Fully Regiocontrolled Synthesis of (±)-12a,12b-Secocolchicine and Studies Concerning its Cyclisation to the Alkaloid Colchicine

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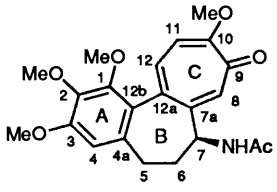
A fully regiocontrolled synthesis of the title compound **6**, an AC-ring analogue of the alkaloid colchicine **1**, is reported. The key step associated with the sequence used was condensation of lithium halogenocarbenoid **10**—a synthetic equivalent for the inaccessible 7-methoxytropon-3-yl anion **12**—with 3,4,5-trimethoxycinnamaldehyde **17** to produce the 1,2-addition product **18** as a mixture of diastereoisomers. Elaboration of compound **18** provided benzoate **23** which, on treatment with base, underwent ring-expansion to give troponoid **24** in excellent yield. Replacement of the C-7 benzoate group in compound **24** by an acetamido moiety was readily achieved and produced compound **6** in good overall yield. Unsuccessful attempts to convert compound **6** and the deacetamido analogue **38** into colchicine and deacetamidocolchicine **3**, respectively, are described.

The alkaloid colchicine **1** isolated from a range of sources including the meadow saffron *Colchicum autumnale*, is a potent antimitotic agent which exerts its effect by binding to tubulin in dividing cells and thereby preventing microtubule formation.[1] The precise manner in which compound **1** binds to this cytoskeletal protein is the subject of considerable research at present.[2] As a result of its antimitotic properties colchicine has been investigated as an agent in the treatment of, *inter alia*, gout,[3] Mediterranean Familial Fever,[3] glaucoma,[4] HIV-1 and -2,[5] multiple sclerosis[6] and hepatitis B.[7] However, the high toxicity of the compound has prevented its extensive clinical application. Nevertheless, certain derivatives of colchicine **1**, most notably the sulfide **2**, retain the potent antimitotic activity of the parent system but display considerably reduced toxicity. As a result of its greatly enhanced therapeutic index, 3-demethyl-10-thiocolchicine **2** has been used in the treatment of various refractory tumours including B16 melanoma.[3]



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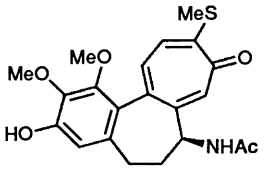

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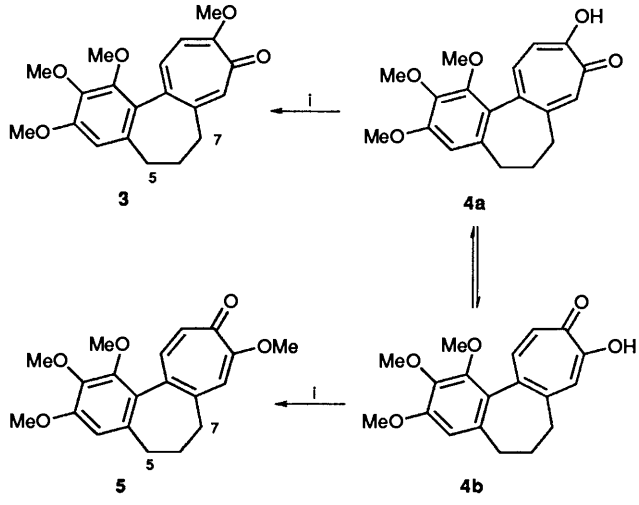
The interesting pharmacological profile of colchicine and its congeners coupled with their novel molecular architectures have made such compounds attractive synthetic targets.[8] To date a total of fifteen total or formal total syntheses of colchicine **1** have been reported.[8,9] Nine of these syntheses rely on the acquisition of compounds **3**, **4** or **5** (Scheme 1), advanced intermediates in Eschenmoser's original synthesis[8a] of the natural product. Three key problems have become apparent as a result of the extensive synthetic work in the area. These are: (i) the absence of flexible methods for preparing α-tropolones[9a] in general (the key structural element associated with the C-ring of colchicine); (ii) the lack of synthetic protocols which allow for the regioselective introduction of the methoxy and carbonyl moieties on the C-ring and (iii) the difficulties associated with regioselective introduction of the C-7 acetamido group in colchicine **1**. The second difficulty arises because O-methylation of unsymmetrical α-tropolones produces mixtures of the regioisomeric methyl ether derivatives. For example, O-methylation of the free tropolone deacetamidocolchiceine **4**, which



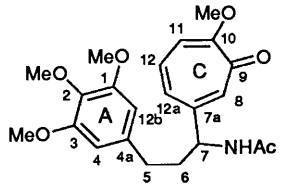
Scheme 1 *Reagents and conditions:* i, CH_2N_2, diethyl ether

exists in two rapidly interconverting tautomeric forms, **4a** and **4b**, affords a ~ 1:1 mixture of regioisomers **3** and **5**.[8a] As an illustration of the third difficulty, attempts to introduce the acetamido group into compound **3** by effecting initial pseudobenzylic bromination at C-7 have failed because the halogen is incorporated exclusively at C-5. In contrast, analogous reaction of compound **5** produced a mixture of the C-5 and C-7 bromoderivatives which could be separated chromatographically.[8a] However, after replacement of the C-7 bromine by an acetamido group, a demethylation/remethylation sequence was necessary in order to establish the required positions for the methoxy and carbonyl groups on the C-ring of the product **1**. Of course, this sequence is inefficient not least because it produces a mixture of colchicine and isocolchicine.

Quite remarkably, only one[8n] of the synthetic strategies described so far for the preparation of colchicine has solved all of the aforementioned problems and allowed for its synthesis in a fully regiocontrolled manner. The enantiocontrolled introduction of the C-7 acetamido group in colchicine **1** has yet to be achieved.

The title compound, (±)-12a,12b-secocolchicine **6**, represents an attractive synthetic target for three reasons. First, any efficient preparation of this compound requires the solution of many of the problems of regiocontrol which need to be addressed in the synthesis of colchicine itself. Secondly, two

research groups have shown that structurally less complex 12a,12b-seco systems, *i.e.* compounds **7**[8e] and **8**,[8g] can be converted, albeit inefficiently, into the colchicine skeleton. On this basis, compound **6** might serve as a precursor to colchicine. The third motivation for attempting to prepare compound **6** was that the acquisition of this compound would allow for an assessment of the significance of the σ-bond between the A and C rings of colchicine (which compound **6** lacks) as a determinant of antimitotic activity.[10]



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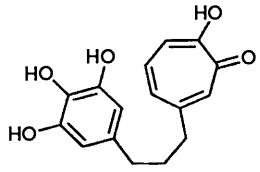

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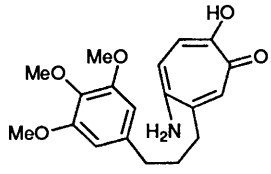

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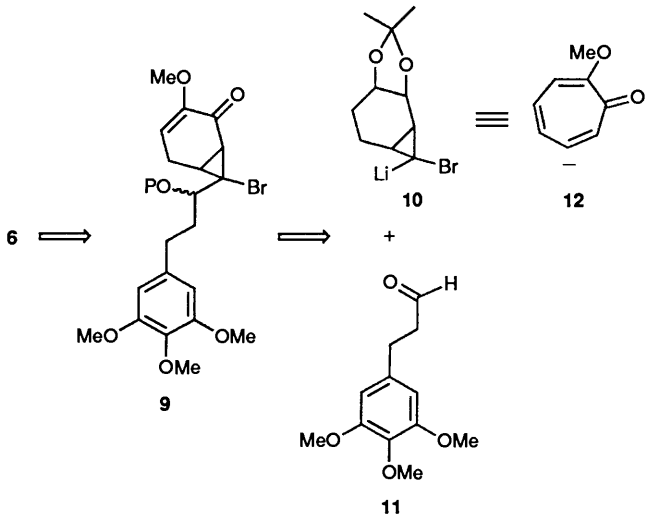
Yamamoto *et al.* have previously reported[11] a non-regioselective synthesis of compound **6** which starts from the naturally occurring tropolone β-thujaplicin. Although elegant in conception, this work does not address the two critical problems (i) and (ii) noted above. We now provide full details[12] of a fully regiocontrolled synthesis of 12a,12b-secocolchicine **6** and describe (unsuccessful) efforts to convert this and related compounds into the tricyclic (ABC) ring-system associated with colchicinoids.

Results and Discussion

1. *Retrosynthetic Analysis for* (±)-12*a*,12*b*-*Secocolchicine* **6**.—On the basis of earlier work, which had established the utility of 7-halogenobicyclo[4.1.0]heptenones as precursors to troponoids,[13] it was expected that the target compound could be prepared, in a fully regiocontrolled manner, using the strategy shown retrosynthetically in Scheme 2. Thus, base-promoted dehydrobrominative ring-expansion of compound **9** should deliver a 12a,12b-secocolchicinoid with a substituent at C-7* capable of conversion into the required acetamido group. Compound **9** should, in turn, be available by condensation of the lithium halogenocarbenoid **10** with 3,4,5-trimethoxydihydrocinnamaldehyde **11**. In effect, then, this strategy would employ compound **10** as a synthetic equivalent for the inaccessible 7-methoxytropon-3-yl anion **12**. The implementation of this approach is detailed in the following section.

