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Enantiodivergent synthesis of cyclobutyl-(*Z*)-α,β-dehydro-α-amino acid derivatives from (−)-*cis*-pinononic acid

Gemma P. Aguado, Albertina G. Moglioni† and Rosa M. Ortuño*

Departament de Química, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain

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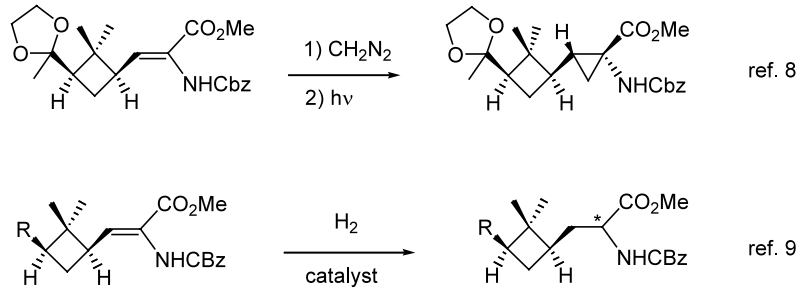
Abstract—The two enantiomers of the title dehydroamino acids (DHAAs) have been synthesized through respective Wadsworth–Emmons condensations of a suitable phosphonate with enantiomeric cyclobutyl aldehydes. These compounds, in turn, were prepared by selective manipulation of the functional groups starting from (−)-*cis*-pinononic acid as the common chiral precursor. The CD spectra of the prepared DHAAs are described. These products are suitable for the stereocontrolled synthesis of diferent types of saturated cyclobutyl amino acids and their derivatives. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Unsaturated amino acids occur in nature, being incorporated into peptides (dehydro-peptides, DHP) present in the structure of enzymes,[1] hormones,[2] antibiotics,[3] and phytotoxins[4] among other biologically active products. These amino acids are responsible for the binding abilities of designed DHPs[5] used as metal ligands and can also act as β-turn inducers.[6] Moreover, α,β-dehydro amino acids (DHAAs) are believed to be biosynthetic precursors to the D-amino acid residues present in some antibiotics.[3b]

In addition, DHAAs are valuable synthetic precursors to a variety of designed saturated amino acids. Thus, according to our research program on the stereoselective synthesis of cyclobutyl amino acids from natural terpenes,[7–11] we have described the preparation of α,β-dehydro amino acids through Wadsworth–Emmons olefination of aldehydes obtained from (−)-α-pinene or (−)-verbenone.[7] Some of these cyclobutyl DHAA underwent 1,3-dipolar cycloaddition of diazomethane to afford pyrazolines that, under photolysis, gave cyclopropanes as single stereoisomers (Scheme 1).[8] The diastereoselectivity of the cycloaddition was governed by the steric hindrance of the bulky cyclobutane moiety, which shields one of the faces of the double bond from the attack of diazomethane.

On the other hand, hydrogenation of the double bond was accomplished by using chiral catalysts based on chiraphos or duphos ligands (Scheme 1). From our



Scheme 1.

* Corresponding author. E-mail: rosa.ortuno@uab.es
† Permanent adress: Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, 1113 Buenos Aires, Argentina.

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preliminary results, we could not conclude whether the configuration of the newly formed stereogenic center depends on the catalyst, on the substrate, or if it results from double asymmetric induction promoted by both reactants.[9] Therefore, to pursue our hydrogenation studies aimed at the diastereocontrolled synthesis of cyclobutyl α-amino acids, we needed to obtain the DHAAs in both enantiomeric forms.

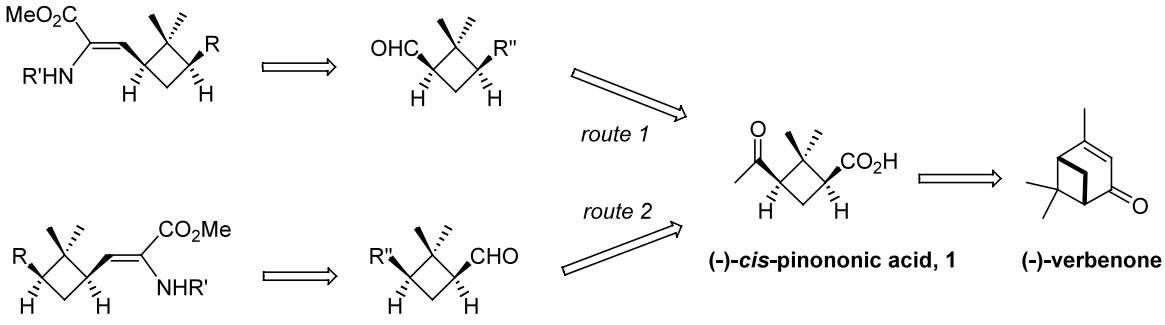
Herein, we describe the stereodivergent synthesis of the two enantiomers of a cyclobutyl DHAA starting from (−)-*cis*-pinononic acid, **1**, as the common chiral precursor (Scheme 2). This compound results from oxidative cleavage of the double bond of (−)-verbenone.[7] Scheme 2 shows the retrosynthetic pathways envisioned. According to route 1, the methyl-ketone group in **1** must be degraded to a formyl group, while the carboxylic acid must be reduced to an aldehyde in route 2. Thus, the synthesis of the two enantiomers of a DHAA, for a given R substituent, was achieved through selective transformations of the functional groups providing enantiomeric cyclobutyl aldehydes and their subsequent condensation with a suitable phosphonate that bears the amino acid function conveniently protected.

