Diastereoselective Diels–Alder Reactions Using Furan Substituted with a Nonracemic Amine

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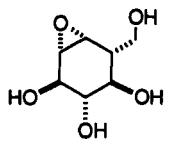
Summary: The furan derivative **1** undergoes diastereoselective Diels–Alder reactions with dienophilic species such as α,β-unsaturated esters, nitriles, sulfones, and imides in good to excellent chemical yields. The oxobicyclic adducts obtained are amenable to chemical transformations which render them useful to natural product synthesis.

Our interest in such structurally diverse substances as cyclophellitol (**2**)[2] and esperamicininone (**3**)[3] prompted us to consider the Diels–Alder reaction to fashion nonracemic cyclohexane ring systems holding ample oxygen substitution. To this end, we sought to examine the behavior of the furan system **1** in the cycloaddition reaction—being aware that asymmetric induction is commonly realized using dienophiles[4] and uncommonly realized using dienes bearing a chiral auxiliary.[5]



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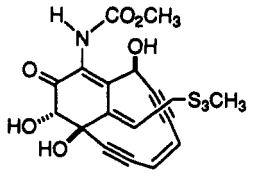

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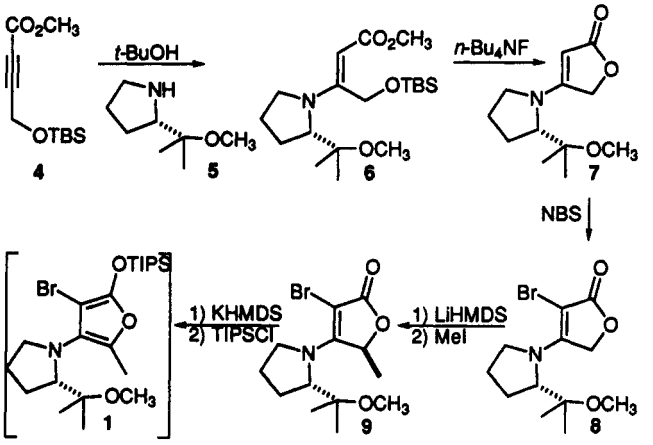
Admixture of acetylene **4**[6] and the proline derivative **5**[7] in *t*-BuOH gave the vinylogous urethane (VU) **6**, which without purification was treated with *n*-Bu_4NF to afford the vinylogous urethane lactone (VUL) **7** (92% yield) from **4**. NBS bromination of **7** in CH_3CN containing Et_3N produced **8** (98%). Deprotonation of **8** with LHMDS in THF at −78 °C followed by treatment of the enolate with MeI resulted in formation of **9** (94%) as a single diastereoisomer.[8] Lastly, the furan **1** was prepared for *in situ* use as a diene by deprotonation of **9** with KHMDS in THF (−78 °C, 3 h) and subsequent reaction with triisopropylsilyl chloride, TIPSCl (0 °C, 10–20 min).[9]

Scheme 1



We began our examination of the Diels–Alder reaction of **1** starting with methyl acrylate by adding 2–4 equiv of the dienophile (1 M in CH_2Cl_2) to the diene and allowing the resulting mixture to stir at 22 °C for 12 h. Analytical HPLC revealed that a 10:1 mixture of *endo* to *exo* adducts **10** and **11** (93%) had formed.[10] Chlorotitanium triisopropoxide $[(CH_3)_2CHO]_3TiCl$, added with the dienophile, enhanced the ratio of adduct **10** relative to **11** (15:1).

Several useful transformations stemming from **10** have been observed; for example, hydrogenolysis of **10** (10% Pd/C and EtOH) with concomitant hydrolysis of the enamine residue afforded the ketone **12** (95%). Chiral stationary-phase HPLC examination of **12** showed it to be contaminated with none of the ketone **22**, the product of

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(2) Atsumi, S.; Umezawa, K.; Iinuma, H.; Naganawa, H.; Nakamura, H.; Iitaka, Y.; Takeuchi, T. *J. Antibiot.* **1990**, *43*, 49–53.

(3) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am.* Chem. Soc. **1987**, *109*, 3462–3464 and references cited therein.

(4) (a) For the first example of a nonracemic dienophile used in the Diels–Alder reaction, see: Walborsky, H. M.; Barash, L.; Davis, T. C. *J. Org. Chem.* **1961**, *26*, 4778–4779. (b) For a recent review which cites several other reviews that deal with nonracemic dienophiles, see: Kagan, H. B.; Olivier, R. *Chem. Rev.* **1992**, *92*, 1007–1019.