2. *Synthesis of* (±)-12*a*,12*b*-*Secocolchicine* **6**.—The tactical details associated with the implementation of the strategy



Scheme 2 P = alcohol-protecting group

defined in Scheme 2 are given in Scheme 3. Treatment of the readily available alkene **13** with catalytic amounts of osmium tetraoxide in the presence of stoichiometric amounts of trimethylamine *N*-oxide[14] produced the diol **14** in 85% yield as a crystalline solid. That *cis*-dihydroxylation had taken place at the less congested α-face of alkene **13** followed from the X-ray crystal structure of a more advanced intermediate (compound **20a**) in the reaction sequence. Reaction of diol **14** with acetone in the presence of perchloric acid resulted in the rapid formation of acetonide **15** (95%), which upon treatment with butyllithium (one mole equivalent) at −100 °C produced the lithium halogenocarbenoid **10**.[15] However, attempts to condense this latter species with 3,4,5-trimethoxydihydrocinnamaldehyde **11**† only resulted in formation of the reductively debrominated product **16**. On the basis that the enolisable aldehyde **11** might be acting as a proton source and quenching anion **10**, this latter species was treated at −100 °C with 3,4,5-trimethoxycinnamaldehyde **17**†·[16] and the 1,2-addition product **18** (77%) was obtained as a 1:1 mixture of diastereoisomers. This mixture of unsaturated alcohols was hydrogenated under standard conditions (1 atm H_2, 10% Pd on C, methanol) to give the corresponding saturated compounds **19** (96%). Conversion of the 1:1 mixture of alcohols **19** into the corresponding benzoates **20**, using benzoyl chloride in pyridine with 4-(dimethylamino)pyridine (DMAP),[17] allowed separation of the resulting diastereoisomeric esters by fractional crystallisation. The structure of the less soluble benzoate **20a** was established by a single-crystal X-ray determination, details of which have been disclosed previously.[12] Hydrolysis of the acetonide group in benzoates **20**§ was accomplished with aqueous acid to give the corresponding diols **21** in high (90%) yield. Gratifyingly, there were no complications associated with acid-promoted ionisation of the benzoate moiety to produce a cyclopropylcarbinyl cation which then suffers ring cleavage.

Oxidation of diols **21** using trifluoroacetic anhydride (TFAA)-activated dimethyl sulfoxide (DMSO)[18] afforded the hydroxy enones **22** which could be O-methylated (using dimethyl sulfate in the presence of potassium carbonate) to produce the α-methoxy enones **23**. Base-promoted ring expansion of compounds **23**, using ten mole equivalents of the weakly nucleophilic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), proceeded rapidly at room temperature to give the troponoid **24** in good yield (85% from **23a** and 80% from **23b**).

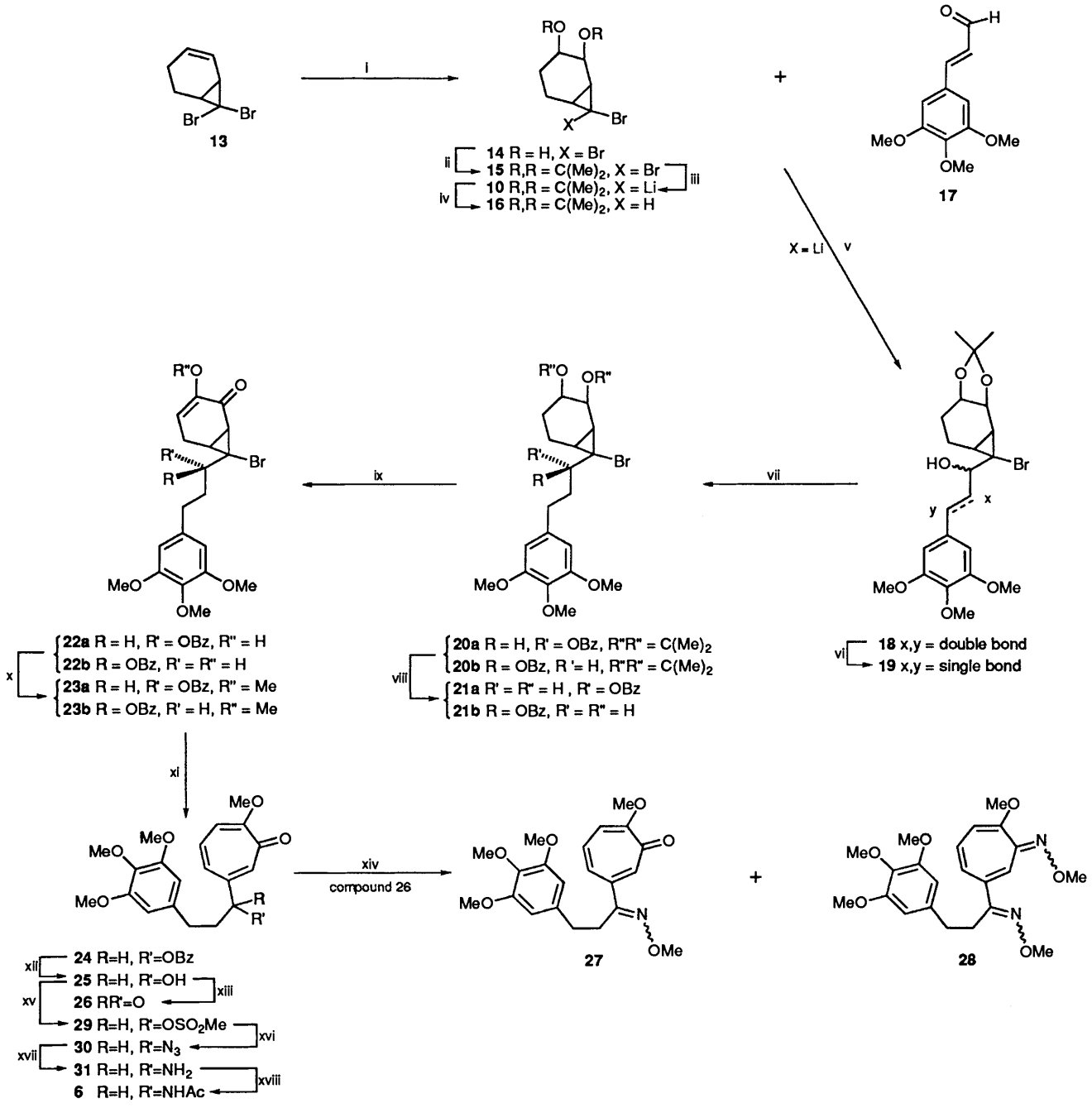
Initial attempts to convert the benzoate moiety of compound **24** into the C-7 acetamido group of our target molecule **6**

* The colchicine numbering scheme has been used throughout the Results and Discussion section of this article for all secocolchicinoids.

† 3,4,5-Trimethoxydihydrocinnamaldehyde **11** was prepared by hydrogenation (at 760 mmHg) of compound **17**,‡,[16] using 5% Pd on carbon as catalyst and ethanol as reaction solvent.

‡ The reported synthesis[16] of 3,4,5-trimethoxycinnamaldehyde **17** proved difficult to reproduce so alternative experimental conditions were developed (see Experimental section for details).

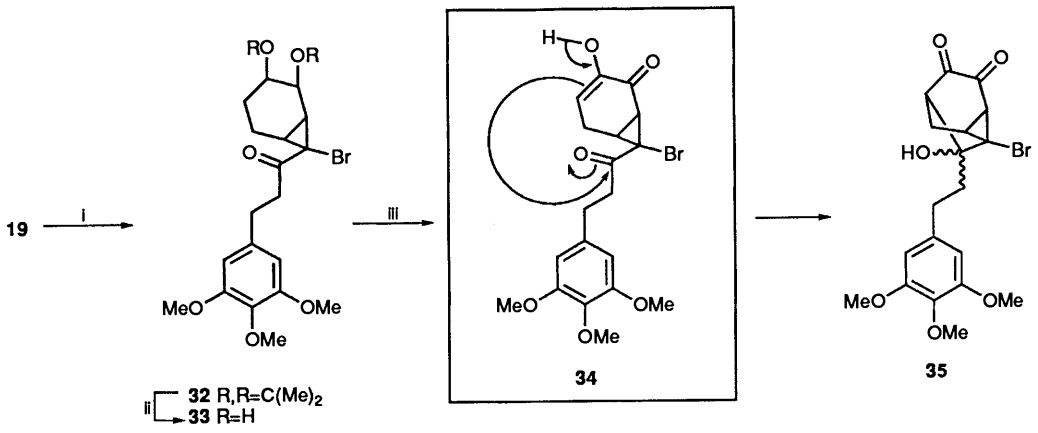
§ From this point on in the synthetic sequence, the separated diastereoisomers **20a** and **20b** were independently subjected to the reaction steps leading to the secocolchicine analogue **24**. Full details are given in the Experimental section.



