Vinyl Benzenes as Dienes in Mild Solid-Phase Diels−Alder Reactions†

Sengen Sun, Ignatius J. Turchi, Dawei Xu, and William V. Murray*

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

Received December 23, 1999

Wang resin-bound intermediates derived from Fmoc-L-phenylalaninal and Fmoc-L-valinal, and a resin supported Horner−Wadsworth−Emmons reaction, were treated with cinnamaldehyde derivatives, acetic acid, and borohydride to give secondary amines which were subsequently benzoylated to afford various derivatives of **3**. Heating **3** at 95 °C induced cycloaddition reactions and produced **4** as the major product. Compounds **3** which were derived from 4-methoxycinnamaldehyde were more reactive, but did not give **4** and **4**−**7g**. The direct cleavage of **3b** using TFA led to the isolation of cycloaddition−demethylation product **10**. The derivative of **3**, which contained an electron-withdrawing nitro group on the phenyl ring, produced a single diastereomer of **4**. The Diels−Alder cycloaddition between two electron-deficient counterparts showed similar reactivity to that of the reactions which have a normal complementary electron-demand.

Introduction

A diene consisting of a side chain double bond and the phenyl ring of styrene can form Diels−Alder cycloadducts with activated dienophiles under certain thermal conditions.[1] The styrene-involved Diels−Alder reactions initially generate a conjugated triene intermediate, followed by a rearomatization process. In some cases, a second round of cycloaddition reactions following the initial Diels−Alder process were observed.[1c,d] These occurred because the conjugated triene intermediates can act as more reactive dienes than the initial diene involving the benzene ring.

Diels−Alder approaches are becoming increasingly important for library generation.[2] Recently, we investigated a class of intramolecular Diels−Alder reactions of amino acid-derived trienes under mild thermal conditions to form hydroisoindolines.[3] These reactions have been easily adapted to a solid support.[4] These mild reaction conditions provided us an opportunity to utilize vinyl benzene moieties as the dienes in the synthesis of libraries on a solid support. Herein we report several examples of the solid-phase Diels−Alder reactions involving vinyl benzenes as the diene component.

Results and Discussion

Wang resin-bound intermediates[4] **1a** and **1b** were treated with cinnamaldehyde derivatives in the presence of acetic acid followed by reduction with sodium triacetoxyborohydride to give **2a**−**h**. Benzoylation afforded the amide intermediates **3a**−**h**. We expected that the tertiary amide precursors **3a**−**h** would be more reactive toward intramolecular Diels−Alder reactions than the secondary amines **2a**−**h** as we reported previously.[3,4] The cycloaddition reactions of **3a**−**h** were carried out at 95−98 °C in DMF (Scheme 1 and Table 1).[4] The expected cycloadducts **4** and related stereoisomers were purified by either column chromatography or preparative HPLC.

Table 1.

precursors	temp, °C	reaction time	yield %	isomer ratio
3a	95−98	20 h	43	1:1:0:0
3b	rt	0 h	27	(**10** only)
3c	95−98	28 h	45	10:4:1:1
3d	95−98	24 h	92	1:0:0:0
3e	95−98	5 days	46	2:1:0:0
3f	95−98	3 days	50	2:1:0:0
3g	rt or 95	−	0	−
2h	95−98	3 days	98	1:0:0:0

The phenylalanine-derived precursors **3a**,**c**,**d** generally required heating for 24 h for the cycloaddition to reach completion. Precursors **3a** and **3c** produced two diastereomers in each case. The structure of the major isomer in each case was established by NMR to be **4a** or **4c**, respectively. As we previously observed,[3,4] these major isomers are trans fused between the 3a and 9a bridgeheads (Scheme 1). The second isomer (**4a′** or **4c′**) in each case gave broad ^{1}H NMR peaks of poor resolution, possibly due to an equilibrium between two conformers for each isomer. The stereo structures of **4a′** and **4c′**, therefore, could not be resolved.

The precursor **3b** derived from *p*-methoxycinnamaldehyde was exceptionally reactive. Without heating, **3b** was immediately treated with TFA in methylene chloride after benzoylation of **2b**. The expected carboxylic acid form of **3b** was not observed, neither was cycloadduct **4b** and related isomers. An isolated compound from preparative HPLC of the cleavage mixture was identified as **10** (Scheme 2). Although the proton NMR coupling constant between H8a and H9 is 8.6 Hz (normally in the range of trans relationship), a 2-D NOE experiment at

† This paper is dedicated to the memory of Professor George Buchi (1921−98).

