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*Original Scientific Paper*

# A Transfer Alkylation Approach to Pentalenolactone*

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Pentalenolactone, an antibiotic and antitumor agent which is a representative of the polycondensed cyclopentanoid natural products, requires the construction of a highly functionalized bicyclo[3.3.0] octyl system. Using the principle of transfer alkylation, a simple route to an acyclic precursor which involves a net $\gamma$ attack of a polyenolate allows the development of a [4 + 1] strategy to the basic ring system. Overall, an eight step route to an excellent precursor to pentalenolactone emerges. Using a further four step sequence, the fully elaborated ring system of pentalenolactone is created. In addition to the transfer alkylation strategy, a novel bromination utilizing liquid bromine as a solvent and a chemoselective unravelling of the resultant tribromide is reported.

The synthesis of the polyquinanes is major field of synthetic endeavor because of their growing importance in natural product and theoretical organic chemistry.[1] We chose pentalenolactone (*1*), an antibiotic and antitumor agent from a stretptomyces broth culture, because of its central role in natural products chemistry. Scheme 1 outlines our retrosynthetic analysis. The key aspect of this analysis is the creation of a linear acyclic precursor to the bicyclic[3.3.0]octane framework of this compound. In this paper, we wish to report the successful deployment of this concept for the synthesis of the bicyclic ring system using the novel concept of transfer alkylation.[7]

The bicyclic ketone *2a* is considered a prime precursor because the conjugated double bond of *2* is »protected« in the form of the $\beta$-hydroxy ester unit, a hydrated analoque, to permit catalytic hydrogenation to be used to create the correct stereochemistry of the endo methyl group of *1*. The stereochemistry of the two esters on the exo face of the bicyclo[3.3.0]octane system is believed to represent the thermodynamically preferred orientation. Thus, the problem factors to creation of the carbon skeleton. A [4+1] type of process is envisioned to form *2* from a totally acyclic system *3* which easily simplifies to the acid *4*.

While many conventional methods of synthesis can be envisioned to create *4*, the notion of transfer alkylation offers the simplest solution. As illustrated in eq. 1, advantage is taken of the propensity for an enolate of

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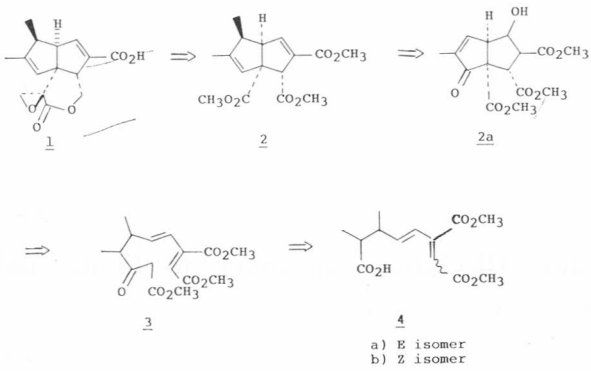
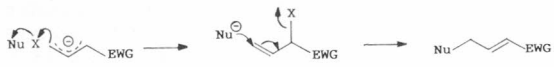
* Dedicated to Professor Mihailo Mihailović on the occasion of his sixtieth birthday.



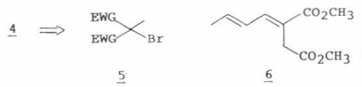

Scheme 1. Retrosynthetic Analysis of Pentalenolactone

a conjugated carbonyl system to undergo $\alpha$ attack. A pro-nucleophile which bears a pro-leaving group that can be transferred as an $X^+$ equivalent must



(1)

be designed. Thus, the alkylation process transfers the original nucleophile from the conjugated enolate by its attacking X to a new carbanion which then can undergo a more normal $S_N2$ type[1] alkylation. For the particular



(2)

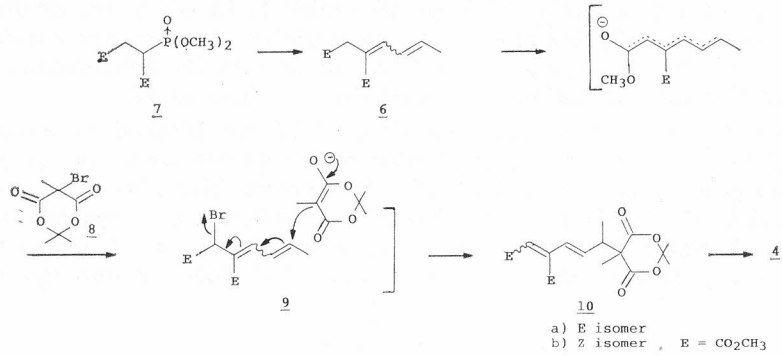
case at hand, eq. 2 illustrates the requisite reacting partners. Scheme 2 summarizes the synthesis of *4*.

Dimethyl dimethylphosphonosuccinate *7*[7,8] is reacted in a Wadsorth--Emmons-Horner reaction with crotonaldehyde yielding alkylidene succinate *6* as a 4 : 1 mixture of *cis:trans* isomers (76%). Addition of *6* to a —78 °C THF-hexane solution of lithium diisopropylamide generates a polyenolate which is quenched in a THF solution of *8*. The polyenolate from *6* undergoes $\alpha$-bromination forming *9* which reacts in the presence of HMPA with the enolate derived from *8* in an $S_N2''$ alkylation. The products *10a* and *10b* are thus obtained in a ratio of 1 : 4.5 (66%).[1] These cyclic esters are readily converted into the desired isomers of *4* by transesterification in trifluoracetic acid and decarboxylation in dimethylsulfoxide yielding *4a* (82%) and *4b* (76%), respectively.

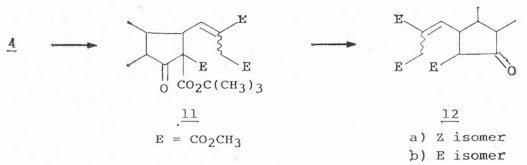
The next goal leading to the synthesis of pentalenolactone was to increase the length of acid *4* by an acetate residue and then to cyclize this acyclic chain in the fewest possible steps to *2*.

The first phase of the conversion of *4* to *2* works marvelously. Activation of either *4a* or *4b* as the methyl carbonic anhydride followed by acylation with *t*-butyl sodiomalonate yields the cyclopentanone *11* directly which, without isolation, is converted into *12* by transesterification and decarboxylation in trifluoroacetic acid in an overall yield of 50% (eq. 3). The structure

Scheme 2. Synthesis of Maleate *4*.

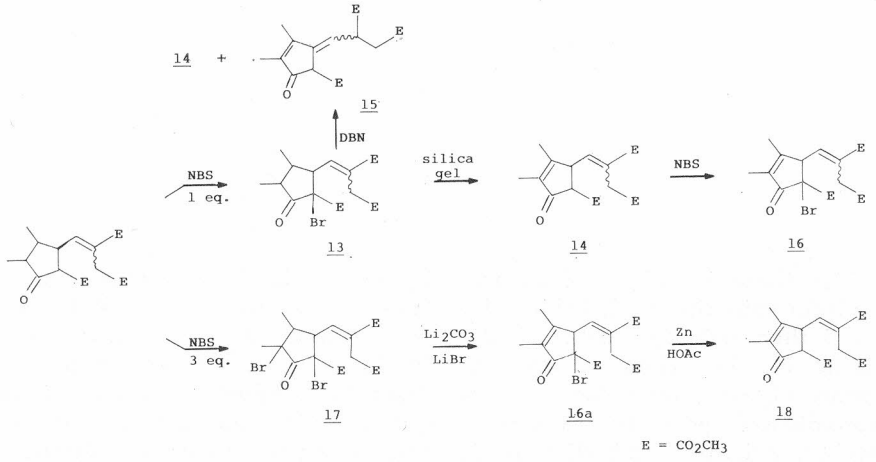



of *12* is based upon its NMR spectrum which exhibits a vinyl proton resonance at $\delta$ 6.67 (*12a*) and $\delta$ 5.78 (*12b*). In isomer *12b* the acetoacetate methine is clearly seen in the NMR spectrum as a doublet at $\delta$ 2.84 ($J$ = 11 Hz).




(3)

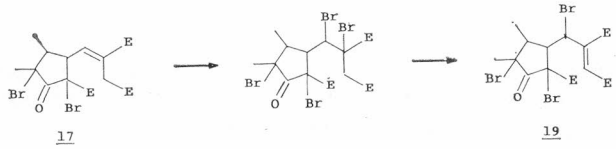
Cyclopentanone *12* is a mixture of geometric isomers, whereas the *cis* geometry is required for ring closure; therefore it was necessary to find conditions which would isomerize *12b* to *12a* (see Scheme 3). Treatment of *12* with one equivalent of NBS in carbon tetrachloride quantitatively produces bromide *13* with no isomerization of the double bond. Bromide *13* is characterized by dehydrobromination with silica yielding *14* or with DBN to *14* and an isomer involving migration of the double bond *15*. Compound *14* is again readily brominated with NBS to yield *16*. The rearrangement of *13* to *14* is characteristic of such reactive bromides.[9]




Scheme 3. Olefin Isomerization of *12* via NBS.

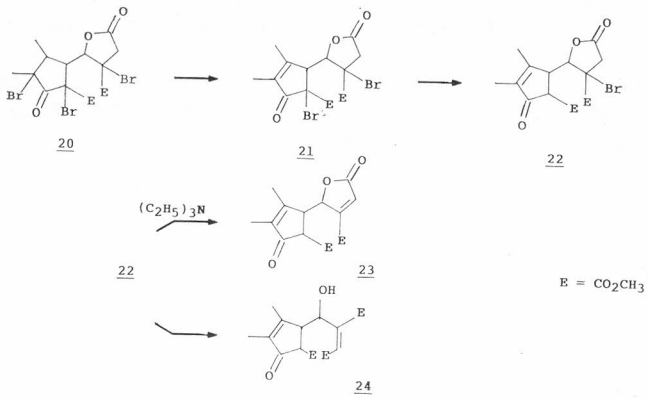
Reaction of *12* with three molar equivalents of NBS in carbon tetrachloride gives a quantitative yield of dibromide *17* in which the double bond has ben isomerized by bromine to the more stable *cis* geometry required for ring closure. The conversion of *17* into *16a* and *18* by dehydrobromination and reductive debromination confirmed the structure of *17*.

Since the two active hydrogen sites of *17* are blocked by bromine, a straightforward method for isomerization of the double bond into conjugation with both esters was conceived in order to overcome $S_N2'$ alkylation problems. Bromination of *17* followed by dehydrobromination was envisioned to yield an allylic bromide *19* which would ring close easily *via* intramolecular $S_N'$ alkylation (eq. 4). However, the double bond of *17* does not undergo addition




(4)

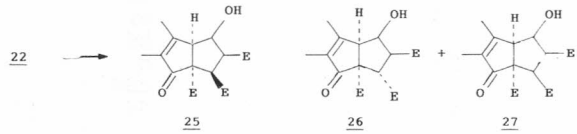
of bromine but rather, in vigorously refluxing bromine, undergoes bromination-lactonization producing *20* in excellent yield. This behavior of alkylidene succinates is also seen when alkylidene succinic acids are treated with bromine.[10] The synthesis of *20* is a beautiful achievement because it has incorporated all the needed structural features of *19*. Dehydrohalogenation of the $\beta$-bromolactone portion of *20* corresponds to a synthon for the double bond of *19* while the lactone linkage itself serves as the allylic bromide in *19*. The structure of *20* is proven by mass spectrometry and by its further conversion into pentalenolactone precursors.




The three bromines of *20* may be each selectively removed by first dehydrobromination with lithium bromide-lithium carbonate in DMF yielding *21* and then reductive debromination with sodium iodide-sodium thiosulfate yielding *22*. The chemoselective elimination of the $\beta$-bromoketone in the presence of the $\beta$-bromolactone is surprising. Bromolactone *22* may be dehydrobrominated with triethylamine yielding butenolide cyclopentanone *23*. However, dehydrobromination of *22* with methanolic sodium methoxide in dichloromethane at 0 °C yields alcohol *24*. Cyclopentanone *24* is formed by

initial dehydrohalogenation to *23* followed by methoxide opening of the lactone ring.

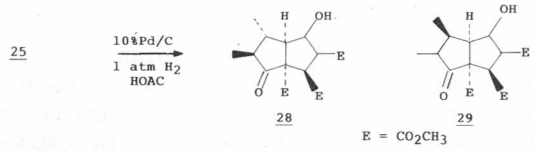
Treatment of methanol solutions of *22*, *23* or *24* at 0 °C with sodium methoxide followed by warming to 25 °C causes conversion of *22* to *23* to *24* and intramolecular Michael addition of *24* yielding the bicyclo[3.3.0]octanes *25*, *26* and *27* all in one pot! A typical preparation from *22* yields *25*, *26* and *27* in a ratio of 4.8 : 1 : 1.6 (67%). Proof of the bicyclo[3.30]octane structure *25*—*27* is based upon spectroscopic analysis. Table I lists the NMR data for *25* as an example




(5)

The *cis* stereochemistry of the ring junction is presumed due to its greater stability over that of the *trans*. The stereochemistry of the methyl esters shown in structures *25* and *26* was assigned on the basis of subsequent chemistry of these compounds and their accompanying spectral data.

