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Divergent Routes to Chiral Cyclobutane Synthons from (−)-α-Pinene and Their Use in the Stereoselective Synthesis of Dehydro Amino Acids

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Several polyfunctionalized cyclobutane derivatives have been synthesized using commercial (−)-α-pinene and (−)-verbenone as chiral precursors. Thus, oxidative cleavage of these compounds by using ruthenium trichloride afforded quantitatively (−)-*cis*-pinonic and (−)-*cis*-pinononic acids, respectively, without epimerization. These products were converted into several types of aldehydes, which are the key intermediates in the synthesis of cyclobutane dehydro amino acids via Wittig−Horner condensations with suitable phosphonates. These reactions are highly stereoselective, affording exclusively (*Z*) isomers, stereochemistry being assessed by NMR experiments. The obtained dehydro amino acids are polyfunctionalized molecules useful for the synthesis of other α-amino acids, with additional chiral centers, whose configuration must be induced by the chirality of the terpene employed as a precursor.

Introduction

The cyclobutane moiety is a structural feature present in several natural or designed products with interesting biological properties. Thus, for instance, the synthesis of cyclobutane analogues of the nucleoside oxetanocin has been the subjet of great interest during the last years because of their activity against human immunodeficiency viruses (HIV).[1]

Cyclobutane amino acids (CBAA) have also received attention. Thus, in 1980, Bell et al., in pioneering work, isolated 2,4-methanoglutamic acid and 2,4-methanoproline from the seeds of the plant *Ateleia herbert smithii*.[2] Another nonprotein amino acid, *cis*-1-amino-3-hydroxymethylcyclobutane-1-carboxylic acid, was isolated also from the same plant.[3] On the other hand, the antibiotic dipeptide X-1092, (1*S*,2*S*)-1-hydroxy-2-[(*S*)-valylamino]-cyclobutane-1-acetic acid, produced by the microorganism *Streptomyces species X-1092*, was isolated in 1983.[4] Since then, other CBAA and related peptides have been obtained from natural sources. Some of these compounds display activities as antiviral or antimicrobial agents, neurotropics, and analgesics. Therefore, great synthetic efforts have been devoted to the production of the natural products and their modified and more active analogues. It is interesing to note that these biologically active products involve derivatives with both the amino and the carboxyl groups directly attached to the cyclobutane ring as well as other compounds in which the amino function and/or the carboxyl are in a side chain. Among these last CBAA, cyclobutylglycine (α-aminocyclobutylacetic acid) can be used as an alternative substrate for valyl transport RNA-synthetase.[5] Moreover, certain (3-aminomethyl-2,2-dimethyl)cyclobutylacetic acid derivatives, readily available from pinonic and pinic acids,[6] display antiviral activity.[7] At present, the studies are mainly focused on the activity of compounds concerning the NMDA, H2−H3, and GABA receptors.[8]

However, in an interesting review, Avotins remarked that, despite the great diversity of CBAA known, the majority of the syntheses described for these products are neither enantio- nor diastereoselective.[9] Among the scarce stereoselective methodologies published, the recent work of Burgess et al. on the synthesis of enantiopure CBAA from (+)-α-pinene and their incorporation in some peptide isosteres is noteworthy.[10] Cyclopropanes have been successfully incorporated in peptide surrogates in order to constrain them conformationally, thus enhancing their properties, or to investigate the topological requirements of the receptor interactions. Since, in certain cases,

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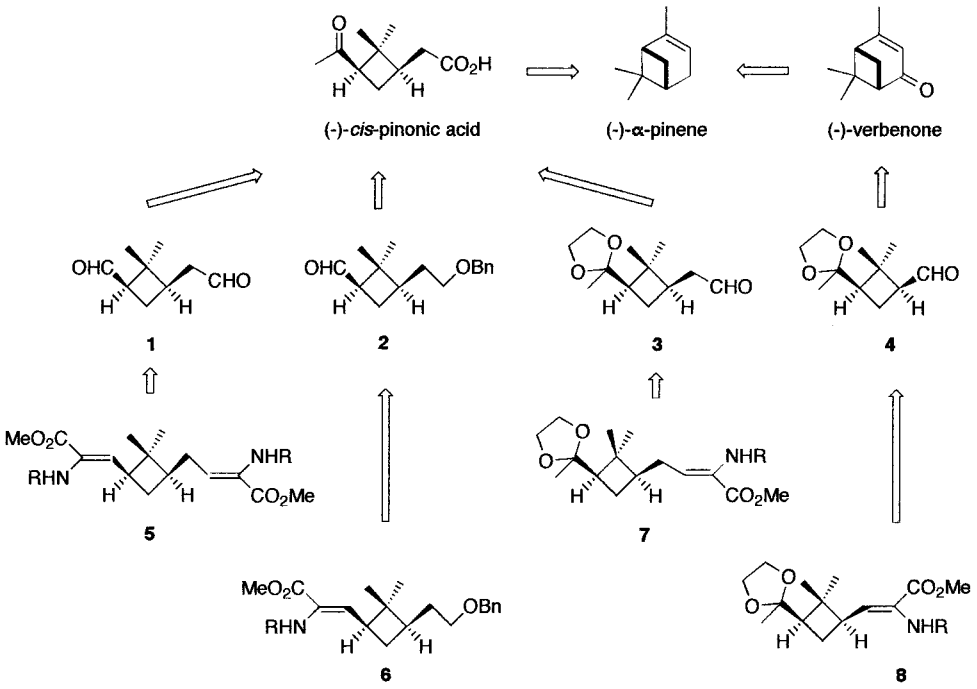
Scheme 1



the highly rigid cyclopropane moiety difficults the suitable folding, it is assumed at present that the more flexible cyclobutane rings can provide peptides with more convenient structural features.[11]

Terpenes are convenient chiral precursors due to their availability and low cost, and among them, α-pinene (both enantiomers) and verbenone are prominent. For instance, pinene has been used as starting material for the production of some compounds of industrial interest[12] and as chiral solvent in the resolution of enantiomers by direct crystallization.[13]

As a part of our research program on the synthesis and structural study of cyclobutane amino acids and related peptides,[14] we have recently reported our preliminary results on the synthesis of chiral polyfunctionalized cyclobutane building blocks as precursors of dehydro amino acids.[14a] In the present paper, we describe several divergent synthetic routes to prepare different aldehydes, which are versatile synthons, and their use in the stereoselective synthesis of novel dehydro amino acids whose stereochemical assignment is provided and discussed. In all cases, (−)-α-pinene was the only starting material affording the cyclobutane ring, as well as two chiral centers with unambiguous absolute configuration and several chemical functions suitable to prepare the target molecules.

