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A facile access to natural and unnatural dialkylsubstituted maleic anhydrides†,‡

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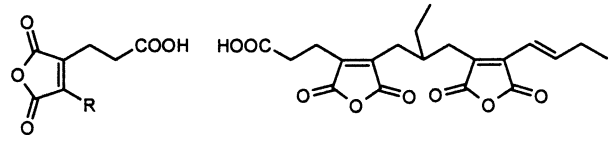
Abstract—A facile new route to naturally occurring 2-carboxyethyl-3-octylmaleic anhydride (**1a**) and unnatural dioctylmaleic anhydride (**11**) has been demonstrated via a chemoselective S_N2' Grignard coupling reaction with dimethyl bromomethylfumarate (**3**) followed by a chemoselective diethyl malonate/Grignard coupling reaction pathway.

During the past decade, several structurally interesting compounds with dialkylsubstituted maleic anhydride moieties have been isolated as bioactive natural products and synthesized in view of their promising bioactivities.[1–3] In 1994, Soda et al. reported[4] the biotransformation of stearic acid with a microbial strain isolated from soil, *Pseudomonas cepacia* A-1419, to produce two new maleic anhydride derivatives **1a** and **1b**, while **1c** was synthesized chemically by dehydration of natural spiculisporic acid.[5] The anhydride **1d** and cordyanhydride A (**2**) have recently been isolated as bioactive fungal natural products.[6,7] The anhydride **1e** has been synthesized as a model compound during the studies on synthesis of part structure of antibiotic tautomycins.[8] Very recently the first general synthetic route to these diverse dialkylsubstituted maleic anhydride analogs was demonstrated[1] by Baldwin et al. using a versatile copper-mediated tandem vicinal difunctionalization of dimethyl acetylenedicarboxylate. In our continuing interest[9] to provide facile synthetic routes to natural and unnatural alkylsubstituted maleic anhydrides, in this letter we report another general approach to this type of compound via the chemoselective S_N2' coupling of a Grignard reagent with dimethyl bromomethylfumarate (**3**) (Scheme 1).

We planned the preparation of (bromomethyl)-octylmaleic anhydride (**8**) as a suitable starting material



1a[4] R = $CH_2(CH_2)_6CH_3$
1b[4] R = $CH_2(CH_2)_4CH_3$
1c[5] R = $CH_2(CH_2)_8CH_3$
1d[6,7] R = $CH_2CH{=}CH{-}CH_3$
1e[8] R = CH_3 (synthetic)

2[6,7]

for the synthesis of the natural product 2-carboxyethyl-3-octylmaleic anhydride (**1a**). Several methods for the synthesis of alkylmethylmaleic anhydrides have been reported,[9a,b] but the NBS-bromination of these anhydrides is known to take place at the allylic methylene carbon[9f] and hence we thought of preparing **8** via a chemoselective S_N2' coupling reaction of a Grignard reagent with **3**.[10] The freshly prepared octylmagnesium bromide was chemoselectively coupled with **3** in an S_N2' fashion to yield the diester **4** in 65% yield. The LiOH induced hydrolysis of **4** followed by bromination of the diacid **5** with molecular bromine gave a mixture of all four possible stereoisomers of **6** in nearly equal proportions with ~100% yield. The diacid **6** in refluxing acetic anhydride yielded the desired (bromomethyl)octylmaleic anhydride (**8**) in quantitative yield and both the dehydrative ring closure of diacid **6** to anhydride **7** and the dehydrobromination took place in the one pot. The highly chemoselective diethyl malonate coupling with **8** in benzene using sodium hydride as base furnished the anhydride derivative **9** in 74% yield. Acid catalyzed hydrolysis of the diester and an in situ decar