The required endo methyl group of pentalenolactone was created by the high yield catalytic hydrogenation of the double bond of *25*—*26* in acetic acid with 10% palladium on carbon. Isomer *25* yields a mixture of reduced products *28* and *29* in a ratio which is dependent upon the ratio of catalyst to

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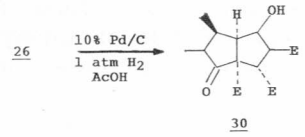


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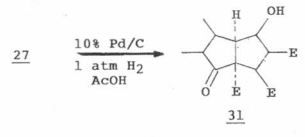
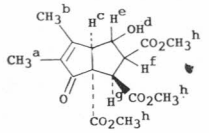



(8)

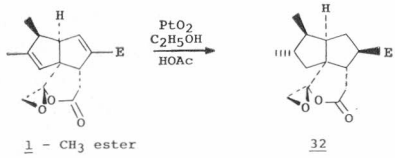
substrate which is used (eq. 6). Higher ratios of catalyst to substrate favor the required isomer *29*. Isomers *26* and *27* yield *30* and *31*, respectively, upon reduction (eq. 7 and 8 respectively). In all cases, the vinyl methyl resonances in the NMR spectra of starting materials were replaced by high field saturated methyl resonances. The stereochemistry of the saturated methyl groups created was deduced from subsequent chemical transformation. The occurrence of isomer *28* requires that the hydrogenation catalyst approach *25* from the concave side of the molecule which was thought to be the sterically less accessible side. A similar result is seen upon catalytic reduction of pentalenolactone methyl ester which yields the tetrahydro derivative *32*.[2b,c] In penta-

TABLE I

*NMR Data for Bicyclo[3.3.0]octane 25.*

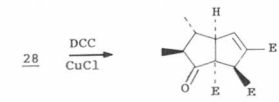


| Proton(s) | Chemical Shift ($\delta$) ($CDCl_3$) | Multiplicity | $J$(Hz) |
|---|---|---|---|
| a | 1.75 | bs | — |
| b | 2.22 | bs | — |
| c | 3.51 | bd | 9 |
| d | 3.18 | d | 4 |
| e | 4.49 | ddd | 10, 9, 4 |
| f | 2.99 | dd | 10, 9 |
| g | 3.94 | one line of d | not observable |
| h | 3.74, 3.77 | s | — |
| e(plus $D_2O$) | 4.49 | dd | 10, 9 |
| d(plus $D_2O$) | disappears | — | — |

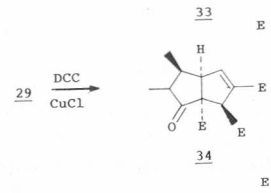


1 - $CH_3$ ester 32

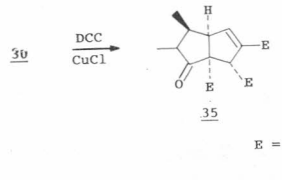
lenolactone methyl ester, catalyst approach from the *exo* face is hindered by the bulky epoxy lactone group. The $\alpha,\beta$-unsaturated acid functionality of pentalenolactone was introduced by dicyclohexylcarbodiimide dehydration[11] of *28—30* in dichloromethane or ether catalyzed by cuprous chloride giving excellent yields of *33—35* (eq. 9—11). These dehydrations could also be effected with phosporous oxychloride or thionyl chloride in pyridine and by mesylation and elimination in pyridine, but the dicyclohexylcarbodi-



(9)



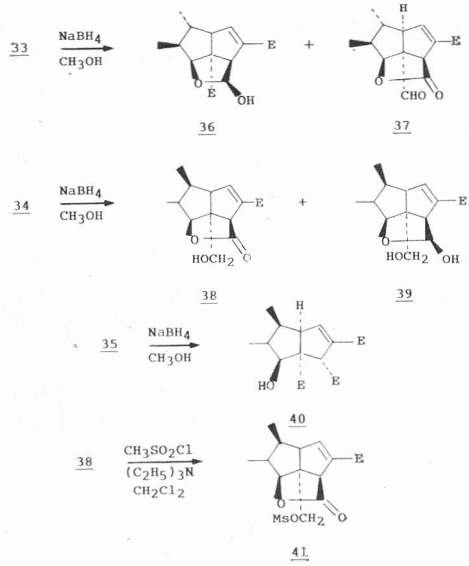
(10)



(11)

imide method gave superior yields and cleaner products. Conditions have not been found to successfully dehydrate isomer *31*.

Proof of the stereochemistry of the endo carbomethoxy group in *33* and *34* and the exo carbomethoxy group in *35* follows from the result of sodium borohydride reduction of the ketone function. Reduction of *33* with sodium borohydride in methanol yields lactol *36* and lactone *37* (eq. 12).



(12)

(13)

(14)

(15)

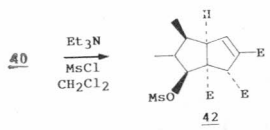
Compound 36 is derived from a precursor lactone and is characterized by a hydroxyl hydrogen stretch in the IR spectrum at 3460 and 3640 $cm^{-1}$ and by a lactol methine at $\delta$ 5.34 in the NMR spectrum. The stereochemistry of the lactol hydroxyl group in *36* is assigned assuming hydride attack from the convex side of the molecule. The fact that lactonization must have occurred leading to *36* proves that the carbomethoxy group of *33* is endo and that hydride reduction of the ketone in *33* occurred from the *exo* face of the molecule. If hydride reduction had occurred from the endo face or if the carbomethoxy group was *exo*, lactonization would have been precluded due to steric strain. Lactone *37* is characterized by a lactone carbonyl stretch in the IR spectrum at 1780 $cm^{-1}$ and an aldehyde proton at $\delta$ 9.82 in the NMR spectrum. Its presence supports the stereochemical assignment of *33*.

Reduction of *34* with sodium borohydride in methanol yields *38* characterized by an alcohol stretch in the IR spectrum at 3505 and a lactone carbonyl band at 1760 $cm^{-1}$ as well as a methylene singlet at $\delta$ 3.72 in the NMR spectrum (eq. 13). Further reduction of *38* is the source of *39* which is characterized by a lactol methine proton at $\delta$ 5.80 in its NMR spectrum. The same arguments concerning stereochemistry apply to *38* and *39* as were rationalized for *36* and *37*. The overreduction seen in *37*, *38* and *39* is typical of $\beta$-ketoesters.

Further proof of structure of *38* was obtained by mesylation with mesyl chloride and triethylamine in dichloromethane[13] to yield *41* (eq. 15). The methylene resonance of *41* moves downfield to $\delta$ 4.38 (s) in the NMR spectrum and *41* does not undergo elimination in refluxing dimethylformamide-pyridine.

Reduction of *35* with sodium borohydride in methanol yields *4* quantitatively (eq. 14). Since *35* does not lactonize during reduction as does *33* and *34*, the carbomethoxy group of *35* must be in the exo geometry. Hydride is assumed to attack *35* from the exo face as is the case with *33* and *34*. Further characterization of *40* is obtained by mesylation with mesyl chloride

and triethylamine in dichloromethane[13] to yield *42* which exhibits a methine at $\delta$ 4.85 ($J = 9$ Hz) in the NMR spectrum (eq. 16). Saponification of *40* in

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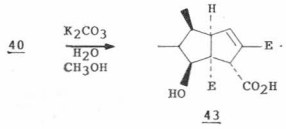
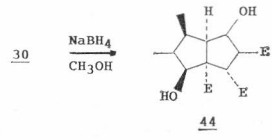



(17)

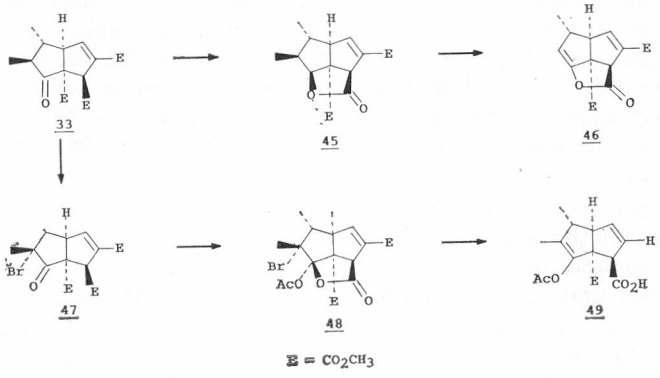
methanol-water with potassium carbonate yields a crystalline monocarboxylic acid *43*. The secondary methyl ester was assumed to have been saponified selectively in preference to the hindered tertiary ester and the less reactive conjugated ester.

Reduction of *28* with sodium borohydride in methanol yields a mixture of lactones and lactols (eq. 9) whereas reduction of *30* yields only diol *44* (eq. 18). This substantiates the above reduction results and stereochemical assignments.




(18)

Attempted enol acetate formation from ketone *33* with acetic anhydride catalyzed by 60% perchloric acid yields acetoxy lactone *45* in 53% yield *via* ketone protonation, intramolecular acylation by the *endo* carbomethoxy group and acetylation. Lactone *45* is characterized by a lactone carbonyl stretch in the IR spectrum at 1795 $cm^{-1}$ and an acetate methyl resonance at $\delta$ 2.12 in the NMR spectrum. Acetate pyrolysis of *45* yields lactone *46* (48% yield) exhibiting a lactone carbonyl stretch in the IR spectrum at 1830 $cm^{-1}$ and a vinyl methyl resonance at $\delta$ 1.65 in the NMR spectrum. The acetate pyrolysis of *45* proceeds *via cis* elimination requiring that the methyl group $\alpha$ to the ketone in *33* be endo.



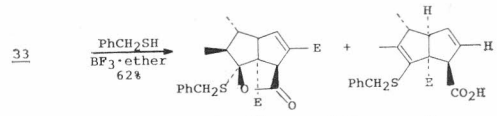

Ketone *33* undergoes nearly quantitative bromination with pyridinium bromide perbromide in acetic acid to yield *47* (97%) assuming bromine

addition from the *exo* face of *33*. Reaction of *47* with acetic anhydride catalyzed by 60% perchloric acid forms acetoxy lactone *48* analogous to *45* in 80% yield. Treatment of *48* with zinc in acetic acid causes 1,2-elimination yielding enol acetate *49* (59% yield). Compound *49* is characterized by a vinyl methyl resonance at $\delta$ 1.53 and an acetate methyl resonance at $\delta$ 2.13 in the NMR spectrum. The conversion of *33* to *49* further substantiates the *endo* geometry of the carbomethoxy group in *33*.

To complete the synthesis of the bicyclo[3.3.0]octane portion of pentalenolactone a method was needed to convert the ketone of *45* into a double bond between the carbonyl and $\alpha$-carbon atoms. The high yield preparation of benzylthioenol ethers from hindered ketones followed by desulfurization to the olefin has been reported.[14,15] Treatment of *33* with benzylmercaptan and borontrifluoride etherate yields benzylthio lactone *50* and benzylthio ether *51* (eq. 19). Compound *50* is characterized by a lactone carbonyl stretch in the IR spectrum at 1800 $cm^{-1}$ and by a resonance at $\delta$ 7.20 for the phenyl ring in the NMR spectrum. Compound *51* exhibits a NMR resonance at $\delta$ 1.93 for a vinyl methyl group and at $\delta$ 7.35 for the phenyl ring. Acid *51* occurs *via* sulfur assisted ionization of the lactone ring followed by proton loss.

Reaction of *34* with benzylmercaptan and boron trifluoride etherate yields benzylthio ethers *52* and *53* (eq. 20). Compounds *52* and *53* exhibit vinyl methyl resonances at $\delta$ 1.63 and 1.60 and an aromatic resonance at $\delta$ 7.30 and 7.36 in their NMR spectra. Ketone *34* tends to undergo less intramolecular acylation than *33* because of the steric crowding caused by the endo methyl group of *34*. The lactone which does form from *34* undergoes complete rearrangement to *53* to relieve the steric strain in the interior of the ring system caused by the *endo* methyl.

