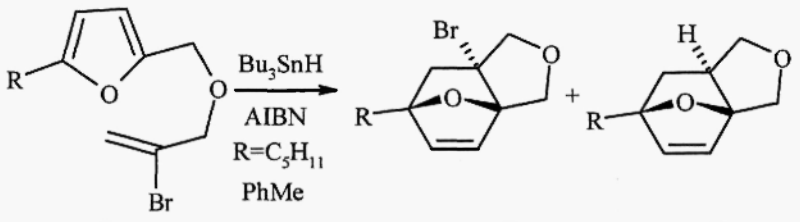
A FACILE SYNTHESIS OF HETEROTRICYCLES FROM FURFURYLBROMOALKENES USING THERMAL IMDA CYCLOADDITION

Aydın Demircan,* Muhsin Karaarslan and Ersen Turaç
Nigde University, Department of Chemistry, Campus, 51100, Nigde, TURKEY
e-mail: ademircan@nigde.edu.tr

Abstract: A variety of key precursors to the IMDA reaction of furan diene have been prepared via facile alkylation. Subsequently, rigid tricyclic compounds (**2a-g**) possessing oxygen, nitrogen, and sulfur has been synthesized by employing thermal intramolecular Diels-Alder reactions. These heterocyclic fused tricycles include a bromo quaternary carbon centre obtained stereoselectively with moderate yields (32-44 % overall).
Keywords: Intramolecular Diels Alder (IMDA), Cycloaddition, Furfurylbromoalkenes.

Introduction

Intramolecular Diels-Alder (IMDA) cycloaddition reactions are of paramount importance in organic synthesis (1). Engagement of diene and a dienophile results usually with a fused six member ring(s). The reaction is usually generated under extremely simple condition for encountering difficult reactions, and takes place with thermal activity, in some cases, Lewis acid or pressures might be needed. Furan is one of the most promising dien and the use of furan IMDA reaction gives useful intermediates for the synthesis of natural products such as carbohydrates and Prostaglandins (2). There are some structural effects for promoting the furan IMDA reactions like Thorpe-Ingold (Scissor), the gem-dialkyl, the reactive rotamer effects and steric buttressing (3). However, the facile retro-Diels-Alder reaction and the low reactivity of furan as a diene as a result of its aromatic character make the Diels-Alder reaction of furan one of the most difficult cycloaddition (4). Additionally, heteroatom in tether of furans has been found to be an internal chiral auxiliary, or ring formation for natural product synthesis (5). We previously reported radical cycloaddition / fragmentation reactions on furan cored compound using tri-*n*-butyltin hydride in the presence of azobisisobutyronitrile (AIBN) (6). (Scheme-1) A few attempts with *O*-bromoallylether **1** in radical conditions underwent cycloaddition to give **2** and **3**.



1 **2** **3**

Scheme-1

After having seen a recent publication of Namboothiri and his-coworkers (7), we proposed to report our new additional findings regarding a series of bromo Diels-Alder cycloadducts; one can utilize these compounds as a powerful strategy at the intermediate stages in a total synthesis, and develop the furan chemistry.

Experimental

Reactions were conducted in flame dried glassware, under nitrogen atmosphere except when noted otherwise. Solvents and reagents were freshly distilled as follows: tetrahyrdofuran (THF) and diethyl

ether (E) were distilled from sodium/benzophenone; dichloromethane (DCM) and toluene were distilled from calcium hydride. Reactions were monitored by thin layer chromatography (TLC) using pre-coated silica plates (Macharey Nagel sil G UV_{254}). Compounds were visualised using ultra-violet fluorescence, alkaline potassium permanganate solution or acidic cerium (IV) sulphate solution. Column chromatography was carried out Macharey Nagel Kieselgel 60 (230-240 mesh). 1H NMR spectra were recorded on a Bruker 300 MHz DPX 300 spectrometer. The chemical shifts are quoted in ppm, as δ values downfield of tetramethylsilane (TMS) or relative to the residual solvent resonance. Infrared (IR) spectra were recorded on a Perkin-Elmer 1720 spectrophotometer; Solid samples were recorded using potassium bromide discs, and liquid samples were recorded as thin films. Elemental analysis were carried out by the microanalytisches laborataorium des institüts für Organische und Biomoleculare Chemie der Universitat Gottingen, electron ionisation mass spectra (EI, 70eV) were obtained on a Fisions VG Autospec mass spectrometer.