(5) (a) For the first example of a nonracemic diene used in the Diels–Alder reaction, see: David, S.; Eustache, J.; Lubineau, A. *J. Chem. Soc., Perkin Trans. 1*, **1974**, 2274–2278. (b) For a review which cites several articles dealing with nonracemic dienes, see ref 4b and: Tashner, M. J. In *Organic Synthesis: Theory and Application Vol. 1*; Hudlicky, T., Ed.; JAI Press: Greenwich, 1989; pp 1–101. (c) For a very recent example of a nonracemic diene in reaction with nitro olefins, see: Enders, D.; Meyer, O.; Raabe, G. *Synthesis* **1992**, 1242–1244. Barluenga, J.; Aznar, F.; Valdes, C.; Martin, A.; Garcia-Granda, S.; Martin, E. *J. Am. Chem. Soc.* **1993**, *115*, 4403–4404. Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *11*, 1582–1584. Enders, D.; Meyer, O.; Raabe, G.; Runsink, J. *Synthesis* **1994**, 66–72.

(6) Schlessinger, R. H.; Iwanowicz, E. J.; Springer, J. P. *Tetrahedron Lett.* **1988**, *29*, 1489–1492. A procedure for the preparation of acetylene **4** is given in the supplementary material.

(7) Enders, D.; Kipphardt, H.; Gerdes, P.; Brenak-Valle, L. J.; Bhushan, V. *Bull. Soc. Chim. Belg.* **1988**, *97*, 691–704.

(8) For examples of highly diastereoselective alkylation and aldol reactions using a very similar VUL, see: Schlessinger, R. H.; Mjalli, A. M. M.; Adams, A. D.; Springer, J. P.; Hoogsteen, K. *J. Org. Chem.* **1992**, *57*, 2992–2993. Both the proton and carbon spectra of **9** suffer from severe problems associated with rotational restrictions. Attempts to better define the spectra by VT NMR at higher temperatures proved futile. The minor isomer could not be separated, so the bromine was removed with 10% Pd/C and atmospheric H_2 to provide a substance that could be separated from its minor isomer. HPLC analysis of this debrominated sample using a 1:1 epimeric mixture as a standard showed the selectivity of this methylation to be greater than 99:1.

(9) Isolation of diene **1**, as well as dienes **13**, **16**, and **17**, is cumbersome to carry out on a routine basis. The Diels–Alder behavior of these dienes was found to be invariant with respect to their use either *in situ* or after isolation. Preparation of the parent vinylogous urethanes is described in the supplementary material. KHMDS in THF was found to be the superior base for these reactions.

(10) This analytical procedure is described in the supplementary material.

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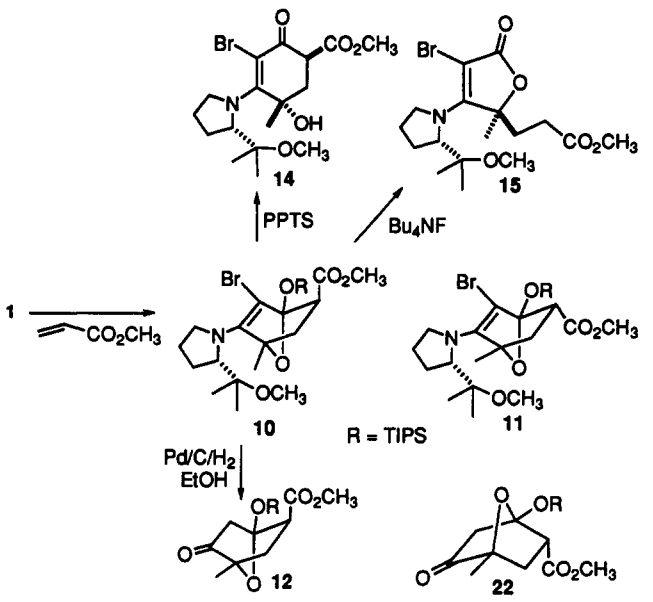
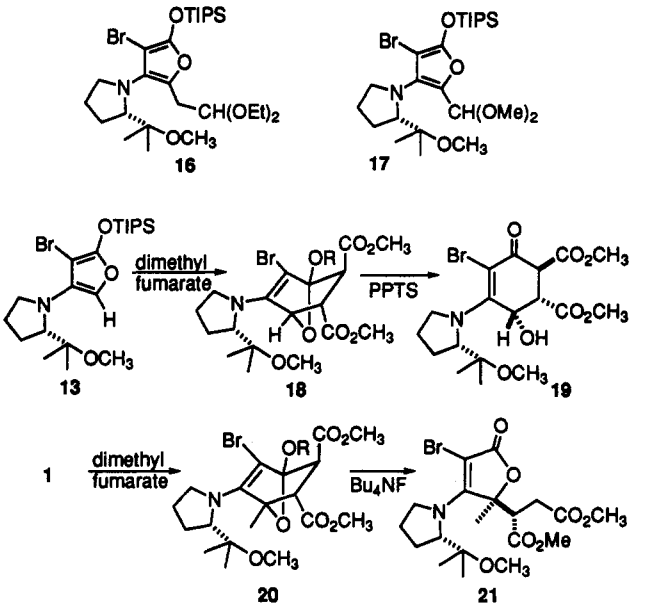
Scheme 2



