Organic Process Research & Development **2009,** *13,* 1141–1144

# Short and Efficient Process for the Synthesis of *trans*-4-Aminocyclohexanecarboxylic Acid Derivatives

Pankaj S. Patil, Ulhas S. Mahajan, Swapnil P. Sonawane,* and Mukund K. Gurjar

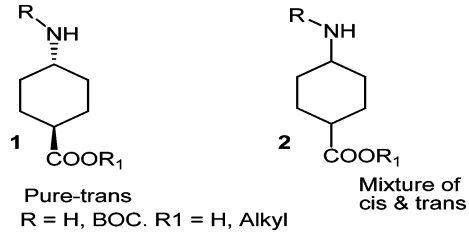
*API R & D Centre, Emcure Pharmaceuticals Ltd., ITBT Park, Phase-II, MIDC, Hinjewadi, Pune - 411057, India*

**Abstract:**

**This contribution relates to an industrially feasible process for the preparation of isomerically pure *trans*-4-amino-1-cyclohexanecarboxylic acid derivatives that are useful building blocks in the synthesis of several pharmacologically active compounds such as glimepiride, L-370518.**

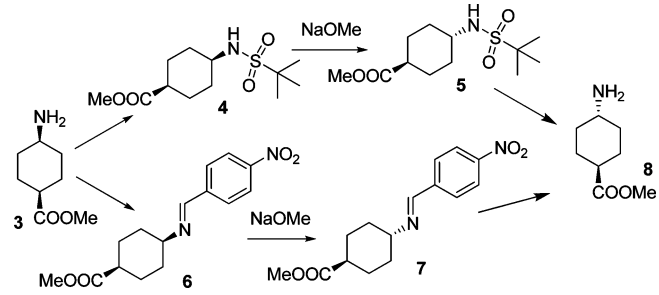
## Introduction

Derivatives of *trans*-4-amino-1-cyclohexanecarboxylic acid (**1**) are known to possess many biological properties. The antihypertensive activity, particularly the prevention and treatment of coronary, cerebral and renal circulatory diseases is most pronounced. 4-Amino-1-cyclohexanecarboxylic acid-derived agents are also useful as neuropeptideYY antagonists,[1] thrombin inhibitors[2] and pesticides.[3]




A literature study reveals very few approaches for preparing the stable *trans*-isomer of 4-amino-1-cyclohexanecarboxylic acid[4a–f] some of which are illustrated in Scheme 1. A straightforward approach for the *trans*-isomer was selective aromatic ring hydrogenation of ethyl 4-hydroxybenzoate with a rhodium catalyst to give a (83:17) *cis*−*trans* mixture of ethyl-4-hydroxycyclohexylcarboxylate,[5] followed by nucleophilic displacement of hydroxyl group with ammonia to give *trans*-4-aminobenzoic acid as a major product. To avoid the use of an expensive rhodium catalyst, hydrogenation was tried with Raney

***Scheme 1***




Ni, Pt/C or Pd/C. However, mixtures of isomers were formed. Due to presence of the ester functionality, epimerization in favor of the *trans*-isomer was reported.[9] Moreover, fractional crystallization of the *trans*-isomer of 4-aminocyclohexanecarboxylic acid methyl ester from the *cis*−*trans* mixture was demonstrated by Aldrich et al.[6]

Aldrich et al. observed that, after repeated crystallization and purification of the isomeric mixture, the *trans*-isomer was isolated with a maximum 90% isomeric purity in 18% yield. In 1988, Toyoshima et al.[7] and Shigetaka et al.[8] independently disclosed that the process for partial epimerization of the pure *cis*-isomer of 4-cyclopropylcyclohexanecarboxylic acid methyl ester to the desired *trans*-isomer could be accomplished by heating, or in combination with sodium hydride under inert and anhydrous atmosphere. This method afforded 80% *trans* product with 70% isomeric purity. The use of stringent conditions and high reaction temperature were the limiting factors of this process. An epimerization process is also described by Masaki et al.[9] using alkali and alkaline earth metals, which provided an equilibrium mixture (80:20) in favor of the desired *trans*-isomer. Recently, Kawanish et al.[10] reported an efficient process for methyl *trans*-4-aminocyclohexanecarboxylic acid, **8**, by epimerization of the *N*-sulphonyl or *N*-benzylidene derivative of the *cis*-isomer of 4-amino-1-cyclohexanecarboxylate using sodium methoxide (Scheme 1, compounds **4** and **6**).

