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Stereoselective Synthesis of Novel Cyclobutane Dehydro Amino Acids from (+)-α-Pinene

Albertina G. Moglioni,[a1] Elena García-Expósito,[a] Graciela Y. Moltrasio,[b] and Rosa M. Ortuño[a*]

a: Departament de Química, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain.

b: Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956, 1113 Buenos Aires, Argentina

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Abstract: Several title compounds have been synthesized in good overall yields through highly stereoselective Wittig-Horner condensations of suitable phosphonates with enantiopure aldehydes easily obtained from α-pinene as chiral precursor. These products, presenting two asymmetric carbons, two or four prochiral centers, and appropriate chemical functions, are versatile precursors to a variety of cyclobutane amino acid derivatives.

The cyclobutane unit is present in an important number of natural products and pharmaceutically interesting compounds.[2] Among them, amino acids and peptides are relevant. Thus, Bell *et al*[3] isolated for the first time, in 1980, 2,4-methanoglutamic acid and 2,4-methanoproline from the seeds of the plant *Atelia Herbert Smithii*. Later, Austin *et al*[4] isolated other non-protein amino acids such as *cis*-1-amino-3-hydroxymethylenecyclobutane-1-carboxylic acid from the same material. These types of compounds have attracted great attention during the last decade because of their biological activity owing to their antiviral, neurotropic, analgesic, depressant, and antimicrobial properties.[5] Moreover, amino acids containing both a cyclobutane and a cyclopropane ring have been synthesized and showed potent anticonvulsant activity.[6] Among the peptides, (1*S*,2*S*)-1-hydroxy-2-[(*S*)-valylamino]-cyclobutane-1-acetic acid is an unusual dipeptide with antimicrobial activity produced by *Streptomyces* species X-1092,[7] and synthetic methano tuftsin analogs show enhanced biological properties with respect to the parent immunomodulatory peptide tuftsin.[8]

Although several cyclobutane amino acids and derivatives have been prepared, the syntheses described for the optically pure products are scarce.[9] Therefore, our own interest in the synthesis of enantiopure carbocyclic amino acids and peptide surrogates[10] prompted us to investigate feasible stereospecific routes to optically active cyclobutane-containing compounds and related chiral synthons.

We present in this paper the efficient syntheses of the enantiopure aldehydes **3** and **4** which are useful chiral building blocks to prepare a variety of products, and their application to the synthesis of the novel cyclobutane dehydro amino acids **1** and **2** (Scheme 1). All these compounds are very versatile precursors to polyfunctional amino acids with conformationally constrained structures. It is noteworthy that molecules **1** and **2** bear two asymmetric carbons with determined absolute configuration, provided by α-pinene, and two or four prochiral centers at the olefinic carbons.

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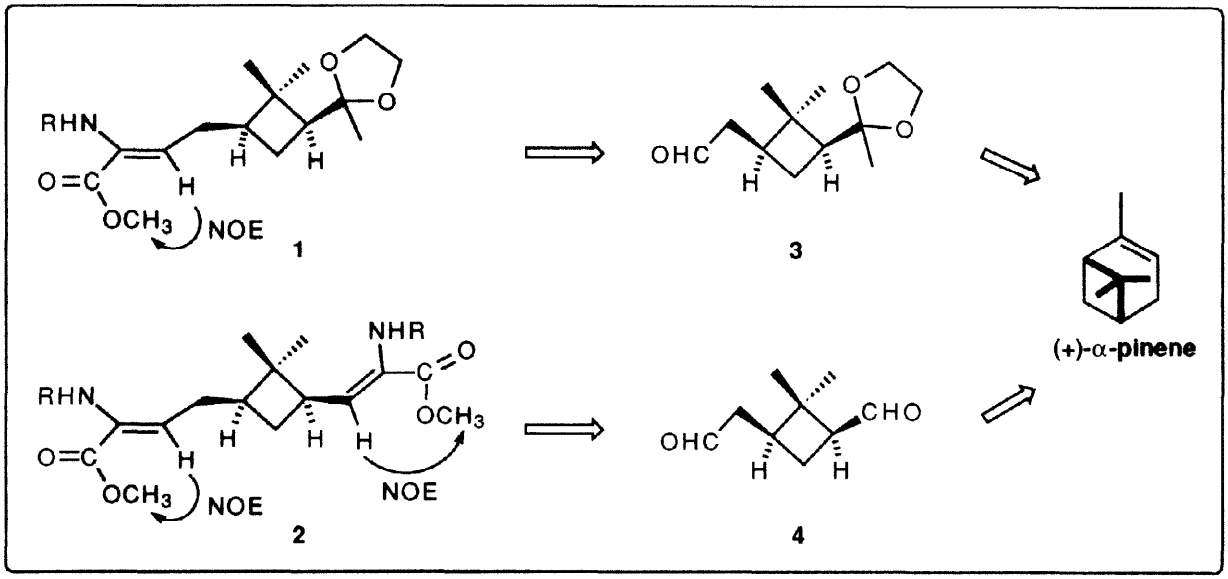