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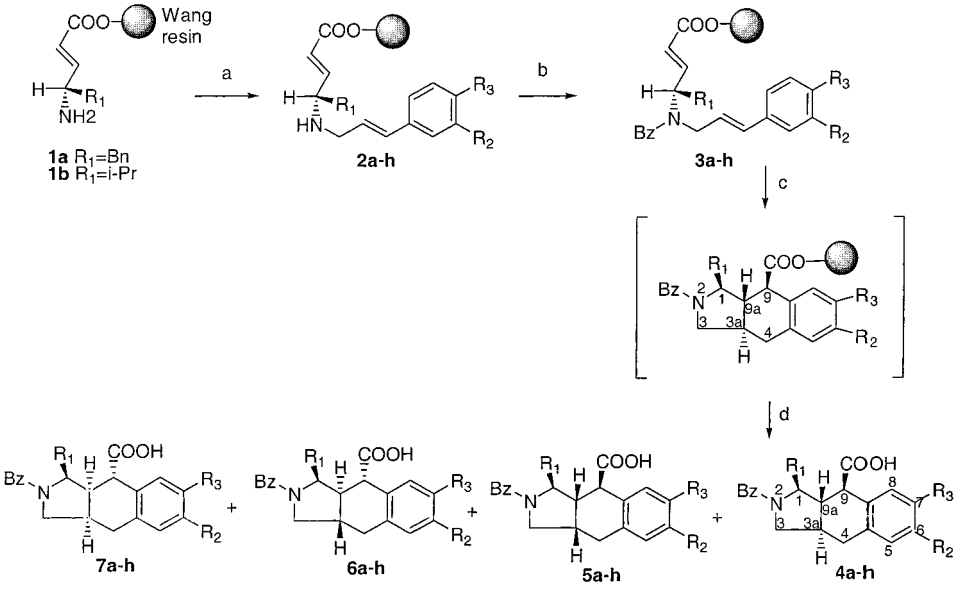
10.1021/jo991956z CCC: $19.00
Published on Web 03/23/2000

Scheme 1[a]

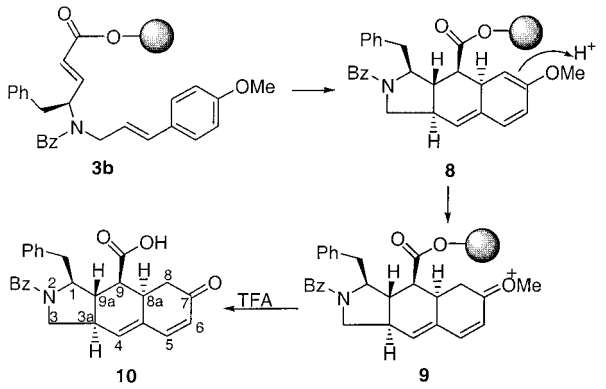


2a,3a R_1=Bn, R_2=R_3=H
2b,3b R_1=Bn,R_2=H, R_3=OMe,
2c,3c R_1=Bn, R_2=OMe, R_3=OH
2d,3d R_1=Bn, R_3=NO_2, R_2=H
2e,3e R_1=*i*-Pr, R_2=R_3=H
2f,3f R_1=*i*-Pr, R_2=OMe, R_3=OH
2g,3g R_1=*i*-Pr, R_3=OMe, R_2=H
2h,3h R_1=*i*-Pr, R_3=NO_2, R_2=H

4-7a R_1=Bn, R_2= R_3=H
4-7b R_1=Bn, R_2=H, R_3=OMe
4-7c R_1=Bn, R_2= OMe, R_3=OBz
4-7d R_1=Bn, R_2=H, R_3= NO_2
4-7e R_1=*i*-Pr, R_2=H, R_3=H
4-7f R_1=*i*-Pr, R_2=OMe, R_3=OBz
4-7g R_1=*i*-Pr, R_2=H, R_3=OMe
4-7h R_1=*i*-Pr, R_2=H, R_3=NO_2

[a] (a) Ar−CH=CH−CHO, $LiBH(AcO)_3$, AcOH, CH_2Cl_2; (b) BzCl, Et_3N, CH_2Cl_2; (c) DMF, 95−98 °C; (d) 20% TFA in CH_2Cl_2.

