Pergamon

Tetrahedron 54 (1998) 2619–2630

TETRAHEDRON

Synthesis of 3,3-Dimethylazetidine-2-carboxylic Acid and Some Derivatives

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Received 7 November 1997; revised 23 December 1997; accepted 8 January 1998

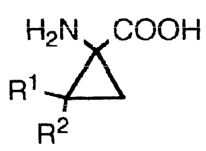
Abstract : γ-Chloro-α-(N-alkylimino)esters were reduced by sodium cyanoborohydride in methanol in the presence of acetic acid with complete selectivity to give rise to either γ-chloro-α-(N-alkylamino)esters (reaction at 0°C) or 1-alkyl-3,3-dimethylazetidine-2-carboxylic esters (reaction at reflux). The isolable γ-chloro-α-(N-alkylamino)esters are suitable sources for 1-(N-alkylamino)-2,2-dimethylcyclopropane-1-carboxylic esters via base-induced 1,3-dehydrochlorination, while the former substrates as transient species undergo 1,4-dehydrochlorination to the corresponding azetidines. The latter process was used for the synthesis of 3,3-dimethylazetidine-2-carboxylic acid, a new non-proteinogenic sterically hindered α-amino acid, via hydrogenolysis of methyl 1-benzyl-3,3-dimethylazetidine-1-carboxylate and subsequent acidic hydrolysis. Reduction of alkyl 4-chloro-3,3-dimethyl-α-(N-alkylimino)butanoates with lithiumaluminiumhydride in diethyl ether afforded 1-alkyl-3,3-dimethyl-2-(hydroxymethyl)-azetidines. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

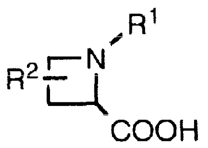
Small ring α-amino acids have been the subject of considerable research in the last decade because of the physiological activities associated with these derivatives. Small ring as well as azacyclic α-amino acids received considerable attention in this respect. 1-Aminocyclopropane-1-carboxylic acids **1-3** have been studied intensively in relation to the unsubstituted α-amino acid **1**, i.e. 1-aminocyclopropane-1-carboxylic acid (ACC), which is omnipresent in plants and which is converted in plants into ethylene by the ethylene forming enzyme via an oxidative decarboxylation process.[1,2] Ethylene is a major natural plant growth regular and is responsible for the germination of seeds, flowering, fruit and leaf drop, and ripening of fruits.[1,2] In general, ethylene is responsible for all factors associated with the senescence of plants. Consequently, a great number of efforts have

PII: S0040-4020(98)00024-6

been devoted to the synthesis of ACC derivatives because of their potential plant growth regulating activity.[3-13] Additionally, ring substituted ACC derivatives **2** and **3** constitute sterically constrained α-amino acids which have an interest in peptide chemistry because of their potential to alter conformations of peptides containing these ACC derivatives. Accordingly, such peptides have been studied as potential enzyme inhibitors. The latter research led to the synthesis of peptide mimetics resistant to proteolytic cleavage.[14-18]



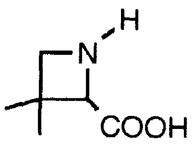
1 $R^1 = R^2 = H$
2 $R^1 \neq H$; $R^2 = H$
3 R^1 and $R^2 \neq H$



4 $R^1 = R^2 = H$
5 $R^1 \neq H$; $R^2 = H$
6 $R^1 = H$; $R^2 \neq H$

Azetidine-2-carboxylic acid **4** and its derivatives **5** are frequently observed in a number of plant sources such as the Liliaceae, Solanaceae, Fagaceae, Fabaceae, Chenopodiaceae and red marine algae.[19,20] Several of these natural derivatives are phytosiderophores, i.e. low molecular weight chelators, which promote uptake and transport of iron in higher plants under iron-deficient conditions.[21] The antifungal antibiotics of the polyoxin group, for example polyoxine A, contain polyoximic acid, an azetidine-2-carboxylic acid, as structural unit.[22] Other azetidine carboxylic acids, also including compounds carrying the carboxyl group at positions different from the α-position, have been shown to display growth regulator activity and male sterilizing activity in cereals,[23-30] while cis-azetidine-2,4-dicarboxylic acid has been reported as a neurotransmitter potentiator.[31, 32]

Cyclopropaneamino acids have become increasingly important as mimics for naturally occurring amino acids. The same is valid for their azetidine based α-amino acids as a result of some special structural features.[33] Peptides containing such small ring amino acids are expected to show improved metabolic stability since tertiary amide bonds are resistant to proteolysis. The reduced conformational space can lead to altered selectivity, while increased ring strain can prove useful for the design of novel peptide-based enzyme inhibitors as exemplified for ACC.[34] While now a number of syntheses on cyclopropanecarboxylic acids **2** and **3** have been published in recent years, few synthetic methods are available for azetidine-2-carboxylic acids.[19,20,35-37]



