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Enantioselective Total Syntheses of Cyclopropane Amino Acids: Natural Products and Protein Methanologs

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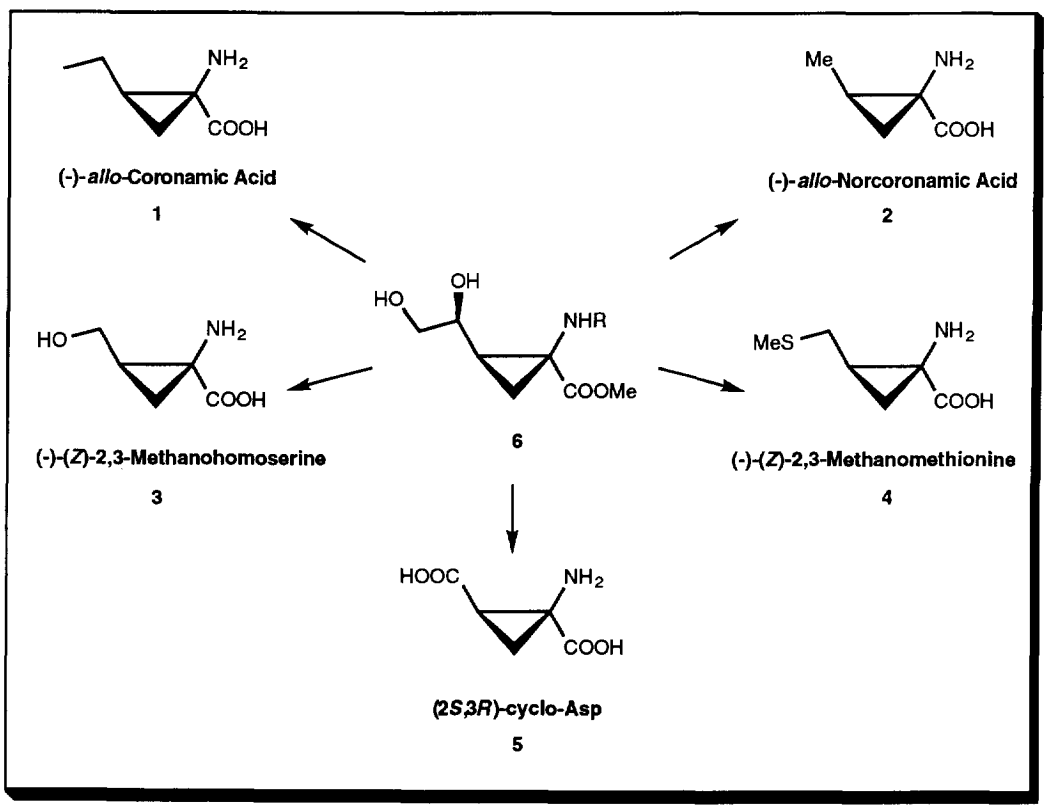
Abstract. The syntheses of (-)-*allo*-coronamic acid, (-)-*allo*-norcoronamic acid, (-)-(*Z*)-2,3-methanohomoserine, (-)-(*Z*)-2,3-methanomethionine, and (2*S*,3*R*)-Cbz-cyclo-Asp-OMe have been achieved in 45-68% overall yields from suitable intermediates derived from homochiral aminopentenoates which were obtained, in turn, from D-glyceraldehyde. The key synthetic step involves the quantitative and highly diastereoselective cyclopropanation of such precursors. The factors dealing with the control of stereoselectivity are highlighted and the main features in side-chain functionalization to the respective target molecules are discussed.

INTRODUCTION

Conformationally restricted cyclopropane amino acids constitute a wide class of compounds that include naturally occurring products and synthetic 2,3-methanoamino acids or methanologs which are structurally related to those found in proteins.[1] For instance, coronamic and norcoronamic acids were isolated from hydrolysis of the plant toxines coronatine[2] and norcoronatine,[3] respectively, and *allo* coronamic acid[4] as well as *allo*-norcoronamic acid[5] play important roles in metabolic pathways in plants. On the other hand, replacement of protein amino acids by methanologs in peptide surrogates often enhances their biological properties with respect to the normal peptides and offers the possibility of using those substrates as biosynthetic and mechanistic probes.

Different approaches have been published on the asymmetric synthesis of β-substituted cyclopropane amino acids.[1] Those using chiral auxiliaries in diastereoselective reactions resulted, in general, in the production of modest amounts of optically active materials. More efficient have proved to be some syntheses from the chiral pool which provides commercially available and often cheap chirons. Among the protocols described, 1,3-dipolar cycloaddition of diazomethane to homochiral dehydroamino acids allows the creation of the two cyclopropane-stereogenic centers in a single step. Face selectivity in this reaction determines the enantiomeric purities of the target molecules, whilst *E/Z* stereochemistry of the β-substituent is predetermined by the configuration of the precursor (see Scheme 2 and Fig 1 for numeration of these compounds).

We describe in this paper, as an illustration of our versatile methodology, the efficient and highly stereocontrolled total syntheses of (-)-*allo*-coronamic acid **1**, (-)-*allo*-norcoronamic acid **2**, (-)-(Z)-2,3-methanohomoserine **3**, (-)-(Z)-2,3-methanomethionine **4**, and (2*S*,3*R*)-Cbz-cyclo-Asp-OMe which is a partially protected derivative of **5**, from diols **6** as a common type of intermediates (Scheme 1).[6] Compounds **6a-c** result from hydrolysis of **11a-c** which are produced by cyclopropanation of the homochiral dehydroamino acid derivatives (Z)-**9** (Scheme 2). These precursors are easily obtained on a multigramme scale through Wittig-Horner condensation of suitable phosphonates **8**[7] and D-glyceraldehyde acetonide **7**. This chiron is commercially available but can be easily obtained from D-mannitol as a primary source of chirality.[8]



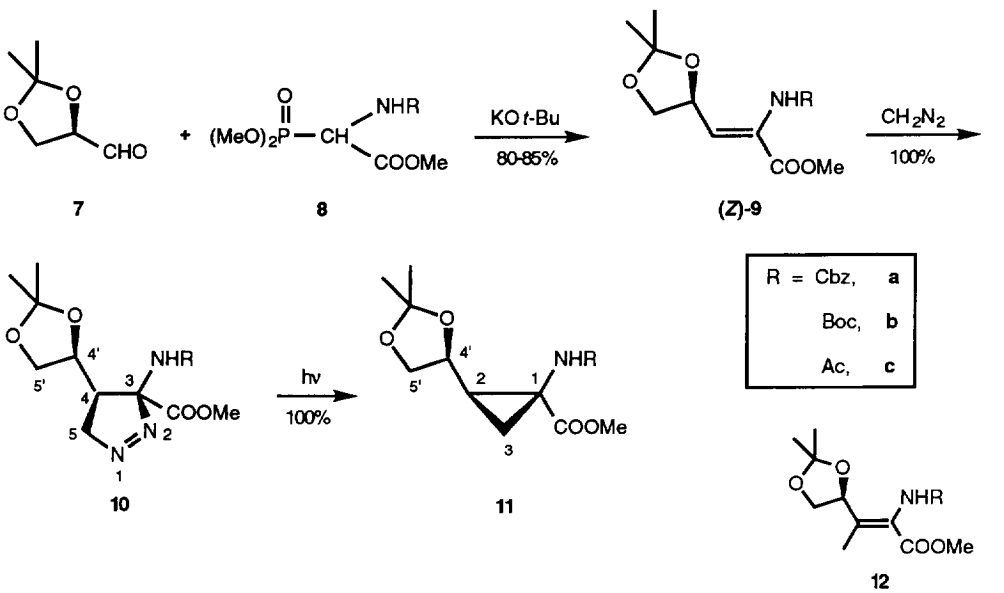
Scheme 1

RESULTS AND DISCUSSION

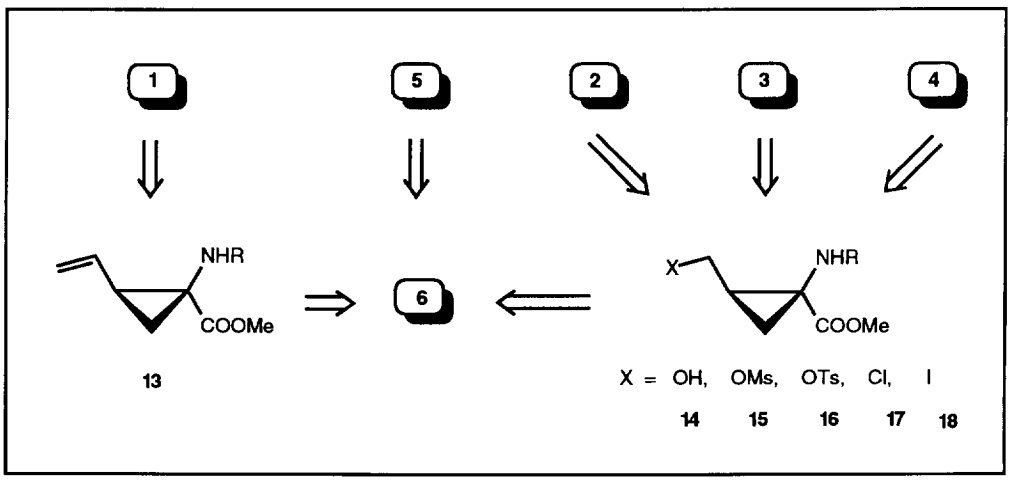
The influence of the reaction conditions on the *E/Z* stereochemistry of the aminopentenoates **9** has been investigated. Cyclopropanation of substrates **9** by addition of diazomethane followed by photochemically induced decomposition of the intermediate pyrazolines **10** afforded cyclopropyl derivatives **11** in quantitative yield each as a single stereoisomer (Scheme 2). Photochemical reaction conditions such as solvent, concentration, temperature and use of photosensitizers have been studied in order to optimize

chemical yields and to avoid the insertion and the cycloreversion products. Different *N*-substituted dehydroamino esters were prepared in order to generalize the excellent diastereoselection observed in these processes and to assure convenient protections of the amino group compatible with the conditions required in the latter reactions.

Subsequently, the synthetic goal was accomplished by transformation of diol **6** into the 2-vinyl, 2-hydroxymethyl, and 2-mesyloxymethyl derivatives, **13**, **14**, and **15**, respectively, as the corresponding key intermediates which led to the target molecules according to divergent synthetic pathways (Scheme 3).



Scheme 2



Scheme 3

1. Synthesis of aminopentenoates 9: Z/E stereochemistry.

Schmidt and Lieberknecht published a general method for the synthesis of *N*-acyl- and *N*-alkoxycarbonyl-2-(dialkoxyphosphinyl)-glycine esters and their condensation with several aldehydes.[7] Potassium *t*-butoxide suspended in dichloromethane at -70° C was used in those works for the condensation of phosphonates **8a** and **8b** with D-glyceraldehyde acetonide **7**, affording dehydroamino pentenoates **9a** and **9b** as 95:5 *Z/E*-mixtures of stereoisomers. We have improved the preparation of **8b** by hydrogenation of **8a** in the presence of Boc_2O by using 20% palladium hydroxide on charcoal as a catalyst at atmospheric pressure instead of 10% palladium on charcoal at 2-3 atmospheres pressure, as in the original method. In this way, a similar yield (85-90%) in **8b** was obtained after a 4 hours period, a much shorter rection time than that required in the conditions previously described.

We have prepared derivatives **9a** and **9b** and the novel N-acetyl analogue **9c**. Conditions that could influence the stereochemistry in these reactions were investigated in order to favour the production of (*E*)-isomers as precursors of (*E*)-cyclopropane derivatives. Phosphonate **8b** was chosen as a model in this study. Several bases such as NaH, BuLi, LDA, DBU, NaOMe, KO*t*-Bu, and solvents of different polarity including dichloromethane, tetrahydrofuran, and methanol were used, and the results compared with those from the previous method.[7] Lithium chloride (1.2 eq) was added in several experiments to realize the influence of lithium cation on the stereochemical outcome of the process. Conditions, ratios of *Z/E*-stereoisomers and chemical yields are summarized in Table 1.

Table 1. Condensation reactions of aldehyde 7 with phosphonate 8b.[(a)]

Entry	Base	Solvent	Eq of LiCl	*Z* : *E* ratio[(b)]	% Yield
(1)	NaH	CH_2Cl_2	---	70 : 30	75
(2)	NaH	THF	---	65 : 35	79
(3)	NaH	THF	1.2	60 : 40	88
(4)	BuLi	CH_2Cl_2	---	62 : 38	96
(5)	BuLi	THF	---	61 : 39	81
(6)	LDA	THF	---	67 : 33	82
(7)	DBU	THF	---	95 : 5	73
(8)	DBU	THF	1.2	70 : 30	79
(9)	DBU	MeOH	1.2	91 : 9	75
(10)	NaOMe	MeOH	---	92 : 8	83
(11)	NaOMe	MeOH	1.2	95 : 5	84
(12)	KO*t*-Bu	CH_2Cl_2	---	95 : 5	92

[(a)] All reactions were performed at 25° C but those in entries 5, 6, and 12 also at -78° C. Results were similar at both temperatures. [(b)] Determined by ^1H NMR analysis.

