

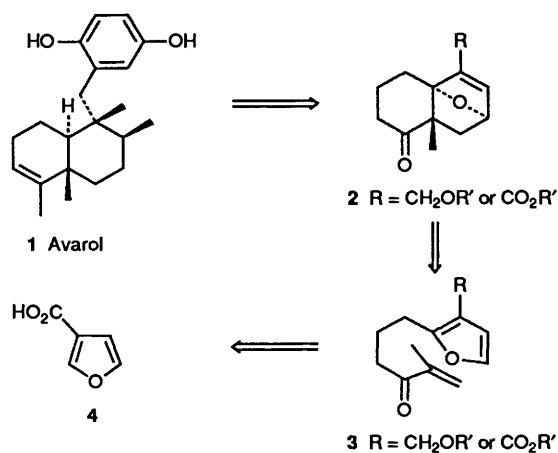
An Improved Synthesis of 2-Substituted-3-furoic Acids Leading to an Intramolecular Diels–Alder Reaction Between a Dienophile and Furan Diene Both Containing an Electron Withdrawing Group

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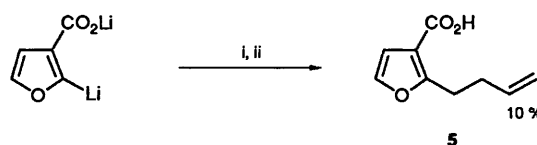
An improved preparation of various 2-substituted-3-furoic acids by lithiation of 2-methyl-3-furoic acid with 2.0 equiv. of butyllithium, and a successful intramolecular Diels–Alder reaction using 0.1 equiv. of methylaluminium dichloride between a dienophile and furan diene, which are both substituted with an electron withdrawing moiety, are described.

Avarol **1** (Scheme 1) is a *trans*-clerodane diterpenoid which has been isolated from the marine sponge *Disidea avara*¹ and



shown to possess potent anti-HIV effect *in vitro*² by inhibition of the t-RNA UAG-termination codon suppressor.³ Although avarol has been synthesized once,⁴ and many synthetic approaches towards other *trans*-clerodanes have been reported,⁵ there is a need for a flexible synthetic pathway towards the synthesis of avarol to allow for the preparation of analogues for structure–activity studies. Our interest in the intramolecular Diels–Alder reaction of the furan diene⁶ (IMDAF) and nucleophilic oxygen-bridge ring-opening reactions of the resultant oxatricyclo adducts⁷ led us to retrosynthesise avarol to bridged adduct **2** (Scheme 1), which should be accessible from the IMDAF precursor **3**. The synthesis of compound **3** should be possible starting with 3-furoic acid **4**. We herein report (1) an improved method for the synthesis of 2,3-disubstituted furans and (2) the synthesis and IMDAF reaction of precursors such as compound **3**.

The C-2 lithiation of 3-substituted furans usually leads to a mixture of C-2 and C-5 mono-anions.⁸ Knight *et al.*⁹ have been the only group to successfully lithiate a 3-substituted furan regioselectively in the C-2 position by treating 3-furoic acid **4** with 2.2 equiv. of LDA (lithium diisopropylamide). Although the C-2 anion could be trapped in high yield with reactive electrophiles (*i.e.* MeI, aldehydes and ketones, yields >90%), poorer yields were obtained when sluggish electrophiles, such as iodoethane and 5-iodopent-1-ene, were employed (yields <42%). In our hands, the reaction of the dianion of 3-furoic acid with 4-bromobut-1-ene provided acid **5** (Scheme 2) in only 10% yield.



Scheme 2 Reagents: i, 4-bromobut-1-ene; ii, H₃O⁺

We have recently reported¹⁰ that 2-methyl-3-furoic acid **6** can be lithiated directly with 2.0 equiv. of butyllithium to form dianion **7** (Table 1).† Trapping this dianion with 3-bromoprop-1-ene provided acid **5**, which was immediately converted into the methyl ester **8** (in 70% yield, two steps) by treatment with diazomethane¹² (Table 1, entry 4).‡§ This reaction was not limited to reactive electrophiles, since electrophiles which are usually sluggish to react with alkylolithium species (entries 2, 3 and 5) provided alkylated products in good to excellent yields after conversion into the methyl ester. The yield of the ester resulting from the addition of 2-(2-bromoethyl)-1,3-dioxolane (entry 1) was low (40%) due to the formation of the corresponding aldehyde upon work-up with 10% HCl; the aldehyde-acid was unstable at room temperature and subsequently decomposed. Finally, aldehydes and ketones (entries 6–8) reacted smoothly to provide the corresponding alcohols in good yield.