4-Bromo-1-(furan-2-yl)-pent-4-en-1-ol. 1a: *n*-Butyllithium in hexane (6.25 mL, 10 mmol, 1.6 M) was added drop-wise to a solution of furan (1 mL, 13.7 mmol) in dry THF (40 mL) maintained at -78°C. The mixture was warmed up to 0°C and stirred 45 min. 4-Bromo-4-pentenal (1.2 g, 7.36 mmol) in 10 mL THF was then added drop-wise to 2-furfuryllithium at -78°C. The reaction mixture was stirred 2 h at room temperature and quenched with NH_4Cl, extracted with diethyl ether. Purification by column chromatography afforded the alcohol with 1.33 g (78 %) yield. TLC, (PE: E; (10:1)), R_f: 0.14; υ_{max}(thin film)/cm^{-1}: 3304(O-H), 2957(C-H), 2930(C-H), 1630(C=C). δ_H ($CDCl_3$): 7.4(d, 1H, *J* 1.8 Hz), 6.36(dd, 1H, J_1 1.8 Hz and J_2 3.3 Hz), 6.25(d, 1H, *J* 3.3 Hz), 5.58(d, 1H, *J* 1.1 Hz), 5.4 (d, 1H *J* 1.1 Hz), 4.7 (t, 1H, 6.2 Hz), 2.3(t, 2H, *J* 7.7 Hz), 2.05(m, 2H), 1.5(br s, 1H). δ_C (75.5 MHz): 156.1, 142.4, 133.8, 117.2, 110.6, 106.0, 66.3, 37.8, 34.2. $^m/_z$ (GC-MS): 215 [M^+-H_2O], 213, 151, 133. EA ($C_9H_{11}O_2{}^{81}Br$): Calc: C 46.78 %, H 4.80 %, Found: C 46.64 %, H 4.92%.

A. Synthesis of 5b-c

To a stirred solution of amine (5.6 mmol) in THF (15 mL) was added 2,3-dibromopropene (0.56 g, 2.8 mmol) and the resulting solution was heated to reflux for 12 h. A portion of potassium carbonate (1.76 g, 12.8 mmol) was then added, and the reaction mixture was heated at reflux for a further 48 h. On cooling a precipitate was formed which was washed with diethyl ether (3x15 mL). The filtrate was extracted with 10% NaOH (15 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography to afford the title compound as colorless oil.

(2-Bromo-allyl)-furan-2-ylmethyl amine. 5b: (0.58 g, 48 %). TLC, (P.E: E) ; (8:2), R_f: 0.24. υ_{max} (thin film)/cm^{-1} : 3322(N-H), 2919(C-H), 2833(C-H), 1206(C-O), 616(C-Br). δ_H ($CDCl_3$): 7.4 (d, 1H, *J* 1.8 Hz), 6.4 (dd , 1H, J_1 3.1 Hz, J_2 1.8 Hz), 6.2 (d, 1H, *J* 3.1 Hz), 5.8 (d, 1H, *J* 2.8 Hz), 5.6(d, 1H, *J* 2.8 Hz), 3.8 (s, 2H), 3.5 (s, 2H), 2.1 (brs, NH). δ_C (100 MHz): 153.2, 142.0, 132.8, 118.1, 110.1, 107.3, 56.3, 44.0.