We have arrived at the following conclusions: (a) Temperature does not exert a practical influence on the *Z/E* ratio. (b) The presence of lithium cation favoured the production of (*E*)-isomer. This effect was

especially noticeable in the cases in which DBU was used (compare entries 7 and 8). (c) A polar and protic solvent such as methanol increased the (*Z*)-isomer ratio. The effect of lithium cation was negligible when reactions were performed in methanol (compare entries 10 and 11). (d) The alternative use of dichloromethane or tetrahydrofuran, both aprotic and low-polarity solvents, did not change sustantially the *E/Z*-ratio (entries 1/4 compared with 2/5).

The results obtained allowed (*E*)-isomers to be prepared in modest yields (30-40%). Alternatively, (*Z*)-isomers **9a-c** were prepared on a multigramme scale in 80-85% yields according to Table 1, and they have been used as synthetic precursors of amino acids **1** - **5**, as described in this paper.

2. Synthesis of cyclopropanes 11a-c through 1,3-dipolar cycloaddition of diazomethane to (Z)-[9a-c]: Facial diastereoselection and some aspects on the photochemical decomposition of the intermediate pyrazolines 10a-c.

Dehydroaminopentenoates (*Z*)-[**9a-c**] were reacted with excess ethereal diazomethane at room temperature to afford pyrazolines **10a-c** (Scheme 2), respectively, in quantitative yield as single diastereoisomers in all cases, as confirmed by ^{1}H and ^{13}C NMR techniques. The same result was obtained when hexane or dichloromethane was used as solvent. The (2*S*,3*R*) absolute configuration of the new stereogenic centers was unambiguously established by X-Ray diffraction analysis of thiocarbonate **19a** (Scheme 5, *vide infra*).[6a] Stereochemistry of the cyclopropanes from series **b** and **c** was assured by comparison of acetonides **11b** and **11c** with **11a**, by means of a detailed ^{1}H NMR study involving n.O.e. difference experiments and 2D-COSY spectra to assign all chemical shifts and coupling constants. The chirality of the cyclopropane ring and the excellent diastereoselection in the cycloaddition can be explained by the preferential attack of diazomethane on the less hindered *re* face of C-2 the double bond of (Z)-**9**, by considering a preferred conformation such as that represented in Fig 1. This conformation has been evidenced in the *N*-acetyl derivative (Z)-**9c** by means of the significant % n.O.e. observed between H_4 and N*H* (Fig 1).

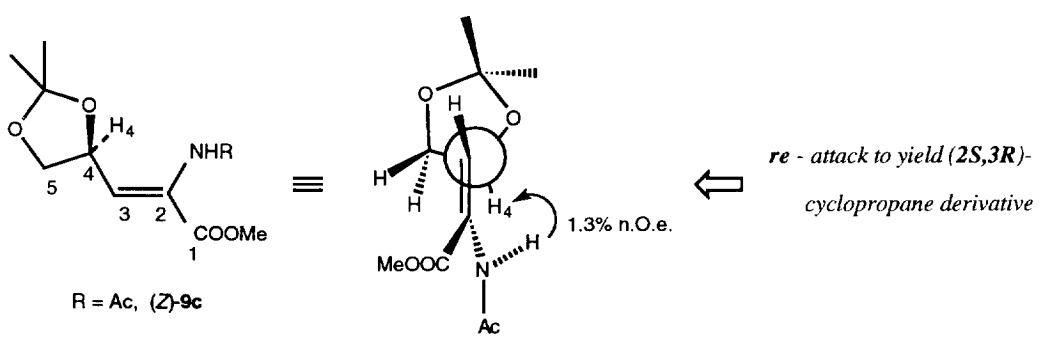


Fig 1. Preferred conformation for aminopentenoates (Z)-[9a-c] explaining re-attack to produce (2S,3R)-cyclopropane derivatives and evidence of such a conformer for (Z)-9c by means of a % n.O.e. value.

Irradiation with a 125 W medium-pressure mercury-lamp of **10a-c** solutions contained in Pyrex reactors afforded cyclopropanes **11a-c**, respectively. Several trials were carried out to develop the optimal conditions. Table 2 summarizes the results of selected reactions of **10a**. Some conclusions are as follows.

Although solvent and temperature influenced the production of both insertion olefin **12a** and cycloreversion product **9a**, the role of benzophenone as a photosensitizer was crucial. Thus, in absence of benzophenone, the reaction was faster at low temperature in dilute toluene solution. Nevertheless, the best result was obtained when 0.015 - 0.04 M solutions of pyrazoline in dichloromethane containing 0.1 equivalents of benzophenone was irradiated at -78° C for about 15 minutes, affording cyclopropane **11a** in quantitative yield. These results were extended to the decomposition of pyrazolines **10b** and **10c** to cyclopropanes **11b** and **11c**, respectively.[9]

*Table 2. Photochemically induced decomposition reactions of pyrazoline **10a**.*

Solvent	Molar concentration	Eq of Ph_2CO	Temp (C)[(a)]	Time	**11a** % Yield	Other products[(b)] % Yield
Toluene	0.17	---	25	14 h	39	8
Toluene	0.11	---	25	10 h	54	13
Toluene	0.11	---	-78	50 min	81	7
Toluene	0.02	---	-78	35 min	80	5
Toluene	0.02	0.1	-78	2.5 h	79	6
CH_2Cl_2	0.02	0.1	25	1 h	86	3
CH_2Cl_2	0.09	0.1	-78	25 min	97	2
CH_2Cl_2	0.02	0.1	-78	13 min	100	--
CH_2Cl_2	0.02	---	-78	1 h	65	30

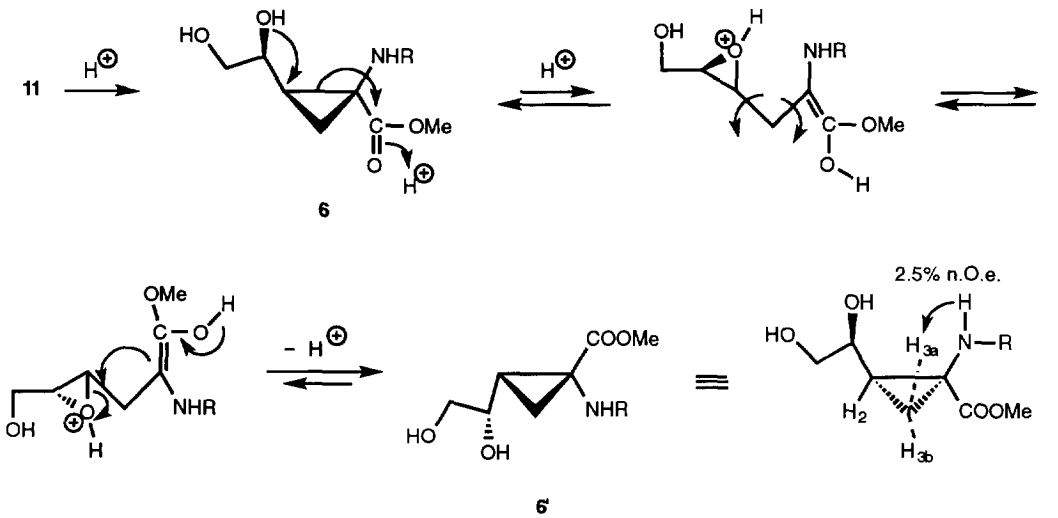
[(a)] Referred to external temperature. [(b)] They include products **9** and **12**.

3. Synthetic routes to amino acids 1 - 5.

The subsequent synthetic step involved hydrolysis of the acetonide in substrates **11a-c**. Mild conditions were needed to avoid the production of epimeric diols as a result of cyclopropane-ring opening and latter closure with the consequent epimerization at *C-1* and *C-2*. Such a process is favoured by the electron-donor neighbouring effect of the secondary hydroxyl group stabilizing a carbocation that results from ester enolization in acid medium, as represented in Scheme 4. Similar processes have been described for related push-pull cyclopropane systems.[10]

Thus, treatment of **11a-c** in methanol with some drops of 5% HCl at room temperature for 4-4.5 hours afforded diols **6a-c**, respectively, in quantitative yields. A 1:1 mixture of diols **6a-c** and **6'a-c** were obtained, respectively, when **11a-c** were treated with acid at room temperature for 5 days.

Epimers were identified by ^1H and ^{13}C NMR being especially significant the absorptions of the cyclopropane proton H_2 at δ 1.78 in **6** and 1.96 in **6'** (data referred to **6a** and **6'a**). Isomers **6'**, as well as isomers **6**, did not undergo lactonization under heating in acid medium as a consequence of the *trans* relationship for the diol and ester substituents. This stereochemistry was also verified by a significant % n.O.e. value between N*H* and H_{3a} protons as shown in Scheme 4. In turn, protons H_{3a} (δ 1.09) and H_{3b} (δ

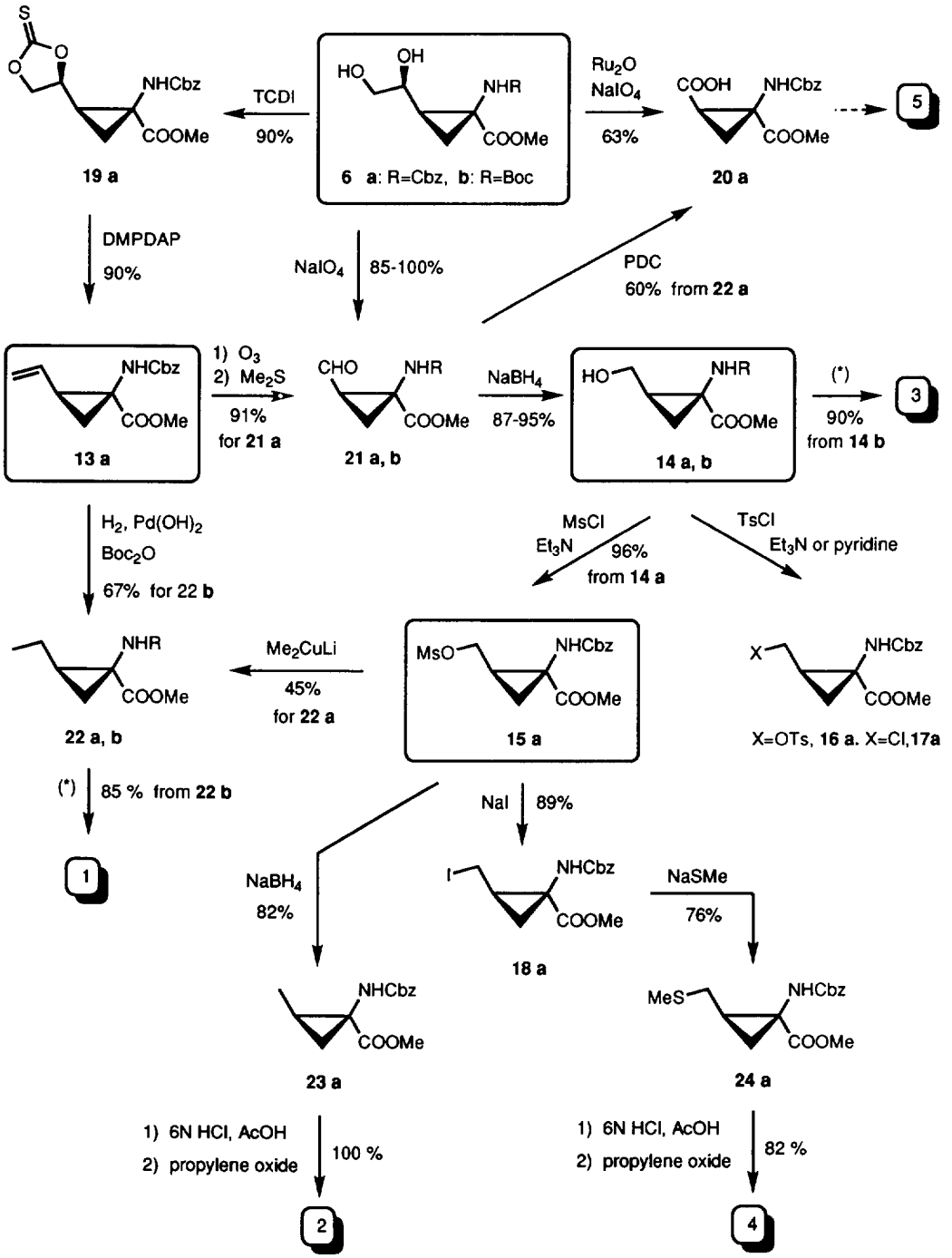


Scheme 4

1.53) were easily assigned on the basis of the coupling costant values $J_{3b,2}$ = 8.0 Hz and $J_{3a,2}$ = 9.5 Hz, corresponding to a *cis* or a *trans* stereochemistry, respectively. Moreover, diol **6'a** was oxidized to a carboxylic acid, m.p. 119-121 C / [α] +110.4, which was the enantiomer of acid **20a**, m.p. 118-119 C / $[\alpha]_D$ -112.0, obtained by oxidation of **6a** (Scheme 5).

