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Diastereoselective Diels-Alder Reactions of Nonracemic 3- and 4-Amino Furans Bound to Polystyrene. A Comparison of These Reactions to Their Solution State Analogues.

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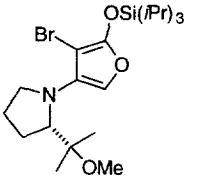
Abstract: The potassium enolates of the 3 and 4-amino furanones **4** and **12** have been silylated with polymer **3**. The resulting polymer-bound nonracemic amino furans **5** and **11** were found to undergo the Diels-Alder reaction with a variety of dienophiles. The *endo*-adducts derived from methyl acrylate were both directly cleaved from the polymer and or synthetically manipulated and then cleaved from the polymer to demonstrate their formation in >99% *de*.

Recent work from these laboratories has demonstrated the utility of Diels-Alder reactions of furans substituted at the 3 or 4 position with a proline derived chiral auxiliary (compounds **1** and **2**).[1] This methodology has been applied toward an enantioselective synthesis of cyclophellitol,[2] and is being applied to total syntheses of the aglycone of esperamicin,[3] zaragozic acid A,[4] ovalicin,[5] fumagillol,[6] fumagillin,[7] the carbosugar analogues of NANA,[8] and β-amino-mannose.[9]



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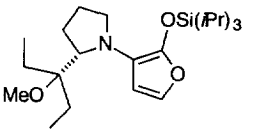

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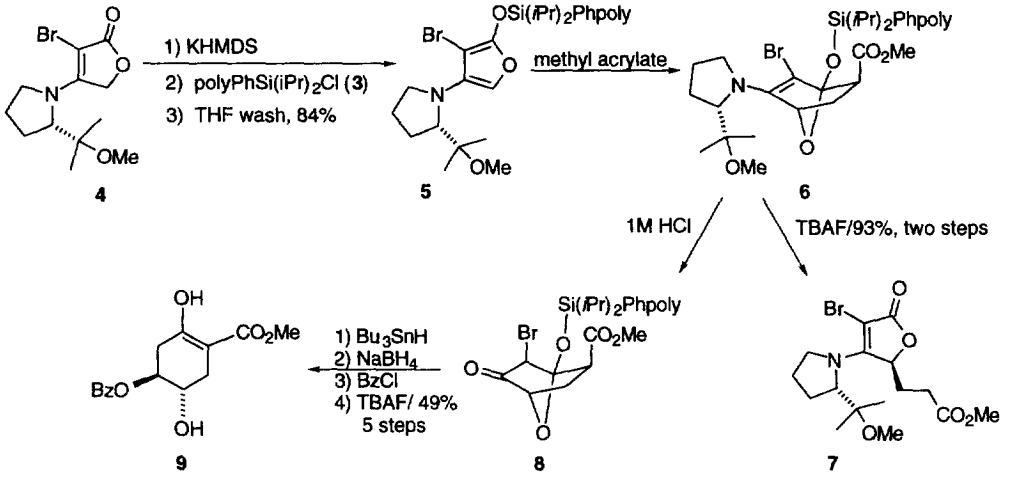
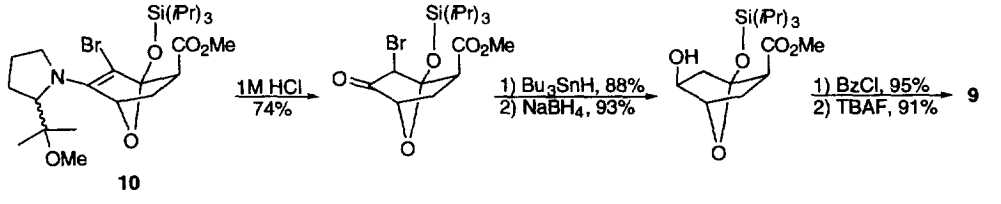
During the course of this work, it occurred to us that this chemistry could be carried out on a solid support—the usual advantages of ease of work-up, ease of isolation, and relative site-site isolation of a reactive polymer-bound substrate (hyperentropic factor) being obvious. Despite the success of polymer-supported reagents or catalysts and polymer-supported synthesis as applied to oligonucleotides,[10] polypeptides,[11] oligosaccharides,[12] and glycopeptides,[13] noniterative multistep enantioselective syntheses of complex molecules on polymer-supports are not well documented.[14] With this in mind, we undertook the following preliminary study to determine if this possibility was a viable one.

