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A Short Synthesis of Naturally Occurring and Other Analogues of Plakinic Acids that Contain the 1,2-Dioxolane Group

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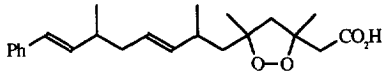
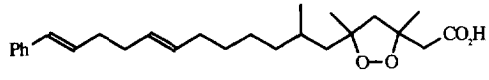
Abstract: Natural and unnatural analogues **4** of plakinic acids A, C and D have been prepared in three steps from alkan-2-ones by (i) LDA-induced condensation with ethyl 3-methylbut-2-enoate to give (2*Z*)-3,5-dimethylalka-2,4-dienoic acids **10**, then (ii) isomerisation to the 2*E*-isomers **5** and finally (iii) peroxymercuriation with 30% hydrogen peroxide and reduction *in situ* with sodium borohydride.

Marine sponges are a rich source of cyclic peroxides many of which exhibit biocidal and cytotoxic properties[1]. Most of these natural products contain 6-membered peroxide rings, but plakinic acid A (**1**)[2], plakinic (and diastereoisomeric epiplakinic) acids C (**2**)[3] and D (**3**)[3] and saturated analogues **4a-e**[4] are exceptional in that they are 1,2-dioxolanes. Other common features of these naturally occurring 1,2-dioxolanes are methyl substituents at the 3- and 5-positions and a CH_2CO_2H group at the 3-position of the five-membered ring. The compounds are claimed to have antitumour, antibacterial and antifungal activity[2-4].



(1)



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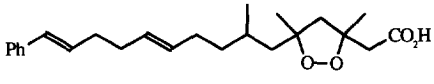

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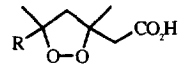


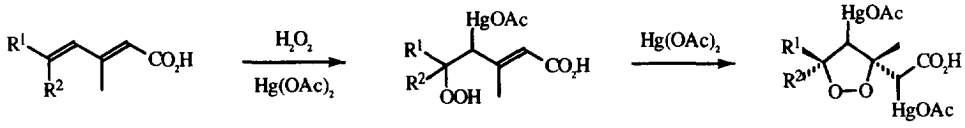
(4)

R	
a	$C_{13}H_{27}$
b	$C_{14}H_{29}$
c	$C_{15}H_{31}$
d	$C_{16}H_{33}$
e	$C_{17}H_{35}$

We set out to develop a general synthesis of compounds of structure **4** that would support a variety of R-groups, including the C_{13}-C_{17} saturated alkyls of the natural products, and would provide a basis for approaching the total synthesis of the plakinic acids. We now report such a method which in its most refined form comprises just three steps.

Our synthetic strategy was based on the belief that the required 1,2-dioxolanes could be created by peroxymercuriation of suitable dienes with hydrogen peroxide[5]. Retrosynthetic analysis on this basis suggested

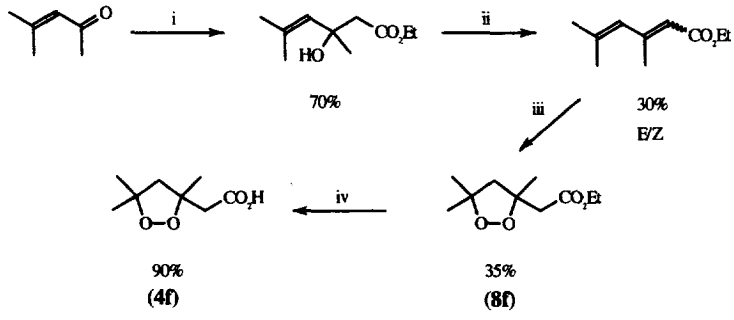
four candidate dienes (ignoring *E/Z* isomerism), of which the αβγδ-unsaturated acid **5** was thought likely to be the most amenable to a general synthesis. With mercury(II) acetate as the electrophile, diene **5** was expected to show 1,2-addition only[6], with the more electron-rich γδ-double bond being the site of initial attack. Thus, hydroperoxymercuriation[7] was expected to give intermediate hydroperoxide **6** which would then undergo intramolecular peroxymercuriation at the αβ-double bond, more easily than the corresponding intermolecular process[8] but with the same orientation, to give the required product in the bis-mercuriated form **7**. Demercuriation of **7** with sodium borohydride[5] would then afford the target 1,2-dioxolane **4**.



