Pergamon

Tetrahedron Letters, Vol. 35, No. 21, pp. 3609-3612, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0604-V

Regioselective Synthesis of Hydroxy Butenolides : A Convenient Synthesis of A-Factor

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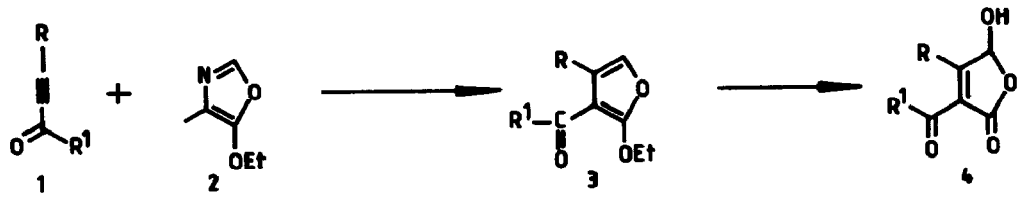
Abstract : An elegant approach for the regioselective preparation of hydroxy butenolide by the oxidation of 2-ethoxyfuran with MnO_2-HCl is described.

Hydroxy butenolide systems are commonly encountered as the main structural core in a variety of natural products[1] having pronounced biological activity. In our ongoing programme on the synthesis of biologically active natural products we faced difficulty in developing such hydroxy butenolide systems. The reported method of photooxidation of furans[2] is devoid of regioselectivity. Lack of a generalized method for regioselective oxidation of substituted furans has hampered the synthesis of many natural products. In this communication, we report a novel and expeditious approach for the regioselective synthesis of functionalised hydroxy butenolides. Our basic strategy delineated in scheme 1 involves a novel MnO_2-HCl oxidation of ethoxy furan 3, which can be prepared easily by a known procedure by employing tandem Diels-Alder and retro Diels-Alder cycloaddition[3] of acetylenic dienophiles 1 with 4-methyl-5-ethoxy oxazole 2.

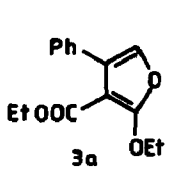
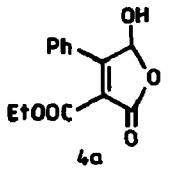
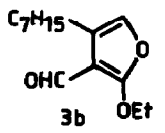
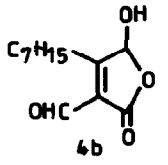
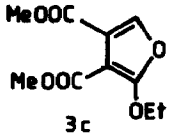
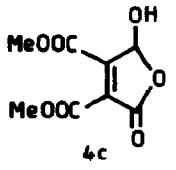
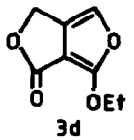
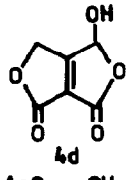
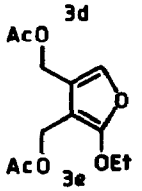
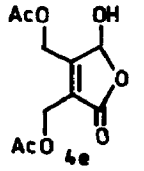
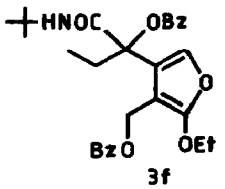
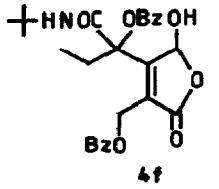
SCHEME - 1



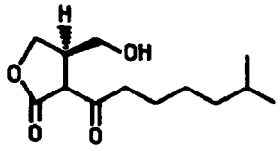
To exemplify, refluxing 3-phenyl propynoate with 4-methyl-5-ethoxy oxazole 2 in toluene for 3h afforded 4-phenyl-3-carbethoxy-2-ethoxy furan 3a in 90% yield in regiomerically pure form, which on treatment with MnO_2-HCl (4:10) gave rise to its hydroxy butenolide system 4a in 78% yield. To demonstrate the generality and functional group compatibility of our methodology, several examples were chosen and obtained the respective hydroxy butenolides in good to excellent yields. Various functionalities such as aldehyde, ester, acetoxy, lactone, amide and alcohol are unaffected indicating the milder reaction conditions (Table 1).

