A Short Stereoselective Preparation of Dienamides from Cyclobutene Compounds. Application in the Synthesis of a New Cyclohexene Nucleoside

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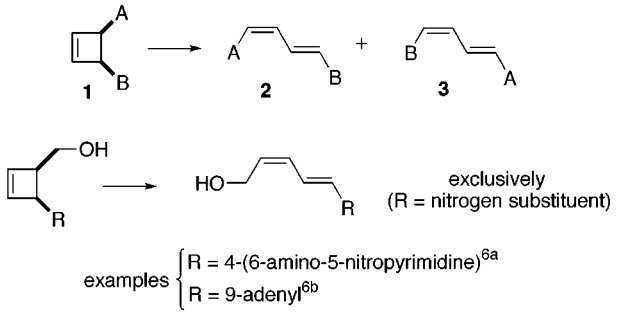
A short stereoselective synthesis of *N*-acylamino-1,3-dienes was developed starting from the cyclobutene lactam **8**, which was obtained from 2-hydroxypyridine by a photochemical electrocyclic reaction. The *tert*-butoxycarbonyl derivative **17** was prepared to facilitate nucleophilic attacks to the carbonyl group, and the subsequent thermal ring opening provided dienes **18**−**21**. One of these (**20**) was used in the synthesis of the cyclohexene nucleoside **30**. A Diels−Alder reaction between diene **20** and maleic anhydride provided the *endo*-cycloadduct **22a**. Three additional steps yielded amine **26**. Construction of the uracil moiety afforded intermediate **29**. Cyclization and removal of the protecting groups occurred in one step in the presence of ammonia, giving the target molecule **30**. Diene **20** also underwent [4 + 2] cycloaddition with methyl acrylate to provide predominantly the *endo*-product **23a**, regioselectively.

Introduction

The use of *N*-acylamino-1,3-dienes in Diels−Alder reactions has become popular, especially in connection with alkaloid synthesis.[1] The first general method for the preparation of dienamides, described by Oppolzer and coworkers,[2] involves the acylation of vinylimines in the presence of a tertiary amine. A second useful approach to these dienes, based on the Curtius rearrangement of dienoic acid azides, was reported by Overman et al.[3] In these literature methods, the C-4 carbon is often substituted by an alkyl or an aryl group.

Herein we present our results on the synthesis of diene carbamates bearing different functionalities at C-4. Our strategy employs cyclobutenes as precursors and allows stereoselective preparation of either (*Z*,*E*) or (*E*,*E*) dienes. The formation of dienes by thermal opening of cyclobutenes is a long established route,[4a] but it suffers from several limitations. For instance, the method is efficient only if the starting cyclobutenes are easily available and if the thermal opening gives a single isomer of the possible dienes. Moreover, this diene must be stable at the temperature required for the opening. When the starting unsymmetrical cyclobutene compound contains two *cis*-substituents at the allylic position (**1**), both (*Z*,*E*)-products **2** and **3** are usually obtained.[4b,c] However, recent theoretical studies from Houk's group[5] and experimental work from our laboratory[6] have shown that nitrogen substituents have a strong outward rotation preference and thus provide excellent stereochemical control (Scheme 1). A subsequent isomerization into (*E*,*E*)-products has been observed upon standing in several cases.

Scheme 1



Such bifunctional (*Z*,*E*)- or (*E*,*E*)-dienes have found several applications as a diene moiety[7] and in annulation reactions.[8] We planed to investigate their use in the preparation of substituted cyclohexene compounds via a Diels−Alder reaction in the course of the synthesis of

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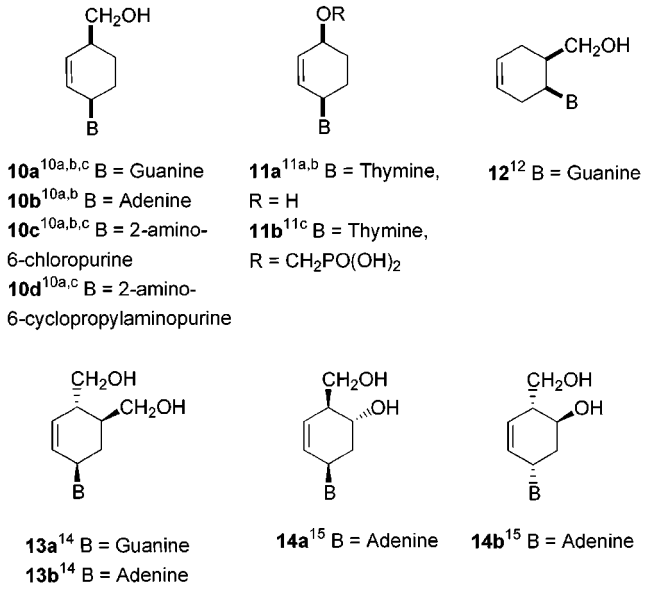
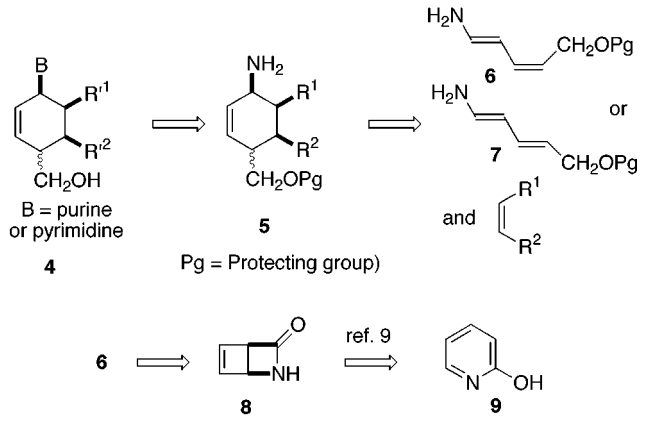


Figure 1. Cyclohexenyl nucleoside analogues.