Diols **6a** and **6b** were chosen to pursue the synthetic sequences (Scheme 5) since the *N*-Cbz and *N*-Boc functions are more convenient and easier to remove than an acetamide. Diol **6a** was converted into the vinyl cyclopropane **21a** in two steps by using the Corey-Hopkins procedure to obtain olefins from 1,2-diols *via* a thiocarbonate derivative as intermediate. This method was modified by using thiocarbonylimidazole (TCDI) in refluxing THF, instead of thiophosgene/DMAP as in the original protocol.[11] In this way, thiocarbonate **19a** was obtained in 90% yield and this compound was treated with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (DMPDAP) to afford **13a** in 90% yield. This product is interesting because simple chemical transformations of the double bond could provide synthetic entries to different cyclopropane derivatives. An application was the synthesis of *allo*-coronamic acid, **1**. This product is a substrate for 1-butene biosynthesis in plants.[4]

Attempts to hydrogenate the double bond in **13a** in the presence of 10% palladium on charcoal in a variety of conditions were unsatisfactory, as was treatment with tosylhydrazine at 150 C. Nevertheles, hydrogenation of **13a** in methanolic solution by using 20% palladium hydroxide on charcoal in the presence of Boc_2O afforded **22b** in 67% yield. This product was hydrolyzed in mild conditions according to a three sequential-step procedure that involved ester saponification with 1N sodium hydroxide and subsequent acid hydrolysis of the carbamate by the action of 1N HCl at room temperature for 24 hours, followed by treatment with a little excess propylene oxide at the same temperature. The resultant aqueous solution was eluted through a commercial C_{18}-reverse phase cartridge to afford free amino acid **1** in 45% overal yield from aminopentenoate (*Z*)-**9a**. This is the highest yield reported for the enantioselective synthesis of *allo*-coronamic acid from an easily available precursor.[12]



(*) 1) 1N NaOH, 2) 1N HCl, 3) propylene oxide.

Scheme 5

Another synthetic route was derived from **13a** *via* aldehyde **21a** which was prepared in 91% yield through ozonolysis of the double bond. This aldehyde could be obtained quantitatively, however, from direct oxidative cleavage of diol **6a** with $NaIO_4$. Similarly, diol **6b** gave aldehyde **21b** in 85% yield.

Aldehydes **21a,b** constitute an important branching point in the divergent synthetic routes to amino acids **2-5**. Thus, they can be oxidized to provide compound **20a**, a precursor of **5**, or reduced to afford alcohols **14a,b** which are precursors of amino acids **2, 3** and **4**.

Aldehyde **21a** was treated with pyridinium dichromate to afford **20a** in 60% yield (60% overall yield from (*Z*)-**9a**). This compound was also obtained from oxidation of diol **6a** with catalytic $Ru_2O.xH_2O$ in the presence of sodium periodate (63% overall yield). The protein amino acid surrogate **20a** is suitably protected for incorporation into peptidomimetics.

Reduction of aldehydes **21a** and **21b** with sodium borohydride in methanol furnished alcohols **14a** and **14b** in 87 and 95% yields, respectively. The synthesis of (-)-(*Z*)-2,3-methanohomoserine **3** was efficiently achieved by hydrolysis of **14b**[13] following the same protocol than that described above for **1**. (*Z*)-2,3-Methanohomoserine is an analogue of the precursor to the plant growth hormone etylene, and has been implicated in the generation of antibodies.[13] Moreover, it has been functionalized to *allo*-coronamic acid[12a] and carnosadine.[14] Our synthetic route provides **3** in 47% overall yield from (*Z*)-**9**, being the shortest and more efficient synthesis described up to present for this amino acid.[13,15]

Amino acids **2** and **4** were also envisaged as synthetic target molecules to explore the versatility and the scope of our methodology. *allo*-Norcoronamic acid has been shown to be a substrate and an inhibitor of the ethylene-forming enzyme (EFE) in mung bean hypocotyls.[5] On the other hand, peptidomimetics of the anti-opiate neuropeptide Phe-Met-Arg-Phe-NH_2 have been synthesized by exchanging the Met with (-)-(*Z*)-2,3-methanomethionine [(-)-(*Z*)-cyclo-Met] **4**, and the other three isomers of cyclo-Met.[16] All four derivatives induced more morphine abstinence signs in morphine addicted rats and exhibited exceptional proteolytic stability towards carboxypeptidase or leucine aminopeptidase digestion, respectively.

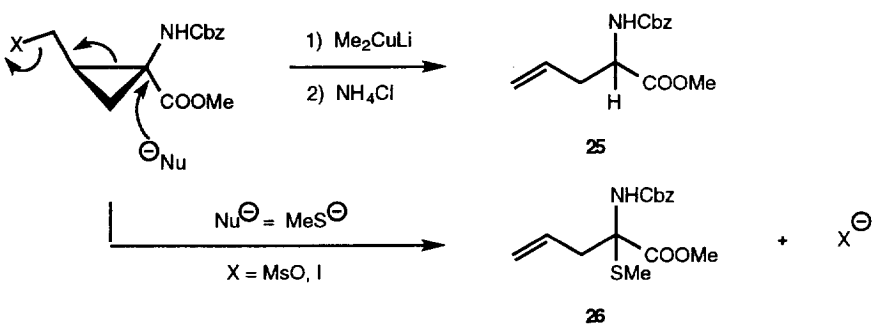
In order to accomplish the syntheses of both amino acids **2** and **4** was necessary to transform the hydroxyl group in **14** into other functionalities able to be reduced to **23**, or to afford **24** according to a nucleophilic substitution process. Mesylate **15a** was a crucial intermediate leading to such amino acids as shown in Scheme 5.

The syntheses of mesylate **15a** and tosylate **16a** were performed in the usual way. Compound **14a** reacted smoothly with tosyl chloride in pyridine or triethylamine to afford mixtures of tosylate **16a**, chloride **17a**,[14] and recovered starting material. Long reaction times favoured the production of chloride **17a** which was obtained in 71% yield along with remaining alcohol **14a** (8%), after a 96 hours period; tosylate **16a** being not detected in this case. In contrast, reaction between **14a** and mesyl chloride in triethylamine for ten minutes afforded mesylate **15a** in 96% yield. This compound was reacted with sodium iodide in acetone to afford iodide **18a** in 89% yield.

Although attempts to reduce chloride **17a** or iodide **18a** by the action of tributyltin hydride or samarium iodide or under catalytic hydrogenation conditions were fruitless, compound **23a** was easily obtained in 82% yield from reduction of mesylate **15a** with sodium borohydride in HMPA. Quantitative acid catalyzed cleavage of the methyl ester and the benzyl carbamate in **23a** by using 6N HCl and some drops of acetic acid furnished (-)-*allo*-norcoronamic acid **2** in 68% overall yield from the precursor aminopentenoate (*Z*)-**9a**.[17,18]

Mesylate **15a** was also reacted with lithium dimethylcuprate giving **22a** in 45% yield along with product **25** which was identified by NMR (Scheme 6). This compound results from cyclopropane-cleavage concomitant to a reductive elimination of mesylate.[19] Ethylcyclopropane **22a** is precursor of (-)-*allo*-coronamic acid **1**, but the low yield of this last reaction confirmed the synthesis through the vinyl derivative **13a** as a more advantageous way (Scheme 5).

In order to realize the synthesis of (-)-(Z)-cyclo-Met **4**, displacement of mesylate from **15a** with thiomethoxide was attempted. Results were, however, discouraging since reaction of **15a** with sodium thiomethoxide in solvents such as DMF, THF or MeOH, in different conditions, afforded always a mixture of **24a** and vinyl acyclic derivative **26** (Scheme 6). This compound results from the preferential nucleophilic attack at the α-carbonyl position in an S_N2'-type sense. A similar product was obtained by Burgess in connection with the synthesis of (*E*)-cyclo-Met.[20]



Scheme 6

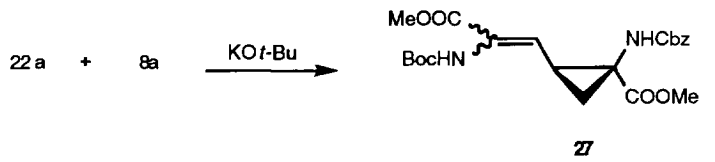
Chloride **17a** remained unaltered under treatment with sodium thiomethoxide but iodide **18a** reacted to give sulfide **24a**. The sequential order in the addition of reactants was critical in this case. Thus, while a mixture of **24a** (45% yield) and **26** (20% yield) was produced when the nucleophile was added to a methanolic solution of **18a**, thioether **24a** was obtained in 76% yield as the only defined reaction product when the reverse addition was performed. Finally, acid hydrolysis of **24a** yielded amino acid **4**, the second asymmetric synthesis of (-)-(Z)-cyclo-Met being thus accomplished in 46% overall yield from precursor (Z)-**9a**.[20]

CONCLUSIONS AND PERSPECTIVES

We have developed a highly versatile, stereocontrolled, and efficient methodology to prepare a variety of cyclopropane amino acids from homochiral aminopentenoates as common precursors, which are easily available on a multigramme scale.

The target molecules of this work include natural products and protein methanologs. Cyclopropane amino acid derivatives bearing substituents in all oxidation levels such as carboxyl, formyl, hydromethyl, and alkyl (methyl, ethyl) have been synthesized. In the same level, sulfonic esters (Ms, Ts), halides (Cl, I) and sulfides have been prepared as alcohol derivatives. All these features verify the scope of our method.

Other synthetic applications based in Wittig-type condensations remain unexplored. For instance, we have prepared compound **27** by condensation of aldehyde **22a** and phosphonate **8a** (Scheme 7).



27

Scheme 7

This molecule contains both a 2,3-methanoamino acid and a 2,3-didehydroamino acid functions. It is interesting to note that the two amines are differently protected thus making possible their selective deprotection in order to incorporate these moieties in conformationally constrained peptide surrogates. Active research in this field is being carried out in our laboratory.

EXPERIMENTAL SECTION

Flash column chromatography was carried out on silica gel (240-400 mesh) unless otherwise stated. Melting points were determined on a hot stage and are uncorrected. Distillation of small amounts of material was effected in a bulb-to-bulb distillation apparatus, with oven temperatures (o.t.) being reported. Electron-impact mass spectra were recorded at 70 eV. Chemical shifts in NMR spectra are given in ppm relative to internal TMS (δ scale).

Methyl (*S*)-(-)-(*Z*)-2-*N*-acetylamino-3-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)-2-propenoate, (*Z*)-9c. Aldehyde **7** (0.9 g, 7.0 mmol) in anhydrous THF (4 mL) was added to a stirred solution of LDA (from 1.1 mL (7.7 mmol) of diisopropylamine and 4.8 mL of a 1.6M solution of BuLi in hexane) in 10 mL of THF at -78° C under nitrogen atmosphere. The mixture was heated at room temperature and then stirred for 3 h. Solvents were removed under vacuo and the residue was poured into dichloromethane (20 mL). The resultant solution was washed with saturated aqueous NaCl (2x10 mL) and extracted with dichloromethane (4x15 mL). The combined organic extracts were dried and the solvent was evaporated at reduced pressure. The residue was chromatographed (1:1 ethyl acetate-hexane) to afford a 4:1 mixture of pentenoates (*Z*)-**9** and (*E*)-**9** (1.3 g, 82% yield). A further chromatography by using 1:6 ethyl acetate-hexane as eluent allowed the obtention of pure (*Z*)-**9** while (*E*)-**9** remained contaminated. Physical and spectroscopic data for (*Z*)-**9** are as follows. O.t. 147-150° C (0.1 mm Hg); $[\alpha]_D$ -78.1 (c= 0.64, $CHCl_3$); IR (film) 3500-3000 (br), 1728, 1665 cm^{-1}; MS, m/e 243 (M, 1), 228 (15), 185 (50), 143 (66), 128 (24), 126 (32), 123 (26), 84 (30), 72 (43), 43 (100); 250 MHz ^{1}H-NMR ($CDCl_3$) 1.30 (s, C*H*$_3$), 1.39 (s, C*H*$_3$), 2.05 (s, C*H*$_3$), 3.73 (s, -OC*H*$_3$), 3.80 (dd, $H_{5a'}$, $J_{5a',5b'}$= 8.8 Hz, $J_{5a',4'}$= 6,2 Hz), 4.28 (dd, $H_{5b'}$, $J_{5b',5a'}$= 8.8 Hz, $J_{5b',4'}$= 6.6 Hz), 4.62 (ddd, $H_{4'}$, $J_{4',3}$= 8.4 Hz, $J_{4',5b'}$= 6.6 Hz, $J_{4',5a'}$= 6.2 Hz), 6.45 (d, $J_{3,4}$= 8.40 Hz), 7.30 (broad s, N-*H*); 62.5 MHz ^{13}C-NMR ($CDCl_3$) 23.4, 25.29, 26.54, 52.58, 68.24, 72.90, 109.57, 125.39, 132.18, 164.62, 168.91. Anal. Calcd. for $C_{11}H_{17}O_5N$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.16; H, 7.28; N, 5.60.