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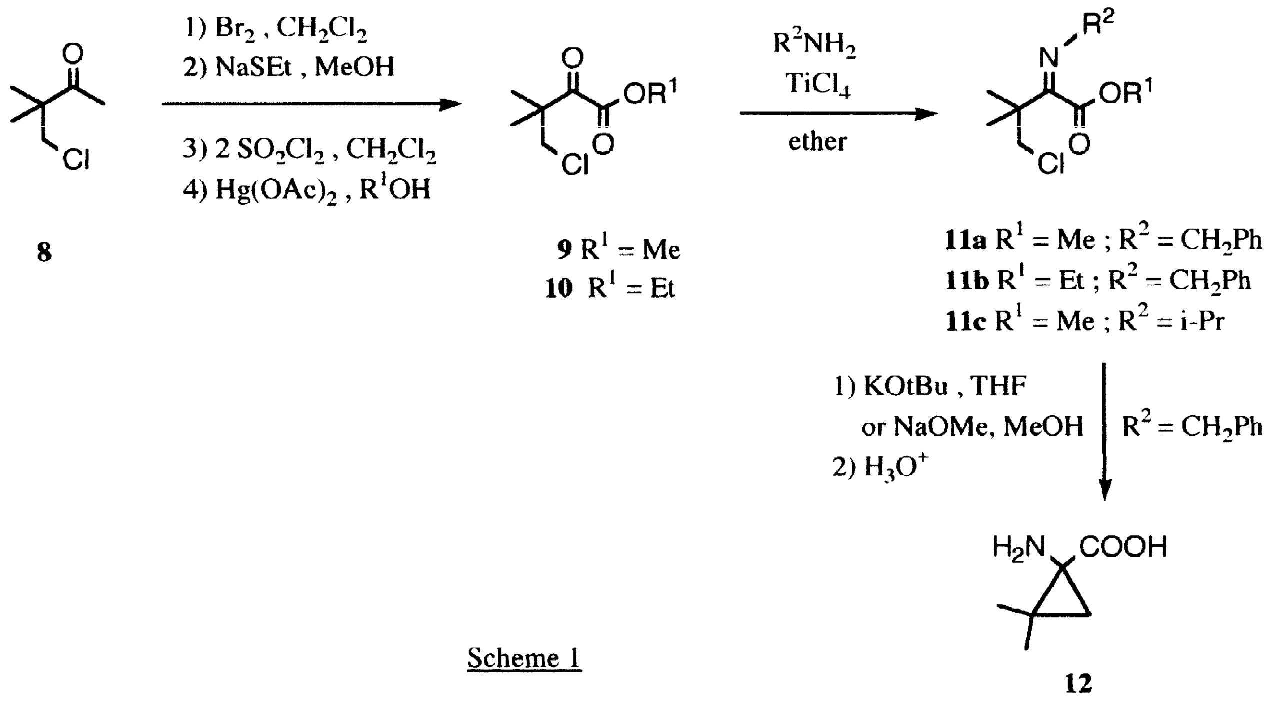
In the present paper, a suitable access to 3,3-dimethylazetidine-2-carboxylic acid **7**, a new small ring unnatural α-amino acid with a sterically hindering geminal dimethyl unit, via selective elaboration of γ-chloro-α-iminocarboxylic esters is disclosed.

RESULTS AND DISCUSSION

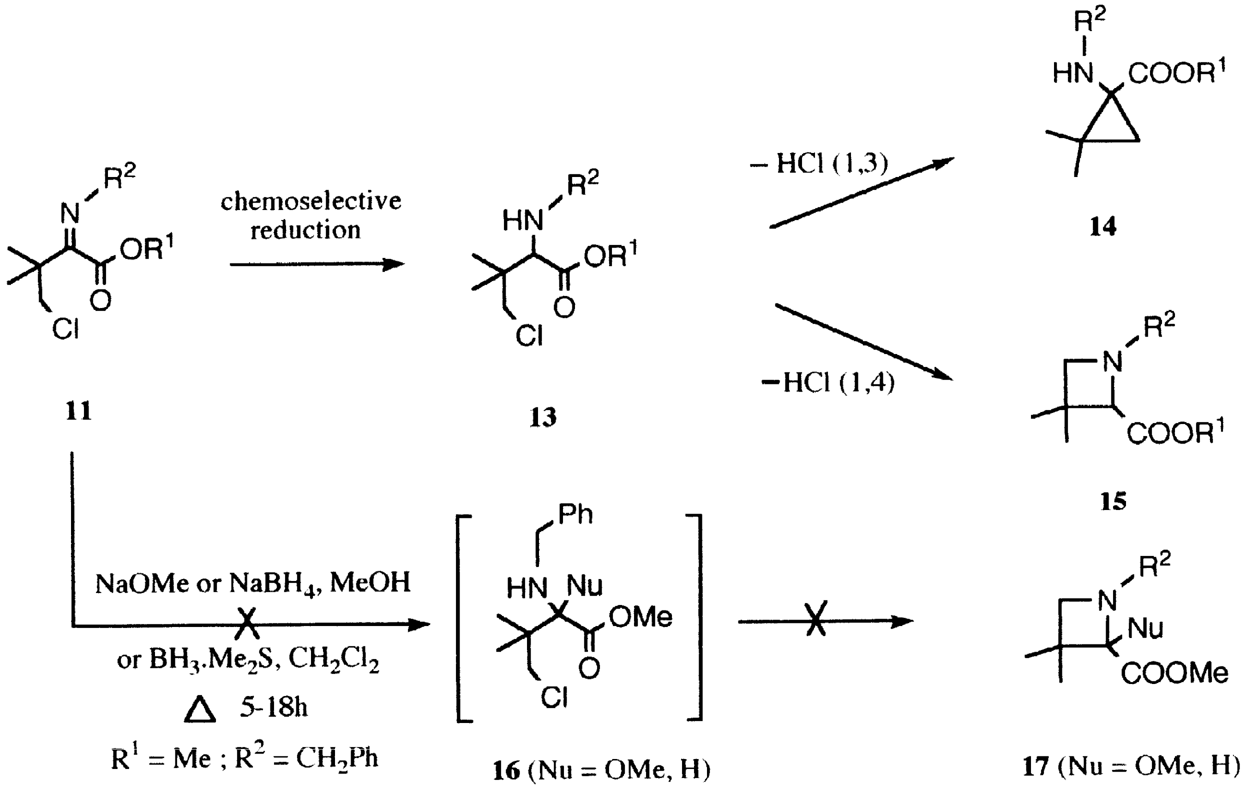
β-Chloro imines have been utilized with success in the synthesis of azetidines via addition of a nucleophile across the imino bond and subsequent intramolecular nucleophilic substitution.[38-40] More functionalized β-halo imines, such as the γ-chloro-α-(N-benzyl)iminocarboxylic esters **11a,b**, have been shown previously to be excellent substrates for the synthesis of 2,2-disubstituted 1-aminocyclopropanecarboxylic acids **12** by base-induced 1,5-dehydrochlorination and subsequent hydrolysis (Scheme 1).[41] γ-Chloro-α-iminocarboxylic esters **11** are suitable trifunctional substrates for selective transformations towards cyclopropanes and azetidines. A selective reduction of the imino function of compounds **11** without interference of the halogen and the carboxylic ester moiety provides a γ-chloro-α-aminocarboxylic ester **13** which either can be converted to ACC derivatives **14** by 1,3-dehydrochlorination or can be ring closed in a 1,4-fashion to provide azetidine-2-carboxylic esters **15** (Scheme 2). The latter aspect is now worked out in the following experiments.

