# Diels−Alder Reactions of Amino Acid-Derived Trienes

William V. Murray,* Sengen Sun, Ignatius J. Turchi, Frank K. Brown, and A. Diane Gauthier

*The R. W. Johnson Pharmaceutical Research Institute, 1000 Route 202, Raritan, New Jersey 08869*

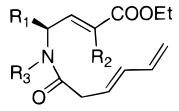
*Received March 12, 1999*

Triene precursors (**1a**−**e**, **2a**−**k**) were constructed for substrate-controlled asymmetric Diels−Alder reactions. Boc-L-phenylalanal and Boc-L-valinal were condensed with triethyl phosphonoacetate or 2-phosphonopropionate to generate the α,β-unsaturated esters as dienophiles. Removal of the Boc group to give free amines **4a**−**d**, which after, or without N-benzylation, were treated with 3,5-hexadienoyl chloride to give **1a**−**e**, or with 2,4-hexadienoyl chloride to afford **2a**−**f**. The trienes **2g**−**i** were prepared via reductive alkylation of amines **4a**−**i** with 2,4-hexadienal. The secondary amide triene **1a** failed to yield any Diels−Alder product when heated at 170 °C. The tertiary amide trienes **1b**−**e** produced in refluxing toluene the major cycloaddition products that were cis-fused and derived from the exo transition states. Trienes **2a**−**k** underwent surprisingly facile Diels−Alder reactions to produce the major trans-fused isomers that were derived from the endo transition states. For trienes **2b**−**h** and **2j**,**k**, Diels−Alder reactions proceeded at room temperature. For the primary amide **2a**, the Diels−Alder reaction proceeded smoothly in refluxing toluene. The tertiary amide triene **22** was constructed to have two electron-withdrawing ester substituents at the termini of the triene. The Diels−Alder reaction of **22** took place spontaneously at room temperature upon benzoylation of the secondary amine **21** and produced a single isomer derived from the endo transition state. 1,3-Allylic strain is discussed as an important factor in control of the diastereoselectivity.

## Introduction

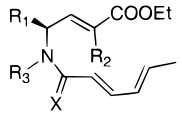
The Diels−Alder reaction is a powerful method for synthesis of many categories of cyclic compounds and possesses considerable potential in synthesis of heterocyclic libraries for drug screening. There have several reports on trienes containing a nitrogen atom within the triene tether.[1] Our goal was to develop an efficient method, based on the intramolecular Diels−Alder reaction of novel amino acid derived trienes, for fast, mild, and selective generation of large number of heterocyclic compounds.

The trienes (**1a**−**e**, **2a**−**k**, Figures 1 and 2) have been designed so that a stereogenic center at the allylic position of the dienophile can provide steric discrimination of the diastereotopic faces of the dienophile.[2] The terminal ethyl ester group may facilitate the cycloaddition process compared with similar published amino acid derived trienes.[1] We report here our surprising observations of the facile intramolecular cycloadditions and our investigation of substituent effects on the reactivity and stereoselectivity.




**1a**. $R_1$=Bn, $R_2$=$R_3$=H
**1b**. $R_1$=$R_3$=Bn, $R_2$=H
**1c**. $R_1$=$R_3$=Bn, $R_2$=Me
**1d**. $R_1$=$Me_2CH$, $R_2$=H, $R_3$=2,4-$(MeO)_2$Bn
**1e**. $R_1$=$Me_2CH$, $R_2$=Me, $R_3$=Bn

**Figure 1.**




**2a.** $R_1$=Bn, $R_2$=Me, $R_3$=H, X=O
**2b.** $R_1$=Bn, $R_2$=H, $R_3$=Bn, X=O
**2c.** $R_1$=Bn, $R_2$=Me, $R_3$=Bn, X=O
**2d.** $R_1$=$Me_2CH$, $R_2$=H, $R_3$=2,4-$(MeO)_2$Bn, X=O
**2e.** $R_1$=$Me_2CH$, $R_2$=Me, $R_3$=2,4-$(MeO)_2$Bn, X=O
**2f.** $R_1$=$Me_2CH$, $R_2$=Me, $R_3$=Bn, X=O
**2g.** $R_1$=Bn, $R_2$=H, $R_3$=H, X=2H
**2h.** $R_1$=$Me_2CH$, $R_2$=Me, $R_3$=Bn, X=2H
**2i.** $R_1$=$Me_2CH$, $R_2$=Me, $R_3$=H, X=2H
**2j.** $R_1$=$Me_2CH$, $R_2$=Me, $R_3$=Bz, X=2H
**2k.** $R_1$=H, $R_2$=H, $R_3$=Bn, X=O

**Figure 2.**

## Results and Discussion

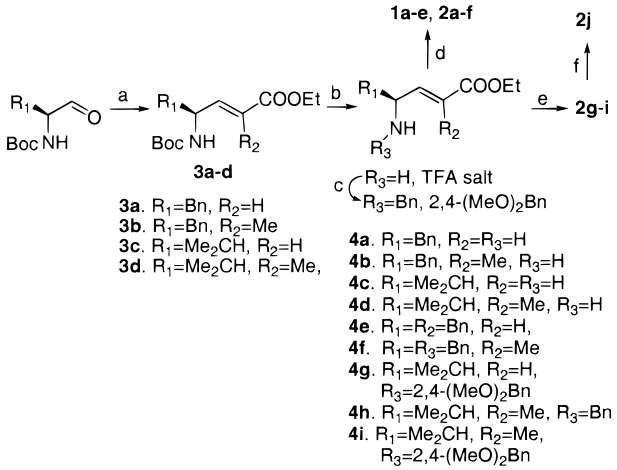
Synthesis of the triene precursors shown in Scheme 1 involves Horner−Wadsworth−Emmons condensation of Boc-L-valinal[3] and Boc-L-phenylalanal[3] with triethyl phosphonoacetate or phosphonopropionate in the pres-

(1) For the syntheses of other hydroisoquinone and hydroisoindole derivatives via Diels−Alder reactions, see: (a) Gutierrez, A. J.; Shea, K. J.; Svoboda, J. J. *J. Org. Chem*. **1989**, *54*, 4335. (b) Moriwake, T.; Hamano, S.; Saito, S.; Torii, S. *J. Org. Chem*. **1989**, *54*, 4114. (c) Martin, S.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem*. **1983**, *48*, 5170. (d) Guy, A.; Lemaire, M.; Negre, M.; Guette, J. P. *Tetrahedron Lett*. **1985**, *26*, 3575. (e) Takeuchi, H.; Fujimoto, T.; Hoshino, K.; Motoyoshiya, J.; Kakehi, A.; Yamamoto, I. *J. Org. Chem*. **1998**, *63*, 7172.

(2) For examples of the discussion on 1,3-allylic strains in Diels−Alder reactions, see: (a) Crisp, G. T.; Gebauer, M. G. *J. Org. Chem*. **1996**, *61*, 8425. (b) Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. *J. Am. Chem. Soc*. **1996**, *118*, 7502. (c) Reetz, M. T.; Kayser, F.; Harms, K. *Tetrahedron Lett*. **1992**, *33*, 3453.

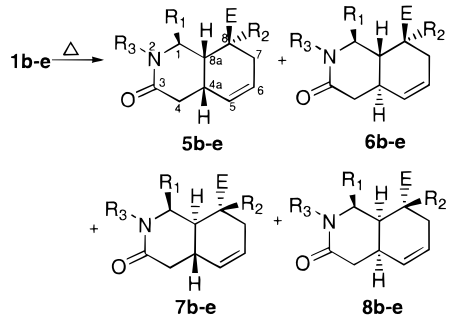
10.1021/jo990459f CCC: $18.00 
Published on Web 07/21/1999

**Scheme 1**[a]




[a] Key: (a) $(EtO)_2P(O)=CR_2COOEt$, THF; (b) 20% TFA in $CH_2Cl_2$; (c) $C_6H_5CHO$ or 2,4-$(MeO)_2C_6H_3CHO$, AcOH, $NaCNBH_3$; (d) (*E*,*E*)-2,4- or (*E*)-3,5-hexadienoyl chloride, 1.5 equiv, $Et_3N$, THF; (e) (*E*,*E*)-2,4-hexadienal, AcOH, $NaBH(OAc)_3$; (f) BzCl, $Et_3N$, THF.

**Scheme 2**[a]




[a] E = COOEt.

ence of a base. Removal of the Boc protecting group afforded amine derivatives **4a**−**d**, which were acylated using 2,4- or 3,5-hexadienoyl chloride to give **1a** and **2a**. **4a**−**d** were alternatively benzylated by reductive alkylation to give **4e**−**i** before installation of the dienes by acylation to generate **1b**−**e** and **2b**−**f**. Compounds **4a**, **4d** (TFA salts), and **4i** were treated with 2,4-hexadienal and a boron hydride in the presence of acetic acid to produce amine-linked trienes (**2g**−**i**). Triene **2i** was benzoylated to afford the amide triene **2j**.

Triene **1a** containing an amide NH group did not produce any cycloaddition products after reflux in toluene for 48 h and decomposed completely under $N_2$ after reflux for 24 h in 1,3-dichlorobenzene. Triene precursor **1b** containing an *N*-benzyl group was converted to Diels−Alder products in excellent yield after reflux in toluene for 16 h. All four possible isomers were observed in a ratio of 33:11:10:3 as shown in Scheme 2 and Table 1. The calculated activation energies for the Diels−Alder reactions of the trienes **1** to the cycloadducts **5**−**8** are presented in the Supporting Information.[4] These values are obtained by taking the difference in energy between an extended, low energy conformer of **1** and the corresponding transition structure leading to the products **5**−**8**. This treatment is not sufficient to explain the lack

**Table 1. Product Ratios Were Obtained by $^1$H NMR Integration of the Crude Reaction Mixtures, or Based on Isolated Yields of the Isomers. Trienes 2b−g and 2j Were Not Characterized Due to the Ongoing Diels−Alder Reactions, and the Yields for These Reactions Are for Two Steps**

| | solvents/temperature | reaction time | yield % | **5**:**6**:**7**:**8** or **9**:**10**:**11**:**12** |
|---|---|---|---|---|
| **1a** | 170 °C | 24 h | 0 | |
| **1b** | toluene, reflux | 16 h | 94 | 33:10:11:3 |
| **1c** | toluene, reflux | 50 h | 85 | 3:1:0:0 |
| **1d** | toluene, reflux | 16 h | 74 | 3:1:0:0 |
| **1e** | toluene, reflux | 6 days | 66 | 5:2:0:0 |
| **2a** | toluene, reflux | 7 h | 93 | 34:11:1:0 |
| **2b** | $CHCl_3$, rt | 12 h | 82 | 10:1:10:1 |
| **2c** | $CHCl_3$, rt | 20 h | 73 | 83:25:1:1 |
| **2d** | $CHCl_3$, rt | 60 h | 91 | 20:2:1:0 |
| **2e** | $CHCl_3$, rt | 80 h | 80 | 185:50:1:0 |
| **2f** | $CHCl_3$, rt | 72 h | − | 6:1:0:0 |
| **2g** | $CH_2Cl_2$/TFA, rt | <6 h | >66 | 5:1:0:0 |
| **2h** | $CHCl_3$, rt | 15 days | 84 | 3:2:0:0 |
| **2j** | $CHCl_3$, rt | 18 h | 61 | 9:1:0:0 |
| **2k** | $CHCl_3$, rt | 18 days | 67 | 6:1:−:− |

of reactivity of **1a**. The lack of reactivity of the triene **1a** may be rationalized by the following computational results. The energy of an extended, low energy conformer of **1** ($R_1$ = Me, $R_2$ = $R_3$ = H) is calculated to be 4.6 kcal/mol (B3LYP/6-31G(d)//RHF/3-21G) lower than a folded (i.e., reactive) conformer. This folded, reactive conformer is a local minimum that would lead to the product **5** ($R_1$ = Me, $R_2$ = $R_3$ = H). Because of this large energy difference between these conformers, compound **1** cannot reach a large enough concentration of the reactive conformer at equilibrium, and consequently, no Diels−Alder reaction is observed. In contrast, introduction of an NMe substituent as in **1** ($R_1$ = Me, $R_2$ = H, $R_3$ = Me) leads to a difference of only 2.5 kcal/mol at the same level of theory between the extended and the folded, reactive conformers. In this case, the concentration of the reactive conformer is high enough at equilibrium for reaction to occur.[5]

For compounds **1c**,**d**, only two diastereomers were present in the crude reaction mixture as seen by $^1$H NMR and were isolated by silica gel column chromatography (Scheme 2, Table 1). The calculated relative activation energies for the reaction of **1** leading to products **5**−**8** at the B3LYP/6-31G(d)//RHF/3-21G level of theory adequately rationalize the observed product distributions assuming similar entropies of activation. In both cases the exo/equatorial transition structure is calculated to be the lowest energy with the endo/equatorial transition structure the next lowest as observed experimentally.

The bond lengths of the forming bonds for the transition structures leading to the products **5**−**8** are given.[6] The formation of the new bonds is asynchronous with the C1−C2 (lactam ring) bond being shorter than the C3−C4 (cyclohexene ring) bond by 0.092 Å (AM1) and 0.267 Å (RHF/3-21G) on average.

It has been reported that cis-fused hydroisoquinolone derivatives are generally the major isomers in cycloadditions of 7-aza-1,3,9-decatrienes.[1] Martin et al. reported a case that the isomeric cycloaddition products can be interconverted at the reaction temperature.[1c] Our trienes

(3) Fehrentz, J.-A.; Castro, B. *Synthesis* **1983**, 676.
(4) Supporting Information Table 2.
(5) Brown, F. K.; Singh, U. C.; Kollman, P. A.; Raimondi, L.; Houk, K. N.; Bock, C. W. *J. Org. Chem.* **1992**, *57*, 4862; Raimondi, L.; Brown, F. K.; Gonzalez, J.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 4796.
(6) Supporting Information Table 3.

