydride as already shown in Scheme 6 (Table 5).

To verify our thesis, we investigated the effect of several Al compounds which were analogous species present in SMEAH. When aluminum tri(isopropoxide), a Lewis acid-type compound, was added to the Red-ALP reduction, although the reaction did not reach completion, 47.8% of by-product **4** was produced (entry 2). The addition of both

Table 5. Effects of additional aluminum compounds on the Red-ALP reduction of **2**

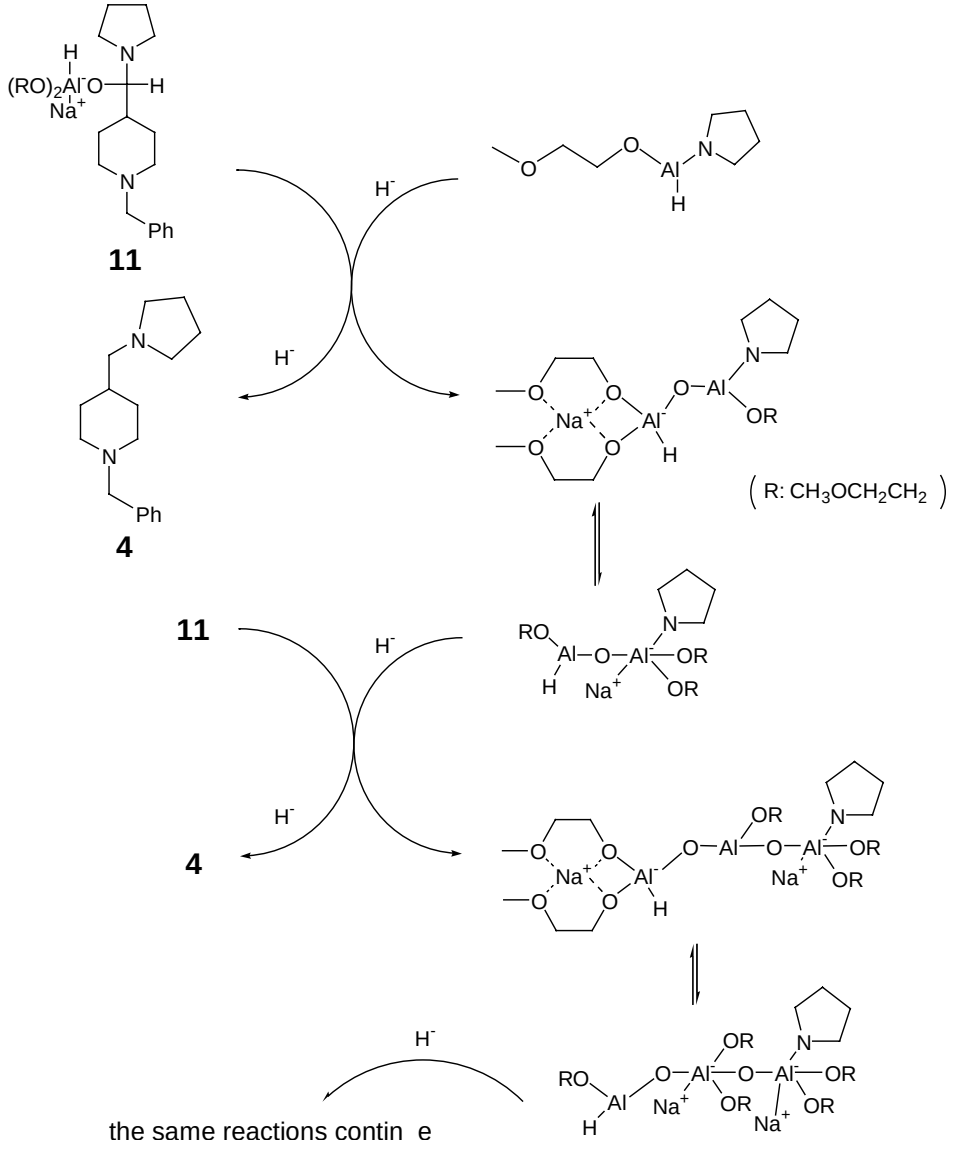
Entry	Time (h)	Additive (additive/SMEAH)	Product ratio[a] (%)				
			1	**2**	**3**	**4**	**5**
1	3	–	65.6	1.8	1.6	30.3	0.3
2	2	$Al(O\text{-}iPr)_3$ (0.14)	37.7	10.8	2.5	47.8	1.9
3		$KOC(CH_3)_3$ (0.07)	96.5	–	2.2	–	1.3
4	1	Entry 3+$Al(O\text{-}iPr)_3$ (0.21)	96.5	–	2.3	–	1.3
5	3	Entry 3+Red-ALP (0.7)	58.2	–	6.7	33.8	1.4
6	1	Entry 3+DIBAL-H (0.07)	67.9	–	6.7	24.6	1.7