Scheme 2



cyclohexene nucleosides **4** (Scheme 2). In this case the dienophile should bear one or two substituents, R^1 and R^2, which can be converted to OH or CH_2OH groups afterward. In our early experiments, with these dienes, the nitrogen-substituted cyclobutenes were prepared via a Hofmann rearrangement.[6a] The synthetic route could be shortened by using a cyclobutene already bearing a nitrogen atom at the allylic position. A potentially interesting compound, from this point of view, was lactam **8**, which is available in one step, through a photochemical electrocyclic reaction, from 2-hydroxypyridine **9**.[9]

The synthesis of nucleoside analogues as potential antiviral and anticancer agents is a very active field of research. In this area, several interesting results have been obtained in the preparation of cyclohexene nucleosides during the past few years (Figure 1). To the best of our knowledge, although several methods have been used for the syntheses of these compounds, only a few of them allow for the introduction of the nitrogen at an early stage. Considerable effort in this area has been devoted to homocarbovir **10**,[10] the cyclohexenyl nucleoside **11a**,[11a,b] and its phosphorylated analogue **11b**.[11c] The syntheses of **11** started from cyclohexadiene and involved either the corresponding monoepoxide,[11a,b] or the 1,4-*trans*-cyclohexenediol[11c] as intermediates. In the case of **10a**,**b** the key step in one of the sequences[10a] was a cycloaddition between cyclohexadiene and chlorosulfonyl isocyanate. In another report, a 1,2-disubstituted product **12** was prepared from phthalic anhydride.[12] *Cis*- and *trans*-1,3-disubstituted products[13] and several trisubstituted products[11b,14,15] such as enantiomerically pure **13** and **14** have also been prepared. The synthesis of **13** was achieved via an enzymatic resolution of *trans*-4,5-bis-(hydroxymethyl)cyclohexene,[14] and **14** was obtained from *R*-(−)-carvone.[15] Cyclohexene compounds substituted at the vinylic position have also been described.[11a,16]

The main advantages of the strategy we envisaged, based on a Diels−Alder reaction, include the short synthetic route and the possibility of introducing several substituents *cis* to the base moiety in one step via *endo* selectivity.

Results and Discussion

Access to Dienes. The starting lactam **8** was obtained from the commercially available 2-hydroxypyridine **9**, in aqueous solution, by the photochemical method previously described by Dilling.[9] However, this reaction must be carried out under very dilute conditions (10^{-3} M) and several days of irradiation in order to provide high yields (88%). Under these conditions, the scale of the reaction is too small for preparative purposes. We found that the scale could be increased with only a modest reduction in the yield. As compound **9** is inexpensive, this lowered yield is tolerable. Performing the reaction at a concentration of 4.7×10^{-2} M provided lactam **8** in an acceptable 46% yield, providing approximately 2.1 g of product on average per run with our photochemical apparatus. When the concentration was increased to 5.2×10^{-2} M, the yield decreased further to 30% providing only 1.50 g of lactam **8**. Under these conditions, the formation of [4 + 4] products becomes competitive.[17]

We had previously synthesized (*Z*,*E*)-diene **18**,[6b] as a single isomer, by the thermal opening of cyclobutene **16**, available in 60% overall yield[6a] from **15**[18] in five steps (Scheme 3). The new experiments with lactam **8** show

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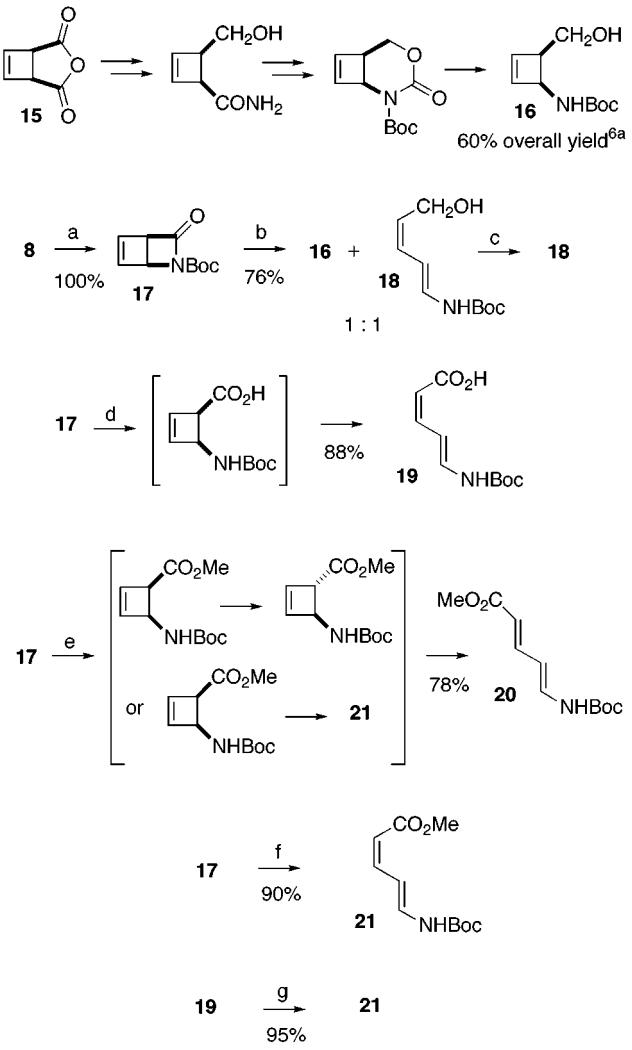
Scheme 3[a]



