Solid Phase Diels−Alder Reactions of Amino Acid Derived Trienes

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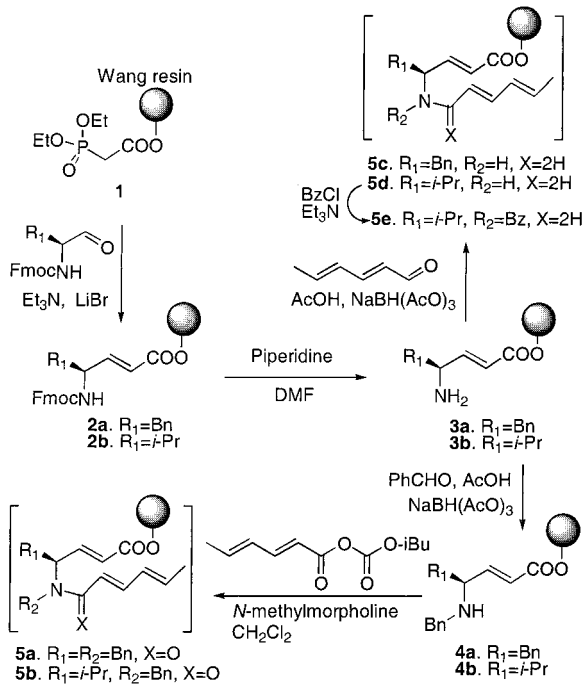
The known diethyl phosphonoacetyl-Wang resin **1** was treated with an Fmoc-protected amino aldehyde in the presence of Et_3N and LiBr. The Fmoc group was then removed with piperidine to give primary amines **3**. With or without N-benzylation, **3** was transformed to resin-bound trienes by either reductive alkylation with dienals or by acylation with activated dienocarboxylic acids. Trienes **5** cyclized at room temperature to give the predominant trans-fused bicyclic products **6**. Trienes **10** containing a furan moiety were constructed similarly, and their cycloadditions also proceeded at room temperature to produce epoxyisohydroindolines **11**, which were derived from an endo transition state pathway. Compounds **12** and **14** containing vinylfuran moieties reacted to form tricyclic products **13** and **15**. These examples demonstrated that furan rings can be used in solid-phase Diels−Alder reactions to generate libraries of functionalized polycyclic compounds.

Diels−Alder reactions were first realized on solid supports 20 years ago.[1] The utilization of Diels−Alder reactions in the construction of combinatorial libraries has been emerging.[2] We believe that there is considerable potential in the use of Diels−Alder reactions to synthesize diverse categories of heterocyclic compounds. We have recently investigated a class of novel amino acid-derived trienes that underwent facile Diels−Alder reactions in the solution phase to produce hydroisoindole derivatives.[3] These mild Diels−Alder reactions, which occur at ambient temperature under normal pressure, are attractive to adapt to resin-based synthesis. Furthermore, the intramolecular Diels−Alder reactions of amino acid-based precursors can provide controlled regioselectivity and diastereoselectivity. These considerations led us to extend our investigation of intramolecular Diels−Alder reactions of amino acid derived trienes onto a solid support. We wish to report several examples of our syntheses of highly functionalized hydroisoindole derivatives.

Results and Discussion

All reactions start from the known phosphonoacetyl-Wang resin **1**,[4] which was treated with an Fmoc-protected amino aldehyde[5a,b] in the presence of Et_3N and LiBr (Scheme 1).[5c,d] The Fmoc group was then removed with piperidine to give primary amines **3**. The primary amines were benzylated to produce secondary amine intermediates **4**. We initially attempted to acylate **4** using 2,4-hexadienoyl chloride and Et_3N in several different ways, none of which were successful. However, coupling **4** with 2,4-hexadienoic acid to afford trienes **5a**,**b** was accomplished using isobutyl chloroformate as an activator.

Scheme 1



(1) Yedidia, V.; Leznoff, C. C. *Can. J. Chem.* **1980**, *58*, 1144 and references therein.

(2) Schlessinger, R. H.; Bergstrom C. P. *Tetrahedron Lett.* **1996**, *37*, 2133. (b) Tietze, L. F.; Hippe, T.; Steinmetz, A. *Synlett* **1996**, 1043. (c) Heerding, D. A.; Takata, D. T.; Kwon, C.; Huffman, W. F.; Samanen, J. *Tetrahedron Lett.* **1998**, *39*, 6815. (d) Ball, C. P.; Barrett, A. G. M.; Commercon, A.; Compere, D.; Kuhn, C.; Roberts, R. S.; Smith, M. L., Venier, O. *Chem. Commun.* **1998**, 2019. (e) Wendeborn, S.; De Mesmaeker, A.; Brill, W. K.-D. *Synlett* **1998**, 865. (f) Paulvannan, K. *Tetrahedron Lett.* **1999**, *40*, 1851.