6,6-Fused transition states corresponding to **1a-e**

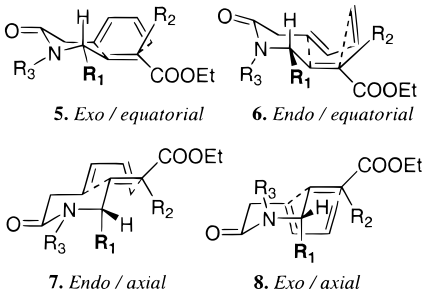



**Figure 3.**

5,6-Fused transition states corresponding to **2a-f**

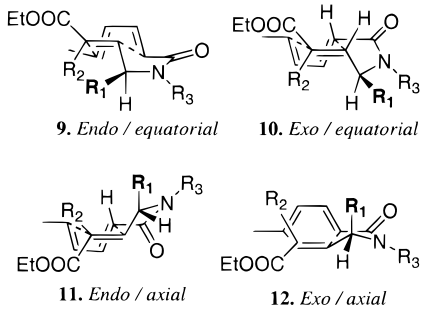
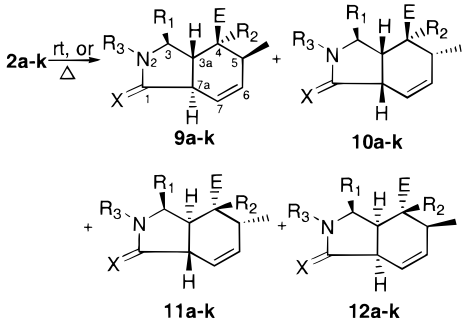



**Figure 4.**

**Scheme 3**[a]




[a] E = COOEt.

**1b**−**d** also gave the major cis-fused products **5**, but derived from the exo transition state (Figure 3). The purified isomers from the cyclizations of trienes **1c**−**e** were not able to be interconverted when reheated at the reaction temperature, suggesting a kinetically controlled mechanism. This observation is surprising as kinetically controlled Diels−Alder reactions usually produce major isomers derived from endo transition states.[7] All of the Diels−Alder reactions described herein are calculated to be exothermic by 9−44 kcal/mol depending on the level of theory.[8] This is consistent with the experimental observations.

This exo selectivity may be a result of the overall conformation that can afford a reaction path of relatively low energy. The sterically more hindered isopropyl group $R_1$, or the size increase of $R_2$ from proton to methyl, may further destabilize the transition states (**7**, **8**) where the $R_1$ group is axial (Figure 3). Overall, the exo transition state with the equatorial $R_1$ (**5**) is favored.

Compound **2b** could not be synthesized in pure form by acylating **4e** with 2,4-hexadienoyl chloride at room temperature due to the facile Diels−Alder cycloaddition that occurred at room temperature. We chose not to isolate the intermediate **2b**, and the crude product **2b** in ether was washed with sodium carbonate and water and was then allowed to stand in $CDCl_3$ or $C_6D_6$ at room temperature. The cycloaddition of **2b** was found to be complete in 12 h (Scheme 3, Table 1). The Diels−Alder cycloaddition reactions of **2c**−**f** also proceeded at room temperature and produced two prominent diastereomers in each case. $^1$H NMR showed endo/exo ratios of from 3:1 to 6:1. The Diels−Alder reaction of **2a** containing a free NH group was sluggish at room temperature. When refluxed in toluene, however, the reaction was complete in 6 h, affording endo selectivity of ∼3:1 and facial selectivity of 34:1. The facial selectivity across the dienophile in these cases appears to be due to the pronounced interaction between the axial $R_1$ group and the $R_2$ methyl group in transition state **11** (Figure 4).

When the TFA salt of **4a** ($R_1$ = Bn, $R_2$ = H) was subjected to reductive alkylation conditions with 2,4-hexadienal, triene **2g** was not detected. Instead, the isomeric cycloaddition products **9g** and **10g** were isolated in a 5:1 ratio. Under the same reaction conditions, pure amine triene **2i** was isolated in a 73% yield from the TFA salt of **4d** and underwent the cycloaddition very slowly (10% conversion in 10 days in $CDCl_3$). The Diels−Alder reaction of **2j** was complete in 18 h after the addition of benzoyl chloride to a THF solution of **2i** containing excess triethylamine. Amine triene **2h** was purified in a 54% yield from a reaction of **4i**. The cycloaddition of **2h** was complete in 15 days (Scheme 3, Table 1). It is apparent in each of these cases that either the interaction between R1 and R3 in the transition state or the planarization of the amine nitrogen to its requisite amide has a profound effect on the rate of the Diels−Alder cycloaddition.

Triene **2k** was prepared by alkylation of benzylamine with 4-bromo-*trans*-crotonic ethyl ester, followed by N-acylation with 2,4-hexadienoyl chloride. Cycloaddition of **2k** took 18 days to complete in either $CDCl_3$ or $C_6D_6$. This result indicated the interaction between $R_1$ and $R_3$ was a key factor to the rate acceleration.

The calculated activation energies for the Diels−Alder reactions of the trienes **2** to the cycloadducts **9**−**12** are given.[9] These values are 3−6 kcal/mol lower for the amides than for the amines with the exception of the amides where the nitrogen substituted with a hydrogen (i.e., **2**: $R_1 = R_2 = Me$, $R_3 = H$ and $R_1 = {}^i$Pr, $R_2 = Me$, $R_3 = H$) at the B3LYP/6-31G(d)//RHF/3-21G level. Also, the amide **2** ($R_1 = {}^i$Pr, $R_2 = Me$, $R_3 = Ac$) has an activation energy for the cycloaddition to **9**−**12** of about 2 kcal/mol lower than the amines at the same level of theory. The calculated values agree at least qualitatively with the observed relative rates for the cycloadditions of **2** to **9**−**12**. Frontier MO theory is inadequate for rationalizing the relative rates of the Diels−Alder reactions of the amides vs the amines since the energy gaps for the frontier orbitals are nearly equal in each case. Thus, subtle steric effects in the transition structures are probably responsible for these rate effects.[6]

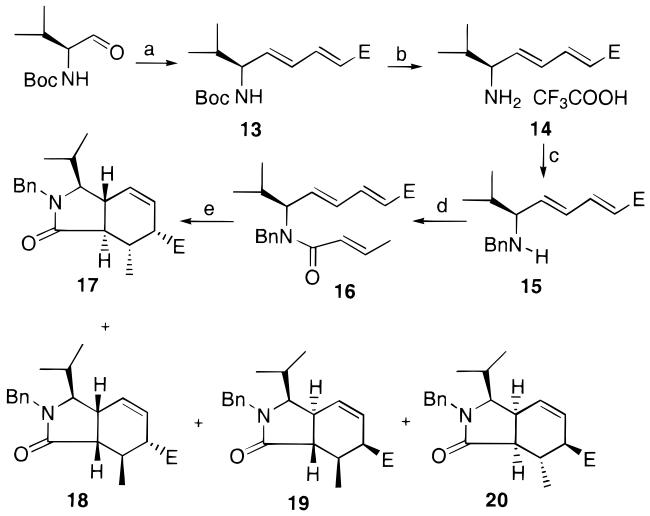
As was the case for the Diels−Alder reactions of **1**, the calculated relative activation energies for the reaction of

(7) Atkinson, R. S. *Stereoselective Synthesis*; John Wiley & Sons: Chichester, 1995; pp 156−180.

(8) Supporting Information Tables 2 and 4.

(9) Supporting Information Table 4.

**Scheme 4**[a]



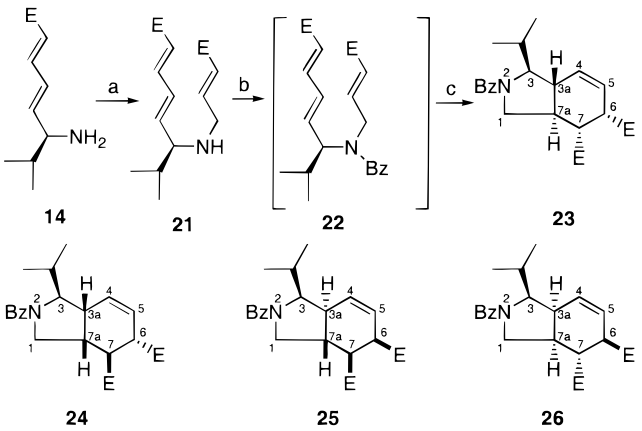
[a] Key: (a) (*E*)-$(EtO)_2P(O)$═CHCH═CHCOOEt, THF; (b) 20% TFA in $CH_2Cl_2$; (c) $C_6H_5CHO$, AcOH, $NaCNBH_3$; (d) (*E*)-crotonyl chloride, $Et_3N$, THF; (e) toluene, reflux, 4 h, 100%, 17:18:19:20 = 10:10:1:1.

**2** leading to cycloadducts **9**−**12** at the B3LYP/6-31G(d)//RHF/3-21G level of theory give a good account of the observed product distributions. In general, the transition structures leading to the endo trans-fused isomers are calculated to be the lowest energy species. Lower levels of theory usually give less satisfactory results.

Amide triene **16** containing an ester-substituted diene was synthesized (Scheme 4). The Horner−Wadsworth−Emmons reaction between valinal and triethyl *trans*-4-phosphonocrotonate gave an inseparable mixture of the major *trans,trans*-diene **13** and a minor *cis,trans*-diene isomer (10:1). The mixture was converted to triene **16** in a pure form. The cycloaddition of **16** was sluggish at room temperature (∼10% conversion in 1 week) and was carried out at reflux in toluene for 4 h to afford four isomers **17**, **18**, **19**, and **20** in a ratio of 10:10:1:1.

It is notable that we are adding an electron-deficient diene and an electron-deficient dienophile for **2a**−**f** to form the 5,6-fused bicycloadducts. Our initial hypotheses for these facile Diels−Alder reactions involved the complementary dipole interaction between the diene and the dienophile in an intramolecular fasion. The similar intermolecular reaction between 2,4-dienoylate and acrylate was apparently disfavored for the regio orientation of the favorable dipole interaction, relative to the regio orientation of apparent dipole repulsion.[11] We believed that matching the presumed negative carbon α to the carbonyl group in the diene to the positive carbon $\beta$ to the carbonyl in the dienophile, as well as the positive carbon $\delta$ to the carbonyl in the diene with the negative carbon α to the carbonyl in the dienophile, we could achieve reasonable orbital overlap, and this could explain the facile nature of the observed Diels−Alder reactions. To test this hypothesis, the diester triene **21** was synthesized (Scheme 5). This compound proved unreactive at room temperature until it was N-benzoylated. Its cycloaddition was initiated upon the benzoylation as

**Scheme 5**[a]



[a] Key: (a) (*E*)-$BrCH_2CHCHCOOEt$, DMAP, THF, 40 h, 52%; (b) PhCOCl, $Et_3N$, THF, 0.5 h; (c) rt, $CDCl_3$ or $C_6D_6$, 40 h, 92% (based on 21), one isomer only.

detected by $^1H$ NMR and was complete in 40 h in either $CDCl_3$ or $C_6D_6$. A single diastereomer **23** was observed and purified in 92% yield as the cycloaddition product. This system eliminates the complimentary polarization that could be in effect in the other examples and demonstrates the requirement for a large group at $R_3$ as well as a planar nitrogen.

For the Diels−Alder reactions of **16** to **17**−**20** and **22** to **23** we were unable to locate transition structures at the RHF/3-21G level of theory using standard or newer techniques such as quadratic synchronous transit methods. Transition structures were located using the AM1 Hamiltonian and single-point calculations using the hybrid HF-DFT method, B3LYP/6-31G(d) were carried out on these two systems. The activation energy for the conversion of **16** to **17**−**20** is about 10−13 kcal/mol higher than for the cycloaddition of **22** to **23**. This is in qualitative agreement with the experimental findings that the triene **22** undergoes cycloaddition much more rapidly than triene **16**. This result can be rationalized based on FMO theory.[6,10] For **16** the interacting orbitals are the HOMO − 1 localized on the diene and the LUMO + 1 localized on the olefinic double bond. The energy gap between these orbitals is 10.1 eV (AM1). For **22**, however, the interacting orbitals are the HOMO localized on the diene and the LUMO + 1 localized on the olefin. In this case the gap is only 9.1 eV (AM1). Other factors such as steric and electrostatic interactions may contribute to the relative reactivity of **16** vs **22**, but these would be more subtle and difficult to visualize.

The relative activation energies for the formation of **17**−**20** accurately reflect the observed product distributions. The transition structures leading to **17** and **18** are calculated to be 3−4 kcal/mol lower in energy than those leading to **19** and **20** at the B3LYP/6-31G(d)//AM1 level of theory. This is not the case for the Diels−Alder reaction of triene **22**. Experimentally, only cycloadduct **23** is observed while the calculations suggest that a mixture of **23** and **24** should be obtained. This incorrect result may be a consequence of using the AM1 geometries for the transition structures leading to **23** and **24** for the single-point B3LYP/6-31G(d) energy calculations.

In contrast to **1b**−**e**, trienes **2a**−**k**, and **22** all cyclized to produce endo-derived trans-fused isomers as the major products. The diastereomeric ratio from the

(10) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: London, 1976.

(11) Overman, L. E.; Taylor, G. F.; Houk, K. N.; Domelsmith, L. N. *J. Am. Chem. Soc.* **1978**, *100*, 3182. (b) Yedidia, V.; Leznoff, C. C. *Can. J. Chem.* **1980**, *58*, 1144.

cycloaddition of triene **2b** (**9b**/**10b**/**11b**/**12b** = 10:1:10:1) reflects a good endo/exo selectivity, but no diastereofacial selectivity. This result indicates that the $A_{1,3}$ interaction between benzyl at $R_1$ and hydrogen at $R_2$ in transition state **11** (Figure 4) is not significant, despite the axial position of $R_1$. As the size of the $R_2$ group increased to a methyl in **2c** and **2e**−**f**, the pathway through the transition states **11** and **12** are largely suppressed and good stereofacial selectivity is achieved. As expected, the reaction of **2d** provided a good diastereofacial selectivity due to the larger isopropyl ($R_1$) and dimethoxybenzyl ($R_3$) groups, as well as good endo/exo selectivity. It appears that the endo selectivity among trienes **2f**, **2h**, and **2j** is rate dependent, as evidenced by the observed endo/exo ratios and reaction times of **2f** (18 h, 9:1), **2h** (15 days, 3:2), and **2j** (80 h, 3:1).