Cycloaddition of diazomethane to pentenoates (Z)-[9a-c]: Synthesis of pyrazolines 10a-c. The general procedure is described for the synthesis of **10a**. An ethereal solution of excess diazomethane was distilled onto (Z)-**9a** (2.3 g, 8.3 mmol) in 4 mL of ether. The light-protected resultant solution was stirred at room temperature for 4 h, then excess diazomethane and solvent were removed and the oily residue was chromatographed (1:1 ethyl acetate-hexane) to give quantitatively pyrazoline **10a** (3.1 g). Pyrazolines **10b** and **10c** were prepared in a similar manner.

Methyl (3*R*, 4*R*, 4'*S*)-(-)-3-*N*-benzyloxycarbonylamino-4-(2', 2'-dimethyl-1', 3'-dioxolan-4'-yl)-1-pyrazoline-3-carboxylate, 10a. Oil, $[\alpha]_D$ -140.0 (c= 1.4, $CHCl_3$); IR (film) 3500-3100 (br), 1736 cm^{-1}; MS, m/e 362 (M-15, 1), 169 (4), 108 (7), 107 (5), 91 ($PhCH_2$, 9), 79 (100); 250 MHz ^{1}H-NMR (acetone d_6) 1.18 (s, CH_3), 1.28 (s, CH_3), 2.81 (dt, H_4, $J_{4,5a}$= 8.4 Hz, $J_{4,4'}$= $J_{4,5b}$= 4.4 Hz), 3.58 (dd, $H_{5a'}$, J'= 7.7 Hz, J"= 5.8 Hz), 3.73 (br s, -OCH_3), 3.94-4.08 (m, 2H, $H_{5b'}$+$H_{4'}$), 4.69 (dd, H_{5a}, $J_{5a,5b}$= 18.3 Hz, $J_{5a,4}$= 8.4 Hz), 4.89 (dd, H_{5b}, $J_{5b,5a}$= 18.3 Hz, $J_{5b,4}$= 4.4 Hz), 5.11 (s, coalesced AB system, -CH_2Ph), 7.35 (broad s, 5H), 7.47 (broad s, N-*H*); 62.5 MHz ^{13}C-NMR (acetone d_6) 25.08, 26.54, 42.15, 53.58, 67.28, 68.68, 74.00, 81.21, 102.76, 109.57, 128.63 (2C), 128.80, 129.18 (2C), 137.60, 155.67, 168.31. Anal. Calcd. for $C_{18}H_{23}O_6N_3$: C, 57.29; H, 6.14; N, 11.13. Found: C, 57.36; H, 6.21; N, 10.96.

Methyl (3*R*, 4*R*, 4'*S*)-3-*N*-*tert*-butoxycarbonylamino-4-(2', 2'-dimethyl-1', 3'-dioxolan-4'-yl)-1-pyrazoline-3-carboxylate, 10b. Oil, IR (film) 3500-3200 (br), 1744, 1725 cm^{-1}; MS, m/e 272 (M-71, 8), 158 (15), 101 (72), 59 (23), 57 (100), 43 (44), 41 (25); 250 MHz ^{1}H-NMR ($CDCl_3$) 1.21 (s, CH_3), 1.33 (s, CH_3), 1.40 (s, 3xCH_3), 2.66 (complex absorption, H_4), 3.47 (complex absorption, $H_{4a'}$), 3.75 (br s, -OCH_3), 4.04 (complex absorption, 2H, $H_{5b'}$+$H_{4'}$), 4.72 (dd, H_{5a}, $J_{5a,5b}$= 18.2 Hz, $J_{5a,4}$= 8.4 Hz), 4.94 (dd, H_{5b}, $J_{5b,5a}$= 18.2 Hz, $J_{5b,4}$= 4.4 Hz), 6.11 (broad s, N-*H*); 62.5 MHz ^{13}C-NMR ($CDCl_3$) 24.78, 26.31, 28.03 (3 x C), 41.56, 53.38, 60.27, 68.11, 73.48, 81.29, 101.36, 109.17, 153.00, 168.83.

Methyl (3*R*, 4*R*, 4'*S*)-3-*N*-acetylamino-4-(2', 2'-dimethyl-1', 3'-dioxolan-4'-yl)-1-pyrazoline-3-carboxylate, 10c. Oil, IR (film) 3500-3100 (br), 1743, 1661 cm^{-1}; MS, m/e 270 (M-15, 3), 226 (5), 200 (5), 156 (31), 126 (33), 114, (33), 101 (33), 43 (100); 250 MHz ^{1}H-NMR ($CDCl_3$) 1.21 (s, CH_3), 1.31 (s, CH_3), 2.07 (s,CH_3), 2.87 (dt, H_4, $J_{4,5b}$=$J_{4,4'}$= 8.04 Hz, $J_{4,5a}$= 3.66 Hz), 3.48 (complex absorption, $H_{4'}$), 3.75 (s, -OCH_3), 3.98 (complex absorption, 2H, $H_{5a'}$+$H_{5b'}$), 4.68 (dd, H_{5a}, $J_{5a,5b}$= 17.9 Hz, $J_{5a,4}$= 3.7 Hz), 5.00 (dd, H_{5b}, $J_{5b,5a}$= 17.9 Hz, $J_{5b,4}$= 8.0 Hz), 7.01 (broad s, N-*H*); 62.5 MHz ^{13}C-NMR ($CDCl_3$) 22,61, 24.60, 26.10, 40.97, 53.56, 67.65, 73.00, 80.50, 102.30, 109.28, 166.99, 169.84.

Photochemically induced decomposition of pyrazolines 10a-c: Synthesis of cyclopropanes 11a-c. The general procedures are described for the decomposition of **10a**.

Method A. A stirred solution of pyrazoline **10a** (1.17 g, 3.10 mmol) in anhydrous toluene (45 mL) contained in a Pyrex reactor under nitrogen atmosphere, cooled at -78° C, was irradiated with a 125 W medium-pressure mercury-lamp for 35 minutes. Solvent was removed and the residue was chromatographed (1:5 ethyl acetate-hexane) to afford the cycloreversion product (Z)-**9a** (71 mg, 7% yield) and cyclopropane **11a** (0.89 g, 83% yield).

Method b. A solution of pyrazoline **10a** (1.07 g, 2.84 mmol) and benzophenone (52 mg, 0.28 mmol) in dry dichloromethane (70 mL) contained in a Pyrex reactor under nitrogen atmosphere, cooled at -78° C, was

irradiated with a 125 W medium-pressure mercury-lamp for 18 minutes. Solvent was removed and the residue was chromatographed (1:3 ethyl acetate-hexane) to give quantitatively cyclopropane **11a** (0.99 g).

Methyl (1*S*, 2*R*, 4'*S*)-(-)-1-*N*-benzyloxycarbonylamino-2-(2', 2'-dimethyl-1', 3'-dioxolan-4'-yl)cyclopropanecarboxylate, 11a. Crystals, m.p. 63-65° C (from ethyl acetate-pentane); $[\alpha]_D$ -57.3 (c= 1.5, $CHCl_3$); IR (KBr) 3500-3150 (br), 1733 cm^{-1}; MS, m/e 258 (M-91, 4), 200 (5), 139 (5), 101 (15), 92 (9), 91 ($PhCH_2^+$, 100), 65 (9), 59 (5), 43 (9); 250 MHz ^{1}H-NMR (acetone d_6) 1.22 (s, C*H*$_3$), 1.23 (dd, H_{3a}, $J_{3a,2}$= 7.6 Hz, $J_{3a,3b}$= 5.1 Hz), 1.35 (s, C*H*$_3$), 1.51 (dd, H_{3b}, $J_{3b,2}$= 9.1 Hz, $J_{3b,3a}$= 5.1 Hz), 1.88 (m , H_2), 3.62 (s, -OC*H*$_3$), 3.70 (m, $H_{4'}$), 3.76 (dd, $H_{5a'}$, $J_{5a',5b'}$= 8.0 Hz, $J_{5a',4'}$=6.0 Hz), 3.98 (dd, $H_{5b'}$, $J_{5b',5a'}$= 8.0 Hz, $J_{5b',4'}$= 6.0 Hz), 5.05 (d, 1H, J_{gem}= 12.4 Hz), 5.13 (d, 1H, J_{gem}= 12.4 Hz), 7.05 (broad s, N-*H*), 7.30-7.37 (complex absorption, 5H); 62.5 MHz ^{13}C-NMR (acetone d_6) 20.35, 25.24, 26.56, 30.09, 38.06, 52.50, 66.85, 69.56, 75.44, 108.59, 127.82 (2C), 128.06, 128.32 (2C), 136.00, 156.49, 172.17. Anal. Calcd. for $C_{18}H_{23}O_6N$: C, 61.86; H, 6.64; N, 4.01. Found: C, 61.72; H, 6.63; N, 4.08.

Methyl (1*S*, 2*R*, 4'*S*)-(-)-1-*N*-*tert*-butoxycarbonylamino-2-(2', 2'-dimethyl-1', 3'-dioxolan-4'-yl)cyclopropanecarboxylate, 11b. Crystals, m.p. 102-104° C (from ethyl acetate-pentane); $[\alpha]_D$ -68.9 (c= 1.03, $CHCl_3$); IR (KBr) 3378, 1730, 1691 cm^{-1}; MS, m/e 315 (M, 1), 258 (29), 200 (24), 139 (27), 101 (83), 57 (100), 43 (22); 250 MHz ^{1}H-NMR ($CDCl_3$) 1.13 (dd, H_{3a}, $J_{3a,2}$= 7.3 Hz, $J_{3a,3b}$= 5.1 Hz), 1.28 (s, C*H*$_3$)1.38 (s, 4 x C*H*$_3$), 1.57 (dd, H_{3b}, $J_{3b,2}$= 9.1 Hz, $J_{3b,3a}$= 5.1 Hz), 1.95 (dd , H_2, $J_{2,3b}$= 9.13, $J_{2.3a}$= 7.6 Hz), 3.64 (s, -OC*H*$_3$), 3.76 (m, 2H, $H_{4'}$+$H_{5a'}$), 4.05 (dd, $H_{5b'}$, $J_{5b',5a'}$= 8.4 Hz, $J_{5b',4'}$= 6.2 Hz), 5.13 (broad s, N-*H*); 62.5 MHz ^{13}C-NMR ($CDCl_3$) 20.43, 25.40, 26.70, 28.08 (3C), 29.93, 38.05, 52.41, 69.72, 75.87, 80.22, 108.60, 155.89, 172.41. Anal. Calcd. for $C_{15}H_{25}O_6N$: C, 57.13; H, 7.99; N, 4.44. Found: C, 57.19; H, 8.01; N, 4.47.

Methyl (1*S*, 2*R*, 4'*S*)-(-)-1-*N*-acetylamino-2-(2', 2'-dimethyl-1', 3'-dioxolan-4'-yl)cyclopropanecarboxylate, 11c. Crystals, m.p. 124-125° C (from ethyl acetate-pentane); $[\alpha]_D$ -100.0 (c= 1.11, $CHCl_3$); IR (KBr) 3500-3100 (br), 1722, 1667 cm^{-1}; MS, m/e 242 (M-15, 10), 200 (28), 157 (22), 140 (46), 114 (17), 108 (20), 101 (56), 80 (37), 59 (18), 43 (100); 250 MHz ^{1}H-NMR ($CDCl_3$) 1.16 (dd, H_{3a}, $J_{3a,2}$= 7.7 Hz, $J_{3a,3b}$= 5.1 Hz), 1.29 (s, C*H*$_3$)1.41 (s, C*H*$_3$), 1.59 (dd, H_{3b}, $J_{3b,2}$= 9.5 Hz, $J_{3b,3a}$= 5.1 Hz), 1.97 (s, C*H*$_3$) , 2.07 (H_2, dt, $J_{2,3b}$= 9.5, $J_{2,3a}$= $J_{2,4'}$= 7.7 Hz), 3.65 (s, -OC*H*$_3$), 3.73 (dd, $H_{4'}$, $J_{4',2}$= 7.7 Hz, $J_{4',5b'}$= 6.2 Hz), 3.85 (dd, $H_{5a'}$, $J_{5a',5b'}$= 8.4 Hz, $J_{5a',4'}$= 6.2), 4.03 (dd, $H_{5b'}$, $J_{5b',5a'}$= 8.4 Hz, $J_{5b',4'}$= 6.2 Hz), 5.97 (broad s, N-*H*); 62.5 MHz ^{13}C-NMR ($CDCl_3$) 19.76, 22.87, 25.50, 26.72, 29.25, 37.59, 52.65, 69.81, 75.25, 108.85, 171.38, 171.56. Anal. Calcd. for $C_{12}H_{19}O_5N$: C, 56.02; H, 7.44; N, 5.44. Found: C, 56.01; H, 7.51; N, 5.44.