(3) Murray, W. V.; Sun, S.; Turchi, I. J.; Brown, F. K.; Guathier, A. D. *J. Org. Chem.* **1999**, *64*, 5930.

(4) Wipf, P.; Henninger, T. C. *J. Org. Chem.* **1997**, *62*, 1586.

(5) Fmoc-protected amino aldehydes derived from phenalanine, valine, and glycine were prepared using a method described by: (a) Fehrentz, J.-A.; Castro, B. *Synthesis* **1983**, 676. (b) Wen, J. J.; Crews, C. M. *Tetrahedron: Asymmetry* **1998**, *9*, 1855. For the discussions of chirality stability of amino aldehyde, see: (c) Rubsam, F.; Evers, A. M.; Michel, C.; Giannis, A. *Tetrahedron Lett.* **1997**, *5*, 1707. (d) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183. Fmoc-aminoaldehydes solidified upon removal of the solvent. After storage for 8 months in the refrigerator (0−4 °C), the Fmoc-aminoaldehydes were used to make **3a** and **3b** (Scheme 1), which were then coupled with Fmoc-NH−Phe-OH. Removal of the Fmoc group and cleavage from the resin gave the crude dipeptide-like compounds NH_2−Phe-NHCH(R_1)CH=CHCOOH. Each crude mixture contained only a single diastereomer as shown by ^1H and ^{13}C NMR. That is, no epimerization took place with the Fmoc-aminoaldehydes under these conditions. Otherwise, there should be a second diastereomer in each case.

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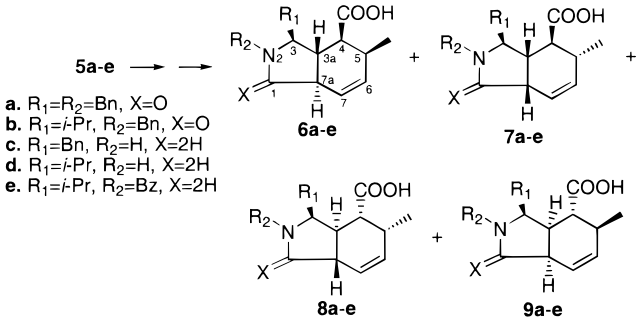
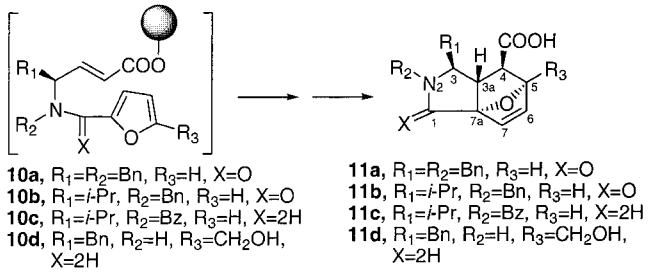
Scheme 2



Scheme 3



After washing, the resin bound trienes **5a**,**b** were allowed to stand in CH_2Cl_2 with occasional swirling. The Diels−Alder reaction was found complete in 30 h for **5a** and in 3 days for **5b** (Scheme 2).[6] After cleavage from the resin, LC−MS showed a single peak for the expected mass of the desired products. The isomer ratio of the crude mixture from triene **5a** could not, however, be determined by ^{1}H NMR integration, due to impurities. A ratio of 10:10:3:1 was estimated from reversed phase HPLC analysis. After preparative HPLC purification, the structures of the two major isomers were assigned to be **6a** and **8a** by ^{1}H NMR coupling constants and by comparison to the corresponding ethyl ester.[3] The total yield of **6a** and **8a** was 38% based on the commercial resin loading of 0.8 mmol/g. The reaction mixture of **5b** also gave a mass spectrum with $MH^+ = 328$, and its ^{1}H NMR spectrum indicated only one major isomer **6b**. The minor isomers could not be clearly identified but were estimated to be less than 10% by ^{1}H NMR. After silica gel flash column chromatography purification, **6b** was obtained in 48% yield. The intramolecular Diels−Alder reactions of resin-bound trienes **5a**,**b** took place at room temperature, while the corresponding intermolecular reaction between resin-bound acryloyl and 2,4-pentadienoyl methyl ester,[1] which was carried out at reflux in toluene, gave a mixture of regio- and stereoisomers.