Scheme 3 *Reagents and conditions:* i, 2.5 wt % OsO_4, Me_3NO, Bu^{t}OH, aq. pyridine, reflux, 2 h; ii, Me_2CO, trace $HClO_4$, 18 °C, 5 min; iii, BuLi (1.0 mol equiv.), THF, −100 °C, 1 h; iv, **11** (1.1 mol equiv.), THF, −100 °C, 2 h; v, **17** (1.1 mol equiv.), THF, −100 °C, 2 h; vi, H_2(1 atm.), 10% Pd on C, MeOH, 18 °C, 1.5 h; vii, PhCOCl (1.35 mol equiv.), DMAP (12 mol equiv.), pyridine, 18 °C, 16 h; viii, 0.5 mol dm^{-3} HCl in 1 : 1 THF–water, 18 °C, 25 h; ix, TFAA (2.0 mol equiv.), DMSO (2.6 mol equiv.), CH_2Cl_2, −60 °C, 1.5 h; then Et_3N (4.5 mol equiv.), −60 °C, 1.5 h; x, $(MeO)_2SO_2$ (44 mol equiv.), K_2CO_3 (30 mol equiv.), Me_2CO, 18 °C, 5 h; xi, DBU (10 mol equiv.), C_6H_6, 18 °C, 1 h; xii, K_2CO_3 (1.2 mol equiv.), MeOH, 18 °C, 2 h; xiii, $(COCl)_2$ (1.2 mol equiv.), DMSO (2.4 mol equiv.), −60 °C, 0.33 h; then Et_3N (5.0 mol equiv.), −60 to 0 °C, 0.33 h; xiv, $MeONH_2$·HCl (1.1 mol equiv.), pyridine, 18 °C, 1.5 h; xv, $MeSO_2Cl$ (1.1 mol equiv.), Et_3N, CH_2Cl_2, 0–5 °C, 0.33 h; xvi, NaN_3 (1.2 mol equiv.), 18-crown-6 (0.1 mol equiv.), THF, 18 °C, 16 h; xvii, H_2 (1 atm.), 10% Pd on C, MeOH, 18 °C, 2.5 h; xviii, Ac_2O, pyridine, 18 °C, 5 min

focussed on formation of a C-7 ketone unit (as in structure **26**). The expectation that reductive amination of such a group might ultimately be carried out in an enantiocontrolled manner provided the impetus for this approach. In the event, the benzoate group of compound **24** was readily removed by treatment with potassium carbonate in methanol and the resulting alcohol **25** was converted into the corresponding ketone **26*** (96%) by Swern oxidation. Following the procedure described by Singh,[19] compound **26** was treated with methoxylamine hydrochloride and pyridine and a ~9 : 1 mixture of the mono- and bis-*N*-methoxyimines, **27** and **28** respectively, resulted (94% combined yield). The two reaction products could be separated chromatographically and the doubling up of signals in both the ^1H and ^{13}C NMR spectra of compound **27** suggested that this material had been obtained as a mixture of

* In an attempt to provide a slightly shorter route (Scheme 4) to ketone **26**, alcohol **19** was oxidised to the ketone **32**. Hydrolytic removal of the acetonide moiety within the latter compound then afforded diol **33**. Subjection of compound **33** to modified Swern conditions then gave the yellow α-diketone **35** as a mixture of epimers at C-8. The desired hydroxy enone **34** was probably the initial product of this last reaction but it could not be isolated as a result of its readily occurring intramolecular aldol condensation to give dione **35**.



Scheme 4 *Reagents and conditions:* i, TFAA (1.8 mol equiv.), DMSO (2.3 mol equiv.), CH_2Cl_2, −60 °C, 1.5 h; then Et_3N (4.0 mol equiv.), − 60 °C, 1.5 h; ii, 0.5 mol dm^{-3} HCl in 1 : 1 THF–water, 18 °C, 30 h; iii, TFAA (3.0 mol equiv.), DMSO (3.9 mol equiv.), CH_2Cl_2, −60 °C, 1.5 h; then Et_3N (7.0 mol equiv.), −60 °C, 1.5 h

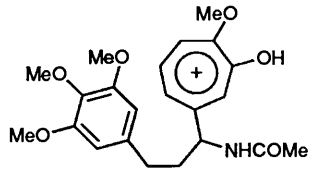
geometric isomers about the C=N bond. The even greater complexity of the ^1H NMR spectrum of compound **28** suggested that the four possible geometric isomers associated with this structure had been obtained. The formation of significant quantities of the bis-*N*-methoxyimine **28** clearly indicated that the troponoid carbonyl group in compound **27** is susceptible to nucleophilic attack. Therefore, it was not surprising that attempts to reduce the imine moiety of compound **27** were unsuccessful, presumably because sodium borohydride attacked at C-8, C-9 and/or C-10 (rather than at C-7), leading to the observed complex mixture of reduction and rearrangement products.[20]

The problems of chemoselectivity associated with competing nucleophilic additions at the sp^2-centres C-7 through to C-10 in systems such as **27** were circumvented by conversion of the C-7 alcohol **25** into the corresponding mesyl ester **29** and then by effecting a nucleophilic substitution with sodium azide in the presence of 18-crown-6.[21] The resulting azido product **30** (86%) was then reduced (1 atm H_2, 10% Pd on C, methanol)[22] and the amine **31** so formed was immediately acetylated[8a] to give the target compound **6** (77% from **30**) as a viscous oil.

Yamamoto *et al.*[11] have previously reported obtaining compound **6** as a crystalline solid; however, all attempts to crystallise our sample of this compound have failed. Nevertheless, the spectral data obtained on our material were in good agreement with the spectral properties described for compound **6** by the Japanese group. In particular, the presence of the expected nineteen signals in the 100 MHz $\{^1H\}^{13}C$ NMR spectrum of compound **6** together with the observation of a molecular ion ($M^{\cdot+}$ 401) in the positive-ion electron-impact mass spectrum strongly supported the assigned structure. Furthermore, diagnostic troponoid absorption bands (at 1595 and 1560 cm^{-1}) were observed in the IR spectrum of compound **6**. The 400 MHz ^1H NMR spectrum of compound **6** also supported the assigned structure. In particular, the observation of a broadened singlet at δ 7.27 (8-H), a doublet ($J_{11,12}$ 10.0) at δ 6.70 (11-H), a doublet of doublets ($J_{12,11}$ 10.0, $J_{12,12a}$ 10.4) at δ 7.07 (12-H) and a doublet of doublets ($J_{12a,12}$ 10.4, $J_{12a,8}$ 1.4) at δ 6.83 (12a-H) served to establish the illustrated substitution pattern on the troponoid C-ring.

3. *Tubulin-binding Properties of* (±)-12a,12b-*Secocolchicine* **6**.—Subjection of compound **6** to a previously described tubulin-binding assay[23] (kindly conducted by Professor A. Brossi and his associates at NIH) established that the compound was inactive. In contrast, racemic colchicine, while less active than the natural enantiomer,[3] displays significant tubulin-binding capacity as do some AC-ring analogues of colchicine **1**.[10] This outcome is fully consistent with Professor Brossi's prediction[24] that an AC-ring axis is an essential requirement for effective tubulin binding within the colchicinoid class.

4. *Attempts to Form the B-Ring of Colchicine by Cyclisation of* (±)-12a,12b-*Secocolchicine* **6** *and Related Compounds.*—With synthetically useful quantities of compound **6** in hand attempts to effect its conversion into colchicine were investigated. Simple storage of compound **6** in mineral acid, in the hope that the derived tropylium ion **36** might act as an internal electrophile and attack the pendant trimethoxyaryl group, only resulted in decomposition of the starting material.