Dehydro amino acids are, in general, molecules of interest to be used as precursors to saturated amino acids through hydrogenation, conjugate addition, or cycloaddition reactions. Actually, the stereochemical outcome of such processes must be presumably influenced by the bulkiness and the chirality of the cyclobutyl moiety contributing to the diastereoselection of the two double-bond faces and, in consequence, to the configuration of the new chiral centers. With the purpose to confirm this hypothesis in connection with the synthesis of polyfunctionalized amino acids with constrained structures, we have prepared the dehydro amino acids depicted in Scheme 1. In **6** and **8** the double bond is directly attached to a stereogenic center of the cyclobutane ring, whereas in **7** the double bond is separated from the carbocycle by a methylene group. Both features coexist in **5**. Moreover, **6** and **8** show reverse chirality.

Results and Discussion

The retrosynthetic pathways connecting the target dehydro amino acids **5**−**8** with the cyclobutyl aldehydes **1**−**4**, as the key intermediates, are shown in Scheme 1. Compounds **5**−**8** result from Wittig−Horner condensations of these aldehydes with phosphonates affording the amino acid function conveniently protected. It is remarkable that dehydro amino acids **5**−**8** bear two asymmetric carbons with determined absolute configuration, provided by (−)-α-pinene, and two or four prochiral centers at the olefinic carbons. In turn, dialdehyde **1** and monoaldehydes **2** and **3** were obtained by functional-group manipulation starting from (−)-*cis*-pinonic acid as a common precursor. (−)-Verbenone is the precursor to aldehyde **4**, which is homologous with **3**. The carbaldehyde group is directly linked to the cyclobutane in compounds **2** and **4**, whereas in **3** this group is separated from the ring by a methylene unit.

Both precursors are easily prepared from (−)-α-pinene as the only primary source of chirality. This compound affords commercially available (−)-verbenone by allylic oxidation. On the other hand, we realized that early classical procedures in the literature for the oxidation of

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pinene[15] provided *cis*-pinonic acid with substantial epimerization of the cyclobutane carbon linked to the ketone carbonyl. This is, indeed, a secondary process concomitant with the oxidation of the double bond under basic or acid conditions, leading to a mixture of two diastereomers whose separation requires tedious successive recrystallizations with the consequent yield decrease. The presence of these isomers was evidenced by the absorption signals for the CH_3 protons of the *gem*-dimethyl substitution, which shows two sets of singlets at 0.84/1.31 ppm (major) and 0.99/1.21 ppm (minor) in the ^{1}H NMR spectrum of the crude mixture. In contrast, we found that the use of ruthenium trichloride is more convenient since it affords the desired product in high yield *without epimerization* as confirmed by the presence of only one set of signals both in the ^{1}H and in the ^{13}C NMR spectra. This method had been previously used in the oxidation of verbenone and verbenol,[10] but not for pinene.

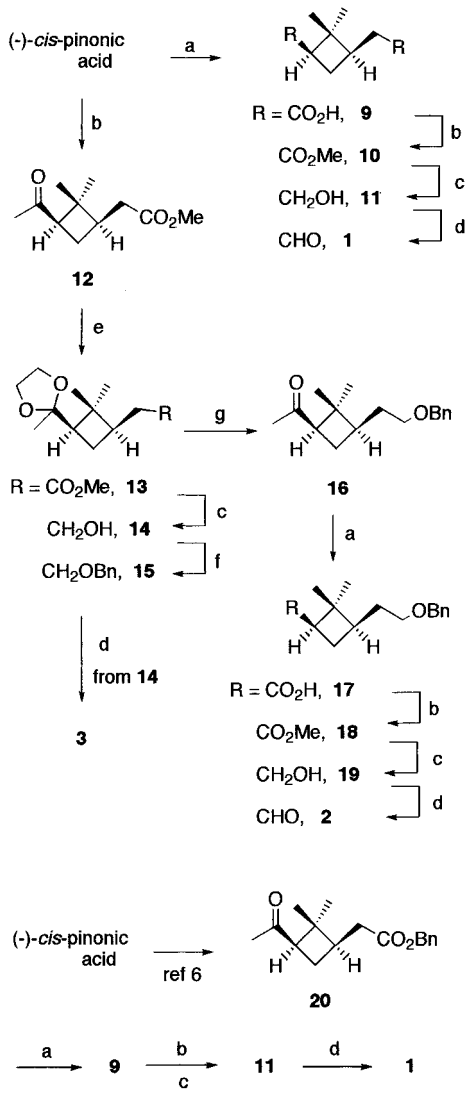
1. Syntheses of Aldehydes 1−4. The divergent synthetic routes toward aldehydes **1**−**3** from (−)-*cis*-pinonic acid are depicted in Scheme 2. Lieben degradation of the methyl ketone function by using aqueous sodium hypobromite furnished (−)-*cis*-pinic acid **9**.[16] Compound **9** also resulted when benzyl ester **20**, obtained from the reaction between the potassium salt of (−)-*cis*-pinonic acid and benzyl chloride, was submitted to Lieben degradation. This concomitant deprotection of the benzyl ester under the basic reaction conditions had not been mentioned by Burgess in his earlier work employing a similar protocol.[10]

Reduction of diacid **9** to diol **1** was attempted with diborane or 9-BBN without satisfactory results. Therefore, **9** was methylated with diazomethane to afford diester **10**.[17] Direct reduction of **10** to dialdehyde **1** by using DIBAL was not successful either. Finally, **10** was reduced with $LiBH_4$ to provide the new alcohol **11** which was oxidized to aldehyde **1**. Among the most common methods, Swern oxidation is very convenient to afford aldehydes from primary alcohols in high yield without epimerization. Dialdehyde **1** was obtained following this procedure, in 70% yield, as an unstable oil which was used immediately in the Wittig−Horner condensation.

According to another synthetic pathway (Scheme 2), ester **12** was obtained by methylation of (−)-*cis*-pinonic acid with diazomethane. Treatment of **12** with ethylene glycol and pyridinium *p*-toluenesulfonate (PPTS) in boiling benzene afforded ketal **13**.[18] Reduction of **13** with $LiBH_4$ gave alcohol **14** which was oxidized to aldehyde **3** alternatively by PDC or Swern reagent. Attempted purification of aldehydes from Swern oxidation by column chromatography resulted in decomposition of the product. On the contrary, treatment with PDC followed by removal of chromium salts by stirring the reaction mixture with Florisil and subsequent filtration afforded pure dialdehyde **3**. Then, this procedure was also used in the synthesis of aldehydes **2** and **4** (see below).

