Tetrahedron Vol 41 No 16 pp 3241 to 3252 1985
Printed in Great Britain

0040-4020/85 $3.00 + .00
Pergamon Press Ltd

SYNTHESIS OF AN 11-DEOXYPRETETRAMIDE DERIVATIVE

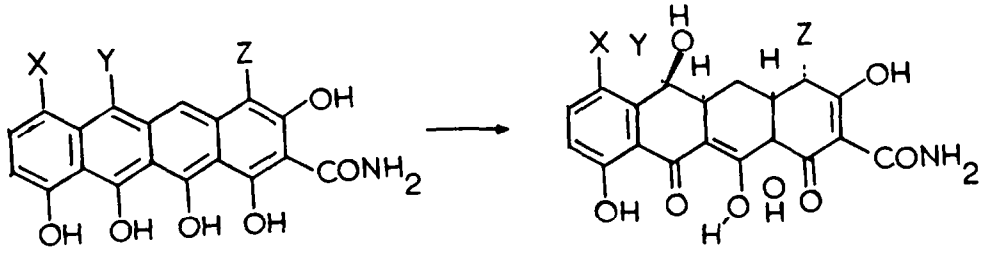
JAMES L. BLOOMER* AND CHRISTIAN S. BROSZ

Department of Chemistry, Temple University,
Philadelphia, Pennsylvania 19122

(*Received in USA 22 April* 1985)

Abstract - A short and efficient synthesis of the 4-oxo-1,2,3,4-tetrahydro-2-naphthalenecarboxylic acid derivative (13a) is described. This synthon may be converted to the dihydronaphthacenone derivative (18) in a regio-controlled manner in only two steps using condensation with 2,5-dimethoxy-benzaldehyde followed by intramolecular acylation. The enol form of the dihydronaphthacenone, (20) corresponds to a derivative of 11-deoxypre-tetramide.

Synthetic approaches to tetracyclines (2) (TC's) stand as significant achievements, owing in no small part to the instability of these substances to both acid and base [1-5] Such instability places severe limits upon possible chemical conversions of naturally occurring TC's to semisynthetic analogs.[6-7]

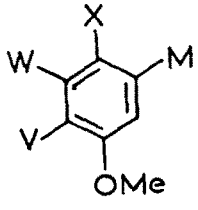


1 2

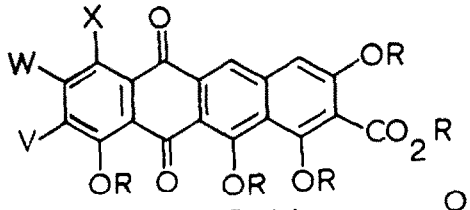
The normal biosynthetic precursors of the tetracyclines (2) (TC) are pretetramide (1, X=Y=Z=H) (PT) and 6-methyl PT (Y=Me) [8-10] Other substituted PT's which have been converted into TC's are 7-chloro PT (X=Cl) and 4-dimethylamino PT ($Z=NMe_2$) [11] The *Streptomyces* strains are thus tolerant of changes in functionality at positions X, Y, and Z of PT (1). Although "methylating" strains[12] will not introduce a 6-methyl[13] onto an existing PT, both the 4-dimethylamino and the 7-chloro substitutents may be introduced.[14] The tolerance of the TC-producing organisms to the structural changes in PT outlined above suggested the feasibility of novel TC's from modified PT's by bioconversion. Since a 4-dimethylamino group is required for TC activity,[15] administered PT's

should contain either H or NMe_2 at carbon 4 Positions on rings C and D of PT, however, were good targets for modification, especially the latter, where three potential sites for modification existed (carbons 7, 8, or 9). While syntheses of PT[17-19] and 6-methyl PT[20] have appeared, none of these are well adapted to the production of ring D analogs.

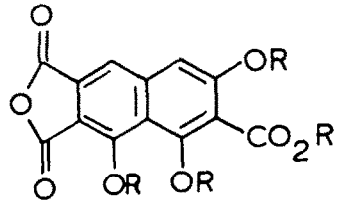
The naphthacenequinone (3) was considered a promising synthetic intermediate, as ample literature precedent existed for the removal of the ring C oxygen at C_6[21-22], the conversion of the ring A ester function at C_2 to the amide,[23] and removal of the protecting groups R=CH_3 in related syntheses.[24] Maximum variation in ring D could be achieved effectively provided the ring D synthon were a simple benzene derivative (4), where M could be either H or an organometallic derivative.[25-26] Variation of groups X, Y, or Z in the benzene synthon (4) would then lead to the corresponding naphthacenequinones (3). Whether or not organometallic derivatives were opted for, the anhydride (5) would be required as countersynthon.



4



3 R=Me

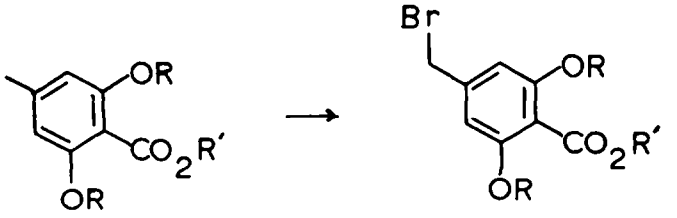


5 R=Me

The intended strategy was to synthesize the anhydride (5) via the tetralone derivative (13b) described below. The latter was preparable in a short and high-yielding synthesis. We were not successful in converting the tetralone (13b) into the desired anhydride (5); however, it was possible to convert the related tetralone (13a) to tetracyclic material in a convergent and regiocontrolled manner requiring only two steps This efficient approach to naphthacene derivatives constitutes the subject of the present paper

From the tetralone carboxylic acid (13a) described below, we were able to prepare a naphthacene derivative corresponding to an 11-deoxypretetramide derivative by the use of a condensation reaction followed by an intramolecular acylation. While the synthetic approach appears applicable to the production of a variety of naphthacene derivatives variously substituted on the terminal rings, A and D, we were unable to overcome the difficulty of the 11-hydroxy function on ring C necessary to prepare a pretetramide. More detailed comments on the scope and limitations of the synthetic sequence are given below

