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A BIOMIMETIC SYNTHESIS OF POLYCYCLIC POLYOXYGENATED AROMATIC COMPOUNDS VIA POLYKETIDES

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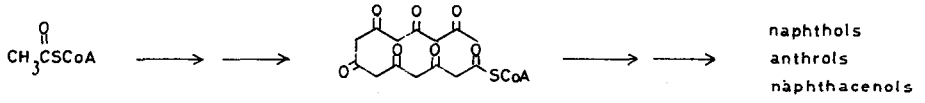
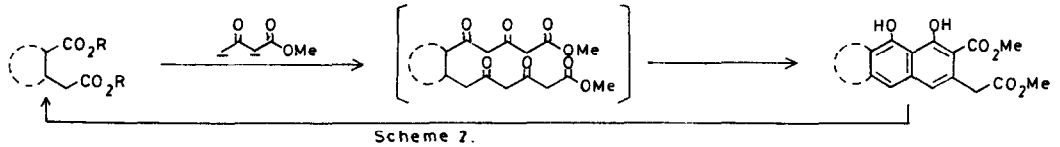
Abstract: Polyoxygenated naphthalenes, anthracenes and a naphthacene are synthesized from glutarates and acetoacetate dianion via polyketides.

The reaction of polyketides is one of the most important biosynthetic route to the polycyclic polyoxygenated aromatic compounds such as phenols, naphthols, anthrols, and naphthacenols. It consists of the Claisen-type condensation of acetates to form β-polycarbonyl compounds followed by its intramolecular condensation (Scheme 1). The organic synthesis of the naturally occurring arenes by the biomimetic process is quite attractive with respect to the construction of the carbon frame-work and the regioselective introduction of oxygen functions.



Scheme 1.

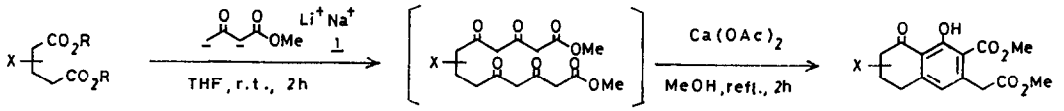
In this communication, we wish to describe a method for the synthesis of polyoxygenated naphthalenes, anthracenes, and a naphthacene through the polyketides. Our strategy is based on the condensation of methyl acetoacetate dianion with glutarates, and successive intramolecular condensation to form 1,8-naphthalendiol moieties (Scheme 2).[2] Although the reaction of acetylacetone dianion with glutarates is known,[3] the present method has the advantage that the resulted products also are glutarates, and further transformations including the extention of the linear ring system is possible.

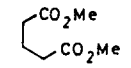
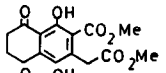
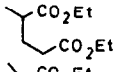
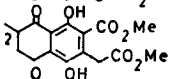
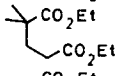
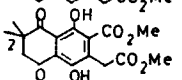
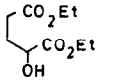
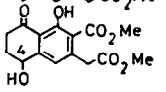


Scheme 2.

At first, tetrahydronaphthalene derivatives are synthesized from simple glutarates. Sodium lithium dianion of methyl acetoacetate (1)[4] (8 equiv.) was reacted with dimethyl glutarate (2) in THF at r.t. for 2h. The reaction was quenched with 1M HCl, extracted with ethyl acetate, dried over Na_2SO_4, and concentrated in vacuo. The residue was treated with $Ca(OAc)_2$[5](4 equiv.) in methanol at reflux for 2h. 1-Oxo-8-hydroxytetrahydronaphthalene 3 was isolated by TLC (silica gel) in 77% yield. In order to examine the regioselectivity of

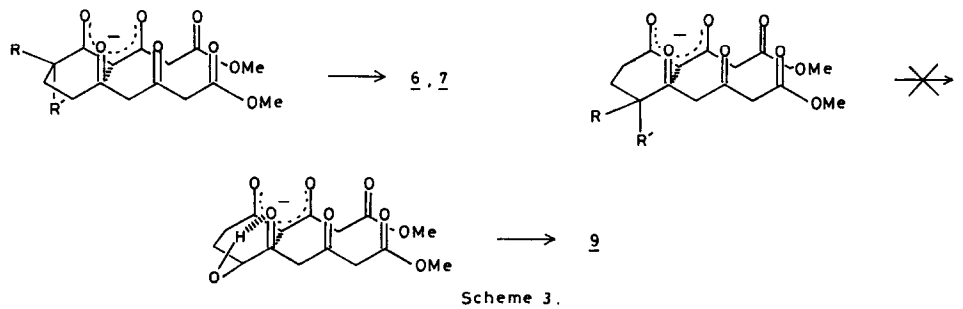
Table 1. Synthesis of 1-Oxo-1,2,3,4-tetrahydronaphthalenes.



glutarate		product		yield(%)
	2		3	77
	4		6	30
	5		7	44
	8		9	36 *)

