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# Tandem Diels–Alder cyclization/aromatization reactions of 5-vinyl-1-acyl-2-aryl-2,3-dihydro-4-pyridones

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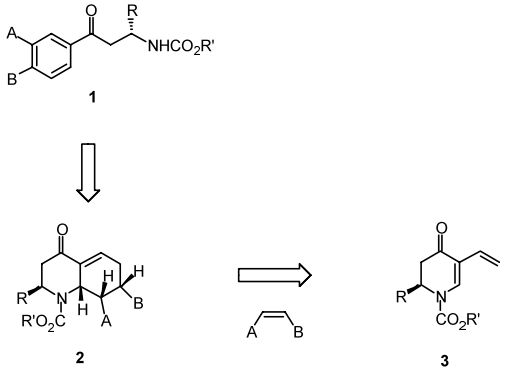
**Abstract**—A tandem Diels–Alder cyclization/aromatization of 5-vinyl-2,3-dihydro-4-pyridones and various dienophiles is reported. The intermediate Diels–Alder cycloadduct undergoes an elimination/aromatization to provide β-amino-ketones, β-amino-alcohols, and unnatural amino acids containing useful functionality. 

The Diels–Alder reaction is well known as a powerful tool for the construction of functionalized six-membered rings. Due to the inherent regio- and stereochemical control usually observed, it is not surprising that the Diels–Alder reaction continues to see a number of advances and synthetic applications for the preparation of complex molecules. The development of heteroatom-assisted Diels–Alder reactions provides increased reactivity and gives access to functional arrays which otherwise would be difficult to obtain.[1–4] Recently, we described a highly regio- and stereoselective synthesis of octahydroquinolines by the Diels–Alder reaction of 5-vinyl-1-acyl-2-aryl-2,3-dihydro-4-pyridones **3** with various dienophiles.[5] During the course of these studies, we observed interesting reactivity of diene **3** with certain dienophiles leading to ring-opening of the initially formed cycloadducts **2**. This process provides access to unique β-amino ketones, alcohols, and amino acids of type **1**. In this letter we disclose our preliminary findings in this area.




The Diels–Alder reaction of **4** with 1,4-naphthoquinone in refluxing toluene afforded the expected cycloadduct **5** in 84% isolated yield as a single diastereomer (Scheme 1). Analysis of the NMR spectrum of the crude product of this reaction showed that **5** was the only isomer present and the stereochemistry was in complete agreement with that observed for similar systems.[5] However, attempted purification of **5** on silica gel resulted in the isolation of a new product which was identified as the anthraquinone derivative **7** on the basis of its spectral properties and high resolution mass spectra. We suspect that **7** arises from silica gel promoted aromatization of the quinone moiety followed by a rapid aromatization of intermediate **6** and ejection of the carbamate functionality. The formation of **7** could be effected in a one-pot procedure by adding silica gel to the Diels–Alder adduct **5** in situ and stirring overnight at room temperature to give **7** in 88% yield from **4**. Reaction of **4** with 1,4-benzoquinone also occurred in refluxing toluene to give, as a single diastereomer, the initially formed cycloadduct **8** in 93% yield. When subjected to silica gel-promoted rearrangement, naphthoquinone derivative **9** was isolated in 69% yield from **4**. In similar fashion, reaction of **10**[5] with 1,4-benzoquinone afforded cycloadduct **11** in 86% yield. Treatment of **11** with silica gel gave β-amino alcohol **12** in 88% yield as a single diastereomeric product.

