Pergamon

Tetrahedron Letters 42 (2001) 5101–5104

TETRAHEDRON LETTERS

Enantioselective synthesis of α-hydroxylated enterolactone and analogs

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Received 16 March 2001; revised 27 March 2001; accepted 28 May 2001

Abstract—A short and general synthesis of enantiomerically pure α-hydroxylated lactone lignans starting from commercially available *i*Pr malate is presented. Key reactions are two stereoselective alkylations of malic acid derivatives. Some enhancements of the alkylation of malic acid esters and a general extension of the alkylation of dioxolanones is reported. Proof of the stereochemical outcome of the alkylation reactions is provided by X-ray diffraction analysis of α-hydroxy-α,β-dibenzyl-γ-butyrolactone, the first crystal structure of an enantiomerically pure α-hydroxylated lactone lignan.

α-Hydroxylated lactone lignans[1] possess many biological activities.[2] Plants containing these lignans are constituents of many Asian traditional medicines. Enantioselective syntheses of α-hydroxylated lactone lignans have been reported in the past. They were based on three general strategies: (a) α-hydroxylation of α,β-dibenzyl-γ-butyrolactone (eight steps/3–6% overall yield);[3] (b) conversion of (+)-arabinose (20/0.5%)[4] or (c) α-alkylation of protected α-hydroxy-β-benzyl-γ-butyrolactones (8/3%).[5] Major drawbacks of these routes were a multistep sequence (b) or a non-selective introduction of either the hydroxy group (a) or the benzyl moiety (c) in α-position to the carbonyl group. Herein we report a short and general synthesis of optically active α-hydroxylated lactone lignans. Key reactions are two stereoselective alkylations of malic acid derivatives at C(2) and C(3) (Fig. 1).

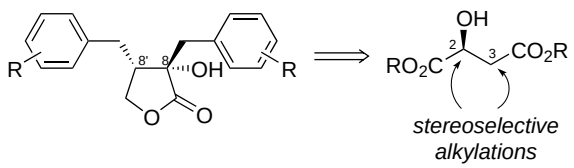

Figure 1.

First, commercially available malic acid esters were alkylated stereoselectively according to the procedure described by Seebach and Wasmuth.[6] Modifications of the reaction procedure involving the ester group of malic acid (*i*Pr malate was used instead of Et or Me malate)[7] and the base (LDA was substituted by LHMDS)[8] have been described. Better yields and/or higher *anti*-selectivity were achieved following these changes.

We have submitted both commercially available malic acid ester, Me and *i*Pr malate (**1** and **2**), in a series of parallel experiments to the standard alkylation conditions. Different bases were employed in order to examine their influence on yield and selectivity (Scheme 1 and Table 1).

We found that neither yield nor selectivity was improved using LHMDS instead of LDA although side reactions were more effectively suppressed with LHMDS as base (indicated by a better mass recovery). The base system *s*-BuLi/TMEDA caused almost complete decomposition of the starting material.

The influence of the alkyl ester was more important: *i*Pr malate (**2**) was alkylated faster and more selective than Me malate (**1**) providing benzylation products **5** and **6** in about 50% yield and 95:5 selectivity compared to ~20% yield and 90:10 selectivity for compounds **3** and **4**. Furthermore, the diastereoisomers of alkylated *i*Pr

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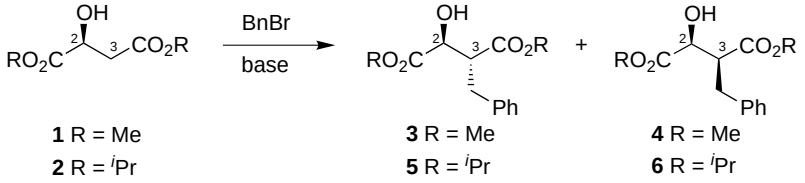
PII: S0040-4039(01)00907-8



1 R = Me
2 R = ^{i}Pr
3 R = Me
5 R = ^{i}Pr
4 R = Me
6 R = ^{i}Pr

Scheme 1.

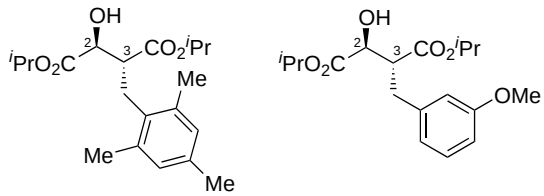
Table 1. Dependence of yield and selectivity on base and alkyl ester

Entry	Base	Yield (%)			
		1	**3**+**4** (d.r.)	**2**	**5**+**6** (d.r.)
1	LDA	30	18 (90:10)	9	45 (95:5)
2	LHMDS	41	17 (91:9)	16	48 (95:5)
3	*s*-BuLi/TMEDA	10	0	15	0

malate can be generally better seperated by column chromatography than those of the corresponding Me malate.[10]

