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Cycloadditions of 4-Pyrones. An Approach to Colchicine

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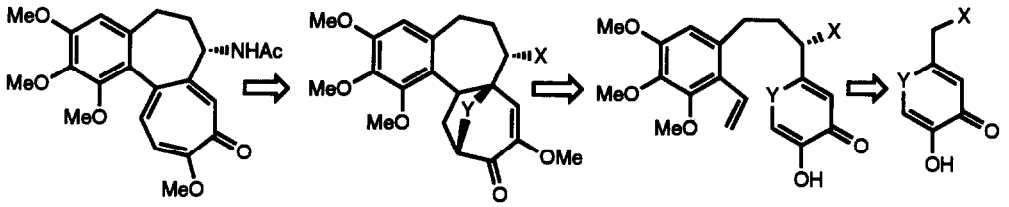
Abstract: *The 4-pyrone, [5-acetoxy-4-oxo-4H-pyran-2-yl]carbonyl chloride was coupled with the malonate anion of bis(2,2,2-trichloroethyl) 2-ethenyl-3,4,5-trimethoxybenzylpropanedioate and analogs thereof. These adducts then underwent intramolecular thermal cyclizations (61-100% yield) to form the two fused seven member rings of the carbon skeleton of colchicine. The malonate moiety was deprotected and decarboxylated quantitatively to provide the desired ring system which contained a bridging ether, from C7a to C11 in the C ring, and a ketone at the 7 position. Removal of the bridging ether as H2O would yield the desired tropolone. Our attempts to remove the ether bridge were unsuccessful.*

INTRODUCTION

Colchicine has been a target for synthetic chemists for the last thirty years. Despite at least eleven distinct routes to colchicine, none of these permit ready formation of modified A-ring analogs.[1] In fact most of the SAR work on colchicine binding to tubulin has been completed on degradation products from the natural material.[2]

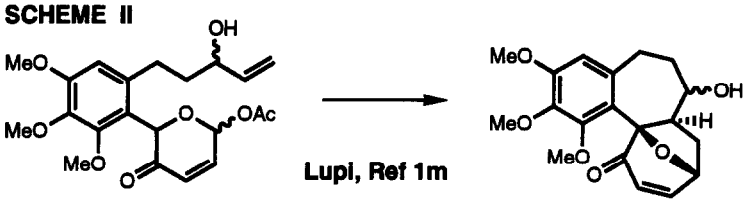
We anticipated that a short synthesis of colchicine would permit the preparation of analogs for such an SAR study. One strategy, outlined in Scheme I, utilizes a [5C + 2C] pyrone cycloaddition as a key step. At the onset of this work quinones[3] such as perezone,[4] oxidopyrylium betaines,[5] oxidopyridinium betaines[6] and pyrones[7] had been reported to undergo this reaction.[8] Few of these examples were intramolecular. Concurrent with our work, the study of these cycloadditions has continued using quinones[9] and pyrylium salts[10] to create several stereocenters in a rigid highly constrained moiety. Although manipulation of these cycloadducts has proven to be a challenge,[11-13] Sammes,[14] Wender,[15] and Williams[16] have used this reaction for sesquiterpene, ingenane, secodolastane synthesis respectively. Lupi, et al.[1m] have reported the cyclization of an

SCHEME I



oxopyrylium salt to give a colchicine precursor (Scheme II). This continued interest in the formation and manipulation of such cycloadducts, prompt us to report the full details of intramolecular pyrone cycloadditions directed toward the synthesis of colchicine and our unsuccessful attempts to convert the adducts into tropolones.[17]

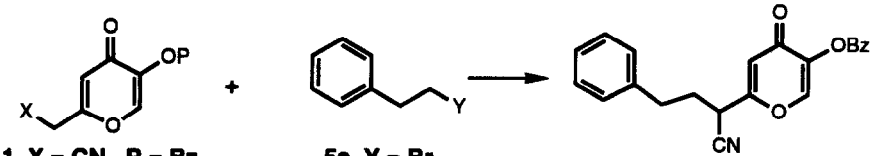
SCHEME II



SYNTHESIS OF STYRYL SUBSTITUTED PYRONES

Initially we attempted to alkylate a 5-substituted-3-hydroxy-4-pyrone with an appropriate halide (Scheme III).[18] This approach used an available pyrone, kojic acid[19] and incorporated an X-group which could be transformed into an acetamido function.[1e] Four pyrone derivatives (1,2,3,4) were examined with several model phenethyl electrophiles (5) without success.[20] Bromide 5a and 1 afforded 6 in 20% yield accompanied by an equivalent amount of dialkylation. Three problems with this alkylation approach are: 1) the electrophile is homoallylic and prone to elimination; 2) the nucleophile is at least as stabilized as a malonate and 3) the pyrone is an excellent Michael acceptor. These problems might be circumvented by completing an aldol-type reaction. Surprisingly, treatment of 1 with phenylacetaldehyde and triethylamine in tetrahydrofuran (THF) yielded the desired 6 in 95% yield.

SCHEME III



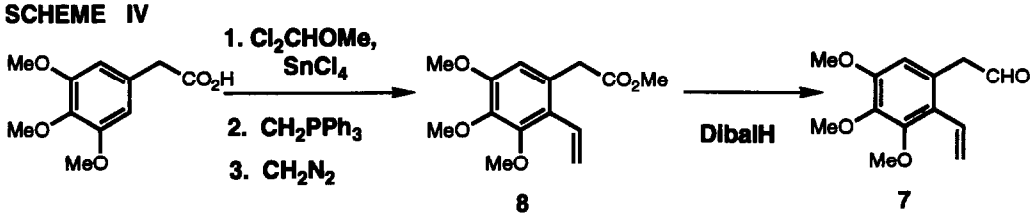
1 X = CN, P = Bz
2 X = CN, P = H
3 X = SO_2Ph, P = Bz
4 X = SO_2Ph, P = H

5a Y = Br
5b Y = I
5c Y = OMes
5d Y = OTf

6

With this model reaction completed, we focused attention on aldehyde 7, the synthesis of which was finally accomplished in the following fashion (Scheme IV). 3,4,5-Trimethoxyphenylacetic acid was reacted with dichloromethyl methyl ether and stannic chloride to form the aldehyde in 95% yield.[21] Wittig olefination in refluxing THF[22] followed by diazomethane treatment afforded ester 8 in 68% yield. Diisobutylaluminum hydride reduction produced the desired aldehyde in 99% yield. Aldehyde 7 was very stable despite being an electron-rich styrene. Treatment of 1 with 7 under a variety of conditions afforded only the aldol dimer of 7, compound 9, with no trace of the desired adduct. The mechanism for the formation of 6 and the failure of 7 to undergo an analogous condensation remain unclear.

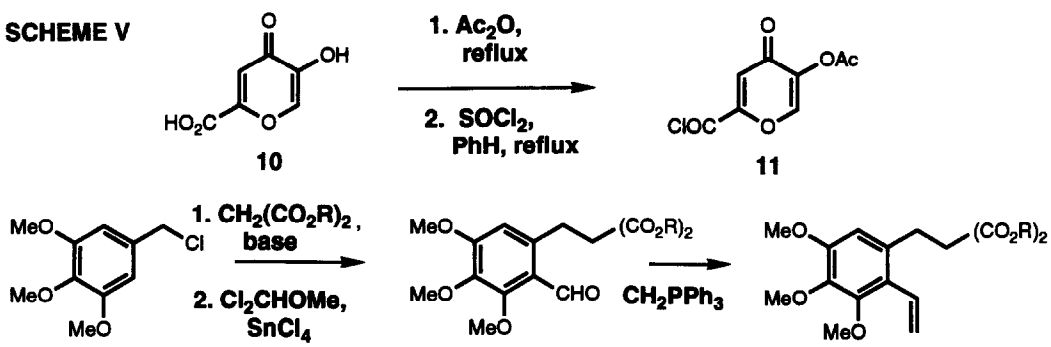
SCHEME IV



8 7

At this time the condensation strategy was reversed. A pyrone containing an electrophile is easily derived from kojic or comenic acid. However, the electrophilic carbon must retain a group which can be converted to an amine. The styrene portion must possess a nucleophile which finishes as a methylene unit in colchicine. To meet these requirements we anticipated acylating a styryl malonate with comenoyl chloride.[23] Cyclization and decarboxylation should provide the requisite intermediate with a ketone available for conversion to the amino group.[24] Previous work indicated that acyl substituted pyrones would undergo this cycloaddition.[8] We felt the carbonyl could be used to assist the formation of the tropolone ring. This strategy ultimately provided several cycloadducts.