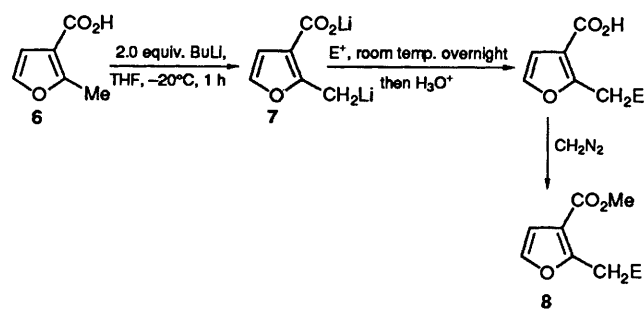
The improved alkylation with compound **6** when compared to those reported⁹ for 3-furoic acid **4** is possibly due to the inherent stability of the dilithio species **7** in tetrahydrofuran (THF) at room temperature, thereby allowing more time for the electrophile to react with the dianion. The dianion of 3-furoic acid when stirred for 2 h at room temperature in THF did not incorporate deuterium when treated with deuterium oxide.

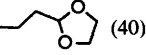
IMDAF precursors **12–14** were prepared as outlined in Scheme 3. Thus, acid **5** was either converted into the isopropyl ester **11**¹³ or reduced with lithium aluminium hydride to provide the corresponding alcohol, which was protected as a methyl **9** or benzyl ether **10**.¹⁴ Hydroboration–oxidation¹⁵ of compounds **9–11**, followed by Swern oxidation¹⁶ provided the corresponding aldehydes. Treatment of the aldehydes with 2-lithiopropene¹⁷ followed by oxidation of the allylic alcohols with Fetizon's reagent¹⁸ provided IMDAF precursors **12–14**, respectively.

† In a similar manner, Tada *et al.* have reported that deprotonation occurs at the C-2 methyl group of 2,4-dimethyl-3-furoic acid when treated with 2.0 equiv. of LDA (see ref. 11).

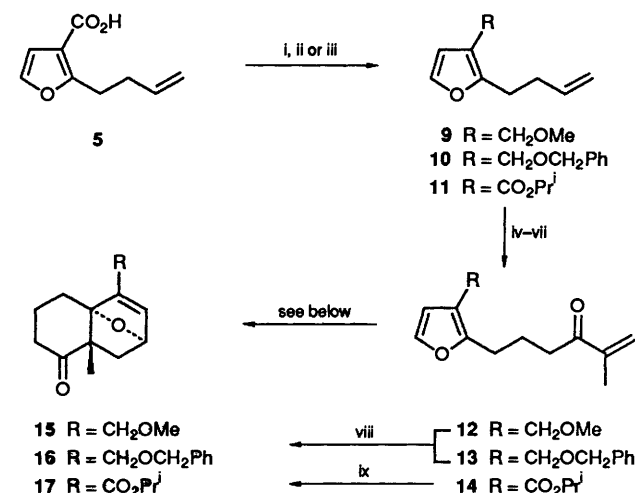
‡ We have found the esters easier to purify than the corresponding carboxylic acids.

§ All compounds provided analytical and/or spectroscopic data consistent with their structures.

Table 1 Results of the lithiation of 2-methyl-3-furoic acid

Entry	Electrophile	Product (8) (% yield) ^a
1	2-(2-bromoethyl)-1,3-dioxolane	E =  (40)
2	iodoethane	E = Et (91)
3	1-chloro-3-iodopropane	E = (CH ₂) ₃ Cl (82)
4	allyl bromide	E = CH ₂ CH=CH ₂ (70)
5	2-iodopropane	E = CHMe ₂ (67)
6	propanal	E = CH(OH)Et (79)
7	benzaldehyde	E = CH(OH)Ph (79)
8	acetone	E = COHMe ₂ (84)

^a Isolated yields after purification.