(2-Bromo-allyl)- (5-methyl-furan-2ylmethyl)-amine. 5c: (0.68 g, 52 %). TLC, (PE : E); (8:2), R_f: 0,22. υ_{max} (thin film)/cm^{-1} : 3337(N-H), 2927(C-H), 2855(C-H), 1120 (C-O), 618(C-Br). δ_H ($CDCl_3$): 6.07 (d, 1H, *J* 2.9 Hz), 5.90 (dd , 1H, J_1 1.1 Hz, J_2 1.9 Hz), 5.82 (d, 1H, *J* 1.6 Hz), 5.61 (d, 1H, *J* 1.7 Hz), 3.7(s, 2H), 3.4 (s, 2H), 2.2 (s, 3H), 1.85 (brs, NH). δ_C (75.5 MHz): 153.7, 153.2, 134.9, 119.9, 110.2, 107.9, 58.3, 46.1, 15.6.

B. Synthesis of furanyl amines 1b-c from 4b-c.

To a solution of furfurylcarbamides, **4b-c** 1.5 mmol in THF (10 mL) was added *n*-BuLi (2.4 M in hexane) (0.64 mL, 1.5 mmol) at -78°C. The reaction mixture was stirred for 30 min, before a solution of 2,3-dibromo propene (0.3g, 1.5 mmol) in THF (5ml) was added dropwise at –78 °C. The solution was then

warmed to ambient temperature, and stirred for additional 2h. The reaction was then quenched with water (15 mL) and extracted with diethyl ether (3x10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash column chromatography to afford amines as yellow oil.

C. Synthesis of furanyl amines 1b-c from 5b-c.
To a stirred solution of **(5b-c)** (2.3 mmol) and di-*tert*-butoxy dicarbonate $(BOC)_2O$ (0.55 g, 2.5 mmol) in DCM (10 mL) was added *N,N*-dimethylaminopyridine (30 mg, 0.25 mmol) at 0°C. The reaction mixture was stirred for 2h at ambient temperature and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to afford **1b-c** as yellow oil.

***N*-(2-Bromoally)-*N*-(tert-butoxycarbonyl)furfurylamine. 1b:** As yellow oil (36 and 83 %). TLC, (PE; E (7:3)), R_f: 0.73; υ_{max}(thin film)/cm^{-1}: 2980(C-H), 1700(C=O), 1640(C=C), 1618, 1108(CO), 663. δ_H ($CDCl_3$): 7.4(d, 1H, *J* 1.4 Hz), 6.3(dd 1H, J_1 1.4 Hz, J_2 2.9Hz), 6.1(d, 1H, *J* 2.9 Hz), 5.98(s, 1H), 5.68(s, 1H), 4.25(s, 2H), 4.0(s, 2H). 1.5(s, 9H). δ_C (75.5 MHz): 155, 151.3, 142.1, 138, 113, 110.3, 108.5, 80.5, 51.9, 42.9, 28.3(3xC). $^m/_z$ (GC-MS): 260[M^+-tBu], 258, 216, 214, 135, 101, 95, 57. EA($C_{13}H_{18}BrNO_3$): Calc: C 49.38 %, H 5.74 %, N 4.43 % Found: C 49.50%, H 5.97 % N 4.32%.

***N*-(2-Bromoally)-*N*-(tertbutoxycarbonyl)-5-methylfurfurylamine. 1c:** As yellow oil (42 and 85 %), TLC, (Hexane: E (7:3)), R_f: 0.63; υ_{max}(thin film)/cm^{-1}: 2960(C-H), 1704(C=O), 1618(CC), 1178, 668. δ_H ($CDCl_3$): 6.0 (d, 1H, *J* 3.0 Hz), 5.8(d, 1H, *J* 3.0 Hz), 5.68(s, 1H), 5.54(s, 1H), 3.95(s, 2H), 3.58(s, 2H), 2.35 (s, 3H), 1.45(s, 9H). δ_C(75.5 MHz): 154.2, 149.4, 144.6, 117.0, 116.3, 105.4, 80.1, 75.4, 64.3, 48.2, 30(3xC), 15.8. $^m/_z$ (GC-MS): 274[M^+-tBu], 272, 230, 228, 149, 109, 81, 57. EA ($C_{14}H_{20}BrNO_3$): Calc: C 50.92 %, H 6.10 % N 4.24 %, Found: C 60.10 %, H 6.26 %, N 4.42 %.

