

complexes as well as into an acetyl palladium(II) trifluoroacetato complex.

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Systematic Study on Bis(dialkylamino) aluminum Hydride: Reexamination of the Reagents for Reduction of Carboxylic Acids to Aldehydes

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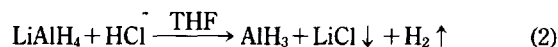
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Some twenty years ago, Muraki and Mukaiyama first prepared various bis(dialkylamino)aluminum hydride and applied them for the reduction of carboxylic acid derivatives to aldehydes.¹ Among the series of reagents, bis(*N*-methylpiperazinyl)aluminum hydride (BMPA) was shown to be the most effective for such conversions. Again, Wiemer and his co-workers confirmed that BMPA is a convenient reagent for the direct reduction of carboxylic acids to aldehydes.²

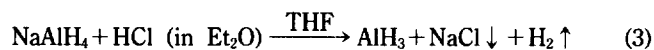
The procedure for the synthesis of the reagents essentially involved the preparation of aluminum hydride solution in THF. The aluminum hydride solution was prepared by treatment of a standardized solution of lithium aluminum hydride in THF with a theoretical quantity of 100% sulfuric acid¹ (eq. 1) or hydrogen chloride² (eq. 2). Even though these procedures provide a pure aluminum hydride solution in THF,



there have been faced problems: some resistance to use of 100% sulfuric acid with lithium aluminum hydride and the solubility of lithium chloride in THF. Lithium chloride dissolves easily in THF to give solution of ~1 M.³ In addition to that, the characterization of aminoaluminum hydrides thus prepared has not been carried out: no systematic study on the preparation of the reagent has been reported.^{1,2}

Consequently, there has been a need for development of a general procedure for the preparation of pure bis(dialkylamino)aluminum hydride reagents with various dialkylamines of different steric environments. In this study, we carried out the systematic study on the preparation of pure solution of bis(dialkylamino)aluminum hydride in THF and re-examined some representative reagents for the reduction of carboxylic acids to aldehydes.

We used sodium aluminum hydride instead of lithium aluminum hydride in the synthesis of a solution of aluminum hydride in THF. The reaction of sodium aluminum hydride in THF and hydrogen chloride in diethyl ether gives an aluminum hydride solution in diethyl ether and THF with a fine solid of sodium chloride³ (eq. 3). The solid slowly settles upon standing.



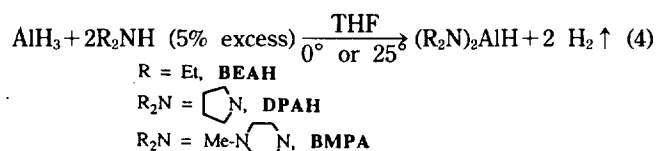
The procedure of a mixed solvent of THF and diethyl ether should not cause any difficulty in typical reactions.^{4,5} However, in this study, we utilized pure aluminum hydride solutions in THF after distilling out diethyl ether in order to match our reaction conditions to those adopted by Muraki *et al.*¹ and Wiemer *et al.*²

A representative series of dialkylamines with various steric and electronic environments were selected for the present study and their reactions with aluminum hydride studied. The stability of the resulting dialkylaminoaluminum hydrides was also examined by ²⁷Al-NMR spectra and measuring the hydride concentration of the reagent solution at appropriate time intervals.

The approximate rates and stoichiometry of the reaction of aluminum hydride with 3 equiv of dialkylamines at 0 or 25 °C were examined in order to establish the generality of this synthesis of dialkylaminoaluminum hydrides. The course of the reaction was monitored by calculating the moles of hydrogen evolved. These results are summarized in Table 1. The reactivity of dialkylamines with aluminum hydride and the stoichiometry of the reaction varied markedly with the steric requirements of the dialkylamines. Thus, in those cases where the alkyl group is a less hindered straight chain, such as diethylamine, di-*n*-butylamine and di-*n*-hexylamine, the reaction evolved 2 equiv of hydrogen within 72 h at 0 or 25 °C and no further hydrogen evolution even in the presence of excess dialkylamines was apparent. However, in case where the alkyl group is a moderately hindered dialkylamine, such as diisobutylamine, the reaction was sluggish at 0 °C but evolved hydrogen slowly to reach the disubstituted stage in 120 h at 25 °C. Cyclic secondary amines,

such as pyrrolidine, piperidine, morpholine and *N*-methylpiperazine, reacted with aluminum hydride readily to evolve more than 2 equiv of hydrogen to indicate the formation of the corresponding trisubstituted derivatives both at 0 and 25 °C, except for the case of pyrrolidine at 0 °C. In these cases the disubstituted derivatives could also be obtained when the reactions were carried out with two equivalents of dialkylamines at 0 °C. Finally, the reaction with diphenylamine evolved 2 equiv of hydrogen to form the corresponding disubstituted derivative at 0 °C, but evolved more than 2 equiv of hydrogen at 25 °C.