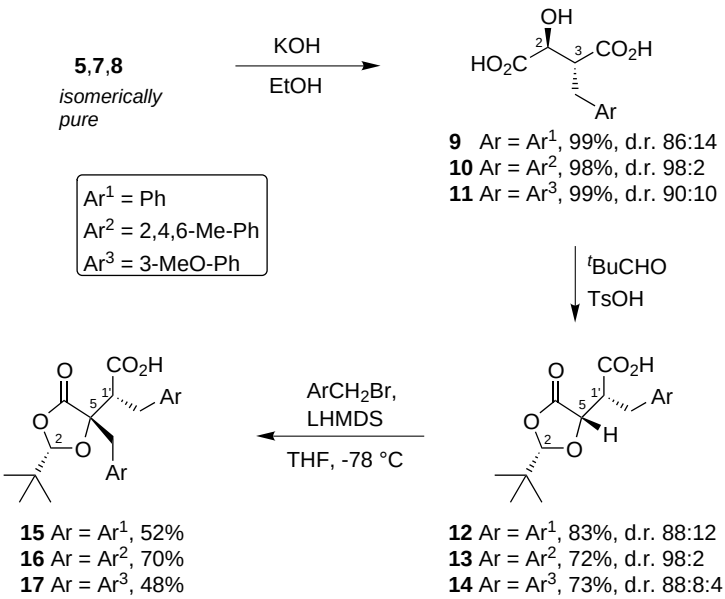
Substituted benzyl bromides were also suitable electrophiles for the alkylation of ^{i}Pr malates. The alkylation products **7** and **8**[9] were obtained in reasonable yields (56 and 65%) using 2,4,6-trimethylbenzyl bromide and 3-methoxybenzyl bromide, respectively (Fig. 2). The stereoselectivity, however, decreased with increased sterical hindrance of the electrophile (*anti*:*syn* 83:17 for **7** and 97:3 for **8**).

Isomerically pure *anti* products **5**, **7** and **8** were quantitatively saponified to the diacids **9**–**11** using KOH in EtOH (3 days, rt). Surprisingly, acids **9** and **11** were isolated as mixtures of diastereoisomers (**9** 86:14, **11** 90:10). The mixtures were used without separation for the subsequent steps (Scheme 2). Diastereoselective alkylation at C(2) was accomplished in analogy to the method described by Seebach et al.[11] Thus, diacids **9**–**11** were converted to the *cis*-1,3-dioxolan-4-ones **12**–**14** upon treatment with pivaldehyde and catalytic amounts of freshly recrystallized TsOH in benzene (72–83%). Since the solvent has a higher boiling point than the aldehyde, continuous addition of pivaldehyde was necessary for complete conversion of the diacids. Reaction in lower boiling solvents like pentane or light petroleum did not afford the dioxolanones. The diastereoisomeric



7 (56%, d.r. 83:17) **8** (65%, d.r. 97:3)

Figure 2.



9 Ar = Ar^{1}, 99%, d.r. 86:14
10 Ar = Ar^{2}, 98%, d.r. 98:2
11 Ar = Ar^{3}, 99%, d.r. 90:10

15 Ar = Ar^{1}, 52%
16 Ar = Ar^{2}, 70%
17 Ar = Ar^{3}, 48%

12 Ar = Ar^{1}, 83%, d.r. 88:12
13 Ar = Ar^{2}, 72%, d.r. 98:2
14 Ar = Ar^{3}, 73%, d.r. 88:8:4

Scheme 2.

purity of dioxolanones **12** and **14** was similar to that of the diacids **9** and **11**. Compound **14** was accompanied by an additional stereoisomer, most likely by the corresponding *trans*-dioxolanone. Dioxolanones **12**–**14** were submitted to the second alkylation without further purification. Addition of 2 equiv. LHMDS to a mixture of the dioxolanone and a small excess of the corresponding benzyl bromide at −78°C afforded the alkylation products **15**–**17** in 48–70% yield. Compounds **15**–**17** were obtained diastereoisomerically pure according to the NMR spectra even when impure starting materials **12** or **14** were employed. Apparently the additional stereocenter in the side-chain caused matched/ mismatched case in which the mismatched dioxolanone did not (or did very slowly) react with the electrophile (Scheme 2).

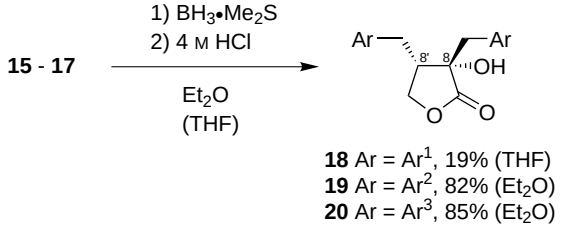
Reduction of the carboxyl group of compounds **15**–**17** using $BH_3{\cdot}Me_2S$ in refluxing diethyl ether followed by acid catalyzed lactonization afforded the enantiomerically pure lignans in over 80% yield (**19**, **20**), except when THF was employed as solvent (**18**, 19% yield) (Scheme 3).

