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Stereoselective synthesis of cyclobutyl α-aminocyclopropyl carboxylic acid derivatives

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Abstract

The highly stereoselective cyclopropanation of chiral cyclobutyl dehydro amino acids, synthesized from (–)-α-pinene or (–)-verbenone, has been achieved by means of a 1,3-dipolar cycloaddition with diazomethane. The proximity of the double bond to the neighbouring stereogenic center of the cyclobutyl moiety is crucial to obtain cyclopropanes as single diastereomers whose configuration has been determined by X-ray structural analysis. DFT theoretical calculations of the more stable conformations allow us to understand the π-facial diastereoselection as the result of steric hindrance by the *gem*-dimethyl substitutuents and the side chain of the cyclobutane-ring. Chiroptical properties of these products have been studied by ORD and CD techniques and their behavior in CSA-NMR experiments has been ascertained.

1. Introduction

Compounds containing the cyclopropane ring are widespread and, among them, amino acids and related products from natural or designed origin are prominent.[1] Due to the relevant biological properties of many of these compounds, synthetic methods based mainly on the use of diazoalkanes, carbenoid species, and phosphorus or sulfur ylides have been developed to prepare cyclopropane derivatives in a stereoselective manner. In our laboratory, we have utilized the 1,3-dipolar cycloaddition of diazomethane to chiral dehydro amino acids, followed by pyrolysis of the resultant pyrazolines, as an efficient procedure for the highly stereoselective synthesis of protein methanologs,[2] non-proteinogenic α- and β-amino acids,[2a,3] peptide surrogates,[3d,4] amino alcohols,[5] hydroxy acids,[6] and cyclopropane carbocyclic nucleosides.[7] The

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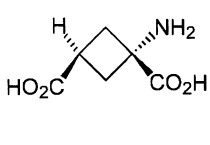
stereoselectivity of these processes has also been observed in the reactions between diazomethane and other olefinic substrates containing electron-withdrawing groups such as ester, nitro or sulphone.[8] The configuration of the new stereogenic centers has been shown to be induced exclusively by the chirality of the asymmetric carbon in the substrate independently of the Z/E geometry of the double bond and of the nature and number of their substituents. Thus, the stereochemical outcome of the cycloadditions was governed by the presence of a dioxolane ring at the allylic stereogenic center of dehydroamino acids obtained from D-glyceraldehyde acetonide,[8] or by a bulky orthoester group in a serine aldehyde OBO ester.[2c] A model based on DFT theoretical calculations has been used to explain and predict the stereoselectivity of this type of cycloaddition. Thus, we have shown that both steric and orbital effects account for the π-facial diastereoselection.[8]

Products containing both the cyclopropane and the cyclobutane moieties are more scarce. Nevertheless, interesting activity of such compounds have been described in connection with the study of the NMDA receptors which are potential targets for therapeutic use in a wide range of neurological processes. In general, the NMDA antagonists possess anticonvulsant, antispastic, and neuroprotective properties. *trans*-2,4-Methanoglutamic acid, **1**, displays an activity similar to glutamic acid as a powerful NMDA agonist. On the other hand, amino acids **2** and **3** have been used to prepare racemic compounds **4** and **5** which have been evaluated as NMDA antagonists. Amino acid **4** is inactive but compound **5** exhibits strong NMDA antagonism showing that the configuration of the molecule plays an important role in the biological activity.[9] Therefore, the development of stereoselective synthetic protocols is crucial to synthesize new compounds to be tested.



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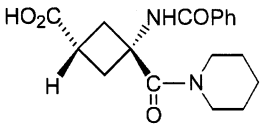

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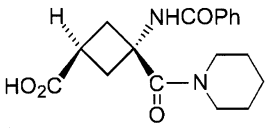

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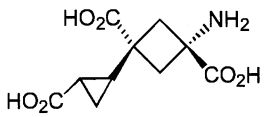

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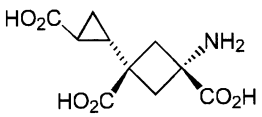

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Herein, we describe the stereoselective synthesis of fully protected amino acids **11** and **15**, as well as the synthesis of **10** as a diastereomeric mixture. All these compounds have an α-amino acid function, directly attached to the cyclopropane ring, and a cyclobutyl unit bearing a functional group capable of being transformed into a carboxylic acid or suitable for the incorporation of these molecules into peptide isosteres.

(−)-α-Pinene or (−)-verbenone have been employed as chiral starting materials providing the cyclobutane moiety and two stereogenic centers. The use of these precursors allowed us to synthesize dehydro amino acid derivatives **6**, **7**, and **13** through stereocontrolled Wittig–Horner condensations with appropriate phosphonates.[10]

We show herein that the *gem*-dimethyl substitution is the main control element responsible for the remarkable stereoselection observed in the cyclopropanation of substrates **7** and **13** which have the double bond attached to the cyclobutane. X-Ray structural analysis led to the unambiguous configurational assignment of the new stereogenic centers, whereas theoretical calculations allowed us to understand the stereochemical outcome of the cycloaddition. Chiroptical measurements and NMR experiments by using the fully deuterated Pirkle alcohol as a chiral solvating agent (CSA) have been also carried out.