The linker length between a diene and a dienophile for a Diels−Alder reaction is believed to affect the orbital overlap.[12] Trienes **2b**−**k** are more reactive toward Diels−Alder reactions to form 5,6-fused cycloaddition products at room temperature, while trienes **1b**−**e** require heating to afford 6,6-fused hydroisoquinones. The enhanced reactivity of compounds **2a**−**k** relative to compounds **1a**−**d** may be attributed to the ring-size difference. That is, the triene system for the smaller 5,6-fused bicycloadducts was able to organize more effectively for the cycloadditions than the system for 6,6-fused rings. It was also shown that the reactivity in these systems was very sensitive to variations of substituents $R_1$, $R_2$, and $R_3$. The relative reactivity in **2a**−**j** decreases when the $R_1$ group is changed from benzyl to sterically more hindered isopropyl. In addition, when we tested triene **2k**, which bears a hydrogen at $R_1$, the cyclization proceeded very slowly (18 days). It appears that an $R_1$ group of moderate size is in the best position to accelerate the cycloaddition. The reaction was slowed when $R_2$ was changed from hydrogen to a methyl group, although the larger $R_2$ group can enhance the diastereofacial selectivity across the dienophile.

Triene **2j** cyclized faster than **2f**, and **2f** cyclized faster than **2h**, suggesting a trend that the tertiary amine reacts more slowly than the tertiary amides. The diene that is free from the conjugation with the amide carbonyl group in triene **2j** is in the best position to cyclize with the dienophile. Trienes **22** cyclized much faster than **16**. This result relates to the corresponding intermolecular cycloaddition between acrylate and 2,4-pentadienoate, which produces the ortho product preferentially via an endo transition state.[10,11]

It is interesting that trienes **2a**−**f**,**k**, **16**, and **22** containing both electron-deficient diene and electron-deficient dienophile cyclized under surprisingly mild conditions. The complementary electron demand is not required between the two reacting partners. There had been occasional examples of facile Diels−Alder reactions in the literature that do not appear to have complementary electronic demand. For example, the dimerization of 2-methoxycarbonyl-1,3-butadiene took place spontaneously at room temperature.[13] These examples were generally limited to theoretical and mechanistic arguments. We are interested in the utilization of these reactions in the stereoselective syntheses of heterocyclic compounds. The mild reaction conditions can facilitate our further implementation of solid-phase technology in the construction of molecular libraries for biological evaluations.

The bond lengths of the forming bonds for the transition structures leading to the products **9**−**12**, **17**−**20**, and **23**−**26** are given.[14] The formation of the new bonds is even more asynchronous than in the 6,6-systems as expected with the $C_1-C_2$ (lactam ring) bond being shorter than the $C_3-C_4$ (cyclohexene ring) bond by 0.37 Å (AM1) and 0.5 Å (RHF/3-21G) on average.

## Conclusion

We have observed a class of cycloadditions of amino acid derived trienes in the synthesis of novel isohydroindole derivatives and found that the major products were derived from endo transition states. The corresponding 6,6 fused hydroisoquinoline derivatives were formed in refluxing toluene through exo transition states. The $A_{1,3}$ interaction between $R_1$ and $R_2$ appears to have an important impact on the diastereomeric distribution of the products. A sterically more hindered $R_1$ or $R_2$ group affords stronger discrimination of the two diastereotopic faces of the dienophile for its access to the diene during cycloaddition.

These reported Diels−Alder reactions to form isohydroindoles lack complementary electronic demand and can take place under mild thermal conditions. Furthermore, the stereoselectivity of the cyclizations between an electron-deficient diene and an electron-deficient dienophile can reach up to 100% to give a single stereoisomer.

Recently, Houk and co-workers published several reports of the successful application of DFT, especially the hybrid HF-DFT gradient corrected methods, to the study of pericyclic reactions.[15] Based on our experimental results, we have shown that the B3LYP energies with a moderate-sized basis set using the RHF/3-21G-optimized geometries gives excellent estimates of the relative reactivity and product distributions of the intramolecular Diels−Alder reactions studied experimentally herein.

We are investigating these reactions to generate complex functionalized heterocyclic libraries.

## Experimental Section

**Computational Details.** The programs GAUSSIAN-94, GAUSSIAN-98, and SPARTAN 5.0 were used for the ab initio and DFT calculations.[16,17] The CAChe (v. 3.8) worksystem[18] was used for the AM1 calculations. Optimized geometries were obtained at the AM1 and RHF/3-21G levels of theory. All stationary points (minima and transition structures) were characterized by calculation of their harmonic vibrational frequencies at the corresponding level (AM1 or RHF/3-21G).

(12) Boeckman, R. K., Jr.; Demko, D. M. *J. Org. Chem.* **1982**, *47*, 1789.

(13) Spino, C.; Crawford, J.; Cui, Y.; Gugelchuk, M. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1499 and references therein.

(14) Supporting Information Table 5.

(15) Yoo, X.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 2877. Wiest, O.; Houk, K. N. *Top. Curr. Chem.* **1996**, 183 (Density Functional Theory IV), 1.

(16) Gaussian 94 and 98: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc., Pittsburgh, PA, 1995, 1998.

(17) SPARTAN (v. 5.0), Wavefunction, Inc., Irvine, CA.

(18) CAChe Scientific, Oxford Molecular, Beaverton, OR.

All minima had no negative eigenvalues of the Hessian and no imaginary frequencies. All first-order saddle points (transition structures) had one negative eigenvalue of the Hessian and one imaginary frequency. Single-point energies were calculated using the Becke three-parameter hybrid Hartree−Fock-DFT method[19] with a 6-31G(d) basis set. ZPE corrections scaled by 0.8929 were applied to the RHF/3-21G calculated energies. B3LYP/6-31G(d)//RHF3-21G and B3LYP/6-31G(d)//AM1 energies are uncorrected.

**General Procedure for Preparation of 3a−d and 13.** To triethyl phosphonoacetate, 2-phosphonopropionate, or 4-phosphono-(*E*)-crotonate (13.4 mmol) in dry THF (50 mL) was added potassium *tert*-butoxide (12 mL, 12 mmol, 1 M in THF) at 0−5 °C. The mixture was stirred at room temperature for 1 h. *N*-Boc-L-phenylalanal or *N*-Boc-L-valine (16.5 mmol) in THF (20 mL) was added slowly at 0−5 °C. Some inorganic salt precipitated as sticky material. The mixture was stirred at room temperature for 2 h. Sodium bicarbonate (5%, 100 mL) was added to quench the reaction. The mixture was extracted with ether (2 × 100 mL). The combined organic phase was dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography. The column was packed with silica gel using a mixture of benzene and hexanes (1:1). The sample was dissolved in the same solvent mixture for loading and was then eluted with 5−10% ethyl acetate in hexanes.

**(4*S*)-4-*N*-*tert*-Butoxycarbonylamino-5-phenyl-2-*trans*-pentenoic Acid, Ethyl Ester (3a).** An oil that solidified slowly was obtained in 75% yield: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.23−7.36 (m, 5H), 6.86−6.94 (m, 1H), 5.84 (d, 1H, $J$ = 17.3 Hz), 4.61 (m, 2H), 4.20 (q, 2H, $J$ = 7.2 Hz), 2.82−2.93 (m, 2H), 1.38 (s, 9H), 1.28 (t, 3H, $J$ = 7.2 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 166.2, 155.0, 147.6, 136.5, 129.4, 128.6, 126.9, 121.1, 79.9, 60.4, 52.3, 40.9, 28.3, 14.2. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.71; H, 7.84; N, 4.39. Found: C, 68.03; H, 7.86; N, 4.27.

**4-*S*-4-*N*-*tert*-Butoxycarbonylamino-5-phenyl-2-methyl-2-*trans*-pentenoic Acid, Ethyl Ester (3b).** An oil that solidified slowly was obtained in 26% yield. A side product, from cyclization of the cis isomer by attack of Boc-protected amino group on the ethyl ester to kick out the ethoxide group, was obtained in 27% yield using 20% ethyl acetate in hexanes as the eluent. For **3b**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.16−7.31 (m, 5H), 6.51−6.54 (m, 1H), 4.65 (m, 2H), 4.17 (q, 2H, $J$ = 7.0 Hz), 2.74−2.94 (m, 2H), 1.69 (d, 3H, $J$ = 1.2 Hz), 1.40 (s, 9H), 1.28 (t, 3H, $J$ = 7.0 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 167.6, 154.8, 140.1, 136.6, 129.4, 128.3, 128.2, 126.5, 79.5, 60.5, 50.2, 41.1, 28.2, 14.1, 12.5; HRMS calcd for $C_{19}H_{28}NO_4$ ($MH^+$) 334.2018, found 334.2021. Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.47; H, 8.11; N, 4.20; found: C, 68.44; H, 8.02; N, 4.11.

**4-*S*-4-*N*-*tert*-Butoxycarbonylamino-5-methyl-2-*trans*-hexenoic Acid, Ethyl Ester (3c).** An oil was obtained in 91% yield: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.51 (dd, 1H, $J$ = 5.6 Hz, 15.6 Hz), 5.57 (dd, 1H, $J$ = 1.5 Hz, 15.6 Hz, 4.80 (d, 1H, $J$ = 9.0 Hz), 3.81 (q, 2H, $J$ = 7.1 Hz), 1.45−1.53 (m, 1H), 1.06 (s, 9H), 5.25 (t, 3H, $J$ = 7.1 Hz), 0.56 (d, 3H, $J$ = 6.7 Hz), 0.55 (d, 3H, $J$ = 6.8 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 165.9, 155.2, 147.2, 121.1, 78.9, 60.0, 56.5, 32.0, 31.7, 28.0, 18.6, 17.8, 13.9; HRMS calcd for $C_{14}H_{25}NO_4$ ($MH^+$) 272.1862, found 272.1871.

**4-*S*-4-*tert*-Butoxycarbonylamino-2,5-dimethyl-2-*trans*-hexenoic Acid, Ethyl Ester (3d).** An oil was obtained in 56% yield. A side product from cyclization of the cis isomer by attack of Boc-protected amino group on the ethyl ester to kick out the ethoxide group was obtained in 37% yield using 15% ethyl acetate in hexanes as the eluent. For **3d**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.51 (dd, 1H, $J$ = 1.1 Hz, 9.2 Hz), 4.58 (s, broad, 1H), 4.20 (q, 2H, $J$ = 7.2 Hz), 1.93 (d, 3H, $J$ = 1.0 Hz), 1.71−1.81 (m, 1H), 1.43 (s, 9H), 0.95 (d, 3H, $J$ = 6.8 Hz), 0.91 (d, 3H, $J$ = 6.7 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 168.0, 155.3, 139.9,129.6, 79.3, 60.6, 53.9, 32.9, 28.4, 18.5, 18.4, 14.2, 13.0; HRMS calcd for $C_{15}H_{28}NO_4$ ($MH^+$) 286.2018, found 286.2014.

**(6*S*)-6-*N*-*tert*-Butoxycarbonylamino-7-methyl-*trans*,-*trans*-2,4-octadienoic Acid, Ethyl Ester (13).** Obtained in 69% yield from column chromatography: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.27 (dd, 1H, $J$ = 10.9 Hz, 15.3 Hz), 6.27 (dd, 1H, $J$ = 11.0 Hz, 15.1 Hz), 5.99 (dd, 1H, $J$ = 6.2 Hz, 15.3 Hz), 5.86 (d, 1H, $J$ = 15.4 Hz), 4.65 (d, broad, 1H, $J$ = 8.2 Hz), 4.19 (q, 2H, $J$ = 7.2 Hz), 1.76−1.85 (m, 1H), 1.45 (s, 9H), 1.29 (t, 3H, $J$ = 7.2 Hz), 0.92 (d, 3H, $J$ = 6.8 Hz), 0.90 (d, 3H, $J$ = 6.8 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 166.8, 155.3, 143.7, 141.8, 128.3, 121.0, 60.1, 57.3, 32.3, 28.3, 28.2, 18.6, 18.0, 14.1.

**General Procedure for Removal of Boc from 3a−d.** Compounds **3a−d** and **13** were treated with 20% trifluoroacetic acid in $CH_2Cl_2$ for 20 min. The mixture was evaporated, coevaporated twice with chloroform, and dried in vacuo to give TFA salts **4a−d** and **14**, which were not purified and characterized, and were used directly for benzylation, 2,4-dimethoxybenzylation, or acylation.

**General Procedure for Reductive Benzylation and 2,4-Dimethyoxybenzylation.** These reactions were performed by strictly following the procedure described in ref 20.

**(4*S*)-4-*N*-Benzylamino-5-phenyl-2-*trans*-pentenoic acid, ethyl ester (4e):** $^1$H NMR ($CD_3OD$) $\delta$ 7.10−7.29 (m, 10H), 6.76 (dd, 1H, $J$ = 8.2 Hz, 15.8 Hz), 5.75 (d, 1H, $J$ = 15.7 Hz), 4.14 (q, 2H, $J$ = 7.1 Hz), 3.75 (d, 1H, $J$ = 13.3 Hz), 3.56 (d, 1H, $J$ = 13.3 Hz), 3.45 (q, 1H, $J$ = 7.4 Hz), 2.72−2.91 (m, 2H), 1.25 (t, 3H, $J$ = 7.2 Hz); HRMS calcd for $C_{20}H_{24}NO_2$ ($MH^+$) 310.1807, found 310.1797.

