Fully Regiocontrolled Synthesis of Deacetamidoisocolchicine: Formal Total Synthesis of Colchicine

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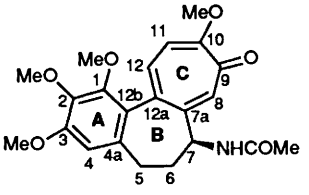
A 19-step synthesis of deacetamidoisocolchicine **4** has been developed starting from commercially available benzaldehyde **10**. Key elements of the strategy used include Robinson annulation of the benzosuberone **15** to produce the tricyclic enone **18** and elaboration of this latter compound to the tetracyclic α-methoxy enone **7a**. Base-promoted ring-expansion of **7a** then provided the title compound **4**, the acquisition of which constitutes a formal total synthesis of the alkaloid colchicine **1**. In connection with efforts to optimise the yield of **4**, the novel acid-catalysed conversion of **32** into dibenzocyclooctene **35** has been observed. The X-ray crystal structures of compound **35** and the novel dichlorocarbene insertion product **24** are reported.

The alkaloid colchicine **1**, which contains two mutually fused seven-membered rings, is a potent antimitotic agent isolated from a variety of sources including the meadow saffron *Colchicum autumnale*.[1] Although the high toxicity of **1** has limited its clinical applications,[2] the compound is used extensively in agricultural[3] and biological research.[2]



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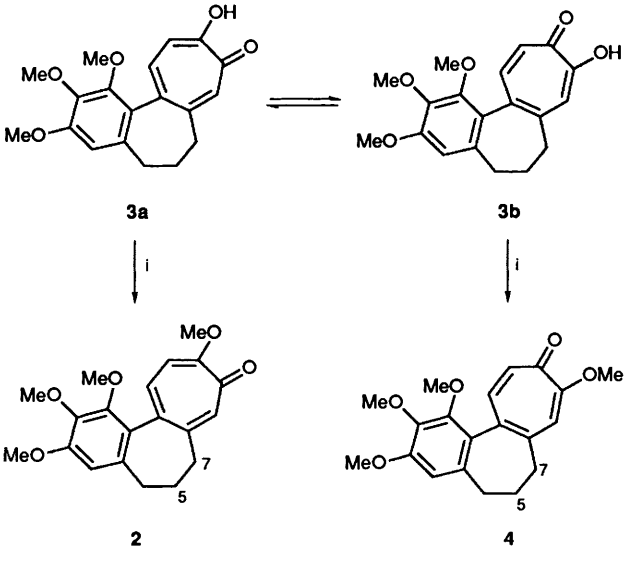
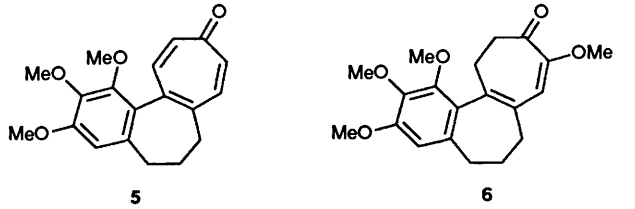
The unusual structural and biological properties of colchicine have not escaped the organic chemist's attention and the molecule has been the subject of a great deal of synthetic effort.[4,5] One of the problems associated with attempts to prepare **1** arises from the lack of general methods for the synthesis of α-tropolones (2-hydroxycyclohepta-2,4,6-trienones) —the key structural element associated the C-ring of the natural product. The first synthesis of colchicine **1**, described by Eschenmoser and Schreiber *et al.*,[4a] also highlighted some important problems of regiochemical control. For example, *O*-methylation of the free tropolone deacetamidocolchiceine **3** (Scheme 1), which exists in two rapidly interconverting tautomeric forms **3a** and **3b**, results in the formation of two distinct regioisomeric products **2** and **4**. Only the former product has the same arrangement of troponoid double bonds and ring substituents as seen in colchicine **1**. However, attempts to convert compound **2** into **1** *via* free-radical bromination have been unsuccessful because functionalisation took place preferentially at the benzylic site C-5. Perversely, analogous treatment of **4** gave the C-7 bromo derivative (together with the C-5 isomer) which could be elaborated to the natural product **1**, although only after the application of a demethylation–remethylation sequence. As a result of Eschenmoser's and Schreiber's pioneering work 7 of the 12 subsequent syntheses of **1** are in fact formal total syntheses of colchicine since they rely on the acquisition of deacetamidoisocolchicine **4** or deacetamidocolchiceine **3**. For example, Boger and Brotherton have described[4k] the application of Diels–Alder chemistry to the preparation of tropone **5** which can be oxidised to tropolone **3**.

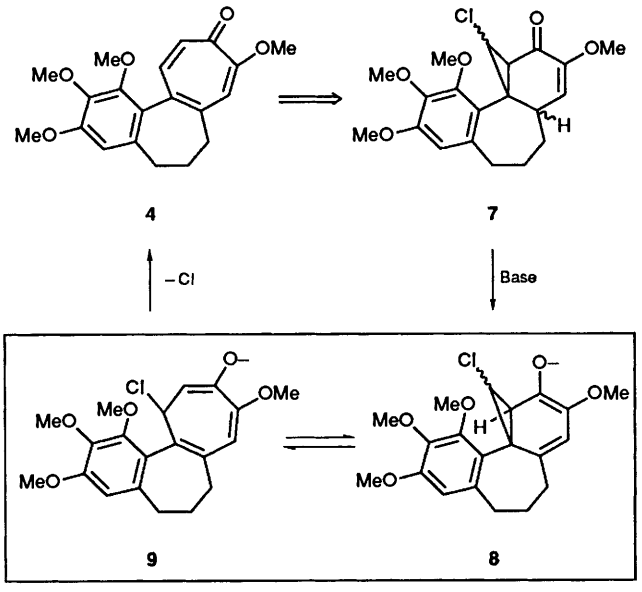


Scheme 1 *Reagents:* i, CH_2N_2

However, this approach does not address the problems of regiocontrol associated with the conversion of **3** into **4** and it has the additional drawback that during the oxidation sequence leading from **5** to **3** a regioisomer of **3** is also produced. An elegant and fully regiocontrolled synthesis of **4** has been reported[4j] by Evans *et al.* who were able to prepare the dihydrotropolone *O*-methyl ether **6** and then convert this material into deacetamidoisocolchicine *via* 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)-promoted dehydrogenation.



Recently we have described[6] efficient new methods for the synthesis of troponoids which involve ring-expansion of 7-halogenobicyclo[4.1.0]heptenones and related compounds. In principle, this methodology could be applied to a fully



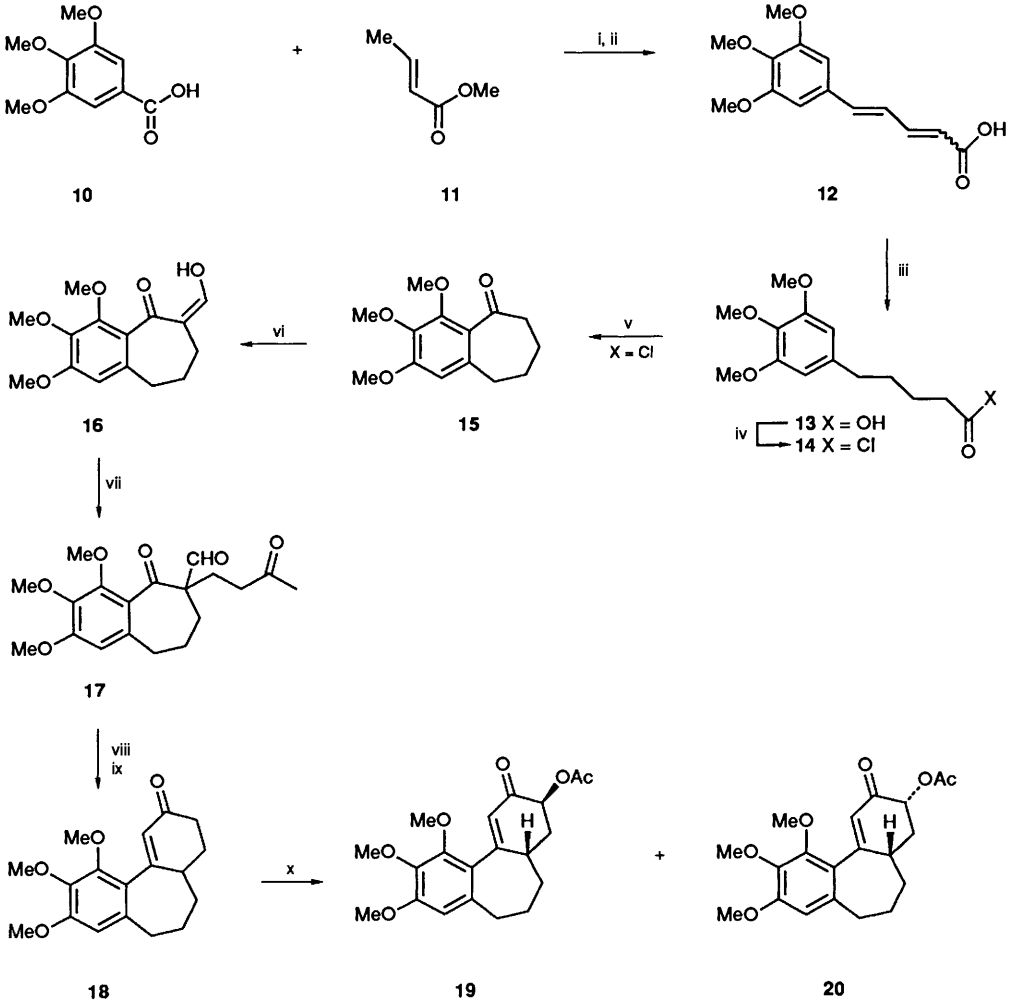
Scheme 2

regiocontrolled and direct (*i.e.* bypassing dihydrotroponoid intermediates which require oxidation) synthesis of deacetamidoisocolchicine **4** using the synthetic plan outlined in Scheme 2. Thus, we expected that any one of the four diastereoisomers depicted by structure **7** should undergo base-promoted conjugate enolisation to give the norcaradienes **8** which should, in turn, undergo electrocyclic ring-opening to the cycloheptatriene **9**. Finally, spontaneous loss of chloride ion from **9** should deliver **4**. We now disclose full details regarding the implementation of this synthetic strategy.[7]

Results and Discussion

The synthetic route employed in preparing compound **7** (and which ultimately provided isomer **7a**) is illustrated in Schemes 3 and 5. Key operations in the early phases (Scheme 3) were the preparation of benzosuberone **15** and its subsequent Robinson annulation with methyl vinyl ketone (MVK) to give the tricyclic enone **18**. Thus, condensation of commercially available 3,4,5-trimethoxybenzaldehyde **10** with the vinylogous enolate anion derived from methyl crotonate **11** afforded, after alkaline hydrolysis of the intermediate methyl esters, the 5-arylpentadieneoic acid **12** as a mixture of geometric isomers. An ethanolic solution of compound **12** was immediately subjected to catalytic hydrogenation and the resulting 5-arylpentanoic acid **13** was obtained as a waxy solid. Treatment of compound **13** with phosphorus pentachloride produced the corresponding acid chloride **14** which was not isolated but immediately subjected to reaction with tin(IV) chloride—the result of which was the efficient formation of the intramolecular Friedel–Crafts acylation product, the crystalline ketone **15**.[8]

Attempts to effect the Robinson annulation[9] of **15** (and thence form enone **18** directly) by treating the compound with



Scheme 3 *Reagents and conditions:* i, Bu^{t}OK, Bu^{t}OH, 18–65 °C; ii, KOH, ethanol, reflux; iii, H_2, Pd on C, ethanol; iv, PCl_5, C_6H_6, reflux; v, $SnCl_4$, C_6H_6, 5–22 °C; vi, NaOMe, HCO_2Et, C_6H_6; vii, MVK, CH_2Cl_2, Et_3N; viii, KOH, ethanol, reflux then excess 2 mol dm^{-3} aq. HCl; ix, K_2CO_3, $(MeO)_2SO_2$, Me_2CO; x, $Mn(OAc)_3$, C_6H_6, reflux

