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THE EFFECT OF SIDE CHAIN SUBSTITUENTS ON THE INTRAMOLECULAR DIELS-ALDER REACTION OF THE FURAN DIENE: THE SYNTHESIS OF (±)-1,4-EPOXYCADINANE

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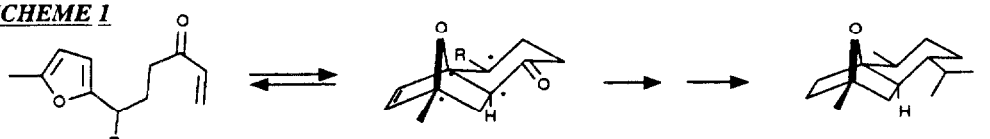
Summary: The effect of side chain substituents on the Intramolecular Diels-Alder reaction of the Furan diene (IMDAF) is reported in which the side chain connecting the furan diene to the dienophile contain four carbon atoms. The synthesis of 1,4-epoxycadinane utilizing this methodology is described.

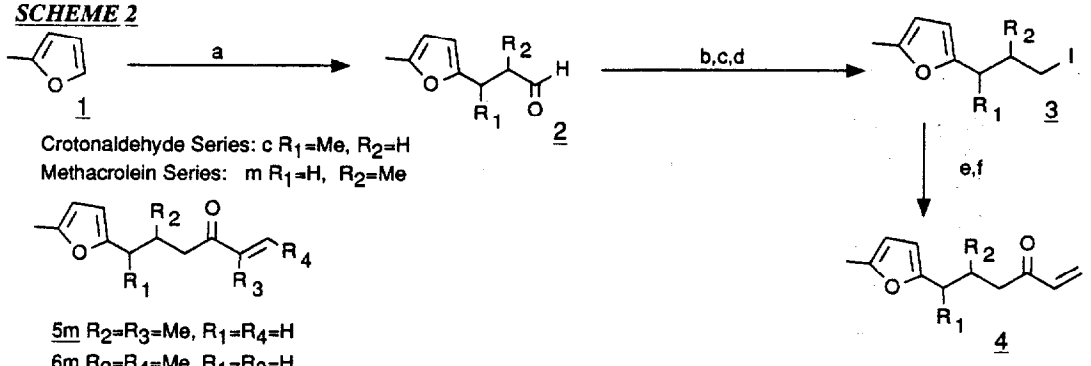
The intramolecular Diels-Alder reaction, with furan as the diene (IMDAF), has been examined by many groups.[1-3] In cases where the side chain connecting the diene and dienophile contain 3 and 4 atoms, only the adduct(s) in which the side arm is orientated exo with respect to the oxygen bridge have been reported to form.[3] This observation led us to believe that considerable advantages could be gained by employing an IMDAF over a normal intramolecular Diels-Alder (IMDA) reaction in which a 4 carbon side chain would contain an asymmetric center (A, Scheme 1). Under thermodynamic conditions the substituent on the side chain should adopt a preferred equatorial position on the newly formed six-membered ring (B). Only one Diels-Alder adduct would therefore be formed, containing a minimum of 4 new chiral centers (*'s), all of known relative stereochemistry. In addition, functionalizing the side chain should accelerate the IMDAF due to the "*gem*-dimethyl effect";[4] the Diels-Alder reaction of similar systems which have unsubstituted side chains are sluggish.[1a] We herein report our findings and apply them to the synthesis of 1,4-epoxycadinane (C).

SCHEME 1



The Diels-Alder precursors 4c and 4m-6m were prepared according to Scheme 2. Thus 2-methylfuran (1) was mixed with either crotonaldehyde or methacrolein and treated with two drops of sulfuric acid, to produce 2c and 2m respectively.[5] Conversion of the aldehydes 2c and 2m into iodides 3c and 3m respectively proceeded without incident. Treatment of iodide 3c with two equivalents of tert-butyllithium at -78°C followed by an acrolein quench[6] and Swern oxidation[7] produced 4c. Treatment of 3m with tert-butyllithium followed by a quench with either acrolein, methacrolein, or crotonaldehyde then Swern oxidation provided 4m-6m respectively. Compounds 7-9 have previously been synthesized.[1a]

SCHEME 2



5m R_2=R_3=Me, R_1=R_4=H
6m R_2=R_4=Me, R_1=R_3=H
7 R_1=R_2=R_3=R_4=H
8 R_1=R_2=R_4=H, R_3=Me
9 R_1=R_2=R_3=H, R_4=Me

a) Methacrolein (53%) or crotonaldehyde (41%), H_2SO_4; b) $NaBH_4$, EtOH (94%); c) Ph_3P, CCl_4 (89%); d) NaI, acetone (83%); e) t-BuLi, Et_2O, -78°, then acrolein (75%);, f) Swern [O] (90%).