Orcinol was converted into p-orsellinic acid (6a) by treatment with CO_2, $KHCO_3$ and glycerol.[27] The acid (6a) was subsequently converted to the dimethoxy methyl ester (6b) using Me_2SO_4, K_2CO_3, and acetone in high yield and purity.[28] The diacetoxy methyl ester (6c) was prepared according to Barton's procedure[29] and also investigated as a ring A synthon. Both esters were readily converted to the corresponding benzylic bromides (7a) and (7b); however, the acetoxy group proved too labile to carbanionic reagents to be of use in subsequent reactions. The carbon skeleton required for intramolecular acylation to give ring B was introduced by nucleophilic substitution of the benzylic halide of the dimethoxy series(7a)using the anion of diethyl

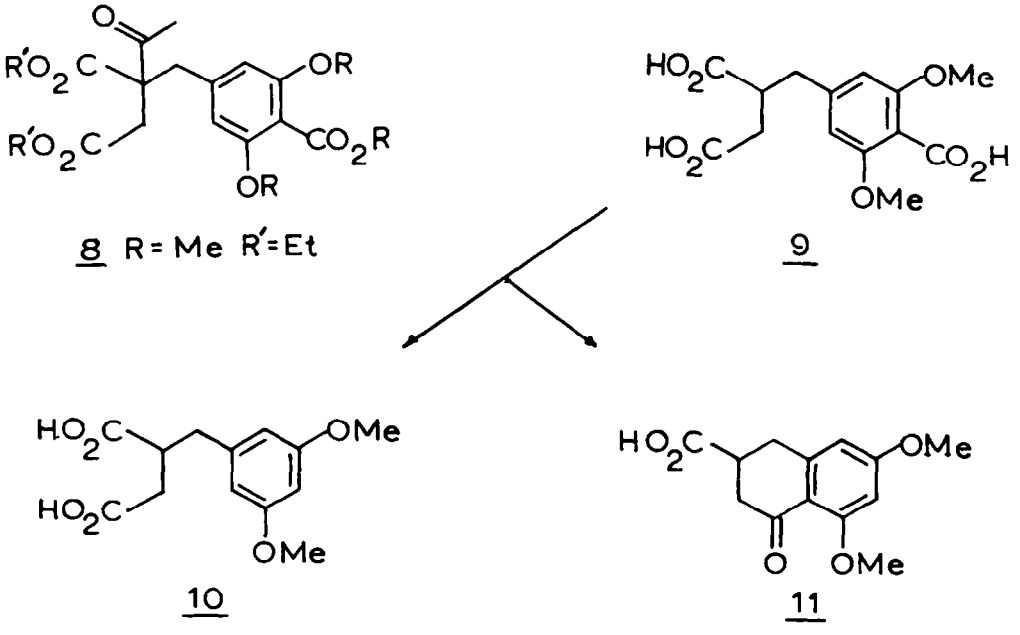


6a R = R′ = H
6b R = R = Me
6c R = Ac R′ = Me

7a R = R = Me
7b R = Ac R′ = Me

acetylsuccinate, which was prepared from the latter with NaH in toluene. An excellent yield of the benzylsuccinate derivative (8), which could be taken directly for the subsequent hydrolyses, was obtained.

Initially, the benzylsuccinic triester (8) was completely saponified with loss of the acetyl group to give the triacid (9). Attempts to cyclize the benzylsuccinic triacid (9) with HF gave only decarboxylated products, the uncyclized diacid (10) and the tetralone acid (11).



8 R = Me R′ = Et

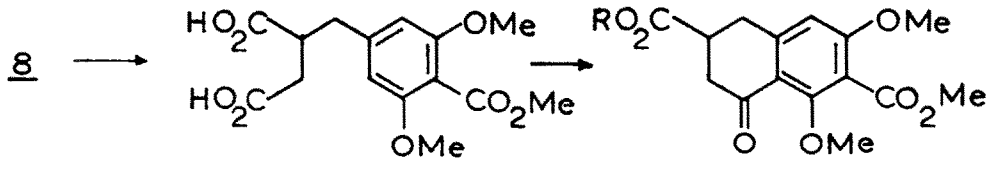
9

10

11

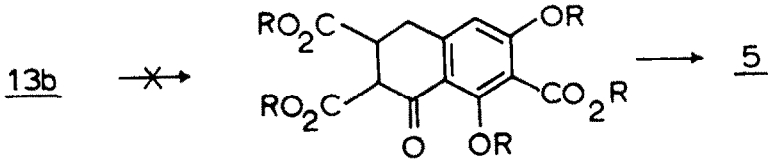
Selective saponification with concomitant deacetylation of the benzylsuccinic triester (8) gave the benzylsuccinic diacid (12), in which the aromatic ester function was retained. The overall yield of the diacid (12) from the benzylic halide (7a) was 83%, with no purification of the intermediate benzylsuccinic ester (8) being required.

The benzylsuccinic acid (12) was cyclized to the desired tetralone carboxylic acid (13a) using polyphosphoric acid at 60° for 3 hrs. The key synthon, tetralone acid (13a) was thus obtainable by a short and efficient synthetic route In the tetralone acid synthon (13a), not only was all required functionality for ring A of pretetramide present, but also the presence of the carboxyl and ring ketone functions presented convenient points for synthetic operations in a regiocontrolled manner.



12 13a R = H 13b R = Me

The most straightforward approach to the correct skeleton for desired 2,3-naphthalenedicarboxylic anhydride (5) appeared to be utilization of carbanionic reactivity at the position alpha- to the carbonyl in tetralone ester (13b). If tetralone triester (14) could be formed, we anticipated, based on literature precedent,[30-33] that it could be aromatized Model studies on 2,3-naphthalenedicarboxylic esters had indicated that this class of compound could be cyclized easily to the requisite anhydride.[34-35] A considerable number of studies involving treatment of the tetralone ester (13b) with a variety of bases and carbon sources such as methyl chloroformate, dimethyl carbonate, etc., were carried out. In these studies, the usual result was that the starting material was recovered in essentially quantitative yield.