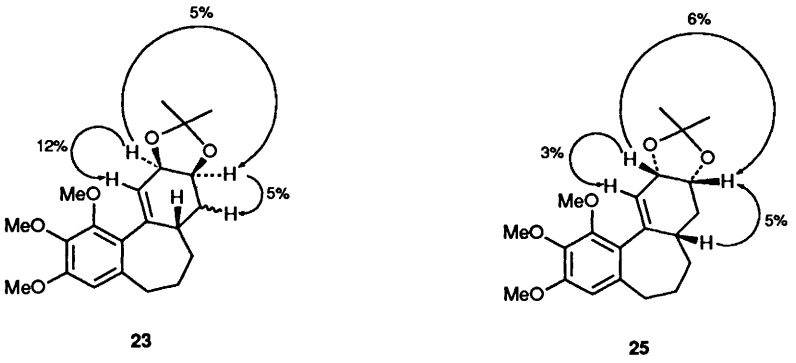
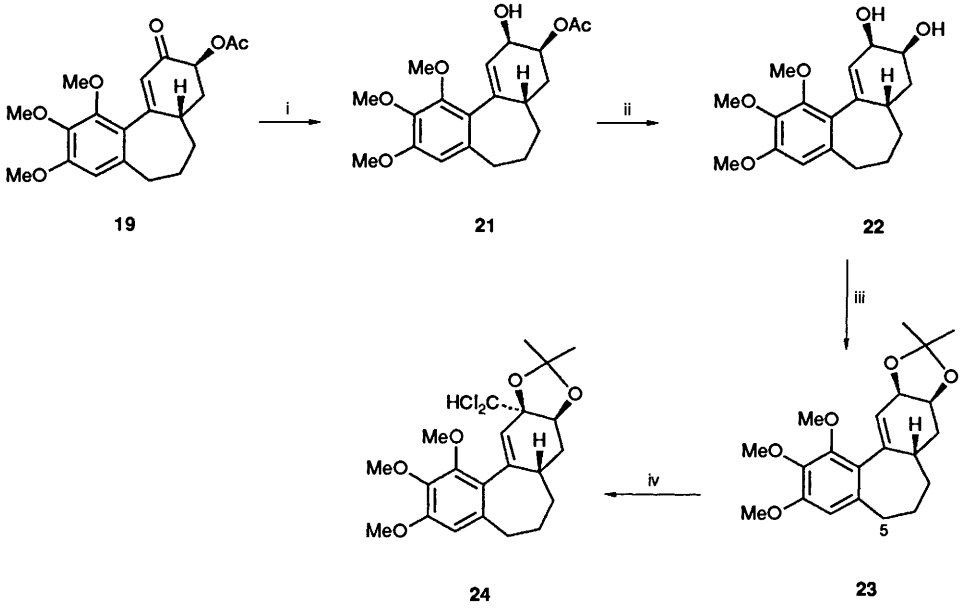


Fig. 1 Selected NOE difference measurements for compounds **23** and **25**



Scheme 4 *Reagents and conditions:* i, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C; ii, KOH, MeOH, 5 °C; iii, Me_2CO, 1 drop $HClO_4$, 0 °C; iv, MeONa, Cl_3CCO_2Et, pentane, 0–18 °C

MVK under either acidic or basic conditions failed. Presumably the slow rate of formation of both the enolate anion and enol derived from **15** meant that Michael addition of these species to MVK failed to compete effectively with polymerisation of the electrophile. To circumvent this problem, α-formylation of ketone **15** was carried out using ethyl formate and freshly prepared sodium methoxide.[10] The resulting product was obtained as a crystalline solid and for convenience this compound is depicted in the α-hydroxymethylene tautomeric form **16**. As expected, reaction of **16** with MVK in the presence of triethylamine[10] resulted in a smooth Michael addition reaction and formation of the alkylated product **17** in high (92%) yield. Intramolecular aldol condensation, dehydration and deformylation of **17** to give **18** was achieved in a one-pot operation by treating the former compound with potassium hydroxide in refluxing ethanol. Since ^1H NMR and TLC analysis of the crude reaction mixture suggested that the enone **18** so formed was contaminated by quantities of demethylated derivatives the crude reaction product was treated with a mixture of dimethyl sulfate and potassium carbonate in acetone. Subsequent work-up then provided the cyclohexenone **18**[11] as a crystalline solid in 64% yield.

α′-Acetoxylation of **18** using manganese triacetate in refluxing benzene[12] provided a *ca.* 1:1 mixture of epimers **19** and **20** which could be separated using flash chromatographic techniques.[13] The assignment of stereochemistry to these acetoxy enones followed from both NMR and X-ray crystallographic analyses of more advanced intermediates along the reaction paths. 1,2-Reduction of the chromatographically more mobile acetoxy enone **19** using $CeCl_3$–$NaBH_4$ in methanol[14] afforded the hydroxy acetate **21** which was immediately hydrolysed to the diol **22**. The latter product was then converted into the corresponding acetonide **23** under standard conditions. An exactly analogous reaction sequence was used to convert the isomeric α-acetoxy enone **20** into the acetonide **25**. A series of NOE difference experiments, the essential details of which are portrayed in Fig. 1, established the illustrated stereochemistries for compounds **23** and **25**.

With the acetonides in hand, efforts to effect dichlorocarbene addition to the alkenic bonds in these compounds were undertaken. However, when substrate **23** was treated with ethyl trichloroacetate and sodium methoxide[15] a complex mixture of products together with traces of starting material was obtained. ^1H NMR analysis of the major reaction product, isolated by flash chromatography, revealed, *inter alia*, a one-proton singlet at δ 5.79 suggesting that the integrity of the double bond associated with **23** had been preserved in this product. Furthermore, the observation of a new singlet at δ 5.62 suggested the presence of a dichloromethyl group. On this basis and with the knowledge that dichlorocarbene is known[15] to insert into activated C–H bonds, the reaction product derived from **23** was tentatively identified as compound **24** (33%) (Scheme 4). This structure was confirmed by single crystal X-ray diffraction analysis (Fig. 2 and Table 1). In view of the poor mass balance

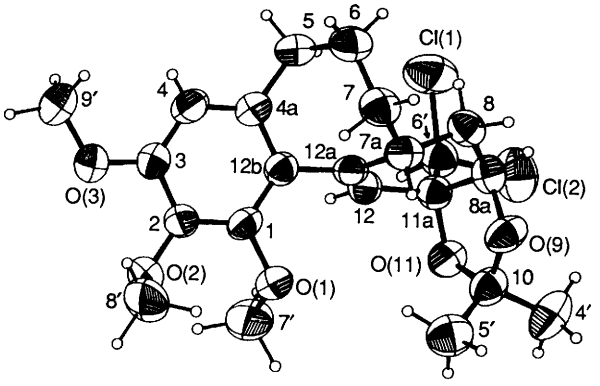


Fig. 2 X-Ray crystal structure of **24**. (Thermal ellipsoids are drawn at the 50% probability level and hydrogen atoms are represented by spheres of arbitrary radius. The C symbol for the carbon atoms has been omitted.)

Table 1 Fractional atomic coordinates C, O ($\times 10^4$), Cl ($\times 10^5$) of the non-hydrogen atoms with esds in parentheses for compound **24**

	x	*y*	*z*
Cl(1)	47 912(12)	10 753(12)	24 860(8)
Cl(2)	60 230(12)	25 472(11)	24 997(8)
C(1)	3 736(3)	791(3)	5 468(2)
O(1)	4 226(2)	1 513(2)	5 686(2)
C(2)	3 460(3)	163(3)	5 938(2)
O(2)	3 728(2)	203(2)	6 597(2)
C(3)	2 915(3)	− 535(3)	5 723(3)
O(3)	2 688(2)	−1 125(2)	6 219(2)
C(4)	2 666(4)	− 578(4)	5 048(3)
C(4a)	2 933(3)	53(3)	4 582(2)
C(5)	2 642(4)	39(4)	3 851(3)
C(6)	1 972(4)	777(4)	3 687(3)
C(7)	2 111(4)	1 638(4)	4 072(3)
C(7a)	3 043(3)	2 048(3)	4 038(3)
C(8)	3 255(3)	2 417(4)	3 340(3)
C(8a)	4 184(3)	2 806(3)	3 316(3)
O(9)	4 227(2)	3 532(2)	3 779(2)
C(10)	5 071(3)	3 579(3)	4 087(3)
O(11)	5 507(2)	2 759(2)	3 921(2)
C(11a)	4 904(3)	2 183(3)	3 567(2)
C(12)	4 587(3)	1 488(3)	4 062(2)
C(12a)	3 761(3)	1 423(3)	4 280(2)
C(12b)	3 493(3)	741(3)	4 793(2)
C(4′)	5 609(5)	4 330(4)	3 791(5)
C(5′)	4 939(6)	3 647(5)	4 838(4)
C(6′)	5 457(4)	1 740(4)	3 006(2)
C(7′)	5 132(4)	1 312(4)	5 867(4)
C(8′)	3 110(5)	622(5)	7 048(3)
C(9′)	2 199(5)	−1 895(4)	6 029(4)

associated with the reaction between **23** and ethyl trichloroacetate–sodium methoxide the formation of the desired dichlorocarbene addition product which then decomposes under the reaction conditions cannot be discounted. Nevertheless, the failure to isolate any adduct capable of subsequent elaboration to the target **4** was a cause for great concern. However, these concerns were alleviated when it was found that the diastereoisomeric alkene acetonide **25** underwent (Scheme 5) smooth dichlorocarbene addition. The product cyclopropane **26** was isolated in *ca.* 70% yield as white needles and the structure of this material was confirmed by X-ray crystallographic methods.*

The divergent behaviour of the alkenes **23** and **25** towards dichlorocarbene is attributed to steric factors. It appears from inspection of molecular models that in the preferred conformation† for **23** 5β-H obscures one face of the alkene double bond while the 1-methoxy group and *endo*-Me group of the 1,3-dioxolane moiety block the other. Since the allylic C–H bond in **23** is *anti*-coplanar with one of the non-bonding electron pairs of the adjacent oxygen, the stereoelectronic requirements for insertion are fulfilled[16] and the observed product results. Although the equivalent C–H bond in **25** is also appropriately orientated for insertion, because the α-face of the alkene residue is unencumbered, carbene addition now competes effectively with insertion and the cyclopropane **26** is formed.

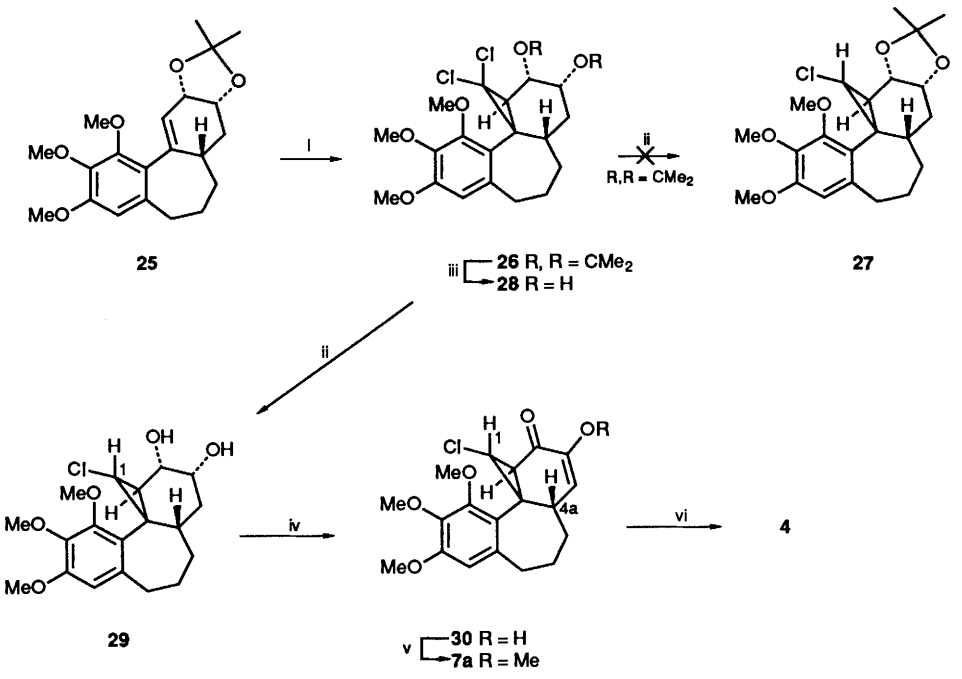
Since dichlorocarbene failed to add to the double bond of acetonide **23**, its precursor, the acetoxy enone **19**, was of no synthetic value. Consequently, in an attempt to convert **19** into its useful epimer **20** (the progenitor of the acetonide **25** and thence the cyclopropane **26**) the former compound was treated with toluene-*p*-sulfonic acid in refluxing benzene. However, aromatisation of **19**, *via* loss of the elements of acetic acid and subsequent dienone to phenol rearrangement, was the only process observed. It is possible that some epimerisation of **19** to **20** did take place under these conditions but this latter compound must then also aromatise. When milder conditions were used, in an effort to isolate any quantities of **20** formed, no reaction was observed.