Scheme 2



500 MHz showed a weak NOE between H8a and H3a, and a stronger NOE between H9 and H3a. The observed NOE between H8a and H9 is stronger than that between H8a and either of the protons at position 8. The NOE NMR analysis supports a cis relationship between H8a and H9. Compound **10** could be formed via the acid-catalyzed demethylation of the intermediate **8** (Scheme 2). Heating the resin-bound intermediate **3b** at 95 °C did not produce any adducts **4b** and **5b**.

The Diels−Alder reaction of **3d** provided us another example of a cycloaddition between two electron-deficient counterparts. This reaction produced a single isomer **4d** as the only observed product.

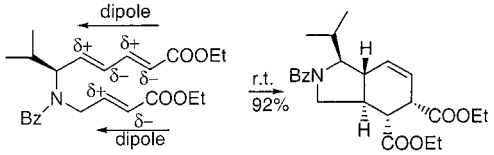
As we expected from our earlier observations,[3,4] cycloadditions of valine-derived precursors **3e**−**g** proceed at a slower rate than phenylalanine-derived precursers (**3a**−**d**). These reactions generally required more than 3 days to reach completion. The cycloadditions of **3e**,**f** produced two stereoisomers in each case. The major isomer in each case is trans-fused **4e** or **4f**. The second isomer was determined to be cis-fused **5e** or **5f** and contained two conformers (4:1 ratio) which interconvert slowly. This is consistent with the observation that **4a′** or **4c′** have two components that exist in a rapid equilibrium.

The *p*-methoxy-derived precursor **3g** did not afford any cycloaddition products. The intermediate **3g** was freshly prepared under a nitrogen atmosphere in two steps from **1b** and was immediately cleaved with TFA. The product was an unknown of molecular weight 426, 32 amu higher than the expected weight for **4g**. Although the structure of the unknown could not be confirmed, we believe that this side reaction involved air oxidation. The air oxidation was faster than the cycloaddition of **3g**. A similar air oxidation product for the precursor **3b** was also observed during the formation of **10**.

In a manner similar to **3d**, the precursor **3h** derived from valine and *p*-nitrocinnamaldehyde produced a single diastereomer **4h** as the only observed product in the crude reaction mixture. The reactivity of **3d** and **3h**, which contain two electron-deficient reacting counterparts, did not appear to be lower than that of the precursors containing electronically deficient-rich complementary counterparts. Further similarity can be found to an intramolecular Diels−Alder reaction of **11** we reported previously,[3] which proceeded at room temperature to afford a single diastereomer (Scheme 3). The dipole repulsion drawn in **11** did not have a significant negative impact on the reactivity, but provided unique stereoselectivity.

The activation energies for the Diels−Alder reaction of **3** (R_1 = Me, R_2 = Ac, R_3 = R_4 = H as the methyl ester) leading to the corresponding primary cycloadducts were calculated at the B3LYP/6-31G(d)//RHF/3-21G level of theory. These values for **4**−**7**, respectively, are 29.0, 29.2,

Scheme 3



11 12

29.7, and 31.2 kcal/mol. In contrast to our previous results,[3] the calculated activation energies preclude the prediction of product ratios at this level of theory. Figure 1 shows calculated (RHF/3-21G) geometries for the transition structures leading ultimately to **4**−**7**. These structures show a high degree of asynchronicity with the C3a−C9a partial bond being between 1.87 and 1.91 Å and the C8a−C9 partial bond being between 2.30 and 2.35 Å. The formation of the product **4** (and in some cases **5** as the minor isomer) in these reactions may be rationalized, at least in part, by a steric interaction between the substituent R_1 (in this case Me) and a hydrogen as shown for the transition structures leading to the primary cycloadducts corresponding to the unobserved aromatized products **6** and **7** (Figure 1). It appears that no such interaction occurs in the transition structures leading to **4** and **5**.