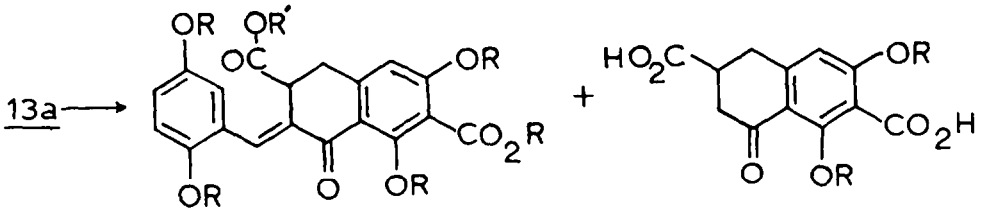


14 R=Me

That the tetralone ester (13b) could be converted into the anion was demonstrated by treatment of the ester with lithium diisopropylamide in THF and then quenching with D_2O. Surprisingly, use of the LDA-THF system with methyl chloroformate carbon source gave only a good recovery of nearly pure starting material plus a few very minor components, none of which gave a positive $FeCl_3$ test.[36]

Although the tetralone ester (13b) failed to respond to a variety of strong base systems usually used for synthetic purposes, we did observe the formation of a benzylidene derivative and the related tetralone acid (13a) in aqueous methanolic NaOH.[37] While the carboxylic acid function of the tetralone acid (13a) would be expected to exist entirely as the carboxylate under these conditions, enolate formation from the tetralone carbonyl was still allowed. We felt that it was preferable to use the carboxyl function as in (13a) rather than the ester function as in (13b), as the latter could be saponified under the reaction conditions, leading to mixtures of products.[38]

In order to produce a D ring corresponding to pretetramide, an ortho-hydroxy function or equivalent was required on the benzaldehyde moiety. In order to facilitate the subsequent intramolecular acylation, a second appropriately placed activating group (e.g. a second hydroxyl or related function) was also desirable The synthon of choice for initial studies was, therefore, 2,5-dimethoxybenzaldehyde Using aqueous methanolic NaOH at 40°, TLC studies indicated that the tetralone acid (13a) required 5 days to give maximum reaction with 2,5-dimethoxybenzaldehyde. Under these conditions, a yield of 43% of the benzylidene tetralone acid (15a) was obtained. A second major component of the reaction mixture was obtained in 37% yield and identified as the ring A carboxylic acid (16) derived from saponification of the aromatic ester



15a R = Me R' = H
15b R = R' = Me

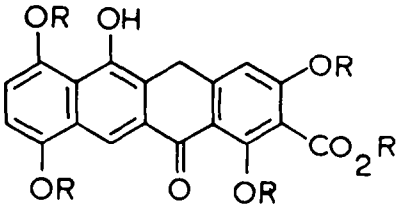
16 R = Me

function of the starting material It was possible to recycle the ring A acid (16) in the following manner: Methylation of the acid (16) gave the diester (13b), the same ester as obtained from monoacid (13a).[39] Selective saponification of diester (13b) regenerated the starting acid (13a).[40]

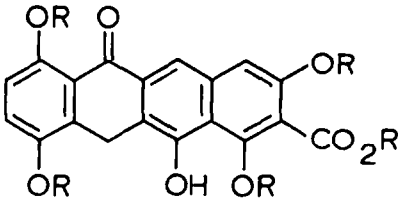
In the benzylidene tetralone acid (15a) obtained above, the ester, unsaturated ketone, and both free and H-bonded carboxylic acid absorptions were clearly visible in the IR spectrum. The acid (15a) was converted to its methyl ester for ^{1}H NMR studies. In the ^{1}H NMR, ester (15b) exhibited a vinylic proton unsplit by long-range coupling (δ 8.02, s, 1H) and protons of the 2,5-dimethoxybenzylidene moiety appeared as a single band (δ 6 89, s, 3H). Other features of the spectrum were unexceptional Structures of the benzylidene derivatives (13a) and (13b) are shown in the E-configuration, as expected for this type of aldol condensation.[41-42]

The intramolecular acylation of the benzylidene tetralone acid (15a) was facilitated by the presence of the meta-methoxy function of the 2,5-dimethoxybenzylidene moiety. When the tetralone acid (15a) was pulverized with NaCl and treated with PPA at 40-45° for 2 hrs, an excellent yield of tetracyclic material (92%) was obtained

The cyclization product from the above procedure exhibited a single phenolic proton in the ^{1}H NMR. In the IR, the O-H stretching was characteristic of hydrogen bonding (3367 cm^{-1}). The UV-VIS spectrum of the cyclization product exhibited no less than five maxima, the longest of which extended into the visible portion of the spectrum (410 nm, ε = 6200). By comparison, the longest maximum of the ester (15b), used for characterization of the starting material, was only 304 nm (ε = 19,600). The vinylic proton in the benzylidene tetralone system (for ester (15b) ^{1}H NMR δ = 8.02, s, 1H), in the cyclized material, was replaced by a new peak further downfield (δ = 8 60, s, 1H) ascribed to a new aromatic ring proton (on ring C). Observation of a doubly benzylic methylene (δ = 4.37, s, 2H) limits the structural possibilities for the cyclized material to the dihydronaphthacenone systems (17) or (18). The former structure is preferred on



17 R=Me

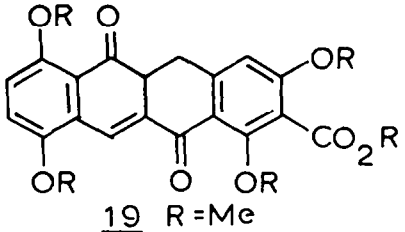


18 R=Me

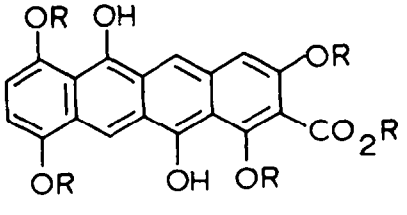
the following basis. In addition to the ^{1}H NMR absorption corresponding to the proton on ring A (δ = 6.93, s, 1H), the protons on aromatic ring D have very similar chemical shifts, indicative of a high degree of electronic symmetry (δ = 6 98, 7 20) The electronic symmetry is in better agreement with structure (17), where the aromatic ring D protons are in a rather similar environment.

Intramolecular acylation of the benzylidene tetralone acid (15a) would be expected to give initially tetrahydronaphthacenedione (19). Simple enolization of the latter would be expected to lead directly to the dihydronaphthacenone (17).[43]

The presence of a potential naphthacene chromophore in dihydronaphthacenone (17) was readily demonstrated by its base-catalyzed isomerization When NaOH was added to (17) in 50% aqueous ethanol, the longest absorption maximum in the UV-VIS spectrum ranged from 418 nm (ε 3400) to 554 nm (ε 12300). Acidification of the basic solution produced a small hypsochromic shift (to 527 nm) with no diminution of epsilon value This was interpreted as an irreversible enolization to the fully aromatic chromophore of (20).