Elaboration of the cyclopropane **26** to the target compound **7a** was not straightforward. Half-reduction of the *gem*-dichlorocyclopropyl moiety in **26** using zinc in ethanolic potassium hydroxide[15] proceeded readily to give the monochloro derivative **27** (85%). The observation of mutually coupled doublets at δ 2.92 and 2.63 with coupling constants of 4.9 Hz suggested a *trans*-relationship between the two cyclopropyl protons in this product.[17] Unfortunately, attempts to remove the acetonide group in **27** only resulted in rapid decomposition of the starting material. All efforts to alter this outcome were fruitless. We rationalise the extreme acid sensitivity of **27** as arising from the capacity of such a system to form a cyclopropylcarbinyl cation as a result of acid-assisted heterolysis of the C–O bond adjacent to the three-membered ring. Subsequent (or concomitant) cleavage of the central bond of the cyclopropane ring would then produce a highly stabilised benzylic cation which could react by a number of pathways to give a plethora of products. On this basis we reasoned that the dichloroacetonide **26** might be less sensitive to acid since the additional chlorine in this compound should, as a result of steric effects, inhibit planarisation at the benzylic centre and, therefore, destabilise any incipient carbocation (steric inhibition to resonance).[18] In the event, treatment of **26** with aqueous acid resulted in its smooth conversion (95%) into the diol **28**. Reductive dechlorination of **28** under the same conditions as employed for the acetonide **26** then provided the monochloro diol **29** in *ca.* 74% yield. Once again, the illustrated *trans*-relationship between the two cyclopropyl hydrogens in **29** followed from the observation of a 4.9 Hz doublet at δ 3.12 for 1-H in the 400 MHz ^{1}H NMR spectrum.

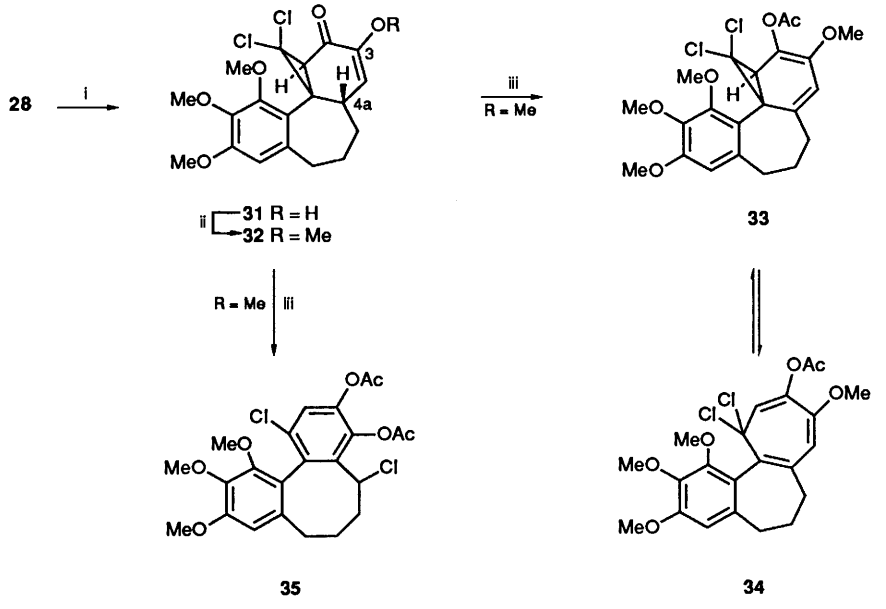
Oxidation of the diol **29** at −60 °C using oxalyl chloride-activated dimethyl sulfoxide (DMSO) (Swern oxidation)[19] produced the desired α-hydroxy enone **30** in only 31% yield. Attempts to enhance the yield in this step by using trifluoroacetic anhydride activated DMSO, a reagent which we have previously identified[20] as being useful for the oxidation of halogenated diols, gave almost none of the desired compound **30**—only complex mixtures of products were observed. The low yields of **30** encountered during the oxidation of diol **29** most likely result from the same sort of acid sensitivity as noted for the related monochloro-acetonide **27**. Confirmation of the

* Details of this structure determination have been disclosed previously.[7]

† As deduced from inspection of the X-ray structure of the insertion product **24**.



Scheme 5 *Reagents and conditions:* i, MeONa, Cl_3CCO_2Et, pentane, 0–18 °C; ii, Zn, KOH, ethanol, reflux; iii, MeOH, 10 mol dm^{-3} aq. HCl; iv, $(COCl)_2$, Me_2SO, −60 °C then Et_3N, −60 °C; v, K_2CO_3, $(MeO)_2SO_2$, Me_2CO; vi, DBU, C_6H_6



Scheme 6 *Reagents and conditions:* i, $(CF_3CO)_2O$, Me_2SO, −60 °C then Et_3N, −60 °C; ii, K_2CO_3, $(MeO)_2SO_2$, Me_2CO; iii, Ac_2O, $HClO_4$

stereochemical relationship between 1-H and 4a-H in the enone **30** was obtained by NOE difference techniques. In particular, irradiation of the signal due to 1-H resulted in a 13% enhancement of the signal due to 4a-H thus establishing the close proximity of these hydrogens. *O*-Methylation of **30** using potassium carbonate and dimethyl sulfate proceeded uneventfully to give the required α-methoxy enone **7a** in 69% yield. Finally, reaction of **7a** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene at room temperature for 48 h afforded deacetamidoisocolchicine as a crystalline solid in 84% yield. The physical and spectroscopic data obtained for **4** were fully in accord with the assigned structure.

In an effort to develop a higher yielding synthesis of **4** we explored ways of avoiding the inefficient oxidation of **29** to **30**. To these ends, the acid stable dichloro diol **28** was treated with trifluoroacetic anhydride-activated DMSO (Scheme 6) and the corresponding α-hydroxy enone **31** was obtained as a yellow oil in 67% yield. *O*-Methylation of **31** then afforded **32** but this latter compound proved completely resistant to base-promoted ring-expansion under a variety of conditions. Presumably, the relatively rigid nature of the carbocyclic framework of **32** together with the presence of a chlorine sitting directly above the γ-hydrogen (4a-H) which must be abstracted for conjugate enolisation conspire to prevent the desired conversion. In an attempt to circumvent this problem, compound **32** was treated with acetic anhydride in the presence of perchloric acid catalyst. However, instead of producing the desired norcaradiene acetate **33** or its valence bond isomer **34** the novel dibenzocyclooctadiene **35** was obtained in 39% yield (at 75% conversion). The structure of **35** was confirmed by X-ray crystallographic methods (Fig. 3 and Table 2) and a possible pathway for its formation from **32** is outlined in Scheme 7. A key step associated

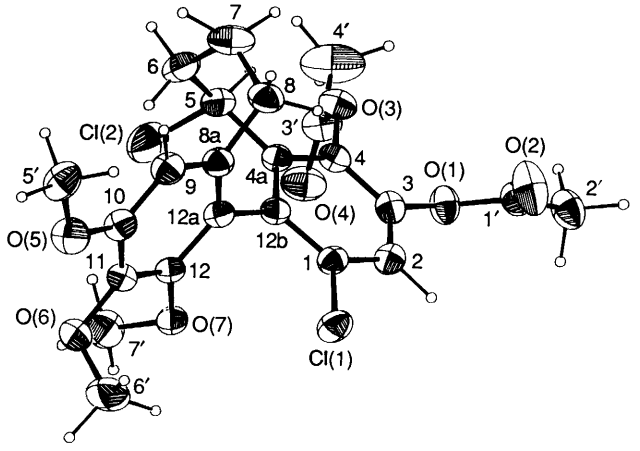


Fig. 3 X-Ray crystal structure of **35**. (Thermal ellipsoids are drawn at the 50% probability level and hydrogen atoms are represented by spheres of arbitrary radius. The C symbol for the carbon atoms has been omitted.)

Table 2 Final atomic coordinates of the non-hydrogen atoms with esds in parentheses for compound **35**

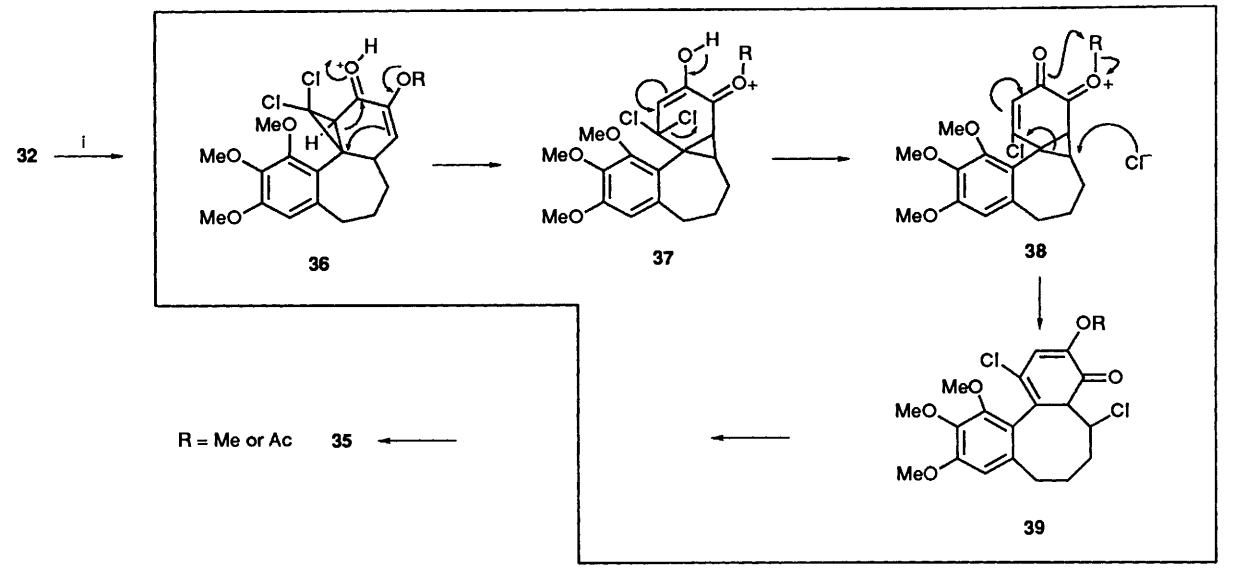
	$10^4 x$	$10^4 y$	$10^4 z$
Cl(1)	970(1)	5231(1)	1446(1)
Cl(2)	3529(1)	580(1)	4219(1)
O(1)	1570(3)	5694(3)	4869(2)
O(2)	2432(5)	7746(4)	3851(3)
O(3)	3734(3)	3711(3)	5037(2)
O(4)	1520(4)	2620(4)	5965(2)
O(5)	4447(3)	1472(3)	−819(2)
O(6)	1613(3)	974(3)	357(2)
O(7)	851(3)	1955(3)	2086(2)
C(1)	1814(4)	4720(4)	2499(3)
C(2)	1372(4)	5425(4)	3237(3)
C(3)	2024(4)	5078(4)	4077(3)
C(4)	3066(4)	4020(4)	4185(3)
C(4a)	3538(4)	3314(4)	3433(3)
C(5)	4669(4)	2162(4)	3643(3)
C(6)	5948(5)	1887(5)	2813(4)
C(7)	6873(5)	3131(6)	2129(4)
C(8)	6028(5)	4091(5)	1384(4)
C(8a)	4829(4)	3331(4)	1082(3)
C(9)	5213(5)	2795(4)	242(3)
C(10)	4174(4)	2007(4)	−4(3)
C(11)	2676(4)	1738(4)	605(3)
C(12)	2305(4)	2220(4)	1467(3)
C(12a)	3358(4)	3036(4)	1703(3)
C(12b)	2892(4)	3671(4)	2569(3)
C(1′)	1759(5)	7098(4)	4657(3)
C(2′)	1010(5)	7634(5)	5517(4)
C(3′)	2813(5)	3013(5)	5919(3)
C(4′)	3629(6)	2833(9)	6770(4)
C(5′)	5985(5)	1605(5)	−1405(3)
C(6′)	611(6)	1833(6)	−221(5)
C(7′)	461(5)	520(5)	2548(4)