On the basis of results in Table 1, we utilized a slight excess dialkylamines (5% excess) in the reaction with aluminum hydride under the practical condition (eq. 4), and the reaction conditions for the synthesis of some representative bis(dialkylamino)aluminum hydrides and the spectral data



are summarized in Table 2. Solution of the aminoaluminum hydrides in THF display typical absorption in the IR: a strong absorption around 1820 cm⁻¹, attributed to the Al-H stretching vibration. The ²⁷Al-NMR spectra of the reagent solutions exhibit a broad singlet peak around δ 130 downfield region relative to [Al(H₂O)₆]³⁺ as a reference. All the reagents examined were stable for an extended period of time provided that the THF solutions of reagents were maintained under a positive pressure of nitrogen at 0°: during the period, no significant change in the hydride concentration was observed.

Table 1. Reaction of Aluminum Hydride with Excess Secondary Amines^a in Tetrahydrofuran

| Amine | Reaction temp. (°C) | Reaction time (h) ^b | | | | | | | |
|----------------------------|---------------------|--------------------------------|------|------|------|------|------|------|-------|
| | | 0.5 | 1.0 | 3.0 | 6.0 | 12.0 | 24.0 | 72.0 | 120.0 |
| Diethylamine | 0 | 1.54 | 1.68 | 1.92 | 2.00 | 2.00 | | | |
| | 25 | 1.78 | 1.84 | 1.98 | 2.00 | 2.00 | | | |
| Di- <i>n</i> -butylamine | 0 | 1.32 | 1.44 | 1.63 | 1.82 | 1.83 | 1.87 | 1.99 | 1.99 |
| | 25 | 1.66 | 1.72 | 1.85 | 1.93 | 1.98 | 2.00 | 2.00 | |
| Diisobutylamine | 0 | 0.91 | 0.97 | 0.99 | 1.07 | 1.08 | 1.13 | 1.27 | 1.38 |
| | 25 | 1.24 | 1.42 | 1.58 | 1.60 | 1.64 | 1.73 | 1.91 | 1.99 |
| Di- <i>n</i> -hexylamine | 0 | 1.24 | 1.43 | 1.61 | 1.73 | 1.78 | 1.84 | 1.98 | 1.99 |
| | 25 | 1.32 | 1.52 | 1.69 | 1.89 | 1.98 | 2.00 | 2.00 | |
| Pyrrolidine | 0 | 1.98 | 1.99 | 2.00 | 2.00 | | | | |
| | 25 | 2.94 | 2.98 | 3.00 | | | | | |
| Piperidine | 0 | 2.43 | 2.50 | 2.54 | 2.58 | 2.61 | 2.64 | 2.77 | |
| | 25 | 2.51 | 2.57 | 2.60 | 2.72 | 2.89 | 3.00 | | |
| Morpholine | 0 | 2.62 | 2.68 | 2.78 | 2.84 | 2.85 | 2.88 | 2.89 | |
| | 25 | 2.93 | 2.98 | 3.00 | | | | | |
| <i>N</i> -methylpiperazine | 0 | 0.98 | 1.13 | 1.34 | 2.21 | 2.46 | 2.55 | 2.70 | 2.85 |
| | 25 | 2.54 | 2.76 | 2.83 | 2.92 | 2.96 | 2.99 | | |
| Diphenylamine | 0 | 0.84 | 0.98 | 1.10 | 1.20 | 1.32 | 1.44 | 1.77 | 1.99 |
| | 25 | 1.44 | 1.55 | 1.61 | 1.64 | 1.87 | 2.33 | 2.59 | 2.71 |

^a Reacted with 3 equiv of dialkylamine. ^b Mmol of hydrogen evolved per mmol of AlH₃.