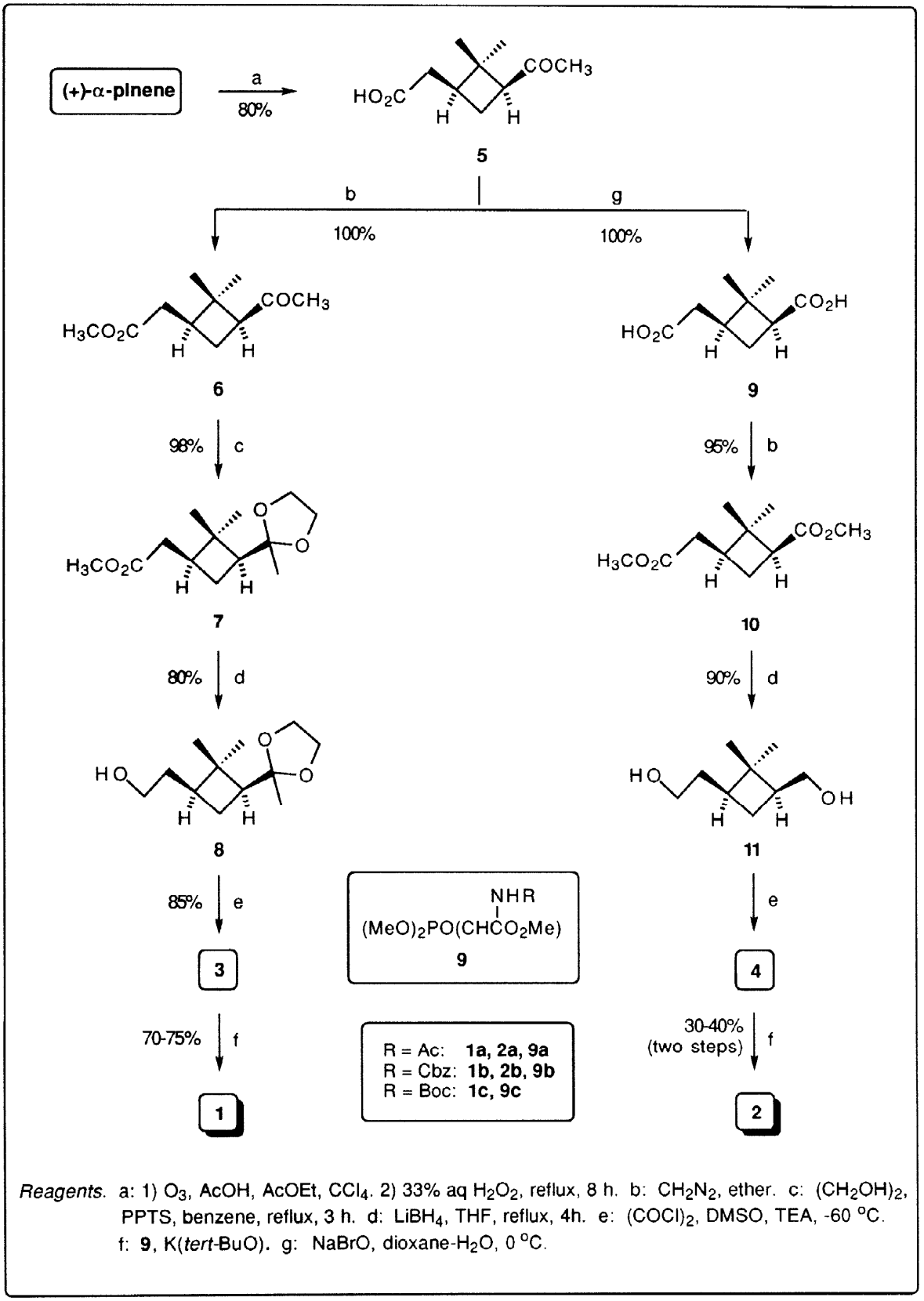
Scheme 1

Oxidation of (+)-α-pinene *via* a literature procedure[11] gave (+)-*cis*-pinonic acid **5** which is the starting material for the two divergent synthetic routes shown in Scheme 2. This acid was methylated with diazomethane to give keto ester **6**[12] which was treated with ethyleneglycol and PPTS in refluxing benzene to afford ketal **7**.[13] The synthesis of aldehyde **3** was achieved through reduction of **7** with $LiBH_4$ in refluxing THF to provide the new alcohol **8**[14] in 80%, followed by Swern oxidation (85% yield). Compound **3** was then obtained in 67% overall yield from keto acid **5**. Wittig-Horner condensation of **3** with phosphonates **9a-c**[15] gave stereoselectively the dehydro amino acid derivatives **1a-c** in about 70-75% yields of purified products. The high stereoselectivity of these condensations leading to the exclusive production of *Z* isomers is remarkable.[16]