γ-Chloro-α-iminoesters **11** were synthesized from β-chloroketone **8** via a sequence of reactions involving α-monobromination, ethylthiolate substitution, dichlorination, Hg^{++}-assisted alcoholysis to give γ-chloro-α-ketoesters **9** and **10**, and $TiCl_4$-mediated imination.[41]

In some preliminary experiments, it was noticed that the trifunctional γ-chloro-α-iminoester **11a** was inert towards nucleophilic attack across the imino double bond. Both sodium methoxide or sodium borohydride were not capable of inducing any reaction, even under more streneous reaction conditions (Scheme 2). Contrary to the imination of **9**, the relative stability of the α-imino ester **11a** towards nucleophilic attack can be interpreted in terms of the higher steric shielding of the imine carbon atom combined with a less electrophilic behaviour of it in comparison with the carbonyl precursors **9** or **10**. While compound **11a** remains unreactive towards sodium borohydride in methanol under reflux for 5h, also a large excess of diborane-dimethyl sulfide complex in dichloromethane under reflux for 18h did not lead to amine **16** (Nu=H) or azetidine **17** (Nu=H). Sodium cyanoborohydride in methanol in the presence of acetic acid proved to be an excellent chemoselective reagent for the reduction of the imino function in compounds **11**.[41] In this way, the electrophilic character of the imino carbon atom is enhanced by conversion into an intermediate iminium ion. This reduction reaction turned out to be an interesting transformation as it could be directed selectively to either the functionalized α-amino esters **13**[41] or the azetidine-2-carboxylic esters **15**. Controlling the reaction conditions allowed to stop the reduction reaction of **11** at the level of α-amino esters **13** when performing the reaction at 0°C for 1h. This conversion offered a route to N-alkylated 2,2-disubstituted-1-aminocyclopropanecarboxylic esters **14** by reac-