[a] Reagents and conditions: (a) Boc_2O, DMAP, Et_3N, CH_2Cl_2; (b) $NaBH_4$, MeOH, −20 °C; (c) toluene, reflux, 10 min; (d) LiOH, H_2O, THF; (e) LiOH, MeOH; (f) NaN_3, MeOH, DMF; (g) CH_2N_2, Et_2O.

that this compound is an excellent precursor to several dienes provided that it is first converted into the *tert*-butoxycarbonyl derivative **17** to facilitate the nucleophilic additions.[6a,19] Reaction with sodium borohydride led to a 1:1 mixture of cyclobutene **16** and diene **18**, which was completely converted to diene **18** by briefly heating the mixture. This diene was therefore easily obtained by a short synthetic route. The reaction of cyclobutene **17** with lithium hydroxide provided (*Z*,*E*)-diene **19**. The facile thermal opening of the cyclobutene intermediate is not surprising and was probably due to the presence, in this case, of two substituents with complementary preferences for the conrotatory mode.[4c,5,6b] The nucleophilic attack of methanol to cyclobutene **17**, under basic conditions, also afforded a diene via a thermally unstable cyclobutene compound. However, in this case, the product was the (*E*,*E*)-isomer **20**. One possible explanation for this result is isomerization of the *cis*-cyclobutene intermediate to the *trans*-compound, under base catalysis, prior to ring opening. However, a more likely explanation is the formation of diene **21** as the primary product followed

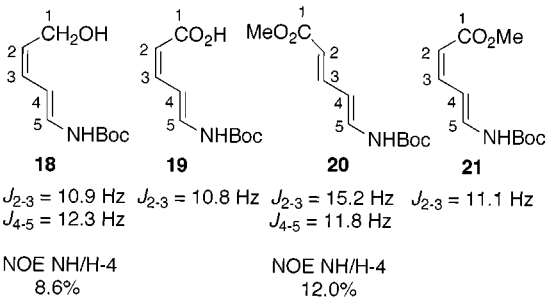


Figure 2. Significant coupling constants and NOE enhancements.

by isomerization to the more stable diene **20** in the basic reaction medium, a type of isomerization for which there is precedent.[20] This is supported by several observations. Treatment of diene **21** with LiOH in MeOH afforded diene **20** in less than 1 h. When the ring-opening reaction of **17** was run in a neutral medium, under the experimental conditions of Palomo et al.,[21] in the presence of sodium azide, the expected (*Z*,*E*)-diene **21** was formed, but it could not be isolated and quickly gave degradation products. On the other hand, esterification of acid **19** under mild conditions with diazomethane afforded diene **21** in a stable form.

The dienes in this paper were identified by ^{1}H NMR spectroscopy (Figure 2). Coupling constants between H-4 and H-5 for **18** and **20**, albeit moderate, were consistent with those observed for *trans*-relationships in similar nitrogen compounds.[6b,7] NOE experiments confirmed these assignments for both compounds. In the cases of **19** and **21**, one of the coupling constants could not be measured due to overlapping signals. However, as **20** was undoubtedly identified, the structure of its isomer **21**, with an expected (*Z*,*E*)-structure, was deduced from the lower J_{2-3}. Compound **19** also exhibited a moderate coupling constant between H-2 and H-3. Moreover, the formation of diene **21** from esterification of acid **19** was consistent with these results.

Cycloadditions and Selectivities. We attempted to carry out Diels−Alder reactions with these dienes. Numerous attempts to cyclize diene **18**, or derivatives of **18** in which both hydrogen atoms were replaced by methyl or benzyl groups, and maleic anhydride, without a catalyst, or in the presence of Lewis acids ($AlCl_3$, $ZnCl_2$, $SnCl_4$, $TiCl_4$), failed to give the expected products due to rapid degradation of the dienes. In contrast, diene **20** reacted readily to provide a single product in 92% yield. This product was clearly identified as the *endo*-adduct **22a** from NOE experiments (Scheme 4). Moreover, analysis of the coupling constants confirmed this identification and showed that the predominant conformation of adduct **22a** was folded rather than extended.[22] Of the main expected conformations of **22a** and the *exo*-isomer **22b**, the small J_{2-3} and J_{4-5} coupling constants, in agreement with a pseudoaxial position for H-2 and H-5, were consistent only with conformations **A** or **D**. However the

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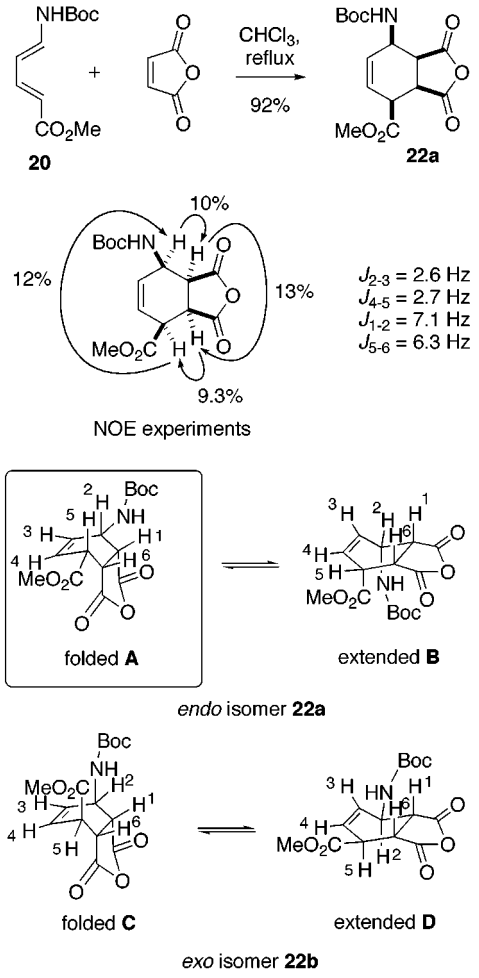
Scheme 4



moderate J_{1-2} and J_{5-6} coupling constants were not consistent with the *trans*-diaxial relationships present in **D**.

