Stereoselective alkylation of tartrate derivatives. A concise route to (+)-*O*-methylpiscidic acid and natural analogues†

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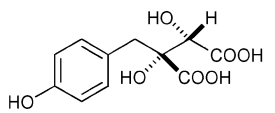
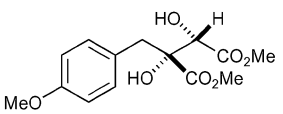
The lithium enolate of (2*S*,3*S*,5*S*,6*S*)-dimethoxy-2,3-dimethyl-1,4-dioxane-5,6-dithiocarboxylate 8 undergoes stereoselective mono- and/or dialkylations to afford two new stereogenic centers. The alkylation products obtained possessed a *cis* stereochemistry, which was confirmed by the synthesis of natural 4′-*O*-methylpiscidic acid dimethyl ester 2.

(+)-Piscidic acid **1** is one of the constituents of the hypnotic and narcotic extracts of *Piscidia erythrina* L. (Jamaica dogwood) and is equally a component of the antitussic extracts isolated from *Dioscorea nipponica*, a medicinal plant used for treating chronic bronchitis.[1,2] Piscidic acid **1** and *O*-methylpiscidic acid have been shown to be linked to phosphorous uptake in pigeon peas, *Cajanus cajan* (L.) Millsp., an important crop in India.[1,2] Furthermore, a commercial remedy for the reduction of menopausal symptoms is based upon an extract of dried *Cimicifuga racemosa* rhizome, which, among other compounds, contains the closely related piscidic and fukiic acid **3** esters.[3] 4′-*O*-Methylpiscidic acid dimethyl ester **2** has been isolated from *Narcissus poeticus* L.[1,2] and the glucoside loroglossin **4** is a characteristic constituent of orchids.[4] Structurally related eucomic acid **5** has been isolated from the bulbs of *Eucomis punctata L'Hérit.*[2]



(+)-Piscidic acid
1



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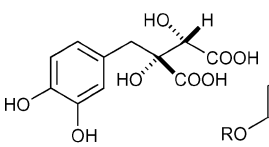
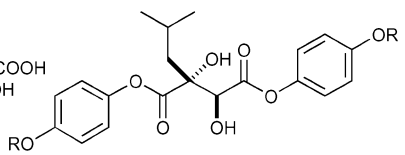
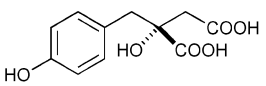


Fukiic acid
3

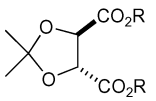


Loroglossin: R= β-D-glucopyranosyl
4

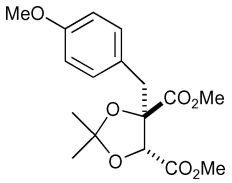


(-)-Eucomic acid
5

Most of these structures can be seen basically as alkylated tartaric acid derivatives and although several syntheses of these compounds have been reported,[1,2,4] the work of Seebach[5] is notable for its concise approach. They reported the alkylation of isopropylidene protected tartaric acid esters **6** and isolated a mixture of the monoalkylated products. The major diastereoisomer, **7**, obtained by this approach, did not have the stereochemistry of natural piscidic acid and was therefore not a precursor for its synthesis or that of stereochemically related natural analogues.



6a: R = CH_3
6b: R = $CH(CH_3)_2$



7

Tartaric acid is an abundant versatile chiral small building block for the asymmetric synthesis of natural products.[6] The dioxane **8**, readily available from tartaric acid,[7] has a rigid structure and undergoes stereoselective aldol reactions possibly *via* a dienolate.[8]

We predicted that the lithium enolate of (2*R*,3*R*,5*R*,6*R*)-dimethoxy-2,3-dimethyl-1,4-dioxane-5,6-dithiocarboxylate **8** would undergo stereoselective mono- or dialkylations to afford new stereogenic centers. If the dienolate was involved then this acetal would provide a chiral memory. It was also expected that this would provide us with the correct stereochemistry for the synthesis of the natural product 4′-*O*-methylpiscidic acid dimethyl ester **2**,[1,2] intermediate for the synthesis of (+)-piscidic acid **1**.[1,2] Other natural products of the same family, such as fukiic acid **3** and its esters,[1–3] loroglossin **4**[4] and eucomic acid **5**[2] could also be available using the same methodology. The synthesis of the well characterised ester **2** would provide a way of confirming the stereochemical outcome of the alkylation reactions.

Alkylation of the lithium dienolate of **8** afforded mono and dialkylated products (Table 1). The degree of alkylation was dependent upon the nature and reactivity of the halide used and thus the proportion of monoalkylated and/or dialkylated compounds obtained. The effect of the size of the halide, the amount of reagent, the presence of HMPA, and the reaction temperature and time were also studied and Table 1 represents a selection of alkylation reactions which gave significant results. HMPA was essential for the successful outcome of the reaction and although DMPU could also be used, the yield of alkylated product was lower and the product was more difficult to purify.