An alternate transformation of the primary amines **3** was to directly connect them to a diene by reductive alkylation with 2,4-hexadienal (Scheme 1).[7] The secondary amine **5c** in solution phase undergoes a very fast Diels−Alder reaction under the conditions of the reductive alkylation.[3] After the reductive alkylation was allowed for 1 h, the resin-bound triene **5c** was thoroughly washed and was allowed to stand in CH_2Cl_2 for 20 h.[6] After cleavage, the Diels−Alder product **6c** was obtained in 55% yield from HPLC and was the only isolated product (Scheme 2). The possible minor isomers could not be confirmed or quantified by HPLC and ^{1}H NMR. The Diels−Alder reaction of **5d** in Schemes 1 and 2 was very slow relative to that of **5c**. This secondary amine triene was transformed to benzoyl amide **5e** to accelerate the cycloaddition (Scheme 1). The cycloaddition was found to be complete in 16 h. ^{1}H NMR showed the existence of two isomers in a ratio of 10:1. A possible third isomer could not be quantified by ^{1}H NMR integration. After purification by column chromatography, the major isomer **6e** was obtained in 32% yield (Scheme 2).

The diastereoselectivity for the solid-phase reactions of trienes **5** follows the same trend as that observed for the corresponding solution-phase reactions.[3] That is, the major diastereomers were derived from the endo transition states, and 1,3-allylic interaction of the dienophile had an important impact on the distribution of product isomers depending on the steric effect of substituent R_1.

The furan ring has been shown to be a highly useful building block to access diversely functionalized compounds and polymers, especially as a diene in Diels−Alder reactions.[8] However, there have been rare examples of solid-phase Diels−Alder reactions involving a furan ring moiety.[2a,f] We, therefore, decided to assemble chiral trienes on the solid support that contain a furan moiety. Thus, furoyl chloride was used to react with **4a,b**, and the resulting trienes **10a** and **10b** were allowed to cyclize for 60 h and 7 days, respectively.[6] Compound **11a** was obtained as the only isolated isomer in 55% yield and **11b** in 52% yield (Scheme 3). The ^{1}H NMR of the crude reaction mixtures indicated the presence of minor impurities, which could not be confirmed to be stereoisomers other than **11a** and **11b**.

A furfuryl group was also tested for the intramolecular Diels−Alder reactions. Amine **3b** was alkylated with furfural under reductive conditions, followed by treatment with PhCOCl and Et_3N to generate triene **10c**. The following cyclization reaction was carried out in CH_2Cl_2 for 60 h to produce a single isolated isomer **11c** in 65% yield after flash chromatography.[6] The secondary amine triene **10d** containing a hydroxymethylfurfuryl group was prepared from **3a** via reductive alkylation and was allowed to cyclize for 4 days.[6] After cleavage from resin, the crude mixture was purified by HPLC to give only one isomer **11d** in 32%.

The resin-bound trienes **10a**−**d** were conveniently constructed using commercially available substituted furan derivatives. Therefore, the epoxyisohydroindoline carboxylic acids **11a**−**d** have been easily accessed in only a few steps (Scheme 3).[9] The endo selectivity was observed in each of our cases, although exo selectivity was also reported by others.[8]

There have been a few reports utilizing vinylfuran derivatives in solution-phase Diels−Alder reactions.[10] We tested the feasibility of using both 2-vinyl- and 3-vinylfuran derivatives as dienes for the solid-phase Diels−Alder reactions (Schemes 4 and 5). Compound **12** was

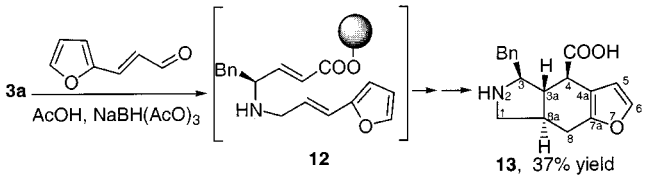
(6) All reaction times and Diels−Alder product yields were unoptimized. No attempt was made to monitor the progress of the solid-phase Diels−Alder reactions. The actual *allowed* reaction times were estimated to be up to twice as long as those of the corresponding solution phase reactions as reported in ref 3, to be sure that the reaction were complete before cleavage from solid support.

(7) Abdel-Magid, A. F.; Harris, B. D.; Maryanoff, C. A. *Synlett* **1994**, 81.

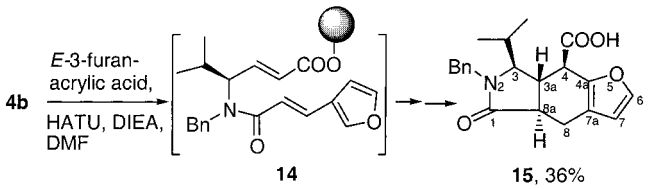
(8) For a recent review, see: Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *42*, 14179 and references therein.