2. Results and discussion

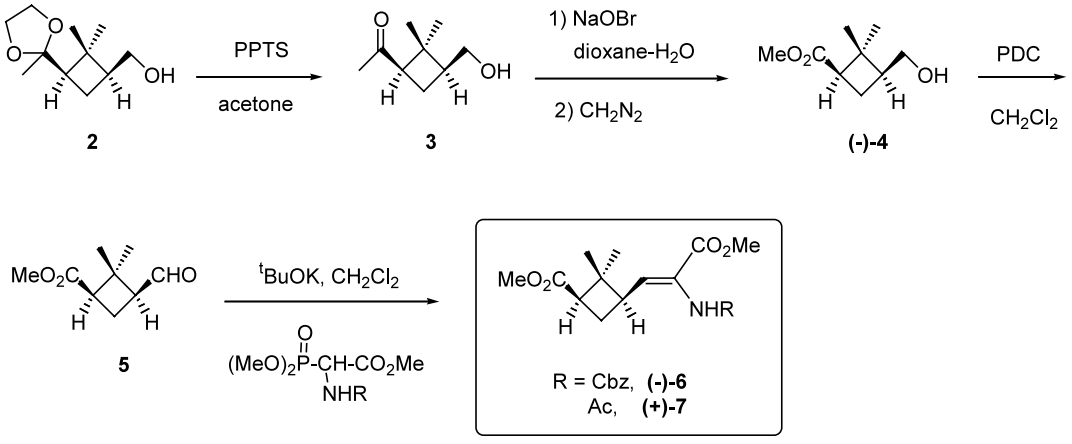
The synthetic sequences developed for the preparation of the two enantiomers (+)- and (−)-**6** are depicted in Schemes 3 and 4, respectively.

Hydroxy ketal **2**, easily prepared from (−)-*cis*-pinononic acid, **1**,[7b] was transformed into hydroxy ketone **3** by treatment with pyridinium *p*-toluenesulphonate (PPTS) in boiling wet acetone for 5 h (Scheme 3). Epimerisation of the α-carbonyl stereogenic centre was prevented under such mild conditions.[12] Lieben degradation of the resultant methyl ketone was achieved through reaction with sodium hypobromite in aqueous dioxane[13] to afford a carboxylic acid that was methylated with diazomethane to produce the hydroxy ester (−)-**4**. Oxidation of the primary alcohol with pyridinium dichromate (PDC) in dichloromethane provided aldehyde **5** that was condensed with the anion (^{t}BuOK) of methyl 2-*N*-benzyloxycarbonylamino-2-dimethoxyphosphinyl acetate[14] giving the DHAA derivative (−)-**6**, $[\alpha]_D$ −6.9. The (*Z*) stereochemistry of the double bond was determined by NMR techniques by means of NOE experiments as previously described for other similar DHAAs.[7] Alternatively, condensation with the *N*-acetyl phosphonate led to compound **7**. These two DHAAs are conveniently protected for use as substrates for asymmetric hydrogenation in the presence of different catalysts.[15]