Hdrolysis of the acetonides: Diols 6a-c and 6'a. A typical experiment to obtain diol **6a** was run as follows. A mixture of **11a** (0.9 g, 2.5 mmol) and ten drops of 5% HCl in methanol (20 mL) was stirred at room temperature for 2.5 h. Then the solvent was evaporated and the residue was chromatographed (4:1 ethyl-acetate-hexane) to afford quantitatively **6a** (0.8 g). If the stirring was continued for several hours, a mixture of **6a** and **6'a** was obtained. Epimer **6'a** was isolated and characterized from such a mixture.

Methyl (1*S*, 2*R*, 1'*S*)-(-)-1-*N*-benzyloxycarbonylamino-2-(1', 2'-dihydroxyethyl)cyclopropanecarboxylate, 6a. Crystals, m.p. 73-76° C (from ethyl acetate-pentane); $[\alpha]_D$ -40.0 (c= 1.25, $CHCl_3$); IR

(KBr) 3700-2900 (br), 1727, 1696 cm^{-1}; MS, m/e 309 (M, 0.7), 158 (6), 127 (6), 126 (6), 108 (8), 107 (6), 92 (8), 91 ($PhCH_2$, 100), 65 (6); 250 MHz ^{1}H-NMR (acetone d_6) 1.23 (dd, H_{3a}, $J_{3a,2}$= 7.3 Hz, $J_{3a,3b}$= 4.7 Hz), 1.61 (dd, H_{3b}, $J_{3b,2}$= 9.1 Hz, $J_{3b,3a}$= 4.7 Hz), 1.78 (m, H_2), 3.46 (m, 1H), 3.61 (broad s, -OCH_3), 4.06 (m, 1H), 4.17 (m, 1H), 5.02-5.13 (dd, AB system, -CH_2Ph, J_{gem}= 12.5 Hz), 7.29-7.37 (complex absorption, 5H); 62.5 MHz ^{13}C-NMR (acetone d_6) 21.34, 31.87, 38.90, 52.47, 66.60, 66.81, 71.53, 128.39 (2C), 128.48, 129.05 (2C), 137.87, 157.39, 173.36. Anal. Calcd. for $C_{15}H_{19}O_6N$: C, 58.23; H, 6.19; N, 4.53. Found: C, 58.10; H, 5.88; N, 4.47.

Methyl (1*R*, 2*S*, 1'*S*)-(+)-1-*N*-benzyloxycarbonylamino-2-(1', 2'-dihydroxyethyl)cyclopropanecarboxylate, 6a'. Crystals, m.p. 100-102° C (from ethyl acetate-hexane); $[\alpha]_D$ +54.4 (c= 1.25, $CHCl_3$); IR (KBr) 3600-2900 (br), 1780, 1703 cm^{-1}; MS, m/e 309 (M, 2), 127 (7), 126 (6), 108 (11), 107 (8), 92 (10), 91 ($PhCH_2$, 100), 65 (4); 250 MHz ^{1}H-NMR (acetone d_6) 1.09 (dd, H_{3a}, $J_{3a,2}$= 8.0 Hz, $J_{3a,3b}$= 5.1 Hz), 1.53 (dd, H_{3b}, $J_{3b,2}$= 9.5 Hz, $J_{3b,3a}$= 5.1 Hz), 1.96 (m, H_2), 3.55-3.64 (complex absorption, 6H, OCH_3+$H_{1'}$+$H_{2a'}$+$H_{2b'}$), 5.12 (d, 1H, CH_2Ph, J_{gem}= 12.7 Hz), 5.17 (d, 1H, CH_2Ph, J_{gem}= 12.7 Hz), 7.14 (broad s, N-*H*), 7.36-7.39 (complex absorption, 5H); 62.5 MHz ^{13}C-NMR (acetone d_6) 20.27, 32.65, 38.27, 52.61, 66.10, 67.21, 72.74, 128.43 (2C), 128.67, 129.13 (2C), 137.55, 159.50, 173.25. Anal. Calcd. for $C_{15}H_{19}O_6N$: C, 58.23; H, 6.19; N, 4.53. Found: C, 58.14; H, 6.19; N, 4.48.

Methyl (1*S*, 2*R*, 1'*S*)-(-)-1-*N*-*tert*-butoxycarbonylamino-2-(1', 2'-dihydroxyethyl)cyclopropanecarboxylate, 6b. Crystals, m.p. 131-132° C (from methanol-ethyl acetate); $[\alpha]_D$ -54.6 (c= 1.08, CH_3OH); IR (KBr) 3500-3100 (br), 1726, 1680 cm^{-1}; MS, m/e 201 (M-56, 3), 114 (21), 83 (11), 59 (11), 57 (100), 54 (14), 43 (10), 41 (32); 250 MHz ^{1}H-NMR (acetone d_6) 1.20 (dd, H_{3a}, $J_{3a,2}$= 7.7 Hz, $J_{3a,3b}$= 4.7 Hz), 1,44 (s, 3xCH_3), 1.59 (dd, H_{3b}, $J_{3b,2}$= 9.5 Hz, $J_{3b,3a}$= 4.7 Hz), 1.77 (m, H_2), 2.10 (broad s, O*H*), 2,91 (broad s, O*H*), 3.46 (m, 1H, $H_{1'}$), 3.66 (s, -OCH_3), 3.98 (d, $H_{2a'}$, J= 5.1 Hz), 4.11 (m, $H_{2b'}$), 6.49 (broad s, N*H*); 62.5 MHz ^{13}C-NMR (acetone d_6) 21.02, 28.17 (3C), 31.64, 38.69, 52.05, 66.70, 71.40, 79.12, 156.60, 175.80. Anal. Calcd. for $C_{12}H_{21}O_6N$: C, 52.35; H, 7.69; N, 5.09. Found: C, 52.48; H, 7.37; N, 5.00.

Methyl (1*S*, 2*R*, 1'*S*)-(-)-1-*N*-acetylamino-2-(1', 2'-dihydroxyethyl)cyclopropanecarboxylate, 6c. Extremely hygroscopic solid. IR (KBr) 3600-3000 (br), 1728, 1667 cm^{-1}; 250 MHz ^{1}H-NMR (acetone d_6) 1.16 (dd, H_{3a}, $J_{3a,2}$=7.3 Hz, $J_{3a,3b}$=5.1 Hz), 1.44 (dd, H_{3b}, $J_{3b,2}$=9.51 Hz, $J_{3b,3a}$=5.1 Hz), 1.91 (complex absorption, CH_3CO + H_2), 3.28 (s, O*H*), 3.60 (s, OCH_3), 3.67 (m, $H_{1'}$), 3.76 (dd, $H_{2'a}$, J=8.4 Hz, J'=5.8 Hz), 3.97 ($H_{2'b}$, J=8.4 Hz, J'=5.8 Hz); 62.5 MHz ^{13}C-NMR (acetone d_6) 20.28, 22.46, 30.37, 37.80, 52.47, 70.50, 76.76, 171.63, 172.69.

Methyl (1*S*, 2*R*, 4'*S*)-(-)-1-*N*-benzyloxycarbonylamino-2-(1', 3'-dioxolan-2'-thiocarbonyl-4'-yl)cyclopropanecarboxylate, 19a. A mixture of diol **6a** (47 mg, 0.15 mmol) and TCDI (58 mg, 0.29 mmol) in 4 mL of anhydrous THF were heated to reflux under argon atmosphere for 6 h. Then the mixture was cooled to room temperature and solvent was removed at reduced pressure. The residue was chromatographed (4:1 ethyl acetate-hexane) to afford thiocarbonate **19a** (47 mg, 90% yield). Crystals, m.p. 108-110° C (from ethyl acetate-pentane); $[\alpha]_D$ -72.3 (c= 1.30, $CHCl_3$); IR (KBr) 3362 (br), 1731, 1694 cm^{-1}; MS, m/e 351 (M, 0.15), 260 (M-91, 0.5), 91 ($PhCH_2^+$, 100), 65 (10), 60 (7), 41 (7); 250 MHz ^{1}H-NMR ($CDCl_3$) 1.30 (dd, H_{3a}, $J_{3a,2}$= 7.3 Hz, $J_{3a,3b}$= 5.8 Hz), 1.74 (dd, H_{3b}, $J_{3b,2}$= 9.3 Hz, $J_{3b,3a}$= 5.8 Hz), 2.26 (m, H_2), 3.69 (s, 3 H,

-OC*H*$_3$), 4.37-4.68 (complex absorption, 3H, $H_{4'}$+$H_{5a'}$+$H_{5b'}$), 5.09 (s, coalesced AB system, -C*H*$_2$Ph), 5.37 (broad s, N-*H*), 7.34 (broad s, 5H); 62.5 MHz ^{13}C-NMR ($CDCl_3$) 20.32, 28.98, 38.79, 53.09, 67.62, 74.46, 82.60, 127.97 (2C), 128.53, 128.61 (2C), 135.62, 156.88, 170.97, 191.67. Anal. Calcd. for $C_{16}H_{17}O_6NS$: C, 54.69; H, 4.88; N, 3.99; S, 9.12. Found: C, 54.68; H, 4.84; N, 3.94; S, 9.05.

Methyl (1*S*, 2*S*)-(+)-1-*N*-benzyloxycarbonylamino-2-vinylcyclopropanecarboxylate, 13a. A mixture of thiocarbonate **19a** (0.5 g, 1.43 mmol) and DMPDAP (0.79 mL, 4.16 mmol) was stirred at 40° C under argon atmosphere for 20 h. Solvent was removed and the oily residue was chromatographed (1:5 ethyl acetate-hexane) to afford vinyl derivative **13a** (0.35 g, 90% yield). Crystals, m.p. 61-62° C (from ethyl acetate-pentane); $[\alpha]_D$ +155.8 (c= 0.95, $CHCl_3$); IR (KBr) 3322 (br), 1732, 1697 cm^{-1}; MS, m/e 276 (M+1, 0.3), 184 (M-91, 9), 92 (10), 91 (100), 80 (13), 65 (15); 250 MHz ^{1}H-NMR ($CDCl_3$) 1.30 (t, H_{3a}, J= J'= 6.3 Hz), 1.93 (dd, H_{3b}, J'= 9.1 Hz, J'= 5.5 Hz), 2.38 (t, H_2, J= J'= 8.3 Hz), 3.59 (broad s, N-), 3.68 (s, 3 H, -OC*H*$_3$), 5.11-5.18 (complex absorption, 3H, $H_{2a'}$ + -C*H*$_2$Ph), 5.24 (d, $H_{2b'}$, J= 17 Hz), 5.49 (m, $H_{1'}$), 7.33 (broad s, 5H); 62.5 MHz ^{13}C-NMR ($CDCl_3$) 22.77, 29.49, 31.30, 39.27, 52.45, 66.84, 118.56, 127.91 (3C), 128.30 (2C), 133.19, 136.03, 156.35, 172.29. Anal. Calcd. for $C_{15}H_{17}O_4N$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.28; H, 6.24; N, 5.09.

Methyl (1*S*, 2*R*)-(-)-1-*N*-*tert*-butoxycarbonylamino-2-ethylcyclopropanecarboxylate, 22b. Boc_2O (0.68 mL, 2.98 mmol) and 20% $Pd(OH)_2$/C (60 mg) were subsequently added to a solution containing **13a** (0.41 g, 1.49 mmol) in 5 mL of MeOH, and the mixture was hydrogenated at room temperature and atmospheric pressure for 4.5 h. Catalyst was removed by filtration and solvent was evaporated. The residue was chromatographed (1:3 ethyl acetate-hexane) to give **22b** as a white solid (0.24 mg, 67%). Crystals, m.p. 59-60° C (from ethyl acetate-pentane); $[\alpha]_D$ -32.0 (c= 1.00, $CHCl_3$); IR (KBr) 3371 (br), 1730, 1692 cm^{-1}; MS, m/e 244 (M+1, 5), 188 (24), 144 (16), 114 (15), 59 (18), 57 (100), 56 (11), 43 (13), 42 (17), 41 (68); 250 MHz ^{1}H-NMR ($CDCl_3$) 0.86 (complex absorption, 1H), 1.00 (t, -C*H*$_3$, J= 7.1 Hz), 1.24-1.35 (m, 2H), 1.43 (s, 3xC*H*$_3$), 1.55-1.63 (m, 2H), 3.66 (s, 3H, -OC*H*$_3$), 4.91 (broad s, N-*H*); 62.5 MHz ^{13}C-NMR ($CDCl_3$) 13.39, 21.39, 22.86 (3C), 28.15, 30.09, 38.28, 52.16, 79.79, 156.27, 173.72. Anal. Calcd. for $C_{12}H_{21}O_4N$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.16; H, 8.73; N, 5.64.