(9) For solution-phase syntheses of epoxyisoindolines, see: (a) Jung, M. E.; Street, L. J. *Tetrahedron Lett.* **1985**, *26*, 3639. (b) Prajapati, D.; Sandhu, J. S. *Heterocycles* **1985**, *23*, 17. (c) Mance, A. D.; Sindler-Kulyk, M.; Jakopcic, K.; Hergold-Brundic, A.; Nagl, A. *J. Heterocycl. Chem.* **1997**, *34*, 1315.

Scheme 4



Scheme 5



synthesized from a reaction between **3a** and *trans*-furylacrolein (Scheme 4), and its cyclization was complete in 2 days. Compound **13** was obtained as the only isolated stereoisomer by HPLC purification. The mechanism for the formation of **13** should involve a Diels−Alder reaction followed by a rearrangement process (aromatization). A side product was detected as dialkylated tertiary amine (an extra furylpropenyl group is on the nitrogen atom of **13**).

The intermediate **14** containing a 3-vinylfuran moiety was then prepared by coupling *trans*-3-furanacrylic acid with **4b** using HATU [*O*-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate]. The following cyclization reaction also proceeded in CH_2Cl_2 at room temperature. After 4 days, the product was cleaved from the resin.[6] Flash column chromatography gave **15** as the only isolated product.

The vinylfuran moieties can be attached to a dienophile on resin either by reductive alkylation of furanacrolein (Scheme 4) or by coupling a furanacrylic acid (Scheme 5). As expected, the side-chain double bond of vinylfuran acted as a part of the diene participating in the Diels−Alder reactions. The aromaticity of the furan ring was restored due to rearrangement after a cycloaddition.[10] The isolated products were also trans fused and were derived from the endo transition states. These examples indicate a potential for extensive exploration of this kind of reaction in the construction of libraries of heterocyclic compounds.

Conclusions

We have demonstrated several examples of facile Diels−Alder reactions of amino acid derived trienes on resin that can be potentially used for rapid stereoselective synthesis of heterocyclic compounds for high throughput drug screening. Furan moieties can be especially useful to access highly functionalized compounds. We will continue to extend our interests in furan ring-based intramolecular cycloadditions on resin, so that the potential in this area can be explored further.

(10) Hayakawa, K.; Nagatsugi, F.; Kanematsu, K. *J. Org. Chem.* **1988**, *53*, 860. (b) Cooper, J. A.; Cornwall, P.; Dell, C. P.; Knight, D. W. *Tetrahedron Lett.* **1988**, *29*, 2107. (c) Fischer, K.; Hunig, S. *Chem. Ber.* **1987**, *120*, 325. (d) Cornwall, P.; Dell, C. P.; Knight, D. W. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2395.

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

Experimental Section

Preparation of 3a,b. Diethyl phosphonoacetyl-Wang resin (1.575 g, 1.103 mmol, 0.70 mmol/g) in THF (15 mL) was treated with Et_3N (1 mL), LiBr (200 mg), and a Fmoc-protected amino aldehyde (3 equiv). The mixture was shaken for 20 h, washed three rounds with MeOH, CH_2Cl_2, and water, dried in vacuo, and treated with 20% piperidine in DMF for 20 min. Filtration followed by washing gave the resin bound amines **3a,b**, which turned blue in a qualitative ninhydrin test.

Procedure for Reductive Alkylation To Make 4a,b, 5c,d, 10c,d, and 12. An amine **3a** or **3b** in CH_2Cl_2 containing glacial AcOH (10%) was treated with an aldehyde (10 equiv; benzaldehyde for **4a,b**, (*E*,*E*)-2,4-hexadienal for **5c,d**, fural for **10c**, 5-hydroxymethylfural for **10d**, or (*E*)-3-furanacrolein for **12**) for 0.5 h on a shaker. The mixture was washed with CH_2Cl_2, DMF, and $CH(OMe)_3$ and was treated with $NaBH(OAc)_3$ (3 equiv) in anhydrous $CH(OMe)_3$ containing 10% glacial AcOH for 1 h.[11] After washing, the resin-bound intermediates were used for the next steps.