**(4*S*)-4-*N*-Benzylamino-5-phenyl-2-methyl-2-*trans*-petenoic acid, ethyl ester (4f):** $^1$H NMR ($C_6D_6$) $\delta$ 6.97−7.24 (m, 10H), 6.81 (dd, 1H, $J$ = 1.2 Hz, 9.5 Hz), 3.94−4.07 (m, 2H), 3.51−3.60 (m, 2H), 3.36 (d, 1H, 13.5 Hz), 2.66 (dd, 1H, $J$ = 6.9 Hz, 13.3 Hz), 2.52 (dd, 1H, $J$ = 6.8 Hz, 13.3 Hz), 1.60 (d, 3H, $J$ = 1.0 Hz), 0.99 (t, 3H, $J$ = 7.2 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 167.8, 139.8, 137.6, 129.5, 129.3, 128.4, 128.3, 127.9, 127.3, 126.9, 126.4, 60.6, 56.6, 51.4, 41.3, 14.2, 12.5; HRMS calcd for $C_{21}H_{26}NO_2$ ($MH^+$) 324.1964, found 324.1958.

**(4*S*)-4-(*N*-2,4-Dimethoxybenzyl)amino-5-methyl-2-*trans*-hexenoic acid, ethyl ester (4g):** $^1$H NMR ($C_6D_6$, 300 MHz) $\delta$ 7.16 (d, 1H, $J$ = 8.0 Hz), 7.05 (dd, 1H, $J$ = 7.9 Hz, 15.9 Hz), 6.43 (d, 1H, $J$ = 2.2 Hz), 6.35 (dd, 1H, $J$ = 2.3 Hz, 8.2 Hz), 6.16 (d, 1H, $J$ = 15.9 Hz), 4.07 (q, 2H, $J$ = 7.2 Hz), 3.91 (d, 1H, $J$ = 13.3 Hz), 3.63 (d, 1H, $J$ = 13.4 Hz), 3.39 (s, 3H), 3.28 (s, 3H), 2.87 (t, 1H, $J$ = 7.0 Hz), 1.49−1.58 (m, 1H), 1.01 (t, 3H, $J$ = 7.3 Hz); $^{13}$C NMR ($C_6D_6$, 75 MHz) $\delta$ 166.1, 160.5, 159.0, 150.1, 130.6, 122.8, 121.6, 103.9, 99.0, 64.6, 60.0, 54.9, 54.7, 46.9, 32.7, 19.0, 18.6, 14.3; HRMS calcd for $C_{18}H_{28}NO_4$ ($MH^+$) 322.2018, found 322.2031.

**(4*S*)-4-*N*-Benzylamino-2,5-dimethyl-2-*trans*-hexanoic acid, ethyl ester (4h):** $^1$H NMR ($C_6D_6$, 300 MHz) $\delta$ 7.08−7.32 (m, 5H, 6.69 (dd, 1H, $J$ = 1.3 Hz, 10.1 Hz), 4.06 (q, 2H, $J$ = 7.1 Hz), 3.65 (d, 1H, $J$ = 13.4 Hz), 3.42 (d, 1H, $J$ = 13.5 Hz), 3.02 (dd, 1H, $J$ = 6.6 Hz, 10.2 Hz), 1.78 (d, 3H, $J$ = 1.3 Hz), 1.47−1.58 (m, 1H), 1.04 (t, 3H, $J$ = 7.1 Hz), 0.87 (d, 3H, $J$ = 6.7 Hz), 0.79 (d, 3H, $J$ = 6.8 Hz); $^{13}$C NMR ($C_6D_6$, 75 MHz) $\delta$ 167.6, 143.6, 141.1, 129.9, 128.4, 127.0, 126.9, 60.8, 60.5, 51.5, 33.3, 19.3, 18.6, 14.3, 13.3; HRMS calcd for $C_{17}H_{26}NO_2$ ($MH^+$) 276.1964, found 276.1973.

**(4*S*)-4-(*N*-2,4-Dimethoxybenzyl)amino-2,5-dimethyl-2-*trans*-hexenoic acid, ethyl ester (4i):** $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.05 (d, 1H, $J$ = 8.1 Hz), 6.61 (dd, 1H, $J$ = 1.3 Hz, 9.9 Hz), 6.38−6.48 (m, 2H), 4.20 (q, 2H, $J$ = 7.1 Hz), 3.80 (s, 3H), 3.79 (s, 3H), 3.75 (d, 1H, $J$ = 13.6 Hz), 3.48 (d, 1H, $J$ = 13.4 Hz), 3.13 (dd, 1H, $J$ = 6.4 Hz, 9.9 Hz), 1.79 (d, 3H, $J$ = 1.2 Hz), 1.67−1.79 (m, 1H), 1.31 (t, 3H, $J$ = 7.1 Hz), 0.91 (d, 3H, $J$ = 6.7 Hz), 0.86 (d, 3H, $J$ = 6.8 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 167.9, 159.9, 158.5, 143.8, 130.3, 129.2, 120.7, 103.4, 98.3, 60.5, 60.3, 55.1, 55.0, 47.0, 32.7, 19.1, 18.4, 14.1, 13.1; HRMS calcd for $C_{19}H_{30}NO_4$ ($MH^+$) 336.2175, found 336.2183.

**(6*S*)-6-*N*-Benzylamino-7-methyl-*trans*,*trans*-2,4-octadienoic acid, ethyl ester (15):** $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.21−7.37 (m, 6H), 6.24 (dd, 1H, $J$ = 11.0 Hz, 15.2 Hz), 5.94 (dd, 1H, $J$ = 8.4 Hz, 15.3 Hz), 5.86 (d, 1H, $J$ = 15.3 Hz), 4.21 (q, 1H, $J$ = 7.1 Hz), 3.80 (d, 1H, $J$ = 13.3 Hz), 3.59 (d, 1H, $J$

(19) Becke, A. D. *J. Chem. Phys.* **1993**, 98, 5648.

(20) Szardemings, A. K.; Burkoth, T. S.; Look, G. C.; Campbell, D. A. *J. Org. Chem.* **1996**, *61*, 6720.

= 13.3 Hz), 2.90 (dd, 1H, $J$ = 6.0 Hz, 8.3 Hz), 1.68−1.79 (m, 1H), 1.30 (t, 3H, $J$ = 7.2 Hz), 0.93 (d, 3H, $J$ = 6.8 Hz), 0.88 (d, 3H, $J$ = 6.8 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 167.0, 144.5, 144.2, 140.5, 129.9, 128.3, 128.0, 126.8, 120.5, 65.5, 60.2, 51.4, 32.6, 19.3, 18.4, 14.3; LC−MS calcd for $C_{16}H_{28}NO_4$ ($MH^+$) 298, found 298.

**General Procedure for Acylation with Hexadienoyl Chloride.** An amine or benzylated amine compound (**4a**−**i**, 1 mmol) in dry THF (20 mL) was treated with triethylamine (0.3 mL) and hexadienoyl chloride (0.2 mL, ∼1.6 equiv) at 0−5 °C. The mixture was stirred at room temperature for 20 min, quenched with 10% sodium carbonate (50 mL), and stirred for another 0.5 h, followed by extraction with ether (100 mL). The ether layer was washed again with 10% sodium carbonate (40 mL), brine (50 mL), and water (2 × 50 mL), dried over sodium sulfate, and evaporated. The residue was dried under high vacuum for 0.5 h before column purification for **1a**−**e** and **2a**. For **2b**−**f**, the crude residue was not purified and was directly dissolved in chloroform for the Diels−Alder reaction to complete.

**(4*S*)-4-[*N*-Benzyl-*N*-(3,5-hexadienoyl)amino]-5-phenyl-2-*trans*-pentenoic acid, ethyl ester (1b):** $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.95−7.54 (m, 11H), 5.67−6.37 (m, 4H), 4.98−5.17 (m, 3H), 4.43 (d, 1H, $J$ = 17.3 Hz), 4.16 (d, 1H, $J$ = 17.0 Hz), 4.13 (t, 2H, $J$ = 7.2 Hz), 2.88−3.21 (m, 4H), 1.24 (t, 3H, $J$ = 7.1 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 171.7, 165.8, 145.2, 137.1, 136.6, 136.3, 136.2, 134.4, 133.8, 129.1, 128.7, 128.4, 127.7, 127.5, 127.0, 126.6, 126.4, 125.3, 122.7, 116.9, 116.5, 60.3, 58.6, 50.2, 38.1, 37.7, 14.0; HRMS calcd for $C_{26}H_{30}NO_3$ ($MH^+$) 404.2226, found 404.2242.

**(4*S*)-4-[*N*-Benzyl-*N*-(3,5-hexadienoyl)amino]-5-phenyl-2-methyl-2-*trans*-pentenoic acid, ethyl ester (1c):** $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.05−7.33 (m, 10H), 6.79 (d, 1H, $J$ = 9.5 Hz), 6.30 (dt, 1H, $J$ = 10.2 Hz, 10.2 Hz, 17.0 Hz), 5.96 (dd, 1H, $J$ = 10.4 Hz, 15.3 Hz), 5.67−5.80 (m, 1H), 5.34 (q, 1H, $J$ = 8.4 Hz), 5.00−5.5.16 (m, 2H), 4.49 (d, 1H, $J$ = 17.6 Hz), 4.35 (d, 1H, $J$ = 17.6 Hz), 4.10 (q, 2H, $J$ = 7.1 Hz), 3.03−3.15 (m, 3H), 2.81 (dd, 1H, $J$ = 8.4 Hz, $J$ = 13.4 Hz), 1.59 (s, 3H), 1.20 (t, 1H, $J$ = 7.2 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 171.5, 167.4, 137.4, 137.2, 136.4, 133.6, 130.9, 129.2, 128.7, 128.3, 127.4, 126.9, 126.5, 126.1, 116.4, 60.5, 55.2, 49.3, 39.0, 38.2, 14.0, 12.6; HRMS calcd for $C_{27}H_{32}NO_3$ ($MH^+$) 418.2382, found 418.2388.

**(4*S*)-4-[*N*-(2,4-Dimethoxybenzyl)-*N*-(3,5-hexadienoyl)-amino]-5-methyl-2-*trans*-hexenoic acid, ethyl ester (1d):** $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.92 (d, 1H, $J$ = 8.0 Hz), 6.80 (dd, 1H, $J$ = 9.2 Hz, 15.8 Hz), 6.27−6.43 (m, 3H), 5.81−6.09 (m, 2H), 5.72 (d, 1H, $J$ = 15.7 Hz), 4.90−5.18 (m, 2H), 4.45 (d, 1H, $J$ = 17.1 Hz), 4.35 (d, 1H, $J$ = 17.2 Hz), 4.11 (q, 2H, $J$ = 7.2 Hz), 3.81 (s, 3H), 3.79 (s, 3H), 3.12−3.27 (m, 3H), 2.17−2.29 (m, 1H), 1.22 (t, 3H, $J$ = 7.1 Hz), 0.86 (d, 3H, $J$ = 6.8 Hz), 0.83 (d, 3H, $J$ = 6.8 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 171.7, 165.9, 160.4, 157.7, 144.8, 136.5, 133.5, 128.8, 127.4, 123.7, 117.0, 116.1, 103.7, 98.3, 63.5, 60.0, 55.2, 55.0, 45.3, 37.9, 28.9, 20.1, 19.3, 14.0; HRMS calcd for $C_{24}H_{34}NO_5$ ($MH^+$) 416.2437, found 416.2453.

**(4*S*)-4-[*N*-Benzyl-*N*-(3,5-hexadienoyl)amino]-2,5-dimethyl-2-*trans*-hexenoic acid, ethyl ester (1e):** $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.09−7.32 (m, 5H), 6.52 (d, 1H, $J$ = 10,3 Hz), 6.31 (dt, 1H, $J$ = 10.1 Hz, 10.1 Hz, 16.9 Hz), 5.78−6.03 (m, 2H), 4.96−5.17 (m, 3H), 4.60 (d, 1H, $J$ = 17.7 Hz), 4.46 (d, 1H, $J$ = 17.7 Hz), 4.00−4.12 (m, 2H), 3.14 (dd, 1H, $J$ = 7.1 Hz, 16.2 Hz), 3.03 (dd, 1H, $J$ = 6.3 Hz, 16.2 Hz), 1.95−2.05 (m, 1H), 1.89 (d, 3H, $J$ = 1.0 Hz), 1.15 (t, 3H, $J$ = 7.2 Hz), 0.94 (d, 3H, $J$ = 6.6 Hz), 0.86 (d, 3H, $J$ = 6.6 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 171.7, 167.4, 138.1, 137.4, 136.4, 133.6, 131.4, 128.5, 127.2, 127.1, 126.0, 116.3, 60.3, 58.0, 48.1, 38.0, 30.4, 19.4, 19.1, 14.0, 13.3; HRMS calcd for $C_{23}H_{32}NO_3$ ($MH^+$) 370.2382, found 370.2369.

**(4*S*)-4-(*N*-2,4-Hexadienoylamino)-5-phenyl-2-methyl-2-*trans*-pentenoic acid, ethyl ester (2a):** $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.08−7.29 (m, 6H), 6.57 (dd, 1H, $J$ = 1.3 Hz, 9.6 Hz), 6.00−6.20 (m, 2H), 5.73 (d, 1H, $J$ = 15.1 Hz), 5.04−5.14 (m, 2H), 4.15 (q, 2H, $J$ = 7.0 Hz), 2.99 (dd, 1H, $J$ = 6.0 Hz, 13.4 Hz), 2.83 (dd, 1H, $J$ = 7.5 Hz, 13.5 Hz), 1.81 (d, 3H, $J$ = 5.4 Hz), 1.73 (s, 3H), 1.26 (t, 3H, $J$ = 7.2 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 167.6, 165.6, 141.4, 139.4, 137.8, 136.6, 129.9, 129.5, 129.3, 128.3, 126.6, 121.1, 60.6, 48.7, 40.6, 18.4, 14.0, 12.6; HRMS calcd for $C_{20}H_{25}NO_3$ ($MH^+$) 328.1913, found 328.1907.