The reaction of diene **20** with excess methyl acrylate in toluene provided a mixture of two adducts **23a** and **23b** in a 90:10 ratio, respectively (Scheme 5). In both isomers, H-1, which was easily assigned by decoupling from NH, was coupled with proton H-6, adjacent to a methoxycarbonyl group. NOE experiments showed that the major product was the *endo*-isomer, and the large $J_{5'-4}$ and $J_{5'-6}$ coupling constants showed that the predominant conformer was **F**. Thus, the cycloaddition occurred with complete regioselectivity and with high *endo*-selectivity.

Synthesis of the Nucleoside Analogue 30. The reduction of **22a**, followed by benzoylation, provided compound **25** in moderate yield (Scheme 6). Several attempts under different experimental conditions failed to improve the yield. Removal of the amine protecting group yielded amine **26**. To avoid an internal acyl transfer, transforming amine **26** to amide **27**, which occurred upon standing, amine **26** was immediately treated with isocyanate **28**[23] to give compound **29**. Finally, cyclization and removal of the protecting group from compound **29** occurred in one step, providing the cyclohexene nucleoside analogue **30**. This compound is the first cyclohexene nucleoside analogue with four substituents in an all *cis*-relationship.

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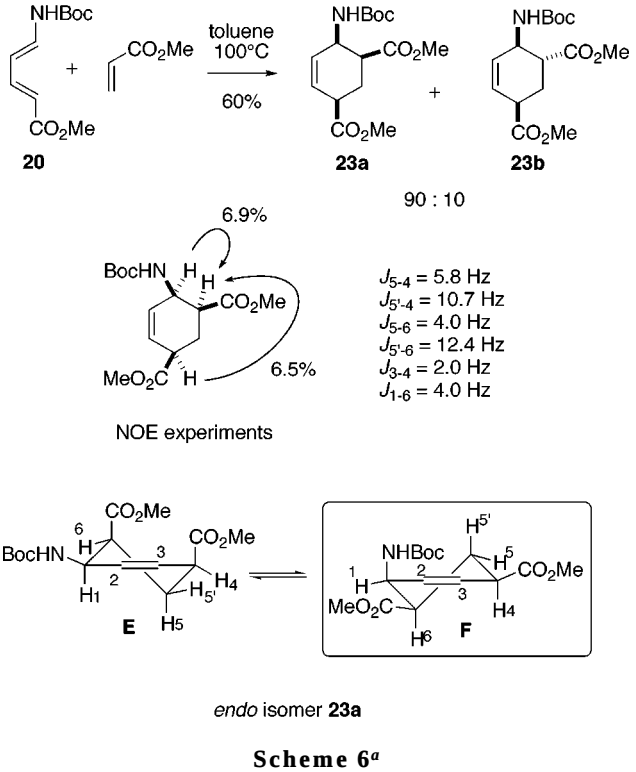
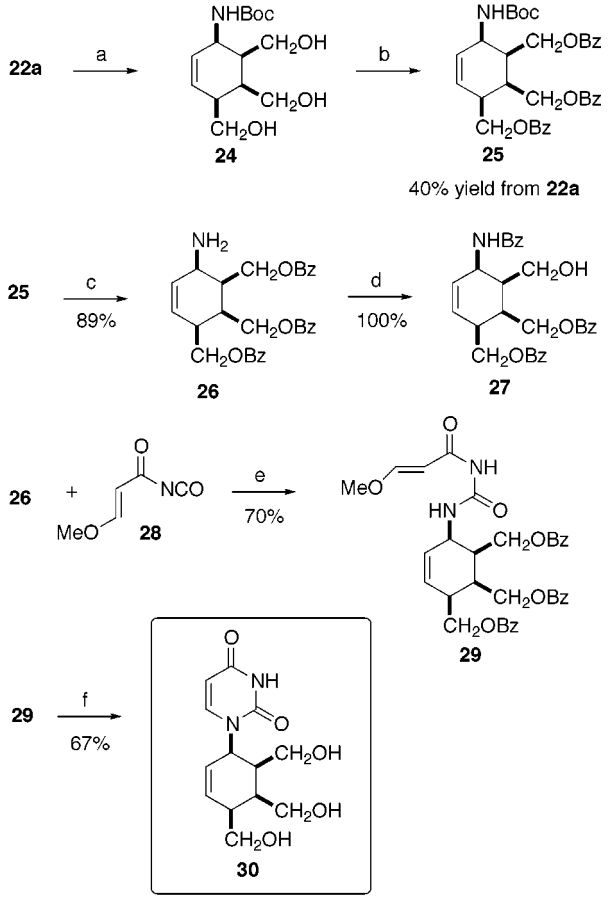
Scheme 5



Scheme 6[a]



[a] Reagents and conditions: (a) $LiAlH_4$, THF, reflux; (b) BzCl, pyridine, CH_2Cl_2; (c) TFA, CH_2Cl_2; (d) upon standing; (e) benzene; (f) NH_3, MeOH.

In conclusion, several diene carbamates were synthesized by a short and selective route. Two examples of

Diels−Alder reactions with one of these dienes provided cycloadducts in high yields with good selectivity. Thus, several cyclohexene derivatives were efficiently obtained from a cyclobutene. The synthesis of the novel cyclohexene nucleoside **30** illustrates the utility of these dienes.