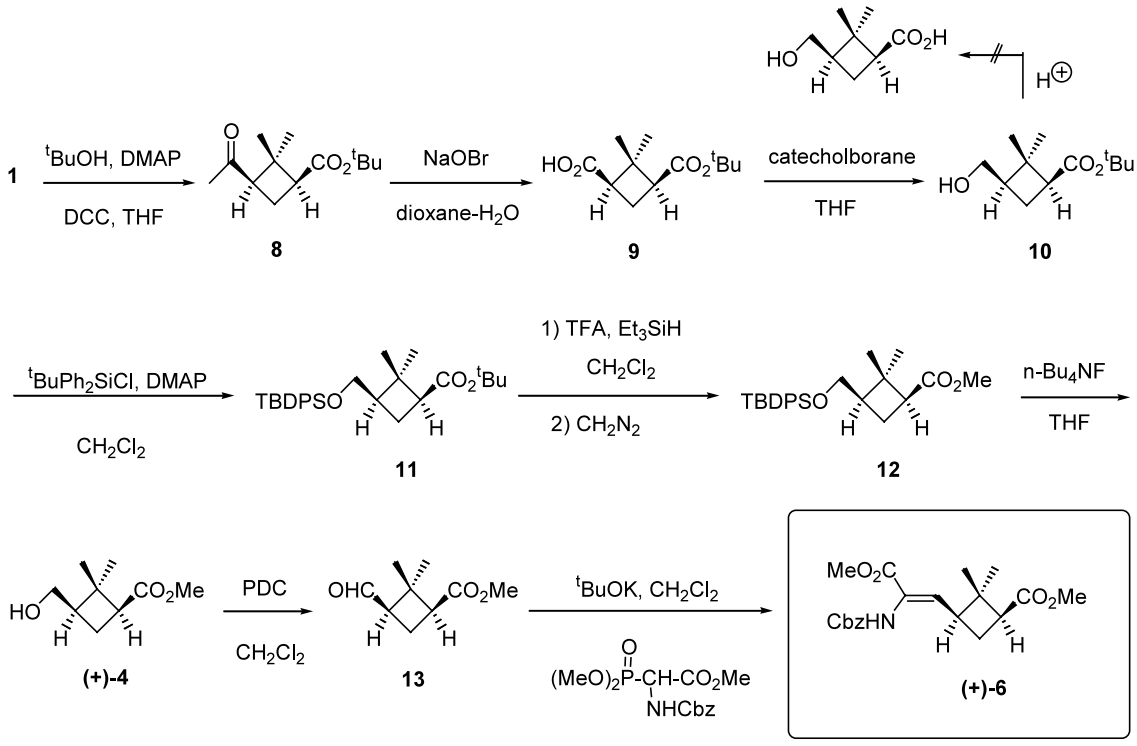
For the synthesis of the enantiomer (+)-**6**, (−)-*cis*-pinononic acid, **1**, was reacted with *tert*-butanol in the presence of dimethylaminopyridine (DMAP) and dicyclohexylcarbodiimide[16] to afford the *tert*-butyl ester **8** (Scheme 4). Lieben degradation of the methyl ketone led to the hemi ester **9** that underwent selective reduc-



Scheme 2.



Scheme 3.



Scheme 4.

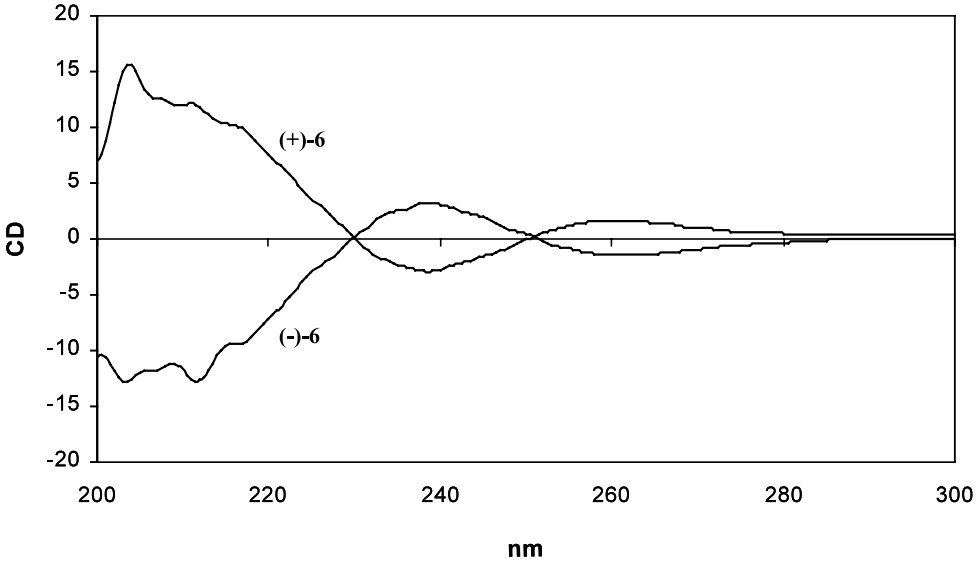


Figure 1. CD spectra (mdeg) of enantiomers (+)-**6** and (−)-**6**.

tion of the carboxyxlic acid group upon treatment with catecholborane.[17] The resultant hydroxy ester **10** did not afford the expected hydroxy acid by treatment under acid conditions. Instead, the corresponding δ-lactone and polymeric side products were obtained. Therefore, protection of the primary alcohol prior to hydrolysis of the *tert*-butyl ester became necessary. Thus, **10** was allowed to react with *tert*-butyldiphenylsilyl chloride in the presence of DMAP affording the silyl ether **11**. Subsequent treatment with trifluoroacetic acid and triethylsilyl hydride in dichloromethane[18] allowed the selective deprotection of the *tert*-butyl ester to give a carboxylic acid that was methylated with diazomethane. The resultant methyl ester, **12**, was allowed to react with *n*-tetrabutyl ammonium fluoride in order to recover the alcohol, giving hydroxy ester (+)-**4**. This compound was oxidized with PDC in dichloromethane to afford the aldehyde **13**. Subsequent condensation with the anion of the *N*-Cbz phosphonate allowed the synthesis of (+)-**6**, $[\alpha]_D$ +6.9, to be accomplished.