## Results and Discussion

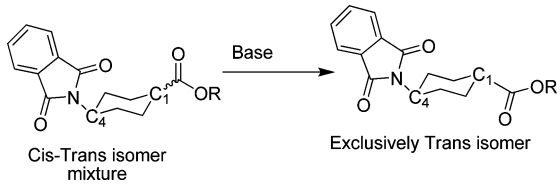
In spite of many strategies being explored towards obtaining *trans*-4-amino-1-cyclohexanecarboxylic acid, **8**, we hoped to develop an alternate method which would be amenable for large-scale production.

* Author to whom correspondence may be sent. Fax: +91-20-39821445. E-mail: Swapnil.Sonawane@emcure.co.in.

(1) Norikazu, O.; Yoshio, O. U.S. Patent 2008161326, 2008.
(2) Cutrona, K. J.; Sanderson, Philip, E. J. *Tetrahdron Lett.* **1996**, *37*, 5045–5048.
(3) Takashi, I.; Akihito, M. U.S. Patent 5,831,118, 1998.
(4) (a) Palaima, A. I. et al., *Bulletin of the Academy of Sciences of the USSR. Division of Chemical Science.*, **1977**; Vol. 26, No. 1. (b) Karpavichyus, K. I.; Kosykhova, L. A.; Pikshilingaite, Yu.-V. K.; Mikul′′skis, P. P.; Knunyants, I. L. *Russ. Chem. Bull.* **1987**, *36*, 1896–1899. (c) Wright, K.; Sarciaux, M.; de Castries, A.; Wakselman, M.; Mazaleyrat, J. P.; Toffoletti, A.; Corvaja, C.; Crisma, M.; Peggion, C.; Formaggio, F.; Toniolo, C. *Eur. J. Org. Chem.* **2007**, *19*, 3133–3144. (d) Ge, P.; Russell, R. A. *Tetrahedron* **1997**, *53*, 17469–17476. (e) Larsen, C. D. *J. Am. Chem. Soc.* **1938**, *60*, 2341–2343. (f) Schneider, W.; Dillmann, R. *Chem. Ber.* **1963**, *96*, 2377–2386.
(5) Wayne, T. World Patent WO05/019221, 2005.
(6) Snyder, K. R.; Murray, T. F.; DeLander, G. E.; Aldrich, J. V. *J. Med. Chem.* **1993**, *36*, 1100–1103.
(7) Shigeshi. T.; Yoshiko. S.; Hisashi S.; Koji, T.; Izumi K. K. U.S. Patent 4,816,484, 1989.
(8) Shigetaka, H.; Tsunenori, F.; Kaoru, K. JP 56120636, 1981.
(9) Fujimoto, M. JP 60258141, 1985.
(10) Yasuyuki, K.; Masaaki, U.; Munenori, M. U.S. Patent 7,314,950, 2005.

10.1021/op900195w CCC: $40.75 
Published on Web 10/14/2009

***Scheme 2***



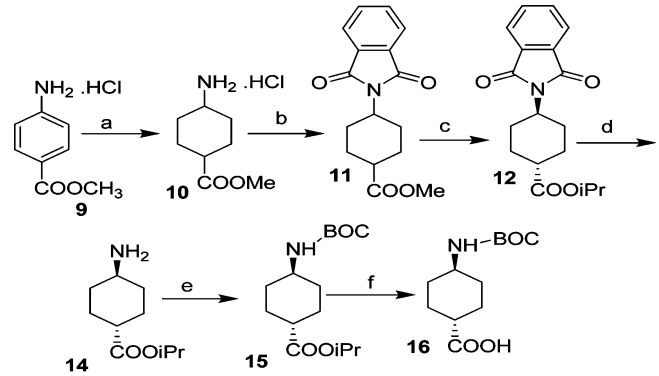

In order to achieve a stereoselective approach to *trans*-4-aminocyclohexanecarboxylic acid, we aimed at starting with a readily accessible substrate, which would be easily converted to the desired *trans*-compound under mild reaction conditions. To achieve our goal, we investigated the use of a phthalimido group as a protecting group for *trans*-4-amino-1-cyclohexanecarboxylate. The intention behind the selection of the phthalimido group of C4-carbon, (Scheme 2) was based on a thought that it will try to remain at an equatorial position so that isomerization can be effectively achieved at the C1 carbon using a base at the ester functionality as shown in Scheme 2.

This task was executed by constructing a phthalimido ring onto the amino group of methyl 4-aminocyclohexanecarboxylate hydrochloride, **10** (*cis*−*trans* isomer), in 75% yield.