Scheme 3 Reagents and conditions: i, LAH, Et₂O; ii, NaH, MeI or BrCH₂Ph; iii, K₂CO₃, 2-iodopropane, DMF, room temp. (83%); iv, BH₃·Me₂S, Et₂O, 0 °C; NaOH, H₂O₂ (76%); v, Swern [O] (89%); vi, 2-bromopropene + Bu^tLi, Et₂O, -78 °C (90%); vii, Ag₂CO₃ on Celite, C₆H₆ (95%); viii, 0.1 equiv. MeAlCl₂, CH₂Cl₂, -78 °C, 1 h (93–95%); ix, 0.1 equiv. MeAlCl₂, CH₂Cl₂, -40 °C, 2 h (63%)

Treatment of either precursor 12 or 13 with 0.1 equiv. of methylaluminium dichloride in methylene chloride at -78 °C for 1 h provided adducts 15 (93%) and 16 (95%) respectively. Only the adducts, in which the methyl group was orientated *anti* to the oxygen bridge, were detected (by ¹H NMR spectroscopy) and isolated.⁶ In order to reduce the number of synthetic steps towards avarol, precursor 14, which has an electron-withdrawing group on both the furan diene and dienophile, was treated with 0.1 equiv. of methylaluminium dichloride in methylene dichloride at -40 °C. Surprisingly, a 35:65 ratio of 14:17* was obtained after 2 h, which did not

* The starting material 14 and adduct 17 are easily separated on silica gel column (20:1; light petroleum-EtOAc) to provide adduct 17 in 63% yield. The recovered starting material was recycled twice to provide adduct 17 in 90% isolated yield.

increase with longer reaction times. Increasing or decreasing the temperature resulted in ratios in favour of starting material 17 [e.g. temperature (14:17 ratio): -78 °C (80:20); -60 °C (75:25); -20 °C (70:30); 0 °C (90:10)]. Although reverse electron demand intramolecular Diels–Alder (IDA) reactions are common, IDA reactions involving electron-withdrawing groups on both the diene and dienophile are rare;¹⁹ only one successful example has been reported, which involved a side arm containing three carbon atoms.²⁰ The successful synthesis of adduct 17 provides a useful intermediate towards the synthesis of avarol. Nucleophilic oxygen-bridge ring-openings of adducts 15–17 are currently under investigation.

In summary, (1) the lithiation of 2-methyl-3-furoic acid and trapping the resulting dianion with electrophiles provides an excellent entry into various 2-substituted-3-furoic acids which were not possible *via* the direct lithiation of 3-furoic acid, and (2) the use of catalytic methylaluminium dichloride in the IMDAF reaction is useful for precursors having substituents in the C-3 position of the furan ring and for systems containing an electron-withdrawing group on both the dienophile and furan ring.

Typical Experimental Procedure.—To a solution of 2-methyl-3-furoic acid¹⁰ 6 (0.1 mmol) in THF at -20 °C was added 2.0 equiv. of butyllithium and the solution stirred for 1 h. The resulting dianion 7 was quenched with a variety of electrophiles (1.5 equiv., room temp., 16 h), which provided upon work-up (10% HCl) the corresponding carboxylic acids (Table 1). The acids were immediately treated with diazomethane in diethyl ether to provide the corresponding methyl esters 8.