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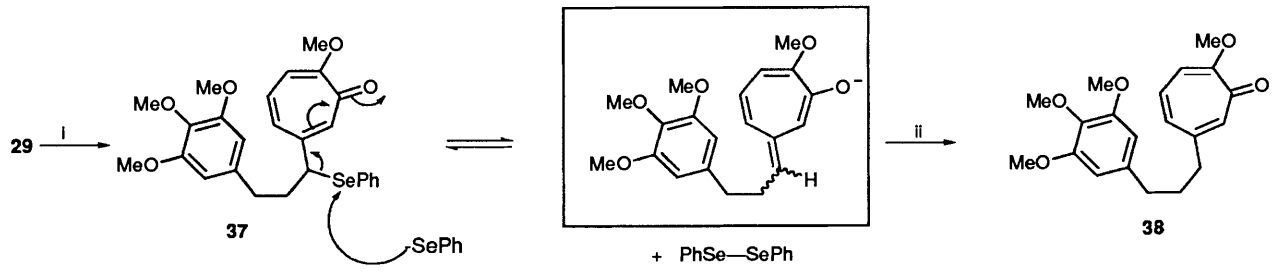
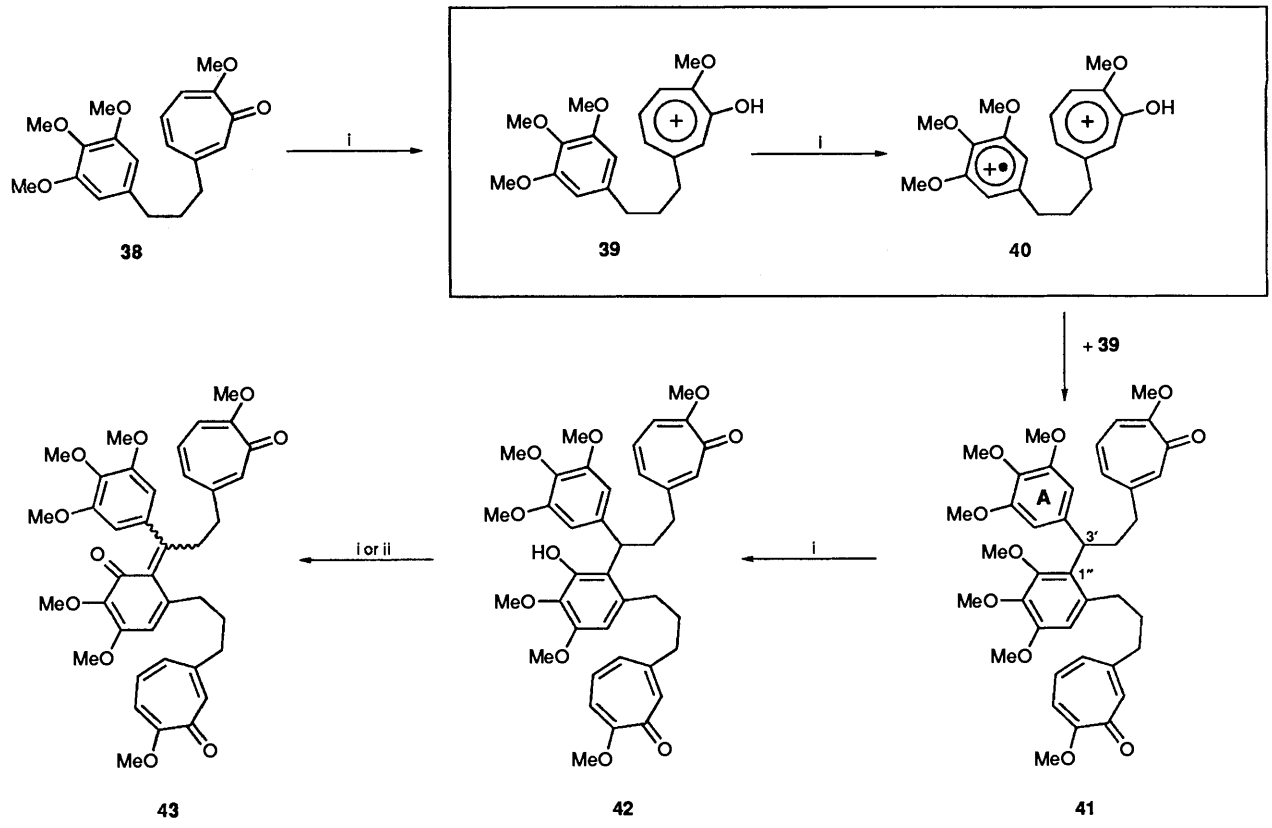
Since there are many examples of intramolecular oxidative coupling of biaryls,[25] this approach for the conversion of compound **6** into colchicine **1** was also investigated. However, when either thallium(III) trifluoroacetate or vanadium trifluoride oxide (VOF_3) was used as coupling reagent only complex mixtures of products were obtained, which proved difficult to analyse or separate by chromatographic means. Since it appeared that the presence of the acetamido group in these products might be contributing to the difficulties of purification we sought to examine the analogous oxidative-coupling reactions of deacetamido-12a,12b-secocolchicine **38**. The preparation of this model system proved unexpectedly straightforward. Thus, simple treatment of the C-7 mesyloxy compound **29** with sodium phenylselenide produced compound **38** (85%) [together with trace amounts (5%) of the substitution product **37**], presumably by the pathway shown in Scheme 5. Support for this reaction pathway followed from the observation that resubjection of selenide **37** to the reaction conditions provided compound **38** in essentially quantitative yield.*

Various methods for effecting the intramolecular oxidative coupling of compound **38** were investigated. While the use of thallium(III)-based oxidants led to low yields of intractable tars (possibly due to aromatic thallation), reaction of compound **38**

* α-Phenylseleno ketones are known to undergo reductive dephenylselenation on treatment with sodium phenylselenide in a protic solvent (ref. 26).



Scheme 5 *Reagents and conditions:* i, $PhSe^- Na^+$ (3.2 mol equiv.), MeOH, 18 °C, 0.25 h; ii, proton source



Scheme 6 *Reagents and conditions:* i, VOF_3 (3.1 mol equiv.), TFA, CH_2Cl_2, −46 °C, 2.5 h; ii, $(COCl)_2$ (10 mol equiv.), DMSO (10 mol equiv.), −60 °C, 0.5 h; then Et_3N, −60 °C, 0.5 h. (*NB:* Although compounds **41**, **42** and **43** will initially be produced as the corresponding tropylium ions, for the sake of brevity only the deprotonated products are shown.)

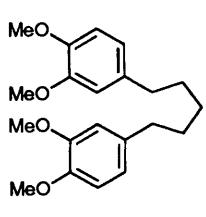
with VOF_3, according to the procedure of Koga and co-workers,[27] provided an orange foam in good yield (greater than 77% of original mass returned). Initial purification of this material by preparative TLC (PLC) provided a yellow oil, which was subjected to reversed-phase semi-preparative HPLC. By using conditions similar to those developed by Klein and Davis[28] for the analysis of colchicine derivatives it was possible to isolate three major chromophoric components from the mixture. On the basis of spectroscopic data obtained for these purified materials the dimeric structures **41** (11%), **42** (27%) and **43** (14%) (Scheme 6) have been proposed. While electron-impact mass spectrometry did not reveal molecular ions for any of these dimeric products, MH^+ ions at *m/z* 687 ($C_{40}H_{46}O_{10}$), 673 ($C_{39}H_{44}O_{10}$) and 671 ($C_{39}H_{42}O_{10}$) were observed in the FAB mass spectra of dimers **41**, **42** and **43** respectively and support the appropriate molecular formulae. The IR spectrum of the bis-tropolone phenol **42** exhibited an O–H stretching band at ν_{max} 3440 cm^{-1} along with intense tropolonic C=C and C=O absorbances at ν_{max} 1628 and 1595 cm^{-1}. Both the ^1H and ^{13}C NMR spectra of dimer **41** are fully consistent with the assigned structure. The presence of two tropolonoid carbonyl resonances at δ_C 179.2 and 179.1 are especially suggestive of a dimeric product. A DEPTD[29] ^{13}C NMR experiment established that compound **42** possesses ten sp^2-hybridised methine carbons, six methoxy carbons, five aliphatic methylene carbons and one aliphatic methine carbon (δ_C 73.4).

The dominant features observed in the IR spectrum of compound **43** were the intense quininoid carbonyl absorption at ν_{max} 1673 cm^{-1} and the tropolonoid olefinic and carbonyl absorbances at ν_{max} 1622 and 1590 cm^{-1}. Again, the ^1H NMR and ^{13}C NMR spectra supported the assigned structure. It is noteworthy that the structure proposed for compound **43** contains the *o*-quinonemethide nucleus. While such entities are known[30] to undergo ready addition of nucleophiles with concomitant aromatisation, the hindered nature of the exocyclic quinonemethide carbon together with the reduced electrophilicity of this same centre (due to conjugation with electron-donating methoxy groups) presumably prevents such processes from taking place in this case.

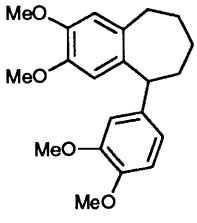
While the ^1H NMR spectrum of compound **41** was similar to that of the dimeric phenol **42**, the former displayed six methoxy methyl resonances and a multiplet at δ 4.12 which is attributed to the doubly benzylic methine proton. In the 100 MHz $\{^1H\}$ ^{13}C NMR spectrum of compound **41** twenty-five sp^2-carbon and seven methoxy methyl carbon resonances are observed. It is believed that this greater than expected number

of signals is a reflection of the restricted rotation about the C-1″/C-3′ bond (see structure **41**) which results in the associated 3,4,5-trimethoxyphenyl unit becoming unsymmetrical. Both the electronic and IR spectra of compound **41** were similar to the corresponding spectra of the starting compound **38**.