(5) **(6)** **(7)**

R^1 = Me, R^2 = R or R^1 = R, R^2 = Me

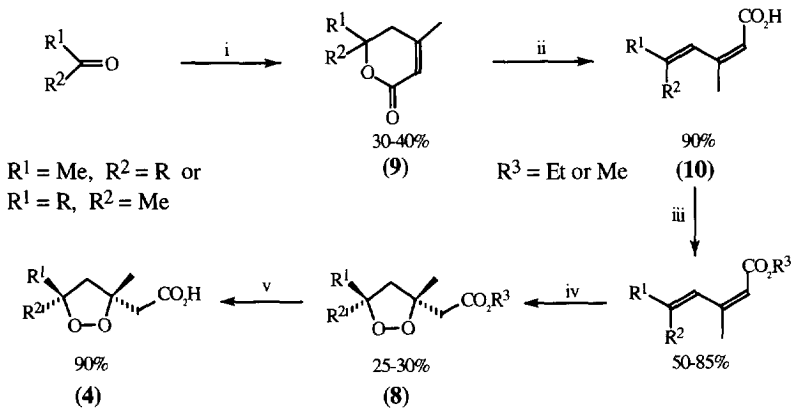
Initial studies centred on 3,5-dimethylhexa-2,4-dienoic acid (**5**, R = Me). An *E/Z* mixture of the ethyl ester of this acid was prepared from 4-methylpent-3-en-2-one (mesityl oxide) by the Reformatsky route[9]. Peroxymercuriation-demercuriation[11] afforded the ethyl ester **8f**[12] of the desired 1,2-dioxolane in 13-35% yield, the *E* ester giving a better yield than the *Z* isomer. Saponification then gave the target acid **4f**[12], the first unnatural analogue of the plakinic acids.



Reagents: i) $BrCH_2CO_2Et$, Zn ii) $POCl_3$ iii) 30% H_2O_2, $Hg(OAc)_2$ then $NaBH_4$, NaOH iv) LiOH then HCl

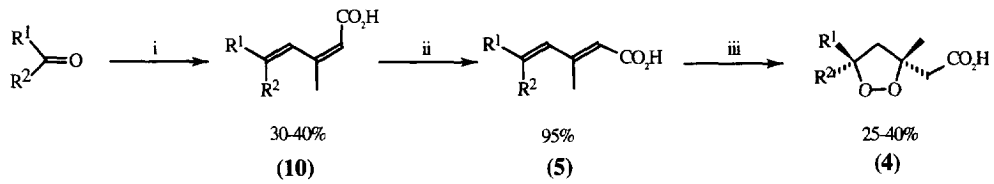
This work established the viability of the peroxymercuriation-based route to plakinic acid analogues, but a different route to the precursor diene was required if the method was to be generally applicable. The route chosen was the condensation of alkan-2-ones with ethyl 3-methylbut-2-enoate to give lactones **9**[13], followed by base-induced ring-opening[14] to provide the 2*Z* diene acids **10** as a 1:2 mixture of the 4*Z* and 4*E* isomers. The diene acids **10** could not be used directly in the peroxymercuriation step because intramolecular acyloxymercuriation, to re-form lactone, was preferred under these conditions. However, by first esterifying the

acids, lactone formation was sufficiently suppressed to allow 1,2-dioxolanes **8** and thence **4** to be prepared in 25-30% yields.



Reagents: i) $Me_2C{:}CHCO_2Et$, LDA, THF (-78°→10°) then aq NH_4Cl ii) NaOEt, EtOH then aq HCl iii) DCC, DMAP, EtOH or $Me_3O^+ BF_4^-$, $^iPr_2NEt$ iv) 30% H_2O_2, $Hg(OAc)_2$ then $NaBH_4$, NaOH v) LiOH then aq HCl

We reasoned that if we could isomerise the 2*Z* diene acids **10** to the 2*E* isomers **5**, which cannot ring-close to the lactone, the esterification and saponification steps of the above synthesis could be eliminated. Several methods of isomerisation were tried, but treatment of **10** with a catalytic amount of thiophenol in carbon tetrachloride at reflux[15] was found to be best, giving a *ca* 4:1 mixture of **5** and **10** which was used in the final step. The synthetic route was further simplified by omitting the isolation of lactone **9** by modifying the work up of the condensation mixture. Accordingly, the current method of choice is shown below.



R^1 = Me, R^2 = R or R^1 = R, R^2 = Me

Reagents: i) $Me_2C{:}CHCO_2Et$, LDA, THF (-78°→20°) then aq HCl ii) cat PhSH, CCl_4, reflux iii) 30% H_2O_2, $Hg(OAc)_2$ then $NaBH_4$, NaOH then aq HCl

Using the three methods described, we have prepared four unnatural plakinic acid analogues, where R = Me (**4f**), Me_2CHCH_2 (**4g**), Ph (**4h**) and C_7H_{15} (**4i**), as well as the naturally occurring analogue **4c**. Each product (apart from **4f**) was obtained as a mixture of *cis* and *trans* isomers, the ratio of which closely matched the ratio of geometric isomers about the γδ double bond of the precursor diene acid or ester. Since the PhSH-

catalysed isomerisation enriched not only the amount of 2*E* isomers but also of 4*E* isomers, the acid route provided 1,2-dioxolanes with greater stereoselectivity.

Work is in progress to try to extend the method to the preparation of the plakinic acids.

ACKNOWLEDGEMENT

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9. Dehydration of the Reformatsky alcohol with anhydrous copper(II) sulfate[10] additionally gave $Me_2C{:}CHC(:CH_2)CH_2CO_2Et$ and (*E/Z*) $CH_2{:}C(Me)CH{:}C(Me)CH_2CO_2Et$, which as expected from the retrosynthetic analysis also afforded **8f** upon peroxymercuriation-demercuriation.
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11. It is noteworthy that all preparations of 1,2-dioxolanes here were effected with 30% H_2O_2 which is safer and more convenient to use than the 80-85% H_2O_2 previously employed[5].
12. All new 1,2-dioxolanes gave consistent ^1H and ^{13}C NMR spectra and correct C/H combustion analyses and/or elemental composition by high resolution mass spectrometry.
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