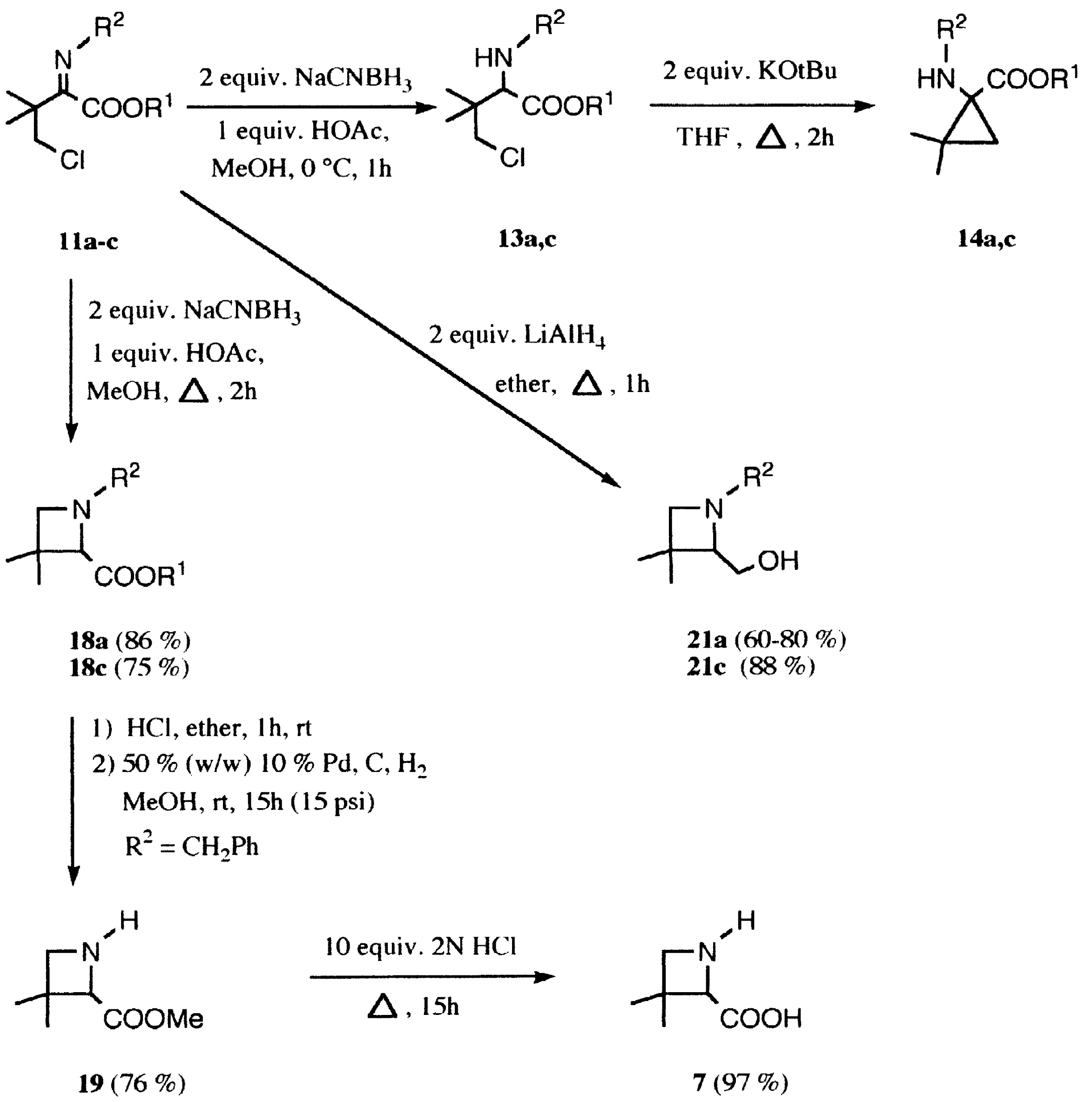


Scheme 1



Scheme 2

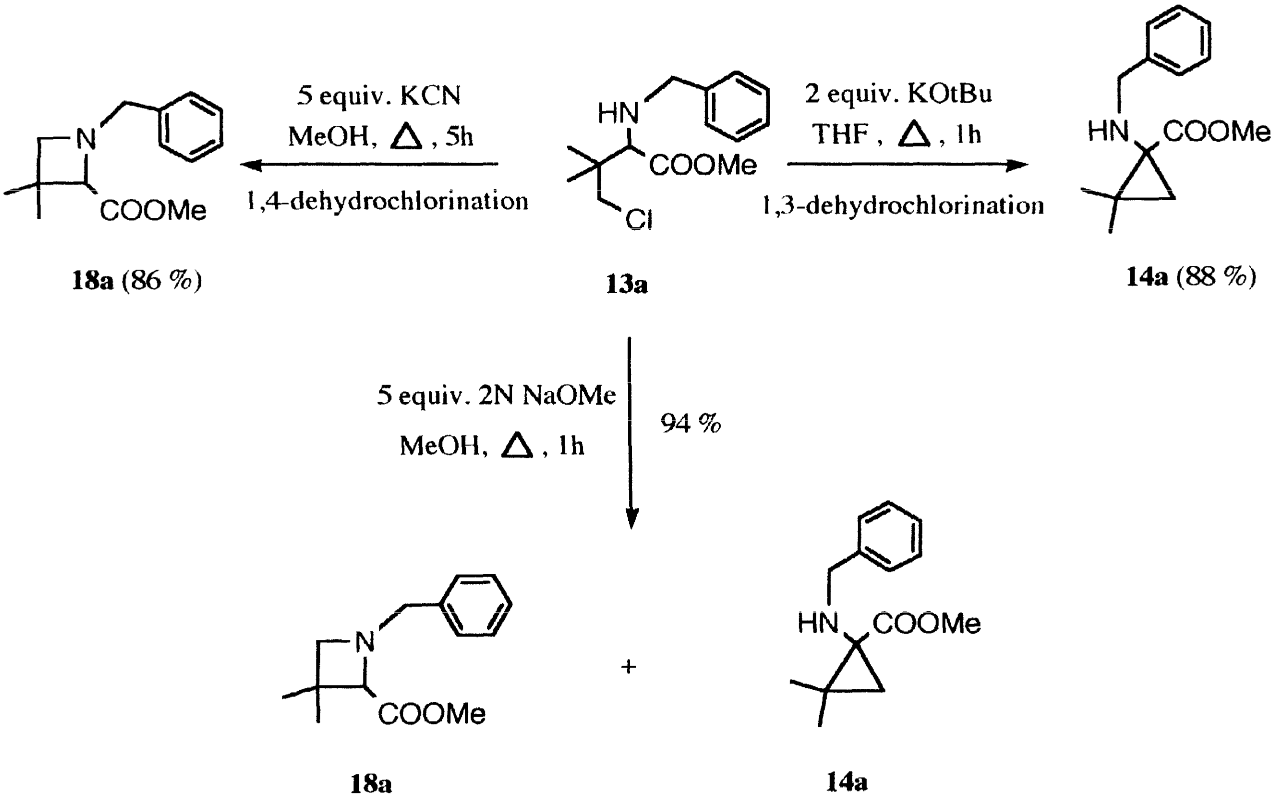
tion of γ-chloro-α-imino esters **13a,c** with potassium t-butoxide in THF under reflux.[41] The temperature of the reductive conversion of compounds **11** with sodium cyanoborohydride proved to be the key to selective reactions. At elevated temperature, the intermediate α-amino esters **13** cyclized in situ to the azetidine-2-carboxylic esters **18**, which were obtained in 75-86% yield. In order to prepare 3,3-dimethylazetidine-2-carboxylic acid **7**, methyl 1-benzyl-3,3-dimethylazetidine-2-carboxylate **18a** was deprotected at the nitrogen atom by



Scheme 3

hydrogenolysis in methanol in the presence of palladium on carbon. This procedure required the use of the azetidine **18a** as the hydrochloride because otherwise the palladium catalyst was poisoned by the N-debenzylated azaheterocycle. This is a common feature for azetidines and is due to the higher basic character compared to other azaheterocycles of different ring size.[42] In addition, relatively large amounts of the palladium catalyst were required in order to obtain methyl 3,3-dimethylazetidine-2-carboxylate **19** in 76% yield. Another prerequisite for a successful conversion of the N-benzylazetidine **18a** into the N-debenzylated derivative **19** concerned the high purity of the starting substrate. A purification of compound **18a** by flash chromatography was absolutely necessary, even when the purity of the compound, as judged from ^{1}H NMR, was higher than 95%. Methyl 3,3-dimethylazetidine-2-carboxylate **19** was hydrolyzed with 10 equiv. 2N hydrogen chloride under reflux for 15h to give 3,3-dimethylazetidine-2-carboxylic acid **20** in virtually quantitative yield.

While the action of relatively strong bases such as potassium t-butoxide on methyl 4-chloro-2-(N-benzylamino)-3,3-dimethylbutanoate **13a** gave rise to methyl 1-(N-benzylamino)-2,2-dimethylcyclopropanecarboxylate **14a**, the reaction of compound **13a** with an excess of potassium cyanide in methanol under reflux for 5h afforded methyl 1-benzyl-3,3-dimethylazetidine-2-carboxylate **18a** in 86% yield. Sodium methoxide in methanol (2N; 5 equiv.) under reflux for 1h converted the γ-chloro-α-amino ester **13a** into a 82:18 mixture (94% yield) of methyl 1-benzyl-3,3-dimethylazetidine-2-carboxylate **18a** and 1-(N-benzylamino)-2,2-dimethylcyclopropanecarboxylate **14a**, respectively (Scheme 4). Accordingly, the presence of relatively stronger bases, such as alkoxides, favors the formation of cyclopropane derivatives **14**, as compared to the formation of azetidines



ratio **18a** : **14a** = 82 : 18

Scheme 4

18 in alcoholic medium in the presence of cyanide or cyanoborohydride.

Treatment of γ-chloro-α-amino esters **11a,c** with lithium aluminium hydride in ether under reflux for 1h gave rise to 1-alkyl-3,3-dimethyl-2-(hydroxymethyl)azetidines **21a,c** in 60-88% yield. Recently, 2-(hydroxymethyl)azetidines have been isolated from marine organisms, i.e. Penares sp.[43-45]. These marine natural products, called penaresidins and penazetidins, displayed an ATP-ase activating property and a protein kinase C inhibition.[42,43]

The methodology, starting with the reductive ring closure of γ-chloro-α-iminocarboxylic esters **11**, is certainly applicable to other 3,3-disubstituted azetidine-2-carboxylic acids and its derivatives. In this way γ-chloro-α-aminocarboxylic esters **11** are elegant sources for the synthesis of strained α-amino acids, i.e. azetidine-2-carboxylic acids and 1-aminocyclopropanecarboxylic acids, with a potential physiological activity.