**(4*S*)-4-(*N*-Benzyl-*N*-hexa-2′,4′-dienyl)amino-2,5-dimethyl-2-*trans*-hexanoic Acid, Ethyl Ester (2h).** To a solution of **4h** (154 mg, 0.56 mmol) in methylene chloride (10 mL) was added hexa-2,4-dienal (0.120 mL, 1.10 mmol), acetic acid (0.2 mL), and sodium triacetoxyborohydride (300 mg, 1.42 mmol) in sequence under nitrogen. The mixture was stirred overnight, quenched with 10% aqueous sodium bicarbonate, and separated between 10% aqueous sodium bicarbonate and methylene chloride. The organic phase was dried over sodium sulfate and concentrated. The residue was purified by column chromatography using a mixture of hexanes and benzene (1:1) to give **2h** (108 mg, 54%). Further elution with benzene gave the cycloaddition products **9h** (19 mg) and **10h** (9 mg). Compound **4h** (21 mg, 14%) was recovered. For **2h**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.7.19−7.36 (m, 5H), 6.72 (dd, 1H, $J$ = 11.0 Hz, 1.3 Hz), 5.97−6.16 (m, 2H), 5.50−5.69 (m, 2H), 4.23 (q, 2H, $J$ = 7.1 Hz), 3.91 (d, 1H, $J$ = 14.2 Hz), 3.19−3.39 (m, 2H), 3.00 (t, 1H, $J$ = 10.4 Hz), 2.83 (dd, 1H, $J$ = 14.4 Hz, 8.5 Hz), 1.80−1.88 (m, 1H), 1.74 (d, 3H, $J$ = 4.4 Hz), 1.73 (d, 3H, $J$ = 1.1 Hz), 1.34 (t, 3H, $J$ = 7.3 Hz), 1.08 (d, 3H, $J$ = 6.5 Hz), 0.73 (d, 3H, $J$ = 6.6 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 167.9, 140.4, 139.9, 132.2, 131.1, 130.7, 129.7, 128.3, 128.1, 128.0, 126.5, 63.0, 60.5, 53.6, 51.4, 29.7, 20.1, 19.9, 17.9, 14.2, 13.3.

**(4*S*)-4-*N*-Hexa-2′,4′-dienyl-2,5-dimethyl-2-*trans*-hexanoic Acid, Ethyl Ester (2i).** Compound **3d** (600 mg, 2.11 mmol) was treated with 20% TFA in methylene chloride (30 mL) for 20 min. The mixture was evaporated to a residue, pumped overnight, and treated by following the procedure to make **2h**. Compound **2i** was purified by elution with 5−8% ethyl acetate in hexane from column chromatography in 410 mg, 73%: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.52 (dd, 1H, $J$ = 10.2 Hz, 1.2 Hz), 5.99−6.13 (m, 2H), 5.53−5.67 (m, 2H), 4.20 (q, 2H, $J$ = 7.1 Hz), 3.18−3.32 (m, 2H), 3.04 (dd, $J$ = 13.8 Hz, 7.1 Hz), 1.85 (d, 3H, $J$ = 1.2 Hz), 1.72−1.80 (m, 1H), 1.74 (d, 3H, $J$ = 6.7 Hz), 1.31 (t, 3H, $J$ = 7.2 Hz), 0.95 (d, 3H, $J$ = 6.7 Hz), 0.88 (d, 3H, $J$ = 6.9 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 167.9, 143.0, 131.8, 131.0, 129.5, 129.3, 128.6, 60.7, 60.5, 49.2, 32.9, 19.3, 18.3, 17.9. 14.2, 13.1.

**(6*S*)-6-(*N*-Benzyl-*N*-*trans*-crotonylamino)-7-methyl-*trans,trans*-2,4-octadienoic Acid, Ethyl Ester (16).** Compound **15** in dry THF was treated with triethylamine and *trans*-crotonyl chloride by following the general procedure for acylation with hexadienoyl chloride. The product was purified by column chromatography and eluted with 5−10% ethyl acetate in hexanes to give **16** in 84% yield: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.91−7.32 (m, ∼7H), 5.89−6.22 (m, 3H), 5.78 (d, 1H, $J$ = 15.4 Hz), 4.46−4.58 (m, 3H), 4.17 (q, 2H, $J$ = 7.1 Hz), 2.05−2.17 (m, 1H), 1.79 (d, 3H, $J$ = 6.6 Hz), 1.27 (t, 3H, $J$ = 6.5 Hz), 0.91 (d, 3H, $J$ = 6.7 Hz), 0.97 (d, 3H, $J$ = 6.5 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 167.3, 166.8, 143.7, 142.7, 140.1, 137.7, 131.5, 128.6, 127.4, 126.6, 122.5, 121.6, 64.6, 60.3, 49.4, 29.7, 20.2, 19.6, 18.2, 14.2; HRMS calcd for $C_{22}H_{30}NO_3$ ($MH^+$) 356.2226, found 356.2217.

**Diels−Alder Reaction To Make Compounds 5b, 6b, 7b, and 8b.** Triene **1b** (92 mg, 0.23 mmol) in toluene (10 mL) was heated under nitrogen at reflux for 16 h. Toluene was removed in vacuo. The residue was purified by slow column chromatography without air pressure: 8% ethyl acetate in hexanes to elute the fast isomer (14 mg, **6b**, pure); 10% ethyl acetate in hexanes to elute a second fraction (5 mg, **8b**, not pure, containing other isomers); 15−20% ethyl acetate in hexanes to elute a third fraction (66 mg as a mixture of **5b** and **7b** with no separation, $^1$H NMR showed a ratio of 3:1). The overall estimated ratio is **5b**:**6b**:**7b**:**8b** = 33:10:11:3, and the total yield is 94%. The fraction for the mixture of **5b** and **7b** was purified in a second round column chromatography using 12% ethyl acetate in hexanes to elute slowly without air pressure. The very initial fractions that were positive in an iodine chamber were identified as **5b** (6 mg). The last half portion of the eluent was combined to give 16 mg (**5b**:**7b** ∼ 1:1), which was purified

in a third round of column chromatography similarly to give **7b** (2 mg) by collecting the very last small fraction.

For **5b**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.11−7.33 (m, 10H), 5.66−5.74 (m, 1H), 5.52−5.61 (m, 1H), 3.29 (d, 1H, $J$ = 14.6 Hz), 3.79−3.90 (m, 2H), 3.59−3.70 (m, 2H), 3.02 (dd, 1H, $J$ = 4.9 Hz, 13.9 Hz), 2.63−2.83 (m, 3H), 2.44 (dt, 1H, $J$ = 6.1 Hz, 10.3 Hz, 10.3 Hz, for H8), 2.26 (dd, 1H, $J$ = 9.1 Hz, 18.0 Hz), 2.09−2.17 (m, 2H), 1.96−2.08 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 174.1, 168.6, 137.6, 137.3, 129.6, 129.1, 128.9, 128.7, 128.6, 127.5, 126.8, 124.6, 60.4, 58.9, 48.6, 40.0, 38.6, 35.6, 34.9, 28.6, 27.8, 13.9; obsd NOE ($CD_3OD$, 270 K, 400 MHz) between H4a and H8a (may be between H7 and H8a due to overlapping of H4a and H7), no NOE between H1 and H8a, H4a and H8, H1 and H4a, H8 and H8a; HRMS calcd for $C_{26}H_{30}NO_3$ ($MH^+$) 404.2226, found 404.2242.

For **6b**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.08−7.34 (m, 10H), 5.65 (d, 1H, $J$ = 14.7 Hz), 5.59−6.64 (m, 1H), 5.39 (d, broad, 1H, $J$ = 9.6 Hz), 4.05−4.19 (m, 2H), 3.75 (d, 1H, $J$ = 14.8 Hz), 3.62 (dt, 1H, $J$ = 6.9 Hz, 3.6 Hz, 3.6 Hz, H1), 3.18 (dd, 1H, $J$ = 3.8 Hz, 14.1 Hz), 2.34−2.45 (m, 3H), 2.20−2.31 (m, 2H), 2.02−2.11 (m, 1H), 1.81 (dt, 1H, $J$ = 6.9 Hz, 10.8 Hz, 10.8 Hz, for H8a), 1.21 (t, 3H, $J$ = 7.2 Hz), 1.06 (dd, 1H, $J$ = 13.7 Hz, 15.9 Hz for H7′); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 175.3, 173.2, 137.5, 136.2, 131.0, 129.3, 129.1, 129.9, 128.5, 127.9, 127.4, 126.2, 61.2, 57.4, 47.0, 45.8, 41.7, 38.6, 37.9, 35.4, 30.3, 14.6; obsd NOE ($CDCl_3$, 400 MHz) between H1 and H4a, H4 and H8a, between H1 and H8a, H8 and H8a, no NOE between H4a and H8a; HRMS calcd for $C_{26}H_{30}NO_3$ ($MH^+$) 404.2226, found 404.2221.

For **7b**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.92−7.33 (m, 10H), 5.62−5.74 (m, 1H), 5.46−5.54 (m, 1H), 5.34 (d, 1H, $J$ = 15.1 Hz), 3.84−3.93 (m, 2H), 3.72 (dt, 1H, $J$ = 4.3 Hz, 4.3 Hz, 8.6 Hz, H1), 3.10 (dd, 1H, $J$ = 3.7 Hz, 13.9 Hz), 3.00 (d, 1H, $J$ = 15.1 Hz), 2.56−2.72 (m, 3H), 2.12−2.38 (m, 3H), 1.97 (dt, 1H, $J$ = 4.1 Hz, 11.5 Hz, 11.5 Hz, H8a), 1.01 (t, 3H, $J$ = 7.1 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 173.9, 169.7, 138.9, 137.4, 129.6, 129.1, 128.8, 128.3, 128.0, 127.8, 127.5, 127.1, 124.8, 60.9, 58.7, 49.2, 42.7, 42.5, 38.0, 37.5, 30.3, 29.6, 14.2; obsd NOE ($CDCl_3$, 400 MHz) between H1 and H8a, between H4a and H-$R_1$, no NOE between H4a and H8a; $^1$H decoupling NMR ($CDCl_3$, 400 MHz) at 1.97 gave $J_{8a-1}$ = 4.3 Hz; HRMS calcd for $C_{26}H_{30}NO_3$ ($MH^+$) 404.2226, found 404.2239.

**Diels−Alder Reaction To Make Compounds 5c and 6c.** Triene **1c** (116 mg, 0.28 mmol) in toluene (10 mL) was heated under nitrogen at reflux for 50 h. Toluene was removed in vacuo. The residue was purified by slow column chromatography without air pressure: a mixture of benzene and hexanes (1:1) was used to pack column and load the sample; 5% and then 10% ethyl acetate in hexanes to elute the unreacted starting material (9 mg, 8%); 15% ethyl acetate in hexanes to elute the fast isomer **6c** (24 mg, 21%, oil); 20% and 30% ethyl acetate in hexanes to elute a second fraction **5c** (74 mg, 64%, oil).

For **5c**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.18−7.38 (m, 10 H), 5.50 (d, 1H, $J$ = 14.4 Hz), 5.37−5.42 (m, 1H), 5.30 (d, broad, 1H, $J$ = 10.3 Hz), 4.02 (q, 2H, $J$ = 7.1 Hz), 3.46 (d, 1H, $J$ = 14.4 Hz), 3.27−3.32 (m, 1H, H1), 3.03 (dd, 1H, $J$ = 6.5 Hz, 13.4 Hz), 2.79 (dd, 1H, $J$ = 5.0 Hz,13.4 Hz), 2.63 (s, broad, 2H, H4a and H8a), 2.24 (dd, 1H, $J$ = 2.8 Hz, 15.5 Hz), 2.04 (dd, 1H, $J$ = 4.4 Hz, 18.1 Hz), 1.91 (dd, 1H, $J$ = 4.3 Hz, 15.5 Hz), 1.16 (t, 3H, $J$ = 7.0 Hz), 0.76 (s, 3H), 0.63 (dd, 1H, $J$ = 2.4 Hz, 17.9 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 176.2, 170.3, 136.7, 136.6, 130.1, 129.6, 128.6, 128.5, 128.1, 127.6, 127.2, 127.0, 60.5, 54.9, 47.4, 45.1, 42.6, 40.5, 36.4, 31.3, 29.4, 23.2, 13.8; obsd NOE ($CD_3OD$, 400 MHz) between H4a and H8a, H1 and Me8, H1 and H7; HRMS calcd for $C_{27}H_{32}NO_3$ ($MH^+$) 418.2382, found 418.2388.

For **6c**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.08−7.36 (m, 10 H), 5.64 (d, 1H, $J$ = 14.7 Hz), 5.55−5.60 (m, 1H), 5.36 (d, broad, 1H, $J$ = 10.7 Hz), 4.08−4.27 (m, 2H), 3.58 (d, 1H, $J$ = 14.5 Hz), 3.49−3.54 (m, 1H, H1), 3.07 (dd, 1H, $J$ = 3.7 Hz, 14.0 Hz), 2.86 (d, broad, 1H, $J$ = 19.6 Hz), 2.30 (dd, 1H, $J$ = 4.4 Hz, 14.0 Hz), 2.20 (dd, 1H, $J$ = 1.9 Hz, 15.6 Hz), 1.85−2.01 (m, 3H), 1.29 (t, 3H. $J$ = 7.2 Hz), 0.98 (dd, 1H, $J$ = 12.7 Hz, 15.4 Hz), 0.69 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 177.0, 173.5, 137.6, 136.5, 131.0, 129.0, 129.0, 128.9, 128.3, 128.0, 127.5, 125.8, 61.4, 55.0, 47.2, 45.2, 44.5, 38.8, 38.2, 37.4, 31.7, 16.2, 14.5; obsd NOE ($CD_3OD$, 400 MHz) between H1 and Me8, and between H4a and Me8; HRMS calcd for $C_{27}H_{32}NO_3$ ($MH^+$) 418.2382, found 418.2382.