SCHEME V



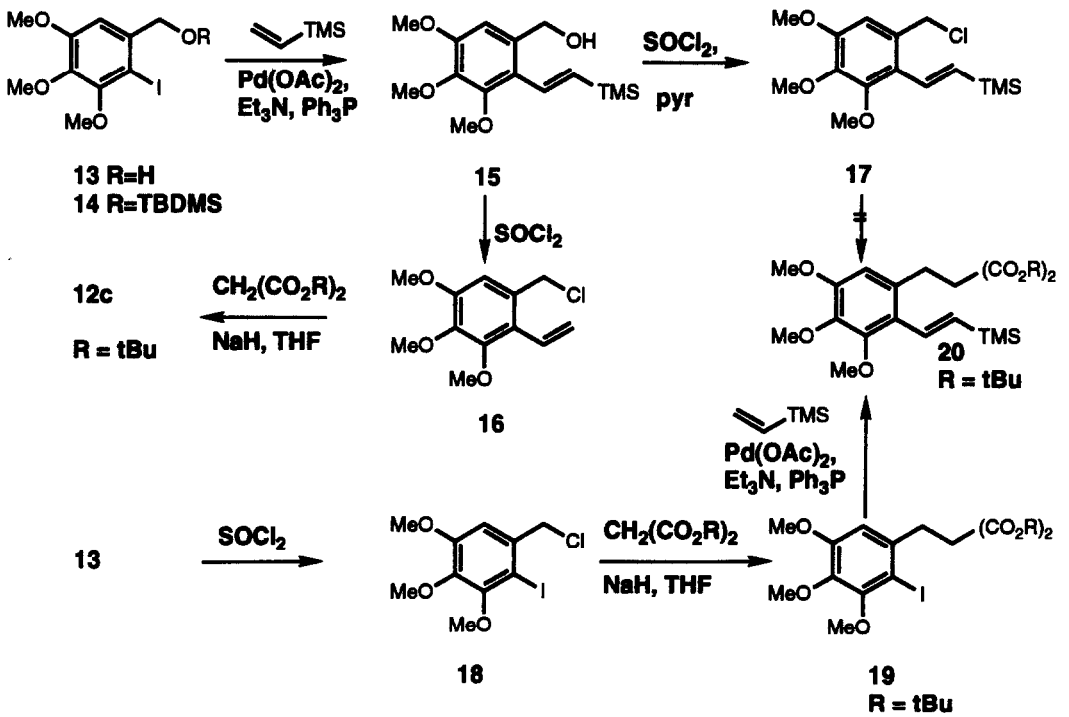
10 11

12a R = Me
12b R = CH_2CCl_3

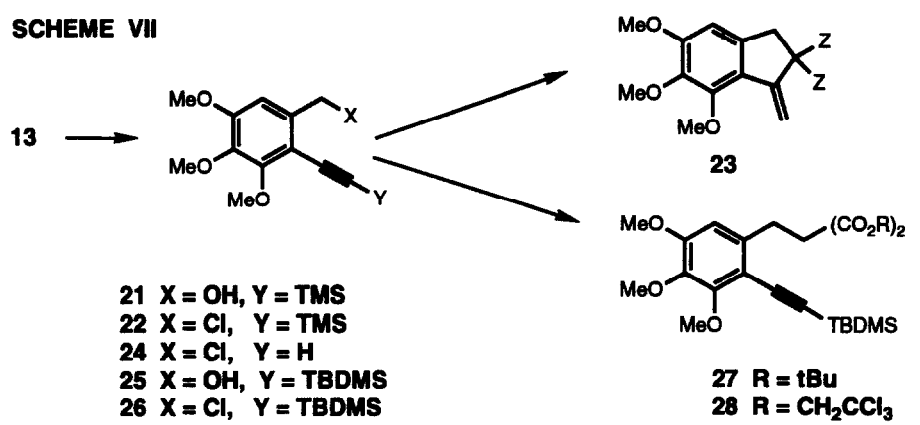
The preparation of the pyrone portion followed simply from crude comenic acid 10.[19] Comenic acid was acetylated with acetic anhydride and acetic acid.[25] This crude material was recrystallized from acetonitrile. Treatment of this acetoxy acid with thionyl chloride in benzene yielded the desired acid chloride 11.

Two general routes to styryl malonates were developed and are illustrated in Schemes V–VII. The first route (Scheme V) started with 3,4,5-trimethoxybenzyl chloride.[26] Malonate displacement and formulation (dichloromethyl methyl/ether stannic chloride) afforded the desired aldehyde in greater than 63% yield. Treatment of this aldehyde with two equivalents of ylide provided the desired olefin 12 in at least 66% yield. This sequence worked well for dimethyl malonate and bis(trichloroethyl) malonate.

SCHEME VI



SCHEME VII



21 X = OH, Y = TMS
22 X = Cl, Y = TMS
24 X = Cl, Y = H
25 X = OH, Y = TBDMS
26 X = Cl, Y = TBDMS

27 R = tBu
28 R = CH_2CCl_3

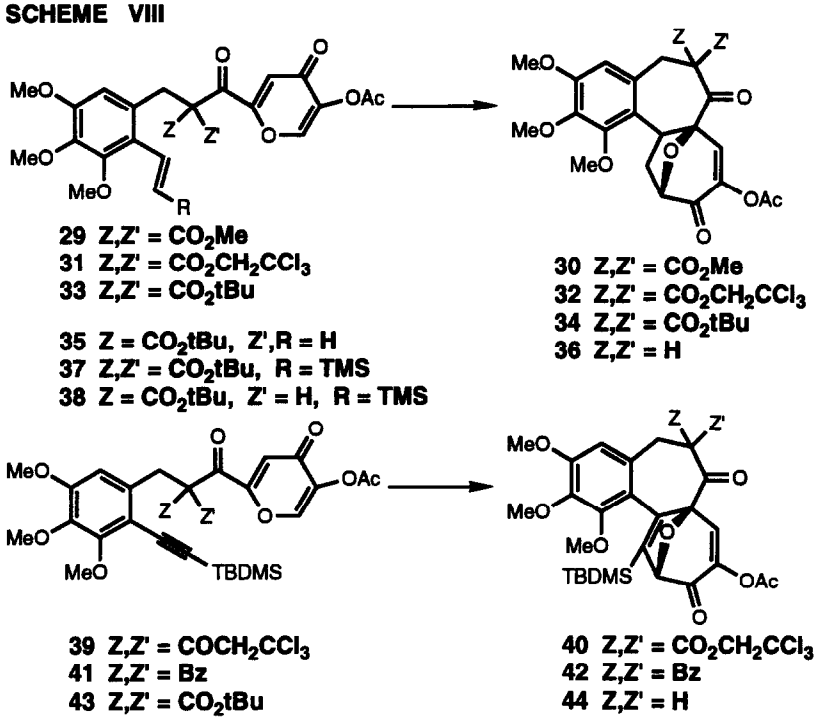
Alternatively, as illustrated in Scheme VI, gallic acid trimethylether was converted into 2-iodo-3,4,5-trimethoxybenzyl alcohol 13 by the method of Ziegler.[27] Conversion of 13 into 17, 22 or 26 was affected by treatment with silyl olefin/acetylene, palladium (II) acetate, triphenylphosphine and triethyl amine as previously reported.[28] Conversion of 15, 19 or 25 into malonates 27 and 28 posed some unique problems. We anticipated protio-desilylation of 15 during conversion into chloride 17. In the presence of pyridine, thionyl chloride treatment of 15 gave silyl styrene 17, however in the absence of pyridine 16 was obtained. Malonate

displacement on styrene 17 could not be affected under numerous conditions. Alternatively, iodoalcohol 13 could be converted into chloride 18 as illustrated in Scheme VI. Transformation of 18 into iodomalonate 19 proceeded smoothly. Coupling of this iodomalonate with trimethylsilylethylene yielded the desired trimethylsilylmalonates 20.

To make the acetylenic malonates, alcohol 13 was converted into 22 and 26 by palladium coupling and thionyl chloride treatment (Scheme VII). Treatment of 22 with malonate gave indane 23 in high yield. The parent acetylene 24 also provided 23. Hindered silyl acetylene 26 was prepared to retard this presumed initial desilylation (22 to 24). Displacement of the chloride on hindered silane 26 yielded the desired malonates 27 and 28 which were used without isolation.

Coupling of all of the malonates 12, 17, 27, and 28 with 11 was effected by sodium hydride in THF. The adducts 29, 31, 31, 39, 41, and 43 could be purified but were often carried on to cyclization without isolation. The yields of this process ranged between 50% and 85%.