Alcohol **14** is also precursor of aldehyde **2** after protection as a benzyl ether to give **15**. Subsequent hydrolysis

Scheme 2[a]



[a] Reagents: (a) aqueous NaOBr; (b) CH_2N_2; (c) $LiBH_4$; (d) PDC or $(COCl)_2$, DMSO, Et_3N; (e) $(CH_2OH)_2$, PPTS; (f) BnBr, NaH, DMF; (g) acetone, PPTS.

of ketal in **15** followed by Lieben degradation of the resultant methyl ketone **16** afforded acid **17**. Methylation to ester **18** and conversion into aldehyde **2**, through alcohol **19**, allowed us to achieve the synthetic goal.

Scheme 3 shows the synthesis of aldehyde **4** from (−)-verbenone. Thus, this compound was treated with $RuCl_3$ to produce (−)-*cis*-pinononic acid **21**, which was reacted with diazomethane to afford methyl ester **22**. Ketone was protected as described above for **12**, affording ketal ester **23**, which was reduced with $LiBH_4$. Finally, the resultant alcohol **24** was oxidized by PDC to aldehyde **4**.

2. Synthesis and Stereochemical Assignment of Dehydro Amino Acids 5−8. The respective Wittig−Horner condensations of aldehydes **1**−**4** with phosphonates **25a**,**b**[19] (Scheme 3), in the presence of KO-*t*-Bu, provided dehydro amino acids **5a**,**b**-**8a**,**b** in which the amino function is protected as a Cbz-carbamate or as an acetamide. It is noteworthy the high stereoselectivity of the reaction, since (*Z*)-isomers were exclusively produced.

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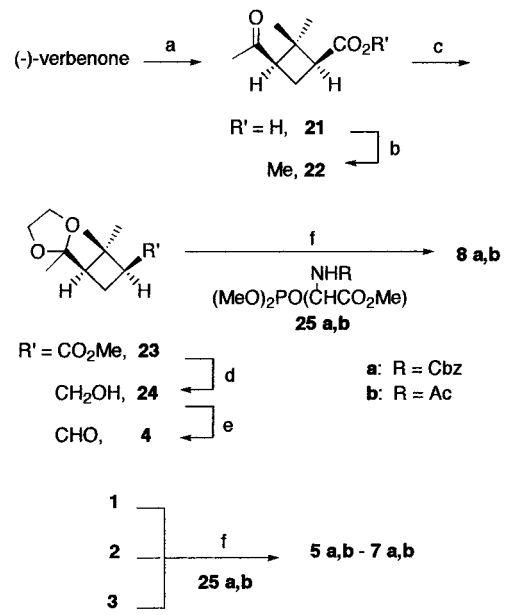
Scheme 3[a]



[a] Reagents: (a) $RuCl_3$; (b) CH_2N_2; (c) $(CH_2OH)_2$, PPTS; (d) $LiBH_4$; (e) PDC; (f) KO*t*-Bu.

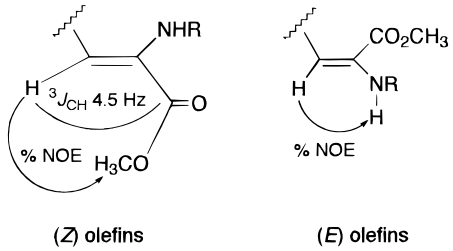


Figure 1. Determined $^3J[^{13}C]^1H$ and significant %NOE enhancements used for the stereochemical assignment of **5**−**8** (see Table 1).

Table 1. Significant % NOE Enhancements for Compounds 5−8[a]

	(*Z*)-**5a**	(*Z*)-**6a**	(*Z*)-**7a**	(*Z*)-**7b**	(*E*)-**7b**	(*Z*)-**8a**	(*E*)-**8a**
=C*H*/OC*H*$_3$	0.24	0.21	0.25	0.35		0.24	
=C*H*/N*H*					0.95		1.80

[a] See Figure 1.

The same diastereoselectivity had been previously observed in our laboratory for the condensations of other aldehydes with phosphonates **25**.[20]

The *Z* geometry of the double bond was determined by NMR techniques by means of NOE experiments. The most significant data are collected in Table 1. Thus, selective irradiation of the olefinic proton (triplet at 6.5 ppm) resulted in enhancement of the absorption due to the methoxyl protons (Figure 1) but NOE on N*H* protons was not observed in any case. In contrast, separate experiments performed on (*E*)-**7b** and (*E*)-**8a** showed NOE on the N*H* proton when the olefinic one (triplet at 6.2 ppm) was selectively irradiated. Diastereomers (*E*)-**7b** and (*E*)-**8a** were obtained by epimerization of (*Z*)-**7b** and (*Z*)-**8a**, respectively, on standing as chloroform solutions for 2 days. These results agree with the determined long-range heteronuclear coupling constant between the carbonyl carbon and the olefinic proton (Figure 1): the value $^3J[^{13}C]^1H = 4.5$ Hz is consistent with (*Z*) geometry for dehydro amino acids **5**−**8**.[21]

Concluding Remarks

(−)-α-Pinene has been shown to be a convenient starting material for the synthesis of a variety of polyfunctionalized cyclobutane synthons, according to divergent synthetic routes which involve selective manipulations of functional groups. These compounds are very attractive for use in the synthesis of different cyclobutane derivatives with, at least, two stereogenic centers of determined absolute configuration. In this paper, we have shown the efficiency of aldehydes **1**−**4** to synthesize dehydro amino acids in stereoselective manner. It is noteworthy that the Wittig−Horner condensations of these aldehydes with phosphonates **25a**,**b** confirm the ability of such reagents to afford (*Z*)-olefins as the exclusive or predominant stereoisomers. This fact had been already observed by us for condensations of **25** with other aldehydes. Finally, we must mention the interest of the obtained molecules for the synthesis of other types of cyclobutane-containing compounds. For instance, our preliminary results on the hydrogenation and on the cyclopropanation of these dehydro amino acids show a high diastereoselectivity allowing the production of saturated amino acids which contain one or two additional stereogenic centers with determined absolute configuration. Further investigation in this field is being currently carried out in our laboratories.

Experimental Section

Commercial (1*S*)-(−)-α-pinene (97% ee/GLC) and (1*S*)-(−)-verbenone (99+%) were used as starting materials without purification. Flash column chromatography was carried out on silica gel (240−400 mesh) unless otherwise stated. Baker-silica (40 μm) was used for the chromatography of acid-sensitive products. 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 (ot) reported. Standard ^1H NMR and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, respectively. Long-range heteronuclear coupling constants, $^3J[^{13}C]^1H$, were determined in a 400 MHz spectrometer from SDEPT-1D spectra.[22] NOE data were extracted from DPFGE-NOE 1D experiments using a mixing time of 800 ms according to ref 23.

