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Synthesis of (+)-wikstromol by double alkylation of malic acid

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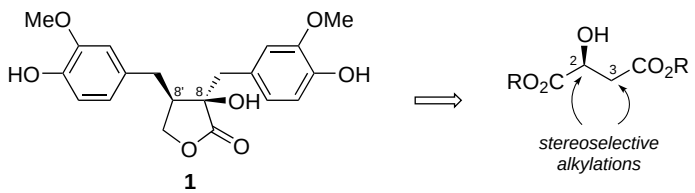
Abstract—The synthesis of (+)-wikstromol in six steps, based on two stereoselective benzylations of unnatural malic acid derivatives, is presented. The influence of the alkyl ester on yield and selectivity in the alkylation of malic acid esters is examined.

(+)-Wikstromol **1**[1] (Scheme 1) is an α hydroxylated lactone lignan possessing anti-leukemic activity in vivo.[2] Despite its attractive biological properties, only one enantioselective synthesis of (+)-wikstromol **1** has been published so far.[3] The overall yield from eight steps was only 5% due to the resolution of a racemic precursor and a non-selective oxygenation reaction α to the carbonyl group in the penultimate step.[3] (±)-Wikstromol was prepared more efficiently, although the hydroxy group was similarly introduced by oxygenation of the corresponding lactone enolate.[4]

Two alternative strategies for the synthesis of α-hydroxylated lactone lignans have been described. One is based on the conversion of arabinose[5] and the other on the alkylation of a protected α-hydroxy-β-benzyl-γ-butyrolactone.[6] The first strategy suffers from a lengthy synthesis (20 steps, 0.5% overall yield) whereas the non-selective alkylation of the γ-butyrolactone is the major drawback of the second route (eight steps, 3% overall yield). Herein, we report a short and efficient synthesis of (+)-wikstromol **1** involving two diastereoselective alkylations of (+)-malic acid (Scheme 1).

The first stereoselective alkylation was the benzylation at C(3) of malic acid ester. This reaction, first reported by Seebach and Wasmuth,[7] is frequently used to prepare enantiopure alkyl succinic acids,[8] although yields and selectivities were very dependent on the electrophile employed.[8] Some years ago Dugger et al. reported that the yield of benzylation of malates was dependent on the ester used.[9] The alkylations of Me and Et malates were less efficient than that of the *iso*-propyl analog, which was attributed to reduced self-condensation of *iso*-propyl malate due to the protection of the carboxyl moieties by sterically demanding *iso*-propyl groups. We reasoned that ester condensation might be efficiently suppressed when a solution of the base is added to a mixture of malate and electrophile at low temperature followed by gradually warming to rt. Additionally, LHMDS was used instead of LDA because Norman and Morris have reported that better yields and selectivities were obtained with this base.[10] Using these conditions we re-examined the steric effects of the ester on the yield and selectivity of the benzylation of malic acid. A series of malic ester analogs **2a**–**2d** (R = Me, Et, *iso*-Pr, *tert*-Bu[11]) were reacted with 4-benzyloxy-3-methoxy-benzyl bromide **3** after addition of two equiv. of LHMDS at −78°C. Subsequent warming to about 10°C afforded the alkylation products **4a**–**4d** and their *syn*-isomers (Scheme 2). The selectivities and yields



Scheme 1. (+)-Wikstromol and malic acid ester as suitable precursor.

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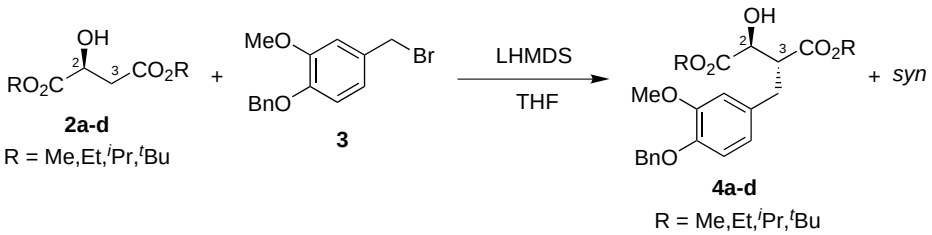


Scheme 2. *Conditions*: 1.4 equiv. **3**, 2.1 equiv. LHMDS, 13 h, −75 to 14°C (for **2a**, **2b**); −75 to 9°C (for **2c**, **2d**). Esters of (−)-malic acid were employed for these experiments.

obtained after chromatographic purification are summarized in Fig. 1. Interestingly, all esters gave reasonably high yields of alkylation product (75–90%). As expected, the lowest yield of 75% was achieved with Me malate **2a** good *anti*-selectivity of 89:11 was also observed. Reaction of Et malate **2b** gave a very good 91% yield of the alkylated product **4b** and a slightly better ratio than with the methyl analog (90:10) was achieved. As described, *iso*-Pr malate **2c** reacted more slowly than the Me and Et analogs and the reaction did not proceed to completion (80% yield + ~10% starting material) although the stereoselectivity of the reaction of **2c** was very good (95:5). Curiously, the more sterically encumbered *tert*-Bu malate reacted efficiently under identical conditions to afford **4d** in 94% yield, however the stereoselectivity was lower (86:14). Therefore, **2c** was chosen for the actual synthesis of (+)-**1** from (+)-malic acid. The low reactivity of **2c** was circumvented easily by increasing the reaction time and elevating the temperature of the reaction. Thus, compound **5** was obtained in 85% yield and 95:5 diastereoselectivity from (+)-*iso*-Pr malate (−75°C to +14°C, 16 h, Scheme 3).