The CD spectra of both enantiomers were superimposed showing good concordance (Fig. 1). A strong positive band with a maximum of +12.2 mdeg at 210 nm and a weak negative band with a minimum of −3.0 mdeg at 238 nm were observed for (+)-**6**. The CD spectrum of (−)-**6** showed two bands of −11.9 and +3.5 mdeg at 210 and 238 nm, respectively (Fig. 1).

Thus, selective manipulation of the functional groups starting from (−)-*cis*-pinononic acid, as the only chiral immediate precursor, allowed the enantiodivergent synthesis of the two DHAA derivatives (+)- and (−)-**6**. These compounds are suitable to be used as synthetic precursors for a variety of enantiomeric saturated amino acids and are also convenient to study the influence of the chiral catalysts in the hydrogenation of the double bond. Such applications are under active investigation in our laboratory.

3. Experimental

3.1. General

(−)-*cis*-Pinononic acid was prepared[7b] from commercial (−)-verbenone (95% e.e.). Flash column chromatography was carried out on Baker® silica gel (40 μM). Melting points ere 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 (ot) reported. CD data were acquired on a spectropolarimeter equipped with a diode-array detector and measurements were made using methanol solutions contained in 1.0 mm path-length cells. The CD spectra are the averages of four scans acquired over a 1 h-period with the base-lines subtracted. ^{1}H and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, respectively. Chemical shifts are given on the δ scale. Electron impact MS and HRMS spectra were recorded at 70 eV.

3.2. (1*R*,3*S*)-3-Hydroxymethyl-2,2-dimethylcyclobutyl methyl ketone, 3

A mixture of ketal **2** (1.4 g, 6.7 mmol) and PPTS (0.6 g, 2.2 mmol) in wet acetone (91 mL) was heated under reflux for 5 h. The reaction mixture was cooled and solvent was removed at reduced pressure. The residue was poured into ether (84 mL) and the resultant solution was washed with saturated aq $NaHCO_3$ and dried ($MgSO_4$). The solvent was evaporated under vacuo and the residue was flash chromatographed (EtOAc) to afford ketone **3** (985 mg, 90% yield) as a hygroscopic oil unsuitable for microanalysis; ot 75–78°C (0.02 torr), $[\alpha]_D$ −42 (*c* 1.33, MeOH). IR (film) 3510–3255 (broad), 1703 cm^{-1}; ^{1}H NMR (acetone-d_6): 0.88 (s, 3H, *c*-2-CH_3), 1.33 (s, 3H, *t*-2-CH_3), 1.62–1.90 (complex absorption, 2H, H_{4a}, H_{4b}), 1.95 (s, COCH_3), 2.08–2.20 (m, 1H, H_3), 2.88 (dd, $J_{1,4a}=7.5$ Hz, $J_{1,4b}=10.0$ Hz, 1H, H_1), 3.34–3.54 (complex absorption, 3H, CH_2O*H*); ^{13}C NMR (acetone-d_6): 17.08 (*c*-2-*C*H$_3$), 20.36 (C_4), 29.95, 31.41 (2C, *t*-2-*C*H$_3$, CO*C*H$_3$), 43.01 (C_2), 44.32 (C_3), 53.98 (C_1), 62.96 (*C*H$_2$OH), 207.93 (*C*=O); MS, *m*/*e* (%) 157 (M+1, 100), 139 ([M+1]–H_2O, 38), 127 ([M+1)–CH_2O, 10).