19 R=Me



20 R = Me

Naphthacene (20) is a derivative of 11-deoxypretetramide Studies directed towards introduction to the 11-hydroxy function at various stages of the synthesis have not been particularly encouraging.[44] Bypass routes from tetralone ester (13b) to the initial anhydride

synthetic objective (5) exist, but are lengthy.[45] Aside from the difficulty with the introduction of the 11-hydroxy function necessary for pretetramide, the synthetic method described here appears to be an efficient and regiocontrolled synthesis of naphthacene derivatives. It seems possible to produce a variety of naphthacene derivatives with different ring A and D substitution patterns, since a number of benzaldehydes are commercially available, and several analogs of the tetralone carboxylic acid (13a) are readily accessible from simple benzaldehyde derivatives via Stobbe condensation and classical cyclization methods.[47-50]

EXPERIMENTAL[51]

Thin Layer Chromatography. The progress of reactions was routinely monitored by thin layer chromatography (TLC) using Analtech and Woelm GF 250 μm silica gel plates. TLC eluents were. Eluent A toluene/ethyl acetate (9:1) and Eluent B toluene/diethyl ether/acetic acid/methanol (120:60:18:1).

Methyl-2,6-diacetyloxy-4-methyl Benzoate, (6c) Prepared according to Barton,[52] mp of 71-72° (lit[52] 70°).
NMR (CCl_4) δ 7 73 (s, 2H), 3 74 (s, 3H), 2.35 (s, 3H), 2.15 (s, 6H)

Methyl-4-bromomethyl-2,6-diacetyloxy Benzoate, (7b). N-Bromosuccinimide (4 88 g, 27.1 mmol) was added to a solution of 6c (7.235 g, 27.1 mmol) in carbon tetrachloride (750 ml). The volume was reduced under nitrogen to 540 ml. Di-t-butyl peroxide (.64 ml) was added and the mixture refluxed for 68 hrs. The volume was reduced further to 270 ml and di-t-butyl-peroxide (.5 ml) was added. The mixture was refluxed 24 hrs. and cooled. After removal of succinimide, evaporation of the solvent gave a crystalline product (9.742 g, in slight excess of theory).
NMR ($CDCl_3$) δ 7.06 (s, 2H), 4 40 (s, 2H), 3 85 (s, 3H), 2.28 (s, 6H) M/e 344 (M^+)

2,6-Dihydroxy-4-methyl Benzoic Acid, (6a) Prepared according to the literature.[53]
UV (EtOH) λ max 212 nm (ε 26000), 250 nm (ε 7700), 308 nm (ε 3000)
IR (KBr) 6.14 μ (1627 cm^{-1}) broad
NMR ($CDCl_3$/DMSO d_6) δ 10.92 (s, 3H), 6.39 (s, 2H), 2 37 (s, 3H)

Methyl-2,6-dimethoxy-4-methyl Benzoate, (6b). A mixture of 6a (1 682 g, 10 mmol), dimethyl sulfate (3 79 ml, 40 mmol), anhydrous potassium carbonate (5.37 g, 40 mmol), and dry acetone (25 ml) was refluxed for 24 hrs. After removal of the carbonate and evaporation of solvent, the residue in ether (75 ml) was washed with 5N NaOH (3 ml), saturated NaCl, and dried Evaporation gave (6b) as irregular crystals (1.997 g, 92%) mp 84-85.5° (lit[54] mp 86°).
IR (KBr) 5.77 μ (1732 cm^{-1})
NMR ($CDCl_3$) δ 6.37 (s, 2H), 3.87 (s, 3H), 3 77 (s, 6H), 2.31 (s, 3H). M/e 210 (M^+)
Anal Calcd for $C_{11}H_{14}O_4$. C, 62 85, H, 6.71, Found. C, 62.67, H, 6.59

Methyl-4-bromomethyl-2,6-dimethoxy Benzoate, (7a) N-Bromosuccinimide (18 g, 100 mmol) was added to a solution of (6b) (21.023 g, 100 mmol) in dry carbon tetrachloride (2000 ml). Di-t-butyl peroxide (2.36 ml) was added, the mixture refluxed 30 hrs The reaction volume was reduced to 500 ml. After removal of succinimide, evaporation of solvent and recrystallization from ether gave the benzylic bromide (7a) 17.73 g (61.4%), mp 99-101°.
IR 5.80 μ (1723), 8.25 (1212, CH_2 deformation), 14.86 (673 cm^{-1}, C-Br stretch).
NMR ($CDCl_3$) δ 6.58 (s, 2H), 4.43 (s, 2H), 3.88 (s, 3H), 3.81 (s, 6H). M/e 288 (M^+)
Anal. Calcd for $C_{11}H_{13}BrO_4$: C, 45 70; H, 4.53; Br, 27.64, Found. C, 46.89; H, 4.65; Br, 27.76.

Diethyl-2-acetyl-2-(4-carbomethoxy-3,5-dimethoxyphenylmethyl)butandioate, (8). Diethyl acetylsuccinate (55.44 g, .256 mol) was added dropwise during 20 min to sodium hydride (10.80 g of 57% oil dispersion, .256 mol), in dry toluene (50 ml) at 0° with stirring. When the sodium hydride had dissolved the solution was brought to room temperature and bromide (7a) (67.4 g, .233 mol) in dry toluene (200 ml) was added over 10 min. The mixture was stirred for 48 hrs A TLC (eluent B) showed no bromide to be present. The mixture was poured into a separatory funnel containing water (100 ml), ice (100 g), and concentrated hydrochloric acid (25 ml). The toluene fraction was separated, the aqueous fraction was extracted with ether (5 x 200 ml), and the combined ether and toluene extracts were dried (sodium sulfate) and evaporated (65°, 2 mm, 2 hrs.) to give a pale yellow viscous liquid (suitable for direct conversion to (12)). A sample of the liquid was triturated with ether and the resulting solid was recrystallized from ether/petroleum ether, mp 62-65°.
IR (KBr) 5.81 μ (1721 cm^{-1}) broad
NMR (CCl_4) δ 6.30 (s, 2H), 4 19 (q, 2H, J = 7 Hz), 3.79 (s, 3H), 3 76 (s, 6H), 3.05-3.43 (AB quartet, 2H, J = 14 Hz), 2.82 (s, 2H), 2 26 (s, 3H), 1.27 (t, 3H, J = 7 Hz), 1 25 (t , 3H, J = 7 Hz)
Anal. Calcd for $C_{21}H_{28}O_9$: C, 59.42, H, 6.65, Found. C, 59 17, H, 6.59.