(-)-*allo*-Coronamic acid, 1. 1N NaOH (4.7 mL, 4.7 mmol) was added to a solution containing **22b** (0.23 g, 0.95 mmol) in MeOH (4 mL) and the mixture was stirred at room temperature for 20 h. Then MeOH was removed and the aqueous solution was acidified to pH 1. The resultant white solid was dissolved by addition of ethyl acetate, the layers were separated and the aqueous layer was extracted with ethyl acetate (2x10 mL). The combined organic phases were dried and solvent was evaporated at reduced pressure to give **(1*S*, 2*R*)-(-)-1-*N*-benzyloxycarbonylamino-2-ethylcyclopropanecarboxylic acid** (0.2 g, 92% yield) which was characterized by their physical and spectroscopic data as follows. Crystals, m.p. 145-148° C (from ethyl acetate-pentane); $[\alpha]_D$ -23.3 (c= 0.60, $CHCl_3$); IR (KBr) 3379 (br), 1694 (br) cm^{-1}; MS, m/e 173 (M-57, 5), 100 (20), 87 (20), 59 (16), 57 (100), 41 (27); 250 MHz ^{1}H-NMR (acetone d_6) 0.80 (m, 1H), 1.02 (t, -C*H*$_3$, J= 7.3 Hz), 1.18-1.29 (m, 1H), 1.43 (complex absorption, 1H + 3xC*H*$_3$), 1.39-1.47 (m, 1H), 1.59-1.70 (m, 2H), 6.39 (broad s, N-*H*); 62.5 MHz ^{13}C-NMR ($CDCl_3$) 13.33, 21.39, 23.40, 28.09 (3C), 30.81, 30.09,

37.90, 79.96, 156.30, 179.14. Anal. Calcd. for $C_{11}H_{20}O_4N$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.55; H, 8.12; N, 5.89.

This acid (0.18 g, 0.81 mmol) was dissolved in THF (6 mL) and then 6N HCl (1.3 mL) was added. The mixture was stirred at room temperature for 24 h. Solvents were removed and the resultant white solid was poured into 3 mL of absolute ethanol and propylene oxide (2 mL) was added to the solution which was heated at 35° C for several minutes. Solvents were removed and the residue was dissolved in water (3 mL) and eluted through a C_{18}-reverse phase cartridge to afford, after evaporation of water, pure **(-)-*allo*-coronamic acid 1** (97 mg, 85% from **22b**). Crystals, m.p. 182-186° C (from H_2O-acetone); $[\alpha]_D$ -58.0 (c= 1.00, H_2O) [Lit ref 12f: m.p. 185-187° C dec, $[\alpha]_D$ -60 (c= 0.4, water); ref 12b: $[\alpha]_D$ -52 (c= 1.83, water)]; IR (KBr) 3600-2000 (br), 1593, 1544, 1516 cm^{-1}; 250 MHz ^{1}H-NMR (D_2O) 0.76-0.84 (complex absorption, CH_3+H_{3a}), 1.07-1.22 (m, H_{3b}), 1.24-1.35 (m, CH_2), 1.38-1.53 (m, H_2), 1.39-1.47 (m, 1H), 1.59-1.70 (m, 2H), 6.39 (broad s, N-*H*); 62.5 MHz ^{13}C-NMR (D_2O-acetone d_6) 12.96, 18.54, 20.67, 26.68, 39.36, 174.96.

Oxidation of diols 6a and 6b with $NaIO_4$: Synthesis of aldehydes 21a and 21b. A typical experiment is described for the synthesis of **21a**. Sodium periodate (0.99 g, 4.63 mmol) was added in portions to a stirred and ice-cooled solution of diol **6a** (0.95 g, 3.01 mmol) in 10 mL of THF and 3 mL of water. The mixture was stirred at 0° C for 20 minutes and ether (6 mL) was then added and the produced solid was filtered off. The organic solvents were evaporated from the filtrate and the resultant aqueous residue was extracted with dichloromethane (4x10 mL). The combined organic extracts were dried and the solvent was removed to give a residue which was chromatographed (ethyl acetate) affording aldehyde **21a** in quantitative yield (0.85 g) as a yellowish oil unsuitable to microanalysis. In a similar way, aldehyde **21b** was prepared in 85% yield.

Methyl (1*S*, 2*R*)-(-)-1-*N*-benzyloxycarbonylamino-2-formylcyclopropanecarboxylate, 21a. Oil; $[\alpha]_D$ -102.4 (c= 1.25 $CHCl_3$); IR (film) 3450-3200 (br), 1712, cm^{-1}; MS, m/e 277 (M, 1), 151 (4), 142 (10), 92 (8), 91 (100), 79 (4), 65 (9); 250 MHz ^{1}H-NMR ($CDCl_3$) 1.87 (complex absorption, H_{3a}+H_{3b}), 2.90 (m, H_2), 3.70 (s, 3H, -OCH_3), 5.07 (s, 2H, coalesced AB system), 5.48 (broad s, N-*H*), 7.31 (s, 5H), 9.42 (broad s, *CH*O); 62.5 MHz ^{13}C-NMR ($CDCl_3$) 20.29, 35.62, 41.59, 52.97, 67.07, 127.85 (2C), 128.29, 128.42 (2C), 135.77, 156.36, 170.40, 195.45.

Methyl (1*S*, 2*R*)-(-)-1-*N*-*tert*-butoxycarbonylamino-2-formylcyclopropanecarboxylate, 21b. Crystals, m.p. 105-106° C (from ethyl acetate-pentane); $[\alpha]_D$ -190.7 (c= 0.96 $CHCl_3$); IR (KBr) 3369 (bb), 1731, 1712 cm^{-1}; MS, m/e 187 (M-56, 5), 143 (8), 127 (12), 126 (12), 114 (13), 84 (12), 59 (11), 57 (100), 43 (5), 41 (24); 250 MHz ^{1}H-NMR ($CDCl_3$) 1.42 (s, 3xCH_3), 1.85 (d, H_{3a}+H_{3b}, J= 8.0 Hz), 2.46 (m, H_2), 3.72 (s, 3H, -OCH_3), 5.16 (broad s, N-*H*), 9.42 (broad s, *CH*O); 62.5 MHz ^{13}C-NMR ($CDCl_3$) 20.20, 28.00 (3C), 35.60, 41.61, 52.90, 80.63, 156.00, 170.65, 195.38. Anal. Calcd. for $C_{11}H_{17}O_5N$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.48; H, 6.75; N, 5.65.

Synthesis of aldehyde 21a through ozonolysis of vinyl derivative 13a. Ozone was bubbled through a stirred solution of **13a** (0.17 mL, 0.62 mmol) in ethyl acetate (15 mL) at -78° C for 20 minutes. Then dimethyl sulfide (0.1 mL, 1.34 mmol) was added and the mixture was stirred at room temperature for 30

minutes. The solvents were removed under reduced pressure and the residue was chromatographed (5:1 ethyl acetate-hexane) to provide **21a** (0.16 g, 91% yield).

Methyl (1*S*, 2*R*)-(-)-1-*N*-benzyloxycarbonylamino-2-carboxycyclopropanecarboxylate, 20a.

(a) From diol 6a. Sodium periodate (0.26 g, 2.84 mmol) and Ru_2O hydrate (15 mg) were added to a solution of **6a** (76 mg, 0.71 mmol) in 2:2:3 CCl_4-CH_3CN-H_2O (7 mL) and the mixture was stirred for 2 h at room temperature. Ether (2 mL) was added and the phases were separated. The aqueous phase was extracted with ether (4x4 mL) and the combined organic extracts were dried. Solvent was removed and the residue was chromatographed (3:1 ethyl acetate-hexane) to give acid **20a** (45 mg, 63% yield).

(b) From aldehyde 21a. Pyridinium dichromate (0.29 g, 0.76 mmol) was added to a solution of **21a** (0.14 g, 0.51 mmol) in freshly distilled DMF and the mixture was stirred at room temperature for 36 h. The solution was acidified to pH 1 with diluted HCl and then water (10 mL) was added. The resultant solution was extracted with dichloromethane (7x10 mL) and the combined organic extracts were dried. Solvents were removed and the residue was chromatographed (4:1 ethyl acetate-hexane) to afford **20a** (90 mg, 60% yield).

Physical and spectroscopic data of **20a** are as follows. Crystals, m.p. 118-119° C (from ethyl acetate-pentane); $[\alpha]_D$ -112.0 (c= 1.25 $CHCl_3$); IR (KBr) 3500-2300 (br), 3358, 1733, 1706, cm^{-1}; MS, m/e 293 (M^+, 1), 108 (25), 107 (20), 91 (100), 79 (28), 77 (20), 55 (20), 54 (22), 44 (25), 43 (18); 250 MHz ^{1}H-NMR ($CDCl_3$) 1.78 (m, H_{3a}), 1.88 (m, H_{3b}), 2.59 (t, H_2, $J_{2,3a}$= $J_{2,3b}$= 7.9 Hz), 3.70 (s, OCH_3), 5.08 (s, coalesced AB system), 5.54 (broad s, N-*H*), 7.29 (complex absorption, 5 H), 8.55-8.91 (broad s, O-*H*); 62.5 MHz ^{13}C-NMR ($CDCl_3$) 21.97, 28.68, 40.57, 53.08, 67.19, 127.90 (2C), 128.06, 128.38 (2C), 135.94, 156.54, 170.65, 172.46. Anal. Calcd. for $C_{14}H_{15}O_6N$: C, 57.32; H, 5.16; N, 4.78. Found: C, 57.31; H, 5.26; N, 4.84.

Reduction of aldehydes 21a,b to alcohols 14a,b. Sodium borohydride (0.14 g, 3.75 mmol) was added in small portions to a stirred and ice-cooled solution of **21a** (0.80 g, 2.91 mmol) in methanol (5 mL) and the mixture was sitrred at 0° C for 20 minutes. Then solvent was evaporated to dryness and the residue was poured into saturated aqueous ammonium chloride (2 mL). The resultant solution was extracted with dichloromethane (4x10 mL) and the combined extracts were dried. Solvent was removed and the residue was chromatographed (4:1 ethyl acetate-hexane) to give alcohol **14a**[14] (0.71 mg, 87% yield) as a very viscous oil. Following the same procedure, alcohol **14b** was obtained (0.29 g, 95% yield) as a hygroscopic solid unsuitable for microanalysis.

Methyl (1*S*, 2*R*)-(-)-1-*N*-benzyloxycarbonylamino-2-hydroxymethylcyclopropanecarboxylate, 14a. Oil, $[\alpha]_D$ -38.1 (c= 1.05 $CHCl_3$) [Lit[14] $[\alpha]_D$ -43.7 (c=1.00, $CHCl_3$)]; IR , ^{1}H and ^{13}C NMR spectra were in good agreement with thosed described for this product in ref 14. Previously undescribed mass spectrum follows. MS, m/e 279 (M, 2), 188 (9), 127 (15), 92 (9), 91 (100), 79 (12), 68 (18), 65 (10), 41 (16).

Methyl (1*S*, 2*R*)-(-)-1-*N*-*tert*-butoxycarbonylamino-2-hydroxymethylcyclopropanecarboxylate, 14b. Crystals, m.p. 73-75° C (from ethyl acetate-pentane); $[\alpha]_D$ -34.1 (c= 0.675 CH_3OH); IR (KBr) 3444 , 3365, 1726, 1693 cm^{-1}; MS, m/e 189 (M-56, 12), 128 (12), 114 (31), 68 (10), 59 (11), 57 (100), 41 (30); 250 MHz ^{1}H-NMR ($CDCl_3$) 0.77 (dd, H_{3a}, $J_{3a,2}$= 7.6 Hz, $J_{3a,3b}$= 4.7 Hz), 1.44 (s, 3xCH_3), 1.53 (dd, H_{3b}, $J_{3b,2}$= 9.5 Hz, $J_{3b,3a}$= 4.7 Hz), 2.24 (m, H_2), 3.18 (t, OH, J= 11.7 Hz), 3.69 (s, 3H, -OCH_3), 3.70 (m, $H_{1a'}$),

3.95 (dt, $H_{1b'}$, J= 11.7 Hz, J'= J"= 2.9 Hz), 5.11 (broad s, N-*H*); 62.5 MHz ^{13}C-NMR (methanol d4) 20.79, 28.62 (3C), 31.15, 39.00, 53.00, 62.10, 81.30, 159.80, 174.70.