Alkylation with MeI afforded the dialkylated product **9** exclusively (Table 1). Our assignment of the *cis* stereochemistry

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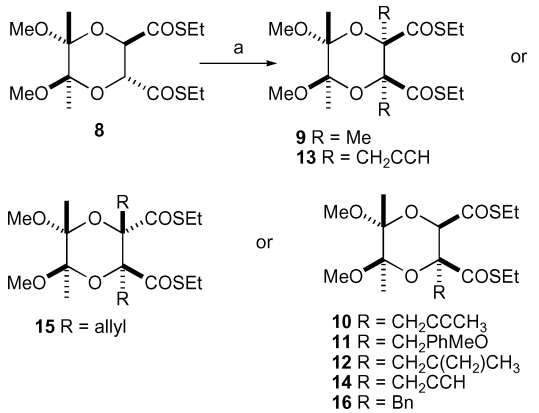
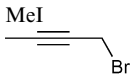
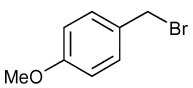
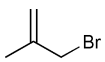
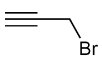
Table 1



Eq. LDA	Halide	Eq. halide	Product/yield (%)
2.2	MeI	5	**9** (99)
2.2		5	**10** (62)
1.5		1.5	**11** (82)
2.2		1.5	**12** (65)
2.2		5	**13** (7), **14** (50)
2.2		3	**15** (62)
2.2	BnBr	3	**16** (60)

a) HMPA, THF, −78 °C to 0 °C, 2 h.

was based upon the non-equivalence of the methyl groups in the NMR spectrum, indicating that the molecule no longer had C_2-symmetry. To further prove that we had the *cis* dimethylated product, cleavage of the acetal afforded a *meso* diol with a rotation of zero. This dialkylation is further proof of the formation of a dienolate and of its higher reactivity since Seebach could only alkylate with more reactive alkyl halides.[5]

Interestingly, no traces of monomethylated products were found, even when the reaction was not complete. The same reaction conditions were reproducible on a larger scale.

Alkylation using 1-bromo-2-butyne afforded a 62% yield of the monoalkylated compound **10** (Table 1). No dialkylated product was detected even when 5 eq. of the halide were used. With the more bulky halides, such as benzyl bromide and 4-methoxybenzyl bromide, no dialkylated products were ever formed. With propargyl bromide 7% of the *cis* dialkylated product was obtained, however when trying this reaction with a small excess of the halide (1.5 eq.), a considerable amount of starting material was recovered. Interestingly, alkylation with allyl iodide afforded the C_2 symmetric *trans* diallylated product **15** as seen by the equivalence of protons in the NMR spectrum.

The obtention of the *cis* product with methyl iodide and the *trans* product with allyl iodide, could be explained by the bulkyness of the alkyl iodide (Fig. 1). The steric hindrance exerted by an alkyl group in the second alkylation of the monoenolate is much larger for the allyl group than the methyl group, as seen in the structures depicted in Fig. 1. The first allyl group can block the attack from the same side and thus the second allyl group enters *trans* to the first. When the installed group is a methyl, the steric hindrance of the thioester group prevails, the second methyl group entering *cis* to the first one.

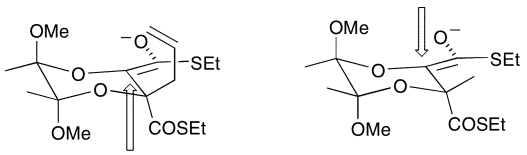
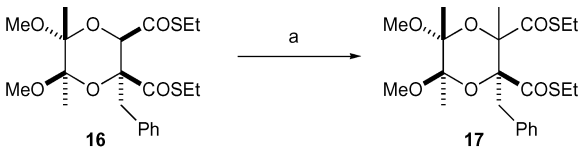


Fig. 1

Steric hindrance also played an important role in the second alkylation of monobenzylated derivative **16** (Scheme 1). It was possible to introduce a methyl group in good yield (82%) to furnish a non-symmetrically dialkylated product **17**. We only can assume that it is the *trans* product since the installed benzyl group is bulky. However, it was not possible to introduce a second benzyl group to the monobenzylated compound indicating that the size of the electrophilic species is also a limiting factor.

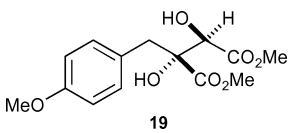


Scheme 1 a) LDA, HMPA, MeI, THF, −78 °C/0 °C, 82%.

The absolute stereochemistry of the monoalkylated products needed confirmation and to resolve this problem we attempted a synthesis of the natural compound **2**.

Monoalkylated product **11**, $[\alpha]_D^{20}$ −14.3 (0.44, $CHCl_3$), (Table 1) was further transformed, to the enantiomer of natural product *ent*-**2**, $[\alpha]_D^{20}$ −43.9 (0.86, $CHCl_3$) (isolated natural product, $[\alpha]_D^{24}$ +44 ± 2, $c = 0.60$, $CHCl_3$;[2] synthesised product, $[\alpha]_D^{25}$ +46 ± 2, $c = 1.01$, $EtOH^2$), as indicated by the opposite optical rotation for the natural compound. Using *ent*-**8** from D-tartaric acid, natural **1** and **2** were obtained (Scheme 2).