SCHEME VIII



29 Z,Z' = CO_2Me
31 Z,Z' = $CO_2CH_2CCl_3$
33 Z,Z' = CO_2tBu

35 Z = CO_2tBu, Z',R = H
37 Z,Z' = CO_2tBu, R = TMS
38 Z = CO_2tBu, Z' = H, R = TMS

30 Z,Z' = CO_2Me
32 Z,Z' = $CO_2CH_2CCl_3$
34 Z,Z' = CO_2tBu
36 Z,Z' = H

39 Z,Z' = $COCH_2CCl_3$
41 Z,Z' = Bz
43 Z,Z' = CO_2tBu

40 Z,Z' = $CO_2CH_2CCl_3$
42 Z,Z' = Bz
44 Z,Z' = H

CYCLIZATION REACTIONS

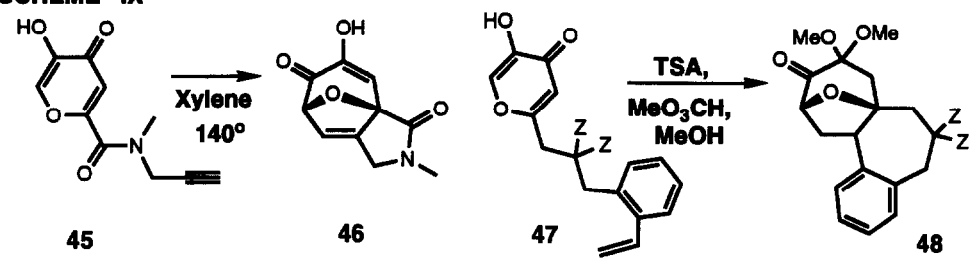
The initial cyclization reaction of 29 to 30 occurred under conditions designed to induce ester hydrolysis (sodium iodide/acetic acid/acetic anhydride at reflux). We were surprised to find 30 amid the products (Scheme IX). We were unable to decarboxylate either 29 or 30 under a range of conditions. Instead, the deacylation reaction predominated. Therefore, alternative esters were prepared. We initially prepared the bis-ß-trichloroethyl and bis-t-butyl esters and later made the dibenzyl malonate derivatives. Compounds 31, 33,

and the dibenzyl analog of 31 cyclized smoothly in refluxing xylenes in 2–4 h. This process did not require acid as often required.8,[17,25] The t-butyl ester (33) underwent decarboxylation in competition with cyclization under cyclization conditions. Thus, heating 33 in refluxing xylene yielded a mixture of compounds including 34, 35, 36 and other uncyclized materials which were partially or completely decarboxylated.

To explore alternative de-oxygenation reactions vinyl silanes 37 and 38 were prepared for cyclization. Both esters 37 and 38 failed to yield any cyclized product both for reasons outlined above and the presumably due to increased steric requirements of the vinyl silane.

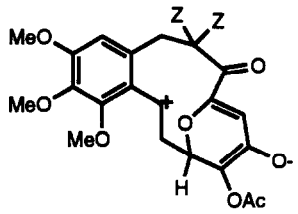
Acetylenes, such as 39, 41, and 43, should be less sterically hindered than 37 and thus might be appropriate candidates for cyclization. Indeed, both the trichloroethylester 39 and the benzyl ester 41 gave excellent yields of 40 and 42 respectively under conditions comparable to the reaction of 31. The di-t-butyl ester 43 afforded some of the desired analog of 44 amid numerous other products.

SCHEME IX



45 46 47 48

Related cyclizations illustrated in Scheme IX[8] proceed more slowly than these. Furthermore, the acetates of 45 and 47 did not cyclize, and the acid conditions required for 47 to 48 were ineffective for either 45 or 29. The enhanced cyclization rate of 29 can be rationalized by the presence of geminal esters (Thorpe-Ingold effect[29,30]) and the keto group (sp^2 center). If this process is not concerted, then a pyrone based intermediate should be electron deficient and made more reactive by an adjacent electron withdrawing keto group. These assumptions plus the increased electrophilicity of styrene 29 (vs. 47) are consistent with 49 rather than other possible intermadiates.

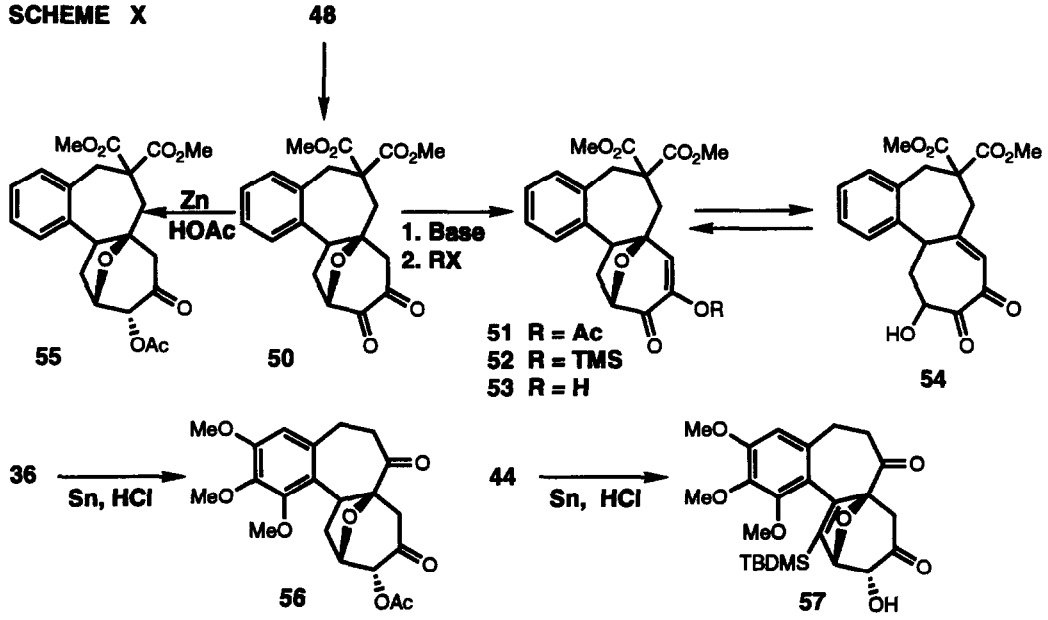


49

The stereochemistry of adducts 30, 32, 34 or 36 has not been determined. NMR experiments available at the time of this work were ambiguous. None of these compounds have been crystalline prohibiting x-ray analysis. Pipitzol and related intramolecular cyclizations proceed via an exo-transition state.[3] The endo transition state of Diels-Alder reactions[31] and intermolecular quinone acetal reactions[3] is sterically inaccessible to the pipitzol-type reactions. Molecular models indicate that either transition state is accessible. We have assigned the indicated stereochemistry for an endo transition state based on adducts based upon the exclusive trans products obtained by Lupi[1m] and Williams[16] in closely related systems.

MANIPULATION OF ADDUCTS: ATTEMPTED DE-OXYGENATION

Conversion of the adducts 30, 32 or 34 into 36 and 40 into 44 presented an initial problem which necessitated the preparation of several different esters. The ester of choice must withstand a range of reaction conditions used in its preparation and must then be removed under mild conditions which leave the sensitive ketone of the ß-tricarbonyl system intact. Eventually, we found that the ß-trichloroethyl group could be removed selectively using the zinc-copper couple in anhydrous THF with two equivalents of water.[32] We were unable to produce all of the desired cyclization precursors with this ester and could not use the efficient pathway outlined in Scheme VI. The di-t-butyl ester was readily prepared but failed to undergo cyclization as desired. We briefly investigated the dibenzyl ester. Preparation and cyclization of this compound proceeded as expected. Preliminary attempts at hydrogenolysis of 42 using palladium on carbon and atmospheric hydrogen afforded substantial amounts of over-reduction.



The second major challenge in this reaction sequence is the elimination of the bridging atom. Noyori, *et al*[33] solved this problem in a system related to 36 by reducing the olefin, effecting the bis-dehydration and reoxidizing the dihydro species. After our work was completed, Shore[11] reported a number of failures in related aromatizations. Sammes[14] developed a technique for reductive removal of oxygen from a 7-oxabicyclo {2.2.1] heptane. Katritzky,[34] Chapman,[35] and Roberts[36] have reported methods for nitrogen removal in related sytems. Buchi[37] has reported a process for CO elimination.

Model compound 48 was chosen for initial investigations. Hydrolysis of the ketal (methanol/0.1 N hydrochloric acid/reflux/ 3 h) afforded diketone 50 (Scheme X). We were unable to effect elimination of water from under a wide range of base conditions. We could trap the enol/enolate from 50 to afford acetate 51 or silane 52.The dihedral angle between the enolate nucleophile and the oxygen leaving group of 50 is between 120° and 150° rather than the normal 180° for E-2 elimination. Other elimination reactions[38] and S_N2 reactions[39] proceed smoothly with less stringent geometrical requirements. Alternatively, the equilibrium between 53 and 54 and their respective anions could favor 54. Vigorous base conditions (strong base/elevated temperature/long reaction times) lead to complete decomposition.

To circumvent the geometrical requirements we anticipated stabilizing the enolate with an exo group illustrated by the X-moiety in Scheme I. Unfortunately, this precursor was not synthetically available. We then assumed that a nitrogen stabilized anion from an oxime or hydrazone would be sufficient to open the bridging system. We were unable to prepare the oxime, hydrazone, tosyl hydrazone or semicarbazone of 36 without substantial decomposition as judged by loss of bridgehead and olefin resonances in the NMR spectra.

To facilitate the ether cleavage, acid catalysis was investigated. Coordination with Lewis acid or protonation of the ether oxygen would make it a better leaving group diminishing the geometrical requirements. Acid catalysis failed to effect any reaction or lead to complete decomposition. This process requires the intermediacy of a carbonium ion adjacent to a carbonyl. The expected product and intermediates such as 54 are probably less stable to acid than the precursor such as 33 or 50.