This was carried out by reacting phthalic anhydride in toluene under reflux in the presence of triethylamine (Scheme 3). Starting amine hydrochloride, **10**, was obtained by aromatic ring reduction of commercially available methyl 4-aminobenzoate hydrochloride, **9**, via hydrogenation using Pt/C catalyst. After having substrate **11** in hand, our ultimate goal was to find optimized reaction conditions for the critical isomerization conversion. Keeping in mind that organic nucleophilic base such as monomethylamine will hydrolyze the phthalimido group of **11**, our first attempt was to use a strong, non-nucleophilic organic base, such as DBU, triethyl amine, Hunig's base in various solvents and reaction conditions. Unfortunately, the first attempt with DBU was unsuccessful; hence, we have not used other non-nucleophilic organic bases. The results are summarized in Table 1 (entries 1−3).

Substrate **11** was found to be inert towards methanol, toluene and THF with DBU under reflux conditions (Table 1, entries 1−3).

***Scheme 3.*** **Reaction pathway for the synthesis of *trans*-4-*tert*-butoxycarbonylamino-1-cyclohexane carboxylic acid (16)**



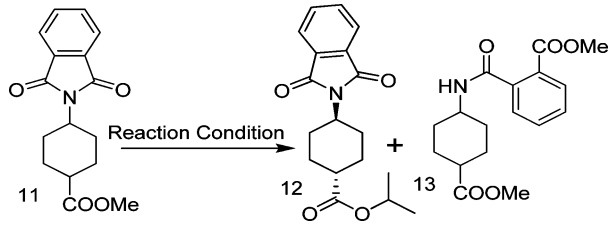

Reaction condition: a) Pt/C, MeOH, $H_2$, 60°C, b) Phthalic anhydride, toluene, $Et_3N$, reflux, c) KO*t*Bu, IPA, 65°C, d) $NH_2$-$NH_2$, MDC/MeOH, RT, e) $(BOC)_2O$, $Et_3N$, MeOH, RT, f)MeOH, Aq. NaOH, RT.

Our next set of conditions was based on the use of alkoxides such as sodium methoxide and potassium *tert*-butoxide. Unfortunately when we performed the reaction on substrate **11** using sodium methoxide in methanol at reflux temperature, the phthalimido ring of **11** was opened, and we ended up with partially hydrolyzed product **13** as shown in Table 1 (entries 4−6). Having these results in hand, we turned our attention toward the use of a bulkier base such as potassium *tert*-butoxide in isopropanol as solvent for isomerization of methyl 4-phthalimidocyclohexanecarboxylate; fortunately, this condition afforded *trans* esterified product with isomerization in 70% yield with isomeric purity of 99.7% (Table 1, entry 7).

Encouraged by the above result, we studied optimized reaction conditions for isomerization with respect to solvents and mole ratio of potassium *tert*-butoxide. The results are cited in Table 2 (entries 1−6).

Finally, we could get an optimized reaction condition using 0.5 equiv of potassium *tert*-butoxide in isopropyl alcohol at 65 °C for the isomerization of methyl 4-phthalimidocyclohexanecarboxylate (**11**), which furnished the desired isopropyl *trans*-4-phthalimidocyclohexanecarboxylate **12** with *trans*-esterifica-

***Table 1.*** **Study of various bases for isomerization**[a]




| rxn | reaction conditions | % isolated yield **12** | % isolated yield **13** | recovered **11** (%) | *cis:trans* ratio[d] |
|---|---|---|---|---|---|
| 1 | $CH_3OH$, DBU, 65 °C,8 h | —[b] | —[b] | 78 | — |
| 2 | toluene, DBU, 110 °C,8 h | —[b] | —[b] | 80 | — |
| 3 | THF, DBU, 66 °C, 8 h | —[b] | —[b] | 82 | — |
| 4 | $CH_3OH$, $NaOCH_3$, 65 °C,6 h | — | quantitative | —[c] | 70:30 |
| 5 | toluene, $NaOCH_3$, 80 °C,5 h | — | quantitative | —[c] | 70:30 |
| 6 | THF, $NaOCH_3$, 65 °C,3 h | — | quantitative | —[c] | 70:30 |
| 7 | IPA, KO*t*Bu, 65 °C,4 h | 70 | — | —[c] | 0.30:99.70 |

[a] Reactions were carried out on 5 mmol scale using 1.0 equiv of base wrt **11**. [b] No reaction. [c] Starting material quantity is specified only when it exceeds 30%. [d] Isomeric purity was calculated by $^1$H NMR and HPLC.