When diene **4** was allowed to react with DMAD or di-*tert*-butylacetylene dicarboxylate in refluxing toluene, the initially formed cycloadducts **13** could not be isolated (Scheme 2). Instead, intermediate **13** rapidly aromatized with ejection of the phenyl carbamate group to give the substituted benzene derivatives **14** and **15** in 71 and 85% yields, respectively. There was no

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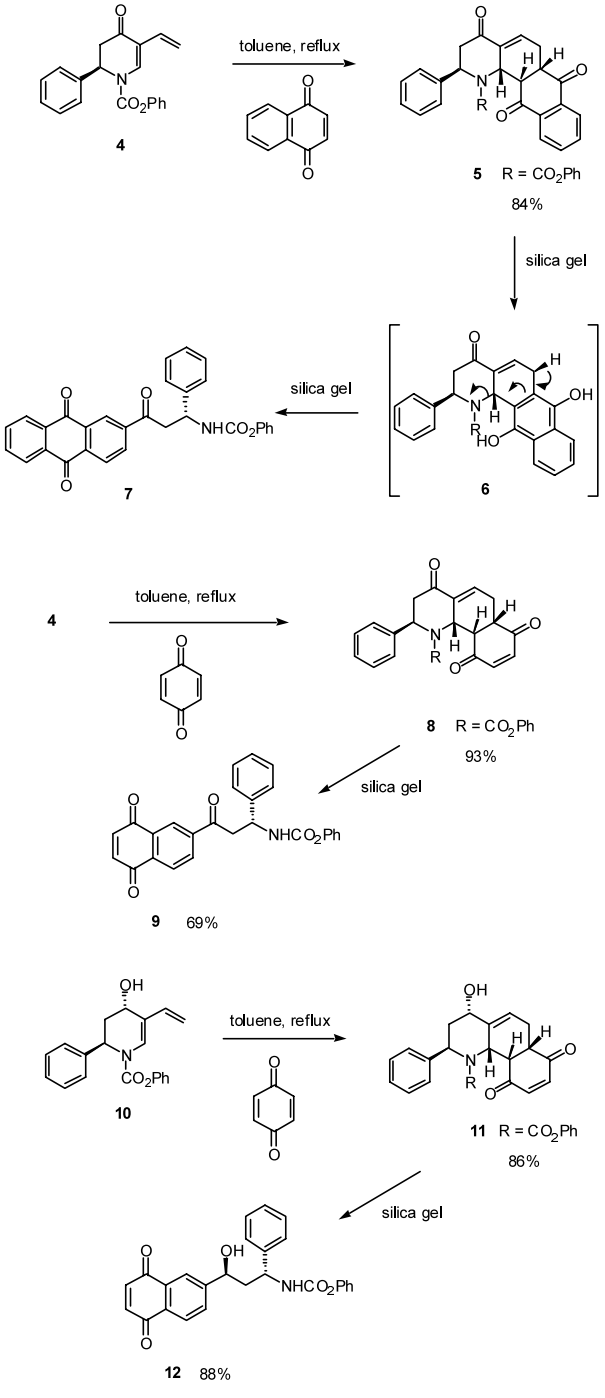
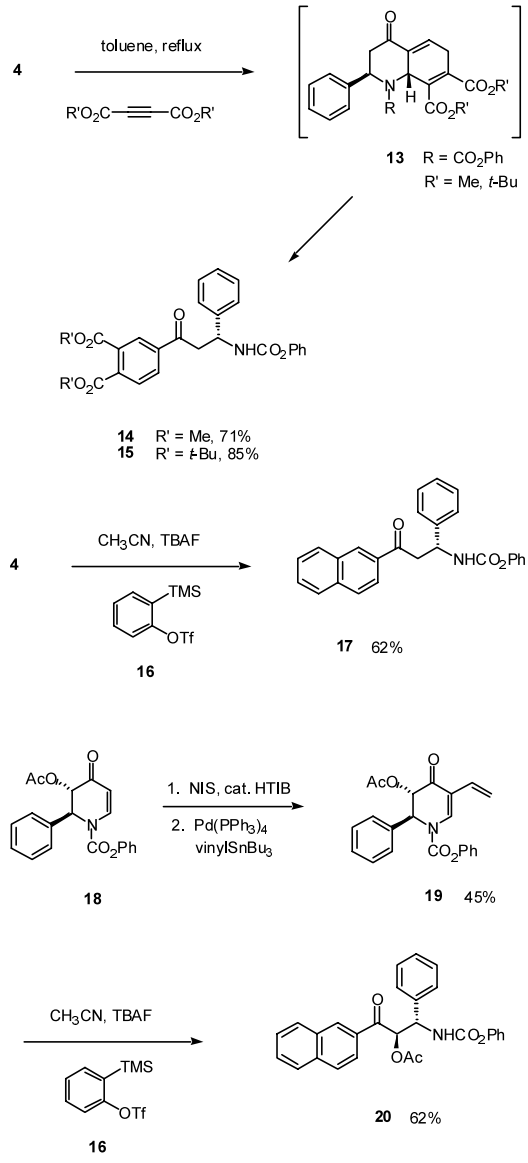
detectable amount of **13** in the crude reaction mixture even when the reaction was stopped prior to complete conversion of starting materials.

