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# Stereoselective Synthesis of Decalines via Tandem Photooxidation - Intramolecular Diels-Alder Reactions of Bis-Furans

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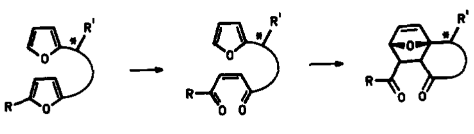
Abstract Selective mono-oxidation of bis-furan compounds using $^1O_2$ followed by intramolecular cycloaddition provides decalines with complete stereocontrol.

The Singlet Oxygen oxygenation of furans has been studied extensively[1] since it was discovered by Schenck,[2] although its application in synthesis has been rather limited sofar. Considering the growing importance of furans as flexible starting materials[3,4] it is noteworthy that furans are mildly and selectively converted into dihydrofurans, butenolides and γ-keto enones using $^1O_2$.[1,5,6] This is further illustrated by the easy access to optically pure γ-alkoxybutenolides which enter a variety of asymmetric syntheses.[7] Furthermore it has been shown that the rate of oxidation of furans with $^1O_2$ critically depends on the substitution pattern i.e. 2,5-dimethylfuran is approximately twice as reactive as 2-methylfuran ($10^2$ β 0.078 and 0.140 respectively).[8] These findings open the interesting possibility that functionalized carbocyclic compounds can be prepared by selective $^1O_2$ oxidation of bis-furans[9] followed by intramolecular Diels-Alder reaction of the furan (IMDAF reaction) (eq. 1). Highly stereocontrolled methodology for the synthesis of carbocyclics via IMDAF reactions has recently been described.[4,10] The readily access to unsymmetrically substituted bis-furans, the in-situ formation of the dienophile and the expected stereoselectivity make this sequence particularly attractive provided that high regioselectivity for the disubstituted furan is reached in the $^1O_2$ addition step.

(1)

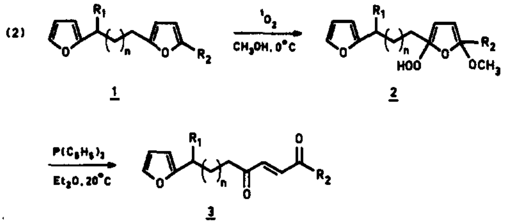


The bis-furans 1a - 1e (eq. 2, table I), with different substituents and lengths of the spacer, were synthesized to test this concept. The methyl- and trimethylsilyl-derivatives of 1a and 1e were prepared via lithiation of furan (n-BuLi, THF, -30°C), alkylation with 1,3-dibromopropane (THF, -40° → 20°C, 61%) and subsequent reaction with 2-lithio-5-methylfuran or 2-lithio-5-trimethylsilylfuran (THF, -30° → 20°C, 70 resp. 60%).

1-(2-Furyl)-1-methoxy-2[5-(methyl)-2-furyl]-ethane (1b) was obtained by alkylation of 5-methylfuryllithium with bromoacetaldehyde diethylacetal (THF, 5h, 55°C, 56%), followed by deprotection of the aldehyde (HCl, acetone, 92%), addition of furyllithium (-40°C) and methylation (NaH, $CH_3I$, 60°C, 43% over 2 steps). 1-(2-Furyl)-1-methoxy-3[5-(methyl)-2-furyl]propane (1c) was obtained in 3 steps (i. NaOH, $CH_3OH$; ii. $LiAlH_4$, $Et_2O$; iii. NaH, $CH_3I$, overall 41%) from 5-

methylfurfural and acetylfuran. 1-(2-Furyl)-1-methoxy-4[(5-methyl)-2-furyl]-butane (1d) was obtained from 5-methylfuryllithium (i. $Br(CH_2)_3Cl$, 16 h, 20°C; ii. Mg, THF, 20° → -20°C, furfural, iii. NaH, $CH_3I$, 50°C, overall 31%).

(2)



The photooxidation of the bis-furans 1 (0.5-2.0 mmol) was performed at 0°C in methanol using Rose Bengal as a sensitizer[1,5,8] (reaction times approx. 0.5-2.0 h). The oxidation could readily be followed by $^1$H NMR to determine the time when the disubstituted furyl group was completely converted into hydroperoxide 2. Prolonged reaction times resulted in the oxidation of the monosubstituted furyl group as well. In this way regioselective and quantitative oxidation of 1a - 1d was achieved with the monosubstituted furyl group completely intact. To determine if similar high selectivities could be reached in an intermolecular competition experiment the photooxidation of equimolar quantities of 2-methylfuran (4) and 2,5-dimethylfuran (5) was executed. Much to our surprise no selective photooxidation of the disubstituted furan 5 was found in contrast to the "intramolecular counterpart" 1a. Before complete conversion of 5 (1h) a major part of 4 was oxidized too. The origin of the slow photooxidation of the monosubstituted furyl moiety in 1 remains obscure at present although a decrease in reactivity towards $^1O_2$ due to a charge transfer interaction with the oxidized part of the molecule is possible. The hydroperoxides 2 were in situ reduced with triphenylphosphine to afford, after chromatography, the pure *trans*-ene dione derivatives 3a - 3d in high yields (table I).[11] The intramolecular Diels Alder reaction of 3c was investigated under a variety of conditions i.e. solvent, temperature, Lewis acid catalyst and reaction time. Some results are summarized in table 2.