(1′*R*,3′*R*)-2-(3′-Acetyl-2′,2′-dimethylcyclobutyl)acetic Acid [(−)-*cis*-Pinonic Acid]. Catalytic $RuCl_3$ hydrate (120 mg) and $NaIO_4$ (13.4 g, 63 mmol) were added to a stirred solution of (−)-α-pinene (2.5 mL, 16 mmol) in 2:2:3 carbon tetrachloride−acetonitrile−water (130 mL). After the mixture was stirred at room temperature for 24 h, ether (100 mL) was added and the mixture was stirred for 5 min and extracted with ether. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was diluted with 50 mL of ether, filtered through Celite, and evaporated to afford quantitatively crude (−)-*cis*-pinonic acid, which can be crystallized but used without purification for

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(21) This constant is in good agreement with that reported for a closely related system: Le Corre, M.; Hercouet, A.; Bessieres, B. *Tetrahedron*: *Asymmetry* **1995**, *6*, 683.

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practical purposes: crystals; mp 65−68 °C (ether) (lit.[15a] mp 68−70 °C); $[\alpha]_D$ −77.8 (*c* 2.03, MeOH) (lit.[24] $[\alpha]_D$ −77.1 (*c* 5.0, $CHCl_3$)); IR and ^1H NMR data were in good accordance with those in ref 24; previously undescribed ^{13}C NMR (acetone-d_6) 17.36, 23.71, 30.09, 30.33, 35.15, 38.68, 43.39, 54.42, 174.38, 207.05.

(1*S*,3*R*)-3-Acetyl-2,2-dimethylcyclobutanecarboxylic acid [(−)-(*cis*)-pinononic Acid, 21]. This compound was prepared starting from (−)-verbenone following the procedure described above. Crude **21** was used without further purification in the next step: yield 2.7 g (100%); $[\alpha]_D$ −34.1 (*c* 1.53, MeOH). Spectroscopic data agree with those in ref 16.

General Procedure for Lieben Degradation. Synthesis of Acids 9 and 17. A typical experiment is described. To a stirred solution of methyl ketone (7.7 mmol) in dioxane (25 mL), cooled at −15 °C was added an aqueous solution of NaOBr prepared from bromine (1.2 mL, 24 mmol), NaOH (4.1 g, 102 mmol), and water (98 mL), and previously cooled to 0 °C. After being stirred at 0 °C for 2 h and at room temperature for 6 h, the solution was extracted with dichloromethane. Aqueous $NaHSO_3$ (40%, 30 mL) and concentrated HCl were subsequently added to the aqueous phase. The resultant acid solution was extracted with ether, the extracts were dried ($MgSO_4$), and solvent was removed to afford the carboxylic acid pure enough to be used in the next step without further purification. Acids **9** and **17** were prepared by this protocol.

(1′*R*,3′*R*)-2-[3′-Carboxy-2′,2′-dimethylcyclobutyl]acetic acid (*cis*-pinic acid, 9): yield 1.0 g (70%); IR (film) 3093, 3079 (broad), 1705 cm^{-1}; ^1H NMR ($CDCl_3$) 0.98 (s, 3H), 1.23 (s, 3H), 1.89 (complex absorption, 2H), 2.32 (complex absorption, 3H), 2.76 (dd, J = 10.2 Hz, J' = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) 17.88, 25.30, 30.24, 35.42, 39.03, 42.80, 46.53, 173.82, 173.91.

(1*R*,3*R*)-3-(2′-Benzyloxyethyl)-2,2-dimethylcyclobutanecarboxylic acid (17): yield 0.8 g (41%); ^1H NMR ($CDCl_3$) 0.96 (s, 3H), 1.18 (s, 3H), 1.53 (m, 1H), 1.67 (m, 1H) y 1.94 (complex absorption, 3H), 2.70 (dd, J = 10.2 Hz, J' = 8.0 Hz, 1H), 3.42 (t, J = 6.6 Hz, 2H), 4.47 (s, 2H), 7.32 (complex absorption, 5H); ^{13}C NMR ($CDCl_3$) 17.80, 25.39, 30.42, 31.30, 40.21, 42.80, 46.56, 69.39, 73.24, 128.06, 128.24, 129.00, 140.00, 174.05.

General Procedure for the Preparation of Methyl Esters 10, 12, 18, and 22. A typical experiment was run as follows. To an ice-cooled solution of carboxylic acid (3 mmol) in ether (40 mL) was added a freshly distilled ethereal solution of diazomethane (from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (3.4 g, 16 mmol) in ether (38 mL) and KOH (0.8 g, 15 mmol) in EtOH (12 mL). The resultant solution was stirred at room temperature for 1 h, and excess diazomethane was destroyed by addition of benzoic acid. The reaction mixture was filtered, solvent was evaporated at reduced pressure, and the residue was chromatographed through Baker-silica (mixtures of EtOAc−pentane) to furnish the corresponding pure ester **10**, **12**, **18**, or **22**. The new compounds **10**, **18**, and **22** are described below.

Methyl (1′*R*,3′*R*)-2-[2′,2′-dimethyl-3′-methyloxycarbonylcyclobutyl]acetate (10): yield 0.6 g (96%); oil; $[\alpha]_D$ +16.17 (*c* 2.4, $CHCl_3$); IR (film) 1737 cm^{-1}; ^1H NMR ($CDCl_3$) 0.88 (s, 3H), 1.18 (s, 3H), 2.02 (complex absorption, 2H), 2.30 (complex absorption, 3H), 2.70 (dd, J = 10.2 Hz, J' = 8.0 Hz, 1H), 3.61 (s, 3H), 3.62 (s, 3H); ^{13}C NMR ($CDCl_3$) 17.56, 24.44, 29.86, 35.06, 38.21, 42.56, 46.09, 51.15, 51.41, 173.17. Anal. calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.61; H, 8.49.

Methyl (1*R*,3*R*)-3-(2′-benzyloxyethyl)-2,2-dimethylcyclobutanecarboxylate (18): yield 0.8 g (92%); oil; $[\alpha]_D$ −2.15 (*c* 0.9, MeOH); IR (film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) 0.89 (s, 3H), 1.16 (s, 3H), 1.54 (m, 1H), 1.65 (m, 1H), 1.97 (complex absorption, 3H), 2.70 (dd, J = 10.2 Hz, J' = 7.3 Hz, 1H), 3.40 (t, J = 6.6 Hz, 2H), 3.59 (s, 3H), 4.47 (s, 2H), 7.32 (complex absorption, 5H); ^{13}C NMR ($CDCl_3$) 17.80, 25.30, 29.48, 31.24, 40.24, 43.03, 46.56, 51.06, 69.33, 73.21, 128.03, 128.20, 128.97, 139.97, 173.35. Anal. calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.81; H, 8.66.