3.3. Methyl (1*R*,3*S*)-3-hydroxymethyl-2,2-dimethylcyclobutane-1-carboxylate, (−)-4

An ice-cooled solution of NaOBr, prepared from bromine (1.08 mL, 21.6 mmol) and NaOH (3.3 g, 82 mmol), in water (43 mL) was added to a solution of ketone **3** (0.6 g, 3.8 mmol) in dioxane (67 mL) cooled at −5°C. The resultant mixture was stirred at 0°C for 3 h and at rt for 4 h. Then the reaction mixture was extracted with ether and 40% aq $NaHCO_3$ and conc HCl was subsequently added to the basic aqueous solution until acid pH was reached. The acid solution was extracted with ether and all the combined ether extracts were dried ($MgSO_4$) and solvents were removed at reduced pressure to afford a crude carboxylic acid (370 mg, 61% yield). This compound was made to react with a freshly distilled ethereal solution of diazomethane at 0°C for 30 min. Then excess diazomethane was destroyed by addition of benzoic acid, the mixture was filtered and the solvent was evaporated at reduced pressure. The residue was flash chromatographed (5:1 ethyl acetate–hexane) to afford pure hydroxy ester (−)-**4** (383 mg, 95% yield) as a hygroscopic oil unsuitable for microanalysis; ot 65–67°C (0.02 torr), $[\alpha]_D$ −9.2 (*c* 0.87, MeOH). IR (film) 3529–3260 (broad), 1735 cm^{-1}; ^{1}H NMR (acetone-d_6): 0.93 (s, 3H, *c*-2-CH_3), 1.21 (s, 3H, *t*-2-CH_3), 1.74–1.95 (complex absorption, 2H, H_{4a}, H_{4b}), 2.06–2.21 (m, 1H, H_3), 2.69 (dd, $J_{1,4a}=7.9$ Hz, $J_{1,4b}=10.0$ Hz, 1H, H_1), 3.41–3.57 (m, 2H, CH_2OH), 3.59 (s, 3H, OCH_3); ^{13}C NMR (acetone-d_6): 17.52 (*c*-2-*C*H$_3$), 21.91 (C_4), 31.16 (*t*-2-*C*H$_3$), 42.52 (C_2), 44.62 (C_3), 46.17 (C_1), 51.12 (O*C*H$_3$), 63.02 (*C*H$_2$OH), 173.64 (*C*=O); MS, *m*/*e* (%) 173 (M+1, 100), 157 (([M+1]–CH_3, 15).

3.4. Methyl (1′*R*,3′*R*)-2-*N*-benzyloxycarbonylamino-3-(2′,2′-dimethyl-3′-methoxycarbonylcyclobutyl)-(*Z*)-2-propenoate, (−)-6, and methyl (1′*R*,3′*R*)-2-*N*-acetylamino-3-(2′,2′-dimethyl-3′-methoxycarbonylcyclobutyl)-(*Z*)-2-propenoate, 7 through aldehyde, 5

A mixture of alcohol **4** (340 mg, 2.0 mmol) and PDC (1 g, 2.7 mmol) in dry dichloromethane was stirred at rt for 6 h under nitrogen atmosphere. Then a small portion of Florisil was added and stirring was pursuit for 30 min. The reaction mixture was filtered on Celite and solvent was removed at reduced pressure to afford crude aldehyde **5** (300 mg, 89% yield) as a rather unstable oil that was identified by their IR and ^{1}H NMR spectroscopic data and immediately used in the condensation step without purification. IR (film) 2926, 1736 (broad, two C=O) cm^{-1}; ^{1}H NMR (acetone-d_6): 0.96 (s, 3H, *c*-2-CH_3), 1.40 (s, 3H, *t*-2-CH_3), 1.07–2.02 (complex absorption, 2H, H_{4a}, H_{4b}), 2.59 (dd, $J_{1,4a}=J_{1,4b}=10.2$ Hz, H_1), 2.80–3.02 (m, 1H, H_3), 3.62 (s, 3H, OCH_3), 9.72 (d, J = 1.5 Hz, C*H*O).

A solution of methyl 2-*N*-benzyloxycarbonylamino-2-dimethoxyphosphinyl acetate (0.9 g, 2.8 mmol) in dry

dichloromethane (4.5 mL) was slowly added to a suspension of K^{t}BuO (0.26 g, 2.3 mmol) in dry dichloromethane (5 mL) cooled at −78°C under nitrogen atmosphere. The mixture was stirred at −78°C for 30 min and aldehyde **5** (0.2 g, 1.2 mmol) in dry dichloromethane (3.5 mL) was added dropwise. The resultant mixture was allowed to warm to rt, then stirred for 64 h. Water (10 mL) was added and layers were separated. The aqueous layer was extracted with dichloromethane (4×25 mL), the combined organic phases were dried ($MgSO_4$) and solvent was removed under reduced pressure. The residue was chromatographed (1:3 ethyl acetate–hexane) to afford (−)-**6** (170 mg, 38% yield) as an oil, $[\alpha]_D$ −6.9 (*c* 0.86, MeOH); IR (film) 3326 (broad), 1729, 1653 cm^{-1}; ^{1}H NMR (acetone-d_6): 0.94 (s, 3H, *c*-2′-CH_3), 1.18 (s, 3H, *t*-2′-CH_3), 2.11–2.21 (complex absorption, 2H, $H_{4'a}$, $H_{4'b}$), 2.70–3.15 (complex absorption, 2H, $H_{3'}$, $H_{1'}$), 3.65 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 5.14 (s, 2H, PhCH_2O), 6.57 (d, $J_{3,1'}$=8.9 Hz, H_3), 7.25–7.49 (complex absorption, 5H, *Ph*), 7.55 (broad s, 1H, N*H*); ^{13}C NMR (acetone-d_6): 18.64 (*c*-2′-*C*H$_3$), 24.63 ($C_{4'}$), 29.38 (*t*-2′-*C*H$_3$), 40.22 ($C_{1'}$), 45.08 ($C_{2'}$), 46.01 ($C_{3'}$), 50.86 (O*C*H$_3$), 51.86 (O*C*H$_3$), 66.63 (Ph*C*H$_2$O), 127.90 (C_α), 128.25, 128.29 (5C, *C*H$_{Ph}$), 137.41 (C_{ipso}), 137.58 (C_β), 154.92 (NH*C*O$_2$CH$_2$Ph), 165.11 (MeO$_2$*C*-C=C-), 172.73 (*C*O$_2$CH$_3$); HRMS: Calcd for $C_{20}H_{25}NO_6$ (M): 375.1682. Found: 375.1669. Calcd for $C_{14}H_{15}NO_4$ [M−$C_6H_{10}NO_2$]: 261.1001. Found: 261.1004.