The energies of reaction were calculated at the same level of theory. These are 4.2, −0.7, 5.4, and 3.4 kcal/mol for the primary cycloadducts leading to **4**−**7**, respectively, suggesting that the reaction is reversible and that a rapid proton migration occurs after cycloaddition to give the aromatized products **4**−**7** which are 37.3, 31.5, 38.4, and 32.9, respectively, lower in energy than the primary cycloadducts.

Conclusions

Vinyl benzenes and their substituted derivatives can act as the diene components in intramolecular Diels−Alder reactions to form novel tricyclic compounds under mild thermal conditions. When the vinyl benzene contains an electron-withdrawing nitro group, only a single diastereomer was observed in a clean, crude reaction mixture. Further purification can, therefore, be avoided in these cases. In contrast, the Diels−Alder reaction precursors, which contain two complementary counterparts, afforded reduced diastereoselectivity and less clean reaction products. Our calculations indicate that these reactions are reversible. If this is the case, the subsequent rearomatization reaction drives the process to completion. These vinyl benzene-involved intramolecular Diels−Alder reactions will be further investigated for the synthesis of libraries for high-throughput screening.

Experimental Section

The intermediate **1a** or **1b** was treated with AcOH (10%) in CH_2Cl_2 and a cinnamyl aldehyde derivative (10 equiv) for 0.5−1 h. The mixture was washed with CH_2Cl_2 and was treated with $NaBH(OAc)_3$ (3−5 equiv) in anhydrous CH_2Cl_2 containing 10% glacial AcOH for 1 h to give **2a**−**f**. After washing and drying under high vacuum overnight, a resin-bound intermediate (**2a**−**f**) was treated with a mixture of PhCOCl (10 equiv) and Et_3N in dry CH_2Cl_2 for 1 h. The intermediate (**3a**−**f**) was washed with CH_2Cl_2 and MeOH and was dried.

Diels−Alder Reaction of 3a To Make 4a. The resin-bound precursor **3a** (156 mg, 0.090 mmol) in DMF was heated at 95−98 °C for 20 h. The product was cleaved using TFA (20%) in CH_2Cl_2. ^{1}H NMR of the crude mixture showed two isomers in a ratio of 1:1. The two isomers were separated using preparative HPLC (Gilson, C-18 column, 50−70% MeCN in water containing 0.1% TFA in 30 min) to give **4a** as a solid (10 mg, 27%, retention time t_R = 16 min) and a second isomer **4a′** (6 mg, 16%, t_R = 22 min). The peaks on the ^{1}H NMR spectrum of **4a′** were very broad even after a second round of purification, or after the same reaction was repeated. The stereo structure of **4a′** could not be confirmed. For **4a**, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10−7.60 (m, 14 H), 4.61 (dd, 1H, J = 8.9 Hz, 4.2 Hz, H1), 3.96 (d, 1H, J = 11.2 Hz, H9), 3.76 (dd, 1H, J = 13.8 Hz, 5.2 Hz), 3.53 (dd, 1H, J = 10.4 Hz, 6.3 Hz), 2.70−2.79 (m, 2H), 2.41−2.55 (m, 3H), 1.82−1.94 (m, 1H, H3a); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 170.0, 136.3, 135.7, 135.0, 133.1, 131.1, 130.8, 129.9, 128.4, 128.1, 127.8, 127.5, 126.9, 126.6, 61.8, 55.5, 51.1, 44.7, 39.9, 34.8, 32.2; NOESY (500 MHz, $CDCl_3$) between H1 and H9, H3a and H9, and no NOE between H1 and H9a. LC-MS calcd for $C_{27}H_{26}NO_3$ (MH^+) 412, found 412.

