A Novel and Convenient Synthesis of 3-Methylfuran-2(5*H*)-one

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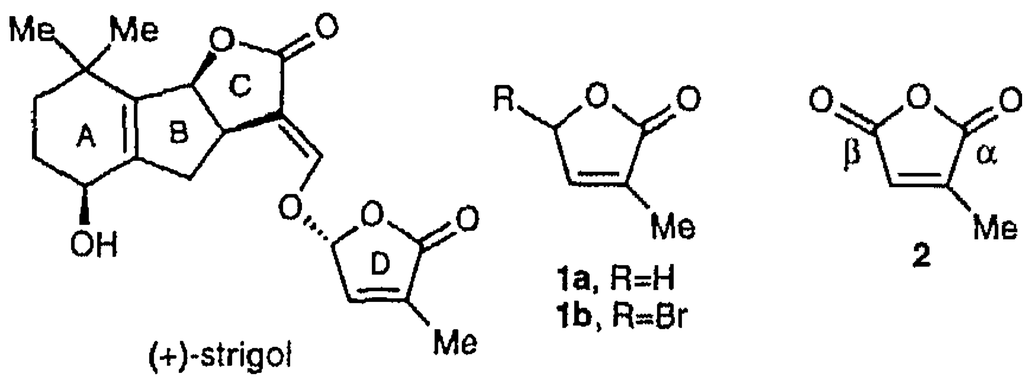
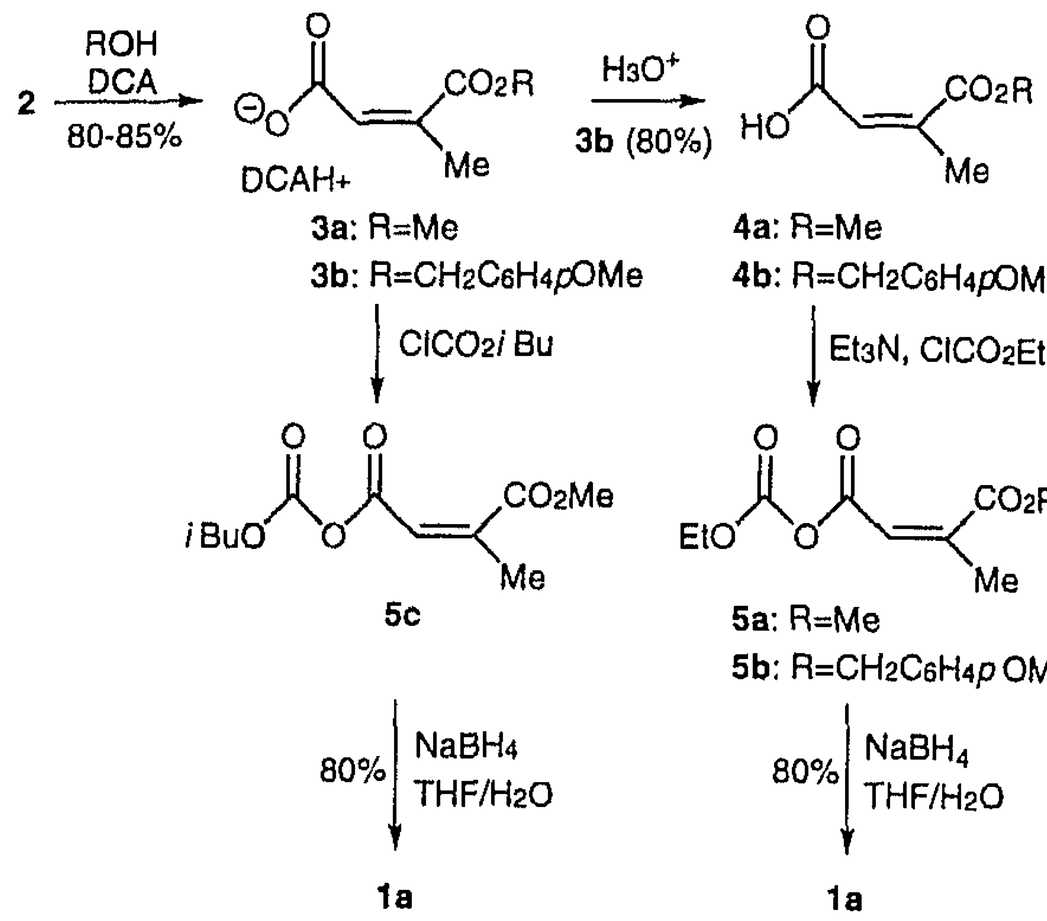
3-Methylfuran-2(5*H*)-one (**1a**), a precursor of strigol and its analogues, is prepared in a highly efficient manner by a regiocontrolled alcoholysis of citraconic anhydride and subsequent reduction via the mixed anhydride **5c**.