Following a similar protocol but using 2-*N*-acetylamino-2-dimethoxyphosphinyl acetate, compound **7** was synthesized in 31% yield as an oil, $[\alpha]_D$ +2.25 (*c* 1.80, MeOH); IR (film) 3274 (broad), 1731, 1668 cm^{-1}; ^{1}H NMR (acetone-d_6): 0.94 (s, 3H, *c*-2′-CH$_3$), 1.20 (s, 3H, *t*-2′-CH$_3$), 1.98 (s, 3H, COCH_3), 2.10–2.17 (complex absorption, 2H, $H_{4'a}$, $H_{4'b}$), 2.77–2.85 (m, 1H, $H_{3'}$), 2.91–3.02 (m, 1H, $H_{1'}$), 3.62 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 6.51 (d, $J_{\beta,1'}$=8.6 Hz, H_β), 8.27 (broad s, 1H, N*H*); ^{13}C NMR (acetone-d_6): 19.05 (*c*-2′-*C*H$_3$), 22.75 (*t*-2′-*C*H$_3$), 25.06 ($C_{4'}$), 30.49 (CO*C*H$_3$), 40.82 ($C_{1'}$), 45.42 ($C_{2'}$), 46.42 ($C_{3'}$), 51.28 (O*C*H$_3$), 52.19 (O*C*H$_3$), 128.44 (C_α), 137.34 (C_β), 165.53 (2×*C*O$_2$CH$_3$), 173.19 (*C*OCH$_3$). Anal. calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.33; H, 7.43; N, 4.76.

3.5. *tert*-Butyl (1*S*,3*R*)-3-acetyl-2,2-dimethylcyclobutane-1-carboxylate, 8

Solutions of *tert*-butanol (0.95 mL, 10 mmol) and DMAP (43 mg, 0.35 mmol) in dry THF (4 mL) and DCC (0.8 g, 3.8 mmol) in dry THF (2 mL) were subsequently added to an ice-cooled solution of acid **1** (0.6 g, 3.5 mmol) in dry THF (4 mL) under nitrogen atmosphere. The mixture was allowed to reach room temperature and stirred overnight. The solid produced was filtered and washed with dichloromethane and the filtrate was subsequently washed with 5% HCl and aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$) and solvents were removed under reduced pressure. The residue was chromatographed (3:1 ethyl acetate–dichloromethane) to afford 0.5 g (60% yield) of pure ester **8** as a white solid; mp 44–47°C; $[\alpha]_D$ −40.6 (*c* 0.64, MeOH); IR (film) 1726, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$): 0.90 (s, 3H, *c*-2-CH_3), 1.39 (s, 3H, *t*-2-CH_3), 1.42 (s, 9H, C(CH_3)$_3$), 1.65–2.01 (m, 1H, H_{4a}), 2.03 (s, COCH_3), 2.48–2.69 (complex absorption, 2H, H_{4b}, H_1), 2.81 (dd, $J_{3,4b}$=10.6 Hz, $J_{3,4a}$=7.9 Hz, 1H, H_3); ^{13}C NMR ($CDCl_3$): 17.81 (*c*-2-*C*H$_3$), 19.14 (C_4), 28.16 (C-(*C*H$_3$)$_3$), 29.93, 30.25 (*t*-2-*C*H$_3$, -CO*C*H$_3$), 44.79 (C_2), 45.82 (C_1), 53.02 (C_3), 80.36 (CO_2-*C*(CH$_3$)$_3$), 171.43 (*C*O$_2$^{t}Bu), 207.20 (*C*OCH$_3$). Anal. calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.74; H, 9.71%.