Table 2. Reaction Condition for the Synthesis of Some Representative Bis(dialkylamino)aluminum Hydrides in Tetrahydrofuran^a and Their Spectra

| (R ₂ N) ₂ AlH | Reaction temp. (°C) | Reaction time (h) | IR ν _{Al-H} , cm ⁻¹ | ²⁷ Al-NMR chemical shift ^b , δ |
|---|---------------------|-------------------|---|--|
| Bis(diethylamino)-aluminum hydride | 25 | 6 | 1822 | 129 |
| Dipyrrolidinoaluminum hydride | 0 | 6 | 1824 | 132 |
| Bis(<i>N</i> -methylpiperazino)-aluminum hydride | 0 | 12 | 1823 | 124 |

^a5% excess dialkylamine utilized. ^bChemical shifts are relative to [Al(H₂O)₆]³⁺. All spectra are broad singlet.

Table 3. Yields of Aldehydes in the Reduction of Carboxylic Acids with Bis(dialkylamino)aluminum Hydrides in Tetrahydrofuran under Reflux

| Acid | Time (h) | Yield of Aldehyde (%) ^a | | | |
|------------------------|----------|------------------------------------|------|------|------|
| | | Ratio of H ⁻ to cpd | BEAH | DPAH | BMPA |
| Caproic | 3 | 2.2 | 68 | 60 | — |
| | 6 | 2.2 | 72 | 72 | 60 |
| | 12 | 2.2 | 70 | 77 | 61 |
| | 48 | 2.2 | — | — | 62 |
| Pentadecanoic | 3 | 4.0 | 59 | 70 | 78 |
| | 6 | 2.2 | 73 | — | — |
| | 12 | 2.2 | — | 76 | — |
| | 48 | 2.2 | — | — | 69 |
| Palmitic | 3 | 4.0 | — | — | 72 |
| | 6 | 2.2 | 60 | — | — |
| | 12 | 2.2 | — | 85 | — |
| | 48 | 2.2 | — | — | 70 |
| Stearic | 3 | 4.0 | — | — | 92 |
| | 6 | 2.2 | 75 | — | — |
| | 12 | 2.2 | — | 80 | — |
| | 48 | 2.2 | — | — | 70 |
| Isovaleric | 3 | 4.0 | — | — | 90 |
| | 6 | 2.2 | 69 | — | — |
| | 12 | 2.2 | — | 43 | — |
| | 48 | 2.2 | — | — | 73 |
| Cyclopropanecarboxylic | 3 | 4.0 | — | — | 62 |
| | 6 | 2.2 | 65 | — | — |
| | 12 | 2.2 | — | 51 | — |
| | 48 | 2.2 | — | — | 61 |
| Cyclohexanecarboxylic | 3 | 4.0 | — | — | 80 |
| | 6 | 2.2 | 72 | — | — |
| | 12 | 2.2 | — | 60 | — |
| | 48 | 2.2 | — | — | 60 |
| Phenylacetic | 3 | 4.0 | — | — | 66 |
| | 6 | 2.2 | 30 | — | — |
| | 12 | 2.2 | — | 32 | — |
| | 48 | 2.2 | — | — | 35 |
| | 3 | 4.0 | — | — | 51 |

Table 3. Continued.