Dissolving metal reductions have often been used to effect α-reductions and may not have the same steric requirements as carbanion eliminations.[40] This reduced product could be dehydrated and reoxidized to give the tropolone. Treatment of 50 with zinc and acetic acid afforded 55 in greater than 90% yield. Treatment of 36 with tin and hydrochloric acid gave 56 and 44 provided 57. Stronger acid with a reducing agent lead to decomposition. Treatment of 56 under a variety of acidic conditions lead only to decomposition products.

Finally, several reagents used to convert epoxides into olefins or to transform 7-oxabicyclo [2.2.1] hept-2-enes into cyclohexadienes or benzenes were investigated. Compound 56 was treated with these reagents including lithium naphthalide,[41] low valent titanium,[42] phosphines,[43] phosphites, palladium (II)[44] and diiron nonacarbonyl.[45] All eventually provided decomposition products without any evidence of tropolones.

We have demonstrated that the cyclo-addition using a pyrone and an olefin can yield bicyclic intermediates of the colchicine type. We have been unable to remove the oxygen atom. An effective synthesis of colchicine by this route requires the unknown thiacomenic acid or the appropriate pyridone.46

EXPERIMENTAL[47]

Flash chromatography was executed on silica gel 60. The silica was packed in hexanes, the sample introduced and eluted with 100% hexanes, 75:25 hexanes:ether, 50:50 hexanes:ether, 25:75 hexanes:ether, and 100% ether each in 200 ml portions. The effluent was collected in a vacuum flask using house vacuum (20-25 mm Hg). Sodium hydride (NaH) was washed with hexanes immediately before use. The weight of NaH recorded was a 50% oil before the hexanes wash. The [4-oxo-5-(phenylmethoxy)-4H-pyran-2-yl]acetonitrile was made by the method of Share.[18] Compounds 14, 15, 20, 21 and 25 have been reported.[28]

Two standard work-up preceedures were used. ***Procedure A***: The reaction mixture was quenched with 10% HCl and extracted with three portions of ether or methylene chloride. The organic extracts were combined and washed with $NaHCO_3$. The organic layer was dried and the solvent was removed under reduced pressure. ***Procedure B***: The mixture was treated with aqueous $NaHCO_3$ and extracted with methylene chloride (3 times). The pooled organics were dried and the solvent was removed under reduced pressure.

4-Phenyl-2-[4-oxo-5-(phenylmethoxy)-4H-pyranyl]butyronitrile (6). Sodium hydride 0.34 g (7.1×10^{-3} mol, 370M%) was suspended in 2.0 ml HMPA at rt. The nitrile (1, 0.0459 g, 1.90×10^{-4} mol, 100M%) was added to the HMPA suspension and stirred for 15 min before 0.50 ml (3.66 x 10-3 mol, 190%M) of 2-bromoethylbenzene was added. The reaction mixture was stirred at rt for 5.5 h and processed by procedure A followed by flash chromatography to give the dialkylated product (0.0177 g, 21% yield, 50:50 hexanes:ether fxn) and the monoalkylated product 6 (0.0203 g, 31% yield, 25:75 hexanes:ether and 100% ether fxn): IR 3030, 2930, 1640, 1452, 1210; 1H NMR 2.23 (m, 2H), 2.83 (bt, J~7 Hz, 2H), 3.59 (t, J~7H, 1H), 5.07 (s, 2H), 6.43 (s, 1H), 7.1-7.4 (m, 10H), 7.52 (s, 1H); MS m/z 345 (M+).

Alternatively, a solution containing 1 (0.0425 g, 1.76 x 10^{-4} mol, 100M%), 0.05 ml (4 x 10^{-4} mol, 240M%) of phenylacetaldehyde and 0.30 ml (2.15 x 10^{-3} mol, 1200M%) of triethylamine in 10 ml THF was heated at reflux for 13 h. The solution eventually turned from yellow to bright red over the course of the reaction. The product 6 was isolated in 95 % yeild (0.057 g, 25:75 hexanes:ether and 100% ether fxns).

Methyl 2-Ethenyl-3,4,5-trimethoxyphenylacetate (8). Tin tetrachloride (0.52 ml, 1.77 x 10^{-2} mol, 250M%) was added to a 0°C solution containing 0.40 g (1.77 x 10^{-3} mol, 100M%) of 3,4,5-trimethoxyphenylacetic acid, and 1.60 ml (1.77 x 10^{-2} mol, 110M%) of dichloromethyl methyl ether (DCME) in 5 ml CH_2Cl_2. The reaction solution turned orange on addition of the $SnCl_4$. The reaction was kept at ~0°C for 20 min, then warmed to rt and stirred for 2 h before it was quenched with water and processed by procedure B to afford 0.43 g (95% yield) of the acid: ^{1}H NMR 3.87 (s, 2H), 3.92 (S, 6H), 4.00 (s, 3H), 6.55 (s, 1H), 10.38 (s, 1H); MS m/z 254 (M+).

NaH (0.50 g, 1.04 x 10^{-2} mol, 118M%) was added to 2.2488 g (8.55 x 10-3 mol, 100M%) of the aldehyde in 40 mL THF at rt. A THF solution of the ylide, prepared from methyltriphenyl phosphonium bromide and n-BuLi was added to the acid anion solution after 15 min. The reaction was stirred at rt for 15 min, then heated to reflux for 5 h. The reaction mixture was then cooled, acidified with 10% HCl and extracted with ether. The ether layer was treated with excess diazomethane. The excess diazomethane was evaporated under a stream of N_2. The ether solution was processed by procedure B and then filtered through silica eluting with 50:50 hexanes:ether to afford 1.61 g (68.4% yield) of 8: IR 2940, 2840, 1735, 1595, 1490, 1455, 1320, 1240, 1195, 1125; ^{1}H NMR d 3.65 (s, 2H), 3.68 (s, 3H), 3.80 (S, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 5.37-5.64 (m, 2H), 6.48-6.82 (m, 1H), 6.57 (s, 1H); MS m/z 266 (M+).

2-Ethenyl-3,4,5-trimethoxyphenylacetaldehyde (7). Diisobutylaluminum hydride (1.85 ml 1.85 x 10^{-3} mol, 150M%) was added to 0.3278 g (1.23 x 10-3 mol, 100M%) of ester 8 in 15 ml dry PhMe at -60°C. The reaction was allowed to stir at -60°C for 1 h. The reaction was quenched while cold with H_2O and processed by a procedure A workup. The reaction gave 0.2871 g (99% yield) of 7: IR 2940, 2840, 1720, 1595, 1490, 1455, 1405, 1335, 1240, 1195; ^{1}H NMR 3.72 (d, J~2 Hz, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 5.32-5.56 (m, 2H), 6.42-6.77 (m, 1H), 6.50 (s, 1H), 9.73 (t, J=2 Hz, 1H); MS m/z 236 (M+).

(5-Acetoxy-4-oxo-4H-pyran-2-yl)carbonyl Chloride (11). Comenic acid (10, 10.00 g, 6.41 x 10^{-2} mol, 100M%) was suspended in 0.5 ml glacial HOAc and 30 ml Ac_2O. The mixture was heated to reflux for 26 h, cooled, placed in ~150 ml ether and filtered. The crude brown product was washed with 100 ml ether then placed in a Soxhlet extraction thimble on top of ~1 g celite and ~1 g activated charcoal. The product was extracted with acetonitrile in a Soxhlet extractor: Mp 201-204°C; ^{1}H NMR (2.30, s, 3H), 7.13 (s, 1H), 8.10 (s, 1H).

The acid (0.92 g, 4.62 x 10^{-3} mol, 100M%) was placed in ~20 ml PhH. Thionyl chloride (0.49 ml, 6.85 x 10-3 mol, 150M%) and 10 drops of DMF were added and the mixture was heated to reflux. After ~20 min all of the acid had reacted as indicated by a homogeneous solution. After the reaction was complete most of the PhH was removed by distillation at atmospheric pressure. Then additional PhH was added and the distillation continued. The remaining solvent was removed at reduced pressure. Carbon tetrachloride (2 x 10 ml) was added and removed under reduced pressure twice to give the solid yellow acid chloride which was always used immediately in the next reaction: IR 3080, 3025, 1730, 1650, 1470; 1H NMR 2.36 (s, 3H), 7.40 (s, 1H), 8.09 (s, 1H).

Dimethyl 2-Ethenyl-3,4,5-trimethoxybenzylpropanedioate (12a). NaH (1.41g, 2.93 x 10^{-2} mol, 150M%) was added in three portions to a solution of 3.87 g (2.93 x 10^{-2} mol, 150M%) of dimethyl malonate in 70 ml THF. After 5 min 4.23 g (1.95 x 10^{-2} mol, 100M%) of 3,4,5-trimethoxybenzyl chloride and a catalytic amount of NaI in ~20 ml THF was added to the anion solution. The reaction was then heated at reflux for 10 h. The reaction was processed according to procedure A. The crude product was purified by medium pressure chromatography eluting with 50:50 hexanes:EtOAc to provide 3.88 g (64% yield) of monoalkylated malonate: IR 2950, 2840, 1735, 1540, 1500, 1460, 1435, 1425, 1345, 1245, 1125; 1H NMR 3.17 (d, J~7 Hz), 2H), 3.72 (t, J~7 Hz, 1H), 3.75 (s, 6H), 3.85 (s, 9H), 6.42 (s, 2H); MS m/z 312 (M+).