***Table 2.*** **Optimization of solvent and molar ratio wrt 11 for isomerization[a]**

| rxn | mol equiv | reaction conditions | yield[b] **12** (%) | recovered **11** (%) | *cis:trans* ratio[d] |
|---|---|---|---|---|---|
| 1 | 1.0 | IPA, 25 °C, 24 h | NA | 80 | − |
| 2 | 0.5 | IPA, 65 °C, 3 h | 70 | − | 0.30:99.70 |
| 3 | 0.25 | IPA, 65 °C, 8 h | 40 | −[e] | 0.30:99.70 |
| 4 | 0.5 | IPA, 65 °C, 8 h | −[c] | 72 | − |
| 5 | 0.5 | toluene, 65 °C, 8 h | −[c] | 60 | − |
| 6 | 0.5 | THF, 65 °C, 8 h | −[c] | 67 | − |

[a] Reactions were carried out on 5 mmol scale using KO*t*Bu. [b] Isolated yields using column chromatography. [c] Trace amount of product. [d] Isomeric purity was calculated by $^1$H NMR and HPLC. [e] Unreacted starting material quantity is specified only when it exceeds 30%.

tion in 70−75% yield with 99.7% isomeric purity as shown by HPLC (Table 2, entry 2).

Subsequently, the *N*-phthalimido group of isopropyl *trans*-4-pthalimidocyclohexanecarboxylate (**12**) was easily deprotected using hydrazine hydrate with quantitative yield to provide the pure *trans*-amino compound (**14**), which on protection using BOC anhydride gave *N*-BOC-isopropyl ester (**15**) in 97.4% yield followed by basic hydrolysis to end up with *N*-BOC-cyclohexanecarboxylic acid (**16**) in 88% yield (Scheme 3).

## Conclusion

Looking at prior articles the process disclosed by us for the synthesis of *trans*-4-aminocyclohexanecarboxylic acid is short, efficient and cost-effective. The overall yield was found to be 68−72% with enhanced isomeric purity. Potassium *tert*-butoxide was shown to be a useful base for the isomerization of methyl-4-phthalimidocyclohexanecarboxylate (**11**) to desired *trans*-isomer in good yields with excellent isomeric purity. We feel that the process may be commercially feasible.

## Experimental Section

All materials were purchased from commercial suppliers. Unless specified otherwise, all reagents and solvents were used as supplied by manufacturers. Melting points were determined by open air capillary with an X-6 melting point apparatus, Beijing Tech instrument Co Ltd., and are uncorrected. $^1$H NMR spectra (400 MHz) and $^{13}$CNMR spectra (100 MHz) were recorded in $CDCl_3$, DMSO-$d_6$, and mass spectra were determined on API-2000LCMS mass spectrometer, Applied Biosciences. HPLC system was Symmetry C18 (4.6 mm × 250 mm) 5 $\mu$, 1.5 mL/min, 205 nm; mobile phase 1.0 mL phosphoric acid in 100 mL of water with pH adjusted to 3.0 using triethylamine.

**Preparation of Methyl 4-Aminocyclohexanecarboxylate Hydrochloride (10).** Methyl-4-aminobenzoate hydrochloride **9** (10.0 kg, 5.33 mol) and methanol (110 L) were mixed together in an autoclave under nitrogen atmosphere at room temperature. Pt/C (100 g, 10% w/w) was added under a nitrogen atmosphere. The autoclave was heated to 60−65 °C at 7−8 kg/cm$^2$ hydrogen pressure for 6−8 h until consumption of the starting material was observed (reaction monitored by TLC analysis). The reaction mass was removed from the autoclave, and Pt/C was filtered through a Hyflo bed. The filtered methanol was distilled under reduced pressure. Dichloromethane (25 L) was added to the residue; concentration of the mother liquor gave crude methyl 4-aminocyclohexanecarboxylate hydrochloride (**10**), which was then crystallized from ethyl acetate (80 L) (Yield 7.4 kg, 71.7%). An analytical sample was obtained by column chromatography.

MS(CI): calcd for $C_8H_{15}NO_2$ HCl (M + H) *m/z*: 158.21; found (M + H) *m/z*: 158.2; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 1.47−1.65 (m, 5H), 1.79−1.82 (m, 2H), 1.97 (m, 3H), 2.08−2.32 (m, 7H), 3.1 (br s, 1H), 3.2 (br s, 1H), 8.2 (d, 4H). Anal. for $C_8H_{15}NO_2$ HCl. Calcd C, 61.12; H, 9.62; N, 8.91. Found C, 60.81; H, 9.02; N, 8.94.