The polymer chosen for these studies was commercially available 1% divinylbenzene-styrene copolymer. This polymer was lithiated using the direct lithiation procedure reported by Frechet and Farrall[15] followed by silylation of the polymer as described by Danishefsky and co-workers[16] to produce **3**. Polymer **3** was determined by acid-base titration after hydrolysis, to contain approximately 1.4 mmoles of silyl chloride per gram of polymer. Compound **3** was treated with four equivalents of the potassium enolate derived from the nonracemic 4-amino furanone **4**.[17] Washing the resulting polymer, **5**, with anhydrous THF to recover the unreacted amino furanone **4** allowed us to determine the amount of enolate that was incorporated onto the polymer was 84%. Polymer-bound nonracemic 4-amino furan **5** was reacted with methyl acrylate to form the

polymer-bound adduct **6**. Compound **6** was then subjected to a 5% aqueous 1M THF solution of TBAF to yield the polymer-free 5-propionate substituted amino furanone **7**.[18] Based on the loading of the enolate derived from **4** onto the polymer, the conversion of polymer-bound amino furan **5** into **7** was determined to be 93% over two steps. This corresponds to a loading of 0.75 mmol of the oxabicycloheptene adduct **6** per gram of polymer.

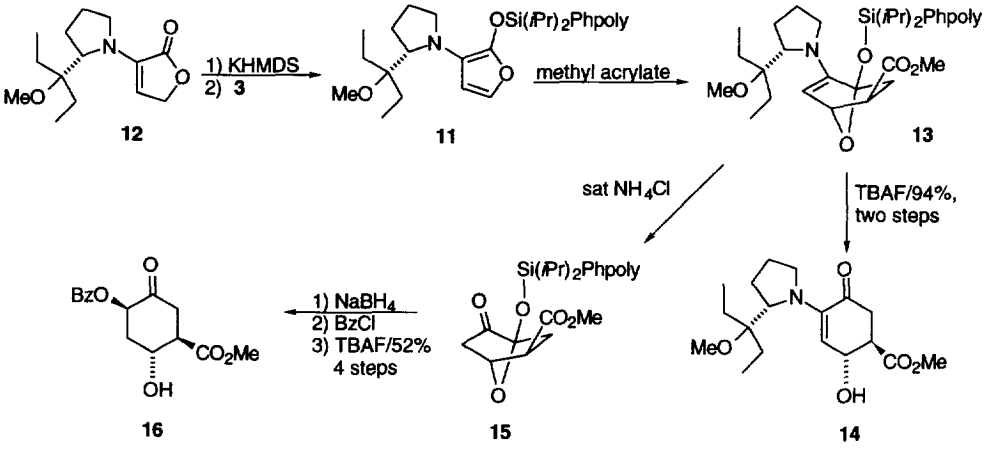


To demonstrate the facial selectivity of the the above cycloaddition reaction, the following reaction sequence was carried out. Polymer bound adduct **6** was hydrolyzed with near quantitative recovery of chiral amine to give the polymer bound oxabicyclo bromo ketone **8**. Tin mediated debromination of **8**, stereoselective $NaBH_4$ reduction of the resulting polymer bound oxabicyclo ketone, benzoylation of the newly formed alcohol residue, and finally TBAF mediated cleavage of the modified adduct from the polymer gave the enolic β-keto ester **9**, essentially pure, in a gratifying 49% overall yield from **6**. Chiral HPLC analysis of **9** compared to a racemic standard confirmed its enantiomeric purity to be greater than 99%.[19] Racemic **9** was prepared in a parallel solution state synthesis commencing from racemic adduct **10** in five steps in 52% overall yield as shown below.[20] A variety of other dienophiles was also examined in reaction with polymer bound furan **5**—these include dimethyl fumarate, dimethyl maleate, acrylonitrile and phenyl vinyl sulphone, among others.



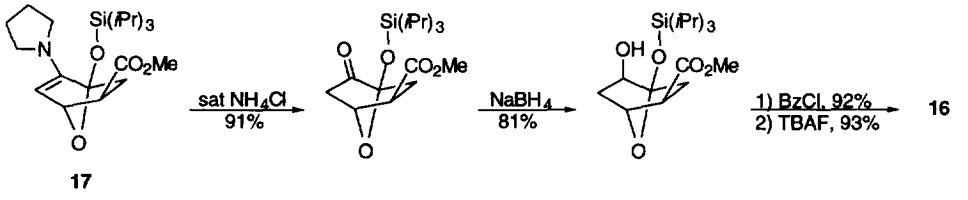
The Diels-Alder behavior of polymer bound nonracemic 3-amino furan **11** with methyl acrylate was also investigated. Nonracemic 3-amino furanone **12** was deprotonated in a similar manner as **4** and the

corresponding enolate was trapped with polymer **3**.[21] The polymer bound 3-amino furan **11** was washed with THF to recover unreacted **12** allowing us to determine that the amount of enolate incorporated onto the polymer was 83%. Polymer-bound 3-amino furan **11** was reacted with methyl acrylate to the produce polymer-bound oxabicycloheptene adduct **13**. TBAF (THF/H_2O) treatment of **13** afforded the amino cyclohexenone derivative **14** in 94% yield over two steps. This corresponds to a loading of 0.78 mmol of the oxabicycloheptene adduct **13** per gram of polymer.