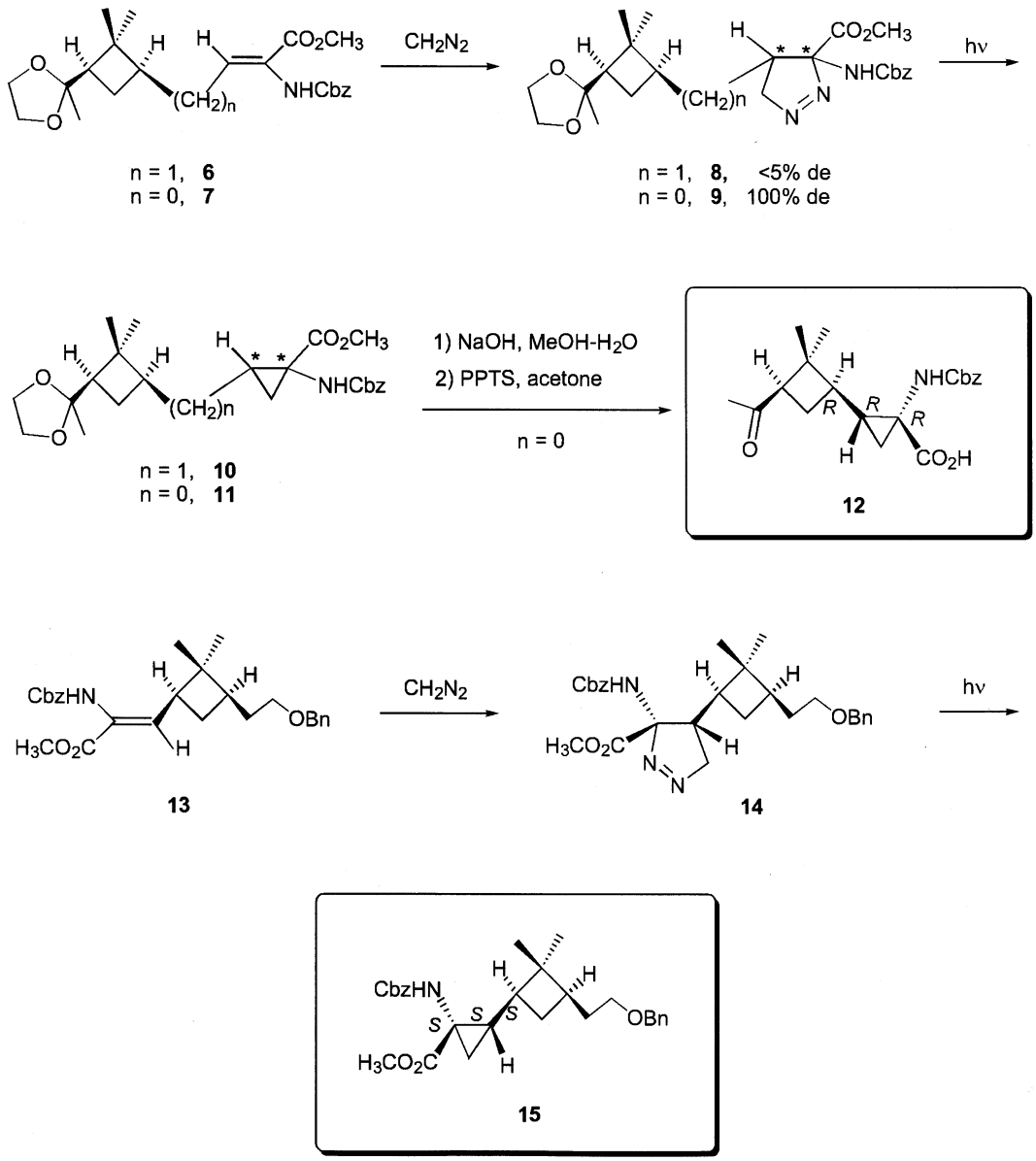
2. Results and discussion

*2.1. Synthesis and stereochemical assignment of amino acids **10**, **11**, and **15***

In a previous paper, we described the syntheses of dehydro amino acids **6** and **13** from (−)-α-pinene and the synthesis of **7** from (−)-verbenone. It is noteworthy that products **7** and **13** show opposite configurations at C-1′ and C-3′.[10b] These substrates were reacted, in separate experiments, with excess ethereal diazomethane, at room temperature for 17–20 h, to afford pyrazolines **8**, **9**, and **14**, respectively, in 80–83% yield (Scheme 1). Photolysis of the pyrazolines was carried out by irradiation with a 125-W medium-pressure mercury lamp of toluene solutions of **8**, **9**, or **14**, contained in Pyrex reactors. In such a way, the corresponding cyclopropanes, **10**, **11**, and **15** resulted in 54–60% yield. NMR analysis showed that **10** was obtained as a mixture of the two possible diastereomers in about a 1:1 ratio. These isomers could not be separated either by HPLC or by using other techniques. On the contrary, compounds **11** and **15** were synthesized in a single isomeric form and they were characterized by their spectroscopic data. While an analytical sample of compound **15** could be obtained and used for specific rotation determination and for microanalysis, compound **11** was an unstable product unable to give the analytical sample. This is due to the high lability of the ketal which is partially removed during the normal purification process.[11] Therefore, compound **11** was submitted to saponification of the methyl ester and subsequent ketal hydrolysis to afford the keto acid **12**. This compound could be fully characterized and, in addition, afforded crystals suitable for X-ray structural analysis. Fig. 1 shows the X-ray structure obtained for **12** allowing the (*R*,*R*)-configuration to be assigned to the two stereogenic centers at the cyclopropane ring.[12] By analogy, the (*S*,*S*)-configuration was assigned to **15**. This stereochemistry is easily rationalized by considering the conformational bias of substrates **7** and **13**, as described in the following section. Otherwise, it is remarkable that the stereoselectivity is excellent when the double bond is directly linked to a stereogenic center of the cyclobutane ring and near, therefore, to the *gem*-dimethyl group. On the contrary, in **6**, the separation of the double bond from the stereogenic carbon by a methylene unit results in a loss of stereocontrol in the cyclopropanation process.