D. Synthesis of furanyl oxa and thioethers.
To a suspension of 0.19 g (4.8 mmol) of NaH (60% in mineral oil) in 50 mL THF at 0°C is added 4.4 mmol of furfuryl oxa or thio alcohols in 5ml THF dropwise, causing evolution of H_2 gas. After this mixture was stirred for 30 minutes at room temperature, 2,3-dibromopropene (6.6mmol) was added. When TLC analysis showed the reaction to be complete, the mixture was re-cooled to 0°C and quenched with saturated NH_4Cl solution. The mixture was extracted with diethyl ether (3x50 mL). The combined extract was washed with brine, dried over $MgSO_4$ and concentrated to give the crude product as pale yellow oil.

2-[(2-Bromoallylthio) methyl]furan. 1f: As pale yellow oil (58 %). TLC, (Hexane:E; (9:1)), R_f: 0,72; υ_{max}(thin film)/cm^{-1}: 2953(C-H), 2924(CH), 1621(C=C), 1206, 604. δ_H($CDCl_3$): 7,37 (d, 1H, *J* 1,9 Hz), 6,32 (dd, 1H, *J* 3,1 Hz, J_2 1,9 Hz), 6,19 (d, 1H, *J* 3,1 Hz), 5,83 (d, 1H, *J* 1,8 Hz), 5,58 (d, 1H, *J* 1,8 Hz), 3,72 (s, 2H), 3,44 (s, 2H).δ_C (75.5 MHz):153,0, 144,3, 131,2, 121,0, 112,4, 109,9, 43,3, 29,4. $^m/_z$ (GC-MS): 233, 231, 187, 185, 152, 113, 81. EA(C_8H_9BrOS): Calc: C 41.22 %, H 3.89 %, Found: C 40.98 %, H 4.12% .

2-[(2-Bromoallythio)methyl]-5-methylfuran. 1g: As yellow oil (60 %). TLC, (PE: E; (10:1)), R_f: 0.5; υ_{max}(thin film)/cm^{-1}: 2928(C-H), 1594(CC), 1564, 1095(C-O). δ_H ($CDCl_3$): 6.1(d, 1H, *J* 3.0 Hz), 5.93 (d, 1H, *J* 3.0 Hz), 5.89(s, 1H), 5.81(s, 1H), 4.59(s, 2H), 4,2(s, 2H), 2.44(s, 3H). δ_C (75.5 MHz): 153.3, 149.5, 129.6, 118.0, 111.3, 106.6, 73.8, 64.3, 16.0. $^m/_z$ (GC-MS): 247, 245, 232, 230, 151, 111, 81. EA ($C_9H_{11}BrOS$): Calc: C 43.74 %, H 4.49 %, Found: C 44.01 %, H 4.63 %.

E. Cycloaddition Reactions of 2a-g.

The ethers and amines (5 mmol) was heated up to 110 °C in 10 mL of toluene for 4 days at which time the reaction mixture was cooled and concentrated. Purification by column chromatography afforded the cycloadducts, and in all cases, the polarity of the cycloadduct was greater that its precursor.