[a] Product ratio was determined by GC.

aluminum tri(isopropoxide) and KTB (entry 4) caused complete suppression of by-product, similar to the result obtained without aluminum tri(isopropoxide) (entry 3). Thus, a Lewis acid type compound affected the Red-ALP reduction, but did not promote the formation of **4**. When further Red-ALP (1.0 equiv.) was added to the reaction of entry 3, the amount of **4** rose from 0 to 33.8%, indicating the presence of an active species (entry 5). The addition of 0.1 equiv. of DIBAL-H, a trivalent aluminum hydride, to the reaction mixture of entry 3 increased the content of **4** from 0 to 24.6% within 1 h, which revealed that the active species was a trivalent aluminum hydride (entry 6).

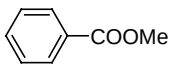
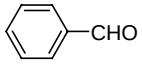
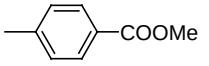
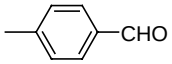
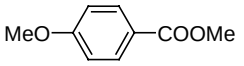
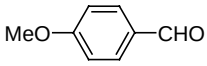
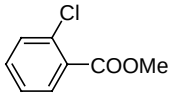
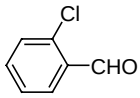
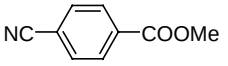
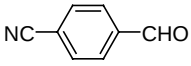
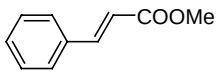
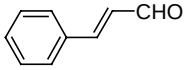
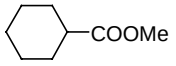
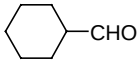
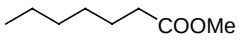
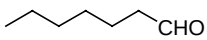
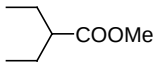
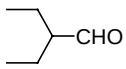
The putative mechanism of formation of the by-product is outlined in Scheme 9. The chain reaction could start with a small amount of trivalent aluminum hydride compound present in the reagent that is active enough to reduce the intermediate **11** to give **4**. After the reaction, the reagent could lose its hydride but maintain its trivalent form. The trivalent aluminum hydride could be regenerated through equilibrium to reduce another molecule **11**. The effect of KTB or other alkaline bases as deterrents of overreduction could be attributed to the transformation of the trivalent aluminum hydride to quadrivalent aluminum hydride, which might be too weak to reduce the intermediate **11**.

Lastly, we explored the scope of this new reduction system. Table 6 shows a summary of the results obtained. In general, benzoic acid esters could be transformed to their corresponding aldehydes in excellent yields, regardless of the electron withdrawing or donating substituents. The Red-ALP KTB system gave a similar yield to that of the SMEAH-*N*-methylpiperazine system[9] (entry 2), indicating that benzoic acid esters can be reduced to aldehydes with either reducing agent effectively. For aliphatic carboxylic acid esters, the Red-ALP KTB system also proved to be effective. The low yield of 2-ethylbutylaldehyde was attributed to its high solubility in water which made it difficult to extract efficiently (entry 11). On the contrary, the Red-ALP KTB system was not effective for cinnnamic acid esters due to the formation of a complex mixture (entry 9).



Scheme 9.

Table 6. Reduction of other substrates with Red-ALP in the presence of KTB

Entry	Substrate	Product	yield (%)
1			93[b]
2[a]			97[b]
3			97[b]
4			100[b]
5			98[b]
6			85[b]
7			39[b]
8			97[c]
9[d]			82[c]
10			70[c]
11			58[c]

[a] *N*-Methylpiperazine was used as the base. [b]Determined by HPLC. [c]Determined by GC. [d]In the absence of KTB. Reaction conditions and procedures are described in Section 2.