Table 1

| bis-furan | | | | photooxidation | | reduction | |
|---|---|---|---|---|---|---|---|
| | $R_1$ | $R_2$ | n | product | yield (%)[a] | product | yield (%)[b] |
| 1a | H | $CH_3$ | 1 | 2a | >98 | 3a | 75 |
| 1b | $OCH_3$ | $CH_3$ | 0 | 2b | >98 | 3b | 75 |
| 1c | $OCH_3$ | $CH_3$ | 1 | 2c | >98 | 3c | 80 |
| 1d | $OCH_3$ | $CH_3$ | 2 | 2d | >98 | 3d | 75 |
| 1e | H | $Si(CH_3)_3$ | 1 | 2e | ≥80 | 3e[c] | 58[d] |

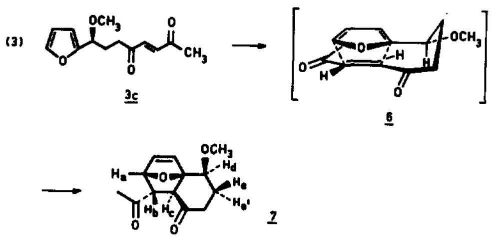
[a] Yield determined by $^1$H NMR; [b] Overall yield isolated after photooxidation-reduction as obtained after flash chromatography ($SiO_2$, $Et_2O$); [c] Cis 3e was obtained; [d] Isolated yield of cycloadduct 7, see text.

It is well precedented that IMDAF reactions lead to equilibrium mixtures of starting materials and cycloadducts.[4,10] As prolonged reaction times did not result in significant alteration of the yield of the cycloadduct of 3c it is presumed that the equilibrium is reached under the appropriate conditions as shown in table 2. Although significant effects of silicagel and florisil were found in accordance with observations made by de Clerck and van Royen[12] on IMDAF reactions, various Lewis acids proved to be more useful. Following earlier results in the intermolecular Diels Alder reaction of furan[13] it turned out that $ZnI_2$ gave the highest yields of 7.

Table 2 Intramolecular Diels-Alder reaction of 3c

| entry | solvent | Lewis acid | temperature (°C) | time (h) | cycloadduct (7) (%) |
|---|---|---|---|---|---|
| 1 | dichloromethane | - | RT | 24 | - |
| 2 | ether | $SiO_2$ | RT | 0.5 | 15 |
| 3 | toluene | 3Å sieves | 110 | 24 | 0 |
| 4 | dichloromethane | 3Å sieves | RT | 24 | 40 |
| 5 | dichloromethane | 3Å sieves | 0 | 6 | 27 |
| 6 | dichloromethane | florisil | RT | 48 | 44 |
| 7 | dichloromethane | $ZnI_2$ | RT | 48 | 67 |

(RT = room temperature)



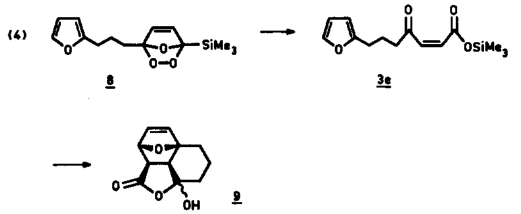
In all cases cycloadduct 7 was obtained as a single diastereomer.[11] The relative stereochemistry was established using 300 MHz $^1H$ and 2D-Cosy NMR. The coupling constants $J_{Ha,Hb}$ and $J_{Hb,Hc}$ of 4.8 and 3.6 Hz unambiguously prove the endo orientation of the acyl group and the trans-relationship between $H_b$ and $H_c$. The proton $H_d$ at the stereogenic center was observed at $\delta$ = 4.13 ppm as a double doublet with $J_{a,a}$ = 12 Hz and $J_{a,e}$ = 4.5 Hz demonstrating the pseudo-equatorial orientation of the methoxy substituent. The exo face selectivity with respect to the β-enone position has precedent in IMDAF reactions.[4,10,14] The high diastereoselectivity towards one of the possible endo diastereomers 7 can be attributed to the favourable pseudo equatorial orientation of the $OCH_3$ substituent in the proposed transtion state for the S-enantiomer 6, whereas in order to obtain the diastereomer an unfavourable axial orientation results in a methoxy substituent directed towards the dienophile as model studies indicate.

The high stereocontrol by the α-methoxy substituent in the IMDAF reaction combined with efficient methodology to prepare optically active furylalcohols[16] will provide attractive routes to enantiomerically pure multifunctional decaline compounds.