***tert*-Butyl-5-bromo-10-oxa-3-aza-tricyclo[5.2.1.0^{1,5}]dec-8-ene. 2b:** As white solid, 0.7 g (44 %), m.p:120-122°C, TLC, (PE : E (7:3)) R_f: 0.16; υ_{max}(thin film)/cm^{-1}: 2980(CH), 1700(CO), 1650(CC), 1200(CO), δ_H ($CDCl_3$): 6.54-6.46(m, 2H), 5.11(dd, 1H, J_1 1.6 Hz, J_2 4.6 Hz), 4.12(dd, 1H, J_1 6.0 Hz, J_2 12.5 Hz), 3.9(d, 1H J 12.5 Hz), 3.8 (dd, 1H, J_1 6.0 Hz, J_2 12.5 Hz), 3.6(d, 1H J 12.5 Hz), 2.54(m, 1H), 1.74(dd, 1H, J_1 4.6 Hz, J_2 12.5 Hz), 1.5 (s, 9H). δ_C (75.5 MHz): 154.4, 137.6, 134, 96.1, 81.2, 80.1, 64.5, 62.0, 46.3, 41.5, 28.7(3xC). $^m/_z$ (GC-MS): 261[M$^+$-*t*Bu, 5%], 259[M$^+$-*t*Bu, 5%], 180[M$^+$-(^{81}Br+*t*Bu), 15%], 81[^{81}Br$^+$, 100%], 57[*t*Bu$^+$, 85%]. EA($C_{13}H_{18}BrNO_3$): Requires: C 49.38 %, H 5.74 %, N 4.43 % Found: C 49.56 %, H 5.51 %, N 4.28 %.

***tert*-Butyl-5-bromo-7-methyl-10-oxa-3-aza-tricyclo[5.2.1.0^{1,5}]dec-8-ene. 2c:.** As a white solids, 0.66 g (40 %) m.p.: 85-87°C. TLC, (Hexane: E; (5:1)) R_f: 0.22; υ_{max}(thin film)/cm^{-1}: 2975(CH), 1699(CO), 1479. δ_H ($CDCl_3$): 6.3(d, 1H, J 5.8Hz), 6.2(d, 1H, J 5.8 Hz), 4.30(dd, 2H, J_1 6.0 Hz, J_2 12.5 Hz), 3.96(dd, 2H, J_1 6.0 Hz, J_2 12.0 Hz), 2.06(d, 1H, J 12.5 Hz), 1.70(d, 1H, J 12.5 Hz), 1.68(m, 1H), 1.5 (s, 3H), 1.45(s, 9H). δ_C (75.5 MHz): 154.5, 136.8, 135, 95.9, 79.8, 75.4, 64.4, 54.5, 51.9, 48.2, 28.7(3xC), 21.5. $^m/_z$ (GC-MS): 331[M$^+$(^{81}Br), 8%], 329[M$^+$(^{79}Br), 8%], 274[M$^+$(^{81}Br)-(^{t}Bu-H), 18%], 272[M$^+$(^{79}Br)-(^{t}Bu-H), 18%], 230[M$^+$(^{81}Br)-(Boc), 44%], 228[M$^+$(^{79}Br)-(Boc), 44%], 57[^{t}Bu$^+$, 100%]. EA ($C_{14}H_{20}BrNO_3$): Requires: C 50.92 %, H, 6.10 %, N, 4.24 %, Found: C 51.22 %, H 5.86 %, N, 4.40 %.