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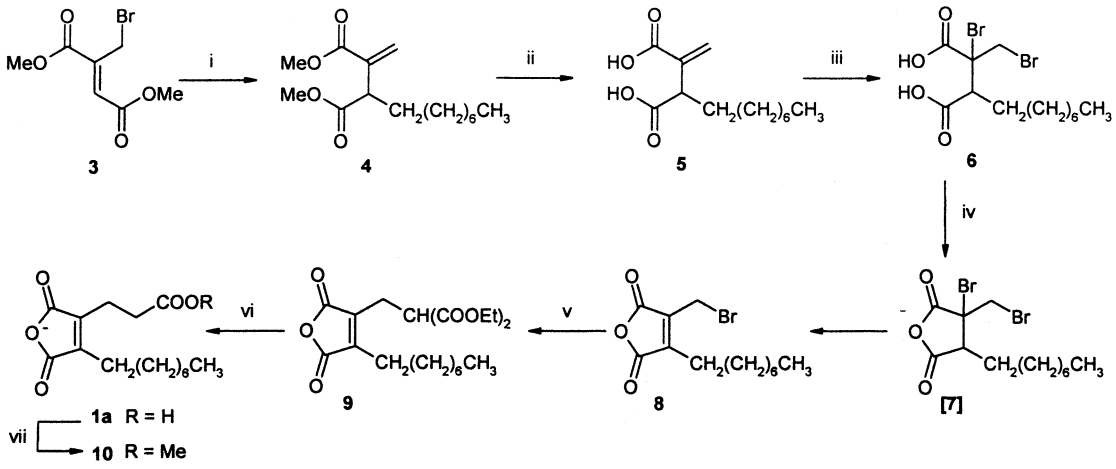
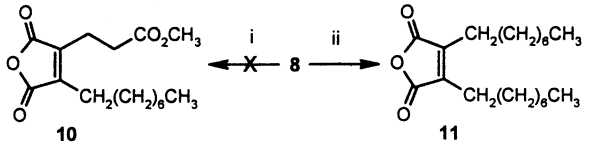


Scheme 1. *Reagents and conditions*: (i) $C_8H_{17}MgBr$ (1.5 equiv.), Et_2O, HMPA, −20°C, 0.5 h (65%); (ii) LiOH (10 equiv.), THF+H_2O (3:1), rt, 18 h (92%); (iii) Br_2 (1.5 equiv.), CCl_4, rt, 6 h (~100%); (iv) Ac_2O, reflux, 1.5 h (~100%); (v) (a) diethyl malonate (1.1 equiv.), NaH (1.1 equiv.), C_6H_6, rt, 8 h; (b) H^+/HCl (74%) (vi) AcOH+HCl (1:1), reflux, 12 h (95%); (vii) CH_2N_2, Et_2O, 0°C, 3 h (95%).



Scheme 2. *Reagents and conditions*: (i) $BrCH_2CO_2Me$ (1.5 equiv.), Zn (2 equiv.), THF, rt/reflux, 12 h (0%); (ii) $C_7H_{15}MgBr$ (5 equiv.), CuI (0.1 equiv.), Et_2O, HMPA, −5 to 0°C (55%).

boxylation of the intermediate *gem*-dicarboxylic acid gave the natural product **1a** in 95% yield. The overall yield of **1a** via the six steps was 42%. The analytical and spectroscopic data obtained for **1a** were in complete agreement with reported data.[4] The anhydride **1a** was also characterized further as the methyl ester **10**.

The chemoselective coupling of freshly prepared heptylmagnesium bromide with **8** in the presence of HMPA and a copper catalyst gave the desired dioctylmaleic anhydride (**11**) in 55% yield, thus providing a new simple route to symmetrical/unsymmetrical dialkylsubstituted maleic anhydrides[9b,e] (Scheme 2). In our hands, all attempts to obtain **10** via a chemoselective Reformatsky reaction with **8** in the presence/absence of HMPA met with failure.

In summary, we have demonstrated a facile general approach to natural and unnatural dialkylsubstituted maleic anhydrides using a new synthetic strategy.

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