A very preliminary study to complete the synthesis of the key precursor of pentalenolactone *2* was initiated. The enol thioether *54* is prepared from the ketone *35* (eq. 21). Raney Ni desulfurization potentially completes the synthesis of *2*. At this point the desulfurization produces largely the fully saturated product with the desired olefin only detected by NMR spectroscopy. Nevertheless, since this result arises from only one attempt,

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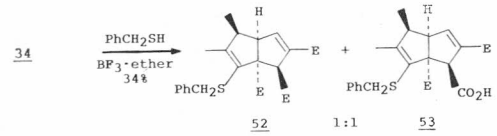
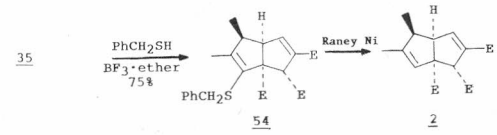



(20)




(21)

E = $CO_2CH_3$

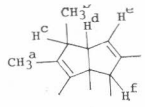
it is felt that this reaction can ultimately be improved. Assignment of the stereochemistry of the saturated methyl group derives from comparison of the NMR shifts of *1*, *51*, *52*, and *54*. From the data in Table II it is seen that the $H^c$ proton in *51* resonates at 0.5 ppm to higher field than in *52* and *54*. This is interpreted as meaning that $H^c$ is experiencing transannular $\sigma$-bond shielding in *51* whereas $H^c$ is deshielded by 0.2 ppm from *1* by the tertiary ester group. Proton $H^f$ is seen to resonate at 0.5 ppm to lower field in *51* and *52*, due to deshielding by the adjacent tertiary ester, than in *54*. The $H^d$ bridgehead proton of *54* resonates at lower field than in *51* or *52* due to deshielding by the exo carbomethoxy group.

## CONCLUSIONS

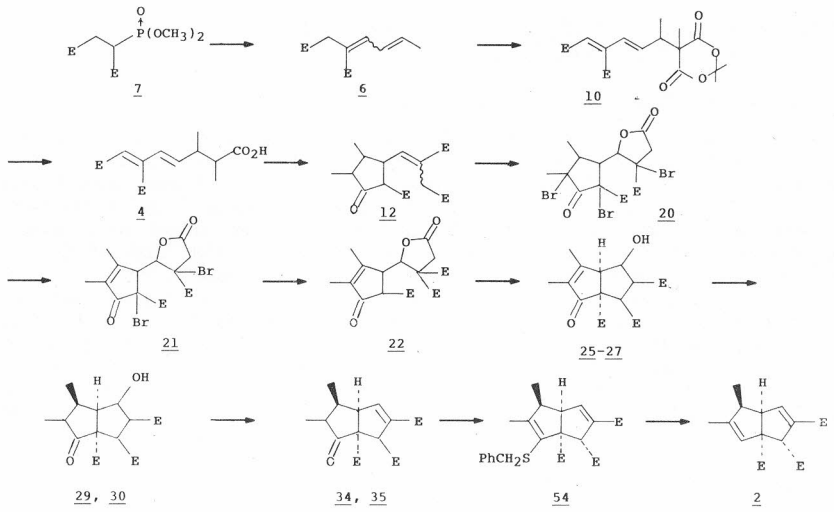
Scheme 4 summarizes the simple twelve step synthesis of the elaborated bicyclo[3.3.0]octyl system of the pentalenolactones. The efficiency of this approach embodying the concept of transfer alkylation is highlighted by the preparation of a highly functionalized bicyclo[3.3.0]octyl building block in only eight steps. The selectivity of the bromination, even in liquid bromine as solvent, and the chemoselective transformation of each bromide is especially noteworthy. Such a strategy could be useful in designing synthesis to other members of this important family of compounds.[3]

TABLE II

*NMR Correlation of 1, 51, 52 and 54.*




| Compound | Proton | Chemical shift ($\delta$) | Multiplicity | $J$ (Hz) |
|---|---|---|---|---|
| 1 | a | 1.65 | t | 1.2, 1.2 |
| 51 | a | 1.93 | s | — |
| 52 | a | 1.63 | s | — |
| 54 | a | 1.45 | d | 1 |
| 1 | b | 1.05 | d | 7.5 |
| 51 | b | 1.19 | d | 7 |
| 52 | b | 1.12 | d | 7.5 |
| 54 | b | 1.10 | d | 7.5 |
| 1 | c | 2.80 | b sextet | 9, 7.5, 2.1, 1.2 |
| 51 | c | 2.59 | b quintet | 6 |
| 52 | c | 3.01 | b quintet | 7.5 |
| 54 | c | 3.17 | b quintet | 7 |
| 1 | d | 3.35 | dq | 9, 3, 2.7 |
| 51 | d | 3.32 | dd | 5, 3 |
| 52 | d | 3.83 | m | — |
| 54 | d | 3.97 | ddd | 7.5, 2, 2 |
| 1 | e | 6.65 | dd | 2.7, 2.1 |
| 51 | e | 6.98 | dd | 3, 2 |
| 52 | e | 6.78 | dd | 2, 2 |
| 54 | e | 6.62 | dd | 2, 1 |
| 1 | f | 3.10 | m | 3, 3, 2.1 |
| 51 | f | 4.65 | bs | — |
| 52 | f | 4.64 | dd | 2, 2 |
| 54 | f | 4.18 | dd | 2.5, 1.5 |



Scheme 4. Linear Sequence for Synthesis of *2*.

## EXPERIMENTAL

All reactions were done under an atmosphere of nitrogen or argon gas. Ethereal solvents were dried by distillation from sodium benzophenone ketyl. Unless otherwise stated, evaporations were done on a Buchi Rotovapor at water aspirator pressure. High vacuum evaporations and drying were conducted at pressures of 0.1—0.01 torr. The silica gel for preparative layer chromatography (plc) and thin layer chromatography (tlc) was from Merck (Silica Gel PF-254). The silica gel for column chromatography was from Davison Chemical or MCB (60—200 mesh). Nuclear magnetic resonance (NMR) spectra were obtained on a Varian Associates A60A, T60 or XL100 spectrometer or a Jeol MH 100 spectrometer. Infrared (IR) spectra were obtained on a Beckman IR8 spectrometer. Ultraviolet (UV) spectra were obtained on a Cary 15 spectrometer. Mass spectra were obtained on an AEC MS-902 spectrometer. Microanalyses were done by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

### *Methyl 3-Carbomethoxy-7-carboxy-6-methyl-cis,trans-2,4-octadienoate (4b)*

A portion (45.8 g, 0.129 mol) of Meldrum's acid analogue *10b*[7] was dissolved in 500 mL of trifluoroacetic acid and stirred at 25 °C for 20 hr. The reaction was then evaporated first at aspirator pressure and then under high vacuum. The remaining portion of *10b* was dissolved in 500 mL of trifluoroacetic acid and stirred at 25 °C for 20 hr. The reaction was evaporated as above. The combined residues were dissolved in 300 mL of DMSO and heated at 120—128 °C for 55 min. The reaction was cooled and poured into 2 L of ice water and 1500 mL of ether. The ether phase was combined with a second 1 L ether extract of the water phase, washed twice with 100 mL of water, once with 500 mL of saturated aqueous sodium chloride solution and dried over magnesium sulfate. The tan, solid residue was powdered in ether, filtered and dried yielding 16 g of white powder. This 16 g of powder was recrystallized from ether-tetrahydrofuran to yield after drying 4.77 g, m. p. 130—131 °C of *4b*. The mother liquor from this recrystallization was reduced in volume and pentane added. The material which crystallized was 4.99 g, m. p. 115—120 °C of *4b*. The total mother liquor was evaporated and recrystallized from ether-pentane to yield 20.28 g of *4b* as a white powder which was pure by NMR analysis. This represents a total yield of 30.0 g (86%) of pure *4b*: IR ($CHCl_3$) OH 3000, C=O 1725 and C=C 1635 and 1615 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.11 (d, methyls, $J = 7$ Hz), 2.1—2.9 (m, two methines), 3.72 and 3.90 (s, $OCH_3$), 5.81 (dd, C—5 vinyl proton, $J = 16$ and 7 Hz), 5.82 (s, C—2 vinyl proton), 6.22 (d, C—4 vinyl proton,

$J$ = 16 Hz) and 13.0 (s, COOH). Anal. Calcd. for $C_{13}H_{18}O_6$ (270.1103): C, 57.75; H, 6.71; Found: C, 57.70; H, 6.57; MW, 270.1103.

*Methyl 3-Carbomethoxy-7-carboxy-6-methyl-trans,trans-2,4-octadienoate (4a)*

A portion (4.73 g, 13.3 mmol) of Meldrum's acid derivative *10a*[7] was dissolved in 50 mL of trifluoroacetic acid and stirred at 25 °C for 20 hr. The reaction was evaporated to a viscous oil which was dissolved in 50 ml of and heated at 130 °C for 40 min. The reaction was cooled, poured into ether-water and extracted twice with ether. The ether extract was washed with water, dried over magnesium sulfate and evaporated to 3.83 g of brown oil. A portion (584 mg) of this oil was purified by lc on silica gel using two elutions with chloroform saturated with formic acid to yield *4a* (325 mg) and *4b* (91 mg). This represents a total yield for the reaction of 76% consisting of 78% *4a* and 22% *4b*. *4a*: IR ($CCl_4$) C=O 1720, 1700, and C=C 1590 and 1625 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 1.17 (d, C—6 methyl and C—8 protons, $J$ = 6 Hz), 2.0—3.0 (m, C—6, 7 methines), 3.73 and 3.80 (s, $OCH_3$), 6.22 (s, C—2 vinyl proton), 6.39 (dd, C—6 vinyl proton, $J$ = 16 and 7 Hz), 7.25 (d, C—4 vinyl proton, $J$ = 16 Hz) and 11.08 (broad, COOH). Anal. Calcd. for $C_{13}H_{18}O_6$: 270.11032. Found: 270.11032.

*cis and trans-2-Carbomethoxy-3-(2',3'-dicarbomethoxyprop-1'-en-1'yl)-4,5--dimethylcyclopentanone (12)*

*Preparation A. Carbonic Anhydride Formation*

To a —78 °C solution of 5.00 g (18.5 mmol) of dienoate *4b* in 50 mL of THF was added 2.58 mL (18.5 mmol) of triethylamine (distilled from KOH) followed after 5 min by the addition of 1.43 mL (18.5 mmol) of methyl chloroformate. The resultant mixture was stirred 2 hr at to —17 °C to 0 °C and then filtered. The filtrate was kept at 0 °C and used below.

*Enolate Generation and Acylation*

To a slurry of 554 mg (23.1 mmol) of sodium hydride (57% in mineral oil) was added dropwise over a 40 min period 3.96 mL (4.01 g, 23.1 mmol) of methyl *t*-butyl malonate. The resultant thick mass was stirred 1 hr at 25 °C. In a glove bag filled with nitrogen gas the enolate mixture was poured into the above prepared carbonic anhydride solution at 0 °C. The resultant reaction mixture was stirred 2 hr at 0 °C and poured into dichloromethane and saturated aqueous ammonium chloride. The organic phase was washed once with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to 8.82 g of oil. This oil was dissolved in 50 mL of trifluoroacetic acid and stirred 12 hr at 25 °C followed by evaporation to give 7.23 g of oil. This residue was purified *via* column chromatography with 700 g (H/D = 28) of silica gel: (fraction (1 l. each), % ether-dichloromethane eluent, weight of evaporated fraction) 1—2, 0, 0; 3—4, 2, 0; 5—7, 3, 0; 8, 3, 39 mg; 9, 5, 511 mg; 10, 5, 1.126 g; 11, 7, 1.042 g; 12, 7, 253 mg; 13, 10, 319 mg; 14, 10, 311 mg; 15—16, 10, 110 mg of crystals. These column fractions were further purified *via* lc on silica gel eluted with 10% ether-dichloromethane. Fraction 9 yielded 400 mg of *12a:* IR ($CCl_4$) C=O 1730 and C=C 1660 $cm^{-1}$; NMR ($CCl_4$) 1.11 (bd, methyls, $J$ = 6 Hz), 1.3—2.4 (m, two methines), 3.0 (m, two methines), 3.38 (s, methylene), 3,65, 3.70 and 3.75 (s, $OCH_3$) and 6.67 (m, vinyl proton): mass spectrum *m/e* (relative intensity) 326(9), 295(28), 294(26), 263(24), 262(100), 234(35), 206(46), 183(53), and 59(47). Anal. Calcd. for $C_{16}H_{22}O_7$: 326.13654. Found: 326.13654. Fraction 12 yielded 185 mg of *12b:* IR ($CCl_4$) C=O 1730 and C=C 1660 $cm^{-1}$; NMR ($CCl_4$) 1.1 (m, two methyls), 1.4—2.5 (m, two methines), 2.84 (d, acetoacetate methine, $J$ = 11 Hz), 3.23 (m, methine) 3.65 and 3.70 (s, three $OCH_3$) and 5.78 (d, viyl) proton, $J$ = 10 Hz); UV $\alpha_{max}^{C_2H_5OH}$ = 217 nm; mas spectrum *m/e* (relative intensity) 326(8), 295(24), 294(34), 263(35), 252(100), 235(30), 234(46), 207(31), 206(59), 183(53), 83(59), 59(71), 56(39), and 55(43). Anal. Calcd. for $C_{16}H_{22}O_7$: 326.13654. Found: 326.13654. Fraction 10 and 11 yielded 840 mg and 883 mg, respectively, of a mixture of *12a* and *12b*. Fractions 15 and 16 are *4b* (2.2%) by m. p. comparison. The total yield of *12a* and *12b* after lc was 2.31 g (38%).

