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STRATEGIES OF SYNTHESIS OF AROMATIC POLYKETIDES USING CYCLOHEXA-1, 4- AND -1, 3-DIENES IN ALDER-RICKERT REACTIONS

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ABSTRACT

Cyclohexa-1, 4-dienes with appropriate substituents, obtained by Birch reduction of the substituted benzene, react directly with derivatives of propiolic ester or aldehyde to yield aromatic polyketides. The following compounds have been synthesised: mycophenolic acid, nidulol methyl ether, the root growth hormone 3, 5-dihydroxy-2-formyl-4-methyl-benzoic acid, antibiotic DB 2073, the macrocyclic lactones lasiodiplodin and dihydrozearalenone and the biphenyl derivatives alternariol and altenusin. Polyketide anthraquinones can be made from naphthoquinone precursors.

DIFFICULTIES in the syntheses of polyketides are due to the relative positions of the variety of OR, alkyl, CO₂H, CHO, COR substituents resulting from the mode of biosynthesis¹. In particular the relative orientations of substituents to each other and to positions of ring-closure often make classical aromatic substitution procedures awkward to apply²⁻⁴.

An alternative is to build up an appropriately substituted aromatic system *de novo* using the Alder-Rickert reaction⁵. This employs a Diels-Alder addition to cyclohexa-1, 3-dienes with a dienophile of such a nature that there can be obtained, directly or

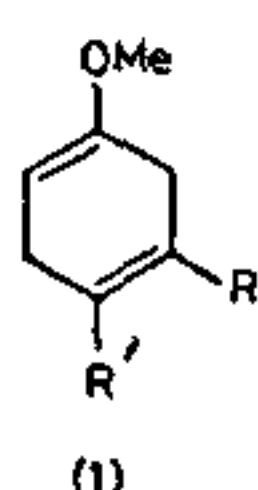
indirectly, a cyclohexa-1, 4-diene with a 2, 5-bridge. Appropriate dienophiles for the direct process are acetylenes activated by an electron-sink such as CO₂Me or CHO, most reactions having previously been carried out with dimethyl acetylenedicarboxylate⁶⁻⁸. Indirect precursors are quinones followed by oxidation of the adduct to regenerate the necessary unsaturation. Thermal removal of the bridge as an olefin occurs readily to form the substituted benzene.

The advantages for polyketide synthesis are: (1) The 1-OMe; 1, 3-diOMe, 3-Me etc. cyclohexa-1,4-dienes needed as precursors are readily available by Birch

reduction of the corresponding aromatic compounds⁹. This range of precursors can be extended by alkylations, adjacent to OMe, of carbanions readily derived from the dihydrobenzenes¹⁰⁻¹². (3) The dienes can be conjugated to the required 1-methoxy-1, 3-dienes¹³⁻¹⁶. (4) Alternatively, the unconjugated dienes can be reacted directly with the acetylenes, conjugation occurring *in situ*, preferably catalysed by a small proportion of added dichloromaleic anhydride. This procedure is more convenient than preliminary conjugation and has the advantage that all of the diene is potentially usable, rather than the maximum of about 70-80% present at equilibrium. (5) A bridge-head OMe facilitates loss of the bridge and good yields result from the fission step.

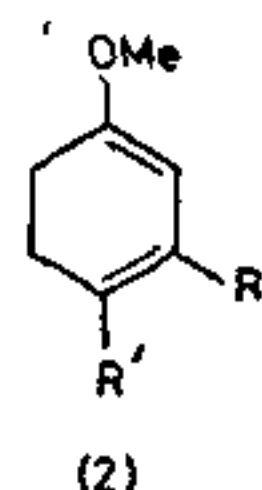
In situ conjugation cannot be carried out with quinones because they oxidise the 1, 4-dienes. However, the catalytically conjugated mixture can be used^{17,18}.