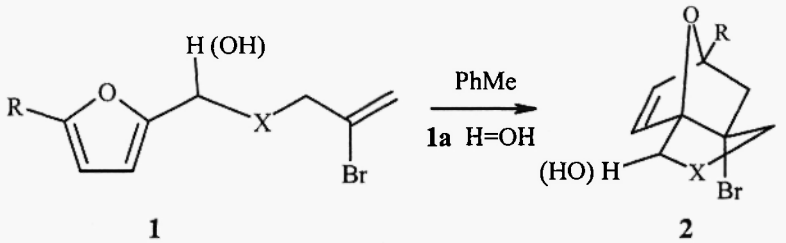
5-Bromo-10-oxa-3-thia-tricyclo[5.2.1.0^{1,5}]dec-8-ene. 2f:. As yellow crystal, 0.41 g (35 %), m.p.: 64-66 °C; TLC, (Hexane:Et_2O; (9 : 1), R_f:0,28; υ_{max} (thin film)/cm^{-1} : 2924(CH), 2856(CH), 1601(CC), 1455, 1218, 620. δ_H ($CDCl_3$): 6,55 (dd, 1H, J_1 5,8 Hz, J_2 1,8 Hz), 6,46 (d, 1H, J 5,8 Hz), 5,10 (dd, 1H, J_1 1,8 Hz, J_2 4,6 Hz), 3,44 (d, 2H, J 12,5 Hz), 3,38 (d, 2H, J 12,5 Hz), 2,56 (dd, 1H, J_1 4,8 Hz, J_2 12,5 Hz), 1,90 (d, 1H, J 12,5 Hz).δ_C (75.5 MHz): 139,1, 138,5, 103,8, 82,6, 71,8, 49,9, 46,2, 31,8. $^m/_z$ (GC-MS): 234[M$^+$(^{81}Br)-, 10%], 232[M$^+$(^{79}Br), 8%], 93[M$^+$-(^{81}Br+CH_2SCH_2), 100%]. EA(C_8H_9BrOS): Requires: 41.22%, H. 3.89 %, Found: C 41.51, H 3.63 %.

5-Bromo-7-methyl-10-oxa-3-thia-tricyclo[5.2.1.0^{1,5}]dec-8-ene. 2g: As a pale yellow solids, 0.4 g (32 %), m.p.: 82-84 °C. TLC, (PE: E; (5:1)) R_f: 0.27; υ_{max}(thin film)/cm^{-1}: 2934(C-H), 2869(CH), 1591(CC), 1196. δ_H ($CDCl_3$): 6.37(d, 1H, J 5.6 Hz), 6.20(d, 1H, J 5.6 Hz), 4.30(dd, 1H, J_1 1.2 Hz, $J_2$10.8 Hz), 3.96(dd, 2H, J_1 1.2 Hz, J_2 10.8Hz), 2.06(d, 1H, J 11.7 Hz), 1.70(d, 1H, J 11.7 Hz), 1.68(m, 1H), 1.51(s, 3H). δ_C (75.5 MHz): 140.4, 135.3, 98.6, 89.9, 82.1, 69.9, 67.3, 46.6, 19.6. $^m/_z$ (GC-MS): 248[M$^+$(^{81}Br), 5%], 246[M$^+$(^{79}Br), 5%], 202[M$^+$(^{81}Br)-(SCH_2), 8%], 200[M$^+$(^{79}Br)-(SCH_2), 8%], 93[M$^+$-(Br+$CH_2SCH_2CH_3$-H), 100%]. EA ($C_9H_{11}BrOS$): Found: Requires: 43.74 %, H. 4.49 %, C 43.88 %, H 4.62 %.

Results and Discussions

A series of IMDA precursors, *N*-, *O*- and *S*- furfurylbromoalkenes **1a-g** were prepared and subsequent transformation of the compounds **1a-g** to the IMDA cycloadducts **2a-g** was studied by heating in toluene. Their tendency to thermal IMDA cyclisation and structural analysis regards to **2a-g** without using radicalic condition (Table-1) was also investigated. The syntheses of **1a-g** were accomplished in a few steps as follows; slow addition of 4-bromo-4-pentenal to 2-furfuryllitium in tetrahydrofuran at –78°C provided bromofurfurylalkenol, **1a** in 78% yield. The process shown in scheme 2 was used to prepare **1b-c**, by starting with commercially available furfuryl amines.