*Preparation B. Carbonic Anhydride Formation*

To a —17 °C solution of 502 mg (1.86 mmol) of *4b* in 7 ml of THF was added 259 μL (1.86 mmol) of triethylamine (distilled from KOH) followed after 5 min by the addition of 1.43 mL (18.5 mmol) of methyl chloroformate. The resultant mixture was stirred 1 hr at —17 °C to —10 °C and then filtered and the filtrate used below. The filtered precipitate was dried yielding 257 mg (99%) of triethylamine hydrochloride.

*Acylation*

The above prepared carbonic anhydride in approximately 15 mL of THF was added over a 7 min period to a slurry of 743 mg (3.79 mmol) of methyl *t*-butyl sodiomalonate in 15 mL of THF at 25 °C. The reaction was stirred an additional 75 min at 25 °C and then evaporated. The residue was dissolved in 25 mL of trifluoroacetic acid and stirred 15 min at 25 °C. The reaction was then evaporated and the residue diluted with 150 mL ether and 50 mL of ice. The organic phase was washed twice with 50 mL of 7% $NaHCO_3$, dried over magnesium sulfate and evaporated to 522 mg of oil. This oil was purified *via* lc on silica gel eluting twice with 60% ether-pentane to yeld 4.7 mg (0.9%) ($R_f$ 0.71) of methyl 3,7-dicarbomethoxy-6-methyl-*cis,trans*-2,4-octadienoate: IR ($CCl_4$) C=O 1730, C=C 1610 and 1635 $cm^{-1}$, NMR ($CCl_4$) 1.05 (d, $CH_3$, $J = 6.5$ Hz), 1.08 (d, $CH_3$, $J = 6.75$ Hz), 2.1—2.8 (m, two methines), 3.64, 3.70 and 3.81 (s, three $OCH_3$), 5.71 (s, C—2 vinyl proton), 5.72 (dd, C—5 vinyl proton, $J = 16$ and 7 Hz) and 6.15 (d, C—4 vinyl proton, $J = 16$ Hz) and 411 mg (68%) ($R_f$ 0.44) of *12a* and *12b* in a ratio of 1 : 1.

*2-Bromo-2-carbomethoxy-3-(2',3'-dicarbomethoxyprop-1'-en-1'-yl)-4,5-dimethylcyclopentanone (13) and 2-Carbomethoxy-3-(2',3'-dicarbomethoxyprop-1'--en-1'-yl)-4,5-dimethylcyclopent-4-enone (14)*

To a solution of 117.8 mg (0.361 mmol) of a 2 : 1 *cis : trans* mixture of cyclopentanone *12* in 3 mL of carbon tetrachloride was added 65.9 mg (0.370 mmol) of NBS and a trace of dibenzoyl peroxide. The reaction mixture was then heated at reflux for 1 hr. The reaction mixture was cooled, filtered and evaporated to a colorless oil. The NMR of this oil shows it to be *13:* NMR ($CCl_4$) $\delta$ 1.0—1.4 (m, methyls), 1.5—2.4 (m, methines), 3.02 (t, methine, $J = 10$ Hz), 3.36 (s, methylene), 3.65, 3.66, 3.75 and 3.78 (s, $OCH_3$), 5.91 (d, vinyl proton, $J = 10$ Hz) and 6.75 (d, vinyl proton, $J = 10$ Hz). Purification of this crude product on silica gel ($CaSO_4$ binder) eluted with 60% ether-hexane yielded 86.8 mg (74%) of a new compound *14*: NMR ($CCl_4$) $\delta$ 1.70 and 2.00 (bs, vinyl methyls), 2.9—3.5 (m, methylene), 3.65 and 3.71 (s, $OCH_3$), 5.70 (d, vinyl proton, $J = 10$ Hz) and 6.59 (d, vinyl proton, $J = 10$ Hz). See preparation of *18* for additional data.

*2-Bromo-2-carbomethoxy-3-(2',3'-dicarbomethoxyprop-1'-en1'-yl)-4,5--dimethylcyclopent-4-enone (16)*

To a solution of 86.8 mg (0.268 mmol) of *cis* and *trans* enone *14* in 3 mL of carbon tetrachloride was added 48.0 mg (0.270 mmol) of NBS and a trace of dibenzoyl peroxide. The reaction mixture was heated at reflux for 0.5 hr. The reaction was cooled, filtered and the filtrate evaporated to an oil. This oil was purified *via* lc on silica gel eluted twice with 60% ether-pentane to yield 75.2 mg (63%) ($R_f$ 0.37) of *16* as two isomers: IR ($CCl_4$) C=O 1725 and C=C 1645; $cm^{-1}$; NMR ($CCl_4$) $\delta$ 1.80 and 2.02 (bs, vinyl methyls), 3.45 and 3.48 (s, methylene), 3.69, 3.76 and 3.80 (s, $OCH_3$), 4.2 (m, methine) and 6.49 and 6.58 (d, vinyl protons, $J = 10$ Hz). See preparation of *16a* for additional data.

*Dehydrobromination of 2-Bromo-2-carbomethoxy-3-(2',3'-dicarbomethoxyprop--1'-en-1'-yl)-4,5-dimethylcyclopentanone (13) with 1,5-Diazabicyclo-[4.3.0]-non--5-ene*

To a solution of 85.5 mg (0.262 mmol) of a 2 : 1 *cis:trans* mixture of cyclopentanone *12* in 3 mL of carbon tetrachloride was added 46.7 mg (0.262 mmol) of NBS and a trace of dibenzoyl peroxide. The reaction mixture was heated at reflux

for 1 hr and then cooled and filtered. Evaporation of the filtrate yielded an oil which was pure *13* by NMR. This crude bromide was dissolved in 3 mL of ether and cooled to —78 °C. To this cold solution was added dropwise 32.8 mg (0.265 mmol) of DBN. The reaction was stirred 20 min at —78 °C with no formation of a precipitate. The reaction was then warmed to —23 °C causing immediate formation of a tan precipitate. The reaction was stirred 10 min at —23 °C and then allowed to warm to 25 °C and poured into ether-water. The ether extract was washed once with water, dried over magnesium sulfate and evaporated to an oil. This oil was purified *via* lc on silica gel eluted twice with 60% ether-pentane to yield 29.5 mg ($R_f$ 0.35) and 12.2 mg ($R_f$ 0.26). The material of $R_f$ 0.26 is mostly *cis* and *trans* cyclopentenone *14* contaminated with a small amount of *15* by NMR analysis (see preparation of *14*). The material of $R_f$ 0.35 was further purified *via* lc on silica gel ($CaSO_4$ binder) eluting once each with 50 and 60% ether-pentane to yield a pure oil removed from the front portion of a band of $R_f$ 0.24: 7.1 mg of 2-carbomethoxy-3-(2,3-dicarbomethoxy-propylidene)-4,5-dimethylcyclopent-4-enone (15): IR ($CCl_4$) C=O 1745, 1710 and C=C 1614 $cm^{-1}$; NMR ($CCl_4$) 1.83 and 2.11 (s, two vinyl methyls), 2.45—2.75 (6 lines, methylene), 3.3—4.0 (m, side chain methine), 3.68 and 3.72 (s, $OCH_3$), 3.90 (bs, cyclopentanone methine) and 5.61 (bd, vinyl proton, $J = 10$ Hz); UV (ethanol) 279 nm; mass spectrum *m/e* (relative intensity) 324(14), 261(18), 260(100), 233(49), 232(42), 200(34), 149(41) and 59(26).

*2-Carbomethoxy-cis-3-(2¹,3¹-dicarbomethoxyprop-1¹-en-1¹-yl)-2,5-dibromo-4,5-dimethylcyclopentanone (17)*

To a solution of 125 mg (0.384 mmol) of a 2 : 1 *cis:trans* mixture of cyclopentanone *12* in 3 mL of carbon tetrachloride was added 206 mg (1.15 mmol) of NBS and a trace of dibenzoyl peroxide. The reaction mixture was heated at reflux for 5 hr, cooled and filtered. The filtrate was evaporated to a yellow oil which appeared to be pure *17* by NMR analysis. This crude product was purified *via* lc on silica gel eluting with 60% ether-pentane to yield 157 mg (84%) ($R_f$ 0.38) of *17*: IR ($CCl_4$) C=O 1730 and C=C 1650 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 1.15 (d, methyl, $J = 6.5$ Hz), 1.90 (s, $CBrCH_3$), 1.4—2.2 (m, methine), 3.40 (s, methylene), 3.35 (dd, allylic methine, $J = 11$ and 10 Hz), 3.67, 3.76 and 3.84 (s, $OCH_3$) and 6.71 (d, vinyl proton, $J = 10$ Hz). Anal. Calcd. for $C_{16}H_{20}Br_2O_7$: 481.9577. Found: 481.9556.

*2-Bromo-2-carbomethoxy-cis-3-(2',3'-dicarbomethoxyprop-1'-en-1'-yl)-4,5-dimethylcyclopent-4-enone (16a)*

To a mixture of 48.1 mg (0.650 mmol) of lithium carbonate and 139 mg (1.60 mmol) of lithium bromide in 1 mL of DMF at 25 °C was added 122 mg (0.252 mmol) cyclopentanone *17* in 2 mL of DMF. After stirring 30 min at 25 °C, the reaction was poured into ether-water. The ether phase was washed twice with water, dried over magnesium sulfate and evaporated to an oil. This oil was purified *via* lc on silica gel eluting with 80% ether-pentane to yield 68.0 mg (68%) ($R_f$ 0.38) of *16a:* IR ($CCl_4$) C=O 1725 and C=C 1650 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 1.80 (bs, vinyl methyl), 2.03 (s, vinyl methyl), 3.45 and 3.48 (s, methylene), 3.69, 3.74 and 3.80 (s, $OCH_3$), 4.20 (m, methine), 6.48 and 6.58 (d, vinyl protons, $J = 10.5$ Hz); mass spectrum *m/e* (relative intensity) 402(0.6), 404(0.6), 323(20), 291(100), 263(100) and 59(10).

*2-Carbomethoxy-cis-3-(2',3'-dicarbomethoxyprop-1'-en-1'-yl)-4,5-dimethylcyclopent-4-enone (18)*

To a solution of 204 mg (0.506 mmol) of bromocyclopentenone *16a* in 1 mL of glacial acetic acid at 25 °C was added 400 mg (6.16 mmol) of zinc dust. The reaction mixture was stirred 20 min at 25 °C and then poured into ether-water. The ether phase was washed twice with water, dried over magnesium sulfate and evaporated to an oil. This oil was purified *via* lc on silica gel eluting twice with 60% ether-pentane to yield 96.6 mg (59%) ($R_f$ 0.32) of 18: IR ($CCl_4$) C=O 1725 and C=C 1650 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 1.70 and 2.00 (bs), vinyl methyls), 3.10 (d, methine, $J = 4$ Hz), 3.41 (s, methylene), 3.66 and 3.70 (s, $OCH_3$), 4.0 (m, methine) and 6.60 (d, vinyl proton, $J = 10.5$ Hz). Anal. Calcd. for $C_{16}H_{20}O_7$: 324.12089. Found: 324.12148.

*2-Carbomethoxy-2,5-dibromo-3-(4'-bromo-4'-carbomethoxy-2'-oxotetrahydrofuran-5'-yl)-4,5-dimethylcyclopentanone (20)*

*Preparation A*

A solution of 728 mg (1.50 mmol) of dibromocyclopentanone *17* in 1.5 mL of carbon tetrachloride and 8 mL of bromine was stirred at 25 °C for 22 hr. The reaction was diluted with dichloromethane and evaporated to an orange oil. This oil was purified *via lc* on silica gel ($CaSO_4$ binder) eluting with 60% ether-pentane to yield 204 mg (24.7%) ($R_f$ 0.50) of *20* and 47.9 mg (6%) ($R_f$ 0.24) of another isomer of *20*. *20* ($R_f$ 0.50: m. p. 164—165 °C from ether: IR ($CHCl_3$) C=O 1790 and 1740 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.28 (d, methyl, $J = 7$ Hz), 191 (s, $CBrCH_3$), 3.22 (q, methine adjacent to methyl, $J = 7.5$ Hz), 3.36 (d, methine, $J = 4$ Hz), 3.54 (s, methylene), 3.73 and 3.89 (s, $OCH_3$) and 5.46 (d, O—C—H, $J = 4$ Hz); NMR ($CDCl_3$ + Eu(fod)$_3$) the four lines of the methine coupled only to adjacent methyl can be seen with $J = 7.5$ Hz and the methylene resonance becomes an AB pattern; NMR (100 MHz) ($CDCl_3$ spin decoupling: irradiation of the $\delta$ 1.28 methylene doublet causes collapse of the $\delta$ 3.22 methine quartet to a singlet and irradiation of the $\delta$ 5.46 doublet causes collapse of the $\delta$ 3.36 doublet; at 100 HMz the methylene resonance changes to an AB pattern. Mass spectrum *m/e* (relative intensity) 553(0.5), 552(2), 551(1), 550(6), 549(1), 548(6), 547(0.5), 546(2), 440(23), 438(44), 436(23), 113(22), 85(52), 80(25), 79(39), 77(25), 59(85), and 55(100). Isomer of *20* ($R_f$ 0.24): m. p. 161—163 °C from ether-chloroform; IR ($CHCl_3$) C=O 1805 and 1745 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.55 (s, methyl), 1.55 (m, methine), 1.82 (s, $CBrCH_3$), 3.44 (part of a methine, $J = 1.5$ Hz), 3.49 (s, methylene), 3.72 and 3.90 (s, $OCH_3$) and 5.06 (d, O—C—H, $J = 1.5$ Hz); mass spectrum *m/e* (relative intensity) 552(0.1), 550(0.3), 548(0.2), 546(0.1), 307(57), 275(21), 135(75), 82(100), 81(66), 80(100), 79(68), 77(36) and 59(33).