**Preparation of Methyl 4-Phthalimidocyclohexanecarboxylate (11).** Methyl 4-aminocyclohexanecarboxylate hydrochloride **10** (10 kg, 5.17 mol), toluene (100 L) and phthalic anhydride (99.5 kg, 6.71 mol) were mixed at room temperature. Triethylamine (13 kg, 12.92 mol) was added dropwise over a period of 30 min at room temperature. The reaction mass was refluxed for 5−6 h by removing water azeotropically using a Dean−Stark apparatus. After completion of the reaction (monitored by TLC), toluene was distilled below 50 °C under reduced pressure. DM water (130 L) was added and stirred for 30 min at ambient temperature, after which methyl 4-phthalimidocyclohexacarboxylate **11** was isolated by filtration (Yield 11.1 kg, 75%). An analytical sample was obtained by column chromatography.

MS (CI): calcd for $C_{16}H_{17}NO_4$ (M + H) *m/z*: 288.32; found (M + H) *m/z*: 288.3. Off-white solid, mp: 130−132 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 1.57−1.62 (m, 4H), 1.65 (m, 1H), 2.12 (m, 1H), 2.28−2.33 (m, 4H), 4.12 (m, 1H), 7.68−7.75 (m, 2H), 7.80−7.83 (m, 2H). Anal. for $C_{16}H_{17}NO_4$. Calcd C, 66.89; H, 5.96; N, 4.87. Found C, 66.77; H, 5.93; N, 4.86.

**Preparation of Isopropyl *trans*-4-Phthalimidocyclohexanecarboxylate (12).** Isopropyl alcohol (100 L) and methyl 4-phthalimidocyclohexanecarboxylate, **11** (10.0 kg, 3.48 mol), were mixed together, and potassium *tert*-butoxide (1.954 kg, 1.74 mol) was added to the mixture at ambient temperature. The reaction mixture was stirred for 2−3 h at 60−65 °C. After completion of the the reaction (monitored by TLC), the pH was adjusted to 7 by using acetic acid at room temperature. The precipitated solid was stirred for 30 min at 10−12 °C; the resultant precipitated solid was filtered, washed with isopropyl alcohol (5 L) and dried at 40−45 °C to get pure product. **12** was isolated and then filtered and washed with isopropyl alcohol (5 L) and dried at 40−45 °C (Yield 7.7 kg, 70.64%). An analytical sample was obtained by column chromatography. MS (CI) calcd for $C_{18}H_{21}NO_4$ (M + H) *m/z* 316.37, found (M + H) *m/z*: 316.3. White solid, mp: 120−122 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 1.22 (d, 6H), 1.65 (m, 2H), 1.75 (m, 2H), 2.11 (m,2H), 2.24 (m,3H), 4.11 (m, 1H), 4.98 (sep,1H), 7.69 (d, 2H), 7.81 (d, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 21.76, 28.39, 28.57, 42.17, 49.79, 67.38, 123.03, 131.93, 133.82,

168.25, 174.84. Anal. for $C_{18}H_{21}NO_4$: Calcd C, 68.55; H, 6.71; N, 4.44. Found C, 68.27; H, 6.67; N, 4.42.

**Preparation of Isopropyl *trans*-4-Amino-1-cyclohexanecarboxylate (14).** Isopropyl *trans*-4-phthalimidocyclohexanecarboxylate, **12** (10 kg, 3.17 mol), was added to a solution of methanol (60 L) and dichloromethane (25 L) at ambient temperature. Hydrazine hydrate (11.1 kg, 19.04 mol) in DM water (50 L) was added dropwise at 25−30 °C under stirring. The reaction mass was stirred for 12−14 h, and the solid was filtered off. DM water (20 L) was added to the filtrate; the dichloromethane layer was separated and concentrated under reduced pressure to give isopropyl *trans*-4-amino-1-cyclohexanecarboxylate **14** (Yield 5.4 kg, 93.1%). An analytical sample was obtained by column chromatography. MS (CI) calcd for $C_{10}H_{19}NO_2$ (M + H) *m/z* 186.27, found (M + H) *m/z*: 186.2. White solid, mp: 89 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 1.11 (m, 2H), 1.22 (d, 6H), 1.37 (m, 2H), 1.48 (m, 2H), 1.98 (m, 4H), 2.16 (m, 1H), 2.65 (m, 1H), 4.98 (Sep, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 21.50, 27.62, 35.37, 42.50, 49.50, 49.61, 66.92, 175.08. Anal. for $C_{10}H_{19}NO_2$: Calcd C, 64.83; H, 10.34; N, 7.56. Found C, 64.63; H, 10.28; N, 7.53.

