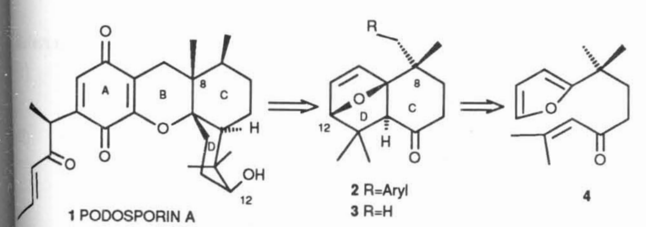
The Effect of Lewis Acids on the Intramolecular Diels–Alder Reaction of the Furan Diene

Christine Rogers, Brian A. Keay*
Department of Chemistry, University of Calgary, Calgary, Alberta T2N 1N4, Canada

Received 8 February 1991

Abstract: Lewis acids have been found to accelerate the intramolecular Diels–Alder reaction of the furan diene in which the diene and dienophile are connected by four-carbon atoms [2-(4-oxo-5-alkenyl)furans]. The methodology has been extended to include acetylenic dienophiles [2-(1,1-dimethyl-4-oxo-5-alkynyl)-furans], which cyclize to give the oxatricyclo ring system (5,6,7,8-tetrahydro-5,5-dimethyl-8-oxo-2*H*-2,4a-epoxynaphthalene).

The antibiotic Podosporin A **1** was isolated from the fungus *Podospora decipiens* and possesses the unique benzo[d]xanthene ring system.[1] Our interest in the intramolecular Diels-Alder[2] reaction of the furan diene (IMDAF) prompted us to investigate the possibility of using the IMDAF to prepare the C-D rings of Podosporin A. Our

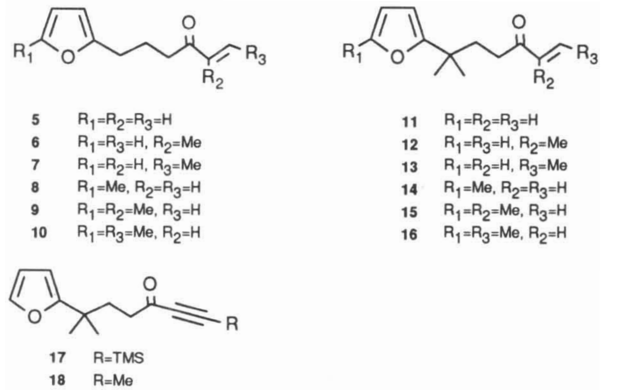


Scheme 1

retrosynthetic analysis provided oxatricyclo adduct **2**, which was further simplified to compound **3** as a model for our study. Since the IMDAF reaction of precursors containing gem-dialkylated four carbon tethers have not been investigated, we chose to explore first the IMDAF reaction involving compounds such as **4**.

The IMDAF reaction of a furan diene connected to the dienophile by a four carbon chain are known to have an equilibrium which lies toward starting material. Methods employed to overcome this unfavourable equilibrium to date include heat[3], β-cyclodextrin[4], aqueous solutions[5], alkylated side chains[6], and high pressure.[7] The success of the first four methods has been limited to precursors having unsubstituted dienophiles. Although high pressure shifted the equilibrium of a variety of systems containing substituted dienophiles to the tricyclo adducts exclusively, they were formed in modest yields ranging from 40-60%. Since the above methods required long reaction times (2-14 days) and/or access to specialized equipment we sought a more generally accessible method to improve the yields of adducts and shorten the reaction times.

Lewis acids have been used successfully to catalyze the intermolecular Diels-Alder reaction employing furan as the diene component.[8] In addition Lewis acids have also been used in the intramolecular Diels-Alder reaction[9]; however, their use in the IMDAF reaction has been limited to one unsuccessful report involving a five carbon atom side arm[7c] and one example involving a three atom side arm (one nitrogen and two carbon atoms) with an internally coordinated magnesium salt.[10] We herein report the effect of Lewis acids on the IMDAF reaction of compounds **4-18** (Schemes 1 and 2).[11]



Scheme 2

Compound **6** was treated with a variety of Lewis acids under various conditions.[12] The most effective catalyst in terms of a starting material:adduct ratio (SM:A, 35:65), yield (97%), and ease of handling was methylaluminum dichloride;[13] the SM:A ratio was attained after only 2.5 hours at -50°C. These results are greatly improved over previous observations employing either florisil or 2.0M calcium chloride;[5a] stirring compound **6** for 4 days in florisil provided no adduct while calcium chloride gave a 50:50 SM:A ratio. Interestingly, zinc iodide was the least effective catalyst (r.t., 39h; SM:A, 65:35) in spite of its proven utility in the intermolecular Diels-Alder reaction with furans.[8c]

The SM:A ratios observed for the Lewis acid $MeAlCl_2$ were shown to be thermodynamic and not kinetic ratios. Treating pure tricyclo adduct **20** with one equivalent of $MeAlCl_2$ in methylene chloride at -50°C for 2.5 hours provided a SM:A ratio of 35:65, which is identical to that obtained when treating precursor **6** under the same conditions.