IICT Communication No. 3326

TABLE . PREPARED HYDROXY BUTENOLIDES

S.No.	3	4	Yield %
1	 3a	 4a	78 %
2	 3b	 4b	65 %
3	 3c	 4c	82 %
4	 3d	 4d	55 %
5	 3e	 4e	80 %
6	 3f	 4f	81 %

We exploited this methodology and successfully accomplished the total synthesis of (±)-A Factor. Khokholv et al discovered A-Factor as the inducer of the biosynthesis of Streptomycin in inactive mutants of Streptomyces griseus.[4] The gross structure of A-Factor was proposed by Russian workers[5] but its absolute structure was established by its synthesis by K. Mori et al.[6]

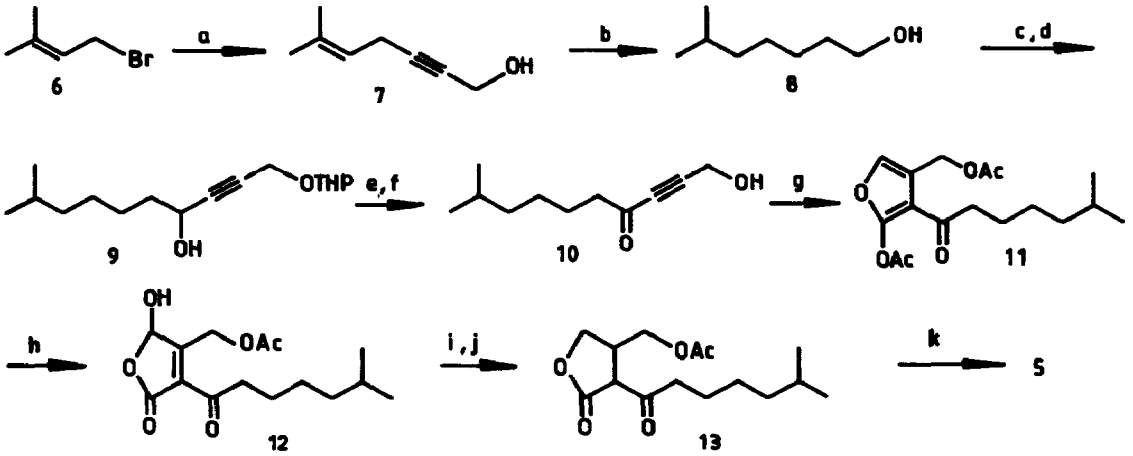


A . Factor
5

Scheme 2 depicts our approach towards the total synthesis of (±) A-Factor.

Alkylation of propargyl alcohol Grignard with prenyl bromide **6** gave **7** in 75% yield. The eneyne was converted to its saturated system **8** in quantitative yield by hydrogenation over Pd-C. Swern oxidation of **8** followed by treatment with th Grignard reagent of protected propargyl alcohol yielded the acetylenic alcohol **9** in overall 78% yield. Collins oxidation of **9** and deprotection of tetrahydropyranyl ether in presence of HCl/AcOH gave the keto alcohol **10** in overall 82% yield. Compound **10** was treated with Ac_2O/Py to give the corresponding acetate which on subsequent refluxing with 4-methyl-5-ethoxy oxazole in toluene resulted in **11** in overall 80% yield. Crucial oxidation of **11** under MnO_2-HCl conditions gave the hydroxy butenolide **12** in 80-85% yield. Chlorination and hydrogenation sequence led to compound **13** in 92% yield. Acetate derivative was treated with catalytic amounts of NaOMe to afford target molecule (±)**5**.

SCHEME-2



a) ≡-CH_2OH, EtMgBr, THF, 0°C; **b)** H_2/Pd-C, MeOH; **c)** $(COCl)_2$, DMSO, TEA, DCM, -78°C; **d)** Li ≡-CH_2-OTHP, -78°C; **e)** AcOH-HCl (4:1), r.t; **f)** PCC, DCM; **g)** (i) Ac_2O, TEA, DMAP, DCM; (ii) 4-Methyl-5-ethoxy oxazole, toluene, 110°C; **h)** MnO_2-HCl (4:10); **i)** $SOCl_2$, DMF(cat), $CHCl_3$; **j)** H_2/Pd-C-MeOH; **k)** NaOMe (cat), MeOH, r.t.

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+ All new compounds are characterised by spectral data and HRMS.

(*Received in UK* 20 *December* 1993; *revised* 7 *March* 1994; *accepted* 24 *March* 1994)