Acylation and Diels−Alder Reactions To Prepare 6a and 8a. To 2,4-hexadienoic acid (163 mg, 1.46 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added *N*-methylmorpholine (1.0 mL) and isobutyl chloroformate (200 μL, 1.39 mmol). The mixture was stirred at room temperature for 15 min and was added to a tube that contained resin-bound intermediate **4a** (610 mg, 0.403 mmol). The tube was shaken overnight. The mixture was then washed with CH_2Cl_2 and MeOH and was allowed to stand in CH_2Cl_2 for a further 30 h with occasional swirling. After filtration, the resin was treated with 20% TFA in CH_2Cl_2 for 20 min. The TFA solution was collected by filtration, and the solid resin residue was washed thoroughly with CH_2Cl_2 and CH_3OH. The combined filtrate was concentrated in vacuo, coevaporated with $CHCl_3$, and dried under high vacuum for 0.5 h. MS analysis of the crude mixture showed a peak of 376 for the protonated molecular ions (MH^+). Reversed phase HPLC analysis on a Gilson C-18 column using a mobile-phase gradient of MeCN (30−70% in 35 min) in water (containing 0.1% TFA) showed a ratio of about 10:10:3:1. After preparative HPLC, **6a** was obtained as a white powder (total 30 mg, 20%), which was the slowest to elute among the four possible isomers. The next slowest isomer **8a** was obtained also as a white powder (total 27 mg, 18%). Immediately before the two major isomers, there were two faster moving peaks, which might be the two minor isomers as judged by the same mass spectrum. But the structures for the two minor fractions were not characterized due to the small quantities and some impurities.

For **6a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12−7.26 (m, ∼8H), 6.89−6.93 (m, 2H), 6.15 (d, 1H, J = 9.7 Hz), 5.54 (dt, 1H, J = 3.2 Hz, 3.2 Hz, 9.6 Hz), 5.12 (d, 1H, J = 15.2 Hz), 4.04 (d, 1H, J = 15.2 Hz), 3.63 (ddd, 1H, J = 3.1 Hz, 5.6 Hz, 9.0 Hz, H3), 3.36 (dd, 1H, J = 3.0 Hz, 15.5 Hz), 2.92−3.03 (m, 2H), 2.71−2.84 (m, 2H), 2.08 (q, 1H, J = 11.0 Hz, H3a), 0.98 (d, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 173.1, 137.3, 136.5, 133.0, 129.5, 128.5, 128.4, 127.7, 127.3, 126.5, 123.0, 59.7, 48.3, 47.7, 44.2, 39.5, 36.2, 33.9, 17.2; LC−MS calcd for $C_{24}H_{26}NO_3$ (MH^+) 376, found 376.

For **8a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23−7.31 (m, ∼6H), 7.11−7.15 (m, 2H), 6.88−6.93 (m, 2H), 6.13 (d, 1H, J = 9.8 Hz), 5.59 (dt, 1H, J = 3.5 Hz, 3.5 Hz, 9.9 Hz), 4.94 (d, 1H, J = 15.1 Hz), 3.96−4.03 (m, 1H, H3), 3.19 (d, 1H, J = 15.0 Hz), 3.07 (dd, 1H, J = 6.8 Hz, 12.0 Hz, H4), 3.00 (dd, 1H, J = 0.9 Hz, 12.7 Hz, H7a), 2.68−2.84 (m, 3H), 2.27 (dt, 1H, J = 6.6 Hz, 12.4 Hz, 12.4 Hz, H3a), 0.96 (d, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 173.0, 137.9, 136.6, 132.8, 129.3, 128.8, 128.6, 128.0, 127.5, 126.9, 122.7, 58.8, 45.2, 44.8, 42.7, 39.5, 34.2, 33.1, 16.9; LC−MS: calcd for $C_{24}H_{26}NO_3$ (MH^+) 376, found 376.

Acylation and Diels−Alder Reaction To Prepare 6b. By following the procedure to prepare **6a** and **8a**, resin **4b** (500 mg, 0.364 mmol) was used, and the triene intermediate **5b** was stored in CH_2Cl_2 for 3 days before cleavage with TFA. Compound **6b** was purified by flash chromatography and eluted using 1−4% MeOH in CH_2Cl_2 to give a solid (57 mg,

48%). For **6b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14−7.33 (m, 5H), 6.44 (dt, 1H, J = 3.0 Hz, 3.0 Hz, 9.0 Hz), 5.64 (dt, 1H, J = 3.0 Hz, 3.0 Hz, 9.0 Hz), 5.20 (d, 1H, J = 15.4 Hz), 3.87 (d, 1H, J = 15.4 Hz), 3.24 (dd, 1H, J = 2 Hz, 10 Hz, H3), 2.82 (t, 1H, J = 9.1 Hz, H4), 2.67 (dd, 1H, J = 2.0 Hz, 12.7 Hz, H7a), 2.50−2.58 (m, 1H), 2.05−2.19 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 174.1, 136.6, 133.2, 128.7, 127.7, 127.4, 126.8, 65.9, 46.5, 45.7, 44.1, 41.4, 32.9, 26.4, 17.9, 16.9, 16.4; NOESY (400 MHz, $CDCl_3$) between H3 and H4, H3 and H7a, H4 and H7a, H5 and H7a; LC−MS calcd for $C_{20}H_{26}NO_3$ (MH^+) 328, found 328.

