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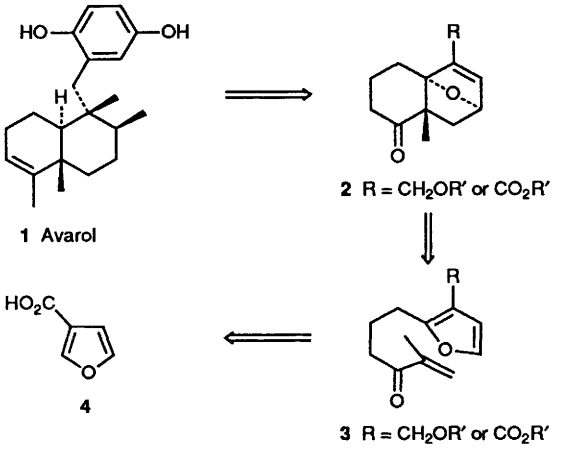
An improved preparation of various 2-substituted-3-furoic acids by lithiation of 2-methyl-3-furoic acid with 2.0 equiv. of butyllithium, and a successful intramolecular Diels–Alder reaction using 0.1 equiv. of methylaluminium dichloride between a dienophile and furan diene, which are both substituted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

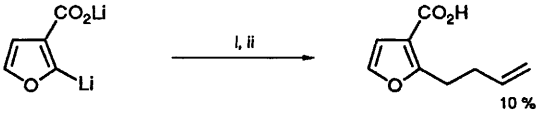
Avarol **1** (Scheme 1) is a *trans*-clerodane diterpenoid which has been isolated from the marine sponge *Disidea avara*[1] and



Scheme 1

shown to possess potent anti-HIV effect *in vitro*[2] by inhibition of the t-RNA UAG-termination codon supressor.[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 diene[6] (IMDAF) and nucleophilic oxygen-bridge ring-opening reactions of the resultant oxatricyclo adducts[7] 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 regiospecifically 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, H_3O^+

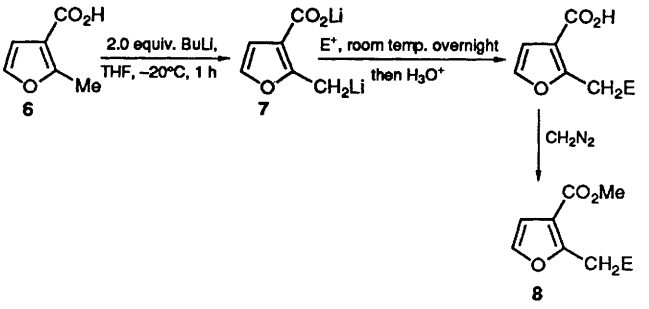
We have recently reported[10] that 2-methyl-3-furoic acid **6** can be lithiated directly with 2.0 equiv. of butyllithium to form dianion **7** (Table 1).† Trapping this dianion with 3-bromoprop-1-ene provided acid **5**, which was immediately converted into the methyl ester **8** (in 70% yield, two steps) by treatment with diazomethane[12] (Table 1, entry 4).‡§ This reaction was not limited to reactive electrophiles, since electrophiles which are usually sluggish to react with alkyllithium 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.

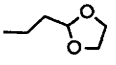
The improved alkylation with compound **6** when compared to those reported[9] for 3-furoic acid **4** is possibly due to the inherent stability of the dilithio species **7** in tetrahydrofuran (THF) at room temperature, thereby allowing more time for the electrophile to react with the dianion. The dianion 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–oxidation[15] of compounds **9–11**, followed by Swern oxidation[16] provided the corresponding aldehydes. Treatment of the aldehydes with 2-lithiopropene[17] followed by oxidation of the allylic alcohols with Fetizon's reagent[18] provided IMDAF precursors **12–14**, respectively.

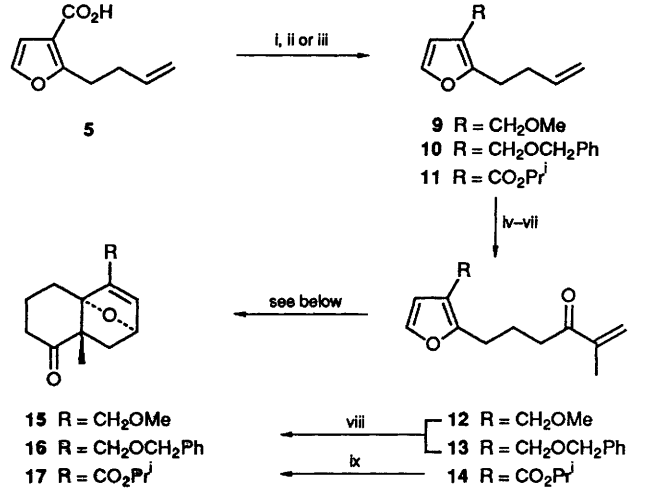
† In a similar manner, Tada *et al.* have reported that deprotonation occurs at the C-2 methyl group of 2,4-dimethyl-3-furoic acid when treated with 2.0 equiv. of LDA (see ref. 11).
‡ We have found the esters easier to purify than the corresponding carboxylic acids.
§ All compounds provided analytical 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 = $(CH_2)_3Cl$ (82)
4	allyl bromide	E = $CH_2CH{=}CH_2$ (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, Et_2O; ii, NaH, MeI or $BrCH_2Ph$; iii, K_2CO_3, 2-iodopropane, DMF, room temp. (83%); iv, $BH_3{\cdot}Me_2S$, Et_2O, 0 °C; NaOH, H_2O_2 (76%); v, Swern [O] (89%); vi, 2-bromopropene + Bu^{t}Li, Et_2O, −78 °C (90%); vii, Ag_2CO_3 on Celite, C_6H_6 (95%); viii, 0.1 equiv. $MeAlCl_2$, CH_2Cl_2, −78 °C, 1 h (93–95%); ix, 0.1 equiv. $MeAlCl_2$, CH_2Cl_2, −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 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 acid[10] **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

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) and the University of Calgary Research Board for financial support.

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* 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.

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Paper 2/04133B
Received 31*st July* 1992
Accepted 3*rd September* 1992