Stereochemistry was assigned on the basis of ^1H NMR techniques including NOE experiments.[17] Thus, selective irradiation of the olefinic proton in **1a-c** (triplet at 6.5 ppm) resulted in enhancement of the absorption due to methoxyl protons (singlet at 3.75 ppm) as shown in Scheme 1. In no case was NOE on N*H* protons (broad singlets at 5.9-6.8 ppm) observed. Moreover, olefin **1a** was partially isomerized on standing as a chloroform solution for several days. Actually, the ^1H NMR spectrum showed two triplets for the two olefinic protons and two singlets at 3.70 and 3.75 ppm. Only the latter, corresponding to the *Z* isomer, was enhanced when both olefinic protons were presaturated.

In the second synthetic route, keto acid **5** was submitted to Lieben degradation by the action of sodium hypobromite in aqueous dioxane to afford (+)-*cis*-pinic acid **10**.[18] This compound was methylated and subsequently reduced to diol **11**. Swern oxidation of **11** provided aldehyde **4** which is an unstable oil that was immediately condensed with phosphonates **9a,b** to afford the bis(didehydroamino acid) derivatives **2a,b** in 30-40% yield for the two steps. Once again, the stereoselectivity of these condensations leading exclusively to *Z* isomers as shown by ^1H and ^{13}C NMR is notable. Stereochemical elucidation was also made through NOE experiments as described above for compounds **1a-c**.

In conclusion, (+)-α-pinene has proved to be a convenient precursor to prepare the new cyclobutane derivatives **1** and **2**. Application of these products to the synthesis of other enantiopure amino acids is under active investigation in our laboratory.



Reagents. a: 1) O_3, AcOH, AcOEt, CCl_4. 2) 33% aq H_2O_2, reflux, 8 h. b: CH_2N_2, ether. c: $(CH_2OH)_2$, PPTS, benzene, reflux, 3 h. d: $LiBH_4$, THF, reflux, 4h. e: $(COCl)_2$, DMSO, TEA, -60 °C. f: **9**, K(*tert*-BuO). g: NaBrO, dioxane-H_2O, 0 °C.

Scheme 2

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Notes and References

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14. All new products were characterized by their physical constants and spectroscopic data and gave satisfactory microanalysis. Some selected data follow. **8**: oil, $[\alpha]_D$ -2.4 (c 2.5, $CHCl_3$). **1a**: oil, $[\alpha]_D$ -5.0 (c 2.0, $CHCl_3$); 250-MHz ^{1}H NMR ($CDCl_3$) 0.99 (s, 3H), 1.08 (s, 3H), 1.19 (s, 3H), 1.54 (m, 1H), 1.89 (complex absorption, 2H), 2.08 (complex absorption, 3H), 2.10 (s, 3H), 3.75 (s, 3H), 3.80 (m, 2H), 3.92 (m, 2H), 6.58 (t, *J*=7.3 Hz, 1H), 6.80 (broad s, 1H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 16.9, 23.5, 23.6, 24.5, 29.6, 31.1, 40.9, 41.1, 49.7, 52.1, 63.47, 65.3, 109.6, 124.8, 137.4, 164.9, 168.4. **1b**: oil, $[\alpha]_D$ +1.8 (c 2.2, $CHCl_3$). **1c**: oil, $[\alpha]_D$ -2.7 (c 2.2, $CHCl_3$). **11**: $[\alpha]_D$ -21.1 (c 1.1, $CHCl_3$). **2a**: oil, $[\alpha]_D$ -5.8 (c 1.0, $CHCl_3$). 250-MHz ^{1}H NMR (CDCl3) 0.96 (s, 3H), 1.07 (s, 3H), 2.03 (m, 1H), 2.06 (complex absorption, 2H), 2.09 (s, 3H), 2.11 (s, 3H), 2.22 (acomplex absorption, 2H), 2.76 (m, 1H), 3.75 (s, 6H), 6.56 (t, *J*=6.6 Hz, 1H), 6.66 (d, *J*=8.8 Hz, 1H), 7.49 (broad s, 1H), 7.49 (broad s, 1H), 62.5-MHz ^{13}C NMR ($CDCl_3$) 14.1, 17.9, 23.4, 29.3, 30.3, 30.4, 41.6, 40.8, 43.1, 52.3, 52.4, 124.7, 124.9, 136.7, 138.8, 165.1, 168.3, 168.5, 171.1.

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