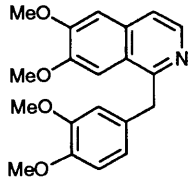
Additional support for the structural proposals outlined above derives from a consideration of the mechanism of formation of compounds **41**–**43**. Although the scope and limitations of the VOF_3-mediated oxidations have been studied extensively,[25,27,31] no mechanism has yet been formulated for coupling reactions employing this reagent. However, related oxidants such as thallium(III) trifluoroacetate are believed to operate *via* single-electron transfer to form radical cations with electron-rich substrates.[32] On this basis, it is proposed that in the present case the arene **38** is protonated (to give **39**) and then oxidised to the radical cation **40**. This latter species then reacts with a second molecule of cation **39** to afford the benzylically coupled dimer **41**. Under the strongly acidic conditions employed, the dimer **41** could then undergo monodemethylation to yield the phenol **42**. Further oxidation of the phenol **42** would then give the observed quinonemethide **43**. There is good experimental evidence to support the structural relationship between these last two compounds. For example, Swern oxidation [18] of compound **42** afforded quinonemethide **43** (47% yield after reversed-phase HPLC purification) identical in all respects with the material isolated from the VOF_3-promoted oxidation. Although benzylic coupling under oxidative cyclisation conditions is not common, it is by no means unprecedented. For example, Ronlán and Parker [33] have reported that cyclisation of the 1,5-diarylpentane **44** under a variety of conditions, including those employing thallium(III) trifluoroacetate, occurs between one aromatic ring and the benzylic position of the other ring to afford the tricyclic compound **45**. The absence of intramolecular coupling products in the reaction mixture derived from treatment of monomer **38** with VOF_3–CF_3CO_2H is attributed to rapid initial protonation of the tropolone ring with concomitant formation of the deactivated tropylium ion **39** (Scheme 6). Some support for such a proposal stems from the work of Kupchan *et al.*[34] who reported that treatment of papaverine **46** with VOF_3 in trifluoroacetic acid (TFA) afforded only the intermolecularly coupled product **47** (80%). These workers proposed that protonation of the nitrogen in papaverine **46** deactivated the isoquinoline ring-system and prevented any intramolecular coupling.



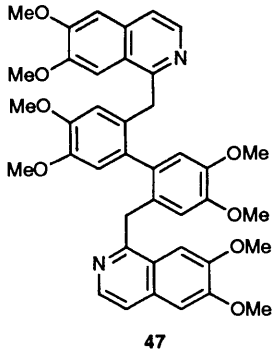
44



45

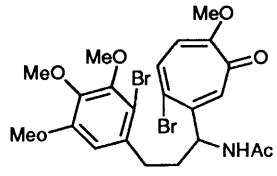


46

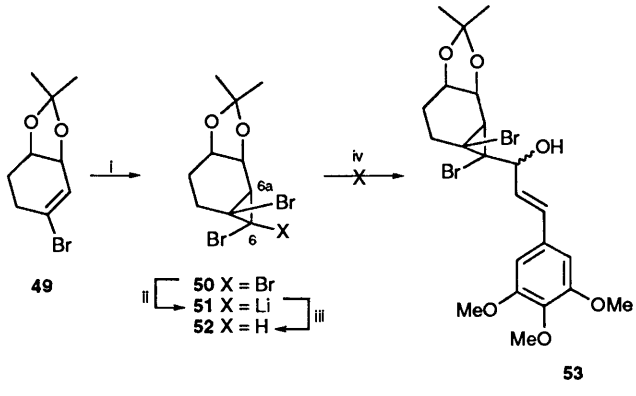


47

Various other attempts to introduce a σ-bond between the A- and C-rings of the 12a,12b-secocolchicinoid **38** were pursued. For example, in an effort to exploit intramolecular Ni^0 couplings of diaryl dihalides,[35] attempts (Scheme 7) were made to adapt the synthesis of compound **6** described earlier so as to allow for the preparation of the dibromo derivative **48**. To these ends, the known vinyl bromide **49** [36] was treated with dibromocarbene (generated by thermolysis of $PhHgCBr_3$ [37]) and the resulting crystalline adduct **50** (43%) was subjected to a metal-for-halogen exchange reaction at −100 °C by using butyllithium. The resulting lithium halogenocarbenoid **51** could be protonated efficiently with methanol to give the unstable dibromocyclopropane **52**. The stereochemistry at C-6 in this product follows from the observation of a doublet at δ 3.32 which is assigned to 6-H. The magnitude of the vicinal coupling (*J* 8.8) between 6-H and 6a-H is indicative of a *cis*-relationship [38] between them and is consistent with the notion that, under the reaction conditions used here, metal-for-halogen exchange reaction results in the formation of the sterically less congested (thermodynamic) product, *i.e.* **52**.[15] Unfortunately, all attempts to intercept anion **51** with 3,4,5-trimethoxycinnamaldehyde failed to produce the desired adduct **53**—only complex mixtures of products containing traces of dibromide **52** were obtained. Presumably the bromine at C-5a in tribromide **50** reduces the rate of attack of this anion on aldehyde **17** and other processes, including α-and β-elimination of the elements of lithium bromide, become competitive.



48

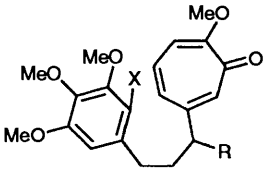


49 **53**

Scheme 7 *Reagents and conditions:* i, $PhHgCBr_3$ (1.2 mol equiv.), C_6H_6, reflux, 1.25 h; ii, BuLi (1.0 mol equiv.), THF, −100 °C, 5 h; iii, MeOH (5.0 mol equiv.), THF, −100 °C, 5 h; iv, **17** (1.0 equiv.), THF, −100 °C, 5 h

In another attempt to introduce a σ-bond between C-12a and C-12b in compound **38** the iodo derivative **54** (prepared in 91% yield by reaction of the former compound with molecular iodine in the presence of silver trifluoroacetate [39]) was treated with palladium acetate in aqueous sodium hydrogen carbonate. However, only the reductive deiodination product **38** was obtained and no evidence was gained to suggest that an intramolecular Heck reaction [40] of iodide **54** had occurred to give deacetamidocolchicine **3**. Similarly, treatment of compound **54** with tributyltin hydride, in the hope that the initially formed C-12b aryl radical would undergo conjugate addition to the pendant troponoid ring, produced only compound **38**. Varying (especially lowering) the stannane concentration failed

to alter this outcome, leading to the proposal that the initially formed aryl radical undergoes intramolecular hydrogen-atom abstraction to produce radical **55**, which reacts with another molecule of hydride in the next step of the chain-propagation sequence.



54 X = I, R = H
55 X = H, R = •

Conclusions.—The methodologies detailed above should allow for the efficient synthesis of various 12a,12b-secocolchicinoids. However, the probable lack of activity associated with such systems, as well as the inability readily to install a C12a–C12b bond within this framework (and thereby form bioactive colchicinoids), make 12a,12b-secocolchicinoids unlikely candidates for further synthetic and biological studies.

Experimental

^{1}H NMR spectra were recorded on a Varian EM 360, Varian T60, JEOL FX-90Q or JEOL JNM GX-400 spectrometer. ^{13}C NMR spectra were recorded on a JEOL JNM-FX-60, JEOL FX-90Q or JEOL JNM GX-400 instrument. Unless otherwise stated all NMR spectra were recorded in deuteriochloroform solution, and *J* values are given in Hz. FAB mass spectra were recorded on a ZAB-2HF mass spectrometer using glycerol matrices and argon as the bombarding gas. During PLC operations the bands obtained after elution were extracted with the same solvent system as used for elution. General experimental details have been reported elsewhere.[8m]

(1α,2β,3β,6α)-7,7-*Dibromobicyclo*[4.1.0]*heptane*-2,3-*diol* **14**.—Osmium tetraoxide (4 mol % of a 2.5% w/w solution in *tert*-butyl alcohol) was added to a mixture of 7,7- dibromobicyclo-[4.1.0]hept-2-ene **13**[41] (920 mg, 3.65 mmol), trimethylamine *N*-oxide dihydrate (604 mg, 5.43 mmol), pyridine (1.45 cm^3), water (11 cm^3) and *tert*-butyl alcohol (55 cm^3). The resulting mixture was heated at reflux under nitrogen for 2 h. The cooled reaction mixture was then concentrated under reduced pressure and the residue was diluted with sodium metabisulfite (20 cm^3 of a saturated aqueous solution) and extracted with dichloromethane (3 × 50 cm^3). The combined organic phases were washed with hydrochloric acid (2 × 30 cm^3 of a 2 mol dm^{-3} aqueous solution), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a dark brown oil. This material was subjected to column chromatography (silica gel; diethyl ether elution), and concentration of the appropriate fractions (R_f 0.5) afforded a solid, which was recrystallised (pentane–dichloromethane) to give the title compound **14**[42] (891 mg, 85%) as needles, m.p. 73–74.5 °C (lit.,[42] 73–74 °C) (Found: M$^+$, 283.9040; C, 29.2; H, 3.6; Br, 56.1%. Calc. for $C_7H_{10}{}^{79}Br_2O_2$: M, 283.9050; C, 29.4; H, 3.5; Br, 55.9%); ν_{max}(KBr)/cm^{-1} 3315, 2920, 1442, 1342, 1218, 1057, 1024, 839, 750 and 700; δ_H(60 MHz) 3.74 (2 H, m, 2- and 3-H), 2.80 (1 H, m, OH) and 2.50–1.30 (7 H, complex m, 1- and 6-H, 4- and 5-H and OH); δ_C(15 MHz) 68.1, 67.1, 35.4, 33.4, 28.1, 25.3 and 16.6; *m/z* (%) 214 (8), 212 (16) and 210 (8) [(M − $C_3H_6O_2$)$^+$], 207 (3) and 205 (3) [(M − Br)$^+$] and 83 (100).