In summary, we established a viable synthetic process for the manufacture of the key intermediate aldehyde **1** for donepezil hydrochloride using a new selective reducing agent, SMEAH modified with pyrrolidine. Furthermore, we proposed the mechanism of overreduction to give the pyrrolidinylmethyl by-product **4**, and revealed the versatility of the new reducing system to other substrates. We believe that our findings could provide a new useful method for the transformation of ester to aldehyde and promote further understanding of the complex reducing agent, SMEAH.

2. Experimental

2.1. General

EI-MS and FAB-MS were obtained with a JEOL JMS HX100. ^{1}H and ^{13}C NMR spectra were measured on a JEOL JNM-α600 using tetramethylsilane as an internal standard. GC conditions were as follows (column: DB-1, column length: 30 m, ID: 0.25 μm, initial temperature: 150°C, final temperature.: 250°C, temperature rate: 5°C/min, initial time: 10 min, final time: 5 min, injection temperature: 250°C, detector temperature: 300°C, injection volume: 2 μL, total flow: ca 60 mL/min, split rate: 1/80, HEWLETT PACKARD 5890 SERIES II). All esters, aldehydes, and alcohols used as substrates, products and authentic samples in Table 6 were obtained from Tokyo Chemical Industry.

2.1.1. *N*-Benzyl-4-ethoxycarbonylpiperidine (2). In a 200 L reactor was placed INPE (165 kg, 1051 mol) and $NaHCO_3$ (89 kg, 1059 mol) in 50% EtOH/H_2O (284 L). To the mixture was added dropwise benzyl chloride (133 kg, 1051 mol) over 1 h at 40°C. After stirring for 2 h at 80°C, *n*-hexane (295 L) and H_2O (295 L) were added, and the organic layer was separated, washed with H_2O (295 L) and concentrated in vacuo to give 241.6 kg of **2** in 93% yield. This product was used for the next step without purification. Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J*=7 Hz, 3H), 1.70–1.90 (m, 4H), 1.95–2.05 (m,

2H), 2.12–2.32 (m, 1H), 2.80–2.90 (m, 2H), 3.48 (s, 2H), 4.12 (q, J=7 Hz, 2H), 7.20–7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.19, 28.28, 41.23, 52.91, 60.22, 63.24, 126.94, 128.16, 129.05, 138.41, 175.25. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.88; H, 8.43; N 5.65. Found: C, 72.84; H, 8.56; N, 5.66.

2.2. Screening of secondary amines

Typical procedure. A solution of *N*-methylpiperazine (2.00 g, 20 mmol) in THF (5 mL) was added dropwise to a 66% toluene solution of SMEAH (20 mmol) in THF (20 mL) around −20°C over 5 min, and the mixture was stirred at room temperature for 1 h. The prepared reducing agent was added dropwise to a solution of **2** (2.48 g, 10 mmol) in THF (10 mL) with ice-cooling over 1 h. After 2 h, the reaction mixture was quenched with 2N NaOH, and extracted with MTBE (100 mL). The organic layer was separated, extracted with 2N HCl solution (20 mL), and the pH of the mixture was adjusted to ca 8.5 with K_2CO_3 solution. The organic layer was subjected to GC analysis.

2.2.1. *N*-Benzyl-4-formylpiperidine (1). *Reduction of (2) without KTB*. In a 200 mL reactor was placed a 66% toluene solution of SMEAH (31.0 g, 101.9 mmol) in MTBE (109 mL) under a nitrogen atmosphere. To the solution was added dropwise a solution of pyrrolidine (7.6 g, 107.0 mmol) in MTBE (25 mL) at −20 and −5°C, and stirred overnight at 20°C to prepare the Red-ALP solution.

In a 300 mL four necked-flask was placed **2** (18.0 g, 72.8 mmol) in MTBE (72 mL). To this solution was added dropwise the prepared Red-ALP solution at 20°C, followed by stirring for 2 h. The reaction mixture was quenched with 4N NaOH solution (86 mL) at 15°C. The aqueous layer was separated, washed with 4N NaOH solution (11 mL) and H_2O (86 mL). To the organic layer was added a solution of conc. HCl (18 mL) in H_2O (68 mL) pre-cooled in an ice-bath at ca. 15°C and stirred for 0.5 h. Then, the pH of the mixture was adjusted with 8N NaOH (16 mL) solution to 8.5. The organic layer was separated, washed with H_2O (61 mL) twice and concentrated in vacuo to give crude 14.1 g of **1** in 95% yield. The mixture ratio was determined by GC. **1/2/3/4/5**=65.6:1.8:1.6:30.3:0.3.