Acknowledgements

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References

- L. Minale, R. Riccio and G. Sodano, *Tetrahedron Lett.*, 1974, **15**, 3401; S. de Rosa, L. Minale, R. Riccio and G. Sodano, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1408; W. E. G. Muller, R. K. Zahn, M. J. Gasic, N. Dogovic, A. Maidhof, C. Becker, B. Diehl-Seifert and E. Eich, *Comp. Biochem. Physiol.*, 1985, **80C**, 47; D. M. Kushlan and D. J. Faulkner, *Tetrahedron*, 1989, **45**, 3307; A. Crispino, A. de Giulio, S. de Rosa and G. Strazzullo, *J. Nat. Prod.*, 1989, **52**, 646; S. Hirsch, A. Rudi and Y. Kashman, *J. Nat. Prod.*, 1991, **54**, 92.
- P. A. Sarin, D. Sun, A. Thornton and W. E. G. Muller, *J. Natl. Cancer Inst.*, 1987, **78**, 663.
- W. E. G. Muller, H. C. Schroder, P. Reuter, P. S. Sarin, G. Hess, K.-H. M. Zum Buschenfelde, Y. Kuchino and S. Nishimura, *Aids Research and Human Retroviruses*, 1988, **4**, 279; E. Sandstrom, *Drugs*, 1989, **38**, 417; Y. Kuchino, M. Mizushima, H. C. Schroder and W. E. G. Muller, *Arch. Aids Res.*, 1990, **IV**, 61.
- A. S. Sharma and P. Chattopadhyay, *J. Org. Chem.*, 1982, **47**, 1727.
- J. W. ApSimon and K. Yamasaki, *Chem. Lett.*, 1977, 1453; S. Takahashi, S. T. Kusumi and H. Kakisawa, *Chem. Lett.*, 1979, 515; A. B. Smith III and R. Mewshaw, *J. Org. Chem.*, 1984, **49**, 3685; A. S. Sharma and A. K. Gayen, *Tetrahedron*, 1985, **41**, 4581; P. Magnus, C. Walker, P. R. Jenkins and K. A. Menear, *Tetrahedron Lett.*, 1986, **27**, 651; T. Tokoroyama, K. Fujimori, T. Shimizu, Y. Yamagiwa, M. Monden and H. Iio, *Tetrahedron*, 1988, **44**, 6607; H. Hagiwara and H. Uda, *J. Org. Chem.*, 1988, **53**, 2308.
- C. Rogers and B. A. Keay, *Can. J. Chem.*, 1992, in the press; C. Rogers and B. A. Keay, *Tetrahedron Lett.*, 1991, **32**, 6477; C. Rogers and B. A. Keay, *Synlett.*, 1991, 353; C. Rogers and B. A. Keay, *Tetrahedron Lett.*, 1989, **30**, 1349; B. A. Keay and P. W. Dibble, *Tetrahedron Lett.*, 1989, **30**, 1045; B. A. Keay, *J. Chem. Soc., Chem. Commun.*, 1987, 419.
- S. Woo and B. A. Keay, *Tetrahedron Lett.*, 1992, **33**, 2661; B. A. Keay, C. Rogers and J.-L. J. Bontront, *J. Chem. Soc., Chem. Commun.*, 1989, 1782.

- 8 (a) S. Katsumura, K. Hori, S. Fujiwara and S. Isoe, *Tetrahedron Lett.*, 1985, **26**, 4625; S. P. Tanis and D. B. Head, *Tetrahedron Lett.*, 1984, **25**, 4451; (b) D. Goldsmith, D. Liotta, M. Saindane, L. Waykole and P. Bowen, *Tetrahedron Lett.*, 1983, **24**, 5835; (c) I. Paterson and M. Gardner, *Tetrahedron* 1989, **45**, 5283; (d) D. L. Commins and M. O. Killpack, *J. Org. Chem.*, 1987, **52**, 104.
- 9 D. W. Knight and A. P. Nott, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1125; D. W. Knight, *Tetrahedron Lett.*, 1979, **20**, 469.
- 10 S. Yu and B. A. Keay, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2600.
- 11 M. Tada, Y. Sugimoto and T. Takahashi, *Chem. Lett.*, 1979, 1441.
- 12 T. H. Black, *Aldrichim. Acta*, 1983, **16**, 3.
- 13 S. C. Welch, C.-Y. Chou, J. M. Gruber and J.-M. Assercq, *J. Org. Chem.*, 1985, **50**, 2668.
- 14 T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 1991, Wiley, New York.
- 15 C. F. Lane, *J. Org. Chem.*, 1974, **39**, 1437.
- 16 A. J. Mancuso and D. Swern, *Synthesis*, 1981, 165.
- 17 W. F. Bailey, T. T. Nurmi, J. J. Patricia and W. Wang, *J. Am. Chem. Soc.*, 1987, **109**, 2442.
- 18 A. McKillop and D. W. Young, *Synthesis*, 1979, 401.
- 19 G. Brieger and J. N. Bennett, *Chem. Rev.*, 1980, **80**, 63; A. G. Fallis, *Can. J. Chem.*, 1984, **62**, 183; E. Ciganek, *Org. React.*, 1984, **32**, 1; B. H. Lipshutz, *Chem. Rev.*, 1986, **86**, 795; D. Craig, *Chem. Soc. Rev.*, 1987, **16**, 187; W. R. Roush, *Adv. Cycloadd.*, 1990, **2**, 91.
- 20 M. E. Jung and K. M. Halweg, *Tetrahedron Lett.*, 1981, **22**, 2735.

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