Diels−Alder Reaction of 3b to Make 10. The freshly prepared resin-bound precursor **3b** (139 mg, 0.079 mmol) was cleaved using TFA (20%) in CH_2Cl_2. ^{1}H NMR of the crude mixture showed a major isomer, which was purified using preparative HPLC (Gilson, C-18 column, 50−70% MeCN in water containing 0.1% TFA in 30 min) to give **10** as a solid (9 mg, 27%, t_R = 12 min). The solubility of **10** is very low in $CDCl_3$, and its ^{1}H NMR in pure CD_3OD had some overlapping peaks that interfered with the assignment of the stereo structure. ^{1}H NMR (300 MHz, CD_3OD:$CDCl_3$ = 1:1) δ 7.27−7.50 (m, 10 H), 7.07 (d, 1H, J = 9.8 Hz), 6.01 (s, broad, 1H), 5.92 (d, 1H, J = 9.8 Hz), 4.34−4.39 (m, 1H, H1), 3.63 (dd, 1H, J = 14.1 Hz, 5.3 Hz), 3.53 (dd, 1H, J = 9.4 Hz, 5.8 Hz), 3.29−3.41 (m, 1H, H8a, overlapped with solvent), 3.20 (dd, 1H, J = 14.0 Hz, 2.4 Hz), 3.15 (dd, 1H, J = 11.3 Hz, 8.6 Hz, H9), 2.65 (dd, 1H, J = 16.2 Hz, 13.6 Hz), 2.55 (dd, 1H, J = 16.2 Hz, 5.8 Hz), 2.45 (dd, J = 11.9 Hz, 9.4 Hz), 2.30−2.40 (m, 1H, H3a), 2.18 (q, 1H, J = 10.7 Hz, H9a); NOESY (500 MHz, CD_3OD:$CDCl_3$ = 1:1) between H1 and H9, H1 and H3a, H3a and H9, H3a and H8a, H4 and both of H3, H4 and H3a; ^{13}C NMR (75 MHz, CD_3OD:$CDCl_3$ = 1:1) δ 199.2, 173.1, 169.9, 147.9, 136.9, 136.3, 135.6, 131.5, 130.7, 130.6, 128.2, 127.7, 127.2, 126.2, 126.1, 60.5, 52.8, 47.7, 42.7, 42.4, 40.9, 36.1, 33.5; LC-MS: calcd for $C_{27}H_{26}NO_4$ (MH^+) 428, found 428.

Diels−Alder Reaction of 3c To Make 4c. The resin-bound precursor **3c** (150 mg, 0.080 mmol) in DMF was heated at 95−98 °C for 28 h. The product was cleaved using TFA (20%) in CH_2Cl_2. Reversed phase HPLC analysis (Gilson, C-18 column, 50−70% MeCN in water containing 0.1% TFA in 30 min) of the crude mixture showed 4 peaks (10:4:1:1) close to each other, and each of them has the same molecular weight of 561. The two major isomers were recovered from the preparative HPLC to give **4c** as a white solid (15 mg, 33%, t_R = 29 min) and an isomer **4c′** (6 mg, 13%, t_R = 24 min). The retention times (t_R) of the two unrecovered isomers are 25 and 27 min, respectively. The cleaved Diels−Alder reaction precursor has a t_R of 15 min. The peaks of the ^{1}H NMR spectrum of **4c′** were very broad, and therefore, its stereo structure could not be confirmed. For **4c**, ^{1}H NMR (300 MHz, $CDCl_3$:C_6D_6 = 1:1) δ 8.17 (d, 2H, J = 7.6 Hz), 7.54−7.56 (m, 2H), 7.46 (d, 2H, J = 7.3 Hz), 7.12−7.23 (m, 10H?), 6.30 (s, 1H), 4.59 (dd, 1H, J = 9.2 Hz, 4.2 Hz, H1), 3.97 (dd, 1H, J = 13.8 Hz, 5.1 Hz), 3.74 (d, 1H, J = 11.0 Hz, H9), 3.20 (dd, 1H, J = 10.0 Hz, 6.3 Hz), 2.93 (d, 1H, J = 13.8 Hz), 2.46 (q, 1H, J = 11.0 Hz, H9a), 2.15−2.27 (m, 2H), 2.07 (t, 1H, J = 12.0 Hz), 1.30−1.50 (m, 1H, H3a); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 169.7, 164.8, 150.3, 138.6, 136.6, 136.1, 133.9, 133.5, 131.1, 130.6, 130.3, 129.2, 128.5, 128.3, 128.0, 127.8, 126.5, 125.8, 122.3, 113.2, 61.7, 55.9, 55.4, 50.3, 44.6, 39.8, 34.6, 32.3; LC-MS: calcd for $C_{35}H_{32}NO_6$ (MH^+) 562, found 562.