Experimental Section

General. All moisture-sensitive reactions were carried out in oven-dried glassware (110 °C) under a nitrogen atmosphere. Commercially available reagents and solvents were purified and dried, when necessary, by standard methods just prior to use. IR spectra were scanned on a FT infrared spectrophotometer. All melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100.6 MHz, respectively. Chemical shifts are reported in ppm downfield from TMS which was used as an internal reference. Multiplicities in the ^{13}C spectra were determined by DEPT experiments, and numerous assignments were obtained by ^{13}C/^{1}H HETCOR experiments. Ratios in mixtures of isomers were calculated from ^{1}H NMR. Elemental analyses were obtained from the Service de Microanalyze, CNRS ICSN, Gif-sur-Yvette. High-resolution mass measurements were performed at the CRMPO, Rennes.

2-Azabicyclo[2.2.0]hex-5-en-3-one (8). Compound **8** was prepared according to the procedure described by Dilling.[9] A solution of 2-hydroxypyridine (4.50 g, 47.32 mmol) in H_2O (2.9 L) was internally irradiated (Mazda, MAF 400 W) at 25−28 °C for 62 h. The water was removed in vacuo, and the residue was purified by sublimation (80 °C, 20−30 mmHg) to give the title compound (2.09 g, 46%) as colorless crystals: mp 67−68 °C (lit.[9] mp 68−69 °C); IR (KBr) 3212, 1720, 1540 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.65 (dd, 1H, H-6, J = 2.5, 2.5 Hz), 6.54 (dd, 1H, H-5, J = 2.5, 1.0 Hz), 6.35 (br s, 1H, NH), 4.44 (dd, 1H, H-1, J = 2.5, 2.5 Hz), 4.17 (m, 1H, H-4).

***N*-*tert*-Butoxycarbonyl-2-azabicyclo[2.2.0]hex-5-en-3-one (17).** Et_3N (3.25 mL, 23.32 mmol), Boc_2O (10.19 g, 46.68 mmol), and DMAP (2.85 g, 23.33 mmol) were added to a cooled (0 °C) solution of lactam **8** (3.70 g, 38.91 mmol) in CH_2Cl_2 (75 mL). The reaction mixture was stirred at room temperature for 2 h and then diluted with CH_2Cl_2 (25 mL). The solution was washed with cool 1 M solution of HCl and then with H_2O and dried over $MgSO_4$. The solvent was evaporated in vacuo to give compound **17** (7.59 g, 100%) as a pale yellow oil (^{1}H NMR estimated purity >98%) which was immediately used in the next step (degradation was observed in the course of column chromatography on silica gel or after storing at −18 °C for 1 week): IR (KBr) 1803, 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.64 (dd, 1H, H-5, J = 2.5, 1.5 Hz), 6.58 (ddd, 1H, H-6, J = 2.5, 2.5, 1.0 Hz), 4.65 (dd, 1H, H-1, J = 2.7, 2.5 Hz), 4.14 (ddd, 1H, H-4, J = 2.7, 1.5, 1.0 Hz), 1.46 (s, 9H, $(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 165.9, 149.0, 141.7, 140.3, 83.0, 56.8, 52.5, 27.8; HRMS calcd for $[(C_{10}H_{13}NO_3) - OC_4H_9]^+$ 122.0242, found 122.0256.

(1*S,2*R**)-*N*-*tert*-Butoxycarbonyl-(2-hydroxymethylcyclobut-3-enyl)amine (16) and (2*Z*,4*E*)-5-(*tert*-Butoxycarbonylamino)penta-2,4-dienol (18).** $NaBH_4$ (4.42 g, 0.12 mol) was added to a solution of compound **17** (7.60 g, 38.93 mmol) in dry methanol (350 mL) at −20 °C. The mixture was stirred at −20 °C for 1 h. A solution of 1 M HCl (40 mL) was then added dropwise while the temperature was slowly allowed to warm to 20 °C, and then the solvents were evaporated to dryness (without heating). The residue was dissolved in CH_2Cl_2 and washed with brine. The aqueous layers were extracted with CH_2Cl_2, and the combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (silica gel, CH_2Cl_2/Et_2O, 4:1) to afford a mixture of compounds **16**[6a] and **18** (5.90 g, 76%) in a 1:1 ratio as a pale yellow solid. This mixture was refluxed in toluene for 10 min to totally convert cyclobutene **16** into diene **18**, isolated as a yellow oil: IR (KBr) 3400−3200, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.76 (br dd, 1H, H-5, J = 12.3, 12.3 Hz), 6.61 (br d, 1H, NH, J = 12.3 Hz), 6.05 (dd, 1H, H-3, J = 10.9, 10.9 Hz), 5.89 (br dd, 1H, H-4, J = 12.3, 10.9 Hz), 5.45 (td, 1H, H-2, J = 10.9, 7.0 Hz), 4.24 (m, 2H, CH_2), 1.48 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ 152.6, 129.1, 128.8, 124.9, 105.4, 79.8, 58.4, 28.2; HRMS calcd for ($C_{10}H_{17}NO_3$) 199.1208, found 199.1207.

(2*Z*,4*E*)-5-(*tert*-Butoxycarbonylamino)penta-2,4-dienoic Acid (19). Solid LiOH (0.37 g, 15.40 mmol) was added to a solution of compound **17** (1.00 g, 5.12 mmol) in THF (20 mL) and water (15 mL). The mixture was stirred at room temperature for 16 h, and the solvent was removed in vacuo. The aqueous layer was acidified with acetic acid to pH 4 and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by recrystallization (MeOH) to give compound **19** (0.96 g, 88%) as colorless crystals: mp 175−179 °C (dec); IR (KBr) 3500, 1698, 1629 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.82 (s, 1H, OH), 9.86 (br s, 1H, NH), 7.05−6.92 (m, 2H, H-4 and H-5), 6.64 (dd, 1H, H-3, J = 10.8, 10.8 Hz), 5.29 (d, 1H, H-2, J = 10.8 Hz), 1.43 (s, 9H, $(CH_3)_3$); ^{13}C NMR (DMSO-d_6) δ 167.8, 152.4, 144.8, 137.3, 111.9, 106.9, 80.1, 27.8. Anal. Calcd for $C_{10}H_{15}O_4N$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.11; H, 6.81; N, 6.42.