Methyl (1S,3R)-3-acetyl-2,2-dimethylcyclobutanecarboxylate (22): yield 0.5 g (98%); oil; $[\alpha]_D$ −7.14 (*c* 0.3, MeOH); IR (film) 1736, 1708 cm^{-1}; ^1H NMR ($CDCl_3$) 0.81 (s, 3H), 1.42 (s, 3H), 1.88 (ddd, J = 11.3 Hz, J' = 7.7 Hz, J'' = 7.7 Hz, 1H), 2.67 (ddd, J = 11.3, J' = 10.8 Hz, J'' = 10.3 Hz, 1H), 2.78 (dd, J = 10.8 Hz, J' = 7.7 Hz, 1H), 2.88 (dd, J = 10.3 Hz, J' = 7.7 Hz, 1H); ^{13}C NMR (acetone-d_6) 18.27, 19.29, 30.09, 30.21, 44.83, 45.36, 51.27, 53.06, 172.85, 206.08. Anal. calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.97; H, 9.02.

General Procedure for the Synthesis of Ketals 13 and 23. A typical experiment is described. A mixture of ketone (7.6 mmol), ethyleneglycol (3 mL, 57.4 mmol), and PPTS (0.3 g, 1.2 mmol) in anhydrous benzene (170 mL) was heated to reflux for 4 h, using a Dean−Stark trap to remove water from the reaction mixture. Solvent was evaporated at reduced pressure, and the residue was poured into ether (240 mL). The resultant solution was subsequently washed with saturated aqueous $NaHCO_3$ and brine and dried ($MgSO_4$). Solvent was removed, and the residue was chromatographed (1:5 ethyl acetate−hexane) to afford pure ketals **13** and **23**.

Methyl (1′*R*,3′*R*)-2-[2′,2′-dimethyl-3′-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]acetate (13): yield 1.5 g (81%); oil; ot 130−134 °C (0.05 Torr) (lit.[12] peb 100−105 °C (0.3 Torr)); $[\alpha]_D$ −6.50 (*c* 2.1, MeOH). Previously undescribed NMR spectra follow. ^1H NMR ($CDCl_3$) 1.00 (s, 3H), 1.09 (s, 3H), 1.21 (s, 3H), 1.57 (m, 1H), 1.87−1.97 (m, 1H) 2.07−2.36 (complex absorption, 4H), 3.60 (3H, s), 3.80−3.93 (complex absorption, 2H); ^{13}C NMR (acetone-d_6) 17.49, 23.95, 25.53, 31.35, 35.40, 39.42, 41.47, 50.87, 51.09, 64.18, 65.95, 110.17, 173.52.

Methyl (1*S*,3*R*)-2,2-dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)cyclobutanecarboxylate (23): yield 1.6 g (90%); oil; $[\alpha]_D$ +10.42 (*c* 1.0, MeOH); IR (film) 1739 cm^{-1}; ^1H NMR ($CDCl_3$) 1.03 (s, 3H), 1.21 (s, 3H), 1.24 (s, 3H), 1.84−1.91 (m, 1H), 2.15−2.31 (m, 2H), 2.57−2.64 (m, 1H), 3.64 (s, 3H), 3.79, 3.96 (complex absorption, 4H); ^{13}C NMR (acetone-d_6) 20.47, 22.91, 26.02, 33.59, 45.98, 48.39, 52.05, 53.30, 66.41, 68.13, 112.07, 175.31. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 62.72; H, 8.76.

General Procedure for the Reduction of Esters to Alcohols 11, 14, 19, and 24. A 2 M solution of $LiBH_4$ in THF (7 mL, 13 mmol) was added to a solution of ester (5.8 mmol) in dry THF (20 mL). The mixture was heated to reflux under nitrogen atmosphere for 6−8 h. Excess hydride was destroyed by slow addition of methanol, and then water (30 mL) was added. The resultant solution was extracted with ethyl acetate, and the combined extracts were dried ($MgSO_4$). Solvents were removed at reduced pressure, and the residue was chromatographed (ethyl acetate) to provide alcohols **11**, **14**, **19**, and **24**.

(1′*R*,3′*R*)-2-(3′-Hydroxymethyl-2′,2′-dimethylcyclobutyl)-1-ethanol (11): yield 0.8 g (85%); oil; $[\alpha]_D$ +26.13 (*c* 1.1, MeOH); IR (film) 3333 (broad) cm^{-1}; ^1H NMR ($CDCl_3$) 0.94 (s, 3H), 1.09 (s, 3H), 1.10−2.15 (complex absorption, 6H), 3.40−3.67 (complex absorption, 6H); ^{13}C NMR ($CDCl_3$) 16.53, 26.36, 30.89, 33.47, 38.97, 39.53, 44.56, 61.53, 63.77. Anal. Calcd. for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.31; H, 11.65.

(1′*R*,3′*R*)-2-[2′,2′-Dimethyl-3′-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]-1-ethanol (14): yield 1.1 g (85%); oil, ot 125 °C (0.01 Torr); $[\alpha]_D$ −1.9 (*c* 2.06, MeOH); IR (film) 3431 (broad) cm^{-1}; ^1H NMR ($CDCl_3$) 0.91 (s, 3H), 0.99 (s, 3H), 1.12 (s, 3H), 1.26−1.89 (complex absorption, 5H), 2.00 (dd, J = 10.9 Hz, J' = 7.3 Hz, 1H), 2.45 (broad s), 3.42 (t, J = 6.9 Hz, 2H), 3.83, 3.72 (complex absorption, 4H); ^{13}C NMR ($CDCl_3$) 16.98, 23.55, 24.63, 31.12, 33.09, 38.99, 40.65, 49.94, 61.06, 63.47, 65.27, 109.82. Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.02; H, 10.15.

(1*R*,3*R*)-3-(2′-Benzyloxyethyl)-2,2-dimethylcyclobutylmethanol (19): yield 1.0 g (68%); oil; ot 115−120 °C (0.01−0.05 Torr); $[\alpha]_D$ +17.8 (*c* 0.4, MeOH); IR (film) 3510−3259 (broad) cm^{-1}; ^1H NMR ($CDCl_3$) 0.93 (s, 3H), 1.07 (s, 3H), 1.50 (complex absorption, 2H), 1.66 (complex absorption, 2H), 1.97 (complex absorption, 3H), 3.37 (t, J = 6.6 Hz, 2H), 3.54 (complex absorption, 2H), 4.46 (s, 2H), 7.31 (complex absorption, 5H); ^{13}C NMR ($CDCl_3$) 16.54, 26.39, 30.51, 30.95, 39.30,

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39.51, 44.56, 63.86, 68.97, 72.94, 127.49, 127.61, 128.34, 138.61. Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.58; H, 9.71.