**Diels−Alder Reaction To Make Compounds 5d and 6d.** Triene **1d** (148 mg, 0.36 mmol) in toluene (20 mL) was heated under nitrogen at reflux for 16 h. Toluene was removed in vacuo. $^1$H NMR of the mixture showed two isomeric products in a 3:1 ratio. The residue was purified by slow column chromatography without air pressure: a mixture of benzene and hexanes (1:1) was used to pack the column and load the sample; 10% ethyl acetate in hexanes to elute a fast unknown; 15% ethyl acetate in hexanes to elute the fast isomer **6d** (28 mg, 19%), and the slow isomer **5d** (82 mg, 55%).

For **5d**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.20 (d, 1H, $J$ = 8.2 Hz), 6.39−6.44 (m, 2H), 5.25 (d, 1H, $J$ = 14.4 Hz), 3.96−4.07 (m, 2H), 3.75−3.88 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.10 (dd, 1H, $J$ = 1.0 Hz, 4.4 Hz, H1), 2.76 (s, broad, 1H, H4a), 2.60 (dd, 1H, $J$ = 7.4 Hz, 17.3 Hz), 2.32−2.51 (m, 2H), 2.07−2.28 (m, 3H), 1.94 (d, broad, 1H, $J$ = 18.1 Hz), 1.14 (t, 3H, $J$ = 7.2 Hz), 1.00 (d, 3H, $J$ = 7.3 Hz), 0.98 (d, 3H, $J$ = 7.0 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 174.4, 169.3, 160.2, 158.6, 132.0, 129.6, 125.0, 117.9, 104.3, 98.1, 62.1, 60.4, 55.32, 55.27, 41.6, 40.3, 36.1, 33.0, 31.5, 28.9, 26.8, 19.9, 18,4, 14.0; obsd NOE ($CDCl_3$, 400 MHz) between H1 and H7 and between H4a and Me of i-Pr.

For **6d**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.23 (d, 1H, $J$ = 9.0 Hz), 6.41−6.44 (m, 2H), 5.63−5.69 (m, 1H), 5.48 (d, broad, $J$ = 9.8 Hz), 5.04 (d, 1H, $J$ = 14.2 Hz), 4.03−4.20 (m, 2H), 3.95 (d, 1H, $J$ = 14.2 Hz), 3.85 (s, 3H), 3.79 (s, 3H), 3.77−3.80 (m, 1H, H1), 2.34−2.59 (m, 3H), 2.18−2.33 (m, 1H), 1.98−2.08 (m, 2H), 1.73 (m, 1H, $J$ = 7.2 Hz), 1.57 (dt, 1H, $J$ = 6.7 Hz, 10.5 Hz, 10.5 Hz, H8a), 1.28 (t, 3H, $J$ = 7.1 Hz), 1.09 (d, 3H, $J$ = 7.3 Hz), 0.84 (d, 3H, $J$ = 6.7 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 174.6, 173.0, 160.0, 158.4, 131.8, 129.1, 125.5, 118.1, 103.6, 98.2, 63.3, 60.6, 55.2, 54.9, 46.4, 46.1, 44.6, 39.2, 35.8, 35.6, 30.0, 22.5, 15.7, 14.0; HRMS calcd for $C_{24}H_{33}NO_5$ ($MH^+$) 416.2437, found 416.2437.

**Diels−Alder Reaction To Make Compounds 5e and 6e.** Triene **1e** (150 mg, 0.41 mmol) in toluene (20 mL) was heated under nitrogen at reflux for 6 days. Toluene was removed in vacuo. $^1$H NMR showed two isomers in a 2.5:1 ratio. The residue was purified by slow column chromatography without air pressure: a mixture of benzene and hexanes (1:1) was used to pack column and load the sample; 5% ethyl acetate in hexanes to elute the fast minor isomer **6e** (31 mg, 21%); 10% ethyl acetate in hexanes to elute the slow isomer **5e** (67 mg, 45%).

For **5e**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.24−7.31 (m, 5H), 5.64 (d, 1H, $J$ = 14.3 Hz), 5.27−5.37 (m, 2H), 4.00−4.09 (m, 2H), 3.62 (d, 1H, $J$ = 14.4 Hz), 3.02 (dd, 1H, $J$ = 3.0 Hz, 5.2 Hz, H1), 2.77 (s, broad, 1H, H4a), 2.61 (dd, 1H, $J$ = 5.4 Hz, 15.8 Hz), 2.50 (d, broad, 1H, $J$ = 6.6 Hz, H8a), 2.37 (dd, 1H, $J$ = 3.5 Hz, 15.7 Hz), 1.97−2.08 (m, 2H), 1.17 (t, 3H, $J$ = 7.1 Hz), 1.13 (d, 3H, $J$ = 7.1 Hz), 1.04 (d, 3H, $J$ = 6.9 Hz), 0.99 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 176.6, 170.9, 136.9, 129.8, 128.4, 127.9, 127.5, 127.4, 60.5, 59.5, 49.4, 45.5, 40.5, 36.9, 36.3, 31.7, 29.9, 23.7, 21.4, 18.6, 13.9; coupling constants, 0 Hz between H4a and H8a, 5.2−6.6 Hz between H1 and H8a (not accurate due to broadness); obsd NOE ($CDCl_3$, 400 MHz) between H1 and H7, H1 and Me8, H4a and H8a. HRMS calcd for $C_{23}H_{32}NO_3$ ($MH^+$) 370.2382, found 370.2383.

For **6e**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.23−7.36 (m, 5H), 5.66 (d, 1H, $J$ = 13.5 Hz), 5.60−5.66 (m, 1H), 5.48 (d, broad, 1H, $J$ = 9.9 Hz), 3.97−4.13 (m, 2H), 3.75 (d, 1H, $J$ = 11.6 Hz), 3.40 (dd, 1H, $J$ = 0.9 Hz, 6.7 Hz, H1), 2.86 (d, broad, 1H, $J$ = 17.4 Hz), 2.55 (d, 1H, $J$ = 13.1 Hz), 2.00−2.18 (m, 2H), 1.86 (dd, 1H, $J$ = 4.7 Hz, 18.3 Hz), 1.64 (dd, 1H, $J$ = 6.8 Hz, 11.2 Hz, H8a), 1.52 (m, 1H, $J$ = 7.0 Hz), 1.24 (t, 3H, $J$ = 7.1 Hz), 1.13 (d, 3H, $J$ = 7.3 Hz), 0.86 (d, 3H, $J$ = 6.7 Hz), 0.67 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 176.5, 173.5, 137.5, 128.6, 128.5, 127.7, 127.5, 60.9, 59.7, 49.4, 48.6, 44.1, 38.9, 36.9, 36.3, 31.9, 23.7, 15.9, 15.5, 13.9; obsd NOE ($CDCl_3$, 400 MHz) between H1 and Me8, H4a and Me8.

**Diels−Alder Reaction To Make Compounds 9a and 10a.** Triene **2a** (96 mg, 0.29 mmol) in toluene (10 mL) was heated under nitrogen at reflux for 7 h. Toluene was removed in vacuo. The residue was purified by slow column chromatography without air pressure: the fast isomer was eluted with 0.5% methanol in methylene chloride to give **9a** (65 mg, 68%). The slow isomer was eluted with 1% methanol in methylene chloride to give **10a** (21 mg, 22%).

For **9a**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.14−7.35 (m, 5H), 6.09 (dt, 1H, $J$ = 2.1 Hz, 2.1 Hz, 9.7 Hz), 5.60 (dt, 1H, $J$ = 3.4 Hz, 3.4 Hz, 9.7 Hz), 5.23 (s, broad, 1H), 4.11−4.28 (m, 2H), 3.74 (ddd, 1H, $J$ = 3.4 Hz, 9.8 Hz, 12.3 Hz, H3), 3.12 (dd, 1H, $J$ = 3.2 Hz, 13.9 Hz), 2.82 (dd, 1H, $J$ = 2.5 Hz, 13.2 Hz, H7a), 2.51 (dd, 1H, $J$ = 12.5 Hz, 13.2 Hz), 2.45 (dd, 1H, $J$ = 9.3 Hz, 13.2 Hz, H3a), 2.18−2.22 (m, 1H), 1.37 (s, 3H), 1.32 (t, 3H, $J$ = 7.1 Hz), 1.01 (d, 3H, $J$ = 7.3 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 175.0, 173.9, 137.9, 133.0, 128.9, 128.6, 126.9, 121.8, 60.6, 56.0, 48.9, 46.3, 43.2, 41.7, 40.5, 18.2, 17.9, 14.0; $^1$H NMR coupling constants, 13.2 Hz between H3a and H7a, 9.3−9.8 Hz between H3 and H3a; HRMS calcd for $C_{20}H_{26}NO_3$ ($MH^+$) 328.1913, found 328.1915.

For **10a**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.13−7.34 (m, 5H), 5.93 (dt, 1H, $J$ = 3.3 Hz, 3.3 Hz, 9.9 Hz), 5.69 (d, 1H, NH), 5.50 (dt, 1H, $J$ = 2.1 Hz, 2.1 Hz, 9.9 Hz), 4.01−4.09 (m, 1H), 3.83−3.95 (m, 1H), 3.52 (t, broad, 1H, $J$ = 6.8 Hz, H3), 3.04 (dd, 1H, $J$ = 3.2 Hz, 8.9 Hz, H7a), 2.88 (d, 1H, $J$ = 8.9 Hz, H3a), 2.72−2.82 (m, 2H), 2.63−2.72 (m, 1H), 1.22 (t, 3H, $J$ = 7.2 Hz), 0.93 (s, 3H), 0.91 (t, 3H, $J$ = 7.3 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 176.03, 175.97, 136.9, 132.3, 129.2, 128.6, 126.7, 121.5, 60.7, 55.5, 48.1, 44.9, 42.2, 39.2, 35.8, 15.9, 14.2, 10.1; obsd NOE ($CDCl_3$, 400 MHz) between H3a and H7a, H3 and Me4, H3a and H5; HRMS calcd for $C_{20}H_{25}NO_3$ ($M^+$) 327.1834, found 327.1829.

**Diels−Alder Reaction To Make Compounds 9b and 11b.** The crude triene **2b**, prepared from **4e** (90 mg, 0.29 mmol) by following the general procedure for acylation, was dissolved in chloroform and kept in the dark. The Diels−Alder reaction was monitored by $^1$H NMR (a small part of the solution was taken in a separate flask; chloroform was blown away with nitrogen; the residue was dissolved in $CDCl_3$). The cycloaddition was complete in 12 h. $^1$H NMR showed an isomeric product ratio of 10:10:1:1. The residue was purified by slow column chromatography without air pressure: a mixture of benzene and hexanes (1:1) was used to pack column and load the sample; 5% ethyl acetate in hexanes to elute the fast isomer **9b** (46 mg, 39%); 8% ethyl acetate in hexanes to elute a second pure isomer **11b** (6 mg) and a third fraction of **11b** (44 mg) containing minor **10b** and **12b**.

For **9b**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.50−7.36 (m, 10H), 6.15 (d, 1H, $J$ = 9.6 Hz), 5.55 (dt, 1H, $J$ = 3.3 Hz, 9.7 Hz), 5.11 (d, 1H, $J$ = 15.3 Hz), 3.96−4.16 (m, 3H), 3.68 (ddd, 1H, $J$ = 3.1 Hz, 5.8 Hz, 9.0 Hz, H3), 3.39 (dd, 1H, $J$ = 3.0 Hz, 15.6 Hz), 3.01 (dd, 1H, $J$ = 5.7 Hz, 15.7 Hz), 2.93 (dd, 1H, $J$ = 6.6 Hz, 11.0 Hz, H4), 2.70−2.87 (m, 2H), 2.12 (dt, 1H, 9.9 Hz, 11.2 Hz, 11.2 Hz, H3a), 1.21 (t, 3H, $J$ = 7.2 Hz), 0.95 (d, 3H, $J$ = 7.2 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 173.0, 172.6, 137.7, 136.7, 133.2, 129.5, 128.5, 128.3, 127.7, 127.2, 126.4, 123.0, 60.4, 59.8, 48.7, 47.7, 44.2, 39.6, 36.2, 34.1, 17.4, 14.2; obsd NOE: between H3a and Me5, H4 and H5, H3 and H4, H3 and H7a, H3 and H3a, H3a and H4; HRMS calcd for $C_{26}H_{30}NO_3$ ($MH^+$) 404.2226, found 404.2241.

For **11b**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$_6.90−7.34 (m, 10 H), 6.12 (d, 1H, $J$ = 9.8 Hz), 5.58 (dt, 1H, $J$ = 3.4 Hz, 3.4 Hz, 9.8 Hz), 4.95 (d, 1H, $J$ = 14.9 Hz), 3.91−4.08 (m, 3H), 3.20 (d, 1H, $J$ = 14.9 Hz), 3.00 (dd, 1H, $J$ = 7.0 Hz, 12.0 Hz, H4), 1.36 (m, 1H, H7a), 2.76 (m, 1H, H5), 2.65−2.78 (m, 2H), 2.78 (dt, 1H, $J$ = 6.5 Hz, 12.6 Hz, 12.6 Hz, H3a), 1.19 (t, 3H, $J$ = 7.2 Hz), 0.89 (d, 3H, $J$ = 7.1 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 172.8, 172.5, 138.1, 136.7, 133.0, 129.3, 128.7, 128.5, 128.1, 127.4, 126.7, 122.8, 60.4, 58.7, 45.2, 45.0, 42.6, 39.8, 34.2, 33.2, 17.0, 14.1; obsd NOE between H4 and H8, H7a and H8, H4 and H7a, H3a and Me5, H4 and H5; HRMS calcd for $C_{26}H_{30}NO_3$ ($MH^+$) 404.2226, found 404.2238.

**Diels−Alder Reaction To Make Compounds 9c and 10c.** Compound **4f** (95 mg, 0.29 mmol) was used by following the procedure for synthesis of **9b** and **11b**. The cycloaddition was found complete in 20 h. $^1$H NMR showed a mixture of isomeric products in a ratio of 83:25:1:1. The residue was purified by slow column chromatography without air pressure: a mixture of benzene and hexanes (1:1) was used to pack column and load the sample; 8% ethyl acetate in hexanes to elute a fraction **9c** (16 mg, pure) and a second fraction (79 mg) as a mixture of **9c** and **10c**. The total recovered yield from **2c** was 73%. The second fraction was purified by a second round of column chromatography: 0.25% and 0.5% ethyl acetate in methylene chloride to elute slowly. The second isomer **10c** was the fast moving in this solvent system, and an early fraction was collected to give **10c** (4 mg).