| | | | | | |
|-------------------------|----|-----|----|----|----|
| Diphenylacetic | 6 | 2.2 | 35 | — | — |
| | 12 | 2.2 | — | 14 | — |
| | 48 | 2.2 | — | — | 40 |
| | 3 | 4.0 | — | — | 61 |
| | 6 | 4.4 | 85 | — | — |
| | 12 | 4.4 | — | 92 | — |
| 1,10-Decanedicarboxylic | 48 | 4.4 | — | — | 92 |
| | 3 | 8.0 | — | — | 96 |
| | 3 | 2.2 | 78 | 68 | 54 |
| Benzoic | 12 | 2.2 | — | 83 | 61 |
| | 48 | 2.2 | — | — | 68 |
| | 3 | 4.0 | — | — | 88 |
| <i>o</i> -Toluic | 3 | 2.2 | 65 | — | — |
| | 12 | 2.2 | — | 45 | — |
| | 48 | 2.2 | — | — | 59 |
| | 3 | 4.0 | — | — | 67 |
| | 3 | 2.2 | 70 | — | — |
| | 12 | 2.2 | — | 50 | — |
| <i>m</i> -Toluic | 48 | 2.2 | — | — | 60 |
| | 3 | 4.0 | — | — | 70 |
| | 3 | 2.2 | 66 | — | — |
| <i>p</i> -Toluic | 12 | 2.2 | — | 71 | — |
| | 48 | 2.2 | — | — | 55 |
| | 3 | 4.0 | — | — | 67 |
| <i>o</i> -Anisic | 3 | 2.2 | 50 | — | — |
| | 12 | 2.2 | — | 48 | — |
| | 48 | 2.2 | — | — | 64 |
| | 3 | 4.0 | — | — | 74 |
| | 3 | 2.2 | 48 | — | — |
| | 12 | 2.2 | — | 56 | — |
| <i>p</i> -Anisic | 48 | 2.2 | — | — | 63 |
| | 3 | 4.0 | — | — | 72 |
| | 3 | 2.2 | 60 | — | — |
| <i>o</i> -Chlorobenzoic | 12 | 2.2 | — | 50 | — |
| | 48 | 2.2 | — | — | 74 |
| | 3 | 4.0 | — | — | 96 |
| | 3 | 2.2 | 59 | — | — |
| | 12 | 2.2 | — | 72 | — |
| | 48 | 2.2 | — | — | 45 |
| <i>p</i> -Chlorobenzoic | 3 | 4.0 | — | — | 97 |
| | 3 | 2.2 | 60 | — | — |
| | 12 | 2.2 | — | 73 | — |
| | 48 | 2.2 | — | — | 74 |
| | 3 | 4.0 | — | — | 98 |
| | 3 | 4.4 | 32 | — | — |
| Phthalic | 12 | 4.4 | — | 30 | — |
| | 48 | 4.4 | — | — | 63 |
| | 3 | 8.0 | — | — | 97 |
| Terephthalic | 3 | 4.4 | 36 | — | — |
| | 12 | 4.4 | — | 37 | — |
| | 48 | 4.4 | — | — | 61 |
| | 3 | 8.0 | — | — | 98 |

^aYields based on 2,4-dinitrophenylhydrazones.

In the reduction of carboxylic acids to aldehydes, we chose bis(diethylamino)aluminum hydride (BEAH), dipyrrolidinoaluminum hydride (DPAH) and bis(*N*-methylpiperazino)aluminum hydride (BMPA) as representatives of the aminoaluminum hydrides. The reduction with these reagents at 0° or 25 °C appeared unsatisfactory: the reaction was very slow and the yields of aldehydes were relatively low. However, refluxing the reaction mixture gave more favorable results. Accordingly, we performed all the reductions under the refluxing conditions, and the results are summarized in Table 3.

In general, the reducing power in the reduction of carboxylic acids is in order of BEAH>DPAH>BMPA. The reactions require 6, 12 and 48 h, respectively, to obtain maximum yields. All the reactions with 10% excess reagents gave moderate yields of aldehydes. There was no significant difference in the yields. However, when a large excess amount of reagent was used in the above experiment, only BMPA gave more favorable results along with the reduction rate enhancement. Such a good result under the drastic conditions is rather surprising. The yields appear to be equally satisfactory both for aliphatic and aromatic derivatives. The reaction conditions adopted by the present study are different from those described in the earlier papers.^{1,2} Even though each result can not be compared directly, the present study confirms that BMPA is a good reagent for conversion of carboxylic acids to aldehydes.

Recently, we reported various methods for the direct transformation of carboxylic acids to aldehydes.⁶⁻⁸ Among them, the 9-BBN system with metal hydrides affords the most satisfactory results.⁸ In addition to that, this work has shown that BMPA provides another useful procedure for such conversion. Furthermore, in contrast to many other commonly used procedures, the procedure for isolation of the product aldehydes is relatively straightforward.² Consequently, this method and other useful ones should combine to effect such conversions much effectively.

Experimental Section

All glassware used in this experiment was dried in a dry oven, assembled hot, and cooled with a stream of dry nitrogen. All reactions were carried out under nitrogen atmosphere. Experimental techniques used in handling air- and moisture-sensitive materials are described elsewhere.⁹ THF was dried over a 4-Å molecular sieve and distilled from sodium benzophenone ketyl just prior to use. Sodium aluminum hydride (SAH) was obtained from the Ethyl Corp. and used directly without further purification. Hydrogen chloride in diethyl ether was purchased from the Aldrich Chemical Co. or synthesized from hydrochloric acid and sulfuric acid using an automatic gasimeter. All of the dialkylamines were high grade commercial reagent and distilled after drying over KOH. ²⁷Al-NMR spectra were recorded on a Bruker WP 80 SY spectrometer and all chemical shifts were reported in δ (ppm) relative to [Al(H₂O)₆]³⁺. IR spectra were recorded on a Perkin-Elmer 1330 spectrometer.