(1*S*,3*R*)-3-(2-Methyl-1,3-dioxolan-2-yl)-2,2-dimethylcyclobutylmethanol (24): yield 1.1 g (95%); oil; $[\alpha]_D$ −10.87 (*c* 1.8, MeOH); IR (film) 3436 (broad) cm^{-1}; ^1H NMR ($CDCl_3$) 0.99 (s, 3H), 1.06 (s, 3H), 1.08 (s, 3H), 1.3−1.49 (m, 1H), 1.62−1.72 (m, 1H), 1.80−2.03 (m, 2H), 3.17 (broad s), 3.31−3.49 (complex absorption, 2H), 3.70, 3.80 (complex absorption, 4H); ^{13}C NMR (acetone-d_6) 17.06, 22.19, 23.88, 32.33, 40.82, 44.86, 50.21, 63.16, 64.05, 65.79, 110.23. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.70; H, 10.19.

Synthesis of (1′*R*,3′*R*)-2-[2′,2′-Dimethyl-3′-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]-1-ethanol (15). To a solution of alcohol **6** (2.0 g, 9.4 mmol) in dry and freshly distilled DMF (21 mL) was added NaH (1.6 g of 60% oil suspension, 65 mmol), and the mixture was stirred under nitrogen atmosphere for 1.5 h. Then benzyl bromide (6 mL, 53 mmol) was added dropwise, and the resultant mixture was stirred at room temperature for 72 h. After removal of excess benzyl bromide, the residue was subsequently poured into dichloromethane (110 mL) and washed with water. The organic solution was dried ($MgSO_4$), and solvent was evaporated at reduced pressure. The residue was chromatographed eluting successively with 1:1 dichloromethane−hexane, dichloromethane, and 1.1 ethyl acetate−hexane: yield 2.6 g (90%); oil; ot 145−150 °C (0.01−0.05 Torr); $[\alpha]_D$ + 4.1 (*c* 3.4, MeOH); ^1H NMR ($CDCl_3$) 0.97 (s, 3H), 1.03 (s, 3H), 1.17 (s, 3H), 1.38−1.80 (complex absorption, 5H) y 1.82−2.13 (m, 1H), 3.34 (t, J = 6.9 Hz, 2H), 3.76−3.88 (complex absorption, 4H), 4.43 (s, 2H), 7.27 (complex absorption, 5H); ^{13}C NMR ($CDCl_3$) 17.07, 23.69, 24.80, 30.21, 31.21, 39.42, 40.77, 50.03, 63.62, 65.38, 69.00, 72.85, 109.01, 127.37, 127.52, 128.26, 138.58. Anal. Calcd for $C_{19}H_{28}O_3$: C,-74.96; H, 9.27. Found: C, 75.20; H, 9.37.

Synthesis of (1*R*,3*R*)-3-(2′-Benzyloxyethyl)-2,2-dimethylcyclobutyl Methyl Ketone (16). A mixture of ketal **15** (2.5 g, 8.3 mmol) and PPTS (1.1 g, 4.3 mmol) in acetone (21 mL) was heated to reflux for 8 h. Then solvent was removed, and the residue was poured into ether (100 mL). The resultant solution was washed with saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). Solvent was evaporated to afford crude ketone **16** pure enough to be used in the next step without further purification: yield 2.1 g (98%); oil; 95−100 °C (0.01−0.05 Torr); $[\alpha]_D$ −30.6 (*c* 3.1, MeOH); IR (film) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) 0.82 (s, 3H), 1.24 (s, 3H), 1.99 (s, 3H), 1.39−2.19 (complex absorption, 5H), 2.78 (dd, J = 9.9 Hz, J' = 7.7 Hz, 1H), 3.36 (t, J = 6.6 Hz, 2H), 4.45 (s, 2H), 7.29 (complex absorption, 5H); ^{13}C NMR ($CDCl_3$) 17.71, 23.00, 30.06, 30.36, 30.83, 38.91, 43.21, 54.27, 68.53, 72.88, 127.44, 127.56, 128.29, 138.47, 207.93. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9,21. Found: C, 77.93; H, 9.31.

General Procedures for the Oxidation of Alcohols 11, 14, 19, and 24: Synthesis of Aldehydes 1, 2, 3, and 4. Method A: Swern Oxidation. A typical experiment was run as follows. To a solution of oxalyl chloride (0.15 mL, 1.7 mmol) in dry dichloromethane (3 mL), cooled at −60 °C, was slowly added dry DMSO (0.2 mL, 2.8 mmol) in dichloromethane (1 mL), keeping the internal temperature below −50 °C. The resultant mixture was stirred for 2 min, and then a solution of alcohol (0.6 mmol) in dichloromethane (2 mL) was very slowly added. The mixture was stirred at −50 °C for 15 min, and freshly distilled triethylamine (1.8 mL, 3.2 mmol) was added. The mixture was allowed to reach room temperature, and water (15 mL) was added. The resultant solution was extracted with dichloromethane, and the combined organic phases were washed with water and dried ($MgSO_4$). Solvent was evaporated to afford the corresponding crude aldehyde. **Method B: Oxidation with PDC.** To a solution of aldehyde (1.2 mmol) in dry dichloromethane (8 mL) was added PDC (0.5 g, 1.3 mmol). After the mixture was stirred at room temperature for 4 h, a small portion of Florisil was added, and stirring was continued for 30 min. The mixture was filtered through Celite, and solvent was removed to afford a crude aldehyde. Aldehydes **1**−**4** were unstable products unusable for microanalysis and for specific rotation measures. They were identified by their IR and ^1H NMR data, as described below, and used immediately in the respective Wittig−Horner condensations without further purification.

(1′*R*,3′*R*)-2-(3′-Formyl-2′,2′-dimethylcyclobutyl)acetaldehyde (1): yield 65 mg (70%) (method A); IR (film) 2726, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) 0.97 (s, 3H), 1.31 (s, 3H), 1.90−2.60 (complex absorption, 5H), 2.85 (m, 1H), 9.70 (d, J = 2.2 Hz, 1H), 9.72 (t, J = 1.47 Hz, 1H).