We also investigated the reaction of **4** with benzyne (Scheme 2). Treatment of a mixture of **4** and triflate **16** in acetonitrile with a 1.0 M solution of TBAF[6] resulted in the rapid formation of ring-opened naphthalene derivative **17** as the sole product in 62% isolated yield. Once again, the initially formed cycloadduct could not be isolated and underwent rapid aromatization by



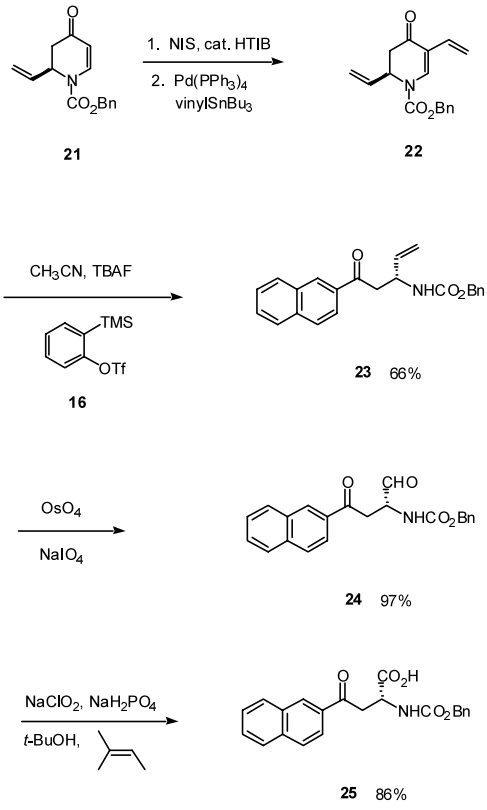

**Scheme 1.**




**Scheme 2.**

ejection of the phenyl carbamate group. In order to investigate the possibility of synthesizing more highly functionalized systems, we prepared diene **19** from the known dihydropyridone **18**.[7] Iodination of **18** with NIS/cat. [hydroxyl(tosyloxy)iodo]benzene (HTIB) followed by Stille coupling with tributyl(vinyl) tin gave **19** in 45% overall yield.[8] Reaction of **19** with benzyne under the conditions described above afforded compound **20** as a single diastereomer in 62% yield with the stereochemistry as shown.

Finally, we investigated an approach to α-amino acids by taking advantage of the vinyl substituent at the C-2 position of diene **22** for further elaboration to the carboxylic acid moiety (Scheme 3). Diene **22** was prepared from dihydropyridone **21** via the iodination/Stille coupling procedure as previously described. Reaction of **22** with benzyne in acetonitrile yielded the expected naphthalene product **23** arising from the tandem Diels–




**Scheme 3.**

Alder cyclization/aromatization protocol in 66% yield. Treatment of **23** with sodium periodate in the presence of osmium tetraoxide gave aldehyde **24** in nearly quantitative yield. Oxidation of **24** to amino acid **25** was accomplished with sodium chlorite/sodium phophate solution in a 2:1 mixture of *t*-BuOH:2-methyl-2-butene to give **25** in 86% yield.