Lignan **18** was crystalline and the *trans* relationship of both benzyl groups of this compound was established by X-ray diffraction, the first crystal structure of an enantiomerically pure α-hydroxylated lactone lignan (Fig. 3). The crystal structure also provides evidence for the stereochemical course of the alkylation of dioxolanones having an additional stereocenter in the side-chain.

Reduction of acid **15** with $BH_3{\cdot}Me_2S$ in refluxing THF provided lactone **18** and several byproducts derived from over-reduction or non-selective reduction probably due to a higher reaction temperature as compared to diethyl ether. Some byproducts, compounds **21**–**23** (Scheme 4), have been characterized. Oxidation of lactol **23** using PDC in CH_2Cl_2 gave formate **24** in 70% yield and not, as expected, lactone lignan **18**.[13]

BBr_3-mediated cleavage of the methylethers of lactone **20** gave the optically pure α-hydroxy analog of enterolactone (**25**) although the conditions were not optimized and the yield was low (Scheme 5).

We have presented a short (five to six steps), efficient (~20% overall yield) and general synthesis of optically active α-hydroxylated lactone lignans. Key reactions were two stereoselective alkylations of malic acid derivatives. Some enhencements of the alkylation of



Scheme 3.

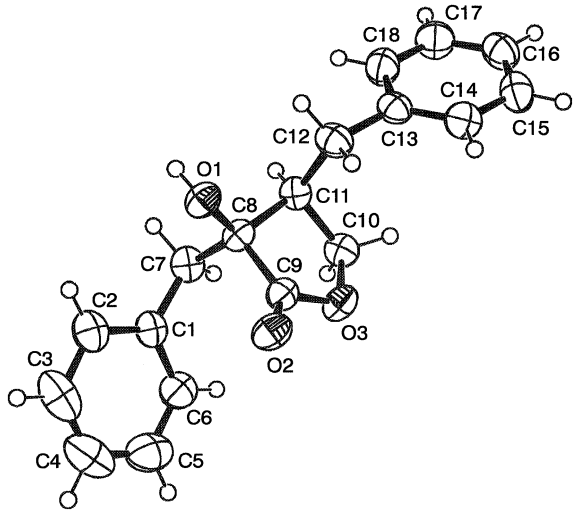
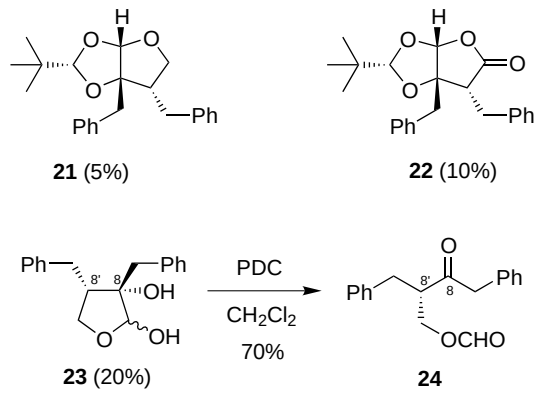
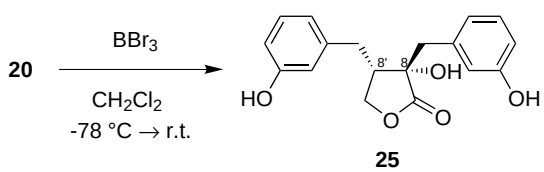


Figure 3. ORTEP plot of compound **18**.[12] Selected distances (Å) and angles (°): C1–C7 1.504(5), C7–C8 1.544(5), C8–C11 1.547(5), C11–C10 1.512(5), C10–O3 1.465(5), O3–C9 1.347(4), C9–C8 1.515(6), C8–O1 1.417(4), C9–O2 1.215(4), C11–C12 1.540(5), C12–C13 1.509(5); C1–C7–C8 115.2(3), C11–C12–C13 112.9(3), C8–C11–C10 100.8(3), C11–C10–O3 104.9(3), C9–O3–C10 109.4(3), O3–C9–C8 110.1(3), C9–C8–C11 100.5(3), O1–C8–C7 112.0(3), O2–C9–C8 129.5(3); C2–C1–C7–C8 81.9(5), C14–C13–C12–C11–111.5-(4), C1–C7–C8–O1 −76.7(4), O2–C9–C8–O1 31.7(5); angle between best planes C_p (C1···C8)–C_p (C14···C18) 61.5(2). Intermolecular hydrogen bonds were found between O1 and O2 to form infinite chains in the *a*-direction (O1–H2 0.86(4), O1···O2 2.887(6), O1–H1···O2 173(3), symmetry operator of O2 is $x-1, y, z$).

malic acid esters and a general extension of the alkylation of dioxolanones is reported. Evaluation of the biological properties of lignans presented herein and the synthesis of unsymmetrically substituted lactone lignans is in progress and will be reported in due course.



Scheme 4.



Scheme 5.

Acknowledgements

M.S. acknowledges the DFG for a habilitation fellowship (Se 875/1-1). Financial support of this work by the Fonds der Chemischen Industrie is gratefully acknowledged.

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