Scheme 3



opposite face addition of acrylate to **1**.[11] PPTS treatment of **10** (benzene, 22 °C, 24 h) results in cleavage of the bridged ether functionality giving rise (80%) to the vinylogous amide **14**.[12] On the other hand, reaction of **10** with $(n\text{-Bu})_4$NF in THF (22 °C, 20 min) leads to C–C bond cleavage and the formation of the VUL **15** (90%) as a single stereoisomer.

Dienophiles, in addition to methyl acrylate, used for cycloaddition in conjunction with diene **1** include dimethyl fumarate, dimethyl maleate, *N*-phenylmaleimide, acrylonitrile, α-chloroacrylonitrile, and phenyl vinyl sulfone. All of these reactions occurred in comparable yields and stereoselectivity to that recorded for **1** and methyl acrylate. Other variations of furan **1** that have been examined for their cycloaddition behavior include **13**, **16**, and **17**. Here again, excellent stereoselectivity and chemical yields were realized.[13] For example, the combination of dienes **1** and **13** with dimethyl fumarate proved very useful. Adducts **18** and **20** obtained from these reactions could be ring opened to the vinylogous amide **19** or the furanone **21**.[14,15] These substances provided X-ray quality crystals that confirmed their absolute stereochemistry.[16,17]

Both the origin of the enantioselection observed for cycloaddition of the furans described in this text as well as their application to total syntheses are under active investigation.

Acknowledgment. Financial support from the NIH and the Merck Sharp and Dohme Corp. is gratefully acknowledged.

Supplementary Material Available: General experimental procedures for **1**, **4**, **6–10**, **12**, **14**, **15**, and **18–21** and copies of ^{1}H NMR of **12**, **15** and **20**. The diastereoselectivities and physical data are given for several examples including acrylonitrile, phenyl vinyl sulfone, dimethyl maleate, dimethyl fumarate, *N*-phenylmaleimide, and dimethyl 2,3-pentadienedioate (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) The other enantiomer could not be detected. It had been synthesized from racemic **9** for HPLC comparison.

(12) Compound **14** initially contained 9% of the epimer about the methine of the β-keto ester. This ratio increased over time (≈24 h) to approximately 1.3:1.0. Compound **14** would eventually aromatize.

(13) A table of selectivities is provided in the supplementary material for the reaction of dienes **1**, **13**, **16**, and **17** with various dienophiles.

(14) Compound **19** was formed from unpurified **18** (OR = OTMS) as a single stereoisomer. There was no epimeric ratio detected about the methine of the β-keto ester even after ≈24 h. The initial bromo enamine adduct **18**, with no substituent at C-4, was found to be *very* unstable toward chromatography and as a result purification of **18** (OR = OTMS/OTIPS) was impossible. The adduct **18** (OR = OTBDPS) could be chromatographed on alumina but did not C–O ring open to **19**; instead, the OTBDPS bromo enamine of **18** hydrolyzed in aqueous HCl to a bicyclic α-bromo ketone with the bromine exclusively in an axial configuration.

(15) The endo and exo isomers of **20** (83:17 with OR = OTIPS) could be easily separated by flash chromatography. Only the endo isomer was carried forward to give **21** as a single stereoisomer. If the OTMS diene were used instead, no exo isomer was detected (>95:5) in **20**.

(16) The absolute stereochemistry of compounds **10** through **15**, as well as **18** and **20**, follows from the structure determination of **19** and **21**.

(17) The author has deposited atomic coordinates for **19** and **21** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.