(1*R*,3*R*)-3-(2′-Benzyloxyethyl)-2,2-dimethylcyclobutanocarbaldehyde (2): yield 270 mg (91%) (method B); IR (film) 1714 cm^{-1}; ^1H NMR ($CDCl_3$) 0.99 (s, 3H), 1.23 (s. 3H), 1.31−2.49 (complex absorption, 5H), 2.73 (dt, J = 8.78 Hz, J' = 2.2 Hz, 1H), 3.38 (t, J = 7.3 Hz, 2H), 4.46 (s, 2H), 7.31 (complex absorption, 5H), 9.66 (d, J = 2.2).

(1′*R*,3′*R*)-2-[2′,2′-Dimethyl-3′-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]acetaldehyde (3): yield 220 mg (92%) (method A); 240 mg (95%) (method B); IR (film) 2720, 1722 cm^{-1}; ^1H NMR ($CDCl_3$) 0.99 (s, 3H), 1.11 (s, 3H), 1.20 (s, 3H), 1.30−2.59 (complex absorption, 6H), 3.87 (complex absorption, 4H), 9.70 (t, J = 2.2 Hz, 1H).

(1*S*,3*R*)-2,2-Dimethyl-3-(2-methyl-1,3-dioxolan-2-yl)cyclobutanocarbaldehyde (4): yield 175 mg (74%) (method B); IR (film) 2713, 1715 cm^{-1}; ^1H NMR (acetone-d_6) 1.11 (s, 3H), 1.16 (s, 3H), 1.32 (s, 3H), 1.71−2.36 (m, 3H), 2.65−2.75 (m, 1H), 3.81 y 3.92 (complex absorption, 4H), 9.70 (d, J = 1.45 Hz).

General Procedure for Wittig−Horner Condensations: Synthesis of Dehydro Amino Acids 5a,b−8a,b. A typical experiment for the condensation of aldehydes **1**−**4** with phosphonate **25a**, to afford Cbz derivatives, is described. In a similar manner, condensations with phosphonate **25b** led to acetyl derivatives.

Phosphonate **25a** (0.4 g, 1.1 mmol) in dry dichloromethane (2 mL) was added to a solution of KO-*t*-Bu (0.1 g, 1.1 mmol) in dichloromethane (2.5 mL) at −78 °C, under nitrogen atmosphere. After the mixture was stirred for 30 min at this temperature, aldehyde (0.6 mmol) in dichloromethane (2 mL) was slowly added. The mixture was allowed to reach room temperature, and stirring was continued for 54 h. Then water (8 mL) was added, layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$), solvent was removed at reduced pressure, and the residue was chromatographed on Baker-silica using mixtures of ethyl acetate−hexane as eluents (solvent ratio is given for each compound).

Methyl (1′*R*,3′*S*)-2-Benzyloxycarbonylamino-4-(2′,2′-dimethyl-3′(2-benzyloxycarbonylamino-2-methoxycarbonyl-(*Z*)-ethenyl)cyclobutyl-(*Z*)-2-butenoate (5a). Chromatographed with 2:1 ethyl acetate−pentane: yield 135 mg (40%); oil; $[\alpha]_D$ +16.42 (*c* 0.7, MeOH); IR (film) 3325 (broad), 1712, 1654 cm^{-1}; ^1H NMR (acetone-d_6) 0.95 (s, 3H), 1.04 (s, 3H), 1.59 (m, 1H), 2.05−2.40 (complex absorption, 4H), 2.90 (complex absorption, 1H), 3.67 (s, 6H), 5.15 (complex absorption, 4H), 6.43 (t, J = 7.3 Hz, 1H), 6.52 (d, J = 9.5 Hz, 1H), 7.36 (complex absorption, 10H), 7.57 (broad s, 1H), 7.70 (broad s, 1H); ^{13}C NMR (acetone-d_6) 20.26, 31.7, 32.1, 32.9, 43.6, 44.8, 46.3, 54.5, 69.1, 69.3, 130.0, 130.4, 130.9, 131.1, 138.3, 140.2, 141.1, 157.4, 167.8. Anal. Calcd for $C_{31}H_{36}N_2O_8$: C, 65.94; H, 6.43; N, 4.96. Found: C, 65.91; H, 6.55; N, 4.95.

Methyl (1′*S*,3′*R*)-2-Benzyloxycarbonylamino-3-[3′-(2-benzyloxy-ethyl)-2′,2′-dimethylcyclobutyl]-(*Z*)-2-propenoate, 6a. Chromatographed with 1:3 ethyl acetate−hexane: yield 140 mg (52%); oil; $[\alpha]_D$ +9.90 (*c* 0.9, $CHCl_3$); IR (film) 3395 (broad), 1729, 1644 cm^{-1}; ^1H NMR ($CDCl_3$) 0.94 (s, 3H), 1.02 (s, 3H), 1.50 (complex absorption, 2H), 1.69 (m, 1H), 1.98 (m, 1H), 2.10 (m, 1H), 2.80 (complex absorption, 1H), 3.39 (t, J = 6.58 Hz, 2H), 3.73 (s, 3H), 4.46 (s, 2H), 5.13 (s, 2H), 5.98 (complex absorption, 1H), 6.60 (d, J = 8.0 Hz), 7.32 (complex absorption, 10H); ^{13}C NMR ($CDCl_3$) 17.95, 29.51, 30.34, 30.45, 39.96, 41.40, 43,15, 52.53, 67.32, 68.82, 72.98, 125.10, 127.51, 127.59, 128.18, 128.23, 128.35, 128.51, 136,08, 138,52, 138,-74, 154.24, 165.11. Anal. Calcd for $C_{27}H_{33}NO_5$: C, 71.82; H, 7.37; N, 3.10. Found: C, 71.79; H, 7.40; N, 3.10.

Methyl (1′*R*,3′*R*)-2-Benzyloxycarbonylamino-4-[2′,2′-dimethyl-3′-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]-(*Z*)-

2-butenoate (7a). Chromatographed with 1:1 ethyl acetate−pentane: yield 155 mg (62%); oil; $[\alpha]_D$ −1.82 (*c* 2.2, $CHCl_3$); IR (film) 3325 (broad), 1722, 1659 cm^{-1}; ^1H NMR (acetone-d_6) 1.01 (s, 3H), 1.08 (s, 3H), 1.15 (s, 3H), 1.57 (m, 1H), 1.84 (complex absorption, 2H), 2.18 (complex absorption, 3H), 3.67 (s, 3H), 3.77−3.90 (complex absorption, 4H), 5.11 (s, 2H), 6.44 (t, J = 7.3 Hz, 1H), 7.36 (complex absorption, 5H), 8.70 (broad s, 1H); ^{13}C NMR (acetone-d_6) 17.35, 23.88, 25.01, 29.92, 31.12, 41.03, 41.51, 50.71, 52.23, 63.63, 65.50, 67.50, 109.9, 125.20, 127.98, 128.01, 128.12, 135.95, 136.8, 153.90, l65.02. Anal. Calcd for $C_{23}H_{31}NO_6$: C, 66.17; H, 7.48; N, 3.35. Found: C, 66.03; H, 7.52; N, 3.46.