(2*E*,4*E*)-5-(*tert*-Butoxycarbonylamino)penta-2,4-dienoic Acid Methyl Ester (20). Solid LiOH (0.92 g, 38.40 mmol) was added to a solution of compound **17** (2.50 g, 12.81 mmol) in dry MeOH (80 mL). The mixture was stirred at room temperature for 3 h, and the solvent was removed in vacuo. The residue was dissolved in EtOAc, washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by recrystallization (Et_2O/petroleum, 2:3) to afford compound **20** (2.27 g, 78%) as yellow crystals: mp 123−125 °C; IR (KBr) 1712, 1639 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.29 (dd, 1H, H-3, J = 15.2, 11.8 Hz), 7.05 (m, 1H, H-5, J = 11.8, 11.8 Hz), 5.80 (br d, 1H, NH, J = 11.8 Hz), 5.73 (dd, 1H, H-4, J = 11.8, 11.8 Hz), 5.71 (d, 1H, H-2, J = 15.2 Hz), 3.73 (s, 3H, OCH_3), 1.49 (s, 9H, $(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 167.9, 152.0, 144.2, 135.0, 115.8, 107.6, 81.7, 51.3, 28.1. Anal. Calcd for $C_{11}H_{17}O_4N$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.21; H, 7.41; N, 6.14.

(2*Z*,4*E*)-5-(*tert*-Butoxycarbonylamino)penta-2,4-dienoic Acid Methyl Ester (21). Method A. NaN_3 (17 mg, 0.26 mmol) and MeOH (12 μL, 0.30 mmol) were successively added to a solution of compound **17** (50 mg, 0.25 mmol) in dry DMF (0.5 mL). The reaction mixture was stirred at room temperature for 16 h and diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give compound **21** (52 mg, 90%) as an orange oil (unstable). **Method B.** A solution of diazomethane (from diazald (260 mg, 1.21 mmol)) in Et_2O (15 mL) was added dropwise to a cooled (0 °C) suspension of acid **19** (200 mg, 0.93 mmol) in Et_2O (5 mL). Excess of diazomethane was destroyed by addition of acetic acid, and the mixture was concentrated in vacuo to afford compound **21** (203 mg, 95%) as an orange oil: IR (neat) 1708, 1668 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.06−7.00 (m, 2H, H-4 and H-5), 6.90 (m, 1H, NH), 6.56 (m, 1H, H-3), 5.49 (d, 1H, H-2, J = 11.1 Hz), 3.71 (s, 3H, OCH_3), 1.49 (s, 9H, $(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 163.3, 152.2, 144.7, 136.3, 111.6, 107.0, 83.5, 50.9, 28.0; HRMS calcd for ($C_{11}H_{17}NO_4$) 227.1158, found 227.1156.

(1*S,2*R**,5*S**,6*S**)-2-*tert*-Butoxycarbonylamino-4-methoxycarbonyl-8-oxabicyclo[4.3.0]non-3-ene-7,9-dione (22a).** A solution of diene **20** (1.90 g, 8.36 mmol) and maleic anhydride (0.90 g, 9.18 mmol) in dry $CHCl_3$ (50 mL) was refluxed for 24 h. The solvent was evaporated in vacuo. A ^{1}H NMR spectrum of the crude product indicated an *endo*-adduct as the sole product. The residue was purified by recrystallization (EtOAc/toluene, 1:1) to give compound **22a** (2.50 g, 92%) as yellow crystals: mp 177−179 °C; IR (KBr) 1845, 1783, 1731, 1687 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.45 (ddd, 1H, H-4, J = 9.7, 2.7, 2.7 Hz), 5.95 (ddd, 1H, H-3, J = 9.7, 2.6, 2.6 Hz), 5.63 (d, 1H, NH, J = 10.5 Hz), 4.46 (m, 1H, H-2), 3.98 (dd, 1H, H-6, J = 10.0, 6.3 Hz), 3.86 (s, 3H, OCH_3), 3.71 (dd, 1H, H-1, J = 10.0, 7.1 Hz), 3.25 (m, 1H, H-5), 1.48 (s, 9H, $(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 170.8, 170.6, 169.5, 155.2, 132.3, 127.0, 80.6, 52.8, 46.5, 43.2, 42.5, 39.6, 28.3. Anal. Calcd for $C_{15}H_{19}O_7N$: C, 55.38; H, 5.89; N, 4.31. Found: C, 55.43; H, 5.65; N, 4.36.