(3aα,5aβ,6aβ,6bα)-6,6-*Dibromo*-2,2-*dimethylhexahydro*-3a*H*-*cyclopropa*[e][1,3]*benzodioxole* **15**.—Perchloric acid (2 drops of 60% aqueous solution) was added to a magnetically stirred solution of diol **14** (240 mg, 0.84 mmol) in dry acetone (4.5 cm^3) maintained at room temperature. The reaction mixture was stirred for 5 min before being diluted with dichloromethane (20 cm^3). The resulting solution was filtered through a pad of anhydrous potassium carbonate and the pad was washed with dichloromethane (3 × 20 cm^3). The combined filtrates were concentrated under reduced pressure to give pure acetonide **15** (260 mg, 95%) as a crystalline solid. Recrystallisation (aq. EtOH) of this material afforded the *title compound* **15** as prisms, m.p. 43–43.5 °C (Found: C, 36.6; H, 4.4; Br, 49.2; $C_{10}H_{14}Br_2O_2$ requires C, 36.8; H, 4.3; Br, 49.0%); ν_{max}(KBr)/cm^{-1} 3005, 2955, 2890, 1375, 1365, 1240, 1210, 1058, 870 and 705; δ_H(60 MHz) 4.25 (1 H, d, *J* 5.0, 6b-H), 3.97 (1 H, m, 3a-H), 2.59–1.52 (6 H, complex m), 1.48 (3 H, s, Me) and 1.40 (3 H, s, Me); δ_C(15 MHz) 107.8, 73.5, 71.0, 34.0, 31.4, 28.3, 28.0, 26.0, 24.9 and 19.5; *m/z* (57 eV) (%) 313 (10), 311 (20) and 309 (10) [(M − CH_3)$^+$] and 43 (100) [$(CH_3CO)^+$].

(E)-3-(3′,4′,5′-*Trimethoxyphenyl*)*prop*-2-*enal* **17**.—Ethereal diazomethane, prepared[43] by the action of aq. potassium hydroxide (3.40 g in 5.0 cm^3) on an ethereal (85 cm^3) solution of *N*-methyl-*N*-nitrosotoluene-*p*-sulfonamide (14.4 g, 67.2 mmol), was added portionwise to a solution of (*E*)-3-(3′,4′,5′- trimethoxyphenyl)prop-2-enoic acid (10.0 g, 42.0 mmol, *ex.* Sigma Chemical Co.) in diethyl ether (50 cm^3). When the yellow colour of diazomethane had discharged (*ca.* 30 min) the organic phase was washed with $NaHCO_3$ (1 × 100 cm^3 of a saturated aqueous solution), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give methyl (*E*)-3-(3′,4′,5′- trimethoxyphenyl)prop-2-enoate (10.23 g, 97%) as an off-white solid, m.p. 95.5–97 °C (lit.,[44] 98 °C); ν_{max}(KBr)/cm^{-1} 3025, 2960, 2855, 1700, 1633, 1585, 1505, 1468, 1425, 1335, 1283, 1245, 1125, 1000, 975, 815 and 628; δ_H(60 MHz) 7.48 (1 H, d, *J* 16.0), 6.67 (2 H, s), 6.18 (1 H, d, *J* 16.0), 3.83 (6 H, s, 2 × OMe), 3.77 (3 H, s, OMe) and 3.73 (3 H, s, OMe); *m/z* (%) 252 (100) (M$^+$), 237 (72) [(M − CH_3)$^+$], 221 (17), 209 (13) and 177 (22).

Diisobutylaluminium hydride (88.4 cm^3 of a 1 mol dm^{-3} solution in hexane, 88.44 mmol) was slowly added to a magnetically stirred solution of methyl (*E*)-3-(3′,4′,5′- trimethoxyphenyl)prop-2-enoate (10.125 g, 40.2 mmol) in dry toluene (210 cm^3) maintained at 0–5 °C under argon. The reaction mixture was stirred for 15 min before being made acidic to litmus by the addition of hydrochloric acid (5 mol dm^{-3} aqueous solution). The resulting mixture was treated with water (200 cm^3) and diethyl ether (300 cm^3). The separated aqueous phase was extracted with diethyl ether (2 × 300 cm^3) and the combined organic phases were dried (Na_2SO_4), then filtered, and concentrated under reduced pressure to give a yellow oil. Subjection of this material to column chromatography (4:1 dichloromethane–diethyl ether elution) afforded, after concentration of the appropriate fractions (R_f 0.3), (*E*)-3-(3′,4′,5′- trimethoxyphenyl)prop-2-en-1-ol[45] (7.94 g, 88%) as a pale yellow oil, ν_{max}(NaCl)/cm^{-1} 3450, 2970, 2880, 1635, 1585, 1505, 1418, 1330, 1240, 1122, 1005 and 730; δ_H(60 MHz) 6.60 (2 H, s), 6.73–6.05 (2 H, complex m), 4.32 (2 H, d, *J* 5.0), 3.90 (6 H, s, 2 × OMe), 3.83 (3 H, s, OMe) and 1.63 (1 H, br s, OH); *m/z* (%) 224 (100) (M$^+$), 209 (9) [(M − CH_3)$^+$], 195 (37), 191 (9) and 181 (62) {[$(CH_3O)_3C_7H_4$]$^+$}.

Barium manganate[46] (4.58 g, 17.9 mmol) was added in one portion to a magnetically stirred solution of (*E*)-3-(3′,4′,5′-trimethoxyphenyl)prop-2-en-1-ol (5.00 g, 2.23 mmol) in dichloromethane (40 cm^3) maintained at room temperature. The resulting dark green suspension was stirred for 4 h before being filtered, and the filtrate was concentrated under reduced pressure to give a yellow oil. Kugelrohr distillation (150–152 °C/0.8 mmHg) of this material afforded the title compound **17** (3.70 g, 75%) as a pale yellow solid, m.p. 110–111.5 °C (lit.,[16] 109–

111 °C); ν_{max}(KBr)/cm^{-1} 3010, 2960, 2860, 1685, 1625, 1585, 1505, 1470, 1335, 1130, 998, 970 and 815; δ_H(60 MHz) 9.73 (1 H, d, *J* 7.0), 7.38 (1 H, d, *J* 14.0), 6.78 (2 H, s), 6.60 (1 H, dd, *J* 14.0 and 7.0) and 3.90 (9 H, s, 3 × OMe); δ_C(15 MHz) 193.3, 153.5, 152.7, 140.9, 129.5, 127.8, 105.8, 60.8 and 56.1; *m/z* (%) 222 (100) (M^+) and 191 (53).

(2E)-1-{(3a'RS,5a'RS,6'SR,6a'SR,6b'SR)-6'-*Bromo*-2',2'-*dimethylhexahydro*-3a'H-*cyclopropa*[e][1',3']*benzodioxol*-6'-*yl*}-3-(3'',4'',5''-*trimethoxyphenyl*)*prop*-2-*en*-1-*ol* **18**.—A solution of *gem*-dibromocyclopropane **15** (870 mg, 2.66 mmol) in tetrahydrofuran (THF) (27 cm^3) contained in a three-necked flask was cooled to −100 °C while being maintained under argon. Butyllithium (1.9 cm^3 of a 1.4 mol dm^{-3} solution in hexane, 2.66 mmol) was added in a dropwise fashion over a period of *ca.* 20 min and the mixture was stirred at −100 °C for 1 h. A solution of the aldehyde **17** (648 mg, 2.92 mmol) in THF (6 cm^3) was added in one portion and the resulting mixture was stirred at −100 °C for a further 2 h, before being quenched with sulfuric acid (1.6 cm^3 of a ~2 mol dm^{-3} solution in THF). The reaction mixture was then warmed to ~0 °C, diluted with water (50 cm^3) and then with dichloromethane (50 cm^3). The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 50 cm^3). The combined organic phases were washed with brine (1 × 100 cm^3) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide a yellow oil. Subjection of this material to flash chromatography (9:1 dichloromethane–diethyl ether elution) afforded two major bands, R_f 0.35 and 0.30.