Diels−Alder Reaction of 3d To Make 4d. The resin-bound precursor **3d** (144 mg, 0.081 mmol) in DMF was heated at 95−98 °C for 24 h. The product was cleaved using TFA (20%) in CH_2Cl_2. A single diastereomer **4d** was indicated by ^{1}H NMR of the crude mixture and was obtained in 34 mg (92%)

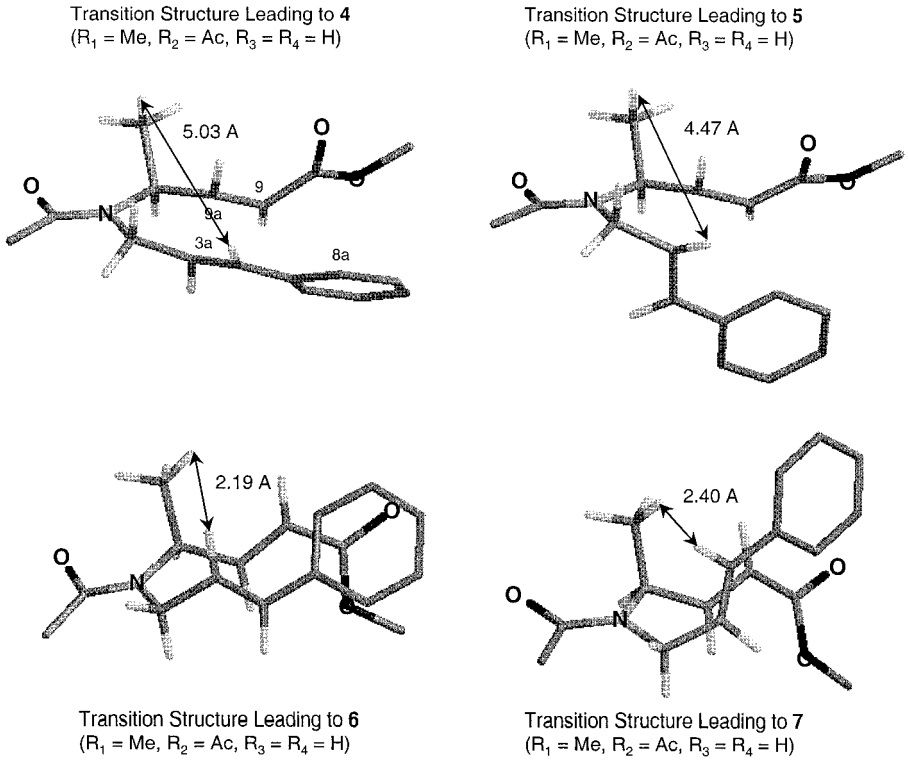


Figure 1.

without any purification. The purity was about 90% by reversed phase HPLC. ^{1}H NMR (300 MHz, C_6D_6) δ 8.30 (s, 1H), 7.69 (dd, 1H, J = 8.5 Hz, 2.1 Hz), 7.47−7.56 (m, 4H), 6.95−7.22 (m, 5H?), 6.38 (d, 1H, J = 8.5 Hz), 4.56 (dd, 1H, J = 9.8 Hz, 5.6 Hz, H1), 3.99 (dd, 1H, J = 13.3 Hz, 5.4 Hz), 3.65 (d, 1H, J = 11.1 Hz, H9), 2.95 (m, 2H), 2.42 (q, 1H, J = 11.0 Hz, H9a), 2.01 (t, 1H, J = 10.9 Hz), 1.87 (dd, 1H, J = 16.6 Hz, 4.1 Hz), 1.69 (dd, 1H, J = 16.6 Hz, 12.2 Hz), 0.92 (m, 1H, H3a); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 171.2, 146.8, 142.7, 135.6, 134.6, 134.0, 131.6, 130.8, 130.3, 128.7, 128.6, 128.3, 127.6, 127.0, 123.5, 122.4, 62.1, 55.3, 50.8, 44.4, 39.3, 34.6, 32.3; LC-MS calcd for $C_{27}H_{24}N_2O_5$ (MH^+) 457, found 457.