Diels−Alder Reaction To Prepare 6c. Freshly prepared **5c** from **3a** (610 mg, 0.48 mmol) was allowed to stand in CH_2Cl_2 for 20 h with occasional swirling. After cleavage with TFA−CH_2Cl_2, the mixture was purified with preparative HPLC (Gilson, C-18 column, 10−40% MeCN in water containing 0.1% TFA in 35 min). Compound **6c** was the only identified isomer and was obtained as a solid (64 mg, 55% yield): ^{1}H NMR (300 MHz, D_2O, the solvent peak was set to 4.63 ppm as the reference) δ 7.16−7.28 (m, 5H), 5.59−5.67 (m, 2H), 3.78 (dt, 1H, J = 3.6 Hz, 11.1 Hz, 11.1 Hz, H3), 3.35 (dd, 1H, J = 3.5 Hz, 14.9 Hz), 3.30 (dd, 1H, J = 7.6 Hz, 11.1 Hz), 2.95 (dd, 1H, J = 7.0 Hz, 11.3 Hz, H4), 2.67−2.79 (m, 3H), 2.43−2.54 (m, 1H, H7a), 1.88 (q, 1H, J = 11.1 Hz, H3a), 0.86 (d, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, D_2O) δ 179.5, 139.2, 137.0, 131.9, 131.5, 130.2, 124.9, 67.4, 49.1, 49.0, 45.7, 44.7, 39.8, 35.2, 19.5; LC−MS calcd for $C_{17}H_{22}NO_2$ (MH^+) 272, found 272.

Benzoylation and Diels−Alder Reaction To Prepare 6e. The secondary amine **5d** after drying under high vacuum overnight was treated with a mixture of PhCOCl (10 equiv) and Et_3N in CH_2Cl_2 for 2 h to give an intermediate **5e**. After filtration and washing with CH_2Cl_2 and MeOH, **5e** was allowed to stand in CH_2Cl_2 for another 16 h. Cleavage of the product gave a crude mixture, whose mass spectrum showed one major peak at 328 (100%) for **6e** (MH^+) and a peak at m/z 391 for an unknown compound. Compound **6e** was isolated by column chromatography, eluted using 0.5−1% MeOH in CH_2Cl_2, and obtained in 32% yield as a solid: ^{1}H NMR (300 MHz, C_6D_6) δ 7.63 (dd, 2H, J = 2.4 Hz, 7.4 Hz), 7.11−7.15 (m, 3H), 5.28−5.38 (m, 2H), 4.52 (d, 1H, J = 9.2 Hz, H3), 3.30 (dd, 1H, J = 6.3 Hz, 9.6 Hz), 2.89−2.96 (m, 1H), 2.80 (dd, 1H, J = 7.1 Hz, 10.3 Hz, H4), 2.67 (dd, 1H, J = 10.2 Hz, 11.9 Hz), 2.49−2.54 (m, 1H), 2.05 (q, 1H, J = 10.4 Hz, H3a), 1.50−1.70 (m, 1H, H7a), 1.39 (d, 3H, J = 7.0 Hz), 1.10 (d, 3H, J = 7.2 Hz), 1.05 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 171.7, 136.7, 134.4, 130.5, 128.3, 128.0, 125.6, 64.7, 54.5, 49.0, 43.9, 43.8, 33.4, 31.5, 21.1, 17.2, 17.0; LC−MS: calcd for $C_{20}H_{26}NO_3$ (MH^+) 328, found 328.

Furoylation and Diels−Alder Reaction To Prepare 11a. Resin **4a** (250 mg, 0.165 mmol) was treated with a mixture of furoyl chloride (0.2 mL, 2.03 mmol) and Et_3N (0.5 mL) in CH_2Cl_2 (6 mL) for 2 h to give **10a**. After washing with CH_2Cl_2, **10a** was kept in CH_2Cl_2 for 60 h with occasional swirling. After cleavage with TFA−CH_2Cl_2, the mixture was purified by flash column chromatography and eluted with 0−0.5% MeOH in $CHCl_3$ to give **11a** as a solid (34 mg, 55%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14−7.38 (m, 8H), 6.96 (m, 2H), 6.76 (d, 1H, J = 5.9 Hz), 6.32 (dd, 1H, J = 1.3 Hz, 5.9 Hz), 5.23 (d, 1H, J = 16.0 Hz), 5.19 (dd, 1H, J = 1.3 Hz, 6.3 Hz), 4.21 (d, 1H, J = 15.4 Hz), 3.54 (ddd, 1H, J = 4.2 Hz, 6.4 Hz, 7.3 Hz, H3), 3.29 (dd, 1H, J = 4.1 Hz, 13.0 Hz), 2.58 (dd, 1H, J = 3.4 Hz, 4.3 Hz, H4), 2.51 (dd, 1H, J = 10.5 Hz, 12.7 Hz), 2.32 (dd, 1H, J = 3.1 Hz, 7.5 Hz, H3a); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 168.0, 135.5, 135.4, 134.9, 134.8, 129.3, 128.9, 128.6, 127.8, 127.7, 127.0, 92.6, 82.7, 63.4, 49.3, 49.1, 44.6, 39.1; NOESY (500 MHz, $CDCl_3$) between H3 and H4, and between H3a and H7; LC−MS calcd for $C_{23}H_{22}NO_4$ (MH^+) 376, found 376.