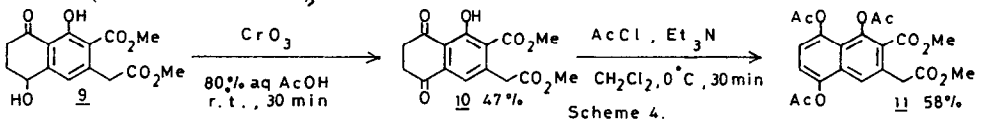
*) The reaction was carried out in THF-HMPA (4:1).

this intramolecular condensation, unsymmetrical glutarates were used (Table 1). α-Methylglutarate 4 and α,α-dimethylglutarate 5 gave 2-methyl and 2,2-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene 6 and 7, respectively, indicating that, in the first cyclization process, the less hindered carbonyl works as the electrophile. Contrary, α-hydroxyglutarate 8 gave 4-hydroxy derivative 9. The hydrogen bonding is presumed to play an important role in this inversion of the regioselectivity (Scheme 3). The structures of 6, 7, and 8 were determined by ^{1}H-NMR: the C-2 methylene of 1-oxo-1,2,3,4-tetrahydronaphthalene derivatives appears at δ 2.6~2.7, and C-4 at δ ~2.9.[2, 6] 6: ^{1}H-NMR ($CDCl_3$-CCl_4) δ 1.28 (3H,d,J=7Hz), 1.6-2.9 (3H,m), 2.94 (2H,t,J=6Hz), 3.69 (5H,s), 3.89 (3H,s), 6.60 (1H,s), 13.06 (1H,s); IR (KBr) 3400, 1735, 1715, 1625 cm^{-1}; $C_{16}H_{18}O_6$ [m/z 306.1101 (M^+)]; Mp 95 °C (benzene-hexane). 7: ^{1}H-NMR ($CDCl_3$-CCl_4) δ 1.24 (6H,s), 1.94 (2H,t,J=6Hz), 2.94 (2H,t,J=6Hz), 3.68 (5H,s), 3.89 (3H,s), 6.59 (1H,s), 13.14 (1H,s); IR (KBr) 3400, 1730, 1625 cm^{-1}; $C_{17}H_{20}O_6$ [m/z 320.1237 (M^+)]; Mp 98 °C (benzene-hexane). 9: ^{1}H-NMR ($CDCl_3$-CCl_4) δ 1.9-2.4 (2H,m), 2.4-2.9 (2H,m), 3.68 (5H,s), 3.89 (3H,s), 4.5-5.0 (1H,m), 6.91 (1H,s), 12.9 (1H,s); IR (neat) 3400, 1740-1710, 1620 cm^{-1}.



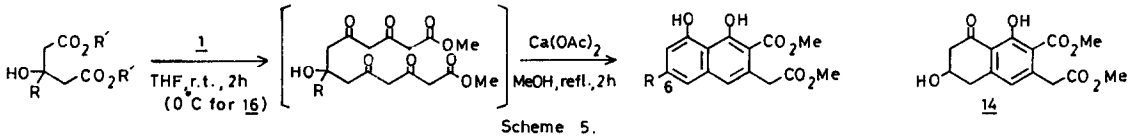
Scheme 3.

Alcohol 9 was oxidized with CrO_3 (2equiv.) in 80% aqueous acetic acid (r.t., 30 min) to diketone 10 (Mp 97 °C (ethyl acetate-hexane)) in 47% yield, which was aromatized to give 1,4,8-triacetoxynaphthalene 11 by acetylation (AcCl, Et_3N, CH_2Cl_2; 0 °C, 30 min) (Scheme 4) [11: ^{1}H-NMR ($CDCl_3$-CCl_4) δ 2.33 (3H,s), 2.36 (3H,s), 2.45 (3H,s), 3.66 (3H,s), 3.88 (5H,s), 7.09 (1H,d,J=8Hz), 7.37 (1H, d,J=8Hz), 7.71 (1H,s); IR (KBr) 1770, 1730 cm^{-1}; $C_{21}H_{20}O_{10}$ [m/z 432.1057 (M^+)]; Mp 146 °C (benzene-hexane)].



Scheme 4.

Direct synthesis of 1,8-naphthalendiols was performed. Diethyl β-hydroxyglutarate 12 was treated as above. Dehydration occurred spontaneously with the polyketide condensation, and the intermediate hydroxyketone 14 was not detected (Scheme 5). Alkyl groups could be introduced at 6-position of the naphthalendiol using tertiary alcohols 15 and 16. In the case of triethyl citrate (16), 1 reacted with the less hindered two ester groups and the other ethoxycarbonyl remained unreacted (Table 2).



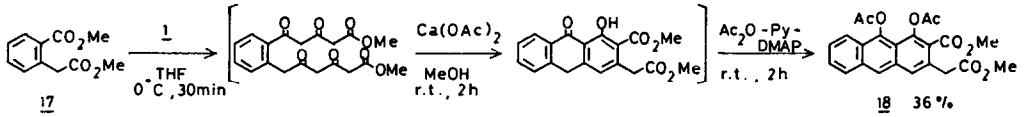
Scheme 5.