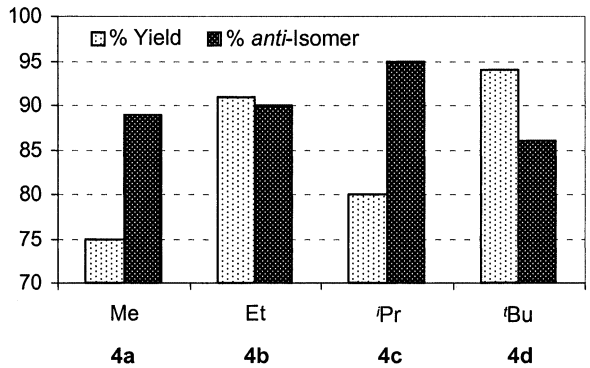
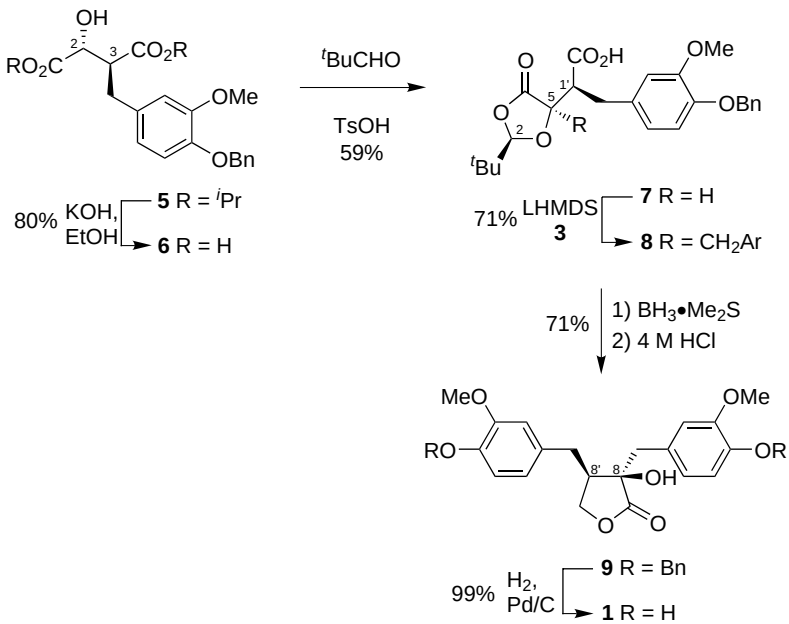


Figure 1. Yields and percent *anti*-isomers of alkylation products **4a**–**4d**.

Saponification of ester **5** using an excess of KOH in EtOH afforded the diacid **6** in 80% yield. Alkylation at C(2) was accomplished by analogy to the methodology developed by Seebach et al.[12] First, acetalization of diacid **6** to 1,3-dioxolan-4-one **7** was effected with pivaldehyde and catalytic amounts of recrystallized TsOH in benzene. Dioxolanone **7** was obtained in 59% yield and ca. 8:1 *cis*:*trans* ratio. Since it is known that acetalization under those conditions generally yielded mixtures of *cis*- and *trans*-dioxolanone an alternative procedure based on the kinetic acetalization of the corresponding tris-trimethylsilyl ether was examined.[13] Unfortunately, no reaction occurred under these condi-



Scheme 3. Synthesis of (+)-wikstromol from malic acid derivative **4c**.

tions. Stereoselective alkylation of an 8:1 mixture of *cis*- and *trans*-dioxolanone **7** was achieved when two equiv. of LHMDS were added to a solution of **7** and 1.3 equiv. of **3** in THF at −78°C. Only one stereoisomer, **8**, was obtained after purification. Apparently the additional stereocenter at C(1′) caused a matched/mismatched case in which the mismatched dioxolanone did not react with the electrophile (or reacted very slowly) (Scheme 3). Dioxolanone **8** was treated with $BH_3 \cdot Me_2S$ in refluxing ether to reduce selectively the carboxyl group and acidic hydrolysis afforded γ-lactone **9** directly in 71% yield. Hydrogenolysis of the two benzyl ethers of lactone **9** provided (+)-wikstromol **1** in quantitative yield.

In summary, (+)-wikstromol **1** was synthesized from *iso*-Pr malate **4d** in six steps and in 20% overall yield. Two stereoselective alkylations of (+)-malic acid derivatives were necessary. The dependence of yield and stereoselectivity on the alkyl ester employed in the alkylation of malic acid was examined. The synthesis of α-hydroxylated lignans and analogs as well as other classes of lignans is currently underway.

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