Table 1 illustrates the effect of $MeAlCl_2$ on the IMDA reaction of compounds **5-16** (entries 1-12) along with the results from stirring the precursors in florisil/methylene chloride. A few points are noteworthy. The Lewis acid mediated IMDAF reactions provides, in all cases, higher SM:A ratios and yields when compared to the results from florisil/methylene chloride.[5a] The starting material and adducts are easily separated by flash chromatography and recycling the starting material provides large quantities of adducts. The *gem*-dimethyl precursors **11** and **14** (unsubstituted dienophile) provided their corresponding adducts in 88% and 96% yield respectively when stirred in florisil/CH_2Cl_2 for 12 hours. This increase in SM:A ratio when compared to the results from compounds **5** and **8** can be attributed to the "*gem*-dialkyl effect".[14,15]

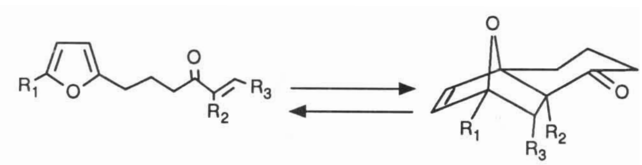
^1H NMR analysis of the adducts obtained from both the florisil- and Lewis acid mediated IMDAF reaction of compounds **5-16**

Table 1: Results of Various IMDAF Reactions

Entry	Compound	Lewis Acid	Temp. °C	Time h	SM:Adduct Ratio	Adduct Yield[a] %
1.	**5**	florisil	25	144	10:90	62 (71)
		$MeAlCl_2$	-78	1	0:100	**19** 99 (99)
		none, 12 kbar	25	25	0:100	51 (51)
2.	**6**	florisil	25	144	100:0	**20** 0
		$MeAlCl_2$	-78	2.5	22:78	76 (96)
3.	**7**	florisil	25	144	100:0	**21** 0
		$MeAlCl_2$	-78	8	78:22	11 (65)
4.	**8**	florisil	25	336	12:88	52 (65)
		$MeAlCl_2$	-78	1	0:100	**22** 99 (99)
		none, 12 kbar	25	24	0:100	55 (55)
5.	**9**	florisil	25	144	100:0	**23** 0
		$MeAlCl_2$	-50	8	19:81	80 (97)
6.	**10**	florisil	25	144	100:0	**24** 0
		$MeAlCl_2$	-78	8	82:18	18 (97)
7.	**11**	florisil	25	12	0:100	**25** 88
8.	**12**	florisil	25	24	83:17	**26** 16 (68)
		$MeAlCl_2$	-78	8	68:32	31 (96)
9.	**13**	florisil	25	192	87:13	**27** 12 (67)
		$MeAlCl_2$	-78	8	73:27	22 (94)
10.	**14**	florisil	25	12	0:100	**28** 96
11.	**15**	florisil	25	240	77:23	**29** 19 (68)
		$MeAlCl_2$	-78	8	78:23	22 (97)
12.	**16**	florisil	25	336	85:15	**30** 13 (62)
		$MeAlCl_2$	-78	8	78:22	18 (93)
13.	**17**	Me_2AlCl	-50	2.5	12:88	**31** 80 (88)
14.	**18**	Me_2AlCl	-50	2.5	0:100	**32** 97

a) number in parentheses is the yield of adduct based on recovered starting material

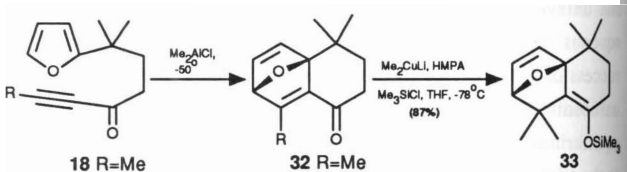
indicated the side arm was orientated *exo* with respect to the oxygen bridge (Scheme 3);[16] adducts resulting from an *endo* side arm transition state were neither detected nor isolated.[17]



Scheme 3

Precursor **4** did not provide any tricyclo adduct **3** (Scheme 1) when treated with $MeAlCl_2$ in methylene chloride at -78°C (by ^1H NMR).[18] This result led us to explore the possibility of employing acetylenic dienophiles in the IMDAF reaction; cuprate addition on the tricyclic α,β-unsaturated ketone **32** would presumably lead to **33** (Scheme 4) which would be equivalent to compound **3** (Scheme 1).