2-(4-Carboxy-3,5-dimethoxyphenylmethyl)butandioic Acid, (9). A mixture of (8) (17.140 g, 40.4 mmol) and 3N sodium hydroxide (60 ml, 180 mmol) was refluxed for 25 hrs The mixture was cooled to 5° and carefully acidified with cold 6N hydrochloric acid to pH 2. The aqueous solution was extracted with ethyl acetate (4 x 50 ml) and the extracts were dried, evaporated and refrigerated to give a pale yellow glass, 14.419 g (12 610 g theory) mp 152-155° Recrystallization from acetone/benzene gave mp 166-168°.
Note: Acids (9), (10), and (11) (abandoned as a synthetic route) were not analyzed.[55]
IR (KBr) 5.92 μ (1689 cm^{-1}) broad
NMR (ACE d_6 δ 6.58 (s, 2H), 3.82 (s, 6H), 2.24-3.54 (m, 5H) M/e 312 (M^+)
The methyl[6] ester gave.
NMR ($CDCl_3$) δ 6.36 (s, 2H), 3.87 (s, 3H), 3 80 (s, 6H), 3.67 (s, 3H), 3 65 (s, 3H), 2.33-3.30 (m, 5H).

5,7-Dimethoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthalenecarboxylic Acid, (11) and 2-(3,5-Dimethoxyphenylmethyl)Butandioic Acid, (10) from HF Cyclization of (9). Hydrogen fluoride at 5° (35 ml) was added with magnetic stirring to (9) (4 36 g, 14 mmol) in a polyethylene centrifuge tube and refluxed (dry ice condenser) for 3 hrs The condenser was then left in place for 20 hrs without the further addition of dry ice. The remaining hydrogen fluoride was removed. Water (nitrogen stream) (35 ml) was added and stirring continued 15 min. The mixture was cooled 30 min (-5°) and centrifuged The aqueous layer was decanted leaving a dark yellow oil which on trituration with ether gave (11) as tan crystals (.275 g) mp 197-199°.
IR (KBr) 5.78 μ (1730), 6.12 (1634 cm^{-1})
NMR ($CDCl_3$/DMSO d_6) δ 6.36 (s, 2H), 3.89 (s, 6H), 3.12 (m, 3H), 2.80 (m, 2H) M/e 250 (M^+)
The methyl ester (CH_2N_2) gave
NMR ($CDCl_3$) δ6.34 (s, 2H), 3 88 (s, 3H), 3.85 (s, 3H), 3.71 (s, 3H), 3.10 (m, 3H), 2 82 (m, 2H). M/e 264 (M^+)
Slow evaporation of the ether solvent yielded uncyclized diacid (10) (.761 g), mp 126-128°. Starting material (.201 g) was also recovered from the mother liquor
IR (KBr) 5.90 μ (1695 cm^{-1}) broad
NMR ($CDCl_3$/DMSO d_6) δ 9.72 (s, 2H), broad, 6.32 (m, 3H), 3 78 (s, 6H), 2 20-2.30 (m, 5H). M/e 268 (M^+)
The methyl ester (CH_2N_2) gave:
NMR ($CDCl_3$) δ 6.31 (s, 3H), 3 76 (s, 6H), 3 67 (s, 3H), 3.64 (s, 3H), 2 25-3 22 (m, 5H).

2-(4-Carbomethoxy-3,5-dimethoxyphenylmethyl)butandioic Acid, (12) A solution of potassium hydroxide (48 93 g of 86%, .75 mmol) in aqueous (20 ml) methanol (200 ml) was added to a solution of (8) (as obtained in the previous step directly) in methanol (200 ml) at 0° The solution was allowed to reach room temperature. After 24 hrs, the bulk of the solvent was removed by rotary evaporation at 25°. Water (400 ml) was added to the viscous residue and the resulting dispersion was extracted with benzene (2 x 400 ml). The collected benzene layers were back extracted with water (2 x 100 ml). The collected aqueous fractions were poured into a mixture of ice (400 g) and concentrated hydrochloric acid (65 ml). After 5 min of stirring a liquid separated which on standing an additional 5 min crystallized. The solid was collected (63 36 g, 83.3% theory from (8)) by vacuum filtration and air dried TLC (eluent B) showed one UV absorbing spot. This material was found suitable for conversion to (13a) Recrystallization (acetone/benzene) gave mp, 188.5-190°.
IR (KBr) 5.75 μ (1739), 5.88 (1701 cm^{-1})

NMR ($CDCl_3$/DMSO d_6 δ 6.53 (s, 2H), 3 82 (s, 9H), 2 00-3.20 (m, 5H). M/e 326 (M^+)
Anal. Calcd for $C_{15}H_{18}O_8$: C, 55.21; H, 5.56, Found: C, 55.41, H, 5.67

6-Carbomethoxy-5,7-dimethoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid, (13a). Very finely divided diacid (12) (5.00 g) as obtained and without further purification from the previous step was stirred with polyphosphoric acid (350 g, practical grade, approximately $H_6P_4O_{13}$) at 60° for 3 hrs using a rotary evaporator as mixer. The yellow reaction mixture was brought to room temperature, treated with ice and water adequate to give 700 ml maintaining < 25°. The solution was allowed to stand overnight at 0-5°. Filtration and air drying gave 4.23 g (90% theory) (13a) Recrystallization (water) gave mp 170°. This was converted to ester (13b) for characterization
IR (KBr) 5 77 μ (1733) broad, 6.03 (1658 cm^{-1})
NMR ($CDCl_3$) δ 9 52 (s, 1H, broad), 6.57 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.77 (s, 3H), 3.19 (m, 3H), 2.85 (m, 2H).
Anal. Calcd for $C_{15}H_{16}O_7$: C, 58.44, H, 5.23, Found: C, 59.01; H, 5.42 See (13b).

Dimethyl-5,7-dimethoxy-4-oxo-1,2,3,4-tetrahydro-2,6-naphthalenedicarboxylate, (13b) Esterification of (13a) with diazomethane gave (13b), used for characterization.
Recrystallization (benzene/pet. ether) gave mp 150.5-151.5°.
UV ($CHCl_3$) λ max 240 nm (ε 13600), 273 nm (ε 16600)
IR (KBr) 5.80 μ (1724), 5.99 (1669 cm^{-1})
NMR ($CDCl_3$) δ 6 57 (s, 1H), 3 88 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.70 (s, 3H), 3.17 (m, 3H), 2 84 (m, 2H). M/e 322 (M^+)
Anal Calcd for $C_{16}H_{18}O_7$: C, 59 62, H, 5 63, Found: C, 59 72, H, 5 67.