The series of dienes (1 a-e) when used directly, reacted as the isomeric dienes (2) resulting from pivoting of the double bond around C-OMe¹³⁻¹⁶. The esters (3 a-d) were found to be applicable, among others. The aromatic pyrolysis products (4 a-f) are examples, formed in 80-90% yields.

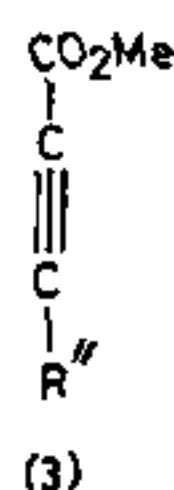


(1)

- (a) R=R'=H
(b) R=OMe; R'=H
(c) R=Me; R'=H
(d) R=H; R'=Me
(e) R=H; R'=n-C₈H₁₈

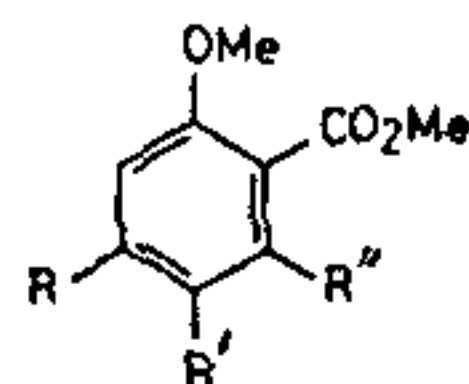


(2)



(3)