Lewis acids were found to accelerate the IMDAF reaction with precursors containing an acetylenic dienophile (entries 13 and 14,



18 R=Me
17 R=$SiMe_3$
32 R=Me
31 R=$SiMe_3$
33

Scheme 4

Table 1). The milder Lewis acid dimethylaluminum chloride was used at -50°C.[19] These conditions provided the highly strained adducts **31** and **32** in 80% and 97% yield respectively with the bulkier trimethylsilylated acetylenic dienophile in precursor **17** providing a lower SM:A ratio (12:88) than the methyl substituted acetylene **18** (0:100).[20] The short reaction times and high yields of adducts **31** and **32** are in contrast with previous reports of thermal IMDA reactions[21] involving internally activated acetylenic dienophiles.[21d-f]

Lithium dimethylcuprate added smoothly to adduct **32** in the presence of HMPA and trimethylsilyl chloride[22] (Scheme 4) to afford adduct **33** in 87% yield. The overall yield of 84% from compound **18** indicates that the IMDAF reaction of systems containing acetylenic dienophiles is a viable synthetic route towards the preparation of Podosporin A.

We have shown that Lewis acids can be employed to accelerate the rate at which equilibrium is achieved in the IMDAF reaction where the dienophile is attached to the diene via a four carbon atom side arm. Reaction times were reduced to a ***few hours*** (instead of days) and in most cases, increased starting material:adduct ratios were observed when compared to the results involving florisil. Application of tricyclo adducts arising from acetylenic precursors towards the preparation of Podosporin A are currently in progress.

Acknowledgement: We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) and the University of Calgary for financial support and NSERC for a post-graduate scholarship (to C.R.).

References and Notes

(1) Weber, H.A.; Baenziger, N.C.; Gloer, J.B. *J. Org. Chem.* **1988**, *53*, 4567.

(2) Ciganek, E. *Organic Reactions*, **1984**, *32*, 1; Fallis, A.G. *Can J. Chem.* **1984**, *62*, 183.

(3) DeClerq, P.J.; Van Royen, L.A. *Synthetic Comm.* **1979**, *9*, 771.

(4) Sternbach, D.D.; Rossana, D.M. *J. Am. Chem. Soc.* **1982**, *104*, 5853.

(5) (a) Keay, B.A. *J. Chem. Soc., Chem. Comm.* **1987**, 419; (b) Sternbach, D.D.; Rossana, D.M. *Tetrahedron Lett.* **1982**, *23*, 303.

(6) (a) Rogers,C.; Keay, B.A. *Tetrahedron Lett.* **1989**, *30*, 1349; (b) Appendino, G.; Hoflack, F.; DeClerq, P.J.; Chiari, G.; Calleri, M. *Tetrahedron* **1988**, *44*, 4605; (c) Jung, M.E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224; Jung, M.E. *Synlett* **1990**, 186; Jung, M.E.; Gervay, J. *J. Am. Chem. Soc.* **1989**, *111*, 5469; Jung, M.E.; Gervay, J. *Tetrahedron Lett.* **1988**, *29*, 2429; (d) Fischer, K.; Hunig, S. *J. Org. Chem.* **1987**, *52*, 564; (e) Sternbach, D.D.; Rossana, D.M.; Onan, K.D. *Tetrahedron Lett.* **1985**, *26*, 591; Sternbach, D.D.; Rossana, D.M. *J. Org. Chem.* **1984**, *49*, 3428; (f) Cauwberghs, S.; De Clerq, P.J.; Tinant, B. DeClerq, J.P. *Tetrahedron Lett.* **1988**, *29*, 2493; (g) Harwood, L.M.; Jones, G.; Pickard, J.; Thomas, R.M.; Watkin, D. *J.C.S. Chem. Comm.* **1990**, 605, 608.

(7) (a) Keay, B.A.; Dibble, P.W. *Tetrahedron Lett.* **1989**, *30*, 1045; (b) Harwood, L.M.; Leeming, S.A.; Isaacs, N.S.; Jones, G.; Pickard, J.; Thomas, R.M.; Watkin, D. *Tetrahedron Lett.* **1988**, *29*, 5017; (c) Burrell, S.J.; Derome, A.E.; Edenborough, M.S.; Harwood, L.M.; Leeming, S.A.; Isaacs, N.S. *Tetrahedron Lett.* **1985**, *26*, 2229; (d) Isaacs, N.S.; Van der Beeke, P. *Tetrahedron Lett.* **1982**, *23*, 2147.