*Preparation B*

To a solution of 9.36 g (28.7 mmol) of *cis* and *trans* cyclopentanone *12* in 75 mL of carbon tetrachloride was added 15.3 g (86.2 mmol) of NBS and a small amount of dibenzoyl peroxide. The reaction mixture was heated at reflux for 11 hr and then cooled. The cold reaction was filtered and its filtrate evaporated to an oil which is pure *17* by NMR analysis. This unpurified *17* was dissolved in 118 mL of bromine and heated at vigorous reflux for 29.5 hr. The reaction was cooled, diluted with dichloromethane and carbon tetrachloride and evaporated to an oil. NMR analysis of this oil shows it to be pure *20*. This crude *20* is then used without further purification in large scale preparations of *21*.

*2-Bromo-2-carbomethoxy-3-(4'-bromo-4'-carbomethoxy-2'-oxotetrahydrofuran-5'-yl)-4,5-dimethylcyclopent-4-enone (21)*

To a solution of 200 mg (0.364 mmol) of lactone *20* (higher $R_f$ isomer) in 2 mL of DMF was added 35.3 mg (0.477 mmol) of lithium carbonate and 131 mg (1.50 mmol) of lithium bromide. The reaction was stirred 5 min at 25 °C, 15 min at 39 °C and 10 min at 42 °C. The reaction was cooled and poured into ether-water. The ether phase was washed twice with water, dried over magnesium sulfate and evaporated to an oil. This oil was crystallized from ether to yield 137.2 mg (81%) of *21*: m. p. 170.5—171.5 °C; IR ($CHCl_3$) C=O 1795, 1730 and C—C 1645 $cm^{-1}$; NMR ($CDCl_3$) 1.83 and 2.30 (bs, vinyl methyls), 3.50 (s, methylene), 3.72 and 3.9 (s, $OCH_3$), 4.14 (bs, methine) and 5.00 (d, $J = 2.5$ Hz). Anal. Calcd. for $C_{15}H_{16}Br_2O_7$: 465.92637. Found: 465.93181.

*2-Carbomethoxy-3-(4'-bromo-4'-carbomethoxy-2'-oxotetrahydrofuran-5'-yl)-4,5-dimethylcyclopent-4-enone (22)*

*Preparation A*

was washed once with water, dried over magnesium sulfate and evaporated. The residue was crystallized from ether yielding 22.15 mg (71%) of *22* (m. p. 162 °C) which exhibited spectral characteristics identical to *22* prepared below.

*Preparation B*

A solution of 15.7 g (28.7 mmol) of lactone (*20*, unpurified) in 25 mL of DMF was added dropwise over a 10 min period to a solution of 8.37 g (96.3 mmol) of lithium bromide and 2.92 g (39.5 mmol) of lithium carbonate in 45 mL of DMF at 52 °C. The reaction was heated an additional 15 min at 52—54 °C and then cooled. The reaction was poured into 500 mL of ether and 300 mL of ice water. The ether phase was washed twice with water and once with saturated sodium chloride solution. The total aqueous phase was extracted with ether and this ether phase washed twice with water and once with saturated sodium chloride solution. The combined ether extract was dried over magnesium sulfate and evaporated to an oil. This oil was dissolved in 50 mL of acetone and added to a 25 °C slurry of 100 g (0.66 mol) of sodium iodide, 71.3 g (0.287 mol) of sodium thiosulfate pentahydrate and 17.1 mL of acetic acid in 200 mL of acetone. The resultant mixture was stirred 70 min at 25 °C and then evaporated to a thick mass. This mass was poured into ether-water. The ether extract along with a second ether extract of the water phase was dried over magnesium sulfate. Evaporation of the ether phase yielded a solid which was washed with ether and dried under vacuum at 50 °C to yield 4.24 g of *22* as a light tan powder. The mother liquor (3.66 g) was purified *via* lc on silica gel eluting with 10% ether-dichloromethane to yield 674 mg after crystallization from ether ($R_f$ 0.53) of *22* (total yield 44%), 521 mg ($R_f$ 0.41) (5.9%) and 285 mg ($R_f$ 0.29) (3.2%) of two isomers of 3-carbomethoxy-3-(4'-carbomethoxy-2'-oxo-2',5'-dihydrofuran-5'-yl)-4,5-dimethyl-cyclopent-4-enone (*23*) identified by comparison of NMR data with samples prepared elsewhere in this experimental. *22:* m. p. 164—164.5 °C from methanol; IR ($CHCl_3$) C=O 1785, 1740, 1710 and C—C 1645 $cm^{-1}$; NMR ($CDCl_3$) (100 MHz) 1.76 and 2.27 (s, vinyl methyls), 3.48 (s, methylene), 3.60 (one line of a methine), 3.68 and 3.86 (s, $OCH_3$), 3.98 (b, methine) and 4.96 (d, O—C—H, $J = 2$ Hz). Anal. Calcd. for $C_{15}H_{17}BrO_7$: C, 46.37; H, 4.45; Br, 20.49. Found: C, 46.26; H, 4.40; Br, 20.56.

*2-Carbomethoxy-3-(4'-carbomethoxy-2'-oxo-2',5'-dihydrofuran-5'-yl)--dimethylcyclopent-4-enone (23)*

To 61.4 mg (158 mol) of cyclopentenone *22* was added 1 mL (7.18 mmol) of triethylamine (distilled from potassium hydroxide). The resultant mixture was stirred 2 hr at 25 °C and then another 1 mL portion of triethylamine was added. After the reaction stirred 1 hr longer at 25 °C, 0.5 mL of dichloromethane was added creating a more homogeneous reaction. The reaction was stirred an additional 1.5 hr at 25 °C and then evaporated, the residue dissolved in dichloromethane and immediately purified *via* lc on silica gel eluting three times with 10% ether-dichloromethane to yield 19.0 mg (39%) *23* ($R_f$ 0.56): IR ($CCl_4$) C=O 1786 and 1725, C=C 1645 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 1.75 (d, vinyl methyl, $J = 1$ Hz), 2.22 (d, vinyl methyl, $J = 1$), 3.55 (m, methine), 3.73 (s, methine), 3.84 (s, $CO_2CH_3$), 6.20 (d, methine, $J = 3$ Hz) and 6.94 (s, vinyl proton); UV (ethanol) 242 nm ($\varepsilon = 11{,}000$) and 214 nm ($\varepsilon = 14{,}120$). Anal. Calcd. for $C_{15}H_{16}O_7$: 308.08959. Found: 308.08763. In addition, 20.0 mg (41%) of a second isomer of *23* ($R_f$ 0.47) is isolated: IR ($CCl_4$) C = O 1793 and 1725 and C=C 1645 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 1.75 (d, vinyl methyl, $J = 1$ Hz), 2.12 (d, vinyl methyl, $J = 2$ Hz), 3.57 (s, methine), 3.60 (m, methine), 3.79 and 3.88 (s, $CO_2CH_3$), 5.08 (d,d, methine, $J = 1.5$ and 1.5 Hz) and 6.28 (d, vinyl proton, $J = 1.5$ Hz); *UV* (ethanol) 237 nm ($\varepsilon = 10{,}248$). Anal. Calcd. for $C_{15}H_{16}O_7$: 308.08959. Found: 308.08984.

*3-Carbomethoxy-3-(2',3'-dicarbomethoxy-1'-hydroxyprop-2'-en-1'-yl)-4,5--dimethylcyclopent-4-enone (24)*

To a solution of 120 mg (308 mol) of cyclopentenone *22* in 1 mL of dichloromethane at 0 °C was added 3 mL of 0.318 M sodium methoxide in methanol (954 $\mu$mol of sodium methoxide) over a 5 min period. After the reaction stirred another 15 min at 0 °C it was poured in 50 mL of dichloromethane and 30 mL of 0.1 M

HCl. The organic phase was dried over magnesium sulfate and evaporated to an oil. This oil was purified *via* lc on silica gel eluting three times with 15% ether--dichloromethane to yield 3.96 mg of $R_f$ 0.62 and 6.92 mg of $R_f$ 0.47 both unidentified as well as 58.6 mg of $R_f$ 0.26 which yielded 41.8 mg (40%) of *24* as white crystals from ether; m. p. 148 °C; IR ($CHCl_3$) OH 3620 and 3380, C=O 1740, 1725 and 1710 and C=C 1648 $cm^{-1}$; NMR ($CHCl_3$) $\delta$ 1.71 (s, vinyl methyl), 2.11 (s, vinyl methyl), 3.00 (d, OH, disappears with $D_2O$ addition, $J = 4$ Hz), 3.36 (m, methines), 3.70, 3.76 and 3.80 (s, $CO_2CH_3$), 4.95 (quintet, H—COH, $J = 4$, 2 and 2 Hz, goes to dd, $J = 2$ and 2 Hz with addition of $D_2O$) and 6.30 (d, vinyl proton, $J = 2$ Hz). Anal. Calcd. for $C_{16}H_{20}O_8$: 340.11580. Found: 340.11828.

*Bicyclo[3.3.0]-3,4-dimethyl-6-hydroxy-2-oxo-1,7,8-tricarbomethoxy--3-octene (25, 26 and 27)*

*Preparation A*

To a slurry of 4.24 g (10.9 mmol) of cyclopentenone (*22*) in 50 mL of methanol (distilled from magnesium) was added dropwise over a 24 min period 10.9 mL of 1.5 M sodium methoxide in methanol (16.4 mmol sodium methoxide). The resultant red-brown solution was stirred 5 min at 0 °C and then allowed to warm to 25 °C and stirred 2 hr. The reaction was poured into ether-water-1 M HCl. The ether extract was dried over magnesium sulfate and evaporated to 3.48 g of orange oil. This oil was purified *via* lc on silica gel eluting twice with 10% ether-dichloromethane to yield a yellow band ($R_f$ 0.76) which must be removed from the silica gel with methanol, 572 mg (15%) ($R_f$ 0.62) of *27*, 76 mg ($R_f$ 0.47), 1.14 g of crystals from ether and 427 mg of mother liquor ($R_f$ 0.29) (43% total) of *25* and 317 mg ($R_f$ 0.15) (9%) of *26*. *25:* m. p. 133.5—134.5 °C from ether-dichloromethane; IR ($CHCl_3$) OH 3560, C=O 1730, 1700 and C=C 1640 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.75 and 2.22 (bs, vinyl methyls), 2.99 (dd, methine, $J = 10$ and 9 Hz), 3.18 (d, $J = 4$ Hz, OH proton which disappears upon addition of $D_2O$), 3.51 (bd, bridgehead methine, $J = 9$ Hz), 3.74 and 3.77 (s, $OCH_3$), 3.94 (one line of a methine) and 4.49 (ddd, O—C—H, $J = 10$, 9 and 4 Hz, collapses to a dd upon addition of $D_2O$ with $J = 9$ and 10 Hz). Anal. Calcd. for $C_{16}H_{20}O_8$: C, 56.45; H, 5.92; MW, 340.11580. Found: C, 56.48; H, 5.90; MW, 340.11915.

*26:* IR ($CCl_4$) OH 3520, C=O 1725 and C=C 1650 $cm^{-1}$; NMR ($CCl_4$) 1.72 (bs, vinyl methyl), 2.10 (bs, vinyl methyl), 2.92 (d, OH, $J = 4$ Hz), 3.4 (m, methines), 3.67, 3.72 and 3.76 (s, $OCH_3$) and 4.70 (m, O—C—H). *27:* IR ($CCl_4$) OH 3450, C=O 1745, 1720 and C=C 1660 $cm^{-1}$; NMR ($CCl_4$) (100 MHz) $\delta$ 1.77, 2.07 and 2.12 (s, vinyl methyls), 2.7—3.2 (m, two methines), 3.2—4 (m, methine), 3.70, 3.74, 3.77, 3.84 and 3.87 (s, $OCH_3$), 4.28 (six line multiplet, methine) and 4.64 (bs, methine).

