Diels–Alder Reactions of 3,4-Dialkoxyfurans: an Application to the Highly Efficient Synthesis of (±)-Methyl Triacetylshikimate

Masato Koreeda,* Kee-Yong Jung, and Junji Ichita
Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109, U.S.A.

Diels–Alder reactions of both 3,4-dimethoxy- and 3,4-dibenzyloxy-furan with various activated dienophiles have been investigated and results applied to the highly expeditious, regio- and stereo-controlled synthesis of (±)-methyl triacetylshikimate.

Notwithstanding their inherent potential as highly oxygenated Diels–Alder dienes, the use of 3,4-dialkoxyfurans in organic synthesis has gained little attention. While there exist a number of reports on the Diels–Alder reaction of 3,4-dimethoxyfuran (**1**),[1] most of these focus on the use of high pressure to effect the reaction with limited types of dienophiles.[2] Furthermore, but few examples[1b,3,4] have been described in the literature for the synthetically more versatile 3,4-dibenzyloxyfuran (**2**). We describe herein the scope of the Diels–Alder reactions of these 3,4-dialkoxyfurans and delineate the efficient four-step synthesis of (±)-methyl triacetylshikimate (**8**) as an application.

As summarised in the Table, both 3,4-dimethoxy-(**1**)[1b] and 3,4-dibenzyloxy-furan (**2**)† underwent smooth reaction with a variety of activated dienophiles, to give the corresponding cycloadducts in excellent yields. A number of cycloadducts, such as those with phenyl vinyl sulphoxide and 2-acetoxyacryronitrile (runs 7 and 8, respectively), indeed illustrate the great potential of these furans in synthesis. Interestingly, while methyl vinyl ketone reacted with (**1**) under reflux in benzene (run 4), similar treatment of cyclohex-2-enone with (**1**) led to complete recovery of the starting furan and enone (run 6). Furthermore, the use of zinc iodide to catalyze the reaction resulted in the formation of the electrophilic substitution product on the furan ring (equation (1)].[5]

(**1**) R = Me
(**2**) R = CH_2Ph(≡Bn)

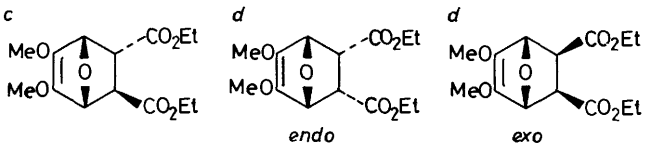
The synthetic utility of these furans was further demonstrated by the following, highly efficient, regio- and stereo-controlled four-step synthesis of (±)-methyl triacetylshikimate[6] (see

† 3,4-Dibenzyloxyfuran (**2**) was prepared in 4 steps from diethyl oxalate and diethyl glycolate in 49.3% overall yield by modifying the original procedure described in ref. 1*b*. Thus, benzylation of 2,5-diethoxycarbonyl-3,4-dihydroxyfuran was achieved with benzyl bromide/K_2CO_3 in acetone, reflux, 4 h (91%) instead of benzyl chloride/NaH in DMF.[1b]

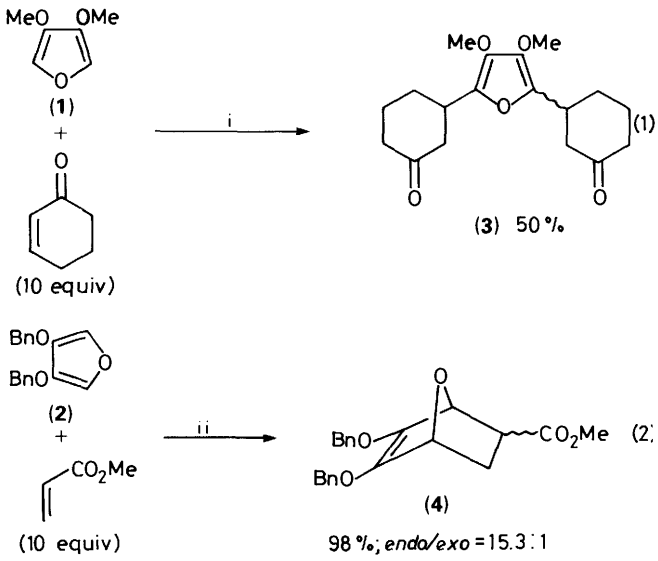
Table. Diels–Alder reactions of 3,4-dialkoxyfurans[a]

Run	Dienophile	% Yield of Diels–Alder adducts[b]	*endo*:*exo* Ratio
	Reactions with furan (**1**)		
1	Methyl acrylate	95	2:1
2	Diethyl fumarate	88	—[c]
3	Diethyl maleate	88	2:1[d]
4	Methyl vinyl ketone	78	1.1:1[e]
5	3-Nitrocyclopent-2-enone	0	
6	Cyclohex-2-enone	0	
7	Phenyl vinyl sulphoxide	98	1.5:1
8	2-Acetoxyacryronitrile	95	4:1[e]
	Reactions with furan (**2**)		
9	Methyl acrylate	88	2:1
10[f]	Dimethyl acetylenedicarboxylate	85	—

[a] The mixture of furan (0.1 mol) and dienophile (0.5 mol) in benzene was heated to reflux for 24 h. [b] Yield of purified product after silica gel chromatography.