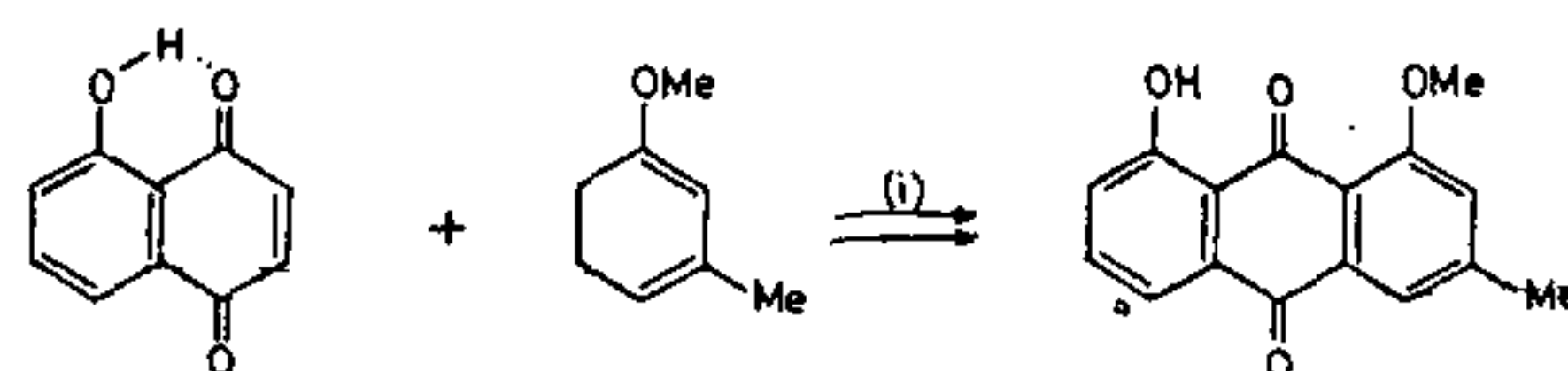
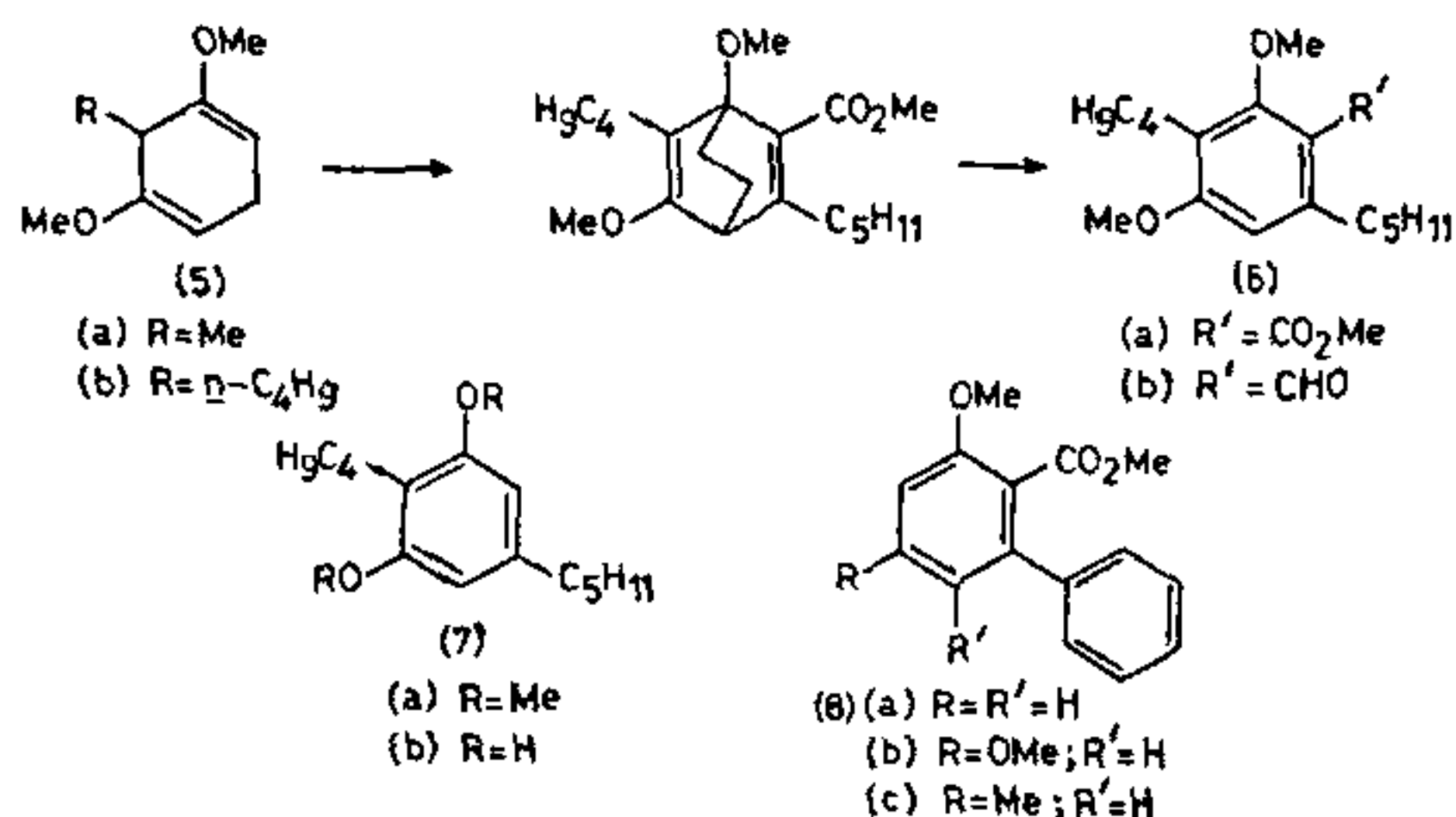
- (a) R''=Me
(b) R''=n-C₄H₉
(c) R''=n-C₅H₁₁
(d) R''=Ph



- (4) (a) R=R'=H; R''=Me
(b) R=OMe; R'=H; R''=Me
(c) R=H; R'=Me=Me
(d) R=OMe; R'=H; R''=C₄H₉
(e) R=OMe; R'=H; R''=C₅H₁₁
(f) R=OMe; R'=H; R''=C₈H₁₈

A convenient experimental procedure for the present work is to heat the two components (1 equivalent each) without solvent (total about 20 g scale) in a sealed tube to 180°/20h and then 220°/10h. The product is worked up by distillation, or by sublimation in appropriate cases. The intermediate bridged ring adduct can be isolated by carrying out the reaction at ambient temperature and 15k bar pressure. However this is not attractive as a preparative method for the aromatic product.