2.2. Theoretical calculations

We have studied the conformations arising from rotation around the C2–C3 bond (see Fig. 2 for atom numeration) for model molecules **16** and **17**. In both structures, the *N*-Ac protection has been considered for simplicity, instead of *N*-Cbz. Thus, structure **17** is analogous to **7**. Moreover, in **16**, the side chain has been changed by a hydrogen atom and, therefore, the cyclobutane has only one stereogenic center. In this way, the steric influence of the second



Scheme 1.

side chain can be evaluated. In both cases, two energy minima with C4–C3–C2–C1 torsion angles of about −130° and +170°, respectively, have been obtained. The first conformer, **a**, is always more stable than the second one, **b**. For **17a** and **17b** we have also considered the rotation around the dioxolane–cyclobutane bond. Fig. 2 presents the more stable structures, and Fig. 3 shows the Newman projection for conformers **a** and **b**. In the most stable conformer **a**, the presence of the *gem*-dimethyl group orients the attack of diazomethane to the (*si*,*re*) face of the double bond, leading to the production of cyclopropanes with (*R*,*R*)-configuration, like compound **11**, or (*S*,*S*)-stereochemistry for substrates with the opposite configuration such as **13**.

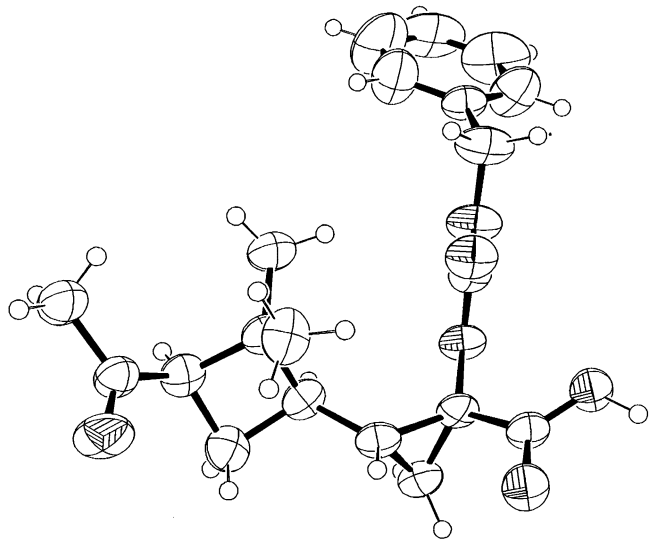


Figure 1. An ORTEP view of the molecular structure of **12**. The thermal ellipsoids enclose 50% probability

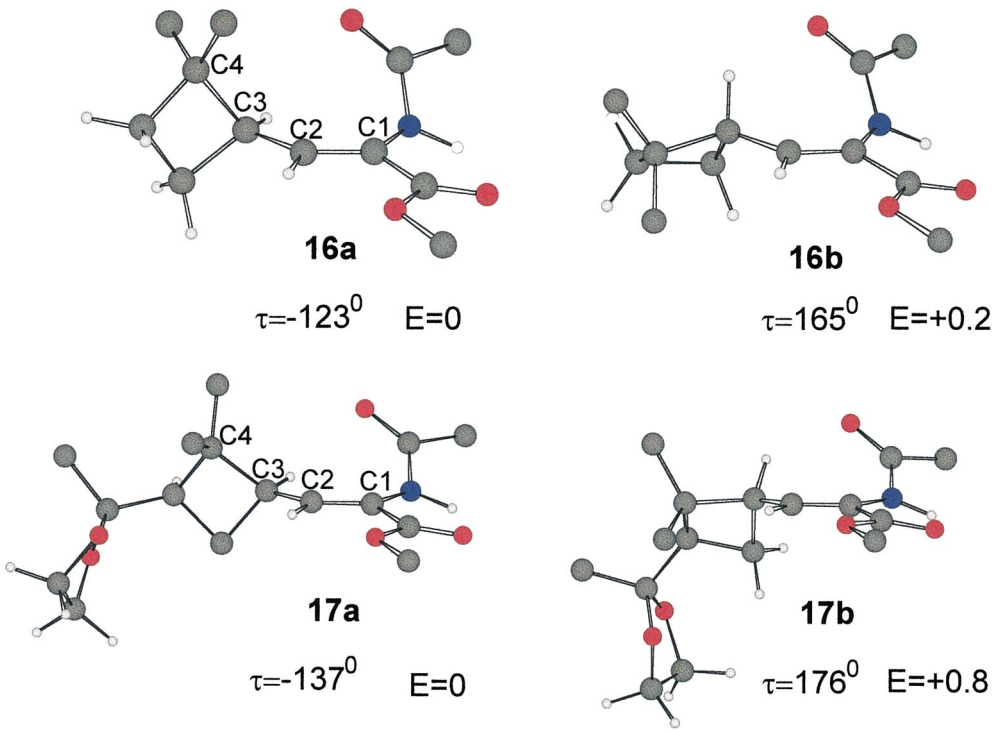


Figure 2. BPW91 optimized geometries of the two conformers **a**,**b** of the model olefins **16** and **17**, respectively. τ is the C4–C3–C2–C1 dihedral angle and relative energies are given in kcal mol^{-1}. Methyl hydrogen atoms have been omitted for clarity