The 3-methylfuran-2(5*H*)-one moiety **1a** is a common structural feature of all known "strigolactones", such as (+)-strigol, which are naturally occurring germination stimulants of seeds of the parasitic weeds *Striga* and *Orobanche* sp.[1-4] Moreover, structure-activity relationship studies revealed that the presence of this structural unit is essential to retain full biological activity, results of which will be published separately.[5]



In view of our interest in the synthesis of simple, biologically active analogues of strigol, which are suitable for weed control purposes,[6,7] a convenient multigram preparation of **1a** is required, using cheap chemicals. This compound can readily be transformed into the corresponding 5-bromo derivative **1b**, which is the D-ring precursor in the synthesis of the strigolactones and their analogues.[8] Several procedures for the synthesis of **1a** have been reported, but none of them fulfils these criteria satisfactorily.[7,9-15] The present paper deals with an improved procedure for the preparation of 3-methylfuran-2(5*H*)-one (**1a**).

An attractive cheap, commercially available starting material is citraconic anhydride (**2**), as it only requires a formal reduction of the β-carbonyl function. However, this approach is not feasible as such, because reduction of the sterically more hindered α-carbonyl function strongly prevails. This observation was supported by ab initio calculations, showing a larger LUMO coefficient on the α-carbonyl.[16] This implies that nucleophilic attack takes place preferentially at the α-carbonyl, which is thus primarily determined by electronic factors. The intrinsic difference in reactivity of both carbonyl functions of **2** could advantageously be used to accomplish the reduction in the desired regiocontrolled fashion in an indirect manner, as is outlined in the Scheme.



Scheme

Alcoholysis of **2** in the presence of dicyclohexylamine (DCA) with either methanol or 4-methoxybenzyl alcohol gave the esters **3a** and **3b**, respectively, isolated as the DCA salts, in high yield (80%) and with high regioselectivity (>90%). In our first approach the DCA salts **3a,b** were converted into the corresponding carboxylic acids **4a,b** by acidification with citric acid or potassium hydrogen sulfate, followed by treatment with ethyl chloroformate in the presence of triethylamine to give the mixed anhydrides **5a,b**. Removal of the $Et_3N \cdot HCl$ precipitate by filtration, immediately followed by addition of the filtrate containing **5a,b** to a saturated aqueous solution of sodium borohydride, smoothly produced **1a**.[17] After conventional workup, butenolide **1a** was isolated in a high overall yield (~80% from crude **3a,b**) after purification by fractional distillation under reduced pressure. The choice of the 4-methoxybenzyl ester was advantageous because carboxylic acid **4b** is much more stable than **4a**. However, the formation of 4-methoxybenzyl alcohol during the reduction process severely complicated the purification of **1a** by distillation. A considerable improvement of the above procedure is the direct formation of mixed anhydride **5c** from **3a** (Scheme). This could be accomplished by treatment of **3a** with isobutyl chloroformate, which circumvented the need to isolate carboxylic acid **4a**. In this experimental setup ethyl chloroformate is not a suitable reagent, as a considerable amount of the corresponding ethyl ester of **4a** was formed under these conditions. The mixed anhydride **5c** was then immediately subjected to reduction with $NaBH_4$, using a reversed addition procedure, i.e. addition of a saturated aqueous solution of $NaBH_4$ to **5c**, which avoids a laborious extractive workup. Crude butenolide