Furoylation and Diels−Alder Reaction To Prepare 11b. Resin **4b** (340 mg, 0.213 mmol) was treated with a mixture of furoyl chloride (0.25 mL, 2.53 mmol) and Et_3N (0.8 mL) in CH_2Cl_2 (8 mL) for 2 h to give **10b**. After washing with CH_2Cl_2, **10b** was kept in CH_2Cl_2 for 7 days with occasional swirling. After cleavage with TFA−CH_2Cl_2, the mixture was purified by flash column chromatography and eluted with 0−2% MeOH in $CHCl_3$ to give **11b** as a solid (36 mg, 52%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18−7.34 (m, 5H), 6.80 (d, 1H, J = 5.9 Hz, H7), 6.46 (dd, 1H, J = 1.6 Hz, 5.9 Hz, H6), 5.37 (dd, 1H, J = 1.3 Hz, 4.5 Hz), 5.28 (d, 1H, J = 15.2 Hz), 3.83 (d, 1H, J = 15.2 Hz), 3.31 (dd, 1H, J = 3.7 Hz, 7.9 Hz, H3), 3.16 (dd, 1H, J = 3.7 Hz, 4.2 Hz, H4), 2.37 (dd, 1H, J = 3.2 Hz, 7.8 Hz, H3a), 2.10−2.00 (m, 1H), 0.86 (d, 3H, J = 5.3 Hz), 0.84 (d, 3H, J = 5.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 168.6, 135.3, 135.24, 135.21, 128.8, 127.7, 127.6, 92.7, 82.3, 65.9, 50.6, 44.1, 42.1, 26.4, 18.1, 14.3; NOESY (400 MHz, $CDCl_3$), between H3 and H4, weak between H3a and H7; LC−MS calcd for $C_{19}H_{22}NO_4$ (MH^+) 328, found 328.

Benzoylation and Diels−Alder Reaction To Prepare 11c. After the benzoylation procedure for **6e** was followed, the Diels−Alder reaction of **10c** was allowed for 60 h in CH_2Cl_2. Compound **11c** was obtained in 65% yield as a solid after flash column chromatography (eluted with 0−1% MeOH in CH_2Cl_2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.53 (m, 5H), 6.44 (d, 1H, J = 5.8 Hz), 6.36 (dd, 1H, J = 1.1 Hz, 5.9 Hz), 5.23 (d, 1H, J = 4.2 Hz), 4.14 (dd, 1H, J = 5.1 Hz, 7.0 Hz), 3.93 (d, 1H, J = 12.8 Hz), 3.88 (d, 1H, J = 12.7 Hz), 3.21 (dd, 1H, J = 3.2 Hz, 4.3 Hz), 2.60−2.69 (m, 1H), 2.40 (dd, 1H, J = 3.0 Hz, 7.1 Hz), 0.98 (d, 6H, J = 6.8 Hz);^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 171.0, 136.7, 135.3, 135.1, 130.3, 128.4, 127.5, 95.3, 80.6, 67.6, 52.6, 46.5, 29.2, 18.8, 15.9; NOESY (400 MHz, $CDCl_3$) between H1a and H3, between H1e and H3a, between H1e and H7, between H3 and H4, weak between H3a and H7; LC−MS calcd for $C_{19}H_{22}NO_4$ (MH^+) 328, found 328.