Methyl (1′*R*,3′*R*)-2-Benzyloxycarbonylamino-3-(2′,2′-dimethyl-3′-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl)-(*Z*)-2-propenoate, 8a. Chromatographed with 1:2 ethyl acetate−pentane: yield 120 mg (50%); oil; $[\alpha]_D$ +17.80 (*c* 0.2, MeOH); IR (film) 3320 (broad) 1722, 1649 cm^{-1}; ^1H NMR (acetone-d_6) 1.03 (s, 3H), 1.10 (s, 3H), 1.16 (s, 3H), 1.76−2.10 (m, 2H), 2.2 (complex absorption, 1H), 2.61−2.80 (m, 1H), 3.67 (s, 3H), 3.70−4.00 (complex absorption, 4H), 5.10 (complex absorption, 2H), 6.54 (d, J = 9.5 Hz), 7.35 (complex absorption, 5H), 7.53 (broad s, 1H); ^{13}C NMR (acetone-d_6) 21.08, 26.10, 27.91, 34.11, 43.32, 46.70, 53.02, 54.43, 66.44, 68.21, 69.18, 112.32, 130.21, 130.87, 131.40, 140.24, 141.43, 157.68, 167.91. Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.49; H, 7.24; N, 3.47. Found: C, 64.99; H, 7.15; N, 3.48.

Methyl (1′*R*,3′*S*)-2-Acetylamino-4-(2′,2′-dimethyl-3′(2-acetylamino-2-methoxycarbonyl-(*Z*)-ethenyl))cyclobutyl-(*Z*)-2-butenoate (5b). Chromatographed with ethyl acetate: yield 155 mg (34%); oil; $[\alpha]_D$ +5.80 (*c* 1.03, $CHCl_3$); IR (film) 3275 (broad), 1728, 1665 cm^{-1}; ^1H NMR (acetone-d_6) 0.96 (s, 3H), 1.06 (s, 3H), 1.97 (s, 3H), 1.99 (s, 3H), 1.60 (m, 1H), 2.00−2.35 (m, 4H), 2.80 (m, 1H), 3.66 (s, 6H), 6.37 (t, J = 7.31 Hz, 1H), 6.46 (d, J = 8.8 Hz, 1H), 8.23 (broad s, 1H), 8.32 (broad s, 1H); ^{13}C NMR ($CDCl_3$) 14.1, 17.9, 23.4, 29.3, 30.3, 30.4, 40.8, 41.6, 43.1, 52.3, 52.4, 124.7, 124.9, 136.7, 138.8, 165.1, 168.3, 168.5, 171.1. Anal. Calcd for $C_{19}H_{28}N_2O_6$: C, 59.99; H, 7.42; N, 7.36. Found: C, 59.49; H, 7.34; N, 7.01.

Methyl (1′*S*,3′*R*)-2-Acetylamino-3-[3′-(2-benzyloxyethyl)-2′,2′-dimethylcyclobutyl]-(*Z*)-2-propenoate (6b). Chromatographed with 1:1 ethyl acetate−hexane: yield 130 mg (30%); oil; $[\alpha]_D$ −2.40 (*c* 2.1, MeOH); IR (film) 3353 (broad), 1729, 1673 cm^{-1}; ^1H NMR ($CDCl_3$) 0.96 (s, 3H), 1.04 (s, 3H), 1.09−2.19 (complex absorption, 5H), 1.96 (s, 3H), 2.78 (complex absorption, 1H), 3.40 (t, J = 6.6 Hz, 2H), 3.66 (s, 3H), 4.46 (s, 2H), 6.48 (d, J = 8.8 Hz), 7.22−7.39 (complex absorption, 5H), 8.21 (broad s, 1H); ^{13}C NMR ($CDCl_3$) 16.92, 22.74, 24.39, 25.98, 31.24, 41.06, 41.68, 43,77, 52.06, 69.50, 73.24, 128.06, 128.23, 129.00, 138.32, 139.29, 140.06, 165.73, 169.11. Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13, N, 3.90. Found: C, 69.93; H, 8.17; N, 3.94.

Methyl (1′*R*,3′*R*)-2-Acetylamino-4-[2′,2′-dimethyl-3′-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]-(*Z*)-2-butenoate (7b). Chromatographed with ethyl acetate: yield 210 mg (54%); oil; $[\alpha]_D$ −6.50 (*c* 2.0, MeOH); IR (film) 3283 (broad), 1729, 1666 cm^{-1}; ^1H NMR (acetone-d_6) 1.00 (s, 3H), 1.08 (s, 3H), 1.15 (s, 3H), 1.54 (m, 1H), 1.87 (complex absorption, 2H), 2.00 (s, 3H), 2.10 (complex absorption, 3H), 3.66 (s, 3H), 3.77−3.89 (complex absorption, 4H), 6.39 (t, J = 7.3 Hz), 8.36 (broad s, 1H); ^{13}C NMR (acetone-d_6) 17.51, 22.74, 23.98, 25.45, 29.59, 31.71, 41.55, 42.18, 50.71, 52.09, 64.18, 65.94, 110.24, 128.06, 135.85, l65.64, 168.82. Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.75; H, 8.36; N, 4.3. Found: C, 62.73; H, 8.27; N, 3.94.

Methyl (1′*R*,3′*R*)-2-Acetylamino-3-(2′,2′-dimethyl-3′-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl)-(*Z*)-2-propenoate (8b). Chromatographed with ethyl acetate: yield 224 mg (60%); oil; $[\alpha]_D$ +38.04 (*c* 0.2, MeOH); IR (film) 3292 (broad), 1726, 1668 cm^{-1}; ^1H NMR (acetone-d_6) 1.07 (s, 3H), 1.11 (s, 3H), 1.16 (s, 3H), 1.76−2.33 (m, 3H), 1.96 (s, 3H), 2.63−2.90 (m, 1H), 3.67 (s, 3H), 3.73−3.97 (m, 4H), 6.49 (d, J = 8.77 Hz, 1H), 8.22 (broad s, 1H); ^{13}C NMR ($CDCl_3$) 18.50, 23.39, 23.62, 24.50, 31.56, 41.33, 43.74, 49.83, 52.33, 63.92, 65.41, 109.67, 124.88, 139.29, 165.11, 168.52. Anal. Calcd for $C_{16}H_{25}O_5N$: C, 61.72; H, 8.09; N, 4.5. Found: C, 61.24; H, 7.90; N, 4.33.

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