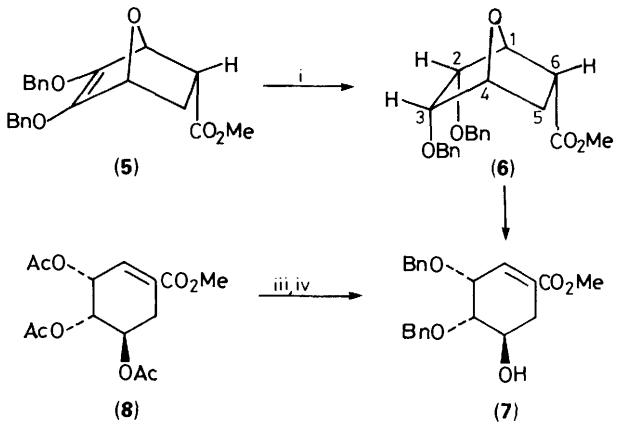
[c] Stereochemistry of the two isomers not assigned. [f] The reaction was complete within 1 h.



Reagents and conditions: i, ZnI_2 (0.1 equiv.), benzene, reflux, 1 h; ii, ZnI_2 (0.1 equiv.), neat, room temp., 1 h

Scheme). The cycloaddition of (**2**) with methyl acrylate was dramatically accelerated by the presence of a catalytic amount of zinc iodide, to give the adduct in 98% yield at room temperature within 1 h with a greatly improved *endo*:*exo* ratio [equation (2)].* Catalytic hydrogenation of the *endo* isomer (**5**)

* The *endo*:*exo* isomers of (**4**) are readily separable by silica gel chromatography with CH_2Cl_2–EtOAc (25:1) as the eluant. However, the stereoisomeric mixture (**4**) can also be efficiently converted into (**8**) in overall 63.9% yield from (**2**). It is of interest to note that catalytic hydrogenation of the *exo* isomer of (**5**) provided the product with the same stereochemistry at C-2 and -3 as in (**6**).



Scheme. *Reagents and conditions:* i, H_2, PtO_2/EtOAc, room temp., 1 h (93%); ii, LiHMDS/THF, −42 °C, 9 h (78%); iii, BF_3·OEt_2, EtSH/CH_2Cl_2, 0 °C, 12 h; iv, Ac_2O/pyridine, room temp., 24 h (90% overall yield for steps iii and iv)

produced the 7-oxabicyclo[2.2.1]heptyl derivative (**6**)† by cleanly introducing hydrogens at C-2 and -3 *cis* to the ether bridge. The opening of the ether bridge with lithium hexamethyldisilazide (LiHMDS), followed by removal of the benzyl group,[7] and subsequent purification of the resulting triol as its triacetate afforded (±)-methyl triacetylshikimate (**8**)[8] in 60% overall yield from 3,4-dibenzyloxyfuran (**2**).[9]

† For (**6**): b.p. 152—154 °C/0.1 mmHg (Kugelrohr bath); δ($CDCl_3$, 300 MHz) 1.835 (dddd, 1 H, $^4J_{3,5\beta}$ = 1.2 Hz, $^3J_{4,5\beta}$ = 4.8 Hz, $^3J_{5\beta,6}$ = 11.5 Hz, $^2J_{5\alpha,5\beta}$ = 12.5 Hz, 5β-H), 2.763 (dd, 1 H, $^3J_{5\alpha,6}$ = 6.4 Hz, $^2J_{5\alpha,5\beta}$ = 12.5 Hz, 5α-H), 3.041 (ddd, 1 H, $^3J_{1,6}$ = 4.8 Hz, $^3J_{5\alpha,6}$ = 6.4 Hz, $^3J_{5\beta,6}$ = 11.5 Hz, 6-H), 3.354 (s, 3 H, OCH_3), 3.809 (ddd, 1 H, $^4J_{3,5\beta}$ = 1.2 Hz, $^3J_{3,4}$ = 4.7 Hz, $^3J_{2,3}$ = 8.4 Hz, 3-H), 3.907 (dd, 1 H, $^3J_{1,2}$ = 4.8 Hz, $^3J_{2,3}$ = 8.4 Hz, 2-H), 4.495 (dd, 1 H, $^3J_{3,4}$ = 4.7 Hz, $^3J_{4,5\beta}$ = 4.8 Hz, 4-H), 4.493 and 4.509 (ABq, J_{AB} = 11.8 Hz, benzylic H), 4.662 and 4.649 (ABq, 2 H, J_{AB} = 8.3 Hz, benzylic H), 4.823 (dd, 1 H, $^3J_{1,2}$ = 4.8 Hz, $^3J_{1,6}$ = 4.8 Hz, 1-H), and 7.23—7.37 (m, 10 H, ArH).

Acknowledgements

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