*Preparation B*

To a 0 °C slurry of 35.8 mg (0.155 mmol) of cyclopentenone *24* in 1 mL methanol was added dropwise 536 μL of 0.318 M sodium methoxide in methanol (0.170 mmol of sodium methoxide). The resultant yellow solution was allowed to warm to 25 °C and stirred 45 min longer. The reaction was diluted with dichloromethane and poured into 50 mL dichloromethane and 30 mL 0.1 M HCl. The organic phases was dried over magnesium sulfate and evaporated to an oil. This oil was purified by lc on silica gel eluting with 20% ether-dichloromethane to yield 2.75 mg (*Rf* 0.37) of unidentified material and 20.3 mg ($R_f$ 0.19) of *25* which yielded 17.4 mg of crystals from ether and 2.95 mg ($R_f$ 0.09) of unidentified material.

*Preparation C*

To a solution of 19.0 mg (61.6 mol) of *23* (lower $R_f$ isomer) in 1 mL of methanol at 25 °C was added 213 μL of 0.318 M sodium methoxide in methanol (0.0677 mmol sodium methoxide). The reaction was stirred 1 hr, diluted with dichloromethane and poured into 15 mL dichloromethane and 5 mL 0.1 M HCl. The organic phase was dried over magnesium sulfate and evaporated to an oil. This oil was purified *via* lc on silica gel eluting with 10% ether-dichloromethane to yield 7.71 mg ($R_f$ 0.53), 7.56 mg (36%) ($R_f$ 0.18) of *25* which crystallized to 4.1 mg of white powder from ether-pentane, 1.98 ($R_f$ 0.09) and 1.19 mg ($R_f$ 0).

*Bicyclo[3.3.0]-3,4-dimethyl-6-hydroxy-2-oxo-1,7,8-tricarbomethoxyoctane (28 and 29)*

To a solution of 2.35 g (6.91 mmol) of diquinane *25* in 25 mL of glacial acetic acid was added 1.2 g of 10% palladium on carbon. The mixture was stirred 24 hr under 1 atm of hydrogen gas pressure with a hydrogen uptake of 284 mL. The reaction was filtered through filter cel with 500 mL of ethyl acetate. The filtrate was evaporated to an oil. This oil was purified *via* lc on silica gel eluting twice with 10% ether-dichloromethane to yield 656 mg (28%) ($R_f$ 0.53) of *29:* IR ($CHCl_3$) OH 3420, C=O 1730 $cm^{-1}$; NMR (100 MHz) ($CDCl_3$) $\delta$ 1.12 (d, methyl, $J$ = Hz), 1.26 (d, methyl, $J$ = 6 Hz), 2.0—2.8 (m, methines), 2.94 (dd, bridgehead methine, $J$ = 7 and 5 Hz), 3.30 (d, methine, $J$ = 1 Hz), 3.78, 3.80 and 3.84 (s, $OCH_3$), 4.02 (d, methine, $J$ = 7 Hz), 4.40 (d, methine, $J$ = 3 Hz) and 4.74 (t, methine, $J$ = 6 Hz). Anal. Calcd. for $C_{16}H_{22}O_8$: 342.13450. Found: 342.13596. In addition there was isolated 1.43 g (61%) ($R_f$ 0.41) of *28:* IR ($CCl_4$) OH 3580 and C = O 1730 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 1.09 (d, methyl, $J$ = 6 Hz), 1.31 (d, methyl, $J$ = 5.5 Hz), 1.5—3.6 (m, methines), 3.71, 3.75 and 3.79 (s, $OCH_3$), 3.98 (one line of a methine) and 4.3—4.7 (m, methine). Anal. Calcd. for $C_{16}H_{22}O_8$: 342.13145. Found: 342.13545.

*Bicyclo[3.3.0]-3,4-dimethyl-6-hydroxy-2-oxo-1,7,8-tricarbomethoxyoctane (30)*

To a solution of 83.0 mg (0.244 mmol) of diquinane *26* in 5 mL of glacial acetic acid was added 91 mg of 10% palladium-on-carbon. The mixture was stirred 20 hr under 1 atm of hydrogen gas pressure with a hydrogen uptake of 9.8 mL. The reaction was diluted with ethyl acetate and filtered through filter cel with 250 mL of ethyl acetate. The filtrate was evaporated to an oil. This oil was purified *via* lc on silica gel eluting with 20% ether-dichloromethane to yield 74.4 mg (89%) ($R_f$ 0.41) of *30* which will grow large crystals in ether: IR ($CCl_4$) OH 3520 and C=O 1730 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 1.06 (d, methyl, $J$ = 6.5 Hz), 1.27 (d, methyl, $J$ — 6.5 Hz), 1.8—2.6 (m, methines), 2.7—3.0 (m, methine, collapses to a dd with $D_2O$ added $J$ = 5 and 3 Hz), 3.25 (bs, OH, disappears with $D_2O$ addition), 3.35 (d, methine, $J$ = 2.5 Hz), 3.49 (one line of a methine), 3.62, 3.66 3.70 (s, $OCH_3$) and 4.5—4.75 (m, methine, still m with $D_2O$ added); mass spectrum *m/e* (relative intensity) 342(86), 311(41), 310(34), 265(21), 264(25), 251(25), 250(75), 241(33), 236(30), 233(21), 222(20), 210(67), 209(81), 205(33), 204(22), 191(21), 181(58), 178(32), 177(100), 169(22), 166(24), 165(23), 163(25), 151(32), 150(32), 139(27), 137(25), 135(22), 119(23), 118(22), 113(23), 93(23), 91(39), 79(38), 77(32), 69(32), 60(48) and 59(97).

*Bicyclo[3.3.0]-3,4-dimethyl-6-hydroxy-2-oxo-1,7,8-tricarbomethoxyoctane (31)*

To a solution of 1.64 g (4.82 mmol) of diquinane *27* in 15 mL of glacial acetic acid was added 900 mg of 10% palladium-on-carbon. The mixture was stirred 24 hr under 1 atm of hydrogen gas pressure with a hydrogen uptake of 183 mL. The reaction was filtered through filter cel with 500 mL of ethyl acetate. The filtrate was evaporated to an oil. This oil was purified *via* lc on silica gel eluting with 10% ether-dichloromethane to yield 1.52 g (92%) ($R_f$ 0.53) of *31* as a mixture of isomers: IR ($CCl_4$) OH 3560, C=O 1725 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 0.65 and 0.66 (d, methyl, $J$ = 7 Hz), 1.05 (d, methyl, $J$ = 7 Hz), 2.3—3.4 (m, methines), 3.68, 3.71 and 3.76 (s, $OCH_3$) and 3.8—4.4 (m, methines).

*Bicyclo[3.3.0]-3,4-dimethyl-2-oxo-1,7,8-tricarbomethoxy-6-octene (33)*

To a solution of 1.43 (4.18 mmol) of diquinane *28* in 5 mL of dichloromethane (distilled from $CaH_2$) was added 1.13 g (5.50 mmol) of DCC and a trace of cuprous chloride. The reaction mixture was heated at reflux for 12 hr, cooled, diluted with ether and filtered. The filtrate was evaporated to an oil. This oil was purified *via* lc on silica gel eluting with 10% ether-dichloromethane to yield 1.00 g (74.5%) ($R_f$ 0.71) of *33* which crystallizes upon standing: IR ($CCl_4$) C=O 1750, 1725, C=C 1640 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 1.09 (d, methyl, $J$ = 6 Hz), 1.29 (d, methyl, $J$ = 6 Hz), 1.4—2.7 (m, methines), 3.32 (dd, bridgehead methine, $J$ = 9 and 2.5 Hz), 3.69 and 3.76 (s, $OCH_3$), 4.60 (d, methine, $J$ = 1.5 Hz) and 7.02 (dd, vinyl proton $J$ = 2.5 and 1.5 Hz). In addition, there is isolated 312 mg (23.1%) ($R_f$ 0.65) of a mixture of two com-

pounds one of which is *34* by comparison of NMR resonances and the other probably an isomer in approximately a 50 : 50 ratio.

*Bicyclo[3.3.0]-3,4-dimethyl-2-oxo-1,7,8-tricarbomethoxy-6-octene (34)*

To a solution of 656 mg (1.92 mmol) of diquinane *29* in 3 mL of dichloromethane (distilled from $CaH_2$) was added 515 mg (2.50 mmol) of DCC and a trace of cuprous chloride. The reaction mixture was heated at reflux for 24 hr, cooled and filtered. The filtrate was evaporated to an oil. This oil was purified *via* lc on silica gel eluting with 10% ether-dichloromethane to yield 31.0 mg ($R_f$ 0.71) of a material derived only from DCC as judged by its NMR spectrum and 547 mg (88%) ($R_f$ 0.53) of 34: IR ($CCl_4$) C=O 1730 and C=C 1645 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 1.06 (bd, methyl, $J$ = 6 Hz), 1.30 (bd, methyl, $J$ = 6 Hz), 1.7—2.4 (m, two methines), 3.65, 3.71 and 3.75 (s, $OCH_3$), 4.51 (dd, methine, $J$ = 2 and 2 Hz) and 6.76 (dd, vinyl proton, $J$ = 2 and 2 Hz).

*Bicyclo[3.3.0]-3,4-dimethyl-2-oxo-1,7,8-tricarbomethoxy-6-octene (35)*

To a solution of 345 mg (1.01 mmol) of diquinane *30* in 2 mL of dichloromethane (distilled from $CaH_2$) was added 271 mg (1.32 mmol) of DCC and a trace of cuprous chloride. The reaction mixture was heated at reflux for 24 hr, cooled and filtered. The filtrate was evaporated to an oil. This oil was purified *via* lc and silica gel eluting with 10% ether-dichloromethane to yield 1.54 mg ($R_f$ 0.68) of material derived only from DCC as judged by its NMR spectrum. There was isolated 280 mg (86%) ($R_f$ 0.53) of *35*: IR ($CCl_4$) C=O 1735 and C=C 1640 $cm^{-1}$; NMR ($CCl_4$) 1.09 (d, methyl, $J$ = 6.5 Hz), 1.30 (d, methyl, $J$ = 6.5 Hz), 1.4—2.6 (m, two methines), 3.62 and 3.69 (s, $OCH_3$), 3.92 (m, two methines) and 6.85 (bs, vinyl proton).

*Bicyclo[3.3.0]-1,7-dicarbomethoxy-3,4-dimethyl-8-formyl-2-hydroxyoct-6-ene hemiketal (36) and Bicyclo[3.3.0]-7-carbomethoxy-1-formyl-8-carboxy-3,4-dimethyl-2-hydroxyoct-6-ene-lactone (37)*

To a 0 °C solution of 121 mg (0.373 mmol) of diquinane *33* in 1 mL of methanol (distilled from Mg) was added 9.2 mg (0.242 mmol) of sodium borohydride (recrystallized from diglyme) in three portions over a 45 min period. The reaction was then poured into 100 mL of ether, 2 mL 1 M HCl and 15 mL of saturated sodium chloride solution. The ether extract was dried over magnesium sulfate and evaporated to an oil. This oil was purified *via* lc on silica gel eluting twice with 10% ether-dichloromethane to yield 11.9 mg ($R_f$ 0.71), 4.6 mg ($R_f$ 0.65), 3.5 mg ($R_f$ 0.59), 28.6 mg ($R_f$ 0.35), 30.7 mg ($R_f$ 0.21) and 13.3 mg ($R_f$ 0.088). The material of $R_f$ 0.21 was further purified *via* lc on silica gel eluting twice with 5% methanol-dichloromethane to yield 3.13 mg ($R_f$ 0.47), 13.3 mg ($R_f$ 0.41), 11.9 mg ($R_f$ 0.29) and 2.24 mg ($R_f$ 0.23). The material of $R_f$ 0.41 is 36: IR ($CCl_4$) OH 3640, 3460, C=O 1725 and C=C 1640 $cm^{-1}$; NMR ($CCl_4$) (100 MHz) $\delta$ 1.03 (d, methyl, $J$ = 6 Hz), 1.11 (d, methyl, $J$ = 6 Hz), 1.4—2.2 (m, two methines), 3.04 (dd, bridgehead methine, $J$ = 7 and 3 Hz), 3.68 (bs, allylic methine), 3.74 (s, $OCH_3$), 4.60 (d, O—C—H, $J$ = 4 Hz), 5.34 (s, lactol methine) and 6.72 (bs, vinyl H). The material of $R_f$ 0.29 is *37*: IR ($CCl_4$) OH 3500, C=O 1780, 1725 and C=C 1630 $cm^{-1}$; NMR ($CCl_4$) (100 MHz) $\delta$ 1.15 (m, methyls), 1.7 (m, methines), 3.20 (dd, bridgehead methine, $J$ = 8 and 3 Hz), 3.80 (s, $OCH_3$), 4.20 (s, methine to lactone), 4.80 (d, O—C—H, $J$ = 4 Hz), 6.84 (bs, vinyl proton) and 9.82 (s, CHO).