EXPERIMENTAL PART

^{1}H NMR spectra were recorded at 60 MHz, 270 MHz or 360 MHz, while ^{13}C NMR spectra were obtained at 67.8 MHz or 90 MHz. IR spectra were measured with a liquid film between NaCl or as a KBr pellet. Mass spectra were recorded at 70 eV, either by the direct inlet mode or via a GC-MS coupling. GC analyses were performed using a capillary column (fused silica, RSL 200, 20 m length, i.d. 0.53 mm, He carrier gas). Flash chromatography was performed using Merck Kieselgel 60 (0.04-0.063 mm) and different solvent combinations, determined via initial tlc analysis (Merck Kieselgel 60 F_{254}, precoated). Melting points were measured on a Kofler Hotbench (Reichert Jung) or with a Büchi 535 melting point apparatus.

Preparation of starting materials

Alkyl 4-chloro-3,3-dimethyl-2-oxobutanoates **9** and **10** were prepared starting from β-chloroketone **8** by consecutive bromination, substitution with sodium ethylthiolate, chlorination with sulfuryl chloride and Hg(II)-acetate mediated alcoholysis.[41] The corresponding γ-chloro-α-(N-alkylimino)esters **11** were synthesized by imination of α-ketoesters **9** and **10** with primary amines (benzylamine or isopropylamine) in the presence of stoichiometric amounts of titanium(IV) chloride in diethyl ether.

Synthesis of N-substituted 3,3-dimethylazetidine-2-carboxylic esters 18

The conversion of methyl 4-chloro-2-(N-benzylimino)-3,3-dimethylbutanoate **11a** into methyl N-benzyl-3,3-dimethylazetidine-2-carboxylate **18a** is representative.

To an ice cooled solution of 4-chloro-2-(N-benzyl)imino-3,3-dimethylbutanoate **11a** (2.67 g, 0.01 mol) in methanol (40 mL) is added sodium cyanoborohydride (1.24 g, 0.02 mol), followed by 98% acetic acid (0.6 g, 0.01 mol). The reaction mixture was stirred for 1h at reflux, poured into water and extracted with

CH_2Cl_2 (3x20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to yield 2.34 g (100%) of methyl 1-benzyl-3,3-dimethylazetidine-2-carboxylic ester **18a**. Purification can be performed by means of flash chromatography or distillation (R_f Et_2O/C_5H_{12} 1/1 = 0.49, bp. 113-117°C / 2 mmHg) to yield the pure compound in 86% and 75% yield, respectively. ^1H NMR ($CDCl_3$, 270 MHz) δ 1.18 and 1.20 (each 3H, each s, $\underline{Me_2}C$); 2.69 and 3.10 (2H, d+dd, AX, J=6.35 and 0.73 Hz, $C\underline{H_2}N$); 3.45 (1H, d, J=0.73 Hz, $C\underline{H}N$); 3.58 and 3.80 (2H, 2xd, AB, J=12.69 Hz, $C\underline{H_2}C_6H_5$); 3.64 (3H, s, $O\underline{Me}$); 7.29 (5H, m, $CH_2C_6\underline{H_5}$). ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 22.93 and 27.73 ($\underline{Me_2}C$); 36.41 ($Me_2\underline{C}$); 51.25 ($O\underline{Me}$); 61.76 ($\underline{C}H_2C_6H_5$), 63.32 (CH_2N); 73.13 ($\underline{C}HN$); 127.13 (Cp); 128.16 and 129.20 (Co and Cm); 137.10 (Cq); 171.93 ($\underline{C}=O$). IR (NaCl, cm^{-1}); 1728-1752 (C=O). MS (70 eV) m/z (rel. int.) 233 (M^+, 1); 174(11); 119(8); 118(7); 117(7); 92(7); 91(100); 65(14); 56(8); 55(5); 42(5); 41(8); 40(11). Elemental analysis : Calcd. 72.07% C, found 72.19% C; calcd. 8.21% H, found 8.10% H; calcd. 6.00% N, found 6.19% N.

Methyl N-isopropyl-3,3-dimethylazetidine-2-carboxylic ester 18c :

^1H NMR ($CDCl_3$, 270 MHz) δ 0.92 and 0.97 (6H, each d, J=6.4 Hz, $CH\underline{Me_2}$), 1.18 and 1.22 (6H, each s, $\underline{Me_2}$); 2.42 (1H, septet, J=6.4 Hz, $C\underline{H}Me_2$); 2.68 and 3.25 (2H, AB, J=6.4 Hz, $C\underline{H_2}N$), 3.40 (1H, s, CHN), 3.77 (3H, s, $O\underline{Me}$). ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 172.28 ($\underline{C}=O$); 73.46 ($\underline{C}HN$); 63.05 ($\underline{C}H_2N$); 58.67 ($N\underline{C}H$); 51.48 ($O\underline{Me}$); 34.55 ($Me_2\underline{C}$); 28.18 and 23.09 ($\underline{Me_2}C$); 19.91 and 19.38 ($CH\underline{Me_2}$). IR (NaCl, cm^{-1}) 1725-1755 (C=O). MS (70 eV) m/z (rel. int.) 186 (M^+ +1, 2); 185 (M^+, 18); 184 (M^+ -1, 2); 170(43); 130(5); 126(100); 115(7); 110(5); 97(8); 88(6); 85(4); 84(51); 83(9); 82(5); 72(6); 71(15); 70(21); 69(9); 68(2); 67(2); 59(5); 57(4); 56(35); 55(12); 54(2); 53(2); 44(4); 43(34); 42(18); 41(18). Elemental analysis : calcd. 64.83% C, found 64.96% C; calcd. 10.34% H, found 10.19% H; calcd. 7.56% N, found 7.50% N.