Attempted Synthesis of Trimethyl-7-dimethoxy-4-oxo-1,2,3,4-tetrahydro-2,3,6-naphthalenetricarboxylate, (14) A solution of (13b) (.161 g, 5 mmol) in benzene (2 ml) was added dropwise (during 45 min) to a mixture of sodium hydride (.059 g, 1.4 mmol as a 57% oil dispersion), dimethyl carbonate (0.84 ml, 1 mmol), and benzene (5 ml) at reflux. After 1.5 hrs the reaction mixture was cooled and acidified (0°) with acetic acid (.5 ml). Water (.5 ml) was added and the solution extracted with benzene (3 x 5 ml). The collected benzene layers were washed, dried and evaporated to give quantitative recovery of starting material

6-Carbomethoxy-1,2-dihydro-5,7-dimethoxy-3-[(2,5-dimethoxyphenyl)methylene]-4(2H)-oxo-2-naphthalenecarboxylic Acid, (15a). A solution of sodium hydroxide (.46 g, 11.5 mmol) in water (8 ml) was added to a solution of 2,5-dimethoxybenzaldehyde (1.66 g, 10 mmol)+(13a) (1 54 g 5 mmol) in methanol (25 ml). The reaction was stirred for 5 days at 20-25°. The methanol was removed under reduced pressure to give a thick brown syrup which was taken up on water (15 ml) The aqueous mixture was extracted with benzene (3 x 50 ml) and then poured onto ice (25 g). Concentrated hydrochloric acid was carefully added with stirring until a brown gum separated from a clear yellow solution. The brown gum was removed and reserved while the solution was further acidified until it became cloudy. After 3 hrs at 20-25°, by-product (16) (.56 g) precipitated as long fine pale yellow needles and was collected by filtration. The brown gum was triturated with methanol to produce a pale yellow powder, (15a) (.62 g, 43%), which gave a single spot on TLC (eluent B) and a melting point greater than 230°.
IR (KBr) 2.93 μ (3413 cm^{-1}), 3 75 (2667), 5.79 (1727), 5.86 (1706), 5.92 (1689), 6.00 (1667).
This was converted to the ester (15b) for characterization.

Dimethyl-1,2-dihydro-5,7-dimethoxy-3-[(2,5-dimethoxyphenyl)methylene]-4(2H)-oxo-2,6-naphthalenedicarboxylate, (15b). A mixture of (15a) (42 g, .92 mmol), potassium carbonate (.17 g, 1.23 mmol), dimethyl sulfate (.11 ml, 1.16 mmol), and dry acetone (15 ml) was refluxed for 7 hrs. The filtered acetone solution gave upon evaporation and addition of methanol rhomboidal plates (.137 g, 85%) mp 170-172°.
UV (EtOH) λ max 206 nm (ε 46600), sh 246 nm, max 304 nm (ε 19600), sh 372 nm.
IR (KBr) 5.80 μ (1724), 6.00 (1667) cm^{-1})
NMR ($CDCl_3$) δ 8.02 (s, 1H), 6.89 (s, 3H), 6.55 (s, 1H), 4.17 (m, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 3.61 (s, 3H), 3 23 (m, 2H). M/e 470 (M^+)
Anal Calcd for $C_{25}H_{26}O_9$ C, 63.82, H, 5.57, Found: C, 63.46; H, 5.65

Methyl-5,12-dihydro-6-hydroxy-12-oxo-1,3,7,10-tetramethoxy-2-naphthacenecarboxylate, (17) A mixture of (15a) (.222 g) and sodium chloride (178 g) was finely pulverized and thoroughly stirred with polyphosphoric acid (25 g) at room temperature for 10 minutes The resulting mixture was stirred at 40-45° for 2 hrs using a rotary evaporator and cooled Ice (25 g) was added and the mixture stirred maintaining < 22° The phosphoric acid solution was shaken with cold ether 5°, 50 ml). The resulting precipitate was collected by vacuum filtration, washed with ice cold water and ether and dried under nitrogen to give golden yellow microneedles (.197 g, 92%); mp 272-275° dec. NOTE. This compound is oxygen-sensitive.
IR (KBr) 5 78 μ (1730 cm^{-1}), 6.02 μ (1661 cm^{-1}), 6.16 μ (1623 cm^{-1})
UV (EtOH) λ max 226 nm (ε 28500), 242 nm (19700), 263 nm (23300), 297 nm (21800), 410 nm (6200)
NMR (DMF-d_7) δ 11.02 (s, 1H), 8.60 (s, 1H), 7 20 (1H) unresolved, 6.98 (1H) unresolved, 6 93 (s, 1H), 4 37 (s, 2H), 4 14 (s, 3H), 4.02 (s, 3H), 3 91 (s, 3H), 3 58 (s, 6H, broad). M/e 438 (M^+)

Anal. Calcd for $C_{24}H_{22}O_8$. C, 65.75; H, 5.05, Found: C, 66 17; H, 4 72. For further mass spectral characterization, (17) was fully methylated (Me_2SO_4/K_2CO_3/acetone) to give material which exhibited M/e 466 (M^+) as would be expected for the dimethyl ether of (20).

ACKNOWLEDGEMENT

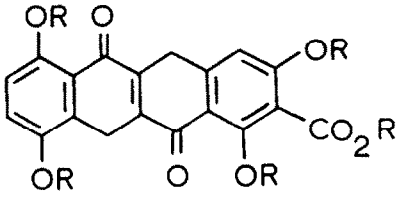
This work was supported in part by the National Science Foundation, Grant No CHE-76-05757 from the National Institutes of Health, and the American Cancer Society.