The Diels-Alder reactions were performed as follows. Compound 4c (100 mg) was dissolved in CH_2Cl_2 (10 mL) containing florisil (1000 mg) and stirred under argon at either room temperature or reflux for an allotted period of time. The mixture was filtered and the CH_2Cl_2 removed *in vacuo* (at r.t.) to provide an oil which was separated by silica gel chromatography to provide adducts 10c and 11c[8] (Scheme 3).

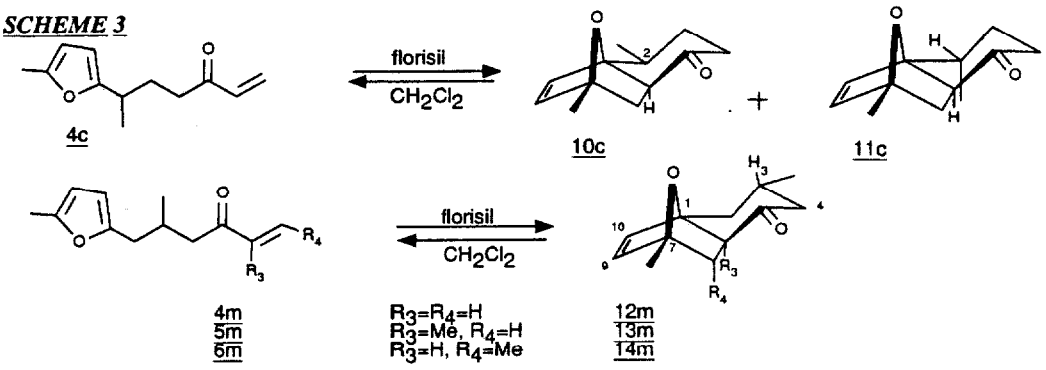
The results from the Diels-Alder reactions are illustrated in Scheme 3 and shown in Table 1. At room temperature precursor 4c produced a 14:86 ratio of starting material(S.M.):adducts after only 12 hours with the two possible adducts (assuming an exo-side arm orientation) present in a 1:1 ratio (by ^{1}H NMR, entry 10, Table 1). Stirring the mixture a further 13 days produced a 6:1 ratio of adducts (containing very little starting material) in favor of the isomer with the C-2 methyl group in an equatorial orientation[9] (entry 11). The reaction ratios observed were thermodynamic and not kinetic ratios since a mixture of 4c, 10c, and 11c containing 11c as the major component (entry 12) when stirred at room temperature for 14 days provided the same equilibrium ratio as entry 11, Table 1 (see entries 12 and 13). This indicates a retro-Diels-Alder--Diels-Alder reaction occurred to preferentially form the more stable C-2 equatorial isomer. The same reaction at reflux reached equilibrium after 1 day with compound 10c predominating (entries 12, 14 & 15).

Compound 4m yielded only one adduct 12m after 12 hours at room temperature (entry 1) in which the C-3 methyl group was equatorial;[10] starting material 4m and the epimeric isomer at C-3 were not detected by ^{1}H NMR. The absence of the epimeric C-3 isomer of 12m may be due to an unfavourable 1,3-diaxial interaction between the C-3 methyl group and the oxygen atom of the bridge (at C-1).[11]

The reaction rate enhancement observed for both 4c and 4m at both room temperature and at reflux (40°C) when compared to the reaction of 7 is noteworthy. In the case of 4c and 4m at room temperature there was essentially no starting material remaining after 6 days[12] and 12 hours respectively, while the Diels-Alder reaction of 7[1a] (Scheme 2), under identical conditions, yielded a 1:7 ratio of S.M.:adducts after 14 days. Refluxing compound 7 in CH_2Cl_2/florisil afforded no adduct whatsoever; however, 4c afforded an equilibrium mixture in favour of adducts after only 1 day (entry 14, Table 1). These results indicate that the placement of a substituent on the side chain accelerates the reaction rate substantially allowing for a higher ratio of S.M.:adduct in a shorter length of time (by reflux).