**Preparation of *trans*-Isopropyl-(4-*tert*-butoxycarbonylamino)-1-cyclohexanecarboxylate (15).** Isopropyl *trans*-4-aminocyclohexanecarboxylate **14** (10 kg, 5.40 mol) was dissolved in methanol (80 L), at ambient temperature. Triethylamine (7 kg, 7.02 mol) was added dropwise at 25−30 °C under stirring. BOC anhydride (11.78 kg, 5.40 mol) in methanol (20 L) was added at 25−30 °C under stirring at 25−30 °C. Reaction mass was stirred for 3−4 h. After completion of the reaction (monitored by TLC) methanol was removed under vacuum completely. DM water (40 L) was added and extracted with dichloromethane (2 × 25 L). The combined dichloromethane layer was dried over sodium sulfate and concentrated under reduced pressure at 40−45 °C to give a white solid, **15** (Yield 15 kg, 97.4%). An analytical sample was obtained by column chromatography. MS (CI) calcd for $C_{15}H_{27}NO_4$ (M + H) *m/z* 286.39, found (M + H)*m/z*: 286.39. White solid, mp: 86−87 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 1.13−1.14 (d, 6H), 1.36 (s, 9H), 1.76−1.82 (m, 4H), 2.12 (m, 1H), 3.16 (m, 1H), 4.82−4.88 (sep, 1H), 6.76 (d, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 21.65, 27.27, 27.65, 28.29, 32.38, 42.49, 48.84, 67.25, 78.95, 155.05, 174.84. Anal. for $C_{15}H_{27}NO_4$: Calcd C, 63.13; H, 9.54; N, 4.91. Found C, 63.01; H, 9.51; N, 4.90.

**Preparation of *trans*-4-*tert*-Butoxycarbonylamino-1-cyclohexanecarboxylic Acid (16).** *trans*-Isopropyl-(4-*tert*-butoxycarbonylamino)-1-cyclohexanecarboxylate, **15** (10 kg, 3.5 mol), was added to methanol (50 L) at 25−30 °C under constant stirring. Sodium hydroxide (3.5 kg, 8.75 mol) in DM water (15 L) was added slowly at 25−30 °C with constant stirring. The reaction mixture was stirred for 11−12 h at 25−30 °C. After completion of the reaction (monitored by TLC) DM water (90 L) and MDC (50 L) were added; the aqueous layer was separated and cooled to below 15 °C under constant stirring. (The MDC layer was discarded.) The pH of the aqueous layer was adjusted to 5−6 with acetic acid (∼14 L) under constant stirring at below 15 °C. During the pH adjustment solid material separated out from the reaction mixture. Precipitated solid was filtered and dried under vacuum to give white to off-white *trans*--*N*-BOC acid, **15** (yield 7.5 kg, 88%). An analytical sample was obtained by column chromatography. MS (CI) calcd for $C_{12}H_{21}NO_4$ (M + H) *m/z* 243.31, found (M − H) *m/z* 242.31. Mp: 181−182 °C (Lit.[11] 182−185 °C). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 1.13 (m, 2H), 1.47 (s, 9H), 1.57 (m, 2H), 2.01 (m, 4H), 2.26 (t, 1H), 3.41 (br s, 1H), 4.41 (m, 1H), 5.3 (br s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 27.59, 28.35, 32.36, 42.24, 48.87, 76.68, 79.27, 155.15, 181.06. Anal. for $C_{12}H_{21}NO_4$: Calcd C, 59.24; H, 8.70; N, 5.76. Found C, 59.12; H, 8.68; N, 5.74.


## Acknowledgment

We thank Mr. Samit Mehta, our management and the IPM group of Emcure Pharmaceuticals Ltd. for their generous support and constant encouragement. Finally, it is a pleasure to acknowledge the reviewers for their suggestions.


## Supporting Information Available

Additional characterization data of compounds **10**−**12** and **14**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.


Received for review July 28, 2009.

OP900195W



(11) Bin, H.; Crider, A. M.; Stables, J. P. *Eur. J. Med. Chem.* **2001**, *36*, 265–28.