Tin tetrachloride (0.92 ml, 7.8 x 10^{-3} mol, 100M%) was added to solution of 2.44 g (7.83 x 10^{-3} mol, 100M%) of malonate and 2.12 ml (2.35 x 10^{-2} mol, 300M%) of DCME in 25 ml CH_2Cl_2 at -78°C. The reaction was stirred at -78°C for 30 min then allowed to warm slowly to rt over 20 min and processed as before to afford after procedure B 2.60 g (98% yield) of aldehyde: IR 2950, 2850, 1735, 1675, 1590, 1560, 1495, 1450, 1435, 1385, 1120, 1025; 1H NMR 3.34 (d, J~7 Hz, 2H), 3.70 (s, 6H), 3.72 (t, 1H), 3.86 (s, 3H), 3.90 (s, 3H), 4.00 (s, 3H), 6.57 (s, 1H), 10.42 (s, 1H); MS m/z 340 (M^+).

The ylide was prepared in the usual way using 0.5945 g (1.47 x 10^{-3} mol, 250M%) of methyltriphenyl phosphonium iodide and n-BuLi (0.7 ml, 1.54 x 10^{-3} mol, 263M%) in 20 ml THF. The ylide was added to a rt solution containing 0.20 g (5.88 x 10-4 mol, 100M%) of the aldehyde in 10 ml THF. The reaction was stirred at rt for 6 h then heated to reflux for 45 min. The reaction was then cooled and processed according to procedure A. The crude product was then purified by flash chromatography (50:50 hexanes ether) to give 0.13 (66% yield) of 12a: IR 2950, 2840, 1735, 1590, 1488, 1450, 1430, 1400, 1340, 1240, 1190, 1125; ^1H NMR 3.39 (d, J~7 Hz, 2H), 3.79 (t, J~7 Hz, 1H), 3.82 (s, 6H), 3.92 (s, 3H), 3.97 (s, 3H), 4.00 (s, 3H), 5.50-5.87 (m, 2H), 6.60-6.95 (m, 1H), 6.61 (s, 1H); MS m/z 338 (M^+).

Bis(2,2,2-trichloroethyl) 2-Ethenyl-3,4,5-trimethoxybenzylpropanedioate (12b). As per 12a, 8.00 g (3.70 x 10^{-2} mol, 100M%) of the benzyl chloride, 23.72 g (6.47 x 10^{-2} mol, 175M%) of bis(trichloroethyl) malonate, 3.26 g (6.79 x 10^{-2} mol, 184M%) of NaH and a trace of NaI in ~100 ml THF afforded 13.31 g (66% yield) of adduct: IR 3000, 1770, 1600, 1520, 1470, 1380, 1340, 1240, 1130; 1H NMR 3.30 (d, J~8 Hz, 2H), 3,82 (s, 3H), 3.85 (s, 6H) 4.00 (t, J~8 Hz, 1H) 4.77 (s, 4H), 6.47 (s, 2H); MS m/z 547 (M+); HRMS, m/z 543.9243 (C17H18Cl6O7 requires 543.9209).

Formylation with 3.24 g (5.93 x 10-3 mol, 100M%) of malonate, 1.61 ml (1.78 x 10-2 mol, 300M%) of DCME, and 0.69 ml (5.99 x 10-3 mol, 100M%) of $SnCl_4$ gave 3.50 g (~100% yield) of aldehyde: IR 2940, 2855, 1770, 1755, 1680, 1595, 1565, 1500, 1455, 1390, 1325; ^1H NMR 3.52 (d, J~6 Hz, 2H), 3.84 (s, 3H), 3.90 (s, 3H), 3.99 (s, 3H), 4.12 (t, 1H), 4.76 (s, 4H), 6.58 (s, 1H), 10.42 (s, 1H); MS m/z 571 (M^+); HRMS 571.9145 ($C_{18}H_{18}Cl_6O_8$ requires 571.9158).

Olefination using 0.4517 g (7.86 x 10^{-4} mol, 100M%) of aldehyde, 0.6986 g (1.73 x 10^{-3} mol, 220M%) of methyltriphenyl phosphonium iodide and 1.07 ml (1.91 x 10-3 mol, 243M%) of n-BuLi afforded 0.4021 g (89% yield) 12b: IR 2990, 1785-1765, 1605, 1500, 1465, 1340, 1130; ^1H NMR 3.40 (d, 2H, J~7 Hz), 3.80 (s, 3H), 3.86 (s, 6H), 4.02 (t, 1H, J~7 Hz), 4.72 (s, 2H), 4.75 (s, 2H), 5.40-5.76 (m, 2H), 6.50-6.90 (m, 1H), 6.56 (s, 1H); MS m/z 569 (M^+); HRMS m/z 569.9370 ($C_{19}H_{20}Cl_6O_7$ requires 569.9369).

Bis(t-butyl) 2-Ethenyl-3,4,5-trimethoxybenzylpropanedioate (12c). NaH (0.22 g, 4.55 x 10^{-3} mol, 110M%), 1.00 g (4.13 x 10^{-3} mol, 100M%) of 16, 0.94 g, (4.34 x 10^{-3} mol, 105M%) of bis(t-butyl) propanedioate, and ~0.1 g sodium iodide in ~15 ml of THF gave 1.42 g (81% yield) of 12c: IR 2975, 2935, 1725, 1595, 1490, 1460, 1370, 1340, 1250; 1H NMR 1.40 (s, 18H), 3.16 (bd, J~7 Hz, 2H), 3.36-3.61 (m, 1H), 3.72-3.97 (m, 9H), 5.37-5.77 (m, 2H), 6.48-6.89 (m, 2H); MS m/z 422 (M^+).

3,4,5-Trimethoxy-2-(2E-trimethysilylethenyl)benzyl Chloride (17). Thionyl chloride (0.49 ml 6.76 x 10^{-3} mol, 400M%) was added to a rt solution containing 0.50 g (1.69 x 10^{-3} mol, 100M%) of the alcohol 15 and 0.27 ml (3.38 x 10^{-3} mol, 200M%) pyr in 15 ml PhH. The reaction was then heated at reflux for 25 min and processed to yield 0.49 g (92% yield) of the chloride 17: IR 2990, 1600, 1500, 1470, 1410, 1330, 1240, 1190, 1120; NMR 0.19 (s, 9H), 3.77 (s, 3H), 3.86 (s, 6H), 4.58 (s, 2H), 6.28 (d, J~20 Hz, 1H), 6.80 (s, 1H), 6.92 (d, J~20 Hz, 1H); MS m/z 314 (M^+).

2-Ethenyl-3,4,5-trimethoxybenzyl Chloride (16). Thionyl chloride (0.12 ml, 1.58 x 10^{-3} mol, 120M%) was added to 0.39 g (1.32 x 10-3 mol, 100M%) of 15 in ~10 ml PhH at rt and heated at reflux for 20 min. The reaction gave a high yield >90% of 16: IR 2990, 1605, 1500, 1465, 1410, 1390, 1335, 1245, 1195, 1125; NMR 3.80, (s, 3H), 3.88 (s, 6H), 4.60 (s, 2H), 5.40-5.80 (m, 2H), 6.60-6.92 (m, 1H), 6.71 (s, 1H); mass spectrum m/z 242 (M^+); HRMS, m/z 242.0712 (Formula $C_{12}H_{15}ClO_3$) requires 242.0731.

2-Trimethylsilylethynyl-3,4,5-trimethoxybenzyl Chloride (22). Thionyl chloride (1.74 ml, 2.38 x 10^{-2} mol, 200M%) was added to 3.49 g (1.19 x 10-2 mol, 100M%) of the benzyl alcohol 21 in ~75 ml of dry PhH at rt and heated to reflux for 1 h. The crude reaction product was processed by procedure B and purified by flash chromatography to give 22 (3.08 g, 83% yield, 75:25 hexanes:ether fxn): IR 2990, 2150, 1600, 1500, 1470, 1450, 1340, 1255, 1200, 1130, 1080; ^{1}H NMR 3.00 (s, 9H), 3.83 (s, 3H), 3.87 (s, 3H), 3.96 (s, 3H), 4.70 (s, 2H), 6.78 (s, 1H); MS m/z 312 (M^+).