Comparable results were obtained with enedione 3a; 50-60% yield of cycloadduct was found. However 3b and 3d were not cyclized under the conditions shown in table 2. Methanol elimination was the major route for 3b, whereas 3d was recovered in most cases quantitatively. The latter result is not unexpected considering the high pressures generally required to obtain useful yields in the formation of cycloheptanes via IMDAF reactions.[17]

Finally the trimethylsilyl derivative 1e was examined. Photooxidation in $CHCl_3$ resulted in rearrangement of the intermediate endoperoxide 8 to provide cis-γ-keto-α,β-unsaturated ester 3e which cyclized partly during the photolysis. Stirring of the resulting mixture for 20 h at 20°C with $ZnI_2$ provided cycloadduct 9 as a single diastereoisomer in 58% yield.[11] Due to the mild conditions the cis-geometry pertains and the exo-cycloadduct is formed exclusively ($J_{Ha,b}$ = 0 Hz, $J_{Hb,c}$ = 7.0 Hz). The stereochemistry of the hemiacetal was not secured due to the labile nature of this center.

This one pot procedure to 7 might provide a very useful route to tetralin natural products such as platyphyllide.



High pressure experiments to force the stereocontrolled formation of cycloadducts with 3d, as well as studies to elucidate the origin of the unexpected high selectivity in the $^1O_2$ addition, are currently under investigation.

References
1. For a review, see: Feringa, B.L., Recl. Trav. Chim. Pays-Bas, 1987, 106, 469.
2. Schenck, G.O., 1947, 80, 289; Gollnick, K.; Schenck, G.O.; in "1,4-Cycloaddition Reactions", Hamer, J. ed., Acad. Press Inc., New York, 1967, chapter 10.
3. Dean, F.M., Adv. Heterocycl. Chem. 1982, 30, 167; Tanis, S.P.; Herrinton, P.M., J. Org. Chem. 1985, 50, 3988; Schreiber, S.L., Science, 1985, 227, 859.
4. For a review: Lipschutz, B.H., Chem. Rev. 1986, 86, 795, and references cited therein; see also: Craig, D., Chem. Soc. Rev., 1987, 16, 187.
5. Feringa, B.L.; Butselaar, R.J., Tetrahedron Lett. 1983, 24, 1193.
6. Feringa, B.L.; Tetrahedron Lett., 1981, 22, 1443.
7. Feringa, B.L.; de Jong, J.C., J. Org. Chem. 1988, 53, 1125; Feringa, B.L.; de Lange, B.; de Jong, J.C., J. Org. Chem. 1989, 54, 2471.
8. Gollnick, K.; Griesbeck, A., Tetrahedron, 1985, 41, 2057; Clennan, E.L.; Mehrsheikh-Mohammadi, M.E., J. Am. Chem. Soc. 1983, 105, 5932.
9. For a related case with a furanophane, see: Wasserman, H.H.; Doumaux, Jr., A.R., J. Am. Chem. Soc. 1962, 84, 4611.
10. Sternbach, D.D.; Rossana, D.M.; Onan, K.D., J. Org. Chem. 1984, 49, 3427; Klein, L.L., J. Am. Chem. Soc. 1985, 107, 2573; van Royen, L.A.; Mijngheer, R.; De Clercq, P.J., Tetrahedron 1985, 41, 4667; Jung, M.E.; Street, L.J., J. Am. Chem. Soc. 1984, 106, 8327.
11. All new compounds were fully characterized and exhibited, spectroscopic data ($^1H$-, $^{13}C$-NMR, IR, HRMS or analysis) in accordance with the structures. Only one enantiomer is shown in eq. 3.
12. De Clercq, P.J.; van Royen, L.A., Synth. Commun. 1979, 9, 771.
13. Brion, F., Tetrahedron Lett. 1982, 23, 5299; Vieira, E., Vogel, P., Helv. Chim. Acta 1983, 66, 1865.
14. Although the effects of substituents in the connecting chain on both rate and selectivity in the IMDAF reaction have been demonstrated,[4,15] the complete diastereocontrol by a single stereogenic center has only very limited precedent, cf. Jung, M.E.; Street, L.J., J. Am. Chem. Soc. 1984, 106, 8327.
15. Cauwberghs, S.; De Clercq, P.J.; Tinant, B.; De Clercq, J.P., Tetrahedron Lett. 1988, 29, 2493; Jung, M.E.; Gervay, J., Tetrahedron Lett. 1988, 29, 2429.
16. Van Oeveren, A.; Menge, W.; Feringa, B.L., Tetrahedron Lett. 1989, 30, 6427.
17. Harwood, L.M.; Jones, G.; Pickard, J.; Thomas, R.M.; Watkin, D., J. Chem. Soc., Chem. Commun. 1990, 605.
18. Bohlmann, F.; Eickeler, E., Chem. Ber. 1979, 112, 2811.

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