Table 2. Synthesis of 1,8-naphthalenediols.

glutarate	product*)	Mp(°C)	yield(%)
12	13	153 (benzene-hexane)	50
15		173 (benzene-hexane)	37
16		125 (benzene-hexane)	24

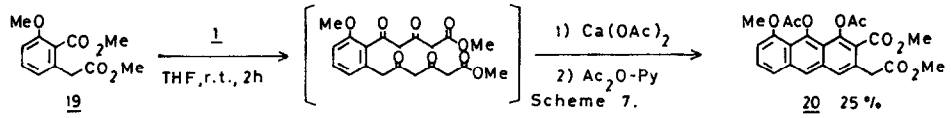
*) All the products gave satisfactory spectral data (^{1}H-NMR, IR, Exact mass).

Next, the synthesis of polyhydroxy anthracenes was examined starting from aromatic glutarates. Methyl 2-methoxycarbonylphenylacetate (17) was reacted with 1 in THF (0 °C, 30 min), and $Ca(OAc)_2$ in methanol (r.t., 2h). The crude products were acetylated (Ac_2O, pyridine, DMAP; r.t., 2h), and methyl 1,9-di acetoxy-2-methoxycarbonyl-3-anthrylacetate (18) was isolated (Scheme 6) [18:



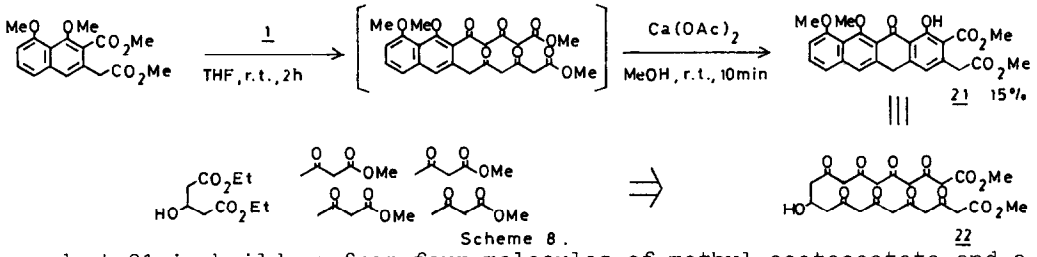
Scheme 6.

^{1}H-NMR ($CDCl_3$-CCl_4) δ 2.39 (2H,m), 2.51 (3H,s), 3.68 (3H,s), 3.90 (5H,s), 7.4-7.6 (2H,m), 7.77 (1H,s), 7.7-8.1 (2H,m), 8.28 (1H,s); IR (KBr) 1770, 1740 cm^{-1}; $C_{23}H_{20}O_8$[m/z 424.1176 (M^+)]; Mp 200 °C (benzene)]. Similarly, 1-methoxy-2-methoxycarbonyl-3-phenylacetate 19[7] gave 1,9-diacetoxy-8-methoxy-2-methoxycarbonyl-3-anthrylacetate 20 in 25% yield (Scheme 7) [20: ^{1}H-NMR ($CDCl_3$-CCl_4) δ 2.41 (3H, s), 2.44 (3H,s), 3.68 (3H,s), 3.91 (5H,s), 3.95 (3H,s), 6.76 (1H,dd,J=1.5,7Hz), 7.2-7.6 (2H,m), 7.74 (1H,s), 8.22 (1H,s); IR (KBr) 1780, 1760, 1740, 1720 cm^{-1}; $C_{24}H_{22}O_9$[m/z 454.1256 (M^+)]; Mp 238 °C (chloroform-hexane)].



Scheme 7.

As aromatic compounds thus obtained also are glutarates, repeated ring formation to polyoxygenated linear arenes could be conducted. An example is shown in the synthesis of a naphthacene. 1,8-Naphthalendiol 13 was methylated (MeI, K_2CO_3, acetone; refl., 3h; 55% yield), and then subjected to the condensation - cyclization procedures. Expected methyl 10,11-dimethoxy-5,12-dihydro-1-hydroxy-2-methoxycarbonyl-12-oxo-3-naphthacenylacetate (21) was obtained in 15% yield after TLC (silica gel) and crystalization from ethyl acetate (Scheme 8) [21: ^{1}H-NMR ($CDCl_3$) δ 3.71 (3H,s), 3.76 (2H,s), 3.95 (3H,s), 3.99 (3H,s), 4.02 (3H,s), 4.38 (2H,s), 6.76 (1H,s), 6.6-6.9 (1H,m), 7.2-7.6 (2H,m), 7.50 (1H,s); IR (KBr) 1740, 1600 cm^{-1}; $C_{25}H_{22}O_8$[m/z 450.1341 (M^+)]; Mp 209 °C (ethyl acetate)].



Scheme 8.

The product 21 is build up from four molecules of methyl acetoacetate and a diethyl β-hydroxyglutarate, and is an equivalent of nonacarbonyl derivative 22. The process constitutes a biomimetic synthesis of arenes via the corresponding polyketides.

Studies directed to the synthesis of natural and unnatural polycyclic polyoxygenated aromatic compounds using this methodology are actively in progress.

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