1a contained a small amount (ca. 1%) of two byproducts, viz. 3-methylfuran-2(5*H*)-one and an as yet unidentified polar product. It is essential to remove this polar byproduct as it substantially suppressed the radical bromination reaction to give **1b** (*vide supra*). This can be achieved by a quick filtration over silica gel. Pure butenolide **1a** was thus obtained in a high overall yield (>80% from **3a**) after fractional distillation.

In conclusion, a convenient and simple preparation of 3-methylfuran-2(5*H*)-one (**1a**), starting from citraconic anhydride (**2**), has been accomplished by making use of the intrinsic difference in reactivity of both carbonyl groups in citraconic anhydride (**2**). The procedure has been performed on at least a 0.2 mole scale using inexpensive ingredients and standard laboratory equipment. This method is therefore superior to all previously reported syntheses.

IR spectra were measured on a Unical Mattson 5000 FT-IR spectrometer. 100 MHz, ^{1}H NMR spectra were recorded on a Bruker AC 100 spectrometer (TMS as internal standard). All coupling constants are given as ^3J in Hz, unless indicated otherwise. GC was conducted with a Hewlett-Packard HP 5890 gas chromatograph, using a capillary column (25 m) of HP-1, and N_2 (2 mL/min, 0.5 atm) as the carrier gas. Mps were measured with a Reichert Thermopan microscope and are uncorrected. Elemental analyses were performed at the Department of Microanalysis of this laboratory.

Solvents were dried using the following methods: CH_2Cl_2 was distilled from P_2O_5; EtOAc was distilled from K_2CO_3; THF was distilled from $LiAlH_4$ just before use. All other solvents were of analytical grade.

Dicyclohexylamine Salt of 2-Methylbut-2-enedioic Acid 1-Methyl Ester (3a):
To a cooled (−15°C) solution of citraconic anhydride (**2**, 56 g, 0.5 mol) in MeOH (400 mL) was added gradually DCA (1.1 equiv). The reaction mixture was stirred for 30 min at r.t. and then concentrated in vacuo, while keeping the temperature below 25°C. EtOAc was added to the residue and after 1 h the product was isolated by filtration and washed with EtOAc to give **3a** (138 g, 85%); mp 121–122°C (propan-2-ol) as colorless crystals.

IR (KBr): ν = 2500–3000 (broad, NH_2^+), 1733 (C=O, ester), 1653 (C=O, carboxylate) cm^{-1}.

^{1}H NMR ($CDCl_3$, 100 MHz): δ = 1.0–2.1 (m, 20 H, cyclohexyl), 1.93 (d, 3 H, ^4J = 1.5 Hz, =CCH_3), 2.8–3.2 (m, 2 H, C*H*N), 3.70 (s, 3 H, OCH_3), 6.05 (q, 1 H, ^4J = 1.5 Hz, =C*H*), 9.63 (br s, 2 H, NH_2).

Analysis ($C_{18}H_{31}NO_4$, 325.45): Calcd C, 66.43; H, 9.6; N, 4.3. Found C, 66.17; H, 9.56; N, 4.41.

Dicyclohexylamine Salt of 2-Methylbut-2-enedioic Acid 1-(4-Methoxybenzyl) Ester (3b):
To a stirred solution of **2** (5.6 g, 0.05 mol) in EtOAc (50 mL) 4-methoxybenzyl alcohol (8.3 g, 0.06 mol) was added. The solution was cooled (−20°C), followed by slow addition of DCA (10.0 g, 0.055 mol), which resulted in the formation of a white precipitate of **3b**. Stirring was continued for 1 h at r.t. The product was isolated by filtration, washed with EtOAc, to give **3b** (17.5 g, 80%); mp 114–115°C (propan-2-ol) as colorless crystals.