Preparation of Aluminum Hydride in THF. The aluminum hydride solution in THF was prepared from the reaction of SAH in THF and hydrogen chloride in diethyl

ether according to the procedure described in our previous paper,³ with the exception that all the diethyl ether solvent was distilled from the solution using an aspirator. Finally, a 1.0 M solution of aluminum hydride in THF was prepared. This solution was used for further reactions.

Reaction of Aluminum Hydride with Excess Dialkylamines. The reaction of AlH₃ with 3 equiv of Et₂NH is representative. An oven-dried, 100 mL, round-bottomed flask with a sidearm, a condenser, and an adaptor was attached to a mercury bubbler. The flask was flushed with nitrogen and maintained under a static pressure of nitrogen. In the flask was placed 10.0 mL of AlH₃-THF solution (1.0 M 10.0 mmol) and the flask was brought to 0 °C by using an ice-water bath. A total of 2.20 g (30 mmol) of Et₂NH was added dropwise with stirring. The evolution of 2.00 equiv of hydrogen was observed in 6 h at 0 °C and no further hydrogen evolution was apparent. An aliquot of the resulting solution was hydrolyzed to evolve 1.00 equiv of hydrogen.

Preparation of Bis(dialkylamino)aluminum Hydride in THF. The preparation of bis(*N*-methylpiperazino)aluminum hydride (BMPA) is illustrative. In a 100 mL, round-bottomed flask was placed 100 mL of a 1.0 M solution of AlH₃ in THF (100 mmol) and the solution was kept at 0 °C by using an ice-water bath. To this solution was added 10.57 g of *N*-methylpiperazine (205 mmol) dropwise with vigorous stirring. The reaction mixture was stirred for 6 h at 0 °C until the evolution of hydrogen was complete. The resulting BMPA solution in THF was 0.8 M, and the ²⁷Al NMR spectrum of the solution showed a broad singlet at δ 124 ppm. The IR spectrum of the solution displayed a strong absorption at 1823 cm⁻¹, attributed to the Al-H stretching vibration.

General Procedure Used for Reductions. The following procedure was used for quantitative studies. The reduction of benzoic acid is described as an example of the experimental procedure. The BMPA solution, 20.0 mL of 0.8 M (16.0 mmol of the reagent), was introduced into a dried, 25 mL flask fitted with a rubber syringe cap on an inlet port, a magnetic stirring bar, and a bent adaptor connected to a mercury bubbler through a reflux condenser. The flask was immersed in a water bath, and 0.49 g of benzoic acid (4.0 mmol) in 4 mL of THF was injected slowly. One equiv of hydrogen was evolved instantly. After the evolution of hydrogen was complete, the stirred solution was heated at reflux. After 3 h, the flask was cooled down to room temperature and the residual hydride was carefully destroyed with water. The reaction mixture was then subjected to analysis with 2,4-dinitrophenylhydrazine, showing a yield of 88%.

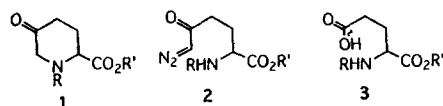
A number of carboxylic acids were reduced in the same manner described above, and the yields of aldehydes were established by the quantitative estimation of the corresponding 2,4-dinitrophenylhydrazones. The identity of the hydrazones was checked through their melting points. The yields of hydrazones are listed in Table 3.

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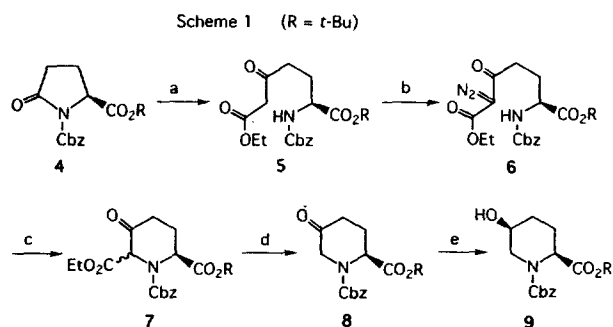
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The β -keto ester **5** prepared by the known reaction⁷ of lithium enolate of ethyl acetate with pyroglutamate **4** was treated with *p*-acetamidobenzenesulfonyl azide⁸ in the presence of Et₃N to give the corresponding α -diazo β -keto ester **6**. Cyclization of diazo compound **6** using the Rapoport protocol (refluxing benzene, 5% rhodium acetate, 30 min)⁹ gave the crude cyclized product **7**, whose IR spectrum lacked the characteristic diazo peak at 2140 cm⁻¹. Without further purification the dealkoxycarbonylation¹⁰ of **7** with LiOH hydrate in THF gave the 5-oxo-L-pipecolic acid derivative **8**. NaBH₄ reduction of **8** gave cis alcohol **9**,¹¹ which showed a complex NMR spectrum due to the presence of several rotamers. However, mass spectrum showed the correct molecular ion at *m/e* 335.