(-)-(*Z*)-2,3-Methanohomoserine, 3. A mixture of compound **14b** (0.25 g, 1.01 mmol) and 1M NaOH in methanol (5 mL) was stirred at room temperature for 19 h. The solvent was removed and the residue was poured into saturated aqueous ammonium chloride (7 mL) and some drops of 5% HCl (pH=3). The solution was extracted with ethyl acetate (5x10 mL) and the combined extracts were dried. Solvent was removed to give a white solid which was crystallized to afford pure **(1*S*, 2*R*)-(-)-1-*N*-*tert*-butoxycarbonylamino-2-hydroxymethylcyclopropanecarboxylic acid** (0.21 g, 90% yield); m.p. 157° C (from ethyl acetate-pentane); $[\alpha]_D$ -37.8 (c= 0.45 CH_3OH) [Lit[13] m.p. 157° C (dec), $[\alpha]_D$ -37.8 (c=0.45, methanol)].

This acid was hydrolyzed as described above for the synthesis of **1**, affording amino acid **3** quantitatively.

(-)-(Z)-2,3-Methanohomoserine, 3. Crystals, m.p. 220° C (dec) (from H_2O-ethanol); $[\alpha]_D$ -70.3 (c= 0.185 H_2O) [Lit ref 13: m.p. 240° C dec, $[\alpha]_D$ -74.5 (c= 0.18, water); ref 15: m.p. 232-234° C dec, $[\alpha]_D$ -71.6 (c= 1.04, water)]; IR (KBr) 3600-2500 (br), 1655 cm^{-1}; 250 MHz ^{1}H-NMR (D_2O) 1.10 (t, H_{3a}, $J_{3a,2}$= $J_{3a,3b}$= 6.6 Hz), 1.37 (dd, H_{3b}, $J_{3b,2}$= 10.2 Hz, $J_{3b,3a}$= 6.6 Hz), 1.78 (m, H_2), 3.64 (dd, $H_{1a'}$, J_{gem}= 12.4 Hz, J'=6.6 Hz), 3.85 (dd, $H_{1b'}$, J_{gem}= 12.4 Hz, J'= 5.1 Hz); 62.5 MHz ^{13}C-NMR (D_2O) 17.10, 26.60, 41.70, 60.80, 177.40.

Methyl (1*S*, 2*R*)-(-)-1-*N*-benzyloxycarbonylamino-2-methanesulfonyloxymethylcyclopropanecarboxylate, 15a. To a stirred and ice-cooled solution of alcohol **14a** (0.25 g, 0.90 mmol) in anhydrous dichloromethane (4 mL) freshly distilled triethylamine (0.25 mL, 1.79 mmol) and mesyl chloride (0.14 mL, 1.79 mmol) were subsequently added under nitrogen atmosphere. The mixture was stirred at 0° C for 10 minutes. Then solvent was evaporated in vacuo and the residue was poured into water (3 mL) and extracted with ethyl acetate (3x10 mL). The combined extracts were dried and the solvent was removed to afford a yellow oil which was chromatographed (1:2 ethyl acetate-hexane) to afford mesylate **15a** as a white solid (0.30 g, 96% yield). Crystals, m.p. 56-58° C (from ethyl acetate-pentane); $[\alpha]_D$ -7.7 (c= 1.30 $CHCl_3$); IR (KBr) 3303 (br), 1754, 1698, cm^{-1}; MS, m/e 293 (4), 172 (21), 159 (23), 127 (26), 126 (28), 91 (100), 68 (49); 250 MHz ^{1}H-NMR (acetone d_6) 1.29 (dd, H_{3a}, $J_{3a,2}$= 7.4 Hz, $J_{3a,3b}$= 5.4 Hz), 1.66 (dd, H_{3b}, $J_{3b,2}$= 9.4 Hz, $J_{3b,3a}$= 5.4 Hz), 2.26 (dddd, H_2, $J_{2,3a}$= 9.4 Hz, $J_{2,3b}$= 7.4 Hz, $J_{2,1b'}$= 7.3 Hz, $J_{2,1a'}$= 7.1 Hz), 3.09 (s, S*CH*3), 3.65 (s, 3H, -O*CH*3), 4.21 (dd, $H_{1a'}$, $J_{1a',1b'}$= 11.0 Hz, $J_{1a',2}$= 7.1 Hz), 4.41 (dd, $H_{1b'}$, $J_{1b',1a'}$= 11.0 Hz, $J_{1b',2}$= 7.3 Hz), 5.10 (t, 2H, coalesced AB system, J_{gem}=11.2 Hz), 7.07 (broad s, N-*H*), 7.29-7.40 (complex absorption, 5H); 62.5 MHz ^{13}C-NMR ($CDCl_3$) 20.03, 25.49, 36.49, 38.44, 51.87, 65.98, 68.88, 127.56 (2C), 127.74, 128.28 (2C), 137.06, 156.91, 171.81. Anal. Calcd. for $C_{15}H_{19}O_7NS$: C, 50.41; H, 5.36; N, 3.92; S, 8.97. Found: C, 50.34; H, 5.40; N, 3.90; S, 8.84.

Reaction of alcohol 14a with tosyl chloride in triethylamine: Methyl (1*S*, 2*R*)-(-)-1-*N*-benzyloxycarbonylamino-2-*p*-toluenesulfonyloxymethylcyclopropanecarboxylate, 16a and methyl (1*S*, 2*R*)-(-)-1-*N*-benzyloxycarbonylamino-2-chloromethylcyclopropanecarboxylate, 17a. To a stirred and ice-cooled solution of alcohol **14a** (70 mg, 0.25 mmol) in anhydrous dichloromethane (2 mL) freshly distilled triethylamine (0.07 mL, 0.50 mmol) and recrystallized tosyl chloride (96 mg, 0.50 mmol) were subsequently added. The mixture was stirred at room temperature for 72 h and the solution was diluted with

dichloromethane (4 mL) and washed with 5% HCl (1x1 mL). The layers were separated and the organic phase was dried and solvent was removed. The residue was chromatographed (1:3 ethyl acetate-hexane) to afford, according to the elution order, chloride **17a**[14] (39 mg, 62% yield based on coverted **14a**), tosylate **16a** (20 mg, 21% yield based on converted **14a**) and 8 mg (11% recovery) of **14a**.

Chloride 17a. Crystals, m.p. 73-75° C (from ethyl acetate-pentane) $[\alpha]_D$ +37.2 (c= 1.00 $CHCl_3$) [Lit[14] m.p. 77-80 C; $[\alpha]_D$ +37.8 (c=1.00, $CHCl_3$)]; IR, ^1H and ^{13}C NMR spectra were in good agreement with those described in ref 14 for this compound although mass spectometric data were not given. MS, m/e 299 (M+2, 1), 297 (M, 3), 262 (4), 218 (13), 208 (4), 206 (11), 149 (10), 91 (100).

Tosylate 16a. Crystals, m.p. 99-101° C (from ethyl acetate-pentane); $[\alpha]_D$ -14.8 (c= 0.27 $CHCl_3$); IR (KBr) 3600-3100 (br), 1763, 1715, cm^{-1}; MS, m/e 349 (2), 156 (6), 139 (6), 101 (14), 92 (10), 91 (100), 65 (7), 43 (8); 250 MHz ^1H-NMR (acetone d_6) 1.15 (t, H_{3a}, $J_{3a,3b}$= $J_{3a,2}$= 6.2 Hz), 1.78 (dd, H_{3b}, $J_{3b,2}$= 9.1 Hz, $J_{3b,3a}$= 6.2 Hz), 1.99-2.12 (m, H_2), 2.38 (s, Ph-C*H*$_3$), 3.64 (s, -OC*H*$_3$), 3.93 (t, $H_{1a'}$, $J_{1a',1b'}$= $J_{1a',2}$= 10.2 Hz), 4.26 (dd, $H_{1b'}$, $J_{1b',1a'}$= 10.2 Hz, $J_{1b',2}$= 5.5 Hz), 5.05 (d, 1H, J_{gem}= 12.4 Hz), 5.11 (d, 1H, J_{gem}= 12.4 Hz), 5.41 (broad s, N-*H*), 7.24-7.33 (complex absorption, 7H), 7.74 (d, 2H, J= 8.0 Hz); 62.5 MHz ^{13}C-NMR ($CDCl_3$) 21.01, 21.54, 25.98, 38.59, 52.71, 67.09, 69.21, 127.76 (2C), 127.91 (2C), 128.14, 128.46 (2C), 129.93 (2C), 132.80, 136.05, 145.04, 156.86, 171.74. Anal. Calcd. for $C_{21}H_{23}O_7NS$: C, 58.18; H, 5.35; N, 3.23; S, 7.38. Found: C, 58.25; H, 5.42; N, 3.24; S, 7.36.

Reaction of mesylate 15a with lithium dimethyl cuprate: Methyl (1*S*, 2*R*)-(-)-1-*N*-benzyloxycarbonyl-amino-2-ethylcyclopropanecarboxylate, 22a. A 1.6M ethereal solution of MeLi (1.08 mL, 1.73 mmol) was added to a stirred emulsion of cuprous iodide (0.16 mg, 0.87 mmol) in anhydrous ether (2.5 mL) at -25° C under nitrogen atmosphere. The mixture was stirred at that temperature for 25 minutes and then a solution of mesylate **15a** (0.10 g, 0.23 mmol) in anhydrous ether (5 mL) was added. After stirring for 5 minutes TLC monitoring showed the total consumption of starting **15a**. Saturated aqueous ammonium chloride (4 mL) was added and the mixture was stirred for 10 minutes whilst heated to room temperature. Layers were separated and the aqueous phase was extracted with ethyl acetate (3x6 mL). The combined organic extracts were dried and solvents were removed to afford a residue which was chromatographed (1:4 ethyl acetate-hexane) to provide **22a** (36 mg, 45% yield) as a white solid along with 18 mg (22% yield) of **methyl 2-(*N*-benzyloxycarbonylamino)-4-pentenoate, 25,** as an oil which was identified by NMR.

Compound 22a. Crystals, m.p. 80-82° C (from ethyl acetate-pentane); $[\alpha]_D$ -20.8 (c= 1.25 $CHCl_3$); IR (film) 3321 (br), 1726, 1691, cm^{-1}; MS, m/e 278 (M+1, 1), 277 (M, 5), 186 (11), 142 (26), 114 (39), 100 (25), 92 (9), 91 (100), 82 (15); 250 MHz ^1H-NMR (acetone d_6) 0.86 (dd, H_{3a} , $J_{3a,2}$= 7.4 Hz, $J_{3a,3b}$= 4.6 Hz), 1.00 (t, 3H, -C*H*$_3$, J= 7.1 Hz), 1.17-1.21 (m, 2H), 1.48 (dd, H_{3b}, $J_{3b,2}$= 9.5 Hz, $J_{3b,3a}$= 4.6 Hz); 1.58-1.70 (m, H_2); 3.61 (s, 3 H, OC*H*$_3$); 5.05 (d, 1H, J_{gem}= 12.8 Hz), 5.09 (d, 1H, J_{gem}= 12.8 Hz), 6.86 (broad s, N-*H*), 7.29-7.37 (broad s, 5 H); 62.5 MHz ^{13}C-NMR ($CDCl_3$) 13.36, 21.39, 22.95, 30.33, 38.39, 52.30, 66.84, 128.01 (2C), 128.11, 128.32 (2C), 136.27, 156.80, 173.41. Anal. Calcd. for $C_{15}H_{19}O_4N$: C, 64.95; H, 6.91; N, 5.05. Found: C, 64.72; H, 6.85; N, 5.08.

Compound 25. 250 MHz ^1H-NMR ($CDCl_3$) 2.52 (m, 2 H_3), 3.66 (broad s, N-*H*), 3.73 (s, OC*H*$_3$), 4.44 (ddd, H_2, J= 8.4 Hz, J'= J"= 5.8 Hz), 5.02-5.13 (complex absorption, C*H*$_2$Ph+H_{5c}), 5.29 (d, H_{5t}, J= 7.7

Hz), 5.58-5.74 (m, H_4), 7.33 (broad s, 5H); ^{13}C-NMR ($CDCl_3$) 36.62, 52.25, 53.19, 66.91, 119.30, 128.01 (2C), 128.10, 128.43 (2C), 131.89, 136.13, 155.61, 172.06.