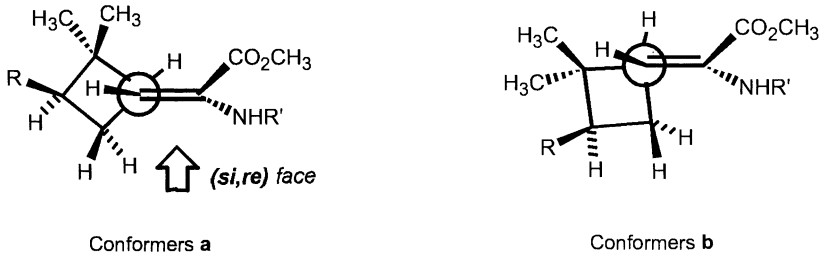


Figure 3. Newman projections for conformers **a** and **b** related to the dehydro amino acids **7**, **13**, **16**, and **17**

2.3. Chiroptical determinations and CSA-NMR experiments

The syntheses of compounds **11** and **15** were accomplished starting from commercial (–)-α-pinene or (–)-verbenone which were used without further treatment. Since the chemical transformations performed on these precursors were all stereocontrolled, the products obtained are, presumably, of high enantiomeric purity, diastereomeric purity being assessed by careful ^{13}C and ^{1}H NMR analysis.

However, optical rotations for these compounds as well as for derivative **12** were near to zero when measured at the sodium D-line (589 nm). For this reason, ORD and CD experiments were undertaken to secure that the synthesized products are optically active. As a representative example, Fig. 4 shows the results for compound **12**.

The ORD curve (MeOH, 20°C) shows a great variation of α depending on the wavelength of irradiation. Also, random oscillations were observed at different recording times, the spectrum shown in Fig. 4(a) being the average of seven scans (see Section 4). A strong decay is observed between 230–240 nm, the magnitude changes from positive to negative values between 240–350 nm and, finally, becomes zero. The region up to 230–240 nm contains the maximal absorption in the UV spectrum (Fig. 4(c)) and is negligible in the CD curve (Fig. 4(b)). On the other hand, CD shows a negative band with a minimum of 200 mdeg at 285 nm. At this wavelength, $[\alpha]_{285} = +435.65$ (*c* 0.07, MeOH).

Finally, stereoisomeric purity was ascertained by ^{1}H NMR by using the (*S*) enantiomer of perdeuterio Pirkle alcohol. This CSA has been recently developed in its perdeuterated version and it has shown its usefulness to resolve mixtures of enantiomers by NMR since the absence of CSA signals simplifies remarkably the spectra allowing accurate determinations.[13] The induced chemical shifts depending on the CSA concentration are represented in the plots shown in Fig. 5 for the protons of the methyl ketone group and for the methyl, from *gem*-dimethyl substitution, *trans* to the cyclopropane ring. The determined slopes of 11.6 and 8.8, respectively, are significant enough to confirm the interaction between the substrate and the CSA. Nevertheless, splitting of the signals was not observed in any case. This result is not in contradiction with the 90% ee previously determined by us for (–)-*cis*-pinononic acid which derives from (–)-verbenone and is the common precursor to **11**, **12**, and **15**.[14]

3. Concluding remarks

The cyclopropanation of cyclobutyl dehydro amino acids, obtained from (–)-α-pinene or (–)-verbenone, has been accomplished in a highly stereoselective manner by means of 1,3-dipolar