*Bicyclo[3.3.0]-7-carbomethoxy-8-carboxy-3,4-dimethyl-2-hydroxy--1-hydroxymethyloct-6-ene lactone (38) and Bicyclo[3.3.0]-7-carbomethoxy-3,4--dimethyl-8-formyl-2-hydroxy-1-hydroxymethyloct-6-ene hemiketal (39)*

To a 0 °C, solution of 113 mg (0.349 mmol) of diquinane (*34*) in 1 mL of methanol (distilled from Mg) was added over a 20 min period 21.1 mg (0.555 mmol) of sodium borohydride (recrystallized from diglyme) in three portions. After stirring an additional 10 min at 0 °C 5 mL of ether and 2 mL of 1 M HCl was added. The reaction was then poured into 60 mL of ether, 5 mL of 1 M HCl and 10 mL of saturated NaCl solution. The organic phase was dried over magnesium sulfate and evaporated

to an oil. This oil was purified *via* lc on silica gel eluting twice with 5% methanol--dichloromethane to yield 2.58 mg ($R_f$ 0.59), 19.15 mg ($R_f$ 0.50), 4.20 mg ($R_f$ 0.41), 44.85 mg ($R_f$ 0.32) and 16.20 mg ($R_f$ 0.23). The material of $R_f$ 0.32 is *38* (48%): IR ($CCl_4$) OH 3505, C=O 1760, 1725 and C=C 1630 $cm^{-1}$; NMR ($CCl_4$) (100 MHz) $\delta$ 1.05 (d, methyl, $J = 6$ Hz), 1.12 (d, methyl, $J = 5$ Hz), 1.25—2.1 (m, two methines), 3.10 (bd, bridgehead methine, $J = 6$ Hz), 3.72 (bs, methylene), 3.69 (s, $OCH_3$), 3.98 (m, methine), 4.24 (O—C—H, $J = 8$ Hz) and 6.98 (dd, vinyl proton, $J = 2$ and 2 Hz); mass spectrum *m/e* (relative intensity) 266(1.9), 204(47), 195(29), 167(30), 145(100), 131(21), 107(28), 105(39), 91(26), 77(25), 74(23), 69(45) and 59(38). The material of $R_f$ 0.23 is *39* (16%) which yielded 9 mg of white crystals from ether-pentane: IR ($CHCl_3$) OH 3340, C=O 1725 and C=C 1630 $cm^{-1}$; NMR ($CDCl_3$) (100 MHz) $\delta$ 1.03 (d, methyl, $J = 6$ Hz), 1.05 (d, methyl, $J = 6$ Hz), 1.2—2.2 (m, two methines), 2.85 (dt, bridgehead methine, $J = 6.5$ and 2 Hz), 3.35 (t, methine, $J = 2$ Hz), 3.78 (s, $OCH_3$), 3.67—3.94 (three lines of an AB pattern, $CH_2OH$), 3.5—4.9 (b, OH), 4.20 (d, O=C—H, $J = 6$ Hz), 5.80 (s, lactol methine) and 6.98 (t, vinyl proton, $J = 2$ Hz); NMR ($CDCl_3 + D_2O$) (100 MHz) the alcohol proton disappears and the AB pattern is clear at $\delta$ 3.71 (d, one proton of $CH_2OH$, $J = 10$ Hz) and 3.87 (d, one proton of $CH_2OH$, $J = 10$ Hz); mass spectrum *m/e* (relative intensity) 250(9), 204(95), 192(25), 191(32), 190(25), 189(55), 167(33), 146(22), 145(100), 137(25), 131(23), 107(39), 105(39), 91(31), 77(30), 69(54), 65(21) and 59(20).

*Bicyclo[3.3.0]-3,4-dimethyl-2-hydroxy-1,7,8-tri-carbomethoxy-6-octene (40)*

To a 0 °C solution of 265 mg (0.818 mmol) of diquinane *35* in 1 mL of methanol was added 14.8 mg (0.390 mmol) of sodium borohydride (recrystallized from diglyme) in two portions over a 10 min period. After an additional 25 min at 0 °C, the reaction was poured into 50 mL of dichloromethane, 40 mL of water and 4 mL of 1 M HCl. The organic phase and a second 50 mL dichloromethane extract of the aqueous phase was dried over magnesium sulfate and evaporated to 271 mg (100%) of *40* as a pure colorless oil: IR ($CCl_4$) OH 3650, 3550, C=O 1735 and C=C 1650 $cm^{-1}$; *NMR* ($CCl_4$) $\delta$ 1.00 (bd, methyls, $J = 5$ Hz), 1.1—2.0 (m, methines), 4.38 (dd, methine, $J = 2.5$ and 2.5 Hz) and 6.68 (dd, vinyl proton, $J = 2.5$ and 2.5 Hz).

*Bicyclo[3.3.0]-7-carbomethoxy-8-carboxy-3,4-dimethyl-2-hydroxy-1--hydroxymethyl-6-octene methanesulfonate lactone (41)*

To a 25 °C solution of 44.0 mg (0.165 mmol) of diquinane (*38*) in 1 mL of dichloromethane (distilled from $CaH_2$) was added 57.5 μL (0.414 mmol) of triethylamine (distilled from KOH). To this solution was added dropwise over a 5 min period 26.6 μL (0.331 mmol) of methanesulfonylchloride.[13] The reaction was stirred 1 hr at 25 °C and then poured into 50 mL of dichloromethane, 5 ml of 1 M HCl, 15 mL of water and 5 mL of ice. The dichloromethane extract was dried over magnesium sulfate and evaporated to an oil. This oil was purified *via* lc on silica gel eluting with 10% ether-dichloromethane to yield 42.3 mg (74%) ($R_f$ 0.21) of *41*; IR ($CHCl_3$) C=O 1775, 1720 and C=C 1630 $cm^{-1}$; NMR ($CDCl_3$) (100 MHz) μ 1.10 (t, methyls, $J = 6$ Hz), 1.3—2.1 (m, two methylenes), 3.10 (s, $CH_3CO_3$), 3.2 (m, bridgehead methine), 3.83 (s, $OCH_3$), 3.89 (t, methine, $J = 2$ Hz), 4.38 (s, methylene) and 6.96 (t, vinyl proton $J = 2$ Hz).

*Bicyclo[3.3.0]-3,4-dimethyl-2-hydroxy-1,7,8-tri-carbomethoxy-6-octene methanesulfonate (42)*

To a solution of 103 mg (0.316 mmol) of diquinane *40* in 1 mL of dichloromethane (distilled from calcium hydride) at 25 °C was added 132 μL (0.948 mmol) of triethylamine (distilled from potassium hydroxide). Over a 5 min period 48.9 μL (0.632 mmol) of methanesulfonyl chloride was added to the stirred reaction.[13] The reaction was stirred an additional 20 min and poured into 50 mL dichloromethane, 30 mL saturated sodium chloride and 4 mL 1 M HCl. The organic phase and a second 50 mL dichloromethane extract of the aqueous phase was dried over $MgSO_4$ and evaporated to an oil, *42*; IR ($CCl_4$) C=O 1735 and C=C 1655 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 1.03 (bd, two methyls, $J = 5$ Hz), 1.2—2.3 (m, two methines), 3.10 (s, $CH_3SO_3$), 3.60, 3.64 and 3.70 (s, $OCH_3$), 4.22 (dd, methine, $J = 2.5$ and 2.5 Hz), 4.85 (d, H—C—$OSO_2$, $J = 9$ Hz) and 6.62 (dd, vinyl proton, $J = 2.5$ and 2.5 Hz).

*Bicyclo[3.3.0]-8-carboxy-7,8-dicarbomethoxy-3,4-dimethyl-2-hydroxy-6-octene (43)*

To a 25 °C solution of impure diquinane *40* (approximately 0.359 mmol contaminated with silicone grease) in 0.75 mL methanol was added 0.5 mL of 1 M potassium carbonate in water. After the reaction had stirred 1 hr an additional 400 mg of potassium carbonate was added creating a two-phase reaction medium which was stirred 10 hr. The reaction was poured into 50 mL dichloromethane and 30 mL 1 M HCl. The organic phase and a second 50 mL dichloromethane extract of the water phase was dried over magnesium sulfate and evaporated. The residue was purified *via* lc on silica gel eluting with ether to yield 40.8 mg (36%) ($R_f$ 0.18), after crystallization from ether and drying under vacuum, of *43*: IR ($CHCl_3$) OH 3000, C=O 1735 qnd C=C 1650 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.00 (bd, methyls, $J = 6$ Hz), 1.2—2 (m, methines), 3.68 (s, $OCH_3$), 3.79 (d, O—C—H, $J = 5$ Hz), 4.5 (m, methine), 5—5.6 (m, COOH and OH) and 6.92 (m, vinyl proton).

*Bicyclo[3.3.0]-3,4-dimethyl-2,6-dihydroxy-1,7,8--tricarbomethoxyoctane (44)*

To a 0 °C solution of 74.4 mg (0.217 mmol) of diquinane *30* in 0.5 mL of methanol (distilled from Mg) was added, over a 1 hr period in three portions, 10.2 mg (0.268 mmol) of sodium borohydride (recrystallized from diglyme). The reaction was stirred 10 min longer and poured into 100 mL of ether, 1 mL of 1 M HCl and 20 mL of 50% saturated sodium chloride. The ether phase was dried over magnesium sulfate and evaporated to an oil. This oil crystallized from ether to yield 30.1 mg (40%) of *44* as a white powder: IR ($CHCl_3$) OH 3620, 3550 and C=O 1725 $cm^{-1}$; NMR ($CDCl_3$) 1.06 (d, methyl, $J = 6$ Hz), 1.15 (d, methyl, $J = 4$ Hz), 1.3—2.5 (m, methylenes), 2.57 (d, methine, $J = 4$ Hz), 2.89 (m, methine), 3.41 (dd, bridgehead methine, $J = 12$ and 3 Hz) and 3.9—4.8 (m, methines).

*Bicyclo[3.3.0]-1-acetoxy-8-carboxy-1,7-dicarbomethoxy-3,4-dimethyl-2--hydroxy-6-octene lactone (45)*

To a solution of 23.1 mg (0.0713 mmol) of diquinane *33* in 250 $\mu$l of acetic anhydride was added 1 drop of 60% perchloric acid. The reaction was stirred 5 hr at 25 °C and then evaporated under high vacuum. The residue was purified *via* lc on silica gel eluting with 80% ether-pentane to yield 13.3 mg (53%) ($R_f$ 0.41) of *45* which crystallizes from ether: IR ($CHCl_3$) C=O 1795, 1750, 1730, C=C 1608 $cm^{-1}$; NMR (100 MHz) ($CDCl_3$) 1.13 (d, methyl, $J = 7$ Hz), 1.16 (d, methyl, $J = 7$ Hz), 1.2——1.8 (m, methine), 2.12 (s, acetate), 2.40 (quintet, methine, $J = 7$ Hz), 3.14 (dd, bridgehead methine, $J = 7.5$ and 3 Hz), 3.80 and 3.94 (s, $OCH_3$), 4.82 (d, methine, $J = 2$ Hz) and 6.78 (dd, vinyl proton, $J = 3$ and 2 Hz); mass spectrum m/e (relative intensity) 324(5), 321(6), 292(12), 266(65), 234(25), 177(24), 150(100), 59(21) and 55(26).

*Bicyclo[3.3.0]-8-carboxy-1,7-dicarbomethoxy-3,4-dimethyl-2-hydroxy-2,6--octadiene lactone (46)*

Diquinane *45* (13 mg, 0.037 mmol) was placed in a 5 mL round-bottomed flask, dried under vacuum and connected to a nitrogen bubbler line. The flask was immersed in a Woods metal bath for a given time and at a given temperature, removed and cooled. The residue was dissolved in deuterochloroform and the NMR spectrum obtained to monitor the percent reaction. The above preparation was then repeated to give the following results: (time, temperature, % reaction) 1 min, 262 °C, 0%; 3 min, 312 °C, 50%; 5 min, 295 °C, 75%. The final residue was purified *via* lc on silica gel eluting with 10% ether-pentane to yield 5.2 mg ($R_f$ 0.41) (48%) *46* and an unmeasured amount of starting material *45* ($R_f$ 0.35). *46*: IR ($CHCl_3$) C=O 1830, 1730 and C=C 1630 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.38 (d, methyl, $J = 7$ Hz), 1.65 (s, vinyl methyl), 2.57 (q, methine, $J = 7$ Hz), 3.37 (bdd, bridgehead methine, $J = 2$ and 2 Hz), 3.77 and 3.78 (s, $OCH_3$), 4.10 (dd, methine, $J = 2$ and 2 Hz) and 6.78 (dd, vinyl proton, $J = 2$ and 2 Hz); mass spectrum *m/e* (relative intensity) 292(44), 232(21), 59(12) and 55(100).