3.6. *tert*-Butyl (1*S*,3*R*)-3-Hydroxymethyl-2,2-dimethylcyclobutane-1-carboxylate, 10 through (1*R*,3*S*)-3-*tert*-butoxycarbonyl-2,2-dimethylcyclobutane-1-carboxylic acid, 9

Following the procedure described above for Lieben degradation of ketone **3**, hemiester **9** was obtained as an oil in 63% yield, identified by their NMR spectroscopic data, and used in the next step without further purification. ^{1}H NMR ($CDCl_3$): 1.01 (s, 3H, *c*-2-CH_3), 1.30 (s, 3H, *t*-2-CH_3), 1.41 (s, 9H, C(CH_3)$_3$), 1.90–2.05 (m, 1H, H_{4a}), 2.39–2.55 (m, 1H, H_{4b}), 2.59–2.86 (complex absorption, 2H, H_1, H_3), 5.42 (broad s, 1H, COO*H*); ^{13}C NMR ($CDCl_3$): 18.16 (*c*-2-*C*H$_3$), 20.06 (C_4), 28.19 (C-(*C*H$_3$)$_3$), 30.03 (*t*-2-*C*H$_3$), 44.44 (C_2), 45.17 (C_3), 46.10 (C_1), 80.55 (CO_2-*C*(CH$_3$)$_3$), 171.50 (*C*O$_2$^{t}Bu), 177.98 (CO_2H).

A mixture of hemiester **9** (200 mg, 0.9 mmol) and catecholborane (2.8 mL of a 1 M solution in THF, 2.8 mmol) was stirred at rt for 12 h under nitrogen atmosphere. Ethanol and water was subsequently added to destroy the excess hydride and solid sodium bicarbonate was added to reach pH 8. The solution was extracted with chloroform and the combined organic extracts were dried ($MgSO_4$). Solvents were removed under reduced pressure and the residue was chromatographed (2:1 dichloromethane–ethyl acetate) to afford hydroxy ester **10** as a pale yellow oil (103 mg, 55% yield), $[\alpha]_D$ +11.4 (*c* 0.88, MeOH); IR (film) 3438 (broad, 1726 cm^{-1}; ^{1}H NMR ($CDCl_3$): 0.99 (s, 3H, *c*-2-CH_3), 1.23 (s, 3H, *t*-2-CH_3), 1.42 (s, 9H, C(CH_3)$_3$), 1.61 (broad s, 1H, O*H*), 1.75–1.97 (complex absorption, 2H, H_{4a}, H_{4b}), 2.07–2.19 (m, 1H, H_3), 2.59 (dd, $J_{1,4a}$= 7.85 Hz, $J_{1,4b}$=10.02 Hz, 1H, H_1), 3.52–3.67 (m, 2H, CH_2OH); ^{13}C NMR ($CDCl_3$): 17.20 (*c*-2-*C*H$_3$), 21.09 (C_4), 28.23 (C(*C*H$_3$)$_3$), 30.95 (*t*-2-*C*H$_3$), 41.84 (C_2), 43.72 (C_3), 46.38 (C_1), 63.42 (*C*H$_2$OH), 80.07 (CO_2-*C*(CH$_3$)$_3$), 172.52 (*C*O$_2$^{t}Bu).

3.7. *tert*-Butyl (1*S*,3*R*)-3-*tert*-butyldiphenylsilyloxymethyl-2,2-dimethylcyclobutane-1-carboxylate, 11

tert-Butyldiphenylchlorosilane (2.1 mL, 8.4 mmol) was added to an ice-cooled solution of alcohol **10** (1.0 g, 4.7 mmol) and DMAP (1.7 g, 14.0 mmol) in anhydrous dichloromethane (5 mL). After stirring at rt overnight, under nitrogen atmosphere, the mixture was diluted with dichloromethane and 1% HCl, and washed with water. The organic phase was dried ($MgSO_4$) and solvent was evaporated under vacuo. The residue was chromatographed (1:1 dichloromethane–hexane) to give

compound **11** (1.8 g, 84% yield) as a colorless oil, $[\alpha]_D$ +5.7 (*c* 0.53, MeOH); IR (film) 1726 cm^{-1}; ^1H NMR ($CDCl_3$): 1.01 (s, 12H, *c*-2-CH_3, SiC(CH_3)$_3$), 1.26 (s, 3H, *t*-2-CH_3), 1.42 (s, 9H, $CO_2C(CH_3)_3$), 1.66–1.85 (complex absorption, 2H, H_{4a}, H_{4b}), 2.11–2.24 (m, 1H, H_3), 2.57 (dd, $J_{1,4a}=8.0$ Hz, $J_{1,4b}=10.2$ Hz, 1H, H_1), 3.49–3.65 (complex absorption, 2H, CH_2OSi), 7.32–7.67 (complex absorption, 10H, 2*Ph*); ^{13}C NMR ($CDCl_3$): 17.09 (*c*-2-*C*H_3), 19.13 (Si*C*(CH$_3$)$_3$), 20.79 (C_4), 26.78 (SiC(*C*H_3)$_3$), 28.27 ($CO_2C(CH_3)_3$), 31.02 (*t*-2-*C*H_3), 42.16 (C_2), 43.54 (C_3), 46.40 (C_1), 64.41 (*C*H_2OSi), 79.89 ($CO_2C(CH_3)_3$), 127.60 (4C, CH_{meta}), 129.54 (2C, CH_{para}), 133.86 (2C, C_{ipso}), 135.55 (4C, CH_{ortho}), 172.57 ($CO_2C(CH_3)_3$). Anal. calcd for $C_{28}H_{40}O_3Si$: C, 74.29; H, 8.91. Found: C, 74.24; H, 8.85.