Thus, alkylation of dithioester *ent*-**8** afforded *ent*-**11**, $[\alpha]_D^{20}$ +15.0 (1.2, $CHCl_3$), as expected. Hydrolysis of the bis-acetal with TFA and water afforded diol **18** in excellent yield (98%). Transesterification with MeONa in MeOH was also accomplished in high yield (95%) and the compound obtained was indeed the natural product **2**, $[\alpha]_D^{20}$ +42.8 (1.02, $CHCl_3$) (isolated natural product,[2] $[\alpha]_D^{24}$ +44 ± 2, ($c = 0.60$, $CHCl_3$); synthesised product, $[\alpha]_D^{25}$ +46 ± 2, ($c = 1.01$, EtOH). Transesterification of the bis-acetal *ent*-**11** was very slow (>24 h), but the transesterification of hydroxyester **18** was much faster (15 min). In this way, we concluded that the stereochemistry of the monoalkylated products was *syn*, whereas Seebach[5] obtained the *anti*-product **19**.



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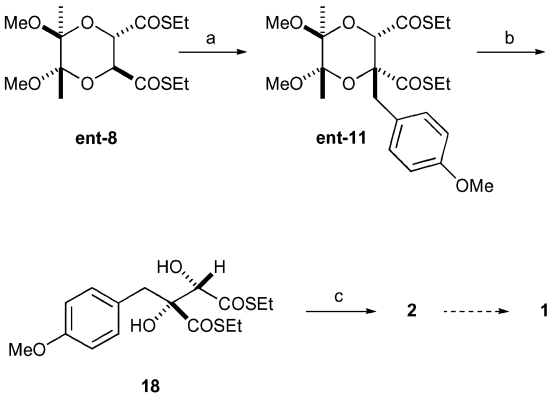
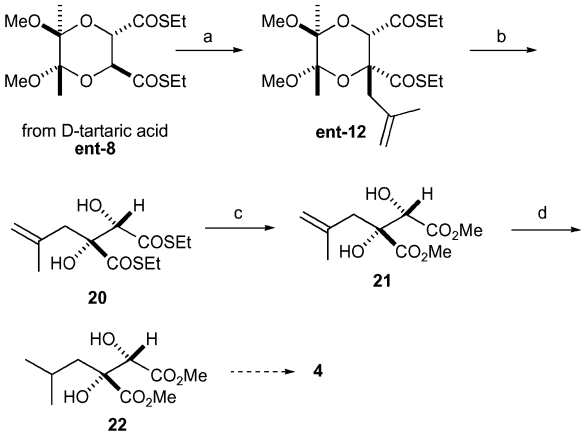


Scheme 2 a) LDA, 4-methoxybenzyl bromide, HMPA, THF, −78 °C/0 °C, 82%. b) TFA, CH_2Cl_2, H_2O, Δ, 98%. c) MeONa, MeOH, rt, 95%.



Scheme 3 a) LDA, 3-bromo-2-methylpropene, HMPA, THF, −78 °C/0 °C, 65%. b) TFA, CH_2Cl_2, H_2O, Δ, 99%. c) MeONa, MeOH, rt, 90%. d) Pd/C 10%, AcOEt, 50 atm, 88%.

In order to introduce the isobutyl group present in loroglossin **4**, alkylation of the dioxane *ent*-**8** was carried out using 3-bromo-2-methylpropene (Scheme 3) to afford *ent*-**12**, $[\alpha]_D^{20}$ +41.2 (2.37, $CHCl_3$), in good yield (65%).

Hydrolysis of the acetal gave diol **20** quantitatively, and transesterification afforded the dimethyl ester **21**. The double bond was saturated using H_2/Pd/C 10%, under 50 atm, and the nucleus of loroglossin **22** ($[\alpha]_D^{20}$ +41.8 (0.29, $CHCl_3$), lit. $[\alpha]_D$ +43 ($CHCl_3$)[4]) was thus obtained in 88% yield (Scheme 3). Further transformation to the *p*-(β-D-glucopyranosyloxy)phenyl esters would afford loroglossin **4**.

All attempts to introduce a protected 3,4-dihydroxybenzyl group, in order to prepare fukiic acid **3** by a simple alkylation were surprisingly unsuccessful, due to the instability of 3,4-dibenzyloxybenzyl bromide and 3,4-dimethoxybenzyl bromide, under the reaction conditions. The synthesis of eucomic acid **5** from **2** has already been described.[2]

In summary, we report the stereoselective mono- and dialkylation of the tartrate derivative **8**, the efficiency of which was shown to be principally dependent upon the nature of the halide employed. This reaction was used as the key step for a short synthesis of 4′-*O*-methylpiscidic acid dimethyl ester **2**, and in the formal syntheses of piscidic acid **1**, loroglossin **4** and eucomic acid **5**.

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