*Bicyclo[3.3.0]-3-bromo-3,4-dimethyl-2-oxo-1,7,8-tricarbomethoxy-6-octene (47)*

To a solution of 124 mg (0.383 mmol) of diquinane *33* in 1 mL glacial acetic acid was added 123 mg (0.383 mmol) of pyridinium bromide perbromide. The reaction was heated at 55 °C for 1 hr and stirred at 25 °C for 4 hr. The reaction was then evaporated under high vacuum to a semisolid. This residue was slurried in carbon tetrachloride, filtered and the filtrate evaporated to an oil. This oil was purified *via* lc on silica gel eluting with 80% ether-pentane to yield 150 mg (97.4%) ($R_f$ 0.57) of *47* which crystallizes upon standing and can be recrystallized from methanol: IR ($CCl_4$) C=O 1765, 1735 and C=C 1640 $cm^{-1}$; NMR ($CCl_4$) 1.30 (d, methyl, $J$ = 6 Hz), 1.68 (s, $CBrCH_3$), 1.5—2.3 (m, methine), 3.48 (two lines of a dd, bridgehead methine, $J$ = 2.5 Hz), 3.66, 3.67 and 3.78 (s, $OCH_3$), 4.12 (d, methine, $J$ = 1.5 Hz) and 6.95 (dd, vinyl proton, $J$ = 2.5 and 1.5 Hz).

*Bicyclo[3.3.0]-1-acetoxy-3-bromo-8-carboxy-1,7-dicarbomethoxy-3,4-dimethyl-2-hydroxy-6-octene lactone (48)*

To a solution of 0.481 mmol of crude diquinane *47* in 1 mL of acetic anhydride was added 7 drops of 60% perchloric acid. The reaction was stirred 20 hr at 29 °C and evaporated under high vacuum. The residue was again dissolved in 1 mL of acetic anhydride and 7 drops of 60% perchloric acid and stirred at 25 ° for 12 hr. The reaction was evaporated under high vacuum and the residue purified *via* lc on silica gel eluting with 80% ether-pentane to yield 165 mg (80%) ($R_f$ 0.53) of *48* which can be crystallized from ether: IR ($CHCl_3$) C=O 1810, 1755, 1730 and C=C 1645 $cm^{-1}$; NMR ($CDCl_3$) (100 MHz) $\delta$ 1.23 (d, methyl, $J$ = 6 Hz), 1.3—1.9 (m, methine), 1.82 (s, $CBrCH_3$), 2.20 (s, acetate), 3.46 (dd, bridgehead methine, $J$ = 11 and 3 Hz), 3.70 and 3.85 (s, $OCH_3$), 4.49 (d, methine, $J$ = 2 Hz) and 6.89 (dd, vinyl proton, $J$ = 3 and 2 Hz); mass spectrum *m/e* (relative intensity) 401(4), 399(4), 388(5), 386(5), 372(5), 370(5), 346(45), 344(46), 150(100), 72(23), 59(13), 57(26) and 55(40).

*Bicyclo[3.3.0]-2-acetoxy-8-carboxy-1,7-dicarbomethoxy-3,4-dimethyl-2,6-octadiene (49)*

To a solution of 165 mg (0.384 mmol) of diquinane lactone (*48*) in 1 mL of glacial acetic acid was added 500 mg of zinc dust. The reaction mixture was heated 10 min at reflux, cooled and poured into 100 mL ether, 50 mL water and 5 mL 3 M HCl. The organic phase was washed once with water, dried over $MgSO_4$ and evaporated to a solid. This solid was dissolved in dichloromethane, filtered and the filtrate evaporated to an oil. This oil was heated at 50 °C while 5 mL of ether was added. Crystallization occurred yielding after washing with ether and drying 79.3 mg (59%) of crystalline *49*: IR ($CHCl_3$) OH 3000, C=O 1725 and C=C 1645 $cm^{-1}$; NMR (100 MHz) ($CDCl_3$) $\delta$ 1.28 (d, methyl, $J$ = 7 Hz), 1.53 (s, vinyl methyl), 2.13 (s, acetate), 2.56 (bg, methine, $J$ = 7 Hz), 3.50 (four lines, bridgehead methine, $J$ = 2 Hz), 3.75 and 3.78 (s, $OCH_3$), 4.33 (dd, methine, $J$ = 2 and 2 Hz) and 6.72 (dd, vinyl proton $J$ = 2 and 2 Hz); mass spectrum *m/e* (relative intensity) 292(23), 224(100), 143(68), 100(21), 99(94), 98(58), 70(26), 61(72), and 59(18).

*Bicyclo[3.3.0]-2-benzylthio-8-carboxy-1,7-dicarbomethoxy-3,4-dimethyl-2-hydroxy-6-octene lactone (50) and Bicyclo[3.3.0]-2-benzythio-8-carboxy-1,7-dicarbomethoxy-3,4-dimethyl-2-6-octadiene (51)*

To a 25 °C solution of 121 mg (0.374 mmol) of diquinane *33* in 0.469 mL (4.00 mmol) of benzyl mercaptan (freshly distilled) was added 1 mL (8.10 mmol) of boron trifluoride etherate. The reaction was then stirred at 45 °C for 24 hr. The reaction was cooled and poured into 50 mL of dichloromethane, 45 mL of 7% sodium bicarbonate and 10 g of ice. The organic phase was dried over magnesium sulfate and evaporated. The water phase was acidified with 3 M HCl, extracted once with 50 mL of dichloromethane, the organic extract dried over magnesium sulfate and evaporated. The two residues were combined and purified *via* plc on silica gel eluting with 80% ether-pentane to yield 44.7 mg (29%) ($R_f$ 0.56) of a mixture of *50* (major) and *51* (minor). *50*: IR ($CCl_4$) C=O 1800, 1736 and C=C 1640 $cm^{-1}$; NMR ($CCl_4$)

$\delta$ 1.14 (bd, methyls, $J = 7$ Hz), 1.5—2.5 (m, methines), 3.3 (m, region of bridgehead methine), 3.55 and 3.65 (two lines of an AB pattern for benzylic methylene), 3.77 and 3.79 (s, $OCH_3$), 4.52 (d, methine, $J = 1.5$ Hz), 6.70 (dd, vinyl proton, $J = 3.5$ and 1.5 Hz) and 7.20 (s, aromatic protons). The latter, 51.3 mg (33%) ($R_f$ 0.22) crystallized from ether-pentane to give 30.0 mg of *51* as a white powder: IR ($CHCl_3$) OH 3000, C=O 1725 and C=C 1745 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.19 (d, methyl, $J = 7$ Hz), 1.93 (s, vinyl methyl), 2.59 (b quintet, methine, $J = 6$ Hz), 3.32 (dd, bridgehead methine, $J = 5$ and 3 Hz), 3.64 and 3.78 (s, $OCH_3$ and benzylic methylene), 4.65 (bs, methine), 6.98 (dd, vinyl proton, $J = 3$ and 2 Hz), 7.35 (s, aromatic protons) and 9.51 (b, COOH); mass spectrum *m/e* (relative intensity) 416(3), 325(12), 307(38), 101(28), 91(100), 84(26), 82(39), 74(28), and 59(68).

*Bicyclo[3.3.0]-2-benzylthio-3,4-dimethyl-1,7,8-tricarbomethoxy-2,6-octadiene (52) and Bicyclo[3.3.0]-2-benzylthio-8-carboxy-1,7-dicarbomethoxy-3,4--dimethyl-2,6-octadiene (53)*

To a 25 °C solution of 475 mg (1.46 mmol) of diquinane *34* in 1.9 mL (16.2 mmol) of benzyl mercaptan (freshly distilled) was added 4 mL (32.4 mmol) of boron trifluoride etherate. The reaction was then stirred at 52 °C for 22 hr. The reaction was cooled, diluted with dichloromethane and poured into 250 mL dichloromethane, 125 mL water and 125 mL ice. The organic phase and a second 200 mL dichloromethane extract of the water phase was dried over magnesium sulfate and evaporated. The residue was purified *via* plc on silica gel eluting with 80% ether-pentane to yield 51.2 mg (19% based upon recovered starting material), ($R_f$ 0.6) of *52* [IR C=O 1725 and C=C 1650 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.12 (d, methyl, $J = 7.5$ Hz), 1.63 (s, vinyl methyl), 3.01 (b quintet, $J = 7.5$ Hz), 3.61, 3.63, 3.67 and 3.72 (s, $OCH_3$ and benzylic methylene), 3.83 (m, part of bridgehead methine), 4.64 (dd, methine, $J = 2$ and 2 Hz), 6.78 (dd, vinyl proton, $J = 2$ and 2 Hz), and 7.30 (s, aromatic protons)] 184 mg (57%) ($R_f$ 0.47) of starting material *34* and 58.8 mg (22% based upon recovered starting material) ($R_f$ 0.33) of *53* which was crystallized from ether to yield 44.9 mg of white crystals; IR ($CHCl_3$) OH 3000, C=O 1725, C=C 1650 and 1610 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.06 (d, methyl, $J = 7.5$ Hz), 1.60 (s, vinyl methyl), 3.30 (b quintet, methine, $J = 8$ Hz), 3.60 and 3.76 (s, $OCH_3$), 3.66 (s, benzylic methylene), 3.88 (part of bridgehead methine), 4.67 (t, methine, $J = 2$ Hz), 6.89 (t, vinyl proton, $J = 2$ Hz), 7.36 (s, aromatic protons) and 9.6 (b, COOH).

*Bicyclo[3.3.0]-2-benzylthio-3,4-dimethyl-1,7,8-tricarbomethoxy--2,6-octadienoate (54)*

To a solution of 67.7 mg (0.209 mmol) of diquinane (*35*) in 117 $\mu$L (1.00 mmol) of distilled benzylmercaptan was added 247 $\mu$L (2.0 mmol) of boron trifluoride etherate. The reaction solution was stirred 39 hr at 25 °C. The reaction was then poured into 50 mL of dichloromethane and 50 mL of cold water. The organic phase along with a second 50 mL dichloromethane extract of the water phase was dried over magnesium sulfate and evaporated to an oil. This oil was purified *via* lc on silica gel eluting with 80% ether-pentane to yield 66.6 mg (74%) ($R_f$ 0.55) of *54:* IR ($CCl_4$) C=O 1735 and C=C 1645 $cm^{-1}$; NMR ($CCl_4$) 1.10 (d, methyl, $J = 7.5$ Hz), 1.45 (d, vinyl methyl, $J = 1$ Hz), 3.17 (b quintet, methine, $J = 7$ Hz), 3.58, 3.63 and 3.67 (s, $OCH_3$ and benzylic methylene), 3.97 (ddd, bridgehead methine, $J = 7.5$, 2 and 2 Hz), 4.18 (dd, methine, $J = 2.5$ and 1.5 Hz), 6.62 (dd, vinyl proton, $J = 2$ and 1 Hz) and 7.10 (s, aromatic protons); UV (ethanol) 265 nm (shoulder) 2130 and 210 nm (end).

*Bicyclo[3.3.0]-3,4-dimethyl-1,7,8-tricarbomethoxy-2,6-octadiene (2)*

To a solution of 64.0 mg (0.149 mmol of bicyclo[3.3.0]-2-benzylthio-3,4-dimethyl--1,7,8-tricarbomethoxy-2,6-octadienoate (*54*) in 1 mL of methanol was added 3 mL of W-2 Raney nickel in methanol. The mixture was heated at reflux for 2.5 hr. The reaction was cooled, filtered and the filtrate evaporated to an oil. NMR analysis shows this oil to be largely bicyclo[3.3.0]-3,4-dimethyl-1,7,8-tricarbomethoxy--2-octene from overreduction: NMR ($CDCl_3$) 1.00 (d, methyl, $J = 6$ Hz), 1.68 (s,

vinyl methyl), 1.8—2.3 (m, methines), 2.7—3.5 (m, methines), 3.56, 3.60 and 3.64 (s, $OCH_3$) and 5.44 (s, vinyl proton). The presence of *2* is evidenced by a vinyl proton resonance at $\delta$ 6.80 and the absence of any aromatic protons.

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## SAŽETAK

### Priprava pentalenolaktona metodom prijenosa alkila

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Pentalenolakton predstavnik je polikondenziranih ugljikovodika, a koristi se kao antibiotik i antitumorski agens. Njegova priprava polazi od visoko funkcionaliziranog biciklo(3.3.0)oktil-sistema. U radu je opisan jednostavan postupak priprave te grupe spojeva iz cikličkih prekursora koji se zasniva na principu prijenosa alkila, kao i njihova daljnja konverzija u konačne pentalenlakotnske produkte.