As compounds 8 and 9, which have unsubstituted side chains (Scheme 2), did not undergo the IMDA reaction at all in florisil/CH_2Cl_2[1a] (at r.t. or reflux) we prepared compounds 5m and 6m to study the effect of a methyl

SCHEME 3



4c 10c 11c

4m 5m 6m R_3=R_4=H R_3=Me, R_4=H R_3=H, R_4=Me 12m 13m 14m

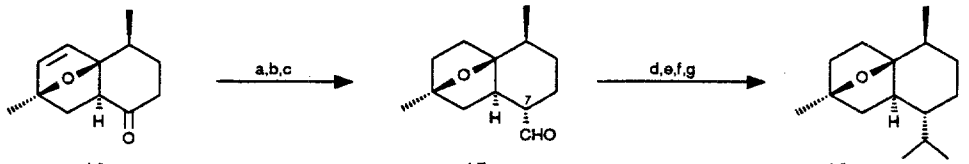
TABLE 1 **IMDAF STARTING MATERIAL TO PRODUCT RATIOS**

Entry	Compound	Temperature	Time	S.M.:Adduct Ratio
				4m:12m
1	4m	r.t.	12 h	0:100
				5m:13m
2	5m	r.t.	5 d	62:38
3		r.t.	9 d	52:48
4		r.t.	19 d	50:50
5		40°C	1 d	55:45
6		40°C	2 d	55:45
				6m:14m
7	6m	r.t.	5 d	83:17
8		r.t.	8 d	81:19
9		40°C	1 d	85:15
				4c:10c:11c
10	4c	r.t.	12 h	14:43:43
11		r.t.	14 d	2:85:13
12			0 d	6:21:73
13		r.t.	14 d	2:85:13
14		40°C	1 d	7:78:15
15		40°C	2 d	7:75:18

substituted side chain on the IMDAF containing substituted dienophiles. The methacrolein series (m) was chosen for this study since only one Diel-Alder adduct was formed from 4m thereby simplifying spectral interpretation. At room temperature compound 5m produced a 3:2 ratio of 5m:13m after 5 days which equilibrated to a 1:1 mixture after 9 days (entries 2-4, Table 1), while 6m produced a 4:1 mixture of 6m:14m after 4 days (entries 7 & 8). Equilibrium was reached in the above cases after 9 days and 5 days respectively (entries 4 & 8). Once again refluxing the mixtures reduced the time necessary to achieve equilibrium; 1 day only at reflux was required for both 5m and 6m (entries 5,6 & 9). In all of the above cases only one adduct was detected and isolated in which the methyl group at C-3 was equatorial and the side arm was exo-orientated with respect to the oxygen bridge.

These results clearly show that the placement of a group on the side chain of these IMDA precursors is useful, not only for reaction rate enhancement, but also for the selective formation of equatorially placed moieties in the newly formed six-membered ring. This additional asymmetric centre of known relative stereochemistry in the side chain becomes useful in the application of this methodology to synthesis; Scheme 4 illustrates the preparation of (±)-1,4-epoxycadinane 16.[13,14]

SCHEME 4



10c 15 16

a) H_2, 10% Pd/C, EtOAc (95%) b) Ph_3P=CHOMe, THF (82%) c) 10% HCl:THF (1:1) (63%)[15] d) MeLi, THF, -78°C (97%) e) Swern [O] (90%) f) Ph_3P=CH_2, THF (76%) g) H_2, PtO_2, EtOH (93%).

ACKNOWLEDGEMENTS

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3) One example, in which the side chain contained 5 carbon atoms, has been reported to produce a mixture of endo- and exo-adducts at 14 kbar: Burrell, S.J.; Derome, A.E.; Edenborough, M.S.; Harwood, L.M.; Leeming, N.S.; Issacs, N.S. *Tetrahedron Lett.*, **1985**, *26*, 2229.

4) For discussions concerning the "*gem*-dimethyl effect", see references 1b and 1c above and references therein.

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7) Mancuso, A.J.; Huang, S.-L.; Swern, D. *J. Org. Chem.*, **1978**, *43*, 2480.

8) All new compounds provided analytical and/or spectroscopic data consistent with their structures.