REFERENCES AND NOTES

1. The most recent synthesis of a tetracycline is that of oxytetracycline, which bears a hydroxyl at carbon 5 (for the numbering system see note 13 below) The synthesis of oxyTC is given in Reference 3.
2. In the regular TC series, syntheses currently proceed via anhydroTC. For recent work see Reference 4. A review of TC chemistry is given in Reference 5.
3. H. Muxfeldt, G. Haas, G. Hardtmann, G. F. Kathawala, J. B. Mooberry, and E. Vedejs, J. Amer Chem. Soc., 101, 689-701 (1979).
4. H. Muxfeldt, H. Dopp, J E. Kaufman, J. Schneider, P. E. Hansen, A Sasak, T. Geiser, Angew Chem. Int. Ed., 12, 497-499 (1973).
5. D. L. J. Clive, Quart Rev. Chem. Soc., 22, 435-456 (1968).
6. To our knowledge, only a very limited number of tetracycline analogs have been subjected to structure-activity studies See Reference 7.

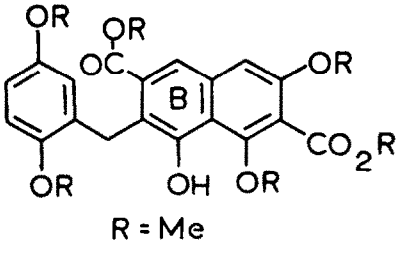
7. R K. Blackwood, A. R. English in D. Perlman (Ed.) "Structure-Activity Relationships Among The Semisynthetic Antibiotics", Academic, New York, pp 397-426 (1977).
8. Biosynthesis of 7-chloroTC has been studied in some detail. For a comprehensive review see References 9-10. The normal precursor of 7-chlorotetracycline is 6-methylpretetramide Presumably, the parent pretetramide is involved in biosyntheses of 6-demethyltetracyclines.
9. J. R. D. McCormick in D. Gottlieb; P. D. Shaw (Eds.), "Antibiotics. Vol. II. Biosynthesis", Springer, New York, pp 113-122 (1967).
10 C. R. Hutchinson, in D. Gottlieb, P. D. Shaw (Eds.), "Antibiotics Vol. IV. Biosynthesis", Springer, New York, pp 1-11 (1981)
11. J. R. D. McCormick, S Johnson, N. O Sjolander, J Amer. Chem Soc., 85, 1692-1694 (1963).
12 That is to say, strains which do not have a metabolic block at the methylation step. These strains are capable of synthesis of TC, which contain the 6-methyl group, de novo, however, when PTs are fed which lack this feature, the methyl group cannot be introduced, and 6-demethylTCs are obtained.
13. In both tetracyclines and pretetramides, the rings are designated A to D from right to left as shown. Pretetramides are derivatives of 2-naphthacenecarboxamide The hydroxyl groups, therefore, occur at positions 1,3,10,11, and 12.
14. J. R D. McCormick, S. Johnson, N. O. Sjolander, J. Amer. Chem. Soc., 85, 1692-1694 (1963).
15. For the ring nomenclature, see note 13.
16. R. K. Blackwood, A. R. English, in D. Perlman (Ed.) "Structure-Activity Relationships Among The Semisynthetic Antibiotics", Academic, New York, pp 397-426 (1977).
17 Syntheses of pretetramide and 6-methylpretetramide are given in the three following references. In the first of these, the ring D synthon is 3-hydroxyphthalic anhydride, for which analogs are by no means easily synthesized. The second synthesis starts with ring D and builds on the other rings sequentially. The third synthesis, while convergent, involves a considerable number of steps. The ring D synthon would be a derivative of 1,5-naphthalenediol, for which analogs satisfactory for this synthesis are not readily obtained.
18. J. R. D. McCormick, J. Reichenthal, S Johnson, N. O. Sjolander, J. Amer. Chem. Soc., 85, 1694-1695 (1963).
19. J. A. Murphy, J. Staunton, J. Chem. Soc. Chem. Commun., 1166-1167 (1979).
20. D H. R. Barton, P. D. Magnus, T. Hase, J. Chem. Soc., (C), 2215-2225 (1971). See note 17 above.
21 For the numbering system, see note 13 above.
22. J. R D McCormick, J. Reichenthal, S. Johnson, N. O. Sjolander, J Amer. Chem Soc , 85, 1694-1695 (1963).
23. D. H. R. Barton, P. D. Magnus, T. Hase, J Chem. Soc , (C), 2215-2225 (1971). See note 17 above.
24. J. A. Murphy, J. Staunton, J. Chem. Soc Chem Commun , 1166-1167 (1979), D H R. Barton, P. D. Magnus, T Hase, J. Chem Soc., (C), 2215-2225 (1971). See note 17 above
25. The Grignard approach was successfully used in the synthesis of islandicin described in the following reference.
26. M Braun, Angew. Chem Int Ed., 17, 945-947 (1978).
27 A Robertson, R. Robinson, J. Chem Soc , 2196-2206 (1927).
28. The dimethoxy ester 6b was reported in the above reference. We found the yield and purity to be improved via use of K_2CO_3 and Me_2SO_4 in acetone.
29. D H. R. Barton, P. D. Magnus, T. Hase, J Chem. Soc., (C), 2215-2225 (1971) See note 17 above.
30. Literature precedent suggests that the tetralone could be converted to the α-naphthol catalytically (Reference 31), or that the tetralone could be brominated (Reference 32) and the bromotetralone converted to an α-naphthol using sodium acetate (Reference 33) or N,N-dimethylaniline (Reference 32)
31 R P Linstead, K. O. A. Michaelis, J. Chem Soc , 1134-1139 (1940).
32. F. Krollpfeiffer, A. Muller, Berichte, 68, 1169-1177 (1935).
33. F. Straus, O. Bernoully, P. Mautner, Annalen der Chemie, 444, 165-194 (1925).
34. As a model, we prepared 1,4-dihydroxy-2,3-naphthalenedicarboxylic acid ethyl ester according to the following reference, and converted it easily to the corresponding anhydride
35. A. H. Hohmeyer, U. S. Patent No. 2,415,884, Feb. 18, 1947.
36. We would expect the beta-ketoester (14) to give a positive test because of enolization. A typical experiment using NaH in benzene is given in the experimental section Quenching studies with D_2O did not indicate exchange of the alpha-hydrogens of the tetralone under these conditions. In further quenching studies, a good exchange of the alpha-hydrogen (0.6 eq.) was achieved with lithium diisopropylamide in THF after only 2 min at ambient temperature; however, attempts to react the enolate with methyl chloroformate still resulted in recovery of almost pure starting material. Trace amounts of products were detected, but none had a positive $FeCl_3$ reaction Later experiments indicated that the enolate of the tetralone function in carboxylic acid (13a) must form under relatively mild conditions (MeO- in MeOH). Satisfactory reactions were observed for the enolate and benzaldehyde or 2,5-dimethoxybenzaldehyde, but when we attempted to use this base/solvent combination on the corresponding tetralone ester (13b) to give a reaction with dimethyl carbonate, again essentially pure starting material was recovered, even after 72 hrs of reflux
37. At room temperature in aqueous methanolic solution, benzaldehyde appeared to be mostly consumed after 15 min. As the parent benzylidene derivative of tetralone acid (13a) would not be a good candidate for cyclization to a PT type, 2,5-dimethoxybenzaldehyde was chosen as the synthon.