Retention time of each compound: **1**=14 min, **2**=20 min, **3**=16 min, **4**=25 min, **5**=32 min, **6**=26 min.

2.2.2. *N*-Benzyl-4-hydroxymethylpiperidine (3). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21–1.35 (m, 2H), 1.42–1.56 (m, 1H), 1.69 (d, J=12 Hz, 2H), 1.90–2.03 (m, 2H), 2.90 (d, J=12 Hz, 2H), 3.46 (d, J=7 Hz, 2H), 3.49 (s, 2H), 7.20–7.36 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.76, 38.53, 53.39, 63.44, 67.79, 126.89, 128.09, 129.21, 138.34. Anal. Calcd for $C_{13}H_{19}NO$: C, 75.81; H, 9.31; N, 6.83. Found: C, 76.06; H, 9.33; N, 6.82. Mass 206 $(M+H)^+$.

2.2.3. *N*-Benzyl-4-(pyrrolidin-1-ylmethyl)piperidine (4). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.35 (m, 4H), 1.40–1.55 (m, 1H), 1.70–1.85 (m, 4H), 1.90–2.03 (m, 2H), 2.29 (d, J=7.3 Hz, 2H), 2.42–2.48 (m, 4H), 2.88 (d, J=11.7 Hz, 2H), 3.49 (s, 2H), 7.20–7.36 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.38, 31.11, 35.35, 53.75, 54.61, 63.13, 63.54, 126.82, 128.07, 129.23, 138.52. Mass 258 $(M+H)^+$.

2.2.4. *N*-Benzyl-4-(pyrrolidin-1-ylcarbonyl)piperidine (5).[14] White wax; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70–2.10 (m, 8H), 2.25–2.40 (m, 1H), 2.85–3.05 (m, 2H), 3.35–3.60 (m, 6H), 3.45 (s, 2H), 7.20–7.45 (m, 5H).

2.2.5. *N*-Benzyl-4-(pyrrolidin-1-ylmethylene)piperidine (6). Colorless oil as a mixture of **1** and **6**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60–1.80 (m, 8H), 2.35–2.45 (m, 4H), 2.70–2.95 (m, 2H), 2.95–3.02 (m, 2H), 3.43–3.44 (m, 2H), 5.67 (s, 1H), 7.20–7.40 (m, 5H).

2.2.6. 1-Benzyl-4-formylpiperidine (1). *Reduction of (2) in the presence of KTB*. In a 500 L reactor was placed a 66% toluene solution of SMEAH (221 kg, 723 mol) in MTBE (242 L) under a nitrogen atmosphere. To the solution was added dropwise a solution of pyrrolidine (60 kg, 838 mol) in MTBE (64 L) at −20°C to −5°C, and the resulting mixture was stirred overnight at around 20°C. Then KTB (5.8 kg, 52.1 mol) in THF (14.8 L) was added in one portion and stirred for 1 h, to give a clear solution of Red-ALP-KTB.

In a 1030 L reactor was placed **2** (120 kg, 485 mol) in MTBE (130 L). To the solution was added dropwise the Red-ALP-KTB agent below 15°C, followed by stirring for 1 h. The mixture was quenched with 4N NaOH solution (572 L) at 15°C. The organic layer was separated, washed with 4N NaOH solution (146 L) and H_2O (580 L). To the organic layer was added a solution of conc. HCl (118 L) in H_2O (448 L) below ca. 15°C and was stirred for 0.5 h. Then the pH of the mixture was adjusted with 25% NaOH solution (117 L) to 8.5–8.7. The organic layer was separated, washed with H_2O (428 L) and concentrated in vacuo to give crude 94.5 kg of **1** in 95% yield. This product was purified by reduced pressure distillation (bp 130–134°C/1 mmHg) to give **1** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62–1.74 (m, 2H), 1.83–1.92 (m, 2H), 2.06–2.14 (m, 2H), 2.18–2.26 (m, 1H), 2.77–2.85 (m, 2H), 3.49 (s, 2H), 7.20–7.35 (m, 5H), 9.64 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.43, 47.98, 52.45, 63.21, 127.00, 128.17, 129.03, 138.24, 203.99. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.66; H, 8.40; N, 6.88. Found: C, 76.81; H, 8.43; N, 6.89.