9) Decoupling the methyl doublet at δ 1.06 of compound 10c collapsed the C-2 hydrogen (δ 2.32-2.42) to a doublet of doublets with couplings of 4.1 and 12.4 Hz. The former is indicative of axial-equitoral coupling while the latter axial-axial coupling thus placing the C-2 hydrogen axial. Compound 10c: oil; IR (neat) 1701, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_4$) δ 1.06 (d, 3H, J=6.9 Hz, C-2 CH_3), 1.54 (s, 3H, C-8 CH_3), 1.55 (dd, 1H, J_{7gem}=11.8, $J_{7\alpha,6\alpha}$=8.2 Hz, $H_{7\alpha}$), 1.6-1.78 (m, 1H, H_3), 1.84-1.91 (m, 1H, H_3), 2.10 (dd, 1H, J_{7gem}=11.8, $J_{7\beta,6\alpha}$=3.4 Hz, $H_{7\beta}$), 2.28 (dd, 1H, $J_{6\alpha,7\alpha}$=8.2, $J_{6\alpha,7\beta}$=3.4 Hz, $H_{6\alpha}$), 2.32-2.42 (m, 1H, $H_{2\beta}$), 2.41-2.46 (m, 2H, $H_{4\alpha}$ and $H_{4\beta}$), 6.08 and 6.17 (ABq, 2H, J=5.6 Hz, H_9 and H_{10}). ^{13}C NMR (75 MHz, $CDCl_4$) δ 16.4, 18.7, 29.7, 33.6, 35.7, 41.6, 53.5, 70.9, 85.7, 137.2, 141.0, 209.8; M.S. 192 (3, M^{+}).

10) The hydrogens $H_{2\alpha}$ and $H_{2\beta}$ showed couplings of 12.0 amd 3.2 Hz respectively to the C-3 hydrogen indicating the C-3 methyl group is equatorial. Compound 12m: mp 62-64.5°C; IR (KBr) 1700, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05(d, 3H, J=7.9 Hz, C-3 CH_3), 1.56 (2, 3H, C-8 CH_3), 1.58 (dd, 1H, J_{7gem}=11.8, $J_{6\alpha,7\alpha}$=8.2 Hz, $H_{7\alpha}$), 1.92 (dd, 1H, J_{2gem}=14.5, $J_{2\alpha,3\beta}$12.0 Hz, $H_{2\alpha}$), 2.12-2.2 (m, 2H, $H_{3\beta}$ and $H_{5\alpha}$), 2.18 (dd, 1H, J_{7gem}=11.8, $J_{7\beta,6\alpha}$=3.4 Hz, $H_{7\beta}$), 2.3 (dd, 1H, $J_{6\alpha,7\alpha}$=8.2, $J_{6\alpha,7\beta}$=3.4 Hz, $H_{6\alpha}$), 2.38 (dt, 1H, J_{2gem}=14.5, $J_{2\beta,3\beta}$= $J_{2\beta,4\beta}$=3.2 Hz, $H_{2\beta}$), 2.45 (ddd, 1H, J_{4gem}=10.2, $J_{4\beta,3\beta}$=2.2, $J_{4\beta,2\beta}$=3.2 Hz, $H_{4\beta}$), 6.15, 6.21 (ABq, 2H, J=6.0 Hz, H_9 and H_{10}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 21.9, 29.1, 35.4, 37.1, 50.0, 52.9, 86.0, 90.4, 137.6, 141.2, 209.2. M.S. 192 (4, M^{+}), 122 (100, -C_4H_6O, McLafferty Rearrangement on retro-Diels-Alder product).

11) Molecular Modeling Software "PCMODEL" calculated a 1.45 kcal/mol difference between the C-3 epimers of 12m in favour of 12m. An axial methyl group at C-3 places one of its hydrogens 0.259 nm away from the oxygen bridge while the axial C-3 hydrogen in 12m is 0.279 nm away from the bridge.

12) The 14 days listed in Table 1 (entry 11) for this reaction is the time required for the equilibration of 11c into 10c to cease. Starting material 4c was not seen past 6 days (by ^1H NMR).

13) 1,4-Epoxycadinane was isolated from the brown algae *Dilophus fasciola*. *See:* Fattorusso, E.; Magno, S.; Mayol, L. *Gazz. Chim. Ital.*, **1979**, *109*, 589.

14) The overall yield was 9% from 2-methylfuran (1). The spectral data of synthetic 1,4-epoxycadinane (M.S., I.R., ^1H and ^{13}C NMR) were identical to those reported by Fattorusso (ref. 13 above).

15) The C-7 hydrogen of compound 15 (δ 2.18), upon decoupling of the aldehyde proton, showed couplings of 3.0, 10.6 and 12.0 Hz; the one axial-equatorial and two axial-axial couplings respectively indicate the C-7 hydrogen is axial.

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