Again, with the goal of determining the facial selectivity for the conversion of **11** to **13**, **13** was hydrolyzed into the polymer bound ketone **15**, as indicated by near quantitative recovery of chiral amine. Stereoselective $NaBH_4$ reduction of **15** followed by benzoylation of the resulting alcohol, and finally TBAF induced cleavage of the resulting modified adduct from the polymer afforded the cyclohexanone derivative **16**, essentially pure in 52% overall yield. Chiral HPLC analysis of **16** compared to its racemic analog determined its enantiomeric purity to again be greater than 99%.[22] Racemic **16** was prepared, as shown below, in the solution state commencing with racemic adduct **17** in 63% overall yield over four steps.[23] As in the case of polymer bound nonracemic 4-amino furan **5**, a variety of other dienophiles was also examined in reaction with the nonracemic 3-amino furan **11**.

The application of these polymer-bound Diels-Alder reactions to total syntheses, as well as the use of substances such as **8** and **15** in combinatorial regimes are planned.



Experimental Procedure for the Diels-Alder Reaction of Polymer Bound 4-Amino Furan 5 with Methyl Acrylate. A 0.85M THF solution of KHMDS (0.55 ml) was added to compound **4** (129 mg,

0.42 mmol) at -78 °C in a centrifuge test tube and stirred for 6h. Polymer **3** (76 mg) was added at -20 °C and stirred for 10h. The resulting slurry was warmed to 0 °C, 0.5 ml of THF was added, and allowed to stir for an additional 6h. This mixture was diluted with 2 ml of anhydrous THF under an inert N_2 atmosphere and centrifuged. The liquid portion was decanted away and this procedure was repeated 3X. The combined liquid phases were added to 1ml of sat. NH_4Cl, extracted with ether (2 X 5 ml), and concentrated to give 102 mg of starting material **4**.

The resulting polymer-bound 4-amino furan **5** was stirred with 0.1 ml of THF and methyl acrylate (0.1 ml, 1.1 mmol) for 12 h at -20 °C and 12h at RT. 4 ml of THF was added and the mixture was centrifuged. The liquid phase was decanted away and a 72 mg portion of the polymer bound Diels-Alder adduct **6** was stirred with 0.1 ml of 1M TBAF in THF at 0 °C for 6h. The mixture was filtered and the polymer was rinsed with THF (3 X 5 ml). The combined filtrate was added to 1 ml of sat. NH_4Cl, extracted with ether (2 X 5 ml), and concentrated to give the 5-propionate substituted amino furanone **7** (32 mg, 0.082 mmol).[24]

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17. For the preparation of vinylogous urethane lactone **4**, see reference 1a.
18. Analytical HPLC analysis of the crude reaction mixture demonstrated that **7** had formed with > 99% de%.
19. Compound **9**, and hence compound **6**, are formed with greater than 99% *ee*. Racemic **9** was chromatographed on a nonracemic HPLC column under conditions which allowed base line separation of racemic **9** into its racemates. Chiral stationary-phase HPLC analyses were performed with a Varian 3010 pump and LDC spectromonitor using a chiralcel OD column supplied by J.T. Baker. The spectra were recorded with a LDC Ultra-Violet/Visible recording spectrometer. UV-Vis (EtOH) λ_S 235nm; $HPLC_{ret}$ 7.12 (50% **9**), 9.46 (50% ent **9**), 95:5-hexane:*i*-propanol, 0.50 ml/min. Under identical conditions, nonracemic **9** did not exhibit a detectable presence of its racemate.
20. Racemic adduct **10** was prepared in an 88% isolated yield from the corresponding racemic furan and methyl acrylate.
21. For the preparation of the nonracemic 3-amino furanone **12**, see reference 1b.
22. A protocol similar to that described in reference 19 was used.
23. Compound **17** was prepared in a 93% crude yield from the corresponding pyrrolidine analogue of **12** and methyl acrylate.
24. All new compounds displayed spectroscopic data consistent with their structural assignments.

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