with this proposal is a rearrangement reaction which produces the cyclopropyl intermediate **37** from **36** and there is some precedent for such a process.[21] Elimination of the elements of HCl from **37** then produces **38** which undergoes further reaction to give, *via* the cyclohexadienone **39**, the observed compound **35**. Unlike a number of other oxonium ions derived from σ-homo-*o*-benzoquinones, **38** presumably does not rearrange to a troponoid[22] because the chlorine in this system inhibits planarisation of the required benzylic cation. As a result, the illustrated fragmentation mode for **38** becomes competitive. The precise timing associated with the replacement of the *O*-methyl group at C-3 in **32** by the *O*-acetyl group in **35** is not known.

Experimental

General Details.—Melting points were recorded on a Kofler hot-stage and are uncorrected. Microanalyses were carried out in the Microanalytical Laboratory at the University of Otago, Dunedin, New Zealand. IR spectra (ν_{max}) were recorded on a Perkin–Elmer 938G spectrometer. Samples were analysed either as thin liquid films on NaCl plates or as KBr discs. Unless otherwise specified ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a JEOL GX-400 spectrometer. ^1H NMR chemical shifts (δ_H) are reported downfield from tetramethylsilane (TMS) as internal standard, while ^{13}C NMR chemical shifts (δ_C) were referenced to the central peak (δ 77.0) associated with the signals due to $CDCl_3$. All *J* values are in Hz. DEPT and INEPT or SFORD techniques were used to determine the degree of substitution associated with various carbons. High and low resolution mass spectra (*m/z*) were recorded on a VG Micromass 7070F using positive ion electron impact techniques. Unless otherwise specified an ionising voltage of 70 eV was used. FAB mass spectra were recorded on a JEOL AX505H mass spectrometer using a thioglycerol matrix and employing xenon atoms of *ca.* 3 eV. Electronic spectra were recorded in the solvent indicated on a Varian Superscan 3 spectrophotometer. Analytical thin layer chromatography (TLC) was conducted on aluminium-backed 0.2 mm thick silica gel 60 GF_{254} plates supplied by Merck and the chromatograms were visualised under a 254 nm UV lamp and/or with anisaldehyde–sulfuric acid–ethanol (2:5:93) spray reagent. Preparative TLC was conducted using 20 × 20 cm glass plates loaded with Merck Kieselgel 60 GF_{254} (35 g per plate) and eluted with the solvent system indicated. The components were located under 254 nm UV light and extracted with the solvents indicated. All solvents were purified according to literature procedures[23] and freshly dried anhydrous solvents were stored over activated 4 Å molecular sieves in tightly stoppered vessels out of sunlight. Other general experimental details have been reported elsewhere.[24]

5-(3′,4′,5′-Trimethoxyphenyl)pentanoic Acid **13**.—A solution of 3,4,5-trimethoxybenzaldehyde **10** (20.0 g, 0.102 mol) and methyl crotonate **11** (15.27 g, 0.15 mol) in *tert*-butyl alcohol (36 cm^3) was added dropwise to a mechanically stirred solution of potassium *tert*-butoxide in *tert*-butyl alcohol (1.5 mol dm^{-3}; 142 cm^3). After addition was complete, the resulting viscous mixture was stirred for a further 4 h while maintaining a reaction temperature of *ca.* 65 °C. The mixture was then cooled, acidified with aq. HCl (2 mol dm^{-3}; 1000 cm^3) and extracted with dichloromethane (3 × 150 cm^3). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting oil was dissolved in absolute ethanol (35 cm^3), treated with water (213 cm^3) and potassium hydroxide (5.68 g) and then heated under reflux for 15 h. The mixture was again cooled and then acidified with aq. HCl (2 mol dm^{-3}; 500 cm^3) and extracted with dichloromethane (3 × 150 cm^3). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow–orange oil which crystallised with time. TLC analysis of this material (diethyl ether elution) revealed two chromophoric spots (R_f 0.4 and 0.7). This material was dissolved in ethanol (200 cm^3) and treated with 3% palladium on carbon (1.00 g). The resulting mixture was stirred under an atmosphere of hydrogen (760 mmHg, 20 °C) for 24 h and the catalyst was then removed by filtration through Celite. The solids thus retained were washed with additional ethanol (*ca.* 100 cm^3). Concentration of the combined filtrates under reduced pressure gave a brown waxy solid. Subjection of this material to purification by flash chromatography (1:199 acetic acid–diethyl ether elution) afforded, after concentration of the appropriate fractions (R_f 0.7), 5-(3′,4′,5′-trimethoxyphenyl)pentanoic acid **13** (23.2 g, 85%



Scheme 7 *Reagents:* i, Ac_2O, $HClO_4$

wrt **10**) as an off-white waxy solid, m.p. 59–61 °C (lit.,[25] m.p. 66–68 °C) (Found: M^+, 268.1311. Calc. for $C_{14}H_{20}O_5$ *M*, 268.1311); ν_{max}(NaCl)/cm^{-1} 2938 br, 1708, 1589, 1506, 1462, 1421, 1238 and 1127; δ_H(90 MHz) 6.38 (s, 2 H, 2′- and 6′-H), 3.83 (s, 6 H, OMe), 3.80 (s, 3 H, OMe), 2.20–2.70 (complex m, 4 H) and 1.52–1.86 (complex m, 4 H); δ_C (22.5 MHz) 179.7 (br), 153.0, 137.7, 136.1, 105.3, 60.7, 56.0, 35.8, 33.9 (br), 30.7 and 24.2; *m*/*z* (%) 268 (83) (M^+), 181 (100), 167 (13) and 151 (10).

6,7,8,9-*Tetrahydro*-2,3,4-*trimethoxy*-5H-*benzocyclohepten*-5-*one* **15**.—A three-necked 1 dm^3 round-bottomed flask equipped with a magnetic stirrer bar was oven-dried then cooled under a stream of dry nitrogen. A solution of the acid **13** (30.14 g, 0.11 mol) in benzene (300 cm^3) was added to this flask and some benzene (*ca.* 40 cm^3) was distilled off. After cooling to room temperature, the stirred solution was treated with PCl_5 (22.90 g, 0.11 mol) and the resulting mixture heated at reflux for 0.75 h and then cooled to 5 °C (ice–water bath). The reaction vessel was fitted with a 100 cm^3 dropping funnel containing a solution of tin(IV) chloride (30.44 g, 0.11 mol) in benzene (67 cm^3). This solution was slowly added to the stirred, cooled mixture over a period of 1.5 h. When addition was complete, the mixture was allowed to warm to 22 °C and stirred at about this temperature for 16 h before being poured onto ice–aq. HCl (2 mol dm^{-3}; 10% excess) and the neutral material extracted with benzene (3 × 500 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light brown solid. Recrystallisation (methanol) of this material gave the title compound **15** (17.48 g, 64%) as white needles, m.p. 99.5–100 °C (lit.,[8] m.p. 100 °C) (Found: C, 67.2; H, 7.5. Calc. for $C_{14}H_{18}O_4$; C, 67.2; H, 7.3%); ν_{max}(KBr)/cm^{-1} 2938, 1672, 1592, 1486, 1454, 1321, 1261, 1194 and 1093; δ_H 6.44 (s, 1 H, 1-H), 3.88(8) (s, 3 H, OMe), 3.88(6) (s, 3 H, OMe), 3.86(0) (s, 3 H, OMe), 2.73–2.70 (complex m, 2 H), 2.63–2.60 (complex m, 2 H) and 1.84–1.78 (complex m, 4 H); δ_C 206.2, 154.7, 151.5, 140.8, 134.7, 127.7, 107.8, 62.3, 60.9, 55.9, 42.0, 32.7, 25.5 and 22.3; *m*/*z* (%) 250 (100) (M^+), 233 (33), 221 (51) and 181 (34).

(Z)-6,7,8,9-*Tetrahydro*-6-*hydroxymethylene*-2,3,4-*trimethoxy*-5H-*benzocyclohepten*-5-*one* **16**.—To a magnetically stirred suspension of alcohol-free sodium methoxide (214 mmol, made from 4.92 g of sodium) in dry benzene (120 cm^3) maintained at room temperature in a flask being flushed with a slow stream of dry nitrogen was added ethyl formate (28.1 cm^3, 348 mmol). The mixture was stirred at room temperature for 1 h and then cooled to 0 °C (ice-bath). A solution of the ketone **15** (16.65 g, 67 mmol) in benzene (180 cm^3) was added in a dropwise fashion over 1 h to the mixture. At the completion of addition the ice-bath was removed and the mixture allowed to warm to room temperature; it was then stirred for a further 15 h. The mixture was cooled to *ca.* 5 °C and then treated with chilled aq. H_2SO_4 (10% v/v; 300 cm^3). The layers were separated and the aqueous phase was extracted with benzene (2 × 200 cm^3). The combined organic layers were washed with water (1 × 250 cm^3) and then extracted with aq. K_2CO_3 (2 mol dm^{-3}; 5 × 200 cm^3). The combined aqueous phases were carefully acidified with aq. H_2SO_4 (2 mol dm^{-3}; 1200 cm^3) and then extracted with dichloromethane (3 × 400 cm^3). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light brown solid. Recrystallisation (diethyl ether) of this material gave the title compound **16** (18.1 g, 98%) as colourless needles, m.p. 110–111.5 °C (lit.,[8] m.p. 110–112 °C) (Found: C, 64.9; H, 6.6 Calc. for $C_{15}H_{18}O_5$: C, 64.8; H, 6.5%); ν_{max}(KBr)/cm^{-1} 2938, 1632, 1591, 1556, 1493, 1461, 1350, 1322, 1198 and 1127; δ_H(90 MHz) 8.00 (d, *J* 6.5, 1 H), 6.49 (s, 1 H, 1-H), 3.90 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 2.58 (t, *J* 6.8, 2 H) and 2.05–1.81 (complex m, 4 H), OH not observed; δ_C(22.5 MHz) 190.4, 175.8, 155.3, 152.4, 141.0, 136.2, 123.5, 112.8, 107.8, 62.1, 60.9, 55.9, 31.2, 30.7 and 23.7; *m*/*z* (%) 278 (100) (M^+), 250 (60) (M^+ − CO), 249 (15) (M^+ − CHO), 235 (46), 221 (51), 207 (18) and 181 (10).