Preparation of the Hydrochloride of Methyl 1-Benzyl-3,3-dimethylazetidine-2-carboxylic ester 18a

A solution of 1.16 g (0.005 mol) of azetidine **18a** in 25 ml of dry ether was treated with an excess of dry hydrogen chloride in ether. The mixture was stirred for 1h at room temperature, after which the precipitated hydrochloride was filtered off and washed with ether. After drying in vacuo, the hydrochloride (1.15 g; yield 85%) was used as such in the next experiment. ^1H NMR ($CDCl_3$, 270 MHz) : 1.45 and 1.54 (each 3H, each s, $\underline{Me_2}$); 3.63 (3H, s, $O\underline{Me}$); 3.7-4.7 (5H, m, $C\underline{H}$-N-$(C\underline{H_2})_2$); 7.3-7.7 (5H, m, $C_6\underline{H_5}$); 12.1 (1H, s, broad, $N\underline{H}$).

Debenzylation of methyl 1-benzyl-3,3-dimethylazetidine-2-carboxylic ester 18a to methyl 3,3-dimethylazetidine-2-carboxylate 19

To a solution of methyl 1-benzyl-3,3-dimethylazetidine-2-carboxylic ester hydrochloride **18a**.HCl (0.81 g, 3 mmol) in methanol (60 mL) was added 10% Pd on carbon (50% w/w, 0.405 g). The amino ester was hydrogenolyzed under a pressure of 50 psi at room temperature for 20h. After the reaction, the suspension was filtered and the filtrate was concentrated in vacuo. The residue was poured into water, neutralized with $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. Purification was performed by flash chromatography to yield 0.33 g (76%) of methyl 3,3-dimethylazetidine-2-carboxylate **19** : R_f MeOH = 0.62. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.10 and 1.39 (6H, each s, $\underline{Me_2}C$); 2.75 (1H, s br, $N\underline{H}$); 3.31 (2H, s, $C\underline{H_2}N$); 3.76 (3H, s, $O\underline{Me}$); 4.02 (1H, s, $C\underline{H}N$). ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 23.29 and 28.05 ($\underline{Me_2}C$); 39.73 ($Me_2\underline{C}$); 51.70 ($O\underline{Me}$); 57.32 ($\underline{C}H_2N$); 67.83 ($\underline{C}HN$); 173.58 ($\underline{C}{=}O$). IR (NaCl, cm^{-1}) 3320 (NH); 1734 (COOMe). Elemental analysis : calcd. 58.72% C, found 58.59% C; calcd. 9.15% H, found 9.19% H; calcd. 9.78% N, found 9.88% N.

Hydrolysis of Methyl 3,3-dimethylazetidine-2-carboxylate 19 to 3,3-dimethylazetidine-2-carboxylic acid 7

A solution of methyl 3,3-dimethylazetidine-2-carboxylate **19** (0.33 g, 2.3 mmol) in 2N HCl (5 ml, 10 mmol) was stirred at reflux for 15h. After the reaction, the solvent was evaporated in vacuo and the residue was chromatographed on Dowex 50x8 to yield 0.28 g (97%) of pure 3,3-dimethylazetidine-2-carboxylic acid **7** : R_f n-BuOH/AcOH/H_2O 4/1/1 = 0.19, mp. 188°C. ^{1}H NMR (D_2O, 270 MHz) δ (Ref. $\underline{CH_3}CN$ = 2.00) 1.17 and 1.33 (6H, each s, $\underline{Me_2}C$); 3.57 and 3.77 (2H, AB, J=10.38 Hz, $C\underline{H_2}N$); 4.40 (1H, s, $C\underline{H}$-N). ^{13}C NMR (D_2O, 67,8 MHz) δ (Ref. Trimethylsilylpropanesulfonic acid sodium salt; δ=0); 24.28 and 29.13 ($\underline{Me_2}C$); 40.14 ($Me_2\underline{C}$); 57.57 ($\underline{C}H_2N$); 71.28 ($\underline{C}HN$); 174.59 ($\underline{C}{=}O$). IR (NaCl, cm^{-1}) ν_{max} = 3420, 3110, 1685, 1610, 1570, 1414 and 1356. MS (70 eV) m/z (rel. int.) no M^+, 179(20); 157(6); 156(31); 147(4); 110(4); 101(5); 100(9); 86(11); 84(15); 83(13); 82(7); 75(22); 74(9); 73(100); 59(8); 56(5); 55(6); 45(20); 44(6); 43(4); 42(5); 41(6); 40(4). Elemental analysis : calcd. 10.84% N, found 10.70% N.

Synthesis of 2-(hydroxymethyl)-3,3-dimethylazetidines 21

The reduction of methyl 4-chloro-2-(N-isopropyl)imino-3,3-dimethylbutanoate **11c** is representative. To an ice cooled solution of 4-chloro-2-(N-isopropyl)imino-3,3-dimethylbutanoate **11c** (25.61 g, 117 mmol) in diethyl ether (300 ml) was added lithiumaluminiumhydride (8.9 g, 234 mmol). The reaction mixture was stirred for 2h at reflux and then poured into ice cold water. The organic phase was separated and the aqueous phase was extracted two times additionally (100 mL) with diethyl ether. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to yield 11.07 (60%) of 1-isopropyl-2-(hydroxymethyl)-3,3-dimethylazetidine **21c**. Recrystallization of the reaction mixture in pentane at -20°C yielded pure azetidine **21c** as a white solid : mp. 67°C. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 0.91 and 0.97 (each 3H, each d, J=6.25 Hz, $CH\underline{Me_2}$); 1.09 and 1.23 (each 3H, each s, $\underline{Me_2}$); 2.48 (1H, septet, J=6.25 Hz, $C\underline{H}Me_2$); 2.71 (1H, d, J_{AB}=7.01 Hz, $\underline{H}CHN$); 2.98 (1H, dxd, J_{AX}=5.94 Hz, J_{BX}=2.28 Hz, $\underline{H}CN$); 3.16 (1H, d, J_{AB}=7.01 Hz, $HC\underline{H}N$); 3.30 (1H, br s, OH); 3.56 and 3.61 (each 1H, ABxd, J_{AB}=10.94 Hz, J_{AX}=5.94 Hz, J_{BX} shows additional broadening, $C\underline{H_2}OH$). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 19.95 and 20.84 ($CH\underline{Me_2}$); 22.23 and 29.33 (Me_2); 32.06 ($\underline{C}Me_2$); 58.08 ($\underline{C}HMe_2$);