Methyl (1*S*, 2*R*)-(-)-1-*N*-benzyloxycarbonylamino-2-methylcyclopropanecarboxylate, 23a. Sodium borohydride (13 mg, 0.34 mmol) was added to a solution containing mesylate **15a** (60 mg, 0.17 mmol) in anhydrous HMPA (3 mL). The mixture was stirred at 40° C for 4 h, then water (3 mL) was added and the resultant solution was extracted with ethyl acetate (3x7 mL). The combined extracts were dried and the solvents were evaporated at reduced pressure. The residue was chromatographed (1:2 ethyl acetate-hexane) to afford compound **23a** as an oil (36 mg, 82% yield). $[\alpha]_D$ -32.9 (c= 1.40 $CHCl_3$); IR (film) 3313 (br), 1765, 1694, cm^{-1}; MS, m/e 264 (M+1, 1), 263 (M, 4), 172 (10), 128 (23), 91 (100), 68 (14), 65 (11); 250 MHz ^{1}H-NMR (acetone d_6) 0.82 (dd, H_{3a}, $J_{3a,2}$= 7.7 Hz, $J_{3a,3b}$= 4.8 Hz), 1.13 (d, C*H*$_3$, J*CH*$_{3,2}$= 5.8 Hz), 1.49 (dd, H_{3b}, $J_{3b,2}$= 9.5 Hz, $J_{3b,3a}$= 4.8 Hz), 1.70 (m, H_2), 3.60 (s, -OC*H*$_3$), 5.05 (d, 1H, J_{gem}= 12.8 Hz), 5.10 (d, 1H, J_{gem}= 12.8 Hz), 6.87 (broad s, N-*H*), 7.29-7.37 (complex absorption, 5H); 62.5 MHz ^{13}C-NMR ($CDCl_3$) 12.91, 23.18, 24.03, 38.23, 52.31, 66.86, 128.02 (3 C), 128.40 (2 C), 136.28, 156.85, 173.49. Anal. Calcd. for $C_{14}H_{17}O_4N$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.55; H, 6.73; N, 5.29.

(-)-*allo*-Norcoronamic acid, 2. A mixture of **23a** (0.14 g, 0.54 mmol), 6N HCl (3 mL) and five drops of glacial acetic acid was stirred at 90° C for 6 h. Solvents were removed and the obtained white solid was poured into absolute ethanol (3 mL) and propylene oxide (1.5 mL) was added. The mixture was stirred at 35° C for 10 minutes. Solution was evaporated to dryness giving a yellowish solid which was poured into water (2 mL) and eluted through a C_{18}-reverse phase cartridge to furnish, after evaporation of water, (-)-*allo*-norcoronamic acid, **2**. Crystals, m.p. 178-181° C (from H_2O-acetone); $[\alpha]_D$ -69.8 (c= 0.43, H_2O) [Lit ref 17: $[\alpha]_D$ -67 (c= 1.5, H_2O); ref 18b: m.p. 215 C (dec), $[\alpha]_D$ -69.7 (c= 0.39, H_2O)]; IR (KBr) 3600-2000 (br), 1729 cm^{-1}; 250 MHz ^{1}H-NMR (D_2O) 0.82 (t, H_{3a}, $J_{3a,3b}$= $J_{3a,2}$= 6.8 Hz), 1.06 (d, C*H*$_3$, J*CH*$_{3,2}$= 6.6 Hz), 1.38 (dd, H_{3b}, $J_{3b,2}$= 9.7 Hz, $J_{3b,3a}$= 6.8 Hz), 1.52-1.66 (m, H_2); 62.5 MHz ^{13}C-NMR (D_2O-acetone d_6) 11.61, 19.11, 19.55, 39.42, 175.23.

Methyl (1*S*, 2*R*)-(+)-1-*N*-benzyloxycarbonylamino-2-iodomethylcyclopropanecarboxylate, 18a. Sodium iodide (0.74 g, 3.98 mol) was added to solution of mesylate **15a** (0.35 g, 0.99 mmol) in freshly distilled acetone and the mixture was stirred at 0° C for 3 h. Solvent was removed and the residue was poured into ethyl acetate (10 mL). 5% Aqueous sodium thiosulfate (4 mL) was added and the layers were separated. The aqueous phase was extracted with ethyl acetate (1x5 mL) and the combined organic phases were dried. Solvents were removed and the residue was chromatographed (1:2 ethyl acetate-hexane) to afford iodide **18a** as a white solid (0.34 g, 89% yield). Crystals, m.p. 93-96° C (from ethyl acetate-pentane); $[\alpha]_D$ +40.0 (c= 1.00 $CHCl_3$); IR (KBr) 3303 (br), 1729, 1696, cm^{-1}; MS, m/e 331 (4), 218 (14), 92 (9), 91 (100); 250 MHz ^{1}H-NMR (acetone d_6) 1.13 (m, H_{3a}), 1.87 (m, H_{3b}), 2.29 (m, H_2), 3.11 (t, $H_{1a'}$, J= J'= 10.1 Hz), 3.30 (t, $H_{1b'}$, J= J'= 8.1 Hz), 3.67 (s, -OC*H*$_3$), 5.13 (d, 1H, J_{gem}= 12.0 Hz), 5.16 (d, 1H, J_{gem}= 12.0 Hz), 5.45 (broad s, N-*H*), 7.35 (broad s, 5 H); 62.5 MHz ^{13}C-NMR ($CDCl_3$) 3.60, 26.16, 31.19, 42.13, 52.70, 67.19, 128.04 (2C), 128.20, 128.47 (2C), 135.91, 156.72, 171.84. Anal. Calcd. for $C_{14}H_{16}O_4NI$: C, 43.21; H, 4.14; N, 3.60; I, 31.61. Found: C, 43.18; H, 4.13; N, 3.55; I, 32.20.

Methyl (1*S*, 2*R*)-(+)-1-*N*-benzyloxycarbonylamino-2-methylthiomethylcyclopropanecarboxylate, 24a. A solution of iodide **18a** (75 mg, 0.19 mmol) in 2 mL anhydrous methanol was added dropwise to a stirred solution of sodium thiomethoxide (27 mg, 0.38 mmol) in 1.5 mL anhydrous methanol under nitrogen atmosphere, and the resultant mixture was stirred at room temperature for 45 minutes. Solvent was removed and the residue was partitioned between water (2 mL) and ethyl acetate (5 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (2x5 mL). The combined organic phases were dried and solvent was removed. The residue was chromatographed (1:2 ethyl acetate-hexane) to provide sulfide **24a** (45 mg, 76% yield) as a solid. Crystals, m.p. 60-62°C (from ethyl acetate-pentane); $[\alpha]_D$ +4.0 (c= 1.00 $CHCl_3$); IR (KBr) 3312 (br), 1732, 1694, cm^{-1}; MS, m/e 262 (M-SCH_3, 5), 218 (9), 142 (11), 126 (13), 92 (8), 91 (100), 65 (7); 250 MHz ^{1}H-NMR ($CDCl_3$) 1.13 (broad s, H_{3a}), 1.83 (m, H_{3b}), 1.97 (m, H_2), 2.18 (s, S-C*H*$_3$), 2.52 (dd, $H_{1a'}$, $J_{1a',1b'}$= 13.2 Hz, $J_{1a',2}$= 8.0 Hz), 2.69 (dd, $H_{1b'}$, $J_{1b',1a'}$= 13.2 Hz, $J_{1b',2}$= 6.8 Hz), 3.66 (s, -OC*H*$_3$), 5.12 (s, coalesced AB system, C*H*$_2$Ph), 5.49 (broad s, N-*H*), 7.32 (broad s, 5H); 62.5 MHz ^{13}C-NMR ($CDCl_3$) 15.30, 23.70, 27.09, 33.08, 38.47, 52.46, 66.90, 127.95 (2C), 128.02, 128.36 (2C), 136.08, 156.84, 172.61 Anal. Calcd. for $C_{15}H_{19}O_4NS$: C, 58.23; H, 6.19; N, 4.53; S, 10.36. Found: C, 58.20; H, 6.30; N, 4.52; S, 10.34.

When the reaction of sodium thiomethoxide was performed with mesylate **15a** as the electrophile, **methyl 2-(*N*-benzyloxycarbonylamino)-2-methylthio-4-pentenoate, 26,** was obtained, along with **24a**, and it was identified by its NMR spectroscopic data as follows. 250 MHz ^{1}H-NMR ($CDCl_3$) 1.99 (s, SC*H*$_3$), 2.79 (d, 1H, C*H*$_2$, J= 7.3 Hz), 2.84 (d, 1H, C*H*$_2$, J= 7.3 Hz), 3.80 (s, OC*H*$_3$), 5.09 (broad s, 4H), 5.51-5.62 (complex absorption, H4), 6.01 (broad s, N-*H*), 7.28-7.35 (broad s, 5 H); ^{13}C-NMR ($CDCl_3$) 15.44, 40.08, 52.57, 52.99, 66.84, 120.07, 128.06 (2C), 128.22, 128.48 (2C), 131.34, 136.17, 156.92, 173.39.

(-)-(*Z*)-2,3-Methanomethionine, 4. A mixture of compound **24a** (98 mg, 0.31 mmol), 6N HCl (3 mL) and glacial acetic acid (3 drops) was stirred at 90° C for 6 h. The solution was evaporated to dryness and the brownish solid thus obtained was treated as described above for amino acid **2,** giving 42 mg of amino acid **4** (82% yield). Crystals, m.p. 194-198° C (from ethanol); $[\alpha]_D$ -22.2 (c= 0.33, H_2O) [Lit[20]: m.p. 195-196° (dec); $[\alpha]_D$ -22.2 (c= 0.33, H_2O)]; IR (KBr) 3600-2000 (br), 1729, 1637, 1602, 1405 cm^{-1}; 250 MHz ^{1}H-NMR (D_2O) 1.05 (t, H_{3a}, $J_{3a,3b}$= 7.1 Hz, $J_{3a,2}$= 7.1 Hz), 1.52 (t, H_{3b}, $J_{3b,2}$= 9.9 Hz, $J_{3b,3a}$= 7.1 Hz), 1.87 (m, H_2), 2.04 (s, -SC*H*$_3$), 2.59 (d, C*H*$_2$, J= 7.7 Hz); 62.5 MHz ^{13}C-NMR (D_2O-methanol d_4) 15.95, 20.45, 25.52, 32.61, 41.02, 175.31.

Methyl (1*S*,2*S*)-(*Z*/*E*)-1-(*N*-Benzyloxycarbonylamino)-2-(2'-*N*-*tert*-butoxycarbonylamino-2'-methoxycarbonylethen-1'-yl)cyclopropane carboxylate, 27. A solution of phosphonate **8a** in dry dichloromethane (2 mL) was added dropwise to an emulsion of potasium *tert*-butoxide (83 mg, 0.74 mmol) in dry dichloromethane (1.5 mL), cooled at -60° C under nitrogen atmosphere and the mixture was stirred for 30 minutes. Then a solution of aldehyde **22a** in dichloromethane (2 mL) was added and stirring was continued at room temperature for 45 minutes. Ether (10 mL) and water (6 mL) were added. The layers were separated and the aqueous phase was extracted with ether (2x5 mL). The combined organic phases were dried and the solvents were evaporated. The residue was chromatographed (4:1 dichloromethane-ether) to afford a 95:5 mixture of (*Z*/*E*)-**27** (163 mg, 54% yield). IR (film) 3500-3100 (br), 1729 (br) cm^{-1}; MS, m/e 151 (14), 149 (12), 108 (42), 107 (17), 91 (100), 90 (12), 79 (25), 71 (14), 65 (15), 57 (35), 55 (18), 43 (34), 41 (22); 250

MHz ^{1}H-NMR ($CDCl_3$) for the major isomer: 1.38 (s, 3xCH_3), 1.53 (t, H_{3a}, $J_{3a,2}$= $J_{3a,3b}$= 6.6 Hz), 2.06 (dd, H_{3b}, $J_{3b,2}$= 8.3 Hz, $J_{3b,3a}$= 6.6 Hz), 2.33 (m, H_2), 3.64 (s, -OCH_3), 3.75 (s, -OCH_3), 5.05 (d, 1H, CH_2Ph, J_{gem}=12.4 Hz), 5.13 (d, 1H, CH_2Ph, J_{gem}= 12.4 Hz), 5.71 (broad s, N-*H*), 6.10 (d, olefinic H, J= 8.8 Hz), 6.29 (broad s, N-*H*), 7.30-7.32 (complex absorption, 5 H); 100 MHz ^{13}C-NMR ($CDCl_3$) for the major isomer: 25.05, 27.87 (3C), 28.12, 40.31, 52.39, 52.44, 66.82, 80.75, 123.29, 127.99 (2C), 128.36, 128.63 (2C), 131.36, 136.21, 152.46, 156.67, 164.47, 172.28. Anal. Calcd. for $C_{22}H_{28}O_8N_2$: C, 58.90; H, 6.30; N, 6.25. Found: C, 58.51; H, 6.59; N, 6.05.

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