IR (KBr): ν = 2500–3000 (broad, NH_2^+), 1737 (C=O, ester), 1647 (C=O, carboxylate) cm^{-1}.

^{1}H NMR ($CDCl_3$, 100 MHz): δ = 1.0–2.1 (m, 20 H, cyclohexyl), 1.92 (d, 3 H, ^4J = 1.5 Hz, =CCH_3), 2.8–3.2 (m, 2 H, C*H*N), 3.79 (s, 3 H, OCH_3), 5.10 (s, 2 H, CH_2), 6.02 (q, 1 H, ^4J = 1.5 Hz, =C*H*), 6.85 (m, 2 H, arom. *H*), 7.30 (m, 2 H, arom. *H*), 9.63 (br s, 2 H, NH_2).

Analysis ($C_{25}H_{37}NO_5$, 431.57): Calcd C, 69.58; H, 8.64; N, 3.24. Found C, 69.11; H, 8.67; N, 3.36.

2-Methylbut-2-enedioic Acid 1-(4-Methoxybenzyl) Ester (4b):
A suspension of DCA salt **3b** (2.0 g, 4.6 mmol) in a mixture of water (10 mL) and EtOAc (25 mL) was acidified by adding $KHSO_4$ until pH < 3, which resulted in a clear two-phase system. The aqueous phase was separated and the organic layer was dried ($MgSO_4$), concentrated in vacuo and crystallized from propan-2-ol to give **4b** in 80% yield; mp 75–76°C (propan-2-ol) as colorless crystals.

IR (KBr): ν = 2900 (broad, OH), 1732 (C=O, ester), 1665 (C=O, carboxy) cm^{-1}.

^{1}H NMR ($CDCl_3$, 100 MHz): δ = 2.08 (d, 3 H, ^4J = 1.6 Hz, =CCH_3), 3.79 (s, 3 H, OCH_3), 5.17 (s, 2 H, CH_2), 5.86 (q, 1 H, ^4J = 1.6 Hz, =C*H*), 6.87 (m, 2 H, arom. *H*), 7.27 (m, 2 H, arom. *H*).

Analysis ($C_{13}H_{14}O_5$, 250.25): Calcd C, 62.39; H, 5.63. Found C, 62.14; H, 5.84.

3-Methylfuran-2(5*H*)-one (1a):
To a cooled (−10°C) solution of DCA salt **3a** (65 g, 0.20 mol) in CH_2Cl_2 (150 mL) isobutyl chloroformate (30 g, 0.22 mol) was gradually added with stirring. During the addition a precipitate of dicyclohexylamine chlorohydrate gradually settled. The mixture was stored overnight at ca. −10°C. Then THF (150 mL) was added and the mixture was allowed to stand for 1 h at the same temperature. The precipitate was removed by filtration, while cooling the filtrate (0°C), and washed with THF (150 mL). To the filtrate containing mixed anhydride **5c**, a cold solution of $NaBH_4$ (15 g, 0.4 mol) in water (30 mL) was added at 0°C, while stirring vigorously, over a 1 h period. Stirring was continued for 2 h at the same temperature and the precipitate was removed by filtration and washed with Et_2O. The filtrate was carefully concentrated in vacuo and the residue was dissolved in *i*-Pr_2O and dried ($MgSO_4$). The solvent was removed in vacuo to give **1a** as a colorless oil, which was purified by fractional distillation at low pressure and subsequently passed over a short column of silica gel, using CCl_4 as the eluent; yield: 17 g (80%) as a colorless oil; bp 80°C/15 Torr. The ^{1}H NMR data were in full agreement with those reported.[18]

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