Methylation of the K salt of the diene (1 b) in ammonia¹⁰⁻¹² yielded (5 a), an intermediate in the synthesis^{4(b)} of nidulol methyl ether and a root growth stimulating fungal metabolite¹⁹.



(i) Addition; purification; reoxidation to quinone; pyrolysis.

Stemphol (7 b) was synthesised by the following procedure. Alkylation of the diene (1 b) with n-butyl bromide gave (5 b) which gave rise to the ester (6 a) in 65% yield on reaction with (3 c). Hydrolysis of the ester proved difficult, so the aldehyde (6 b) was prepared by substituting oct-2-yne-1-al for the propiolic ester. Decarbonylation of (6 b) by the catalytic procedure with triphenylphosphinechlororhodium²⁰ was smooth, to give the ether (7 a). Demethylation with silicon tetrachloride and sodium iodide in acetonitrile gave a stemphol (7 b) identical with authentic material²¹.

With (3, B₂ = Ph) reaction on (1/a, b, c) gave the biphenyl derivatives (8) in 80% yields. Introduction into the Ph of p-Me or OMe or 3, 4-OCH₂O- did not affect the course of the reaction.

Hydrolysis and decarboxylation of (4 e) represents a convenient synthesis of olivetol dimethyl ether.

The synthesis of polyketide anthraquinones, such as (10) takes advantage of the hydrogen-bonding in the quinone precursor (9) to ensure the correct polyketide orientation of the two end rings^{17,18}.

The structural result of the sequence with acetylenes is to attach to the side of the triple bond four appropriately substituted and oriented carbons to complete the aromatic ring. The approach also has the advantage that in syntheses of analogues of biologically active compounds a large number can be made from the same acetylene by the use of readily available alternative dienes.

A Diels-Alder approach with open-chain dienes, such as that used to synthesise lasiodiplodin²², is more limiting in the necessity to make unusual diene precursors which contain enol TMS ethers, less stable than the present OMe derivatives.

The present strategy has been used, additionally to the syntheses noted above, in the syntheses of the heavily substituted benzene derivatives mycophenolic acid^{4c}, antibiotic DB-2073, a degradation product of the polyketide phomazarin²³, the biphenyl derivatives alternariol²⁴, and altenuisins²⁴ and the macrocyclic lactone, lasiodiplodin²⁵. The hydroxy-acid corresponding to the dimethyl ether of the medium ring lactone curvularian has been made²⁵ but so far without success in ring closure. Full details of this work will be published elsewhere.

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CONFORMATIONAL STUDIES OF PHENYL AND ISOXAZOLYL PENICILLINS

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ABSTRACT

Conformational energy calculations have been carried out on a few representative β -lactamase-resistant and susceptible, phenyl and isoxazolyl penicillins. These studies, in agreement with those of earlier workers, show that the 6 β -side chains of resistant penicillins are highly rigid as compared to those of susceptible penicillins. The present studies also suggest that the degree of resistance to β -lactamases depends not only on the rigidity of the side chain but also on the nature and orientation of the substituent, beyond the amide carbonyl group in the side chain. The overall shapes of these penicillins correlate well with their antibacterial properties.

INTRODUCTION

THE search for β -lactam antibiotics resistant to β -lactamases has resulted in the synthesis of penicillins such as oxacillin, ancillin, etc (Figure 1) where the α -carbon atom in the 6 β -side-chain is incorporated in an aromatic or hetero-aromatic ring. In these penicillins, the resistance to β -

lactamases has been attributed to the steric effects around the amide-carbonyl in their 6 β -side-chain^{1,2}.

From a number of chemical studies, it has been postulated that penicillins (A-type) which show resistance to β -lactamases bring about a conformation change in the active site of the enzyme that is unfavourable for catalytic reaction and hence lead to a lower, but constant level of enzymic activity. On the