61.11 (CH_2OH); 63.92 (CH_2N); 72.94 (CHN). IR (KBr, cm^{-1}) 3100 (OH, br). MS (70 eV) m/z (rel. int.) 158 (M^+ +1, 2); 157 (M^+, 8); 142(12); 127(8); 126(100); 114(4); 101(4); 100(7); 85(6); 84(68); 82(4); 81(4); 72(31); 71(4); 70(58); 69(6); 68(4); 67(3); 60(4); 58(10); 57(7); 56(27); 55(18); 54(3); 53(4); 44(26); 43(88); 42(36); 41(38). Elemental analysis : calcd. 68.74% C, found 68.79% C; calcd. 12.18% H, found 12.03% H, calcd. 8.91% N, found 8.99% N.

1-Benzyl-2-(hydroxymethyl)-3,3-dimethylazetidine **21a**

^1H NMR ($CDCl_3$, 360 MHz) δ 1.10 and 1.21 (each 3H, each s, Me2); 2.60 (1H, br s, OH); 2.73 (1H, d, J=6.83 Hz, $\underline{H}CHN$); 3.01 (1H, b, J=4.61 Hz, HCN); 3.15 (1H, d, J=6.83 Hz, $HC\underline{H}N$); 3.45 (2H, d, J=4.61 Hz, $C\underline{H}_2OH$); 3.60 and 3.72 (each 1H, each d, AB, J_{AB}=12.79 Hz, $\underline{CH_2}C_6H_5$); 7.29 (5H, br s, C_6H_5). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 22.24 and 28.79 (Me_2); 33.91 ($\underline{C}Me_2$); 60.71 (CH_2N); 62.55 (CH_2OH); 65.46 ($\underline{C}H_2C_6H_5$); 74.51 (CHN); 127.20 (Cp); 128.38 and 128.71 (Co and Cm); 138.46 (Cq). IR (NaCl, cm^{-1}) 3300 (OH, br). MS (70 eV) m/z (rel. int.) 205 (M^+, 3); 175(4); 174(31); 131(3); 120(5); 118(5); 105(2); 92(11); 91(100); 71(3); 65(7); 56(4); 55(3); 42(4); 41(6); 40(21). Elemental analysis : calcd. 76.06% C, found 76.02% C; calcd. 9.33% H, found 9.24% H; calcd. 6.82% N, found 6.93% N.

Reaction of 4-chloro-2-(N-benzylamino)-3,3-dimethylbutanoate **13a** with Potassium Cyanide or Sodium Methoxide in Methanol

A solution of 0.54 g (0.002 mol) of **13a**[41] in 6 ml methanol was treated with 0.65 g (0.01 mol) of potassium cyanide. After reflux for 5h, the reaction mixture was poured into water and was extracted with dichloromethane to give 0.40 g (86%) of pure methyl 1-benzyl-3,3-dimethylazetidine-2-carboxylic ester **18a** (purity > 96%). The same experiment with 0.54 g (0.002 mol) of compound **13a** and 5 ml 2N sodium methoxide in methanol (0.01 mol) under reflux for 1h afforded 0.47 g (94%) of an 82:18 mixture of azetidine **18a** and methyl cyclopropanecarboxylic ester **14a**, respectively, as judged from ^1H NMR and GC analysis (workup as above). The spectral data of compound **18a** were given above while the spectral data of compound **14a** were identical with data from the literature.[41]

Acknowledgement

The authors are indebted to the "Fund for Scientific Research-Flanders" and EC-INTAS for financial support of the research.

References

1. Yang, S.F.; Hoffman, N.E. *Ann. Rev. Plant Physiol.* **1984**, *35*, 155-189.
2. Yang, S.F. in Plant Nitrogen Metabolism, Chapter 8, pp. 263-287, Ed. Poulton, J.E.; Romeo, J.T. and Conn, E.E. Plenum Press : New York, 1989.
3. De Kimpe, N.; Sulmon, P.; Brunet, P. *J. Org. Chem.* **1990**, *55*, 5777-5784, and references cited therein.
4. Pirrung, M.C.; McGeehan, G.M. *Angew. Chem.*, **1985**, *97*, 1074-1075.
5. Pirrung, M.C.; McGeehan, G.M. *J. Org. Chem.*, **1986**, *51*, 2103-2106.
6. Toshima, H.; Niwayama, Y.; Nagata, H.; Greulich, F.; Ichihara, A. *Biosci. Biotech. Biochem.* **1993**, *57*, 1394-1395.
7. Hoffman, N.E.; Yang, S.F.; Ichihara, A.; Sakamura, S. *Plant Physiol.* **1982**, *70*, 195-199.
8. Charette, A.B.; Côté, B. *J. Am. Chem. Soc.* **1995**, *117*, 12721-12732.
9. Jiménez, J.M.; Rifé, J.; Ortuño, R.M. *Tetrahedron Asym.* **1996**, *7*, 537-558.
10. Baldwin, J.E.; Adlington, R.M.; Rawlings, B.J. *Tetrahedron Lett.*, **1985**, *26*, 481-484.
11. Burgess, K.; Ho, K.-K.; Moye-Sherman, D. *Synlett.* **1994**, 575-583.
12. Wick, L.; Tamm, C.; Boller, T. *Helv. Chim. Acta*, **1995**, *78*, 403-410.
13. Pirrung, M.C.; Cao, J.; Chen, J. *J. Org. Chem.*, **1995**, *60*, 5790-5794.
14. Stammer, C.H. *Tetrahedron* **1990**, *46*, 2231-2254, and references cited therein.
15. Burgess, K.; Ho, K.-K.; Pal, B. *J. Am. Chem. Soc.* **1995**, *117*, 3808-3819.
16. Mendel, D.; Ellman, J.; Schultz, P.G. *J. Am. Chem. Soc.* **1993**, *115*, 4359-4360.
17. Burgess, K.; Ho, K.-K.; Pettitt, B.M. *J. Am. Chem. Soc.* **1995**, *117*, 54-65.
18. Burgess, K.; Ke, C.-Y. *J. Org. Chem.*, **1996**, *61*, 8627-8631.
19. Moore, J.A.; Ayers, R.S. in "The Chemistry of Heterocyclic Compounds", Ed. Weissenberger A. and Taylor E.C., J. Wiley, New York, 1983, Vol. 42, "Small Ring Heterocycles", Part 2, Ed. A. Hassner.
20. De Kimpe, N. in "Comprehensive Heterocyclic Chemistry - Three- and Four-Membered Rings, with All Fused Systems Containing Four-Membered Rings"; Vol. 1B, Chapter 1.18 "Azetidines, Azetines and Azetes : Monocyclic", p. 507-589. Eds. Padwa A., Katritzky A.R., Rees C.W., Scriven E.F.V., Pergamon, Elsevier, Oxford (1996).
21. a) Sugiura, Y.; Tanaka, H.; Mino, Y.; Ishida, T.; Ota, N.; Inoue, M.; Nomoto, K.; Yoshioka, H.; Takemoto, T. *J. Am. Chem. Soc.* **1981**, *103*, 6979. b) Oida, F.; Ota, N.; Mino, Y.; Nomoto, K.; Sugiura, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3436-3437. c) Noma, M.; Noguchi, M.; Tamaki, E. *Tetrahedron Lett.* **1971**, 2017-2020. d) Ohfune, Y.; Tomita, M.; Nomoto, K. *J. Am. Chem. Soc.* **1981**, *103*, 2409. e) Hamada, Y.; Shioiri, T. *J. Org. Chem.* **1986**, *51*, 5489-5490. f) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1992**, *51*, 7917-7920. g) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Asymm.* **1992**, *3*, 1069-1074. h) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1992**, *51*, 7921-7924.

i) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1994**, *50*, 265-274. j) Shioiri, T.; Hamada, Y.; Matsuura, F. *Tetrahedron* **1995**, *51*, 3939-3958.

22. Hanessian, S.; Fu, J.-M.; Chiara, J.-L.; Di Fabio, R. *Tetrahedron Lett.*, **1993**, *34*, 4157-4160.
23. Nielsen, E.; Forlani, G.; Cella, R.; Parisi, B. *Plant Sci.* **1986**, *44*, 147; *Chem. Abstr.* **1986**, *105*, 112253.
24. Fowden, L. *Phytochemistry* **1991**, *30*, 3859-3860.
25. Devlin, B.R.J. US Pat. 4560401 (1985); *Chem. Abstr.* **1986**, *105*, 42626.
26. Verbrugge, P.A.; De Waal, J. US Pat. 4812581 (1989); *Chem. Abstr.* **1989**, *111*, 57527.
27. Wood, D.; Mason, R. Eur. Pat. 131435 (1985); *Chem. Abstr.* **1985**, *103*, 195984.
28. B.V. Maatschappij (Shell Int. Res.) Jpn. Kokai 6281367 (1987); *Chem. Abstr.* **1987**, *107*, 134187.
29. De Nie-Sarink, M.; Mason, R. Eur. Pat. 165636 (1985); *Chem. Abstr.* **1986**, *105*, 6400.
30. De Nie-Sarink, M.; Scholes, G. Eur. Pat. 165637 (1985); *Chem. Abstr.* **1986**, *105*, 224786.
31. Kozikowski, A.P.; Wroblewski, J.; Costa, E. Eur. Pat. 299513 (1989); *Chem. Abstr.* **1989**, *111*, 7211.
32. Kozikowski, A.P.; Tuckmantel, W.; Reynolds, I.; Wroblewski, J. *J. Med. Chem.* **1990**, *33*, 1561-1571.
33. Blythin, D.J.; Green, M.J.; Lauzon, M.J.R.; Shue, H.-J. *J. Org. Chem.* **1994**, *59*, 6098-6100 and references cited therein.
34. a) Masaki, M.; Uehara, M.; Hirate, K.; Isowa, Y.; Sato, Y.; Nakashima, Y. Eur. Pat. Appl. EP 393934, A1 901024; *Chem. Abstr.* **1990**, *114*, 164815. b) Zagari, A.; Nemethy, G.; Scheraga, H.A. *Biopolymers* **1990**, *30*, 951. c) Zagari, A.; Nemethy, G.; Scheraga, H.A. *Biopolymers* **1990**, *30*, 961. d) Tsai, F.H.; Overberger, C.G.; Zand, R. *Biopolymers* **1990**, *30*, 1039.
35. Cromwell, N.H.; Phillips, B. *Chem. Rev.* **1979**, *79*, 331-358.
36. Backes, J. in Organische Stickstoffverbindungen III (Houden-Weyl), Band E16c, pp. 729-909, Ed. Klamonn, D., G. Thieme Verlag, Stuttgart, New York (1992).
37. Dureault, A.; Portal, M.; Carreoux, F.; Depezay, J.C. *Tetrahedron* **1993**, *49*, 4201-4210.
38. Sulmon, P.; De Kimpe, N.; Schamp, N. *Tetrahedron* **1988**, *44*, 3653-3670.
39. Sulmon, P.; De Kimpe, N.; Schamp, N. *Tetrahedron* **1989**, *45*, 2937-2955.
40. De Kimpe, N.; Stevens, C. *Synthesis* **1993**, 89-91.
41. Boeykens, M.; De Kimpe, N.; Abbaspour Tehrani, K. *J. Org. Chem.* **1994**, *59*, 6973-6985.
42. Fedor, L.R.; Bruice, T.C.; Kirk, K.L., Meinwald, J. *J. Am. Chem. Soc.*, **1966**, *88*, 108.
43. Kobayashi, J.; Cheng, J.; Ishibashi, M.; Wälchli, M.R.; Yamamura, S.; Ohizumi, Y. *J. Chem. Soc. Perkin Trans I*, **1991**, 1135-1137.
44. Alvi, K.A.; Jaspars, M.; Crews, P.; Strulovici, B.; Oto, E. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2447-2450.
45. Kobayashi, J.; Tsuda, M.; Cheng, J.-F.; Ishibashi, M.; Takihawa, H.; Mori, K. *Tetrahedron Lett.* **1996**, *37*, 6775-6776.