(1*R,4*R**,6*S**)-*N*-*tert*-Butoxycarbonyl-(4,6-dimethoxy-**

carbonylcyclohex-2-enyl)amine (23a) and Its (6*R)-Isomer (23b).** A solution of diene **20** (150 mg, 0.66 mmol), methyl acrylate (0.75 mL, 6.60 mmol), and a trace of hydroquinone in toluene (2 mL) was heated in a sealed tube at 100 °C for 72 h. The reaction mixture was concentrated in vacuo. The residue was purified by chromatography (silica gel, cyclohexane/EtOAc, 4:1) to yield a mixture of adduct **23a** and **23b** (125 mg, 60%) in a 90:10 ratio as a colorless oil: IR (neat) 1716, 1705, cm^{-1}; ^1H NMR ($CDCl_3$) major isomer **23a** δ 5.95 (m, 1H, H-2), 5.86 (m, 1H, H-3), 4.69 (br d, 1H, NH, J = 9.0 Hz), 4.58 (m, 1H, H-1), 3.71 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 3.12 (m, 1H, H-4), 2.76 (m, 1H, H-6), 2.19 (m, 1H, H-5), 1.94 (m, 1H, H-5′), 1.42 (s, 9H, $(CH_3)_3$), minor isomer **23b** (partially hidden by the major compound) δ 5.95−5.75 (m, 2H, H-2 and H-3), 4.70−4.47 (m, 2H, NH and H-1), 3.70 (s, 3H, CH_3), 3.69 (s, 3H, CH_3), 3.23 (m, 1H, H-4), 2.76 (m, 1H, H-6), 2.19 (m, 1H, H-5), 1.94 (m, 1H, H-5′), 1.43 (s, 9H, $(CH_3)_3$); ^{13}C NMR ($CDCl_3$) major isomer **23a** δ 173.2, 172.9, 154.7, 128.2, 127.5, 79.6, 52.1, 51.8, 45.0, 42.9, 41.0, 28.2, 22.6, minor isomer **23b** (partially hidden by the major compound) δ 173.2, 172.9, 154.74, 129.2, 127.0, 79.6, 52.8, 52.1, 45.8, 43.3, 41.6, 28.2, 24.0; HRMS calcd for $[(C_{15}H_{23}NO_6) + H - C_4H_9]^+$ 257.0895, found 257.0894.

(1*R,4*S**,5*S**,6*S**)-*N*-*tert*-Butoxycarbonyl[4,5,6-tris(hydroxymethyl)cyclohex-2-enyl]amine (24).** A solution of adduct **22a** (1.90 g, 5.84 mmol) in dry THF (15 mL) was added dropwise to a cooled (0 °C) suspension of $LiAlH_4$ (0.70 g, 0.17 mol) in dry THF (35 mL). The reaction mixture was refluxed for 16 h and then cooled to −5 °C. A saturated solution of Na_2SO_4 (1.5 mL) was carefully added and, after addition of Et_2O, the suspension was stirred at room temperature for 15 min. The precipitate was removed by filtration and washed with THF and Et_2O. The combined filtrates were concentrated in vacuo, and the residue was dissolved in CH_2Cl_2. The solution was dried over $MgSO_4$, and the solvent was removed under vacuum to give compound **24** (0.50 g, 78% crude) as a pale yellow oil used in the next step without purification: IR (neat) 3600−3100, 1681 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.81 (m, 1H, H-2), 5.72 (m, 1H, H-3), 5.56 (d, 1H, NH, J = 16.4 Hz), 4.34 (m, 1H, H-1), 3.84−3.50 (m, 9H, CH_2 and OH), 2.61 (m, 1H, H-4), 2.14 (m, 1H, H-6), 1.96 (m, 1H, H-5), 1.45 (s, 9H, $(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 157.6, 130.8, 128.0, 80.2, 63.7, 62.6, 59.2, 44.0, 43.8, 41.7, 38.4, 28.3; HRMS calcd for $C_{14}H_{25}NO_5$ 287.1733, found 287.1729.

(1*R,4*S**,5*S**,6*S**)-*N*-*tert*-Butoxycarbonyl[4,5,6-tris(benzoxymethyl)cyclohex-2-enyl]amine (25).** Pyridine (4.00 mL, 40.0 mmol) and benzoyl chloride (4.50 mL, 40.0 mmol) were successively added to a cooled (0 °C) solution of crude compound **24** (1.25 g, 4.35 mmol) in dry CH_2Cl_2. The reaction mixture was stirred at room temperature for 16 h and diluted with CH_2Cl_2. The solution was washed with 1 M aqueous HCl, water, 10% $NaHCO_3$, and brine. The aqueous layers were extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (silica gel, CH_2Cl_2 then CH_2Cl_2/EtOAc, 95:5) to afford compound **25** (1.33 g, 51%) as a colorless oil: IR (neat) 1718, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.12−7.94 (m, 6H, C_6H_5), 7.63−7.32 (m, 9H, C_6H_5), 5.87 (m, 2H, H-2 and H-3), 4.70−4.53 (m, 6H, H-1, NH and CH_2), 4.44 (m, 2H, CH_2), 2.98 (m, 1H, H-4), 2.78 (m, 1H, H-5 or H-6), 2.64 (m, 1H, H-5 or H-6), 1.36 (s, 9H, $(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 171.2, 166.4, 166.3, 155.4, 133.5, 133.1, 133.0, 132.9, 130.1, 129.8, 129.7, 129.51, 129.49, 129.0, 128.4, 128.32, 128.28, 128.0, 79.8, 65.3, 63.7, 61.7, 45.4, 40.5, 39.2, 34.0, 28.2; HRMS calcd for $[(C_{35}H_{37}NO_8) - C_4H_9 - CO_2C_6H_5]$ 421.1519, found 421.1529.

(1*R,4*S**,5*S**,6*S**)-[4,5,6-Tris(benzoxymethyl)cyclohex-2-enyl]amine (26).** Trifluoroacetic acid (5 mL) was added to a solution of compound **25** (500 mg, 0.83 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temperature for 1.5 h and then cooled to 0 °C. A 20% NaOH solution was carefully added until pH 10, and the mixture was extracted with CH_2Cl_2. The combined extracts were dried over K_2CO_3, and the solvent was removed under reduced pressure to give **26** (371 mg, 89%) as a colorless oil: IR (neat) 1727 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.06−7.94 (m, 6H, C_6H_5), 7.59−7.28 (m, 9H, C_6H_5), 5.95 (m, 1H, H-2 or H-3), 5.74 (m, 1H, H-2 or H-3), 4.89 (dd, 1H, H-7, J = 11.0, 8.7 Hz), 4.81 (dd, 1H, H-8, J = 11.9, 3.8 Hz), 4.67 (dd, 1H, H-7′, J = 11.0, 6.5 Hz), 4.53−4.42 (m, 3H, H-8′, H-9 and H-9′), 3.66 (m, 1H, H-1), 2.96 (m, 1H, H-4), 2.69 (m, 1H, H-5), 2.42 (m, 1H, H-6), 1.45 (br s, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ 168.2, 168.1, 168.0, 134.7, 134.6, 134.5, 134.0, 131.9, 131.7, 131.6, 131.3, 131.2, 130.1, 130.0, 127.8, 67.5, 66.5, 64.0, 47.6, 43.4, 41.8, 36.9; HRMS calcd for $C_{30}H_{29}NO_6$ 499.1995, found 499.1998.