6-*Formyl*-6,7,8,9-*tetrahydro*-2,3,4-*trimethoxy*-6-(3′-*oxobutyl*)-5H-*benzocyclohepten*-5-*one* **17**.—Triethylamine (0.4 cm^3, 2.9 mmol) was added dropwise to a magnetically stirred solution of compound **16** (12.52 g, 45 mmol) and MVK (7.5 cm^3, 90 mmol) in dichloromethane (19 cm^3) maintained at 0 °C (ice–water bath) under an atmosphere of nitrogen. After being stirred at 0 °C for 1 h, the resulting solution was allowed to warm to room temperature and stirred for a further 18 h. Analytical TLC (1:9 diethyl ether–dichloromethane elution) after this time revealed a single major chromophoric component (R_f 0.5). Concentration of the crude mixture under reduced pressure gave a red–brown oil which crystallised with time. Recrystallisation (methanol) of this material gave the *title compound* **17** (14.4 g, 92%) as powdery, white crystals, m.p. 92–94 °C (Found: C, 65.3; H, 7.0. $C_{19}H_{24}O_6$ requires C, 65.5; H, 6.9%); ν_{max}(KBr)/cm^{-1} 2838, 1709br, 1669, 1592, 1488, 1458, 1405, 1350,

1327, 1317, 1253 and 1134; δ_H(90 MHz) 9.83 (s, 1 H, CHO), 6.40 (s, 1 H, 1-H), 3.90 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 2.61–2.39 (m, 4-H), 2.17–1.64 (m, 6 H) and 2.11 (s, 3 H, COMe); δ_C 207.1, 205.6, 201.5, 155.1, 150.9, 140.9, 133.1, 126.8, 107.8, 64.8, 62.4, 60.9, 56.1, 37.6, 32.5, 29.9, 29.6, 28.4 and 22.3; *m/z* (%) 348 (7) (M^+), 320 (14) ($M^+ - CO$), 291 (100) ($M^+ - CO - CHO$), 263 (43), 221 (42), 207 (42) and 43 (30).

3,4,4a,5,6,7-*Hexahydro*-9,10,11-*trimethoxy*-2H-*dibenzo*[a,c]-*cyclohepten*-2-*one* **18**.—The aldehyde **17** (10.0 g, 28.7 mmol) was dissolved in ethanolic potassium hydroxide (8% w/v solution; 370 cm^3) and the resulting mixture was heated at reflux for 1 h under a nitrogen atmosphere. After cooling to room temperature the mixture was diluted with aq. HCl (2 mol dm^{-3}; 200 cm^3) and then water (1000 cm^3) and extracted with dichloromethane (5 × 70 cm^3). The combined organic layers were washed with water (1 × 500 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a reddish brown oil. This material was dissolved in acetone (100 cm^3) and then treated with potassium carbonate (14 g, 114 mmol) and dimethyl sulfate (5.0 cm^3, 839 mmol). The reaction mixture was stirred vigorously under a nitrogen atmosphere for 18 h at room temperature then quenched with water (50 cm^3) and stirred for a further 18 h. The acetone was then removed from the mixture under reduced pressure and the oily residue extracted with dichloromethane (3 × 50 cm^3). The combined organic layers were washed with water (1 × 100 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a red oil. TLC analysis (1:9 diethyl ether–dichloromethane elution) of this material indicated the presence of a single major component (R_f 0.4). Trituration (methanol) of the oil gave the title compound **18** (5.55 g, 64%) as light yellow prisms, m.p. 112–113 °C (lit.,[11] m.p. 103–103.5 °C) (Found: C, 71.7; H, 7.0. Calc. for $C_{18}H_{22}O_4$: C, 71.5; H, 7.3%); ν_{max}(KBr)/cm^{-1} 2935, 1659, 1612, 1592, 1489, 1407, 1369, 1347, 1322, 1293, 1241, 1199, 1130, 1092 and 1050; δ_H(90 MHz) 6.46 (s, 1 H, 8-H), 5.93 (s, 1 H, 1-H), 3.83 (s, 6 H, OMe), 3.74 (s, 3 H, OMe), 2.60–2.22 (complex m, 6 H) and 2.01–1.90 (complex m, 5 H); δ_C 199.2, 163.1, 152.6, 149.9, 140.5, 135.1, 128.4, 127.5, 108.3, 61.3, 60.7, 55.8, 38.8, 34.7, 34.3, 33.8, 30.1 and 26.3; *m/z* (%) 302 (100) (M^+) and 287 (17) ($M^+ - Me$).

(3α,4aα)-3-*Acetoxy*-3,4,4a,5,6,7-*hexahydro*-9,10,11-*trimethoxy*-2H-*dibenzo*[a,c]*cyclohepten*-2-*one* **19** *and* (3α,4aβ)-3-*Acetoxy*-3,4,4a,5,6,7-*hexahydro*-9,10,11-*trimethoxy*-2H-*dibenzo*-[a,c]*cyclohepten*-2-*one* **20**.—Manganese(III) acetate (22 g) was added to a solution of the cyclohexenone **18** (4.28 g, 14.2 mmol) in benzene (240 cm^3). The reaction vessel was equipped with a magnetic stirrer bar, a Dean–Stark trap and a Liebig condenser and a nitrogen atmosphere was established. The mixture was then stirred and heated at reflux for 12 h before being cooled to room temperature and diluted with ethyl acetate (200 cm^3) and aq. HCl (2 mol dm^{-3}; 200 cm^3). The resulting dark-brown suspension was filtered through Celite and the filtrate layers were separated. The organic layer was washed with aq. HCl (2 mol dm^{-3}; 1 × 200 cm^3), aq. $NaHCO_3$ (saturated; 1 × 300 cm^3) and then brine (1 × 300 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an orange oil which crystallised with time. TLC analysis (1:9 diethyl ether–dichloromethane elution) of this material suggested the presence of two diastereoisomeric acetates (R_f 0.6 and 0.4). Separation of these components was achieved using flash chromatography (5:95 diethyl ether–dichloromethane elution, silica). After concentration of the appropriate fractions the chromatographically less mobile product was recrystallised (ethanol) to give the *acetoxy-enone* **20** (1.99 g, 39%) as off-white needles, m.p. 172–174 °C (δ sublimation) (Found: C, 66.6; H, 6.8. $C_{20}H_{24}O_6$ requires C, 66.7; H, 6.7%); ν_{max}(KBr)/cm^{-1} 2992, 2961, 1752, 1692, 1613, 1592, 1490, 1446, 1402, 1369, 1318, 1243, 1225 and 1209; δ_H(90 MHz) 6.47 (s, 1 H, 8-H), 5.97 (s, 1 H, 1-H), 5.69 (m, 1 H, 3-H), 3.84 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 3.73 (s, 3 H, OMe), 2.75–1.76 (complex m, 9 H) and 2.18 (s, 3 H, OCOMe); δ_C(22.5 MHz) 193.7 (C), 170.3 (C), 162.7 (C), 152.7 (C), 150.0 (C), 140.5 (C), 135.8 (C), 127.6 (CH), 127.4 (C), 108.5 (CH), 70.2 (Me), 61.4 (Me), 60.8 (Me), 55.9 (Me), 40.6 (CH), 37.2 (CH_2), 36.8 (CH_2), 36.0 (CH_2), 28.1 (CH_2) and 20.9 (Me); *m/z* (%) 360 (13) (M^+), 300 (100) ($M^+ - MeCO_2H$), 285 (16) ($M^+ - MeCO_2H - Me$) and 43 (32) ($MeCO^+$). The chromatographically more mobile product was recrystallised (methanol) to give *acetoxy enone* **19** (2.04 g, 40%) as coarse light-yellow needles, m.p. 121–123 °C (Found: C, 66.5; H, 6.9. $C_{20}H_{24}O_6$ requires C, 66.7; H, 6.7%); ν_{max}(KBr)/cm^{-1} 2934, 1743, 1685, 1606, 1485, 1454, 1238, 1209, 1132, 1112 and 1083; δ_H 6.49 (s, 1 H, 8-H), 6.03 (d, *J* 2.7, 1 H, 1-H), 5.55 (dd, *J* 12.6 and 5.6, 1 H, 3-H), 3.88 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 2.90–3.00 (m, 1 H, 4a-H), 2.69–2.53 (m, 2 H), 2.33–2.18 (m, 2 H), 2.21 (s, 3 H, OCOMe) and 1.73–1.50 (m, 4 H); δ_C(22.5 MHz) 193.7 (C), 170.2 (C), 164.0 (C), 153.7 (C), 150.0 (C), 140.8 (C), 133.6 (C), 127.8 (CH), 124.8 (C), 107.9 (CH), 74.5 (CH), 61.6 (Me), 60.9 (Me), 56.0 (Me), 37.6 (CH), 34.9 (CH_2), 31.1 (CH_2), 28.0 (CH_2), 21.6 (CH_2) and 20.9 (Me); *m/z* (%) 360 (100) (M^+), 300 (17) ($M^+ - MeCO_2H$), 285 (20), 274 (52), 259 (64) and 243 (88); λ_{max}(ethanol)/nm: 306 (ε 7200), 232 (16 400) and 202 (25 400).

(7aα,8aβ,11aβ)-5,7,7a,8,8a,11a-*Hexahydro*-1,2,3-*trimethoxy*-10,10-*dimethyl*-6H-*benzo*[3,4]*cyclohepta*[1,2-f][1,3]*benzodioxole* **23**.—The α′-acetoxy enone **19** (770 mg, 2.14 mmol) and cerium(III) trichloride heptahydrate (797 mg, 2.14 mmol) were dissolved in methanol (15 cm^3) and the solution cooled to 0 °C. The magnetically stirred solution was then treated with sodium borohydride (97 mg, 2.57 mmol) in three approximately equal portions. The mixture was allowed to warm to room temperature and stirred for a further 30 min before being poured into water (30 cm^3). Extraction of this mixture with dichloromethane (1 × 20 cm^3) gave an emulsion which was readily dispersed upon acidification with a small amount of aq. HCl (2 mol dm^{-3}). The aqueous layer was extracted with further dichloromethane (2 × 20 cm^3), then the combined organic extracts were washed with water (1 × 20 cm^3), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a yellow oil (the crude *acetoxy alcohol* **21**). Dissolution of the above oil in methanol (10 cm^3) afforded a light yellow solution which was cooled to *ca* 5 °C (ice–water). The magnetically stirred solution was treated with finely ground potassium hydroxide (146 mg, 2.60 mmol) and allowed to warm to room temperature. After being stirred for 30 min, the mixture was poured into water (50 cm^3) and the aqueous suspension extracted with diethyl ether (3 × 50 cm^3). Drying of the combined organic layers ($CaCl_2$) followed by filtration and concentration under reduced pressure gave the *diol* **22** as an off-white sold. The diol **22** was dissolved in acetone (15 cm^3) and the magnetically stirred suspension cooled to 0 °C. The mixture was treated with aq. perchloric acid (60%; 1 drop) and stirred for 1 h at 0 °C. During the course of reaction, the solution became homogeneous. The mixture was filtered through a 2 cm deep plug of K_2CO_3 and the plug washed with dichloromethane (*ca.* 50 cm^3). The combined filtrates were concentrated under reduced pressure to give a yellow oil. Subjection of this material to preparative TLC (1:9 diethyl ether–dichloromethane elution) gave a single major chromophoric band (R_f 0.4) which was extracted (diethyl ether) to give a colourless oil that crystallised with time. Recrystallisation (methanol) of this material afforded the title *alkene acetonide* **23** (560 mg, 73%) as a white crystalline solid, m.p. 95–97.5 °C (Found: C, 70.0; H, 8.0. $C_{21}H_{28}O_5$ requires C, 70.0; H, 7.8%); ν_{max}(KBr)/cm^{-1} 2978, 2941, 2859, 1594, 1488, 1453, 1404, 1319, 1126, 1088, 1049, 1022, 990 and 865; δ_H 6.44 (s, 1 H, 4-H), 5.70

(br s, 1 H, 12-H), 4.66 (t, *J* 6.0, 1 H, 11a-H), 4.50 (dd, *J* 12.0 and 6.0, 1 H, 8a-H), 3.85 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 3.75 (s, 3 H, OMe), 2.70–2.38 (m, 3 H), 1.90–1.67 (m, 4 H), 1.58–1.41 (m, 2 H), 1.52 (s, 3 H, Me) and 1.42 (s, 3 H, Me); δ_C 151.8, 150.5, 142.7, 140.6, 135.5, 128.6, 123.8, 108.3, 107.8, 72.2, 71.8, 61.4, 61.0, 55.9, 34.9, 33.7, 33.1, 32.5, 27.8, 26.0 and 24.9; *m/z* (%) 360 (100) (M^+), 302 (79) ($M^+ - Me_2CO$), 274 (81), 270 (58) and 259 (38); λ_{max}(ethanol)/nm 246 (ε 8800) and 214 (26 200).