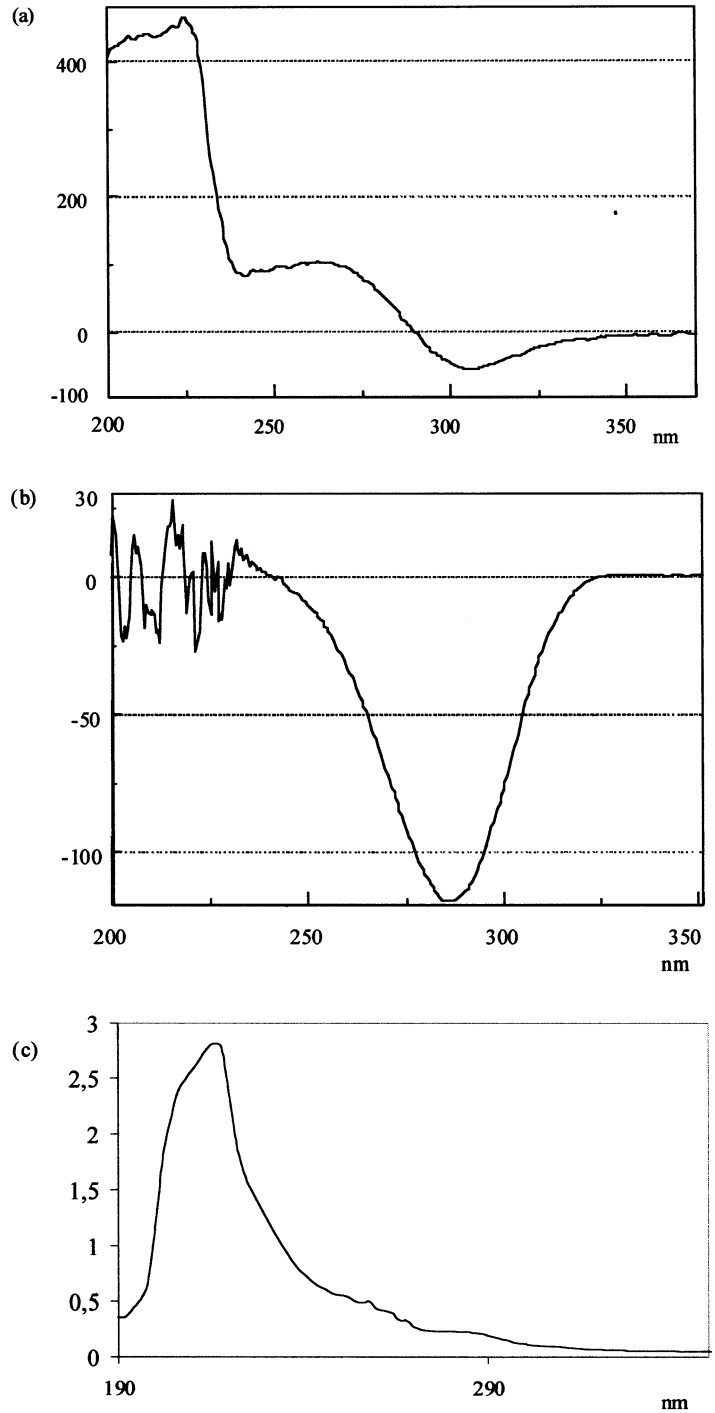


Figure 4. (a) ORD spectrum (mdeg), (b) CD spectrum (mdeg), and (c) UV absorbance of compound **12** as a 1.9×10^{-3} M methanol solution in 1.0 cm path-length cell at 20°C

cycloaddition to diazomethane. The cyclobutyl moiety plays the role of a chiral inducer governing the π-facial diastereoselection whose efficiency depends strongly on the proximity of

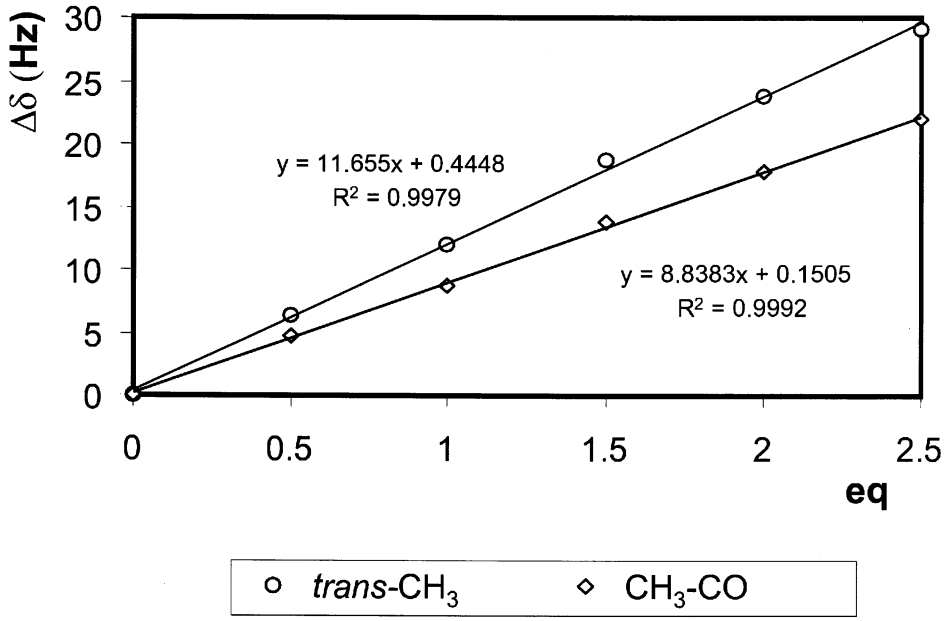


Figure 5. The variation of the chemical shift of the *trans*-CH_3 and CH_3CO protons of **12** when perdeuterio (*S*) Pirkle alcohol was added (constant volume) at several ratios

the double bond to the cyclobutane. In the most favorable cases, diazomethane attacks exclusively the face opposite to the *gem*-dimethyl substituent.

4. Experimental

4.1. General

Commercial (−)-α-pinene (97% ee) and (−)-verbenone (90% ee)[14] purchased from Aldrich were used without further purification. Flash column chromatography was carried out on silica gel (240–400 mesh). Melting points were determined on a hot stage and are uncorrected. UV spectra were acquired on a HP-8453 apparatus with software UV–vis ChemStation. ORD and CD data were acquired on a Jasco J-715 spectropolarimeter with software J-700 for Windows. Both spectrometers were equipped with a diode-array detector and measurements were made using methanol solutions contained in 1.0 cm path-length cells. The ORD and CD spectra are the averages of seven scans acquired over a 1 h-period with the base lines subtracted. ^{1}H NMR and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, respectively, unless otherwise stated. CSA-NMR experiments were carried out at constant volume in a Bruker ARX-400 spectrometer. The sample was prepared by dissolving compound **12** (4 mg, 11.2×10^{-3} mmol) in $CDCl_3$ (0.5 mL). Four portions of CSA (1.6 mg, 5.6×10^{-3} mmol, 0.5 equiv.) were successively added to the solution. After each addition, a ^{1}H NMR spectrum was recorded. $\Delta\delta$ were determined with respect to the chemical shifts of the involved protons in the absence of CSA.

4.2. Computational details

Preliminary geometry optimizations have been done using the semiempirical AM1[15] method. The most significant structures have been optimized through density functional calculations using the gradient-corrected Becke's[16] exchange functional and Perdew–Wang[17] correlation functional (BPW91) with the standard 6-31G(d) basis set.[18] All calculations have been done using the Gaussian-98 program.[19]

4.3. General procedure for the synthesis of pyrazolines **8**, **9**, and **14**

These compounds were synthesized from amino acids **6**, **7**, and **13**, respectively, which were previously described. A typical experiment is described for the preparation of pyrazoline **8**. An ethereal solution of excess diazomethane (ca. 10 equiv.) was distilled onto **6** (0.11 g, 0.24 mmol) in 10 mL of ether. The light-protected resultant solution was stirred at room temperature overnight, then excess diazomethane was destroyed by addition of $CaCl_2$ and solvent was removed to afford oily pyrazoline **8** (90 mg, 82% yield) as a 1:1 diastereomeric mixture which was used in the next step without further purification. Pyrazolines **9** and **14** were prepared and used in a similar manner.