Bis(t-butyl) 1,3-Dihydro-5,6,7-trimethoxy-1-methylene-2H-indene-2,2-dicarboxylate (23). NaH (0.52 g, 1.09 x 10^{-2} mol, 110M%) was added to a solution containing 3.08 g (9.87 x 10^{-3} mol, 100M%) of 22, 0.07 g (5 x 10^{-4} mol, 5M%) of NaI and 2.13 g (9.87 x 10^{-3} mol, 100M%) of bis(t-butyl) malonate in 30 ml THF at rt and heated to reflux for 17 h. Procedure B yielded the crude mixture of products which contained the indane and alkyne malonates in approximately equal portions by proton NMR. The mixture was not separable by medium pressure or flash chromatography. The spectrum contained singlet proton resonances at 5.53 and 6.15 ppm which were consistent with the indane structure. The infrared absorption at 2120 cm^{-1} shows that alkyne is still present in the mixture. The mass spectrum shows the molecular ion m/z 420 (M^+) for the desilated alkyne and/or the indane.

2-Ethynyl-3,4,5-trimethoxybenzyl Alcohol (24). The silyl acetylene 21 (0.22 g, 6.01 x 10^{-4} mol, 100M%) in ~15 ml MeOH was treated with anhydrous K_2CO_3 (0.20 g). After 5 h at rt, processing according to procedure B gave 0.18 g of 24 (>100% yield) which was used in subsequent reactions: IR 3600-3200 broad, 2940, 2840, 2100, 1595, 1490, 1405, 1335, 1250, 1120; ^{1}H NMR 3.42 (s, 1H), 3.83 (s, 3H), 3.87 (s, 3H), 3.95 (s, 3H), 4.70 (6s, 2H), 6.78 (s, 1H); MS m/z 222 (M^+).

2-t-Butyldimethylsilylethynyl-3,4,5-trimethoxybenzyl Chloride (26). Thionyl chloride (3.84 ml, 5.27 x 10 ^{2} mol, 250M%) was added to 7.08 g (2.11 x 10-2 mol, 100M%) of 25, and 4.26 ml (5.27 x 10^{-2} mol, 250M%) pyr in ~75 ml PhH at rt and refluxed for 30 min. Removal of the PhH and processing (procedure B) yielded 5.92 g (79%) of 26: IR 2930, 2840, 1580, 1485, 1325, 1120; 1H NMR 0.22 (s, 6H), 1.01 (2, 9H), 3.86 (s, 3H), 3.88 (s, 3H), 3.97 (s, 3H), 4.70 (s, 2H), 6.75 (s, 1H); MS m/z 354 (M^+).

2-Iodo-3,4,5-trimethoxybenzyl Chloride (18). From 13 (4.04 g, 1.25 x 10^{-2} mol, 100M%) and 1.82 ml (2.49 x 10^{-2} mol, 200M%) of thionyl chloride in 60 ml of PhH, 3.97 g (93%) of 18 was obtained: IR 2940, 2840, 1600, 1465, 1400, 1215 cm-1; NMR d 3.90 (2, 9H), 4.69 (s, 2H), 6.92 (s, 1H).

Bis(t-butyl) 2-Iodo-3,4,5-trimethoxybenzylpropanedioate (19). As per 12a, 0.30 g (6.3 x 10^{-3} mol, 110M%) of NaH, 1.24 g (5.74 x 10-3 mol, 105M%) of bis(t-butyl) propanedioate and 1.87 g (5.47 x 10^{-3} mol, 100M%) of 18 in ~40 ml THF afforded 2.72 g (95% yield) of 19: IR 2975, 2935, 1740, 1730, 1560, 1480, 1390, 1370, 1160, 1140, 1105; ^{1}H NMR 1.42 (s, 18H), 3.21 (bd, J~7 Hz, 2H), 3.60 (m, 1H), 3.78-3.96 (m, 9H), 6.70 (s, 1H); HRMS, m/z 522.1114 ($C_{12}H_{31}IO_7$ requires 522.1159).

Dimethyl [(5-Acetoxy-4-oxo-4H-pyran-2-yl)carbonyl]-[2-ethenyl-3,4,5-trimethoxybenzyl]propanedioate (29). NaH (0.20 g, 4.2 x 10^{-3} mol, 430M%) was added to 0.32 g (9.61 x 10^{-4} mol, 100M%) of 12a in 30 ml THF at rt. The anion of 12a solution was allowed to stir at rt for 15 min and added via cannula to freshly prepared 11 (0.38 g of 10, 200M%). After 11 h at rt the crude product was filtered through celite followed by flash chromatography to afford 0.33 g (67% yield) of 29 (25:75 hexanes:ether fxn): IR 3000, bd 1700-1735, 1660, 1600, 1500, 1470, 1410, 1345, 1250, 1200, 1130; ^{1}H NMR 2.29 (s, 3H), 3.71 (s, 6H), 3.73 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 5.33-5.62 (m, 2H), 6.34-6.70 (m, 1H), 6.61 (s, 1H), 7.06 (s, 1H), 7.78 (s, 1H); MS m/z 518 (M^+).

Dimethyl (7aα,11α,12aß)-9-Acetoxy-10,11,12,12a-tetrahydro-1,2,3-trimethoxy-7,10-dioxo-5H-7a,11-epoxybenzo[a]heptalene-6,6(7H)-dicarboxylate (30). NaI (0.025 g, 1.72 x 10^{-4} mol, 208M%) was added to 0.0428 g (8.26 x 10^{-5} mol, 100M%) of 29, 3.0 ml of Ac_2O and 2.5 ml of HOAc. This mixture was then heated at reflux for 4.5 h. The solvent was removed and the crude product was filtered through silica to provide 12a (50:50 hexane:ether fxn) and 30 ($CHCl_3$ fxn): IR 3000, broad 1760-1735, 1605, 1495, 1470, 1410, 1200, 1125; ^{1}H NMR 2.78 (s, 3H), 2.0-2.6 (m, 2H), 3.2-3.5 (m, 2H), 3.75 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 4.2-4.5 (m, 1H), 4.92 (bd, J~8 Hz, 1H), 6.67 (s, 1H), 7.58 (s, 1H); MS m/z 518 (M^+).

Bis(2,2,2-trichloroethyl) [(5-Acetoxy-4-oxo-4H-pyran-2-yl)carbonyl]-[2-ethenyl-3,4,5-trimethoxybenzyl]propanedioate (31). As per 29, 2.19 g (4.02 x 10^{-3} mol, 100M%) of 12b, 1.59 g (8.05 x 10^{-3} mol, 200M%) of acid 10, 0.50 g (1.0 x 10^{-2} mol, 260M%) of NaH and 100 ml THF gave 1.61 g (47% yield) of 31: IR 3000, 2940, broad 1780, 1660, 1595, 1490, 1365, 1330, 1175, 1125, 1095, 1045; 1H NMR 2.24 (s, 3H), 3.70 (s, 3H), 3.75 (s, 3H), 3.80 (s, 3H), 3.90 (s, 1H), 4.45 (d, J~10 Hz, 2H), 4.78 (d, J~10 Hz, 2H), 5.32-6.62 (m, 2H), 6.37-6.72 (m, 1H), 6.68 (s, 1H), 7.16 (s, 1H), 7.67 (s, 1H); ^{13}C NMR 182.4 (s), 171.2 (s), 166.7 (s), 2-162.9 (s), 155.6 (s), 151.8 (s), 151.6 (s), 146.7 (d), 142.1 (s), 141.5 (s), 130 (d), 126.7 (s), 125.7 (t), 120.0 (s), 117.3 (d), 110.1 (d), 2-93.0 (s), 2-75.0 (t), 66.9 (s), 60.4 (q), 60.1 (q), 55.5 (q), 34.1 (t), 19.8 (q); HRMS m/z 749.942 ($C_{27}H_{24}Cl_6O_{12}$ requires 749.943).

Bis(2,2,2-trichloroethyl) (7aα,11α,12aß)-9-Acetoxy-10,11,12,12a-tetrahydro-1,2,3-trimethoxy-7,10-dioxo-5H-7a,11-epoxybenzo[a]heptalene-6,6(7H)-dicarboxylate (32). The substrate 31 (0.97 g, 1.13 x 10^{-3} mol, 100M%) was heated at reflux in 20 ml Ac_2O for 3.5 h. After solvent evaporation, chromatography afforded 0.59 g (61% yield, 50:50 hexanes:ether fxn) of 32: IR 2940, 2840, 1770, 1735, 1715, 1600, 1490, 1450, 1410, 1370, 1330, 1235, 1195, 1045; 1H NMR 2.00-2.70 (m, 2H), 2.22 (s, 3H), 3.41 (d, 2, J~14 Hz, 1H), 3.79 (s, 3H), 3.82 (s, 3H), 3.86 (s, 3H), 3.98 (d, J~14 Hz, 1H), 4.30-5.03 (m, 6H), 6.70 (s, 1H), 3.98 (d, J~14 Hz, 1H), 4.30-5.03 (m, 6H), 6.70 (s, 1H), 7.57 (s, 1H); ^{13}C NMR 194.0 (s), 188.2 (s), 167.5 (s), 164.4 (s), 163.7 (s), 151.9 (s), 151.4 (s), 143.6 (s), 141.4 (s), 137.4 (d), 128.2 (s), 123.3 (s), 112.5 (d), 93.7 (s), 93.1 (s), 87.1 (s), 82.7 (d), 75.6 (t), 74.7 (t), 70.1 (s), 61.0 (q), 60.4 (q), 55.7 (q), 47.9 (d), 35.9 (t), 34.5 (t) and 20.0 (q); MS m/z 752, 754 (M^+); HRMS, 751.9412 ($C_{27}H_{24}Cls(35,5)Cls(37,1)O_{12}$ requires m/z 751.9404), m/z, 753.9326 ($C_{27}H_{24}Cls(35,4)Cls(37,2)O_{12}$ requires 753.9374).