Diels−Alder Reaction of 3e To Make 4e and 5e. The resin-bound precursor **3e** (250 mg, 0.150 mmol) in DMF was heated at 95−98 °C for 5 days. The product was cleaved using TFA (20%) in CH_2Cl_2. ^{1}H NMR of the crude mixture showed two major isomers in a ratio of 2:1. The isomers were separated using column chromatography and were eluted 0.5−2% methanol in chloroform to give **4e** (17 mg, 31%) and **5e** (8 mg, 15%). ^{1}H NMR of **5e** showed two components in an equilibrium state (6:1). Reversed phase HPLC of **5e** (Gilson, C-18 column, 50−70% MeCN in water containing 0.1% TFA in 30 min) gave a single sharp peak. For **4e**, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11−7.58 (m, 8H?), 4.42 (dd, 1H, J = 10.8 Hz, 2.3 Hz, H1), 3.96 (d, 1H, J = 11.1 Hz, H9), 3.77 (dd, 1H, J = 10.5 Hz, 6.2 Hz), 3.27 (t, 1H, J = 11.1 Hz), 2.85 (dd, 1H, J = 15.8 Hz, 4.6 Hz), 2.75 (t, 1H, J = 15.6 Hz), 2.42 (q, 1H, J = 11.0 Hz, H9a), 2.20−2.32 (m, 1H), 1.82−1.98 (m, 1H, H3a), 1.13 (d, 3H, J = 6.9 Hz), 1.03 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4, 172.2, 135.2, 135.1, 133.0, 131.2, 130.3, 128.6, 128.3, 127.9, 127.5, 127.0, 66.9, 56.4, 51.6, 46.0, 41.2, 32.2, 31.7, 20.4, 17.1. For the major component of **5e**, ^{1}H NMR (300 MHz, C_6D_6) δ 7.27 (d, 1H, J = 7.3 Hz), 6.99−7.10 (m, 7H?), 6.65 (d, 1H, J = 7.3 Hz), 4.24 (dd, 1H, J = 7.1 Hz, 1.8 Hz, H1), 3.65 (d, 1H, J = 4.5 Hz, H9), 2.96 (dd, 1H, J = 11.6 Hz, 8.0 Hz), 2.84 (m, 1H, H9a), 2.64 (dd, 1H, J = 11.5 Hz, 2.4 Hz), 2.40 (dd, 1H, J = 15.1 Hz, 6.2 Hz), 2.18−2.26 (m, 1H, H3a), 1.70−1.79 (m, 2H), 0.93 (d, 3H, J = 6.5 Hz), 0.92 (d, 3H, J = 6.6 Hz); NOESY (500 MHz, C_6D_6) between H1 and H9, H3a and H9a; ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 170.2, 136.2, 135.8, 132.7, 130.0, 128.9, 128.3, 128.2, 127.8, 127.1, 126.9, 67.4, 55.9, 49.5, 41.5, 35.6, 32.3, 31.5, 19.1, 18.6.

Diels−Alder Reaction of 3f To Make 4f and 5f. The resin-bound precursor **3f** (148 mg, 0.085 mmol) in DMF was heated at 95−98 °C for 3 days. The product was cleaved using TFA (20%) in CH_2Cl_2. ^{1}H NMR of the crude mixture showed two major isomers in a ratio of 2:1. The isomer **4f** was isolated using column chromatography and was eluted using 0.5−1% methanol in chloroform to give a white solid (14 mg, 32%). The isomer **5f** was eluted using 2−3% methanol in chloroform to give a white solid (8 mg, 18%). ^{1}H NMR of **5f** showed two components in an equilibrium state (4:1). Reversed phase HPLC of **5e** (Gilson, C-18 column, 50−70% MeCN in water containing 0.1% TFA in 30 min) gave a single sharp peak. For **4f**, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, 2H, J = 7.2 Hz), 7.41−7.63 (m, 8H), 7.04 (s, 1H), 6.69 (s, 1H), 4.40 (d, 1H, J = 8.7 Hz, H1), 3.84 (d, 1H, J = 10.7 Hz, H9), 3.76 (s, 3H), 3.75−3.81 (m, 1H), 3.23 (t, 1H, J = 11.0 Hz), 2.67−2.83 (m, 2H), 2.38 (q, 1H, J = 10.9 Hz, H9a), 2.14−2.26 (m, 1H), 1.84−1.96 (m, 1H, H3a), 1.10 (d, 3H, J = 6.9 Hz), 0.99 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 171.0, 164.5, 150.1, 138.3, 136.4, 134.0, 133.3, 130.4, 130.1, 129.0, 128.3, 128.1, 127.8, 125.4, 122.3, 113.1, 66.0, 56.0, 55.7, 50.6, 45.9, 41.0, 32.1, 31.6, 20.4, 16.8; LC-MS calcd for $C_{31}H_{34}NO_6$ (MH^+) 514, found 514. For the major component of **5f**, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, 2H, J = 7.4 Hz), 7.30−7.64 (m, 8H), 7.10 (s, 1H), 6.60 (s, 1H), 4.15 (s, broad, 1H, H1), 3.72 (s, 3H), 3.65−3.80 (m, 2H), 3.15 (d, 1H, J = 11.4 Hz), 2.92 (m, broad, 1H, H9a), 2.74−2.84 (m, 2H), 2.13 (dd, 1H, J = 13.0 Hz, 6.8 Hz), 2.06−2.18 (m, 1H), 1.05 (d, 3H, J = 7.0 Hz), 1.02 (d, 3H, J = 7.1 Hz); NOESY (500 MHz, C_6D_6) between H1 and H9, H3a and H9a; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 170.2, 164.7, 150.6, 138.4, 136.6, 134.4, 133.4, 130.3, 129.9, 129.3, 128.5, 128.2, 127.3, 124.6, 123.2, 112.3, 67.0, 55.9, 55.8, 48.1, 41.3, 35.4, 32.0, 31.4, 19.1, 18.7; LC-MS calcd for $C_{31}H_{34}NO_6$ (MH^+) 514, found 514.