4.3.1. (3R,4R,1′S,3′R) and (3S,4S,1′S,3′R)-3-N-*Benzyloxycarbonylamino-4-[2′,2′-dimethyl-3′-(2-methyl-1,3-dioxolan-2-yl)cyclobutylmethyl]-3-methoxycarbonyl-1-pyrazoline*, **8**

IR (film): 3406–3300 (broad, NH), 2955, 2885, 2859, 1732 (C=O_{ester}), 1500, 1243, 1038 cm^{-1}. ^1H NMR (acetone-d_6): 0.91 and 0.92 (s, 3H, *t*-2′CH_3), 1.02 and 1.04 (s, 3H, *c*-2′-CH_3), 1.13 (s, 3H, CH_3), 1.15–2.10 (complex absorption, 6H, R-CH_2-R_1/$H_{1'}$/$H_{4'a}$/$H_{4'b}$/$H_{3'}$), 2.35 (m, 1H, H_4), 3.78 and 3.76 (s, 3H, OCH_3), 3.70–3.95 (m, 4H, 2×OCH_2); 4.50 (dd, 1H, H_{5a}, J_{gem} = 17.6 Hz, J' = 6.6 Hz), 4.85 (dd, J = 8.0 Hz, J_{gem} = 17.6 Hz, 1H, H_{5b}), 5.10 (complex absorption, 2H, CO_2CH_2Ph), 7.20 (broad s, 1H, N*H*), 7.35 (complex absorption, 5H). ^{13}C NMR (acetone-d_6) 16.83 and 17.13 (*t*-2′-CH_3), 23.54/24.86/25.48/27.69/27.83/30.89/31.07 (4C, *c*-2′-CH_3/RCH_2R^1/$C_{4'}$/CH_3), 36.48/37.13/40.89/41.07/41.48/41.92/50.07/50.33/53.30 (5C, $C_{1'}$/$C_{2'}$/$C_{3'}$/C_4/OCH_3), 63.74/65.51/66.65 (CO_2CH_2Ph/2×CH_2O/OCH_2Ph), 84.03 and 84.30 (C_5), 101.89 (C_3), 109.77 (C_q), 128.15/128.27/128.35/128.82 (5C, $C_{aromatic}$), 137.32 (1C, $C_{aromatic}$), 154.68 (*C*=$O_{carbamate}$), 168.97 and 169.06 (*C*=O_{ester}).

4.3.2. (3S,4S,1′R,3′R)-3-N-*Benzyloxycarbonylamino-4-[2′,2′-dimethyl-3′-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]-3-methoxycarbonyl-1-pyrazoline*, **9**

Yield: 85 mg, 80%. IR (film): 3550–3300 (broad, N*H*), 2956, 1730 (C=O_{ester}), 1500, 1317, 1041 cm^{-1}. ^1H NMR (acetone-d_6): 0.87 (s, 3H, *t*-2′-CH_3), 0.99 (s, 3H, *c*-2′-CH_3), 1.11 (s, 3H, CH_3), 1.40–2.10 (complex absorption, 4H, $H_{1'}$/$H_{4'a}$/$H_{4'b}$/$H_{3'}$), 2.42 (m, 1H, H_4), 3.84 (s, 3H, OCH_3), 3.70–4.00 (m, 4H, 2×OCH_2); 4.48 (dd, 1H, H_{5a}, J_{gem} = 17.5 Hz, J' = 7.3 Hz), 4.88 (dd, 1H, H_{5b}, J_{gem} = 17.5 Hz, J = 9.5 Hz), 5.01 (d, 1H, J_{gem} = 12.4 Hz, CO_2CH_2Ph), 5.10 (d, 1H, J_{gem} = 12.4 Hz, CO_2CH_2Ph), 6.98 (broad s, 1H, N*H*), 7.40 (complex absorption, 5H). ^{13}C NMR (acetone-d_6): 18.05 (*t*-2′-CH_3), 23.81/24.20/31.71 (3C, *c*-2′-CH_3, $C_{4'}$ and CH_3) 40.42/41.11/41.50/49.76 (4C, $C_{1'}$/$C_{2'}$/$C_{3'}$/C_4), 54.17 (OCH_3), 64.12/65.84/67.22 (3C, CO_2CH_2Ph/2×CH_2O), 83.70 (C_5), 100.19 (C_3), 110.09 (C_q), 128.89, 129.19 (5C, $C_{aromatic}$), 137.48 (1C, $C_{aromatic}$), 154.47 (*C*=$O_{carbamate}$), 169.92 (*C*=O_{ester}).

*4.3.3. (3*R,*4*R,*1′*S,*3′*R*)-3-*N*-*Benzyloxycarbonylamino-4-[3′-(2-benzyloxyethyl)-2′,2′-dimethylcyclobutyl]-3-methoxycarbonyl-1-pyrazoline*, ***14***