In conclusion, we have developed a tandem Diels–Alder cyclization/aromatization reaction of 5-vinyl-1-acyl-2-substituted-2,3-dihydro-4-pyridones as a means of stereoselectivity preparing β-amino ketones, alcohols, and amino acids with a variety of functional arrays. Although this study used racemic starting materials, the methodology can lead to enantiopure products by starting with readily available nonracemic dihydropyridones.[9] This new synthetic protocol may be useful for the preparation of stereodefined hydroxy amino-alcohols and hydroxy amino acids, functional arrays which are well recognized as important components for various protease inhibitors and other potential pharmaceuticals.[10] Application of this chemistry toward the synthesis of other complex molecules is currently under investigation and will be reported in due course.[11]

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11. The structure assigned to each new compound is in accord with its IR and $^{1}H$ and $^{13}C$ NMR spectra and elemental analysis or high-resolution mass spectra. Selected characterization data:
Compound **12**: colorless oil; IR (thin film) 3353, 3063, 2923, 1714, 1666, 1600, 1530, 1489, 1306, 1206 $cm^{-1}$; $^{1}H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 2.18 (m, 1H), 2.39 (m, 1H), 4.76 (m, 1H), 4.99 (q, 1H, $J=6.6$ Hz), 5.76 (m, 1H), 6.95 (s, 1H), 7.06 (m, 1H), 7.17 (m, 1H), 7.33 (m, 11H), 7.71 (d, 1H, $J=7.8$ Hz), 8.00 (m, 1H); $^{13}C$ NMR ($CDCl_3$, 75

MHz) $\delta$ 45.8, 54.3, 71.8, 121.7, 123.7, 125.6, 126.8, 127.2, 128.3, 129.3, 129.5, 131.3, 132.2, 138.8, 139.0, 141.3, 151.0, 151.2, 154.4, 184.9, 185.2; HRMS calcd for $C_{26}H_{21}NO_5$: 428.1498 $[M+H]^+$; found, 428.1517 $[M+H]^+$. Compound **20**: colorless oil; IR (thin film) 3330, 2919, 1740, 1694, 1488, 1370, 1203 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 2.24 (s, 3H), 5.54 (m, 1H), 6.22 (d, 1H, $J=8.0$ Hz), 6.61 (d, 1H, $J=3.4$ Hz), 7.11–7.40 (m, 11H), 7.57 (m, 2H), 7.88 (m, 3H), 8.41 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 21.0, 56.6, 75.4, 121.7, 124.0, 125.7, 127.1, 127.6, 128.0, 128.7, 129.0, 129.2, 129.6, 130.2, 131.0, 132.6, 136.1, 151.7, 154.4, 170.4, 194.6; HRMS calcd for $C_{28}H_{23}NO_5$: 454.1654 $[M+H]^+$; found, 454.1639 $[M+H]^+$.

Compound **23**: white solid; mp 98–99°C (EtOAc/pentane); IR (thin film) 3335, 3060, 1713, 1508, 1468, 1251, 1184 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 3.36 (dd, 1H, $J=16.9$ and 5.7 Hz), 3.57 (d, 1H, $J=16.9$ Hz), 4.80 (m, 1H), 5.11 (s, 2H), 5.14 (d, 1H, $J=10.7$ Hz), 5.24 (d, 1H, $J=17.2$ Hz), 5.67 (br s, 1H), 6.00 (m, 1H), 7.33 (s, 5H), 7.58 (m, 2H), 7.88 (m, 2H), 7.99 (m, 2H), 8.45 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 42.9, 50.5, 67.0, 115.8, 123.8, 127.1, 128.0, 128.3, 128.8, 129.8, 130.2, 132.7, 134.3, 135.9, 136.7, 137.6, 139.1, 155.9, 174.1. Anal. calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.68; H, 5.98; N, 3.79.