The more mobile band afforded (*E*)-1-(3',4',5'-trimethoxyphenyl)hept-1-en-3-ol[47] (72.1 mg, 10% based on butyllithium used) as an oil, ν_{max}(NaCl)/cm^{-1} 3500, 2955, 2880, 1595, 1510, 1465, 1420, 1235, 1125 and 730; δ_H(60 MHz) 6.55 (2 H, s), 6.47 (1 H, d, *J* 16.0), 6.03 (1 H, dd, *J* 16.0 and 6.0), 4.30 (1 H, m), 3.87 (6 H, s, 2 × OMe), 3.83 (3 H, s, OMe), 1.88 (1 H, br s), 1.82–1.12 (6 H, complex m) and 1.12–0.70 (3 H, complex m); *m/z* (6 eV) (%) 280 (42) (M^+), 262 (35) [$(M - H_2O)^+$], 195 (100) and 181 (55) {$[(CH_3O)_3C_7H_4]^+$}.

Further elution of the column yielded a 1:1 mixture of the *title compounds* **18** (973 mg, 77%) as a pale yellow oil (Found: M^+, 468.1130. $C_{22}H_{29}{}^{79}BrO_6$ requires M, 468.1148); ν_{max}(NaCl)/cm^{-1} 3470, 2950, 2860, 1585, 1508, 1460, 1415, 1230, 1120 and 725; δ_H(60 MHz) 6.78–5.92 (2 H, complex m), 6.60 (2 H, s), 4.58 ($\frac{1}{2}$ H, m), 4.24 ($\frac{1}{2}$ H, m), 4.08–3.28 (2 H, complex m), 3.88 (6 H, s, 2 × OMe), 3.83 (3 H, s, OMe), 2.94–0.78 (7 H, complex m), 1.48 (3 H, br s, Me) and 1.37 (3 H, br s, Me); δ_C(15 MHz) 149.7, 135.0, 129.0, 128.9, 128.7, 125.8, 125.3, 105.4, 105.3, 101.4, 72.9, 70.3, 70.2, 67.1, 67.0, 54.8, 44.4, 44.0, 28.3, 28.2, 27.5, 27.4, 25.4, 25.3, 24.9, 16.7 and 16.5 (eleven signals superimposed); *m/z* (%) 470 (5) and 468 (5) (M^+), 452 (41) and 450 (40) [$(M - H_2O)^+$], 388 (17) [$(M - HBr)^+$], 181 (77) {$[(CH_3O)_3C_7H_4]^+$} and 45 (100).

1-{(3a'RS,5a'RS,6'SR,6a'SR,6b'SR)-6'-*Bromo*-2',2'-*dimethylhexahydro*-3a'H-*cyclopropa*[e][1',3']*benzodioxol*-6'-*yl*}-3-(3'',4'',5''-*trimethoxyphenyl*)*propan*-1-*ol* **19**.—The mixture of allylic alcohols **18** (0.35 g, 0.75 mmol) obtained from the reaction described above was dissolved in methanol (33 cm^3) containing 10% palladium on charcoal (50 mg) and the resulting magnetically stirred mixture was maintained under hydrogen (1 atm) for 1.5 h. After this time the catalyst was removed by filtration through a Celite pad and the pad was washed with dichloromethane (2 × 50 cm^3). The combined filtrates were concentrated under reduced pressure to afford a 1:1 mixture of the *title alcohols* **19** (337 mg, 96%) as a foam, ν_{max}(NaCl)/cm^{-1} 3510, 2950, 2880, 2850, 1590, 1505, 1458, 1420, 1232, 1122, 870 and 725; δ_H(60 MHz) 6.42 (2 H, s), 4.47 (1 H, br d, *J* 6.0), 3.86 (6 H, s, 2 × OMe), 4.05–3.50 (2 H, complex m), 3.81 (3 H, s, OMe), 3.14–0.56 (11 H, complex m), 1.43 ($\frac{3}{2}$ H, s, Me), 1.38 ($\frac{3}{2}$ H, s, Me), 1.33 ($\frac{3}{2}$ H, s, Me) and 1.21 ($\frac{3}{2}$ H, s, Me); *m/z* (8 eV) (%) 472 (5) and 470 (5) (M^+), 390 (6) [$(M - HBr)^+$] and 181 (100) {$[(CH_3O)_3C_7H_4]^+$}.

(3aRS,5aRS,6SR,6aSR,6bSR)-6-[(1'RS)-1'-*Benzoyloxy*-3'-(3'',4'',5''-*trimethoxyphenyl*)*propyl*]-6-*bromo*-2,2-*dimethylhexahydro*-3aH-*cyclopropa*[e][1,3]*benzodioxole* **20a** *and* (3aRS,5aRS,6SR,6aSR,6bSR)-6-[(1'SR)-1'-*Benzoyloxy*-3'-(3'',4'',5''-*trimethoxyphenyl*)*propyl*]-6-*bromo*-2,2-*dimethylhexahydro*-3aH-*cyclopropa*[e][1,3]*benzodioxole* **20b**.—Freshly distilled benzoyl chloride (825 mg, 5.87 mmol) was added to a magnetically stirred solution of the 1:1 mixture of alcohols **19** (2.05 g, 4.35 mmol) in dry pyridine (43.5 cm^3) maintained at room temperature. DMAP (6.60 g, 54 mmol) was then added in one portion. The resulting mixture was stirred overnight at ambient temperature before being poured onto crushed ice and extracted with dichloromethane (3 × 220 cm^3). The combined organic phases were washed successively with cold HCl (2 × 220 cm^3 of a 2 mol dm^{-3} aqueous solution) and $NaHCO_3$ (1 × 220 cm^3 of a saturated aqueous solution), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield a yellow oil. Subjection of this material to column chromatography (9:1 dichloromethane–diethyl ether elution) provided, after concentration of the appropriate fractions (R_f 0.4) and trituration (hexane–ethanol) of the resulting oil, a 1:1 mixture of diastereoisomeric benzoates **20a** and **20b** (2.26 g, 90%) as a solid. Recrystallisation (methanol) of this material yielded epimerically pure (3aRS,5aRS,6SR,6aSR,6bSR)-6-[(1'RS)-1'-*benzoyloxy*-3'-(3'',4'',5''-*trimethoxyphenyl*)*propyl*]-6-*bromo*-2,2-*dimethylhexahydro*-3aH-*cyclopropa*[e][1,3]*benzodioxole* **20a** as needles, m.p. 156.5–158 °C (Found: C, 60.2; H, 6.4; Br, 13.6. $C_{29}H_{35}BrO_7$ requires C, 60.5; H, 6.1; Br, 13.9%); ν_{max}(KBr)/ cm^{-1} 2950, 1705, 1590, 1465, 1450, 1428, 1265, 1242, 1117, 1050, 842 and 712; δ_H(60 MHz) 8.45–8.14 (2 H, complex m), 7.80–7.43 (3 H, complex m), 6.58 (2 H, s), 6.55 (1 H, m), 4.35 (1 H, br d, *J* 5.0), 4.23–3.79 (1 H, complex m), 3.94 (6 H, s, 2 × OMe), 3.88 (3 H, s, OMe), 2.96–0.66 (10 H, complex m), 1.45 (3 H, s, Me) and 1.30 (3 H, s, Me); δ_C(15 MHz) 165.7, 153.1, 136.6, 136.4, 133.4, 129.9, 129.6, 128.5, 107.7, 105.6, 73.3, 72.3, 68.5, 60.8, 56.1, 41.8, 37.1, 31.6, 30.2, 27.9, 26.1, 25.9, 24.9 and 16.1; *m/z* (6 eV) (%) 576 (8) and 574 (7) (M^+), 495 (0.5) [$(M - Br)^+$], 181 (100) {$[(CH_3O)_3C_7H_4]^+$} and 105 (48) [$(C_6H_5CO)^+$].

Concentration of the mother liquors from above followed by recrystallisation (aq. MeOH) of the resulting solid gave (3aRS,5aRS,6SR,6aSR,6bSR)-2,2-*dimethyl*-6-[1'-*benzoyloxy*-3'-(3'',4'',5''-*trimethoxyphenyl*)*propyl*]-6-*bromo*-2,2-*dimethylhexahydro*-3aH-*cyclopropa*[e][1,3]*benzodioxole* **20b** as fine needles, m.p. 109–111 °C (Found: C, 60.5; H, 6.3; Br, 13.7%); ν_{max}($CDCl_3$)/cm^{-1} 3020, 2950, 1710, 1590, 1508, 1465, 1422, 1265, 1220, 1125, 1055, 790, 710 and 665; δ_H(60 MHz) 8.28–8.02 (2 H, complex m), 7.68–7.41 (3 H, complex m), 6.53 (2 H, s), 4.76 (1 H, m), 3.91 (6 H, s, 2 × OMe), 3.84 (3 H, s, OMe), 3.97–3.49 (2 H, m), 2.94–1.45 (10 H, complex m), 1.44 (3 H, s, Me) and 1.22 (3 H, s, Me); δ_C(15 MHz) 165.8, 153.2, 136.5, 133.4, 130.0, 129.7, 128.5, 107.9, 105.8, 74.0, 72.3, 68.5, 60.8, 56.1, 42.3, 37.8, 31.5, 29.8, 28.0, 26.7, 25.8, 24.9 and 16.0 (one peak obscured/overlapping); *m/z* (11 eV) (%) 576 (7) and 547 (7) (M^+), 454 (3) and 452 (3) [$(M - C_6H_5CO_2H)^+$], 373 (5) [$(M - C_6H_5CO_2H - Br)^+$], 181 (100) {$[(CH_3O)_3C_7H_4]^+$} and 105 (29) [$(C_6H_5CO)^+$].