Yield: 100 mg, 83%; IR (film): 3406 (broad, NH), 2954, 2929, 2859, 1731 (C=O_{ester}), 1498, 1454, 1266, 1213, 1099, 1027 cm^{-1}. ^1H NMR (acetone-d_6): 0.77 (s, 3H, *t*-2′CH_3), 0.93 (s, 3H, *c*-2′-CH_3), 1.05–2.05 (complex absorption, 6H, RCH_2CH_2OR_1/$H_{1'}$/$H_{4'a}$/$H_{4'b}$/$H_{3'}$), 2.45 (m, 1H, H_4), 3.36 (t, $J_{1,2}$=6.6 Hz, 2H, RCH_2CH_2OR_1), 3.83 (s, 3H, OCH_3), 4.45 (m, 3H, OCH_2Ph/H_{5a}), 4.83 (dd, 1H, H_{5b}, J_{gem}=17.5 Hz, J=8.8 Hz), 4.98 (d, J_{gem}=12.1 Hz, 1H, CO_2CH_2Ph), 5.11 (d, J_{gem}=12.1 Hz, 1H, CO_2CH_2Ph), 6.95 (broad s, 1H, N*H*), 7.35 (complex absorption, 10H). ^{13}C NMR (acetone-d_6): 17.38 (*t*-2′-*C*H_3), 28.89/30.74/31.05 (3C, *c*-2′-*C*H_3/$C_{4'}$/R*C*H_2CH_2OR_1), 40.00/40.44/40.69/41.39 (4C, $C_{1'}$/$C_{2'}$/$C_{3'}$/C_4), 54.11 (O*C*H_3), 67.19/69.36 (2C, CO_2CH_2Ph/RCH_2*C*H_2O), 73.19 (O*C*H_2Ph), 83.64 (C_5), 100.10 (C_3), 128.05/128.19/128.96/129.21 (10C, $C_{aromatic}$), 134.73/139.99 (2C, $C_{aromatic}$), 154.47 (*C*=$O_{carbamate}$), 169.99 (*C*=O_{ester}).

4.4. General procedure for the photolysis of the pyrazolines: cyclopropanes ***10***, ***11***, *and* ***15***

Photolysis of **8** is described as a typical instance. A stirred solution of **8** (100 mg, 0.2 mmol) in anhydrous toluene (30 mL) contained in a Pyrex reactor under an argon atmosphere, cooled at −78°C, was irradiated with a 125 W medium-pressure mercury lamp for 1.5 h (reaction was monitored by UV following the disappearance of the band at ∼330 nm). Solvent was removed and the residue was chromatographed (mixtures of ethyl acetate–hexane) to afford cyclopropane **10** as a mixture of diastereomers (50 mg, 58% yield). The single stereoisomers could not be isolated by the usual chromatographic techniques.

*4.4.1. Methyl (1*R,*2*S,*1′*S,*3′*R*)- and (1*S,*2*R,*1′*S,*3′*R*)-1-*N*-*benzyloxycarbonylamino-2-[2′,2′-dimethyl-3′-(2-methyl-1,3-dioxolan-2-yl)cyclobutylmethyl]cyclopropanecarboxylate*, ***10***

IR (film): 3330 (broad, NH), 2978, 2885, 1729 (C=O_{ester}), 1268, 1237, 735 cm^{-1}. ^1H NMR ($CDCl_3$): 0.97 (s, 3H, *t*-2′-CH_3), 1.07 and 1.08 (s, 3H, *c*-2′-CH_3), 1.20 (s, 3H, CH_3), 0.99–2.15 (complex absorption, 9H, RC$H_2$$R^1$/$H_{1'}$/$H_{4'a}$/$H_{4'b}$/$H_{3'}$/$H_2$/$H_{3a}$/$H_{3b}$), 3.65 (s, 3H, OC$H_3$), 3.75–3.95 (4H, m, 2×OCH_2); 5.10 (s, 3H, -OCH_2Ph and N*H*), 7.34 (complex absorption, 5H). ^{13}C NMR ($CDCl_3$): 16.98 and 17.18 (*t*-2′-CH_3), 22.95 and 23.42 (C_3), 23.68/24.68/24.89/27.18/28.33/28.42/31.15 (5C, *c*-2′-*C*H_3/$C_{4'}$/CH_3/C_2/R*C*$H_2$$R^1$), 37.62/38.33/40.83/40.89/42.09/49.83/49.91 (4C, $C_{1'}$/$C_{2'}$/$C_{3'}$/C_1), 52.35 (*C*H_3), 63.62/65.41/66.88 (3C, CO_2CH_2Ph, 2×*C*H_2O), 109.85 (C_q), 128.08/128.44 (5C, $C_{aromatic}$), 136.29 (1$C_{aromatic}$), 156.82 (*C*=$O_{carbamate}$), 173.43 (*C*=O_{ester}). Anal. calcd for $C_{24}H_{33}NO_6$: C, 66.80; H, 7.71; N 3.25. Found: C, 66.85; H, 7.78; N, 3.50.

*4.4.2. (−)-Methyl (1*R,*2*R,*1′*R,*3′*R*)-1-*N*-*benzyloxycarbonylamino-2-[2′,2′-dimethyl-3′-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]cyclopropanecarboxylate*, ***11***

Yield: 50 mg, 60%. This compound was an unstable oil not suitable for [α] determination and for microanalysis. IR (film): 3445–3353 (broad, NH), 2953, 1721 (C=O_{ester}), 1455, 1226, 1154 cm^{-1}. ^1H NMR ($CDCl_3$): 1.06 (s, 3H, *t*-2′CH_3), 1.10 (s, 3H, *c*-2′-CH_3), 1.19 (s, 3H, CH_3), 1.10 (m, 1H, H_{3a}), 1.40–2.15 (complex absorption, 6H, $H_{1'}$/$H_{4'a}$/$H_{4'b}$/$H_{3'}$/H_2/H_{3b}), 3.66 (s, 3H, OCH_3), 3.75–3.95 (m, 4H, 2×OCH_2); 4.98 (broad s, N*H*), 5.11 (m, 2H, -OCH_2Ph), 7.33 (complex absorption, 5H). ^{13}C NMR (acetone-d_6): 17.71 (*t*-2′-*C*H_3), 20.21 (C_3), 23.18/23.45/27.83/30.89 (4C, *c*-2′-*C*H_3/$C_{4'}$/CH_3/C_2), 38.07/40.30/41.57/50.01 (4C, $C_{1'}$/$C_{2'}$/$C_{3'}$/C_1), 51.89 (O*C*H_3), 63.71/65.45/66.06 (3C, CO_2CH_2Ph/2×*C*H_2O), 109.85 (C_q), 128.09/128.65 (5C, $C_{aromatic}$), 137.79 ($C_{aromatic}$), 156.85 (*C*=$O_{carbamate}$), 173.29 (*C*=O_{ester}); MS, *m*/*e* (%) 418 (M+1, 23.6), 373 (10.5), 356 (24.5), 304 (100), 260 (27.8), 205 (21.4).