(7aα,8aα,11aα)-5,7,7a,8,8a,11a-*Hexahydro*-1,2,3-*trimethoxy*-10,10-*dimethyl*-6H-*benzo*[3,4]*cyclohepta*[1,2-f][1,3]*benzodioxole* **25**.—Following the same procedures as used for the epimer **19** (see above), the acetoxy enone **20** was converted into the alkene acetonide **25**. The crude product was obtained as a white solid which was recrystallised (methanol) to give the *title compound* **25** (82%) as fine white needles, m.p. 60–62 °C (Found: M^+, 360.1935; C, 69.8; H, 7.8. $C_{21}H_{28}O_5$ requires M, 360.1937; C, 70.0; H, 7.8%); ν_{max}(KBr)/cm^{-1} 2931, 1651, 1593, 1486, 1454, 1404, 1134 and 1093; δ_H 6.43 (s, 1 H, 4-H), 5.70 (br s, 1 H, 12-H), 4.71 (ddd, *J* 6.0, 3.5 and 1.5, 1 H, 12a-H), 4.44 (ddd, *J* 6.0, 4.5 and 4.5, 1 H, 8a-H), 3.85 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 3.75 (s, 3 H, OMe), 2.54 (m, 1 H), 2.50 (dt, *J* 14 and 4.5, 1 H), 2.19 (m, 1 H), 1.98 (dt, *J* 13.5 and 4.5, 1 H), 1.87 (m, 3 H), 1.70 (m, 1 H), 1.51 (s, 3 H, Me), 1.47 (m, 1 H) and 1.39 (s, 3 H, Me); δ_C 151.9 (C), 150.7(C), 141.3 (C), 140.7 (C), 136.1 (C), 128.6 (C), 124.9 (CH), 108.5 (C), 108.0 (CH), 73.3 (CH), 72.5 (CH), 61.3 (Me), 60.9 (Me), 56.0 (Me), 35.7 (CH), 34.0 (CH_2), 33.3 (3) (CH_2), 3.32 (7) (CH_2), 33.1 (CH_2), 28.0 (Me) and 25.7 (Me); *m/z* (%) 360 (50) (M^+), 302 (49) ($M^+ - Me_2CO$) and 274 (100).

(7aα,8aβ,11aβ)-11a-*Dichloromethyl*-5,7,7a,8,8a,11a-*hexahydro*-10,10-*dimethyl*-1,2,3-*trimethoxy*-6H-*benzo*[3,4]*cyclohepta*[1,2-f][1,3]*benzodioxole* **24**.—A solution of the alkene **23** (100 mg, 0.29 mmol) in dry pentane (7 cm^3) was added to freshly prepared sodium methoxide (1.08 g, 20 mmol) and the resulting suspension cooled to 0 °C with vigorous stirring. Ethyl trichloroacetate (0.77 cm^3, 5.59 mmol) was slowly added (syringe pump) to the stirred, cooled solution over a period of 1 h. After the completion of addition, the mixture was allowed to warm slowly to room temperature. After a further 24 h the mixture was poured into water (15 cm^3) and extracted with pentane (2 × 15 cm^3). The combined pentane layers were washed with water (2 × 20 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (2:98 diethyl ether–dichloromethane elution, silica) gave, after concentration of the appropriate fractions (R_f 0.5), a crystalline solid. Recrystallisation (twice from methanol) of this material gave the *title compound* **24** (42 mg, 33%) as colourless prisms, m.p. 157–158 °C (Found: M^+, 442.1316; C, 59.6; H, 6.4; Cl, 16.3. $C_{22}H_{28}Cl_2O_5$ requires *M*, 442.1314; C, 59.6; H, 6.4; Cl, 16.0%); ν_{max}(KBr)/cm^{-1} 2933, 1595, 1483, 1460, 1408, 1227, 1135 and 1069; δ_H 6.48 (s, 1 H, 4-H), 5.79 (s, 1 H, 12-H), 5.62 (br s, 1 H, $HCCl_2$), 4.56 (s, 1 H, 8a-H), 3.87 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 3.80 (s, 3 H, OMe), 2.70–2.90 (m, 2 H), 2.45 (dd, *J* 12.8 and 6.8, 1 H), 2.03 (td, *J* 13.9 and 4.4, 1 H), 1.81 (m, 1 H), 1.68–1.38 (m, 3-H), 1.54 (s, 3 H, Me), 1.51 (s, 3 H, Me) and 0.87 (m, 1 H); δ_C 152.4 (C), 150.2 (C), 144.7 (C), 140.7 (C), 134.4 (C), 127.2 (C), 122.1 (CH), 109.4 (C), 107.6 (CH), 81.8 (C), 76.0 (CH), 75.9 (CH), 61.6 (Me), 60.9 (Me), 56.0 (Me), 31.2 (CH_2), 30.7 (CH), 27.7 (Me), 27.5 (Me), 27.4 (CH_2) and 2 × CH_2 not observed; *m/z* (%) 442 (32), 444 (22), 446 (4) (M^+), 384 (4), 386 (3), 388 (< 1) ($M^+ - Me_2CO$), 359 (100) ($M^+ - CCl_2H$), 301 (37) ($M^+ - Me_2CO - CCl_2H$) and 273 (73); λ_{max}(ethanol)/nm 242 (ε 8200) and 212 (27 700).

Acetonide of (1aα,2α,3α,4aβ,11bβ)-1,1-*Dichloro*-1a,2,3,4,4a,5,6,7-*octahydro*-9,10,11-*trimethoxy*-1H-*benzo*[a]-*cyclopropa*[1,6]*benzo*[1,2-c]*cycloheptene*-2,3-*diol* **26**.—Conditions for the formation of this material from precursor **25** were identical with those employed for the conversion of **23** into **24** except that the mixture was stirred at room temperature for 4 h instead of 24 h. Subjection of the crude reaction product to preparative TLC (2:98 diethyl ether–dichloromethane elution) afforded a weakly chromophoric band (R_f 0.5) which was extracted (diethyl ether) to give a light yellow oil. This material was triturated with and then recrystallised from methanol to give the *title acetonide* **26** (91 mg, 71%) as white needles, m.p. 102.5–103.5 °C (Found: M^+, 442.1311; C, 59.8; H, 6.5; Cl, 16.2. $C_{22}H_{28}Cl_2O_5$ requires *M*, 442.1314; C, 59.6; H, 6.4; Cl, 16.0%); ν_{max}(KBr)/cm^{-1} 2933, 1600, 1453 and 1100; δ_H 6.49 (s, 1 H, 8-H), 4.48 (d, *J* 6, 1 H, 2-H), 4.11 (p, *J* 6, 1 H, 3-H), 3.87 (1) (s, 3 H, OMe), 3.86 (7) (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 3.02 (s, 1 H, 1a-H), 2.79 (td, *J* 20 and 8, 1 H), 2.58 (dd, *J* 13.5 and 7, 1 H), 1.74 (m, 2 H), 1.56 (m, 2 H), 1.52 (s, 3 H, Me), 1.41 (s, 3 H, Me), 1.29 (dd, *J* 25 and 11, 1 H), 0.99 (ddd, *J* 18, 12.5 and 5.5, 1 H) and 0.87 (m, 1 H); δ_C 153.8, 152.8, 141.0, 137.3, 121.1, 107.7, 107.0, 75.1, 70.7, 70.6, 61.7, 60.8, 55.8, 37.8, 37.3, 35.3, 33.8, 31.2, 30.4, 28.0, 25.5 and 24.7; *m/z* (%) 444 (1.4), 442 (1.8) (M^+), 415 (3), 413 (17), 411 (25) and 43 (100) ($MeCO^+$).

Acetonide of (1α,1aα,2α,3α,4aβ,11bα)-1-*Chloro*-1a,2,3,4,4a,5,6,7-*octahydro*-9,10,11-*trimethoxy*-1H-*benzo*[a]-*cyclopropa*[1,6]*benzo*[1,2-c]*cycloheptene*-2,3-*diol* **27**.—A magnetically stirred solution of the acetonide **26** (473 mg, 1.07 mmol) in ethanol (27 cm^3) was treated sequentially with zinc (5.25 g) and then potassium hydroxide (2.51 g) and the resulting suspension heated at reflux for 16 h. After this time, the hot mixture was filtered through a 2 cm deep pad of Celite and the retained solids washed with copious amounts of hot ethanol (*ca.* 200 cm^3). The combined filtrates were concentrated under reduced pressure (water bath temperature below 30 °C) and the residue was partitioned between water (50 cm^3) and dichloromethane (30 cm^3). The aqueous layer was extracted with further dichloromethane (4 × 25 cm^3) and the combined organic layers were washed with brine (1 × 100 cm^3) and then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the *title compound* **27** (370 mg, 85%) as fine white needles, m.p. 134–135 °C (Found: M^+, 408.1703. $C_{22}H_{29}{}^{35}ClO_5$ requires *M*, 408.1703); ν_{max}(KBr)/cm^{-1} 3054, 2984, 2934, 1596, 1377, 1368, 1351, 1244, 1107 and 1052; δ_H 6.50 (s, 1 H, 8-H), 4.62 (d, *J* 5.6, 1 H, 2-H), 3.95 (p, *J* 5.6, 1 H, 3-H), 3.88 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 2.92 (td, *J* 13.2 and 7.8, 1 H), 2.92 (d, *J* 4.9, 1 H), 2.63 (d, *J* 4.9, 1 H), 2.58 (dd, *J* 13.2 and 6.8, 1 H), 1.70 (m, 1 H), 1.52 (s, 3 H, Me), 1.41 (s, 3 H, Me), 1.46–1.23 (complex m, 4 H) and 1.08–0.94 (complex m, 2 H); δ_C 154.3, 152.5, 141.0, 137.4, 120.7, 107.9, 107.0, 75.7, 71.4, 61.8, 60.8, 55.7, 44.9, 40.2, 35.1, 32.2, 31.3, 30.4, 28.2, 25.9 and 24.9 (one signal unobserved); *m/z* (%) 408 (17), 410 (5) (M^+), 379 (35), 377 (100) ($M^+ -$ OMe) and 255 (96).

(1aα,2α,3α,4aβ,11bβ)-1,1-*Dichloro*-1a,2,3,4,4a,5,6,7-*octahydro*-9,10,11-*trimethoxy*-1H-*benzo*[a]*cyclopropa*[1,6]*benzo*-[1,2-c]*cycloheptene*-2,3-*diol* **28**.—The acetonide **26** (88 mg, 0.21 mmol) was dissolved in methanol (4 cm^3) and the magnetically stirred solution cooled to 0 °C. Aq. HCl (1 mol dm^{-3}; 1 cm^3) was added dropwise to the stirred, cooled solution. Upon completion of addition, the mixture was allowed to warm to room temperature and was then stirred for 1 h before being poured into water (20 cm^3). The cloudy suspension was extracted with chloroform (3 × 15 cm^3) and the combined organic layers were washed with water (1 × 20 cm^3), dried ($MgSO_4$), filtered and concentrated to give a yellow oil. Subjection of this material to preparative TLC (1:1 diethyl ether–chloroform elution) revealed a weekly chromophoric, mobile component (R_f 0.6) which was extracted (warm THF) to give a colourless oil. This material crystallised with time and

was recrystallised (three times from ethanol) to give the *title compound* **28** (80 mg, 95%) as tan clusters, m.p. 148–149 °C (Found: M^+, 402.1001; C, 56.7; H, 6.0; Cl, 17.9. $C_{19}H_{24}Cl_2O_5$ requires M, 402.1001; C, 56.6; H, 6.0; Cl, 17.6%); ν_{max}(KBr)/cm^{-1} 3417, 2938, 1596, 1485, 1407, 1322 and 1112; δ_H 6.55 (s, 1 H, 3-H), 3.90 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 3.34 (d, *J* 10.5, 1 H, 1a-H), 2.94 (m, 2 H), 2.59 (dd, *J* 13.7 and 8.3, 1 H, 3-H), 2.32 (d, *J* 4.9, 1 H), 2.01 (m, 1 H), 1.75 (m, 2-H), 1.58 (m, 2 H), 1.41 (dm, *J* 14.2, 1 H), 1.29 (td, *J* 13.7 and 4.9, 1 H) and 0.71 (ddd, *J* 18.6, 13.5 and 5.1, 1 H); δ_C 152.9, 152.0, 140.5, 137.6, 119.7, 108.1, 70.2, 69.4, 67.8, 61.1, 60.8, 55.8, 38.7, 38.0, 36.6, 32.2, 30.7, 30.1 and 23.3; *m/z* (%) 402 (6), 404 (4) (M^+), 353 (43), 355 (28), 357 (5) ($M^+ - OMe - H_2O$) and 317 (100) and 319 (36) ($M^+ - OMe - H_2O - HCl$).