For **9c**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.18−7.22 (m, 6H), 6.96−6.99 (m, 2H), 6.83−6.87 (m, 2H), 6.37 (dt, 1H, $J$ = 2.8 Hz, 2.8 Hz, 9.2 Hz), 5.62 (dt, 1H, $J$ = 3.0 Hz, 9.2 Hz), 4.98 (d, 1H, $J$ = 15.4 Hz), 4.02 (d, 1H, $J$ = 15.4 Hz), 3.99 (t, 2H, $J$ = 7.1 Hz), 3.80 (ddd, 1H, $J$ = 3.7 Hz, 6.2 Hz, 10.1 Hz, H3), 3.00 (dd, 1H, $J$ = 3.8 Hz, 15.6 Hz), 2.71−2.81 (m, 2H), 2.45 (dd, 1H, $J$ = 10.0 Hz, 13.0 Hz, H3a), 1.88−2.04 (m, 1H), 1.16 (s, 3H), 1.14 (t, 3H, $J$ = 7.2 Hz), 0.99 (d, 3H, $J$ = 7.3 Hz); $^{13}$H NMR ($CDCl_3$, 75 MHz) $\delta$ 175.2, 173.3, 137.5, 136.6, 133.8, 128.8, 128.5, 128.3, 127.3, 127.0, 126.3, 125.9, 60.5, 58.0, 48.8, 46.2, 44.2, 43.2, 42.2, 37.1, 18.3, 16.3, 13.9; HRMS calcd for $C_{27}H_{32}NO_3$ ($MH^+$) 418.2382, found 418.2381.

For **10c**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.20−7.34 (m, 8H), 7.06 (d, 2H, $J$ = 6.7 Hz), 5.94 (dt, 1H, $J$ = 3.4 Hz, 3.4 Hz, 9.9 Hz), 5.42 (dt, 1H, $J$ = 2.6 Hz, 2.6 Hz, 9.2 Hz), 4.92 (d, 1H $J$ = 14.3 Hz), 4.13 (d, 1H, $J$ = 14.5 Hz), 3.72−3.84 (m, 1H), 3.37−3.47 (m, 2H), 2.78−2.85 (m, 2H), 2.69 (d, 1H, $J$ = 8.7 Hz), 2.53 (m, 1H), 1.03 (t, 3H, 7.2 Hz), 0.75 (d, 3H, $J$ = 7.3 Hz), 0.46 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 175.5, 173.1, 136.6, 135.8, 132.0, 129.32, 129.29, 128.5, 128.3, 127.8, 126.7, 122.1, 60.4, 58.7, 48.0, 45.0, 42.3, 40.0, 37.8, 35.7, 15.8, 13.9, 9.4; obsd NOE between H3a and H5, H7a and H8, between Me4 and Me5, H3 and Me4; HRMS calcd for $C_{27}H_{32}NO_3$ ($MH^+$) 418.2382, found 418.2376.

**Diels−Alder Reaction To Make Compounds 9d.** Compound **4g** (302 mg, 0.94 mmol) was used by following the procedure for synthesis of **9b** and **11b**. The cycloaddition was complete in 60 h. $^1$H NMR showed a very clean mixture of three isomeric products in a ratio of 20:2:1. The major isomer could not be isolated by three rounds of slow column chromatography using different solvent systems. A total of 355 mg product (91% from **4g**) was recovered from column chromatography. The stereochemistry of **9d** was assigned using the product mixture.

For **9d**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.05 (d, 1H, $J$ = 9.1 Hz), 6.42−6.46 (m, 3H), 5.64 (dt, 1H, $J$ = 3.0 Hz, 3.0 Hz, 9.1 Hz), 4.98 (d, 1H, $J$ = 15.4 Hz), 4.15 (q, 2H, $J$ = 7.1 Hz), 4.02 (d, 1H, $J$ = 15.5 Hz), 3.81 (s, 3H), 3.80 (s, 3H), 3.20 (dd, 1H $J$ = 2.2 Hz, 9.8 Hz, H3), 2.81 (t, 1H, $J$ = 9.2 Hz), 2.46−2.62 (m, 2H), 2.19−2.34 (m, 1H), 2.12 (dt, 1H, $J$ = 9.6 Hz, 9.6 Hz, 12.7 Hz, H3a), 1.27 (t, 3H, $J$ = 7.2 Hz), 1.11 (d, 3H, $J$ = 7.4 Hz), 0.84 (d, 3H, $J$ = 7.3 Hz), 0.79 (d, 3H, $J$ = 7.0 Hz); obsd NOE ($CDCl_3$, 400 MHz) between H3 and H4, H3 and H7a, H4 and H5, H4 and H7a, weak between H4 and Me5; HRMS calcd for $C_{24}H_{34}NO_5$ ($MH^+$) 416.2437, found 416.2455.

**Diels−Alder Reaction To Make Compounds 9e and 10e.** Compound **4h** (225 mg, 0.82 mmol) was used by following the procedure for synthesis of **9b** and **11b**. The cycloaddition completed in 80 h. $^1$H NMR showed a mixture of three isomeric products in a ratio of 185:50:1. The residue was purified by slow column chromatography without air pressure: a mixture of benzene and hexanes (1:1) was used to pack column and load the sample; 3−5% ethyl acetate in hexanes to elute. Three fractions were collected to give a first fraction of 24 mg (mixture), a second fraction of 203 g (mixture), and a third fraction of 14 mg (pure **9e**). The total recovery yield was 80% based on **2e**. The first fraction of 24 mg was again purified using the same solvent system to give the fast moving isomer **10e** (8 mg).

For **9e**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.23−7.35 (m, 3H), 7.17 (d, 2H, $J$ = 6.7 Hz), 6.50 (dt, 1H, $J$ = 3.2 Hz, 3.2 Hz, 9.9 Hz), 5.66 (dt, 1H, $J$ = 2.9 Hz, 2.9 Hz, 10.0 Hz), 5.20 (d, 1H, $J$

= 15.4 Hz), 4.12 (q, 2H, *J* = 7.2 Hz), 3.88 (d, 1H, *J* = 15.5 Hz), 3.37 (dd, 1H, *J* = 2.2 Hz, 10.0 Hz, H3), 2.68 (dq, 1H, *J* = 2.7 Hz, 2.7 Hz, 2.7 Hz, 12.8 Hz, H7a), 2.42 (dd, 1H, *J* = 10.0 Hz, 12.8 Hz, H3a), 1.89−2.03 (m, 2H), 1.25 (t, 3H, *J* = 7.1 Hz), 1.15 (s, 3H), 1.04 (d, 3H, *J* = 7.4 Hz), 0.78 (d, 3H, *J* = 7.1 Hz), 0.76 (d, 3H, *J* = 7.2 Hz); $^{13}$C ($CDCl_3$, 75 MHz) *δ* 175.8, 173.9, 136.6, 134.1, 129.0, 128.6, 127.6, 127.3, 61.9, 60.6, 46.7, 46.4, 44.3, 43.7, 42.9, 27.0, 18.3, 17.4, 16.6, 15.5, 14.1; HRMS calcd for $C_{23}H_{32}NO_3$ ($MH^+$) 370.2382, found 370.2379.

For **10e**: $^1$H NMR ($CDCl_3$, 300 MHz) *δ* 7.29 (s, 5H), 6.03 (dt, 1H, *J* = 3.4 Hz, 3.4 Hz, 9.9 Hz), 5.45−5.51 (m, 1H), 4.79 (d, 1H, *J* = 14.4 Hz), 4.09−4.20 (m, 1H), 4.05 (d, 1H, *J* = 14.5 Hz), 3.90−4.01 (m, 1H), 3.14 (dt, 1H, *J* = 3.2 Hz, 3.2 Hz, 9.2 Hz, H7a), 3.09 (d, 1H, *J* = 3.1 Hz, H3), 2.69−2.73 (m, 1H), 2.64 (d, 1H, *J* = 9.2 Hz, H3a), 2.00−2.11 (m, 1H), 1.21 (t, 3H, *J* = 7.1 Hz), 0.75−0.84 (m, 9H), 0.53 (s, 3H); $^{13}$C NMR ($CDCl_3$, 300 MHz) *δ* 176.2, 173.3, 136.2, 131.9, 129.2, 128.5, 127.8, 122.7, 62.8, 60.7, 48.6, 44.8, 41.9, 38.7, 36.0, 28.4, 18.2, 16.2, 15.6, 14.1, 9.2; obsd NOE ($CDCl_3$, 400 MHz) between H3 and Me4, H3a and H7a, Me4 and Me5, H5 and Me4; HRMS calcd for $C_{23}H_{32}NO_3$ ($MH^+$) 370.2382, found 370.2371.

**Diels−Alder Reaction To Make Compounds 9f and 10f.** Followed exactly the same procedure to make **9b** and **11b**. Proton NMR of the crude but clean Diels−Alder reaction mixture showed two isomeric products **9f** and **10f** in a 6:1 ratio, as compared with that of the crude reaction mixture of **9e** and **10e**.

**Diels−Alder Reaction To Make Compounds 9g and 11g.** Compound **3a** (110 mg, 2.11 mmol) after removal of Boc group was used for reductive alkylation with 2,4-hexadienal by following the procedure to make **2i** and **2h**. The reduction was allowed for 6 h after addition of triacetoxyborohydride. $^1$H NMR of the crude mixture indicated the completion of the cycloaddition of **2g**, and showed two diastereomers (**9g**:**11g** = 5:1). The major and more polar isomer **9g** was isolated in pure form (68 mg, 66%), eluted with 20−30% ethyl acetate in hexanes from column chromatography: $^1$H NMR ($CDCl_3$, 300 MHz) *δ* 7.16−7.31 (m, 5H), 5.75 (dt, 1H, *J* = 9.8 Hz, 1.7 Hz), 5.56 (dt, 1H, *J* = 9.7 Hz, 3.3 Hz), 4.18 (q, 2H, *J* = 7.1 Hz), 3.20−3.29 (m, 2H), 3.03 (dd, 1H, *J* = 8.5 Hz, 7.0 Hz, H1), 2.90 (dd, 1H, *J* = 11.3 Hz, 6.8 Hz, H4), 2.74−2.85 (m, 1H, H5), 2.59 (dd, 1H, *J* = 12.5 Hz, 10.0 Hz, H-$R_1$), 2.53 (dd, 1H, *J* = 11.9 Hz, 8.6 Hz, H1′), 2.36−2.46 (m, 1H, H7a), 1.75 (q, 1H, *J* = 11.1 Hz, H3a), 1.30 (t, 3H, *J* = 7.1 Hz), 1.02 (d, 3H, *J* = 7.2 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) *δ* 173.4, 140.0, 132.9, 129.0, 128.2, 125.8, 61.3, 60.0, 48.2, 47.6, 45.2, 44.6, 41.5, 33.5, 29.6, 17.8, 14.2; HRMS calcd for $C_{19}H_{26}NO_2$ ($MH^+$) 300.1965, found 300.1953.

**Diels−Alder Reaction To Make Compounds 9h and 10h.** Compound **2h** (101 mg), after isolation from column chromatography, was immediately dissolved in deuterated chloroform. The cycloaddition was complete in 15 days as monitored by $^1$H NMR and gave two isomers in a 3:2 ratio. The mixture was eluted first with a mixture of benzene and hexanes (1:1) to remove impurities and then with benzene to give the minor isomer **10h** (32 mg) and finally with 5% ethyl acetate in hexanes to give the major isomer **9h** (52 mg). Total yield was 84%.

For **9h**: $^1$H NMR ($CDCl_3$, 300 MHz) *δ* 7.19−7.41 (m, 5H), 5.71 (dt, 1H, *J* = 9.6 Hz, 2.0 Hz), 5.54 (dt, 1H, *J* = 9.6 Hz, 3.0 Hz), 4.02−4.22 (m, 2H), 3.85 (d, 1H, *J* = 13.4 Hz), 3.66 (d, 1H, *J* = 13.4 Hz), 2.61−2.68 (m, 2H), 2.52 (t, 1H, *J* = 11.0 Hz, H1), 2.22−2.32 (m, 1H, H7a), 2.16 (dd, 1H, *J* = 11.5 Hz, 9.7 Hz, H3a), 2.12 (m, 1H, H5), 1.70 (m, 1H, isopropyl), 1.28 (t, 3H, *J* = 7.1 Hz), 1.25 (s, 3H), 0.97−1.02 (5 peaks, 9H); $^{13}$C NMR ($CDCl_3$, 75 MHz) *δ* 176.2, 141.7, 133.6, 128.1, 128.0, 127.4, 126.5, 69.8, 63.7, 60.2, 55.5, 48.5, 46.8, 42.2, 37.5, 30.7, 22.4, 18.3, 18.1, 15.8, 14.2; HRMS calcd for $C_{23}H_{34}NO_2$ ($MH^+$) 356.2589, found 356.2578; obsd NOE ($CDCl_3$, 600 MHz) H3-Me4, H7a-Me4, H3-H5, H5-Me4.

For **10h**: $^1$H NMR ($CDCl_3$, 300 MHz) *δ* 7.18−7.34 (m, 5H), 5.62 (dt, 1H, *J* = 9.9 Hz, 3.2 Hz), 5.36 (d, broad, 1H, *J* = 9.9 Hz), 3.98−4.24 (m, 3H), 3.55 (d, 1H, *J* = 13.6 Hz), 2.94 (t, 1H, *J* = 7.9 Hz), 2.74−2.90 (m, 3H), 2.37 (dd, 1H, *J* = 8.5 Hz, 2.2 Hz, H3a), 2.16 (dd, 1H, 12.0 Hz, 8.2 Hz), 1.67−1.80 (m, 1H), 1.28 (t, 3H, *J* = 7.1 Hz), 1.00 (s, 3H), 0.94 (d, 3H, *J* = 6.8 Hz), 0.88 (d, 3H, *J* = 7.3 Hz), 0.84 (d, 3H, *J* = 6.9 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) *δ* 177.3, 140.9, 130.9, 128.2, 128.1, 126.6, 125.7, 60.5, 59.3, 58.3, 48.2, 46.4, 39.5, 37.1, 32.8, 18.5, 17.9, 16.5, 14.1, 13.3; obsd NOE ($CDCl_3$, 400 MHz) H3a-H5, H3a-H7a, H3-Me4.