*4.4.3. Methyl (1*S,*2*S,*1′*S,*3′*R*)*-N-benzyloxycarbonylamino-2-[3′-(2-benzyloxyethyl)-2′,2′-dimethylcyclobutyl]cyclopropanecarboxylate*, ***15***

Yield: 50 mg, 54%. Oil, $[\alpha]_{285}=-164.83$ (*c* 0.09, MeOH). IR (film): 3339 (broad, NH), 2952, 2859, 1728 (C=O_{ester}), 1498, 1454, 1270, 1236, 1197, 1163, 1093, 738, 698 cm^{-1}. ^1H NMR ($CDCl_3$): 0.92 (s, 3H, *t*-2′CH_3), 1.01 (s, 3H, *c*-2′-CH_3), 0.99–2.10 (complex absorption, 9H, RCH_2CH_2OR_1/$H_{1'}$/$H_{4'a}$/$H_{4'b}$/$H_{3'}$/H_2/H_{3a}/H_{3b}), 3.35 (t, $J_{1,2}=6.6$ Hz, 2H, RCH_2CH_2OR_1), 3.66 (s, 3H, OCH_3), 4.45 (broad s, 2H, OCH_2Ph), 4.97 (broad s, 1H, N*H*), 5.12 (m, 2H, CO_2CH_2Ph), 7.32 (complex absorption, 10H). ^{13}C NMR (acetone-d_6): 16.86 (*t*-2′-CH_3), 20.21 (C_3), 27.65/30.30, (4C, *c*-2′-CH_3/$C_{4'}$/RCH_2CH_2OR_1/C_2), 37.45/39.42/40.18/40.45 (4C, $C_{1'}$/$C_{2'}$/$C_{3'}$/C_1), 51.65 (OCH_3), 65.89/68.71 (2C, CO_2CH_2Ph/RCH_2O), 72.45 (OCH_2Ph), 127.12/127.26/127.65/128.03/128.18 (10C, $C_{aromatic}$), 136.97/138.85 (2C, $C_{aromatic}$), 156.47 (*C*=$O_{carbamate}$), 172.91 (*C*=O_{ester}). Anal. calcd for $C_{28}H_{35}NO_5$: C, 72.23; H, 7.58; N, 3.01. Found: C, 72.35; H, 7.61; N, 3.09.

*4.5. (1*R,*2*R,*1′*R,*3′*R*)-1-*N*-benzyloxycarbonylamino-2-[3′-acetyl-2′,2′-dimethylcyclobutyl]-cyclopropanecarboxylic acid*, ***12***

A mixture of ester **11** (150 mg, 0.3 mmol) and 1N aq. NaOH (1.6 mL) in methanol (1.5 mL) was stirred at room temperature for 20 h. The reaction mixture was extracted with dichloromethane and the aqueous layer was acidified with 5% HCl and then extracted with dichloromethane. This last extract was concentrated under vacuum and the residue was poured into wet acetone (1 mL). Then PPTS (25 mg) was added and the resultant solution was heated to reflux for 5 h. Solvent was evaporated and the residue was subsequently dissolved in ether and washed with water. The organic phase was dried ($MgSO_4$) and solvent was removed to afford keto acid **12** (45 mg, 35% yield) as a solid mp 163–165°C (from ethanol–water), $[\alpha]_{285}=+435.65$ (*c* 0.07, MeOH). IR (film): 3451 (broad, OH), 3350 (broad, NH), 2959, 1708 (C=O), 1433, 1258, 1082 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 0.91 (s, 3H, *t*-2′CH_3), 1.28 (s, 3H, *c*-2′-CH_3), 2.01 (s, 3H, CH_3), 1.12 (1H, m, H_{3a}), 1.60–1.80 (complex absorption, 3H, $H_{4a/b}$/H_{3b}), 2.05 (2H, m, $H_{1'}$/H_2), 2.78 (1H, m, H_3), 5.03 (broad s, 1H, N*H*), 5.12 (complex absorption, 2H, OCH_2Ph), 7.33 (broad s, 5H). ^{13}C NMR (acetone-d_6): 17.18 (*t*-2′-CH_3), 19.41 (C_3), 21.03/27.06/29.47 (4C, *c*-2′-CH_3/$C_{4'}$/CH_3/C_2), 37.53/39.56/41.35/43.15 (4C, $C_{1'}$/$C_{2'}$/$C_{3'}$/C_1), 53.26 (OCH_3), 65.73 (CO_2CH_2Ph), 127.73/128.29 (5C, $C_{aromatic}$), 137.38 ($C_{aromatic}$), 156.64 (*C*=$O_{carbamate}$), 173.52 (*C*=O_{ester}), 206.14 (*C*=O_{ketone}). Anal calcd for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90. Found: C, 66.54; H, 7.26; N, 3.83.

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