2.3. Reduction of other substrates

Typical procedure. A solution of pyrrolidine (1.1 g, 15.4 mmol) in MTBE (3.3 mL) was added dropwise to a 66% toluene solution of SMEAH (14.7 mmol) in MTBE (8.9 mL) around −20°C over 20 min and stirred at room temperature for 1 h. A solution of KTB (16.5 mg, 1.47 mmol) in THF (0.7 mL) was added to the mixture. The above reducing agent was added dropwise to a solution of methyl 4-methylbenzoate (1.1 g, 7.3 mmol) in MTBE (4.0 mmol) around 10°C over 1 h and stirred for 2 h. The reaction mixture was quenched with 2N HCl (80 mL) and the organic layer was separated. The content of 4-methylbenzaldehyde was determined by HPLC using authentic material.

For entries 1–7, the reactions were carried out in a similar

manner to that described above and the yields were calculated by HPLC using authentic samples.

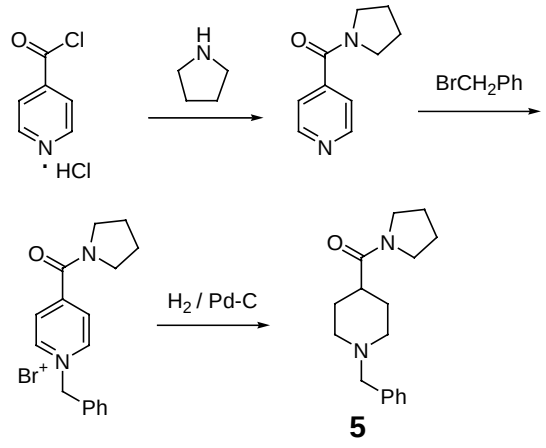
For entries 8–11, the yields were calculated by GC using authentic samples.

HPLC conditions; L-column (4.6 mm×250 mm), Detection 254 nm, flow rate=1.0 mL/min, mobile phase; for entries 1,2,3,5,7; $CH_3CN/H_2O/70\%HClO_4$=400:600:1, and for entries 4,6; CH_3OH/H_2O=750:250.

GC conditions; column: DB-1, column temperature: 100°C, injection temperature: 160°C, detector temperature: 160°C, other conditions were the same as those described in the general procedure.

References

1. Sugimoto, H.; Tsuchiya, Y.; Sugumi, H.; Higurashi, K.; Karibe, N.; Iimura, Y.; Sasaki, A.; Kawakami, Y.; Nakamura, T.; Araki, S.; Yamanishi, Y.; Yamatsu, K. *J. Med. Chem.* **1990**, *33*, 1880–1887.
2. Sugimoto, H.; Tsuchiya, Y.; Sugumi, H.; Higurashi, K.; Karibe, N.; Iimura, Y.; Sasaki, A.; Araki, S.; Yamanishi, Y.; Yamatsu, K. *J. Med. Chem.* **1992**, *35*, 4542–4548.
3. Sugimoto, H.; Iimura, Y.; Yamanishi, Y.; Yamatsu, K. *J. Med. Chem.* **1995**, *38*, 4821–4829.
4. As of 31 July, 2000.
5. Sugimoto, H.; Tsuchiya, Y.; Higurashi, K.; Karibe, N.; Iimura, Y.; Sasaki, A.; Yamanishi, Y.; Ogura, H.; Araki, S. EP 296560 A2; *Chem Abstr.* **1989**, *110*, 173102.
6. Hermans, B.; Van D, P. *Chem Abstr.* **1969**, *70*, 57585.
7. Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, *2*, 109.
8. Chen, Y. L. EP 441517 A2; *Chem Abstr.* **1991**, *115*, 232222.
9. Kanazawa, R.; Tokoroyama, T. *Synthesis* **1976**, 526–527.
10. Muraki, M.; Mukaiyama, T. *Chem. Lett.* **1975**, 875–878.
11. Muraki, M.; Mukaiyama, T. *Chem. Lett.* **1974**, 1447–1450.
12. Muraki, M.; Mukaiyama, T. *Chem. Lett.* **1975**, 215–218.
13. Cerny, Z. *J. Organomet. Chem.* **1996**, *516*, 115–122.
14. The authentic sample was prepared by the following route.



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