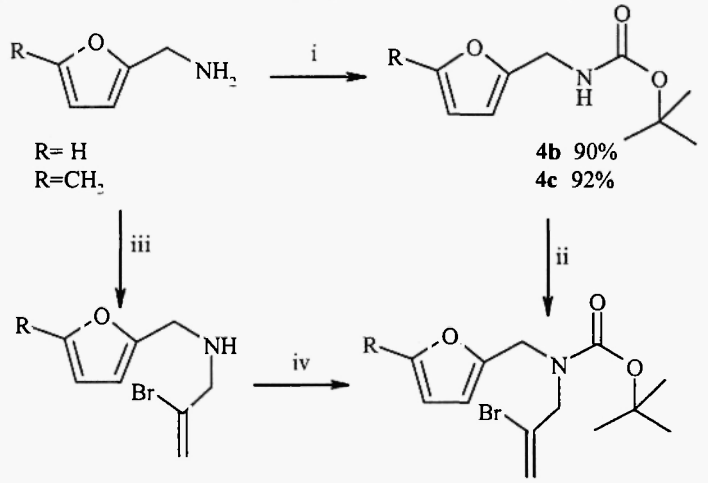
Table-1



1 2

Entry		Substrates			Open: Cyclic
		R	X		1:2
1	**1a**	H	CH_2	**2a**	100:0
2	**1b**	H	*N*-$CO_2{}^tBu$	**2b**	56:44
3	**1c**	CH_3	*N*- $CO_2{}^tBu$	**2c**	60:40
4	**1d**	H	O	**2d**	62:38
5	**1e**	CH_3	O	**2e**	67:33
6	**1f**	H	S	**2f**	65:35
7	**1g**	CH_3	S	**2g**	68:32

The protection was achieved under standard condition (8) to generate carbamides, **4b-c** quantitatively and used as a crude. Following alkylation using *n*-butyllitium and 2,3-dibromopropene gave the IMDA precursors, **1b-c** in 36% and 42% yield. Alternatively, the alkylation of amines with 2,3-dibromopropene in the presence of potassium carbonate and then protection of **5b-c** performed the desired precursors, **1b-c** in 83% and 85% yield. Bromoalkenes, **1d-g** were generated by Williamson ether synthesis; Furfurylalcohols (6) and furfurylthiols were added to the suspension of sodium hydride in tetrahydrofuran at 0 °C and followed by addition of 2,3-dibromopropene provided furfurylbromoalkenes, **1d-g**.



R= H **4b** 90%
R=CH_3 **4c** 92%

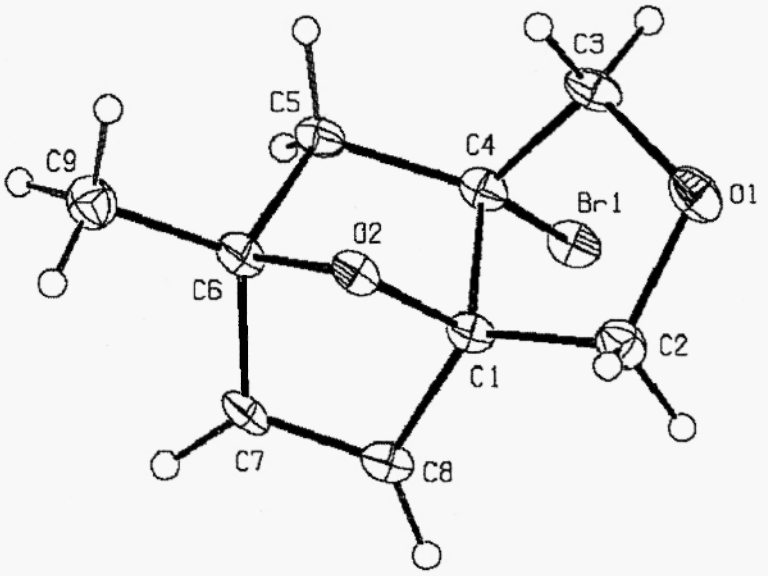
R=H **5b** 48%
R=CH_3 **5c** 52%

83% **1b** 36%
85% **1c** 42%

i. $(BOC)_2O$, DMAP, DCM, 0°C, 2h; ii. K_2CO_3, 2,3-dibromopropene, THF, reflux, 3d; iii. *n*-BuLi, 2,3-dibromopropene, THF, -78°C; vi. $(BOC)_2O$, DMAP, DCM, 0 °C.