Diels−Alder Reaction To Prepare 11d. Freshly prepared **10d** from **2a** (268 mg, 0.168) mmol) was kept in CH_2Cl_2 for 4 days with occasional swirling. After cleavage with TFA−CH_2Cl_2, ^{1}H NMR of the crude mixture showed two isomers in a ratio of 2:1. The major isomer was isolated only using preparative HPLC (Gilson, C-18 column, 1−7% MeCN in water containing 0.1% TFA in 30 min) to give a solid (16 mg, 32% yield): ^{1}H NMR (300 MHz, CD_3OD) δ 7.26−7.35 (m, 5H), 6.64 (d, 1H, J = 5.7 Hz), 6.35 (d, 1H, J = 5.7 Hz), 4.13 (d, 1H, J = 12.7 Hz), 4.08 (d, 1H, J = 12.7 Hz), 3.96 (d, 1H, J = 13.7 Hz), 3.64−3.72 (m, 1H), 3.53 (d, 1H, J = 13.7 Hz), 3.10−3.19 (m, 2H), 2.89 (d, 1H, J = 2.9 Hz), 2.61 (dd, 1H, J = 2.8 Hz, 10.5 Hz, H3a); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 137.5, 136.9, 136.6, 130.2, 128.6, 96.4, 67.4, 61.2, 56.2, 50.2, 47.3, 38.2; NOESY (500 MHz, $CDCl_3$), between H1a and H3, between H1e and H3a, between H1e and H7, between H3 and H4, and between H3a and H7; LC−MS calcd for $C_{17}H_{20}NO_4$ (MH^+) 302, found 302.

Diels−Alder Reaction To Prepare 13. Freshly prepared **12** from **3a** (180 mg, 0.126) mmol) was allowed to stand in CH_2Cl_2 for 48 h with occasional swirling. After cleavage with TFA−CH_2Cl_2, ^{1}H NMR and MS of the crude mixture showed partial dialkylation during the preparation of **12**. The major product was isolated in pure form using preparative HPLC (Gilson, C-18 column, 10−55% MeCN in water containing 0.1% TFA in 30 min) to give a white powder 14 mg (37% yield): ^{1}H NMR (300 MHz, CD_3OD) δ 7.28−7.43 (m, 6H), 6.35 (d, 1H, J = 1.9 Hz), 3.82 (dt, 1H, J = 2.6 Hz, 10.7 Hz, 10.7 Hz, H3), 3.68 (d, 1H, J = 9.5 Hz, H4), 3.51 (dd, 1H, J = 7.2 Hz, 11.4 Hz), 3.26 (dd, 1H, J = 3.0 Hz, 15.1 Hz), 3.11 (t, 1H, J = 11.0 Hz), 2.95 (dd, 1H, J = 3.3 Hz, 15.0 Hz), 2.86 (dd, 1H, J = 11.5 Hz, 15.1 Hz), 2.48−2.63 (m, 2H), 2.41 (q, 1H, J = 10.5 Hz, H3a); ^{13}C NMR (75 MHz, CD_3OD) δ 175.9, 151.0, 143.7, 137.4, 130.3, 129.8, 128.7, 117.1, 110.3, 66.1, 48.5, 43.7, 41.4, 38.1, 27.2; LC−MS calcd for $C_{18}H_{20}NO_3$ (MH^+) 298, found 298.

Acylation and Diels−Alder Reaction To Prepare 15. The secondary amine **4b** (350 mg, 0.24 mmol) after drying under high vacuum overnight was treated with a mixture of *trans*-3-furanacrylic acid (167 mg, 1.21 mmol), DIEA (0.5 mL), and HATU (460 mg, 1.21 mmol) in CH_2Cl_2 (8 mL) for 2 h. This coupling procedure was repeated two more times to give an intermediate **5e**. After filtration and wash with CH_2Cl_2 and MeOH, **5e** was allowed to stand in CH_2Cl_2 for another 4 days. Cleavage of the product gave a crude mixture containing the major product **15**, which was isolated by column chromatography, eluted using 0−0.5% MeOH in CH_2Cl_2, and obtained as a solid in 31 mg (37% yield): ^{1}H NMR (300 MHz, C_6D_6) δ

6.95−7.12 (m, 6H), 5.89 (d, 1H, J = 1.9 Hz), 5.23 (d, 1H, J = 15.5 Hz), 3.64 (d, 1H, J = 15.4 Hz), 3.29 (d, 1H, J = 9.8 Hz, H4), 2.97 (dd, 1H, J = 1.6 Hz, 11.3 Hz, H3), 2.92 (ddd, 1H, J = 1.8 Hz, 5.1 Hz, 15.5 Hz), 2.22 (dt, 1H, J = 9.7 Hz, 9.7 Hz, 12.6 Hz, H3a), 2.41 (ddd, 1H, J = 2.6 Hz, 11.9 Hz, 15.4 Hz), 1.86−1.99 (m, 2H), 0.76 (d, 3H, J = 7.3 Hz), 0.75 (d, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, C_6D_6) δ 175.3, 174.9, 146.1, 142.8, 136.2, 128.7, 127.6, 127.5, 119.5, 110.8, 65.6, 46.0, 44.9, 44.4, 40.8, 26.8, 21.8, 17.2, 17.0; LC−MS calcd for $C_{21}H_{24}NO_4$ (MH^+) 354, found 354.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for the 11 purified Diels−Alder reaction products and a statement of stereo structural assignments based on NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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