a: CH₃CO₂Et, LiN(SiMe₃)₂, THF, -78 °C, 67%. b: *p*-AcNHC₆H₄SO₂N₃, Et₃N, CH₃CN, 86%. c: 5% Rh₂(OAc)₄, benzene, reflux. d: LiOH·H₂O, THF, 58%. e: NaBH₄, EtOH, 93%.

A Convenient Synthesis of 5-Oxo-L-pipecolic Acid Derivative from L-Glutamic Acid

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2-Pipecolic acid derivatives are currently drawing interest since they can serve as starting materials for potential enzyme (e.g. protein kinase C) inhibitors,¹ synthetic drugs and natural products such as the immunosuppressant FK506,² the antifungal antibiotics demethoxyrapamycin³ and mycotoxic alkaloid verruculotoxin.⁴ Therefore many synthetic efforts have been devoted to the preparation of 2-pipecolic acid derivatives.⁵ Previously, we reported that 5-oxo-L-pipecolic acid derivatives **1** can be prepared by rhodium(II) acetate catalyzed cyclization of diazoketones **2** derived from L-glutamic acids **3**.^{5e} However, one drawback of this approach lies in the use of explosive and toxic diazomethane for the conversion of **3** to **2**, which is not suitable for scale-up. We thought that α -diazo β -keto ester **6**, prepared by the diazo transfer reaction of β -keto ester **5**, can be used as an alternative substrate for the rhodium-catalyzed cyclization, as shown in Scheme 1.⁶ In this note we report that this approach can be successfully utilized for the preparation of **1**.

In summary, we have achieved a short, straightforward synthesis of **8** from L-glutamic acid, which is amenable to scale-up and adaptable for the synthesis of pipecolic acids protected with other groups.

Experimental Section

***t*-Butyl L-N-Benzyloxycarbonylpyroglutamate (4)**. was prepared according to the known procedure¹² from L-N-benzyloxycarbonylglutamic acid in 64% yield, mp 48-50 °C (lit.¹² mp 48-52 °C); *R*_f=0.67 (hexane:ethyl acetate=1:1); [α]_D²⁰ = -39.4 (c=2.21, CH₂Cl₂) [lit.¹² [α]_D²⁰ = -36.9 (c=4.5, CH₂Cl₂); ¹H NMR (200 MHz, CDCl₃) δ 7.4-7.3 (m, 5H), 5.29, 5.26 (AB q, 2H, *J*=12 Hz), 4.55 (dd, 1H, *J*=3, 9 Hz), 2.7-2.5 (m, 2H), 2.45-2.25 (m, 1H), 2.1-2.0 (m, 1H), 1.39 (s, 9H); ¹³C NMR (50.3 MHz, CDCl₃) δ 173.0 (CO₂-*t*-Bu), 169.9, 150.7 (NHCO₂Bn), 134.9, 128.4, 128.2, 128.0, 82.3 (CO₂CMe₃), 68.0 (OCH₂Ph), 59.2, 30.8, 27.6, 21.7.

1-*t*-Butyl 7-ethyl 2-L-(benzyloxycarbonyl)amino-5-oxopimelate (5). A solution of ethyl acetate (2.11 g, 24 mmol) in dry THF (40 mL) was treated with 1 M lithium bis(trimethylsilyl)amide in THF (24 mL, 24 mmol) at -78 °C. After stirring for 30 min a solution of pyroglutamate **4** (2.55 g, 8.0 mmol) in THF (10 mL) was added dropwise to the above solution and the whole mixture was stirred for 30 min. TLC showed the absence of starting material. The reaction mixture was quenched with sat NH₄Cl (3 mL) at