**Diels−Alder Reaction To Make Compound 9j.** To the primary amine triene **2i** (110 mg, 0.415 mmol) in THF (10 mL) were added $Et_3N$ (0.4 mL) and PhCOCl (70 mL, 0.60 mmol). The mixture was stirred for 0.5 h, quenched with 5% $NaHCO_3$ (50 mL), and extracted with ether. The ether layer was dried over $MgSO_4$ (0.5 h), evaporated, and pumped under high vacuum for 1 h. A part of the residue was dissolved in $CDCl_3$, and the second part was dissolved in $C_6D_6$. The reaction was monitored by $^1$H NMR and was found complete in 18 h in either $CDCl_3$, or $C_6D_6$ (the time was counted immediately after the addition of PhCOCl). The $^1$H NMR showed a mixture of 2 isomers in a ratio of 9:1. Column chromatography using 5−10% ethyl acetate in hexanes gave the pure major isomer **9j** (89 mg, 58%) and a fraction of mixtures (5 mg, 3%). The total yield is 61%. For **9j**: $^1$H NMR ($C_6D_6$, 300 MHz) *δ* 7.64−7.68 (m, 2H), 7.09−7.16 (m, 3H), 5.42−5.52 (m, 2H), 4.63 (d, broad, 1H, *J* = 8.2 Hz, H1), 3.84−3.95 (m, 2H), 3.45 (dd, 1H, *J* = 6.6 Hz, 9.6 Hz), 2.84 (dd, 1H, *J* = 10.3 Hz, 11.6 Hz), 2.56−2.68 (m, 1H), 2.43 (dd, 1H, *J* = 10.0 Hz, 11.8 Hz, H3a), 1.72−1.80 (m, 2H), 1.21 (d, 3H, *J* = 7.0 Hz), 1.17 (s, 3H), 0.90 (m, 9H); $^{13}$C NMR ($CDCl_3$, 75 MHz) *δ* 176.0, 171.0, 137.0, 134.8, 133.6, 130.3, 128.4, 128.3, 127.9, 127.6, 61.5, 60.5, 54.4, 49.5, 47.4, 42.0, 40.4, 30.7, 19.8, 18.8, 17.4, 16.7, 14.2; obsd NOE ($C_6D_6$, 400 MHz) H3-Me4.

**Compounds 9k.** To benzylamine (1.60 mL, 14.6 mmol) in methylene chloride (20 mL) were added ethyl 4-bromocrotonate (1.0 mL, 7.3 mmol) and 4-(dimethylamino)pyridine (200 mg). The mixture was stirred overnight and separated between ether (200 mL) and water (200 mL). The ether layer was dried over $Na_2SO_4$ and concentrated. The residue was purified by column chromatography and eluted using 10−20% ethyl acetate in hexanes to give ethyl 4-benzylaminocrotonate (0.81 g, 51%): $^1$H NMR ($CDCl_3$, 300 MHz) *δ* 7.22−7.34 (m, 5H), 7.00 (dt, 1H, *J* = 15.6 Hz, 5.3 Hz, 5.3 Hz), 6.01 (dt, 1H, *J* = 15.6 Hz, 1.6 Hz), 4.18 (q, 2H, *J* = 7.1 Hz), 3.78 (s, 2H), 3.39 (dd, 2H, *J* = 1.5 Hz, 5.3 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) *δ* 166.3, 146.6, 139.7, 128.3, 128.0, 127.0, 121.5, 60.1, 53.1, 49.4, 14.1; LC−MS calcd for $C_{13}H_{17}NO_2$ ($MH^+$) 220, found 220.

To ethyl 4-benzylaminocrotonate (125 mg, 0.571 mmol) in THF (10 mL) were added triethylamine (0.2 mL) and 2,4-hexadienoyl chloride (100 mL, ∼0.75 mmol). The mixture was stirred for 0.5 h, quenched with 5% $Na_2CO_3$ (50 mL), and extracted with ether (50 mL). The ether layer was dried over $MgSO_4$ (∼0.5 h), evaporated, and pumped under high vacuum for 1 h. A part of the residue was dissolved in $CDCl_3$, and the second part was dissolved in $C_6D_6$. The reaction was monitored by $^1$H NMR and was found complete in 18 days in either $CDCl_3$ or $C_6D_6$. The $^1$H NMR showed a mixture of two isomers in a ratio of 6:1. Column chromatography using a mixture of methylene chloride and hexanes (3:2) gave the pure major isomer **9k** (109 mg, 61%) and a fraction of mixtures (11 mg, 6%). The total yield is 67%. For **9k**: $^1$H NMR ($CDCl_3$, 300 MHz) *δ* 7.21−7.35 (m, 5H), 6.12 (d, 1H, *J* = 9.9 Hz), 5.59 (dt, 1H, *J* = 3.1 Hz, 3.1 Hz, 9.9 Hz), 4.58 (d, 1H, *J* = 14.7 Hz), 4.37 (d, 1H, *J* = 14.7 Hz), 4.08−4.21 (m, 2H), 3.54 (dd, 1H, *J* = 6.3 Hz, 9.5 Hz), 2.98 (t, 1H, *J* = 9.9 Hz), 2.82−2.89 (m, 2H), 2.69 (d, broad, 1H, *J* = 12.5 Hz, H7a), 2.27 (dq, 1H, *J* = 6.3 Hz, 11.3 Hz, 11.3 Hz, 11.3 Hz, H3a), 1.25 (t, 3H, *J* = 7.1 Hz), 0.93 (d, 3H, *J* = 6.9 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) *δ* 172.7, 172.6, 136.7, 133.3, 128.7, 128.1, 127.5, 122.4, 60.4, 49.3, 47.3, 47.0, 46.7, 35.8, 33.2, 16.9, 14.2; LC−MS calcd for $C_{19}H_{24}NO_3$ ($MH^+$) 314, found 314.

**Diels−Alder Reaction To Make Compounds 17 and 18.** Triene **16** (96 mg, 0.33 mmol) in toluene (10 mL) was heated under nitrogen at reflux for 4 h. Toluene was removed in vacuo. $^1$H NMR showed the two major isomers in a ratio of 1:1. The residue was purified by slow column chromatography using 2−3% ethyl acetate in methylene chloride to elute the fast isomer **17** (39 mg, pure). A second fraction was then

collected to give a mixture of **17** and a minor isomer **19** or **20** (total 3 mg). A third fraction eluted with 5% ethyl acetate in hexanes was obtained in 49 mg, which was a mixture of the major isomer **18** and some starting material **16** (**18**:**16** = 3:2). A fourth fraction eluted with 6% ethyl acetate in hexanes gave a mixture (5 mg, not pure) of **18** containing a second minor isomer **20** or **19**. The total yield was 84% (Diels−Alder products only) or 100% based on the recovery of **16**. For **17** (structural assignment was from $^1$H NMR coupling constants): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.15−7.34 (m, 5H), 6.12 (d, 1H, $J$ = 9.9 Hz), 5.60 (dt, 1H, $J$ = 3.2 Hz, 3.2 Hz, 9.8 Hz), 5.17 (d, 1H, $J$ = 15.2 Hz), 4.10−4.22 (m, 2H), 3.74 (d, 1H, $J$ = 15.2 Hz), 3.25 (dt, 1H, $J$ = 3.3 Hz, 3.3 Hz, 6.8 Hz, H6), 3.16 (dd, 1H, $J$ = 3.2 Hz, 10.2 Hz, H3), 2.52 (t, 1H, $J$ = 11.8 Hz, H7a), 2.28−2.39 (m, 2H), 2.16−2.23 (m, 1H), 1.42 (d, 3H, $J$ = 6.8 Hz), 1.29 (t, 3H, $J$ = 7.1 Hz), 0.99 (d, 3H, $J$ = 7.1 Hz), 0.83 (d, 3H, $J$ = 6.8 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 175.4, 172.9, 136.8, 130.4, 128.6, 127.9, 127.3, 127.1, 62.0, 60.7, 48.5, 45.8, 43.4, 39.4, 33.6, 27.0, 19.7, 15.2, 15.0, 14.3; HRMS calcd for $C_{22}H_{29}NO_3$ ($MH^+$) 356.2226, found 356.2240.

For **18**, the fraction 4 containing a minor isomer was used for NMR analyses: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.22−7.32 (m, 5H), 5.59−5.76 (m, 2H), 5.05 (d, 1H, $J$ = 15.1 Hz), 4.12−4.22 (m, 1H), 3.85 (d, 1H, $J$ = 15.0 Hz), 3.06 (t, 1H, $J$ = 3.8 Hz, H3), 2.79 (s, broad, 1H, H6), 2.64 (s, broad, 1H, H3a), 2.49−2.58 (m, 1H, H7), 2.44 (dd, 1H, $J$ = 6.9 Hz, 8.0 Hz, H7a), 1.99−2.08 (m, 1H), 1.28 (t, 3H, $J$ = 7.3 Hz), 1.25 (d, 3H, $J$ = 6.5 Hz), 0.92 (d, 3H, $J$ = 6.9 Hz), 0.78 (d, 3H, $J$ = 6.9 Hz); obsd NOE ($CDCl_3$, 400 MHz) H3a-H7a, H6-H7a, H3-H7.

**Compounds 23.** To amine **14** (224 mg, 1.14 mmol) in THF (10 mL), were added ethyl 4-bromocrotonate (282 $\mu$L, 1.50 mmol) and 4-(dimethylamino)pyridine (70 mg, 0.57 mmol). The mixture was stirred overnight and separated between ether (100 mL) and water (100 mL). The ether layer was dried over $Na_2SO_4$ and concentrated. The residue was purified by column chromatography and eluted using 10% ethyl acetate in hexanes to give **21** (184 mg, 52%): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.28 (dd, 1H, $J$ = 11.0 Hz, 16.1 Hz), 6.96 (dt, 1H, $J$ = 5.3 Hz, 5.3 Hz, 15.8 Hz), 6.23 (dd, 1H, $J$ = 11.0 Hz), 5.83−6.01 (m, 3H), 4.16−4.24 (m, 4H), 3.40 (ddd, 1H, $J$ = 2.0 Hz, 5.8 Hz, 16.8 Hz), 3.25 (ddd, 1H, $J$ = 1.4 Hz, 5.8 Hz, 16.4 Hz), 2.91 (dd, 1H, $J$ = 5.8 Hz, 8.3 Hz), 1.65−1.79 (m, 1H), 1.26−1.32 (m, 6H), 0.94 (d, 3H, $J$ = 6.7 Hz), 0.89 (d, 3H, $J$ = 6.8 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 167.0, 166.4, 146.9, 143.8, 143.6, 130.1, 121.4, 120.7, 65.7, 60.2, 47.8, 32.6, 19.3, 18.2, 14.23, 14.18; LC−MS calcd for $C_{17}H_{28}NO_4$ ($MH^+$) 310, found 310.

The second amine triene **21** (85 mg, 0.275 mmol) in THF (5 mL) was treated by following the procedure to make **9j**. A part of the residue was dissolved in $CDCl_3$, and the second part was dissolved in $C_6D_6$. The reaction was monitored by $^1$H NMR and was found complete in 40 h in either $CDCl_3$ or $C_6D_6$ (the time was counted immediately after the addition of PhCOCl). The $^1$H NMR of the reaction mixture showed a single isomer. Column chromatography using 5−10% ethyl acetate in hexanes gave the pure **23** (105 mg, 92%): $^1$H NMR ($C_6D_6$, 300 MHz) $\delta$ 7.59 (t, 2H, $J$ = 3.6 Hz), 7.02−7.06 (m, 3H), 5.84 (d, 1H, $J$ = 9.8 Hz), 5.61 (dt, 1H, $J$ = 3.5 Hz, 9.8 Hz), 4.28 (dd, 1H, $J$ = 6.2 Hz, 10.2 Hz), 4.09 (dd, 1H, $J$ = 6.0 Hz, 11.1 Hz, H3), 3.70−3.92 (m, 4H), 3.60−3.64 (m, 1H, H6), 2.96−3.05 (m, 2H), 2.47 (dq, 1H, $J$ = 6.1 Hz, 11.4 Hz, 11.4 Hz, 11.4 Hz, H7a), 2.13 (dd, 1H, $J$ = 6.3 Hz, 11.5 Hz, H7), 2.02 (t, broad, 1H, $J$ = 12.0 Hz, H3a), 0.85−0.99 (m, 9H), 0.78 (t, 3H, $J$ = 7.1 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 171.8, 171.5, 170.6, 136.8, 131.1, 130.3, 128.1, 127.8, 124.8, 63.7, 61.1, 60.6, 55.4, 44.7, 44.5, 43.8, 39.9, 28.4, 19.4, 16.1, 14.1, 13.8; HRMS calcd for $C_{24}H_{32}NO_5$ ($MH^+$) 414.2281, found 356.2263.

**Acknowledgment.** We thank Drs. G. H. Kuo and P. Connolly for helpful discussions, M. Evangelisto for purification of compound **10b**, and W. J. Jones for HRMS. Elemental analysis was performed by Quantitative Technologies, Inc., NJ.

**Supporting Information Available:** The compound purity is exemplified by $^1$H and $^{13}$C NMR spectra for the Diels−Alder reaction products of trienes **2a**−**f** and **22**. Calculated structures (Cartesian coordinates) and energies of all ground and transition structures are given. This material is available free of charge via the Internet at http://pubs.acs.org.

JO990459F