Diels−Alder Reaction of 3h To Make 4h. The resin-bound precursor **3d** (100 mg, 0.057 mmol) in DMF was heated at 95−98 °C for 3 days. The product was cleaved using TFA (20%) in CH_2Cl_2. A single diastereomer **4h** was observed by ^{1}H and ^{13}C NMR of the crude mixture and was obtained (23 mg, 98%) without any purification. The purity was about 90% by reversed phase HPLC. Product **4h** has a better solubility in a mixture of chloroform and methanol. ^{1}H NMR (300 MHz,

$CD_3OD + CDCl_3$, 1:1) δ 8.17 (d, 1H, $J = 1.8$ Hz), 8.03 (dd, 1H, $J = 8.3$ Hz, 2.0 Hz), 7.41−7.57 (m, 5H), 7.29 (d, 1H, $J = 8.6$ Hz), 4.40 (dd, 1H, $J = 8.5$ Hz, 1.7 Hz, H1), 3.91 (d, 1H, $J = 10.8$ Hz, H9), 3.80 (dd, 1H, $J = 10.7$ Hz, 6.3 Hz), 3.28 (t, 1H, $J = 11.0$ Hz), 2.98 (dd, 1H, $J = 16.6$ Hz, 4.4 Hz), 2.86 (dd, 1H, $J = 12.0$ Hz, 9.4 Hz), 2.42 (dt, 1H, $J = 11.3$ Hz, 11.3 Hz, 8.8 Hz, H9a), 2.19−2.30 (m, 1H), 1.81−2.00 (m, 1H), 1.15 (d, 3H, $J = 7.1$ Hz), 1.05 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, $CD_3OD + CDCl_3$, 1:1, CD_3OD as the internal reference) δ 176.7, 172.9, 147.6, 144.6, 137.3, 137.1, 131.8, 131.7, 129.4, 128.6, 124.4, 122.7, 67.5, 57.0, 53.0, 47.1, 41.7, 33.2, 32.9. 21.3, 17.5; LC-MS: calcd for $C_{23}H_{24}N_2O_5$ (MH^+) 409, found 409.

Computational Details. The programs GAUSSIAN-98 and SPARTAN 5.0.3 were used for the ab initio and DFT calculations.[6,7] Optimized geometries were obtained at the RHF/3-21G level of theory. All stationary points (minima and transition structures) were characterized by calculation of their harmonic vibrational frequencies at the RHF/3-21G level. 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[8] with a 6-31G(d) basis set. B3LYP/6-31G(d)//RHF3-21G energies are uncorrected for ZPE.

Supporting Information Available: The compound purity is exemplified by ^{1}H and ^{13}C NMR spectra for the 11 purified Diels−Alder reaction products. 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.

JO991956Z

(5) The progress of the reactions was monitored by cleavage of the product from solid support.

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