(1α,1aα,2α,3α,4aβ,11bα)-1-*Chloro*-1a,2,3,4,4a,5,6,7-*octahydro*-9,10,11-*trimethoxy*-1H-*benzo*[a]*cyclopropa*[1,6]*benzo*[1,2-c]-*cycloheptene*-2,3-*diol* **29**.—Reductive dechlorination of the diol **28** (60 mg, 0.15 mmol), using the same reaction conditions as employed for the conversion of **26** into **27**, afforded a viscous, light yellow oil (63 mg) on work-up. Trituration and then recrystallisation with ethanol gave the *title compound* **29** (41 mg, 74%) as fine white needles, m.p. 147.5–148.5 °C (Found: C, 61.7; H, 7.1; Cl, 10.4. $C_{19}H_{25}ClO_5$ requires C, 61.9; H, 6.8; Cl, 9.6%); ν_{max}(KBr)/cm^{-1} 3417, 2927, 1595, 1454, 1352, 1319 and 1059; δ_H 6.53 (s, 1 H, 8-H), 4.24 (m, 1 H, 2-H), 3.93 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 3.49 (m, 1 H, 3-H), 3.12 (d, *J* 4.9, 1 H, 1-H), 2.93 (m, 2 H), 2.59 (dd, *J* 13.7 and 6.8, 1 H), 2.13 (dd, *J* 4.6 and 2.7, 1 H, 1a-H), 1.70 (m, 2-H), 1.53 (m, 2 H), 1.35 (m, 2 H), 1.26 (m, 1 H) and 0.88 (m, 1-H); δ_C 153.0, 152.7, 140.5, 137.7, 120.2, 107.3, 70.3, 67.4, 61.4, 60.8, 55.9, 44.8, 40.9, 36.0, 34.8, 31.2, 30.2, 29.4 and 25.0; *m/z* (%) 368 (12), 370 (4) (M^+), 319 (100), 321 (34) ($M^+ - OMe - H_2O$), 283 (92) ($M^+ - OMe - H_2O - HCl$) and 255 (85) ($M^+ - OMe - H_2O - HCl - CO$).

(1α,1aα,4aβ,11bα)-1-*Chloro*-1,1a,4a,5,6,7-*hexahydro*-3-*hydroxy*-9,10,11-*trimethoxy*-2H-*benzo*[a]*cyclopropa*[1,6]-*benzo*[1,2-c]*cyclohepten*-2-*one* **30**.—Freshly distilled oxalyl chloride (125 mm^3, 1.44 mmol) was dissolved in dichloromethane (freshly distilled from phosphorus pentoxide) (3 cm^3) and the magnetically stirred solution cooled to −60 °C (solid CO_2–chloroform) under a nitrogen atmosphere. DMSO (4.4 mol dm^{-3} solution in dichloromethane; 652 mm^3, 2.87 mmol) was added dropwise over 5 min to the stirred, cooled solution and after stirring for 5 min at −60 °C the diol **29** (150 mg, 0.41 mmol) dissolved in 4.4 mol dm^{-3} DMSO in dichloromethane (200 mm^3) was added dropwise over 5 min. The resulting solution was stirred for 10 min at −60 °C before triethylamine (800 mm^3, 5.74 mmol) was added dropwise. After being stirred for 5 min at −60 °C, the now yellow suspension was allowed to warm to room temperature and stirred for a further 1 h. After this time the mixture was partitioned between diethyl ether (20 cm^3) and aq. NaOH (1 mol dm^{-3}; 20 cm^3). The organic layer was extracted with additional aq. NaOH (1 mol dm^{-3}; 3 × 20 cm^3) and the combined aqueous layers were then washed with diethyl ether (1 × 20 cm^3) before being acidified with aq. HCl (2 mol dm^{-3}). The aqueous suspension was extracted with dichloromethane (4 × 20 cm^3) and the combined organic layers were washed with water (1 × 30 cm^3) then dried ($MgSO_4$), filtered and concentrated to give a yellow oil that crystallised upon trituration with diethyl ether. This material was recrystallised (twice from dichloromethane–diethyl ether) to give the *title compound* **30** (46 mg, 31%) as fine, light yellow needles, m.p. 129.5–131 °C (Found: M^+, 364.1079; C, 62.3; H, 5.8; Cl, 9.9. $C_{19}H_{21}ClO_5$ requires M, 364.1077; C, 62.6; H, 5.8; Cl, 9.7%); ν_{max}(KBr)/cm^{-1} 3442, 1654, 1632, 1594 and 1196; δ_H 6.52 (s, 1 H, 8-H), 6.13 (s, 1 H, OH), 5.75 (d, *J* 3, 1 H, 4-H), 3.87 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 3.76 (d, *J* 4.5, 1 H, 1-H), 3.67 (s, 3 H, OMe), 3.22 (d, *J* 4.5, 1 H, 1a-H), 2.92 (td, *J* 20 and 6.5, 1 H), 2.74 (br d, *J* 13.5, 1 H), 2.67 (dd, *J* 13.5 and 5, 1 H), 1.84 (m, 1 H), 1.56 (m, 2 H) and 1.30 (m, 1 H); δ_C 189.1, 154.4, 153.2, 145.1, 141.2, 136.9, 120.8, 119.4, 107.2, 61.7, 61.1, 55.8, 47.8, 40.0, 37.8, 37.5, 31.4, 30.4 and 26.9; *m/z* (%) 366 (24), 364 (72) (M^+) and 329 (100) ($M^+ - Cl$).

(1α,1aα,4aβ,11bα)-1-*Chloro*-1,1a,4a,5,6,7-*hexahydro*-3,9,10,11-*tetramethoxy*-2H-*benzo*[a]*cyclopropa*[1,6]*benzo*[1,2-c]*cyclohepten*-2-*one* **7a**.—The α-hydroxy enone **30** (37 mg, 0.1 mmol) was dissolved in dry acetone (3.3 cm^3) and treated with dimethyl sulfate (218 mm^3, 2.3 mmol) and then potassium carbonate (221 mg, 1.6 mmol). The suspension was magnetically stirred in a sealed flask under nitrogen for 14 h before being quenched with water (1 cm^3) and stirred for a further 22 h. After this time, the mixture was partitioned between water (10 cm^3) and dichloromethane (10 cm^3). The aqueous layer was extracted with further dichloromethane (2 × 10 cm^3) and the combined organic extracts were washed with water (1 × 20 cm^3) and then dried (Na_2SO_4), filtered and concentrated to give a light yellow oil (72 mg). Subjection of this material to preparative TLC (5:95 diethyl ether–dichloromethane elution) gave a major chromophoric band (R_f 0.4) which was extracted (diethyl ether) to give a light yellow oil. Subjection of this material to semi-preparative HPLC (70:30 hexane–ethyl acetate elution, 2 cm^3 min^{-1}, μ-Porasil column) provided two major components with retention times of 14.2 and 26.3 min. Concentration of the less mobile fraction afforded a colourless oil which upon trituration (7:3 hexane–ethyl acetate) crystallised to give the *title compound* **7a** (26 mg, 69%) as white crystalline needles, m.p. 102–104 °C (Found: M^+, 378.1235. $C_{20}H_{23}{}^{35}ClO_5$ requires *M*, 378.1234); ν_{max}(KBr)/cm^{-1} 2938, 1677, 1624 and 1595; δ_H 6.42 (s, 1 H, 8-H), 5.28 (d, *J* 2.7, 1 H, 4-H), 3.77 (s, 3 H, OMe), 3.72 (s, 3 H, OMe), 3.58 (s, 3 H, OMe), 3.58 (dd, *J* 4.4 and 0.5, 1 H, 1-H), 3.50 (s, 3 H, OMe), 3.09 (d, *J* 4.4, 1 H, 1a-H), 2.83 (ddd, *J* 19.8, 6.6 and 6.6, 1 H), 2.58 (m, 2 H), 1.75 (m, 1 H), 1.50 (m, 2 H) and 1.23 (m, 1 H); δ_C 187.8, 154.4, 153.1, 149.8, 141.2, 136.9, 119.4, 118.9, 107.1, 61.6, 61.1, 55.8, 55.1, 47.4, 40.1, 39.1, 35.8, 31.3, 31.0 and 26.7; *m/z* (%) 378 (40), 380 (13) (M^+), 342 (65) ($M^+ - HCl$), 314 (85) ($M^+ - HCl - CO$) and 84 (100). Concentration of the more mobile fraction afforded a colourless oil (7 mg). The structure of this material remains unidentified.

Deacetamidoisocolchicine **4**.—A magnetically stirred solution of the α-methoxy enone **7a** (20.1 mg, 0.053 mmol) dissolved in freshly distilled benzene (2.2 cm^3) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (115 mm^3, 0.77 mmol). After being stirred at ambient temperatures for 48 h, the mixture was poured into dichloromethane (10 cm^3) and washed with aq. HCl (2 mol dm^{-3}; 2 × cm^3), aq. $NaHCO_3$ (saturated; 1 × 10 cm^3) and water (2 × 10 cm^3). After being dried ($MgSO_4$), the yellow solution was concentrated under reduced pressure to give a brown oil (18.7 mg). This material was subjected to semi-preparative HPLC (ethyl acetate elution, 2 cm^3 min^{-1}, μ-Porasil column, R_t 17 min) to give a light yellow oil which when triturated with diethyl ether gave the title compound **4** (15.7 mg, 84%) as a light yellow solid, m.p. 148.5–149 °C (lit.,[4j] m.p. 147–148 °C) (Found: M^+, 342.1463. Calc. for $C_{20}H_{22}O_5$ *M*, 342.1461); ν_{max}(KBr)/cm^{-1} 2955, 1611, 1588, 1573, 1446, 1398, 1256, 1135 and 1094; δ_H 7.37 (d, *J* 12.7, 1 H, 12-H), 7.15 (d, *J* 12.7, 1 H, 11-H), 6.77 (s, 1 H, 8-H), 6.56 (s, 1 H, 4-H), 3.99 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 3.67 (s, 3 H, OMe), 2.31–2.55 (complex m, 4 H) and 2.10–2.27 (complex m, 2 H); δ_C 179.4 (C), 163.2 (C), 153.3 (C), 150.5 (C), 144.1 (C), 141.3 (CH), 140.9 (C), 135.8 (C), 135.4 (C), 133.3 (CH), 126.9 (C), 116.9 (CH), 107.3 (CH), 61.2 (Me), 60.8 (Me), 56.1 (Me), 56.0

(Me), 37.4 (CH_2), 33.1 (CH_2) and 30.8 (CH_2); *m/z* (%) 342 (100) (M^+), 314 (73) ($M^+ - CO$) and 299 (15) ($M^+ - CO - Me$); λ_{max}(ethanol)/nm 350 (ε 20 200) and 247 (35 000).