(1*R,4*S**,5*S**,6*S**)-*N*-[4,5-Bis(benzoxymethyl)-6-hydroxymethylcyclohex-2-enyl]benzamide (27).** If compound **26** was not rapidly used in the next step, it rearranged to give compound **27**: IR (neat) 3400−3200, 1714, 1643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.06−7.26 (m, 15H, C_6H_5), 6.23 (d, 1H, NH, J = 8.5 Hz), 6.03 (m, 2H, H-2 and H-3), 4.98 (m, 1H, H-1), 4.55 (dd, 1H, H-8, J = 11.8, 5.0 Hz), 4.53−4.42 (m, 3H, H-9, H-9′ and OH), 4.26 (dd, 1H, H-8′, J = 11.8, 6.3 Hz), 3.87 (dd, 1H, H-7, J = 11.2, 11.2 Hz), 3.69 (dd, 1H, H-7′, J = 11.2, 3.9 Hz), 3.09 (m, 1H, H-4), 2.60 (m, 1H, H-5), 2.43 (m, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ 169.0, 166.4, 166.3, 133.4, 133.2, 133.0, 132.0, 130.5, 129.7, 129.6, 129.5, 129.3, 128.7, 128.6, 128.4, 127.5, 126.9, 65.2, 62.4, 61.9, 44.7, 44.4, 39.9, 34.6.

(1*R,4*S**,5*S**,6*S**)-[4,5,6-Tris(benzoxymethyl)cyclohex-2-enyl]-3-(3-methoxyacryloyl)urea (29).** Thionyl chloride (0.15 mL) was added to a solution of 3-methoxyacrylic acid (120 mg, 1.20 mmol) in dry CH_2Cl_2 (1 mL). The reaction mixture was refluxed for 3 h and concentrated to dryness. The residue was dissolved in dry benzene, and AgOCN (0.31 g, 2.1 mmol) was added. The suspension was refluxed for 30 min to afford **28** and cooled to 0 °C, and the supernatant liquor was added to amine **26** (300 mg, 0.60 mmol). The mixture was stirred at room temperature for 20 h and concentrated in vacuo. The residue was purified by chromatography (silica gel, cyclohexane/EtOAc, 1:1) to give compound **29** (263 mg, 70%) as a white solid: mp 56−59 °C; IR (KBr) 1720, 1673 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.75 (s, 1H, NH), 9.01 (d, 1H, NH, J = 9.8 Hz), 8.05−7.93 (m, 6H, C_6H_5), 7.55−7.29 (m, 10H, C_6H_5 and H-3″), 5.95 (m, 1H, H-2′ or H-3′), 5.88 (m, 1H, H-2′ or H-3′), 5.25 (d, 1H, H-2″, J = 12.3 Hz), 4.87 (m, 1H, H-1′), 4.79−4.48 (m, 6H, CH_2), 3.62 (s, 3H, CH_3), 2.99 (m, 1H, H-4′), 2.81 (m, 1H, H-5′ or H-6′), 2.70 (m, 1H, H-5′ or H-6′); ^{13}C NMR ($CDCl_3$) δ 168.0, 166.27, 166.25, 166.20, 163.6, 155.1, 132.94, 132.86, 132.8, 130.1, 129.9, 129.8, 129.6, 129.5, 128.5, 128.3, 128.2, 128.1, 97.3, 65.3, 63.8, 61.6, 57.7, 44.1, 40.4, 39.4, 34.1; HRMS calcd for $[(C_{35}H_{34}N_2O_9) + H]^+$ 627.2343, found 627.2348.

(1*R,4*S**,5*S**,6*S**)-1-[4,5,6-Tris(hydroxymethyl)cyclohex-2-enyl]uracil (30).** A solution of compound **29** (100 mg, 0.16 mmol) in NH_4OH 20% (1.5 mL) and MeOH (1.5 mL) was heated in a sealed tube at 85 °C for 48 h. The mixture was concentrated in vacuo, and the residue was purified by chromatography (silica gel, CH_2Cl_2/MeOH, 9:1) to give compound **30** (29 mg, 67%) as a yellow oil: IR 3500−3200, 1710, 1695 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.14 (br s, 1H, NH), 7.38 (d, 1H, H-6, J = 7.9 Hz), 6.14 (m, 1H, H-2′ or H-3′), 5.85 (m, 1H, H-2′ or H-3′), 5.48 (d, 1H, H-5, J = 7.9 Hz), 5.07 (m, 1H, H-1′), 3.56−3.19 (m, 9H, CH_2 and OH), 2.38 (m, 2H, H-4′ and H-6′), 2.12 (m, 1H, H-5′); ^{13}C NMR (CD_3OD) δ 168.3, 155.1, 146.6, 137.3, 127.1, 103.3, 64.9, 64.1, 61.1, 58.7, 42.6, 42.5, 42.4; HRMS calcd for $C_{13}H_{18}N_2O_5$ 282.1215, found 282.1216.

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Supporting Information Available: ^1H NMR spectra of compounds **16**−**21**, **22a**, **23**−**27**, **29**, and **30**, and several NOE spectra of **18**, **20**, **22a**, and **23a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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