3.8. Methyl (1*S*,3*R*)-3-*tert*-butyldiphenylsilyloxymethyl-2,2-dimethylcyclobutane-1-carboxylate, 12

A mixture of **11** (0.5 g, 1.1 mmol), triethylsilane (0.4 mL, 2.5 mmol) and trifluoroacetic acid (1.2 mL, 15.6 mmol) in anhydrous dichloromethane (3 mL) was stirred at rt for 1 h. The solution was concentrated at reduced pressure, water was added and the resultant aqueous solution was extracted with ether. The combined organic extracts were dried ($MgSO_4$) and solvent was removed under vacuo to afford a carboxylic acid (330 mg, 75% yield) that was used in the next step without purification. Thus this acid (250 mg, 0.6 mmol) was reacted with excess diazomethane in the usual way (see Section 3.2) to provide a methyl ester that was purified by flash column chromatography (2:1 dichloromethane–hexane) to provide pure **12** (232 mg, 90% yield) as a colorless oil, $[\alpha]_D$ +6.8 (*c* 0.73, MeOH); IR (film) 1736 cm^{-1}; ^1H NMR ($CDCl_3$): 0.97 (s, 3H, *c*-2-CH_3), 1.01 (s, 9H, SiC(CH_3)$_3$), 1.28 (s, 3H, *t*-2-CH_3), 1.73–1.91 (complex absorption, 2H, H_4), 2.14–2.28 (m, 1H, H_3), 2.67 (dd, $J_{1,4a}=8.2$ Hz, $J_{1,4b}=9.9$ Hz, 1H, H_1), 3.50–3.66 (complex absorption, 2H, CH_2OSi), 3.63 (s, 3H, CO_2CH_3), 7.32–7.65 (complex absorption, 10H, 2*Ph*); ^{13}C NMR ($CDCl_3$): 17.29 (*c*-2-*C*H_3), 19.14 (Si*C*(CH$_3$)$_3$), 20.80 (C_4), 26.82 (SiC(*C*H_3)$_3$), 31.04 (*t*-2-*C*H_3), 42.30 (C_2), 43.65 (C_3), 45.67 (C_1), 51.09 (CO_2CH_3), 64.34 (*C*H_2OSi), 127.61 (4C, CH_{meta}), 129.58 (2C, CH_{para}), 133.87 (2C, C_{ipso}), 135.58 (4C, CH_{ortho}), 173.51 (*C*O_2Me). Anal. calcd for $C_{25}H_{34}O_3Si$:, 73.12; H, 8.35. Found: C, 73.06; H, 8.41.

3.9. Methyl (1*S*,3*R*)-3-hydroxymethyl-2,2-dimethylcyclobutane-1-carboxylate, (+)-4

A mixture of compound **12** (1.4 g, 3.4 mmol) and *n*-Bu_4F (4.9 mL of a 1 M solution in THF, 4.9 mmol) in anhydrous THF (3 mL) was stirred at rt for 30 min. Then solvent was removed and the residue was chromatographed (1:2 ethyl acetate–hexane) to give hydroxy ester (+)-**4** as an oil (470 mg, 80% yield), $[\alpha]_D$ +9.8 (*c* 0.41, MeOH). The IR, ^1H and ^{13}C NMR spectroscopic data were in good agreement with those described above for its enantiomer, (−)-**4**.

3.10. Methyl (1′*S*,3′*S*)-2-*N*-benzyloxycarbonylamino-3-(2′,2′-dimethyl-3′-methoxycarbonylcyclobutyl)-(*Z*)-2-propenoate, (+)-6

Following the same procedure described above in Section 3.3, compound (+)-**6** was synthesized from (+)-**4** in 36% yield. $[\alpha]_D$ +6.9 (*c* 0.87, MeOH). The IR, ^1H and ^{13}C NMR spectroscopic data were in good agreement with those described above for its enantiomer, (−)-**6a**. Anal. calcd for $C_{20}H_{25}NO_6$: C, 63.98; H, 6.71; N, 3.73. Found: C, 63.93; H, 6.79; N, 3.62%.

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