(1aα,4aβ,11bα)-1,1-*Dichloro*-1,1a,4a,5,6,7-*hexahydro*-3-*hydroxy*-9,10,11-*trimethoxy*-2H-*benzo*[a]*cyclopropa*[1,6]-*benzo*[1,2-c]*cyclohepten*-2-*one* **31**.—Trifluoroacetic anhydride (30 mm^3, 0.21 mmol) was added dropwise to a magnetically stirred solution of DMSO (19 mm^3, 0.24 mmol) in dichloromethane (1.0 cm^3) maintained at −60 °C (solid CO_2–chloroform) under a nitrogen atmosphere. The solution was stirred for 10 min before a solution of the diol **28** (30 mg, 0.074 mmol) in dichloromethane (300 mm^3) was added dropwise to it. The mixture was then stirred at −60 °C for 90 min, after which triethylamine (69 mm^3, 0.49 mmol) was added and stirring continued for a further 90 min at −60 °C; the mixture was then allowed to warm to room temperature. The now yellow solution was poured into aq. HCl (2 mol dm^{-3}; 10 cm^3) and extracted with chloroform (3 × 10 cm^3). The organic layers were washed with water (1 × 10 cm^3), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to preparative TLC (5:95 diethyl ether–dichloromethane elution) provided a single major and chromophoric band (R_f 0.7) which was extracted (diethyl ether) to give the *title compound* **31** (20 mg, 67%) as a light yellow oil (Found: M^+, 398.0688. $C_{19}H_{20}Cl_2O_5$ requires *M*, 398.0688); ν_{max}(KBr)/cm^{-1} 3429, 2936, 1714, 1666, 1596, 1487,1462, 1408, 1197 and 1108; δ_H 6.51 (s, 1 H, 8-H), 5.89 (d, *J* 3.2, 1 H, 4-H), 3.86 (s, 3 H, OMe), 3.80 (s, 3 H, OMe), 3.65 (s, 3 H, OMe), 3.16 (m, 1 H), 2.68 (m, 2 H), 1.89 (m, 1 H), 1.72 (dd, *J* 13.9 and 6.4, 1 H), 1.55 (m, 1 H) and 1.35 (m, 1 H); δ_C 184.9, 153.8, 153.4, 146.7, 141.0, 136.5, 123.0, 120.2, 107.2, 68.5, 61.9, 61.1, 55.8, 43.7, 41.6, 35.7, 31.3, 30.0 and 26.9; *m/z* (%) 398 (31), 400 (22), 402 (4) (M^+), 367 (39), 369, (26), 371 (6) ($M^+ - OMe$), 363 (35), 365 (15) ($M^+ - HCl$), 331 (87) and 267 (100).

(1aα,4aβ,11bα)-1,1-*Dichloro*-1,1a,4a,5,6,7-*hexahydro*-3,9,10,11-*tetramethoxy*-2H-*benzo*[a]*cyclopropa*[1,6]*benzo*[1,2-c]*cyclohepten*-2-*one* **32**.—The α-hydroxy enone **31** (50 mg, 0.12 mmol) was dissolved in dry acetone (4.1 cm^3) and treated with dimethyl sulfate (272 mm^3, 2.87 mmol) and then potassium carbonate (276 mg, 2.00 mmol). The suspension was magnetically stirred in a sealed flask under nitrogen for 14 h before being quenched with water (1 cm^3) and stirred for a further 22 h. After this time, the mixture was partitioned between water (10 cm^3) and dichloromethane (10 cm^3). The aqueous layer was extracted with further dichloromethane (2 × 10 cm^3) and the combined extracts were washed with water (1 × 20 cm^3), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a light yellow oil. Subjection of this material to preparative TLC (1:9 diethyl ether–dichloromethane elution) gave a single chromophoric band (R_f 0.6) which was extracted (diethyl ether) to give a light yellow oil. This material was triturated with and then recrystallised from methanol to give the *title compound* **32** (22 mg, 46%) as small needles, m.p. 197–199 °C (Found: M^+, 412.0844. $C_{20}H_{22}Cl_2O_5$ requires M, 412.0844); ν_{max}(KBr)/cm^{-1} 2933, 1681, 1619, 1454, 1200, 1148 and 1107; δ_H 6.51 (s, 1 H, 8-H), 5.52 (d, *J* 2.7, 1 H, 4-H), 3.87 (s, 3 H, OMe), 3.80 (s, 3 H, OMe), 3.66 (s, 3 H, OMe), 3.61 (s, 3 H, OMe), 3.59 (br s, 1 H, 1a-H), 3.13 (d, *J* 12.2, 1 H), 2.69 (m, 2 H), 1.92 (m, 1 H), 1.75 (dd, *J* 13.9 and 6.3, 1 H), 1.57 (m, 1 H) and 1.36 (m, 1 H); δ_C 183.5, 153.9, 153.4, 151.2, 141.1, 136.6, 120.5, 120.2, 107.2, 68.4, 61.8, 61.1, 55.8, 55.3, 42.9, 42.0, 35.5, 31.3, 30.7 and 26.7; *m/z* (%) 412 (51), 414 (34), 416 (5) (M^+), 397 (13), 399 (7) ($M^+ - Me$), 345 (39), 341 (34), 310 (42) and 31 (100).

3,4-*Diacetoxy*-1,5-*dichloro*-5,6,7,8-*tetrahydro*-10,11,12-*trimethoxydibenzo*[a,c]*cyclooctene* **35**.—A magnetically stirred solution of the α-methoxy enone **32** (6 mg, 14.5 μmol) in dichloromethane (300 mm^3) under a nitrogen atmosphere was cooled to 0 °C. Acetyl chloride (5 mm^3, 70 μmol) was added followed by 70% aq. perchloric acid (0.5 mm^3). The dark brown solution was stirred at room temperature for 4 h and then diluted with dichloromethane (2 cm^3) and water (2 cm^3). The layers were separated and the aqueous layer extracted with further dichloromethane (2 × 10 cm^3). The combined organic extracts were washed with brine (5 cm^3), dried (Na_2SO_4), filtered and concentrated to give a tan oil (7 mg). Subjection of this material to HPLC (70:30 hexane–ethyl acetate, 2 cm^3 min^{-1}, Porasil) gave two major components with retention times of 14 and 17 min. The less-mobile component was found to be unchanged enone **32** (1.5 mg, 25% recovery) by comparison with an authentic sample. The more mobile material could be crystallised from ethanol to give the *title compound* **35** (2 mg, 39% at 75% conversion) as elongated plates, m.p. 154–156 °C; ν_{max}(KBr)/cm^{-1} 2928, 1778, 1596 and 1197; δ_H 7.41 (s, 1 H, 2-H), 6.49 (s, 1 H, 9-H), 5.40 (d, *J* 9.5 and 4.6, 1 H, 5-H), 3.91 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 2.47 (m, 1 H), 2.37 (s, 3 H, OCOMe), 2.30 (s, 3 H, OCOMe), 2.22 (m, 1 H) and 1.98–1.66 (m, 4 H); δ_C 167.6, 167.5, 154.4, 151.7, 141.6, 140.1, 138.9, 135.3, 135.0, 133.5, 133.3, 124.0, 122.6, 106.6, 60.9, 60.8, 55.9, 54.5, 34.2, 30.9, 25.6, 20.8 and 20.4; *m/z* (%) (FAB–MS) 505 (32), 507 (22), 509 (6), ($M + Na^+$), 482 (92), 484 (68), 486 (17) (M^+), and 447 (100) and 449 (49) ($M^+ - HCl$); λ_{max}(ethanol)/ nm 293 (ε 3300) and 227 (19 800).

Single-Crystal X-*Ray Diffraction Analyses of Compounds* **24** *and* **35**.—*Crystal Data.* Compound **24**; $C_{22}H_{28}Cl_2O_5$, M = 443.4, orthorhombic space group *Pbca* (No. 61), a 15.138(1), b = 15.071(1), c = 19.726(1) Å, V = 4500.4(9) $Å^3$, λ = 1.5418 Å, Z = 8, D_m = 1.300(5), D_c = 1.309 g cm^{-3}. Colourless prisms. Crystal dimensions (distances of faces from centre): 0.128 (0 0 1, 0 0 $\bar{1}$) × 0.128 (1 1 0, $\bar{1}$ $\bar{1}$ 0) × 0.218 (1 $\bar{1}$ 0, $\bar{1}$ 1 0) mm, μ(Cu-Kα) = 27.21 cm^{-1}.

Crystal Data. Compound **35**; $C_{23}H_{24}Cl_2O_7$, M = 483.35, triclinic space group $P\bar{1}$(No. 2), a = 8.796(1), b = 10.048(1), c = 14.028(2) Å, α = 75.26(1), β = 78.40(1), γ = 88.26(1)°, V = 1174.3(3) $Å^3$, λ = 1.5418 Å, Z = 2, D_c = 1.309 g cm^{-3}. Colourless tablet. Crystal dimensions (distances of faces from centre): (0 $\bar{2}$ 1, 0 2 $\bar{1}$) × 0.150 ($\bar{1}$ $\bar{2}$ 0, 1 2 0) × 0.288 (0 1 2, 0 $\bar{1}$ $\bar{2}$) mm, μ(Cu-Kα) = 28.71 cm^{-1}.

Data Collection and Processing. Accurate unit cell parameters by least-squares refinement on diffractometer angles for 25 automatically centred reflections. Rigaku-AFC diffractometer at 291(1) K, $\omega/2\theta$ mode with scan range ($\Delta\omega$) 1.2° + 0.5° tanθ, 2θ scan rate 2° min^{-1}, graphite monochromated Cu-Kα radiation. Data to $2\theta_{max}$ 130° recorded yielded for **24** 3791 unique reflections (h 0 to 17, k 0 to 17, l 0 to 23) and for **35** 3934 unique reflections (h −10 to 10, k −11 to 11, l 0 to 16). Analytical absorption corrections were made [max., min transmission factors for **24** 0.57, 0.51 giving 2382 with $I \geqslant 2\sigma(I)$, for compound **35** 0.68, 0.26 giving 2819 with $I \geqslant 3\sigma(I)$, which were used in the refinements]. There was no crystal decay for **24**, but a linear and approx. isotropic crystal decay of *ca.* 4.3% for **35** was corrected during processing.

Structure Analysis and Refinement. Direct methods with SHELXS-86.[26] Full-matrix least-squares refinement with all non-hydrogen atoms anisotropic. For **24**, the hydrogens were given individual isotropic temperature factors, and apart from those of the methoxy hydrogens on ring A which were included at idealised positions, their positional coordinates were refined. The weighting scheme was $w = [\sigma^2(F_o) + 0.0025 F_o^2]^{-1}$. Five intense low order terms (2 2 0, 1 1 2, 0 2 2, 2 2 3, 0 0 6) seriously affected by extinction were omitted from the final refinement. Final R and R_w 0.073, 0.090, and $(\Delta\rho)_{max}$, $(\Delta\rho)_{min}$ were +0.28, −0.41 e $Å^{-3}$. For **35**, the methyl hydrogens were included at idealised positions with a common isotropic temperature factor

B_{iso} = 11.6(6) Å^2; refinement [x, y, z, U_{iso}] of the remaining H atoms. The weighting scheme was $w = [\sigma^2|F_o| + 0.0096|F_o|^2]^{-1}$. Final R and R_w 0.074, 0.102 and $(\Delta\rho)_{max}$, $(\Delta\rho)_{min}$ were +0.74, −0.55 e Å^{-3}. The intensities for both the structures were corrected for Lorentz and polarisation factors. The absorption corrections and refinements [function minimised $\Sigma w[|F_o| - |F_o|]^2$ were made with SHELX-76[27] on a VAX8800 computer. Atomic scattering factors and anomalous dispersion factors applied to the non-H atoms were those supplied in SHELX-76.[27] Figs. 2 and 3 were prepared from the output of ORTEPII.[28] Bond lengths and valence angles for the non-hydrogen atoms, anisotropic thermal parameters and atomic parameters for the hydrogen atoms for both the structures, together with their estimated standard deviations, have been deposited at the Cambridge Crystallographic Data Centre.* The molecular conformations of **24** and **35** are illustrated in Figs. 2 and 3, respectively.

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