(8) (a) Lipshutz, B.H. *Chem. Rev.* **1986**, *86*, 795; (b) Nugent, W.A.; McKinney, R.J.; Harlow, R.L. *Organometallics* **1984**, *3*, 1315; (c) Brion, F. *Tetrahedron Lett.* **1982**, *23*, 5299; (d) Kotsuki, H.; Asao, K.; Ohnishi, H. *Bull. Chem. Soc. Jpn.* **1984**, 3339; (e) Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1982**, *65*, 1700; (f) Moore, J.A.; Partain, E.M. *J. Org. Chem.* **1983**, *48*, 1105.

(9) (a) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187; (b) Marshell, J.A.; Audia, J.E.; Grota, J.; Shearer, B.G. *Tetrahedron*, **1986**, *42*, 2893; Shea, K.J.; Gilman, J.W. *Tetrahedron Lett.* **1983**, *24*, 657; Sakan, K.; Smith, D.A. *Tetrahedron Lett.* **1984**, *25*, 2081; Sakan, K.; Craven, B.A. *J. Am. Chem. Soc.* **1983**, *105*, 3732; Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1981**, 29; Roush, W.R.; Gillis, H.R. *J. Org. Chem.* **1980**, *45*, 4267.

(10) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1981**, 29 and references therein.

(11) Compounds **5-10** were prepared as previously described.[5a] Compounds **4** and **11-18** were prepared by standard methods and will be presented in detail in a full paper.

(12) The Lewis acids employed in CH_2Cl_2 (conditions; starting material:adduct ratios) were: $SnCl_4$ (-78°, 1h; 24:76); $BF_3 \cdot Et_2O$ (-50°, 3h; 28:72); $TiCl_4$:$Ti(O^iPr)_4$ (-50°, 2h; 32:68); Me_2AlCl, $EtAlCl_2$ and Et_2AlCl (-50°, 2h; 35:65).

(13) A typical procedure for the Lewis acid mediated IMDAF is as follows: To a solution, at -78°C, of a precursor (0.34 mmol) in methylene chloride (10 ml, dry, distilled) under an atmosphere of argon was added 1.1 equivalents of a Me_2AlCl. The solution was warmed to the appropriate temperature and after 2-3 hours quenched with cold sodium bicarbonate (10%) and extracted with methylene chloride. The solvent was removed *in vacuo* (no external heating). The ratio of starting material:adduct was determined by integrating the ^1H NMR spectrum.

(14) Beesley, R.M.; Ingold, C.K.; Thorpe, J.F. *J. Chem. Soc.* **1915**, *107*, 1080.

(15) For discussions concerning the "*gem*-dialkyl effect" in other systems see references 6b and 6c above. See also: (a) Curtin, M.L.; Okamura, W.H. *J. Org. Chem.* **1990**, *55*, 5278; (b) Allinger, N.L.; Zalkow, V. *J. Org. Chem.* **1960**, *25*, 701.

(16) The stereochemistry of the adducts was determined by using a combination of coupling constants and n.O.e. experiments.

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

(18) The major product was identified as a dimer of compound **4** arising from an intermolecular Friedel-Crafts reaction of the alkene of one molecule on the furan ring of a second molecule.

(19) For a recent example of a Lewis acid (Et_2AlCl) mediated intramolecular Diels-Alder reaction with a side arm activated acetylenic dienophile, see: Taschner, M.J.; Cyr, P.T. *Tetrahedron Lett.* **1990**, *37*, 5297.

(20) Optimization of the experimental conditions may result in complete adduct formation for the trimethylsilyl substituted precursor **17**.

(21) For examples of thermal IMDA reactions involving acetylenic dienophiles, see: (a) Hecker; S.J.; Heathcock, C.H. *J. Org. Chem.* **1985**, *50*, 5159; (b) Hall, S.E.; Roush, W.R. *J. Org. Chem.* **1982**, *47*, 4611; (c) Roush, W.R.; Peseckis, S.M. *J. Am. Chem. Soc.* **1981**, *103*, 6696; (d) Jacobi, P.A.; Walker, D.G. *J. Am. Chem. Soc.* **1981**, *103*, 4611; Jacobi, P.A.; Walker, D.G.; Odeh, I.M.A. *J. Org. Chem.* **1981**, *46*, 2065; (e) Kraus, G.A. *J. Am. Chem. Soc.* **1980**, *102*, 1974; (f) Klemm, L.H.; McGuire, T.M.; Gopinath, K.W. *J. Org. Chem.* **1976**, *41*, 2571.

(22) Johnson, C.R.; Murren, T.J. *Tetrahedron Lett.* **1987**, *28*, 27.