Scheme-2

Furans, **1a-g** were subsequently refluxed in toluene (110°C) for 4 days at which time most of systems had reached their equilibrium mixtures. Attempted IMDA reaction with furfuryl moiety **1a** without possessing a heteroatom failed even under forcing conditions. However, much of our interest with bromoalkenylfurans, **1b-g** underwent thermal IMDA reaction with reasonable yields and high stereoselectivity. Cycloaddition attempt with **5b-c** was also found problematic due to the thermodynamic equilibrium often disfavours the cycloadduct (9). The use of protecting group like *tert*-butyl carboxylate encouraged IMDA cycloaddition reactions and increased the yield of cycloadducts against the benzyl protective group, **2b-c**. This cycloaddition could be alternative to Gschwend's work in which nitrogen tricycles opened and gave acyclic product as soon as the carbonyl group has been reduced (10).



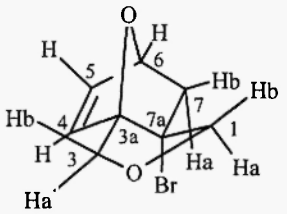
Molecular structure of 6-bromo-4-methyl-8-oxa-1,4-epoxybicyclo[4.3.0]non-2-ene, **2e** in the crystal (12). *Orthorhombic* crystal of space group $Pna2_1$, Z=4, unit cell dimensions a=7.4583(8)Å, b=16.185(2)Å, c=7.4735(8)Å, V=902.1518Å^3. 4123 reflections collected with λ=0.71073Å, θ=2.52-27.98° μ=4.512mm^{-1}.

Scheme-3

The structure and stereochemistry of the cycloadducts were determined by 2D-NMR experiments and further confirmed by X-ray crystallography. X-ray diffraction of **2e** and **2g** (11) attributed that the process is generated over facile *exo* transition state. Bromine is in *endo* position according to epoxy bridge (O2) and preferably being at sterically hindered side of the rings.

The structure of newly formed ring is *exo* fused in **2b-g** and give evident from their relevant ^{1}H-^{1}H couplings. (Table 2) For instance, oxygen possessed moiety **2d** can be representative of three five-membered fused systems. Thus, out of two geminal protons H-*7a* and *7b*, only H-*7b* couples with H-*6* (J = 4.5Hz) (Entry 2). No-coupling between H-*7a* and H-*6* is attributable to dihedral angle of ca. 90° between the two protons. This particular thermal intramolecular Diels-Alder cycloaddition leaded us to consider influence of electronic effect on the reaction besides Thorpe-Ingold and steric buttress effect (13). Such sequential reactions offer a high degree of synthetic efficiency in that they permit complex molecules to be constructed in a simple manner with great elegance and selectivity.

Table 2: NOE data represents **2d.**



Entry	^{1}H-^{1}H	*J* in Hz	NOE
1	6-7a	0.0	-
2	6-7b	4.5	weak
3	7a-7b	12.5	strong
4	1a-1b	10.5	strong
5	3a-3b	10.5	strong
6	3-4	-	-
7	4-5	5.6	medium

The salient features of the strategy include high degree stereoselectivity in the cycloaddition, atom and step economy, and generation of multiple chiral centers and functionalities. The ability to obtain a quaternary carbon originating in the dienophile can significantly extend the scope of the furan based IMDA reaction. Bromine can encourage the transformation of the furan to an indole, isobenzofuran and isobenzothiophene derivatives by cleavage of epoxy-bridge of adduct and concomitant aromatization and, the availability of a large number of functionalized furans. Further progress in this area will be reported in due course.

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