Bis(t-butyl) [(5-Acetoxy-4-oxo-4H-pyran-2-yl)carbonyl]-[2-ethenyl-3,4,5-trimethoxybenzyl]propanedioate (33). The anion from 0.59 g (1.23 x 10-2 mol, 400M%) of NaH, 1.30 g (3.08 x 10^{-3} mol, 100M%) of 12c and 3 drops of MeOH in ~10 ml THF at reflux for 3 h was treated with 11 (0.92 g, 150M% of 10) in 5 ml of THF. After 1.5 h at reflux and 12 h at rt, the crude product mixture was processed as per 29 to afford 0.5 g (28% yield) of 33: 1H NMR 1.30 (s, 18H), 2.30 (s, 3H), 3.80-4.00 (m, 11H), 5.42-5.67 (m, 2H), 6.50-6.84 (m, 1H), 6.86 (s, 1H), 7.16 (s, 1H), 7.82 (s, 1H); MS m/z 602 (M^+).

Bis(t-butyl) [(5-Acetoxy-4-oxo-4H-pyran-2-yl)carbonyl]-[3,4,5-trimethoxy-2-(2E-trimethylsilyl)ethenylbenzyl]propanedioate (37). As per 33, NaH (0.50 g, 1.03 x 10^{-2} mol, 400M%), 1.27 g (2.57 x 10^{-3} mol, 100M%) of 20 in ~15 ml THF and 11 in ~15 ml THF (from 0.61 g, 120M% of 10) afforded 0.52 g (35% yield) of 37: IR 2970, 1730, 1645, 1595, 1490, 1455, 1370, 1250; ^{1}H NMR 0.18 (s, 9H), 1.28 (S, 18H), 2.28 (s, 3H), 3.67-3.84 (m, 11H), 6.15 (d, J~20 Hz, 1H), 6.83 (d, J~20 Hz, 1H), 6.86 (s, 1H), 7.12 (s, 1H), 7.70 (s, 1H).

Bis(2,2,2-trichloroethyl) [(5-Acetoxy-4-oxo-4H-pyran-2-yl)carbonyl]-[2-t-butyldimethylsilyethynyl-3,4,5-trimethoxybenzyl]propanedioate (39). As per 12c, 5.92 g (1.67 x 10^{-2} mol, 100M%) of 26, 6.12 g (1.67 x 10^{-2} mol, 100M%) of bis(trichloroethyl) malonate, 0.96 g (2.00 x 10^{-2} mol, 120M%) NaH and ~0.3 g NaI in ~100 ml THF gave crude 28: ^{1}H NMR 0.18 (5, 6H), 1.00 (s, 9H), 3.40 (m, 2H), 3.70 - 3.95 (m, 10H), 4.75 (s, 4H), 7.60 (s, 1H). Without purification crude 28, 2.40 g (5.01 x 10^{-2} mol, 300M%) of NaH and 11 (from 6.44 g, 195M% of 10) were combined and processed as described in the synthesis of 43 to afford 6.03 g (41% yield from 26) of 39 after purification by MPLC: IR 2930, 2840, 2135, 1770, 1655, 1585, 1485, 1170; ^{1}H NMR 0.20 (s, 6H), 1.00 (s, 9H), 2.22 (s, 3H), 3.74-3.94 (m, 9H), 4.01 (s, 2H), 4.52-4.85 (m, 4H), 6.72 (s, 1H), 7.12 (s, 1H), 7.61 (s, 1H); HRMS m-C_4H_9 m/z 806.9446 + ($C_{29}H_{27}O_{12}Cls(35,5)Cls(37,1)$ requires 806.9412).

Bis(t-butyl) [(5-Acetoxy-4-oxo-4H-pyran-2-yl)carbonyl]-[2-t-butyldimethylsilylethynyl-3,4,5-trimethoxybenzyl]propanedioate (43). As per 12c, 0.60 g (2.8 x 10^{-3} mol) of bis(t-butyl) propanedioate, 0.63 g (2.6 x 10^{-3} m) of 26, 0.15 g (3.0 x 10^{-3} mol) of NaH and a trace of NaI in THF of 1.0 g (81% yeild) of crude 27: 1H NMR 0.18 (s, 6H), 1.00 (s, 9H), 1.40 (m, 18H), 3.25 (m, 2H), 3.80 - 3.90 (m, 10H), 7.60 (m, 1H). Crude 27, NaH (0.50 g, 1.04 x 10^{-2} mol, 560M%) and 11 (from 0.44 g, 120M% of 10) was manipulated as per 43 to afford 0.56 g (56% yeild) of 12c (75:25 hexanes:ether fxn) and 0.44 g (33% yield) of 43 (25:75 hexanes:ether fxn): IR 2950, 2105, 1775, 1730, 1660, 1595, 1490, 1460, 1405, 1370, 1345, 1250, 1180; ^{1}H NMR 0.20 (s, 6H), 1.00 (s, 9H), 1.37 (s, 18H), 2.27 (s, 3H), 3.74-3.98 (m, 11H), 6.88 (s, 1H), 7.08 (s, 1H), 7.78 (s, 1H); MS m/z 657 (M^+ - C_4H_9).

Bis(2,2,2-trichloroethyl) cis-9-Acetoxy-12-t-butylyldimethylsilyl-1,2,3-trimethoxy-7-10-dioxo-5H-7a,11-epoxybenzo[a]heptalene-6,6(7H)-dicarboxylate (40). The alkyne 39 (2.73 g) was heated at reflux in xylenes for 20 h and upon removal of the solvent afforded 2.73 g (100% yield) of pure 50: IR 2960, 2875, 1780, 1720, 1675, 1490, 1470, 1200; NMR –0.12 (s, 3H), 00.00 (s, 3H), 0.90 (s, 9H), 2.15 (s, 3H), 3.40-3.92 (m, 11H), 4.56-5.03 (m, 4H), 5.35 (s, 1H), 6.77 (s, 1H), 7.36 (s, 1H).

(7aα,11α,12aβ)-9-Acetoxy-10,11,12,12a-tetrahydro-1,2,3-trimethoxy-5H-7a,11-epoxybenzo[a]heptalene-7,10(6H,11H)-dione (36). Zn-Cu couple[32] (0.72) g was added to 32 (0.0983 g, 1.14 x 10^{-4} mol, 100M%) dissolved in ~20 ml anhydrous THF which was heated to reflux. Water (3 drops) was added. After 15 min, then more water (12 drops) was added to ensure an excess. Procesing left 0.0475 g (~100% yield) of 36: IR 2940, 2840, 1770, 1715, 1600, 1495, 1455, 1415, 1330; ^{1}H NMR 2.22 (s, 3H), 2.1-3.5 (m, 6H), 3.74 (s, 3H), 3.78 (s, 3H), 3.90 (s, 3H), 4.16-4.40 (m, 1H), 4.95 (bd, J~7 Hz, 1H), 6.43 (s, 1H), 7.62 (s, 1H); MS m/z 402 (M^+); HRMS, m/z 402.1317 ($C_{21}H_{22}O_8$ requires 402.1346).

cis-9-Acetoxy-12-(t-butyl)dimethylsilyl-1,2,3-trimethoxy-5H-7a,11-epoxybenzo[a]heptalene-7,10-(6H,11H)-dione (44). Zn-Cu couple (~3g) was added to 4.43 g (5.12 x 10-3 mol, 100M%) of 40 in ~100 ml THF at 50° C and the reaction was heated to reflux. Water ~1 ml was slowly added to the refluxing reaction which was open to the air. The addition of water caused a great deal of foaming. The reaction was heated for 1 h and processed by filtration through (20 g) silica with ether to afford 2.33 g (89% yield) of 44 which could be recrystallized from ether and hexanes: Mp 147-148°C; IR 2940, 2870, 1780, 1715, 1485, 1465, 1200, 1105; ^{1}H NMR –0.11 (s, 3H), 0.00 (s, 3H), 0.90 (s, 9H), 2.18 (s, 3H), 2.50-3.37 (m, 4H), 3.68 (s, 3H), 3.77 (s, 3H), 3.83 (s, 3H), 5.41 (s, 1H), 6150 (s, 1H) and 7.33 (s, 1H); MS m/z 514 (M^+).