38. Although one could carry out the condensation using methoxide catalysis in methanol, the condensation step itself generates water, which would lead to hydroxide formation and ester saponification, which would give a mixture of products
39. Identified by TLC, IR and melting point.
40. The ring A ester reacts so slowly that a selective saponification of (13b) to (13a) is quite feasible. This process may be used to convert the benzylidene tetralone diester (16b) to the monocarboxylic acid (16a).
41. The usual result of the aldol condensation is to give an E-alkene. Although (16a-b) appear crowded in the planar representation here, the aliphatic acid group of (16a) e.g may rotate in addition to the group being out of plane due to the sp^3 hybridization of the attached carbon. Data on simple aldol condensations is given in the following reference. Ease of cyclization also supports the E- form
42. H. O. House, "Modern Synthetic Reactions", Second Edition, Benjamin, Menlo Park, CA, 635, (1972).
43. Conversion of enedione (19) to dihydronaphthacenone (18) is difficult to conceive of without passing through a second enedione



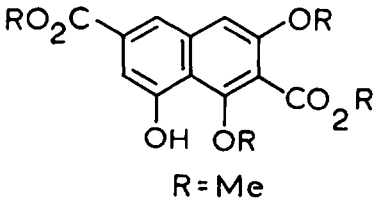
which would be expected to yield a mixture of (17) and (18), whereas only one of these was obtained.

44. The naphthacenone (20) contains a phenolic function in ring B as well as ring C, precluding any selective oxidation of ring C While dihydronaphthacenone (17) could be oxidized in ring C, avoidance of enolization of ring B (and subsequent oxidation) would appear to be a significant problem. The best approach appeared to be via isomerization of the benzylic tetralone system (15b) to the following naphthol derivative.



The naphthol of ring B could be methylated prior to cyclization to stabilize it against subsequent oxidation.
When the ester (15b) was refluxed in decalin with 30% Pd/C, after an hour, only slight conversion was indicated by TLC. After 10 days at these vigorous conditions, starting material had disappeared, but a mixture of products was observed The latter, a series of poorly resolved bands at R_f higher than the starting material in eluent B, exhibited positive $FeCl_3$ tests.
Treatment of ester (15b) with $RhCl_3$ in EtOH/$CHCl_3$ (1:1) at 50° for 16 hrs gave no significant isomerization. Refluxing ester (15b) with Et_3N after 46 hrs gave only slight conversion; likewise, tBuOK in tBuOH after 16 hrs reflux gave no phenolic material. Although ester (15b) reacted rapidly with NaH in DMF at room temperature, a mixture of many components was obtained upon acidification as evidenced by TLC.

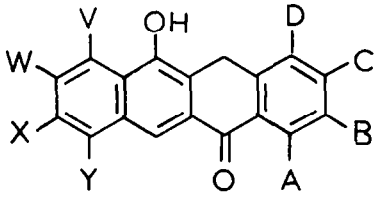
45. As described in Note 30, tetralone synthons have been aromatized either directly or via halogenation/dehydrohalogenation Such procedures applied to the tetralone ester (13b) should yield the following naphthol.



R=Me

Introduction of a C_1 unit at the position indicated by the arrow could be achieved by the classical technique of allylation of the naphthol function, followed by Claisen rearrangement, isomerization of the resultant C-allyl group, and subsequent ozonolysis.

46. Specifically, one should be able to produce dihydronaphthacenones of the general type shown



provided groups A and C allow initial tetralone formation, and also provided that groups V and X allow cyclization of the intermediate benzylidene tetralone

47. A variety of different benzaldehydes are either commercially available or else easily synthesized. Simpler analogs of our tetralone carboxylic acid (13a) have also been prepared by cyclization of benzylsuccinic acids, but these latter compounds are most readily synthesized via the Stobbe condensation of a benzaldehyde derivative with succinate, followed by reduction of the intermediate benzylidene succinic acid derivative. The following references are pertinent The first, Reference 48, is a general one. Reference 49 describes a 5,8-dimethoxy derivative used as an anthracyclinone synthon. Reference 50 describes a 1-methyl-5-chloro-8-methoxy analog which was used in anhydroaureamycin synthesis.

48. E C. Horning, G N Walker, J Amer. Chem Soc., 74, 5147-5151 (1952)
49. C. M. Wong, R. Schwenk, D. Popien, and T -L. Ho, Can. J. Chem., 51, 466-467 (1973)
50. H Muxfeldt, E Jacobs, K. Uhlig, Chem. Ber , 95, 2901-2911 (1962) The simpler tetralone lacking the 1-methyl was also prepared

51. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn Melting points were observed on a Kofler Micro Hotstage and are corrected.
NMR spectra were obtained using the Varian XL-100-15 and the Perkin-Elmer R32 spectrometers using TMS as the internal reference standard. IR spectra were obtained on the Beckman IR5A and the Perkin Elmer 621 spectrometers. Solid IR samples were nominally 1% solutions in potassium bromide and were prepared with a Wilks mini-press; liquid samples were taken neat on 25 mm sodium chloride windows. The Cary 14 spectrometer was used to obtain visible and ultraviolet (UV) spectra. Mass spectra were taken on the Hitachi-Perkin-Elmer RMU 6H instrument by Messrs Michael Frey, Gordon Hanson, and Richard Dunphy of Temple University. All reactions were run under high purity, dry-grade nitrogen unless otherwise specified.

52 D. H R. Barton, P. D. Magnus, T. Hase, J. Chem Soc (C), 2215-2225 (1971) See note 17 above.
53. A Robertson, R. Robinson, J Chem Soc , 2196-2206 (1927).
54 A. Robertson, R. Robinson, J Chem Soc , 2196-2206 (1927)

55. The acids had very poor solubility characteristics in all common NMR solvents, and were converted to esters (CH_2N_2) for NMR characterization.