Dimethyl [(5-Hydroxy-4-oxo-4H-pyran-2-yl)methyl]-[2-ethenylbenzyl]propanedioate (47). Diester 47 was prepared in six steps from isochroman. Isochroman was converted into 1-chloromethyl-2-(2-mesyloxyethyl) benzene by an established route.[48] 2-Chloromethyl styrene was made from treatment of the above mesylate (4.00 g, 1.62 x 10^{-2} mol) with fresh KOt-Bu (1.89 g, 4.86 x 10-2 mol of K in 25 ml t-BuOH) in 50 ml THF at rt for 40 min. Processing according to procedure A yielded 2.27 g (93% yield) of the styrene: NMR d 4.60 (s, 2H), 5.34 (d, J~11 Hz, 1H), 5.65 (d, J~15 Hz, 1H), 6.82-7.58 ppm (m, 5H).

Sodium (1.59 g, 6.91 x 10-2 mol, 100M%) was added to 50 ml of absolute MeOH and was stirred at rt until all the metal had reacted. Dimethyl malonate (9.13 g, 6.91 x 10^{-2} mol, 100M%) was added to the NaOMe solution and stirred for 15 min before 10.44 g (6.91 x 10-2 mol, 100M%) of the styrene was added. The reaction was then heated to reflux for 5 h. The reaction was processed according to procedure A after most of the MeOH had been distilled to afford 13.98 g (82% yield) of oily product alkylated malonate: IR 1750, 1430, 1335, 1225, and 1145 cm-1, NMR d 3.28 (d, J~6 Hz, 2H) 3.61 (s, 7H), 5.31 (d, J~10 Hz, 1H), 5.62 (d, J~16 Hz, 1H), 6.77-7.58 ppm (m, 5H).

A solution containing 13.88 g (5.60 x 10-2 mol, 100M%) styryl malonate in ~200 ml THF was cooled in an ice bath and 2.96 g (6.16 x 10^{-2} mol, 110M%) of NaH was added in 1 gram portions over ~15 min. This mixture was warmed to rt and stirred for 40 min before 21.60 g (5.60 x 10-2 mol, 100M%) of the kojic acid tosylate[49] was added. The reaction was then stirred at rt for 12 hr and then processed according to procedure A followed by filtration through florisil (ether wash) to yield 18.26 g (71% yield) of the oily O-benzylated 47: IR 2945, 1732, 1644, 1435, 1212: ^{1}H NMR 3.02 (s, 2H), 3.41 (s, 2H), 3.62 (s, 6H), 5.02 (s, 2H), 5.23 (d, J~10 Hz, 1H), 5.57 (d, J~16 Hz, 1H), 6.18 (s, 1H), 6.70-7.55 (m, 11H).

To remove the benzyl protecting group, a solution containing 6.54 g (1.42 x 10^{-2} mol, 100M%) of o-benzyl 47 in ~75 ml CH_2Cl_2 was cooled to -78°C and 15.57 ml (1M in CH_2Cl_2, 1.56 x 10^{-2} mol, 110M%) of BBr_3 was then added. The reaction was stirred for 2 h and quenched with a solution of KH_2PO_4 (30 ml ~0.2M) while still at -78°C. The reaction mixture was then warmed to rt and the aqueous layer was extracted with ~(2 x 30 ml) CH_2Cl_2. The organic layers were combined, dried and filtered. The solvent was removed to afford an oily product mixture. The oil was triturated with a mixture of ether and hexanes (1:3) to remove the benzyl bromide. The gummy solid product was placed under high vacuum to remove the remaining solvents to yield 5.18 g (98%) of the solid product 47 which could be recrystallized from ethyl acetate and hexanes: M.P. 154-155°C; IR 1740, 1620, 1435 and 1215 cm-1; NMR d 3.11 (s, 2H), 3.48 (s, 2H), 3.73 (s, 6H), 5.28 (d, J~10 Hz, 1H), 5.64 (d, J~16 Hz, 1H), 6.56 (s, 1H), 6.72-7.60 (m, 5H) and 8.03 ppm (s, 1H); mass spectrum m/z 372 (M+); HRMS, m/z 372.1222 ($C_{20}H_{20}O_7$ requires 372.1238).

Dimethyl (7aα,11α,12aß)-8,9,10,11,12,12a-Hexahydro-9,9-dimethyoxy-10-oxo-5H-7a,11-epoxybenzo[a]heptalene-6,6(7H)-dicarboxylate (48). Methanesulfonic acid (0.44 ml, 6.8 x 10^{-3} mol, 250M%) and trimethylorthoformate (0.18 ml, 1.62 x 10^{-3} mol, 60M%) were added to a rt solution containing 1.00 g (2.70 x 10^{-3} mol, 100M%) of 47 in 40 ml MeOH. The reaction was heated to reflux for 12 h then most of the MeOH was removed at reduced pressure. The reaction mixture was processed by procedure B and then purified by flash chromatography to give 0.9874 g (87% yeild) of pure amorphous solid product 48 (50:50 hexanes:ether fxn): IR 2955, 1730, 1450, 1432, 1280, 1260, 1208, 1178, 1130, 1100, 1065; NMR 2.0-2.90 (m, 6H), 3.00-3.60 (m, 3H), 3.24 (s, 3H), 3.39 (s, 3H), 3.70 (s, 3H), 3.80 (s, 3H), 4.52-4.68 (m, 1H), 6.92-7.20 (m, 4H); MS m/z 418 (M+); HRMS m/z 418.1626 ($C_{22}H_{26}O_8$ requires 418.1665).

Dimethyl (7aα,11α,11aß)-8,9,10,11,12,12a-Hexahydro-9,10-dioxo-5H-7a,11-epoxybenzo[a]heptalene-6,6(7H)-dicarboxylate (50). A solution of 0.92 g (2.21 x 10^{-3} mol, 100M%) 48 in 40 ml 10% aqueous HCl and 40 ml MeOH was heated to reflux for 3 h. Processing by procedure B afforded 0.71 g of 50 (80% yield) which contained an extra molecule of MeOH: IR 2950, 1730, 1438, 1266, 1220, 1080; NMR 2.0-3.6 (m, 9H), 3.72 (s, 3H), 3.80 (s, 3H), 4.4-4.7 (m, 1H) and 6.93-7.25 (m, 4H); MS m/z 372 (M+).

Dimethyl (7aα,11α,12aß)-10,11,12,12a-Tetrahydro-9-acetoxy-10-oxo-5H-7a,11-epoxybenzo[a]heptalene-6,6[7H]-dicarboxylate (51). A solution of 0.068 g (1.84 x 10^{-4} mol) of 50 in 20 ml of THF was cooled to -78°C and treated with 1.90 x 10^{-4} mol LDA in 1 ml THF. After 1 h, the solution was warmed to -10°C and quenched with 0.5 ml Ac_2O. Processing as per usual afforded 0.06 g of 51: ^1H NMR 2.20 (s, 3H), 2.25-2.40 (m, 4H), 3.00-3.60 (m, 3H), 3.24 (s, 3H), 3.39 (s, 3H), 4.90 (d, J = 7.5 Hz, 1H), 6.92-7.20 (m, 5H); MS m/z 414 (M+).Quenching with TMS afforded 52 and 10% HCl, 53 in comparable amounts.

Dimethyl (7aα,10ß,11α,12aß)-10-Acetoxy-8,9,10,11,12,12a-hexahydro-9-oxo-5H-7a,11-epoxybenzo[a]heptalene-6,6(7H)-dicarboxylate (55). A solution of 0.37 g (9.23 x 10^{-4} mol, 100M%) of 50 and 1.00 g of Zn dust in 10 ml of Ac_2O and 10 ml of HOAc was heated to reflux for 2h. The reaction was then cooled to rt and diluted with ~50 ml water. Processing (procedure B) afforded 0.370 g (96.4% yield) of 55: IR 2962, 1733, 1437, 1375, 1284, 1263, 1235; NMR 2.00-2.20 (m, 2H), 2.20 (s, 3H), 2.50-2.80 (m, 4H), 3.10-3.30 (m, 2H), 3.55-3.67 (m, 1H), 3.70 (s, 3H), 3.74-3.80 (m, 1H), 3.84 (s, 3H), 4.70 (t, J~6.3 Hz, 1H), 5.35 (d, J~6.3 Hz, 1H, coupled to 4.70), 6.98-7.21 ppm (m, 4H); MS m/z 416 (M+).

(10ß)-cis-10-Acetoxy-12-t-butyldimethylsilyl-1,2,3-trimethoxy-5H-7a,11-epoxybenzo[a]heptalene-7,9(6H,11H)-dione (57). Tin powder (0.009 g, 7.6 x 10^{-5} mol, 150M%) was added to 0.026 g (5.04 x 10^{-5} mol, 100M%) of 44, 1 ml of water and 0.25 ml cHCl in ~5 ml absolute EtOH at rt. After 14 h at reflux most of the EtOH was removed by distillation. Processing by procedure B afforded 0.024 g (100% yield) of 57: IR 2940, 2860, 1720, 1485, 1465, 1350 and 1110 cm-1; NMR d 0.00 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 2.30-3.23 (m, 4H), 3.74 (s, 3H), 3.80 (s, 3H), 3.85 (s, 3H), 4.47 (s, J~5 Hz, 1H), 5.50 (d, J~5 Hz, 1H), and 6.43 ppm (s, 1H); MS m/z 474 (M+).

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