(1RS,2SR,3RS,6RS,7SR)-7-[(1'SR)-1'-*Benzoyloxy*-3'-(3'',4'',5''-*trimethoxyphenyl*)*propyl*]-7-*bromobicyclo*[4.1.0]*heptane*-2,3-*diol* **21a**.—Hydrochloric acid (5.7 cm^3 of a 1 mol dm^{-3} aqueous solution) was added to a magnetically stirred solution of acetonide **20a** (114 mg, 0.20 mmol) in THF (5.7 cm^3)

maintained at room temperature. The mixture was stirred at room temperature for 25 h, when the reaction mixture was diluted with water (11 cm^3) and extracted with dichloromethane (3 × 15 cm^3). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the *title diol* **21a** (96 mg, 90%) as an oil, ν_{max}(NaCl)/cm^{-1} 3470, 2960, 1710, 1590, 1507, 1455, 1420, 1265, 1125 and 710; δ_H(60 MHz) 8.35–7.92 (2 H, m), 7.78–7.30 (3 H, m), 6.47 (2 H, s), 4.85 (1 H, m), 4.00–3.83 (2 H, m), 3.90 (6 H, s, 2 × OMe), 3.82 (3 H, s, OMe), 3.12 (2 H, br s) and 2.88–0.67 (10 H, complex m); *m/z* (%) 536 (0.6) and 534 (0.6) (M^+) and 181 (100) {$[(CH_3O)_3C_7H_4]^+$}. This material was of sufficient purity for use in the next step of the reaction sequence.

(1RS,2SR,3RS,6RS,7SR)-7-[(1'RS)-1'-*Benzoyloxy*-3'-(3'',4'',5''-*trimethoxyphenyl*)*propyl*]-7-*bromobicyclo*[4.1.0]*heptane*-2,3-*diol* **21b**.—Hydrolysis of the epimerically pure acetonide **20b** (82 mg, 0.14 mmol) using the above procedure but employing a 58 h reaction time afforded the *title diol* **21b** (68 mg, 91%) as an oil, ν_{max}(NaCl)/cm^{-1} 3450, 2950, 1708, 1590, 1505, 1450, 1420, 1265, 1240, 1123, 755 and 710; δ_H(60 MHz) 8.30–7.88 (2 H, complex m), 7.65–7.35 (3 H, complex m), 6.53 (2 H, s), 4.82 (1 H, m), 3.90 (6 H, s, 2 × OMe), 3.82 (3 H, s, OMe) and 3.73–1.03 (14 H, complex m); *m/z* (%) 536 (4) and 534 (4) (M^+) and 181 (100) {$[(CH_3O)_3C_7H_4]^+$}. This material was of sufficient purity for use in the next step of the reaction sequence.

(1RS,6RS,7SR)-7-[(1'SR)-1'-*Benzoyloxy*-3'-(3'',4'',5''-*trimethoxyphenyl*)*propyl*]-7-*bromo*-3-*hydroxybicyclo*[4.1.0]*hept*-3-*en*-2-*one* **22a**.—TFAA (30 mm^3, 0.21 mmol) was added to a stirred solution of DMSO (19 mm^3, 0.26 mmol) in dichloromethane (1.4 cm^3) maintained at −60 °C under argon. After 20 min a solution of the alcohol **21a** (54 mg, 0.10 mmol) in a minimum amount of dichloromethane–DMSO (1:1) was added in one portion to the reaction mixture. The solution thus obtained was stirred at −60 °C for 1.5 h, then triethylamine (63 mm^3, 0.45 mmol) was added to the reaction mixture and the mixture was stirred for a further 1.5 h at −60 °C. The reaction mixture was warmed to room temperature, diluted with HCl (10 cm^3 of a 2 mol dm^{-3} aqueous solution) and extracted with dichloromethane (3 × 10 cm^3). The combined organic phases were washed sequentially with HCl (1 × 5 cm^3 of a 2 mol dm^{-3} aqueous solution) and water (1 × 5 cm^3) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield a yellow oil which, upon subjection to PLC (1:19 diethyl ether–dichloromethane), afforded a single major and chromophoric band (R_f 0.4). Extraction of this band yielded the *title α-hydroxy enone* **22a** (41.5 mg, 75% overall yield based on acetonide **20a**) as a pale yellow oil, ν_{max}(NaCl)/cm^{-1} 3445, 2950, 1710, 1665, 1650, 1588, 1505, 1450, 1420, 1260 and 1120; δ_H(60 MHz) 8.32–7.90 (2 H, complex m), 7.80–7.33 (3 H, complex m), 6.47 (2 H, s), 5.60–5.23 (3 H, complex m), 3.93 (6 H, s, 2 × OMe), 3.87 (3 H, s, OMe) and 3.00–1.60 (8 H, complex envelope); δ_C(15 MHz) 186.0, 165.5, 153.3, 147.0, 136.7, 136.2, 133.2, 129.9, 129.4, 128.3, 113.6, 105.6, 69.2, 60.8, 56.1, 42.9, 38.1, 36.6, 31.6, 29.7 and 20.1; *m/z* (%) 532 (3) and 530 (3) (M^+), 329 (10) [(M − Br − $C_6H_5CO_2H$)$^+$] and 181 (100) {$[(CH_3O)_3C_7H_4]^+$}.

(1RS,6RS,7SR)-7-[(1'RS)-1'-*Benzoyloxy*-3'-(3'',4'',5''-*trimethoxyphenyl*)*propyl*]-7-*bromo*-3-*hydroxybicyclo*[4.1.0]*hept*-3-*en*-2-*one* **22b**.—Oxidation of the epimerically pure diol **21b** (76 mg, 0.14 mmol) according to the above procedure gave the *title α-hydroxy enone* **22b** (48.8 mg, 68%) as a pale yellow solid, m.p. 123–125 °C (Found: M^+, 530.0950. $C_{26}H_{27}{}^{79}BrO_7$ requires M, 530.0940); ν_{max}(KBr)/cm^{-1} 3530, 2950, 1710, 1690, 1590, 1510, 1460, 1423, 1255, 1240, 1125, 1105 and 710; δ_H(60 MHz) 8.23–7.87 (2 H, complex m), 7.70–7.27 (3 H, complex m), 6.28 (2 H, s), 5.85 (1 H, m), 5.22 (1 H, m), 4.28 (1 H, br s), 3.85 (6 H, s, 2 × OMe), 3.80 (3 H, s, OMe) and 2.97–1.67 (8 H, complex m); *m/z* (%) 532 (9) and 530 (8) (M^+), 450 (2) [(M − HBr)$^+$], 329 (11) [(M − Br − $C_6H_5CO_2H$)$^+$] and 181 (100) {$[(CH_3O)_3C_7H_4]^+$}.

(1RS,6RS,7SR)-7-[(1'SR)-1'-*Benzoyloxy*-3'-(3'',4'',5''-*trimethoxyphenyl*)*propyl*]-7-*bromo*-3-*methoxybicyclo*[4.1.0]*hept*-3-*en*-2-*one* **23a**.—Freshly distilled dimethyl sulfate (0.50 cm^3, 5.28 mmol) and anhydrous potassium carbonate (0.50 g, 3.60 mmol) were added to a magnetically stirred solution of epimerically pure α-hydroxy enone **22a** (63.5 mg, 0.12 mmol) in dry acetone (4.0 cm^3) maintained at room temperature. The reaction mixture was stirred at ambient temperatures for 5 h before being diluted with water (20 cm^3). The aqueous phase was extracted with dichloromethane (3 × 20 cm^3) and the combined organic phases were then washed with water (2 × 20 cm^3), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown liquid. Residual dimethyl sulfate was removed by warming (~50 °C) of the crude material under vacuum (3 mmHg). Subjection of the residue to PLC (7:3 dichloromethane–diethyl ether elution) afforded a single major and chromophoric band (R_f 0.4), which upon extraction gave *α-methoxy enone* **23a** (48.8 mg, 75%) as a pale yellow solid, m.p. 125–131 °C (Found: M^+, 544.1089. $C_{27}H_{29}{}^{79}BrO_7$ requires M, 544.1097); ν_{max}($CHCl_3$)/cm^{-1} 3020, 1715, 1625, 1590, 1505, 1460, 1415, 1268, 1215, 1120, 705 and 660; δ_H(60 MHz) 8.30–7.93 (2 H, complex m), 7.67–7.33 (3 H, complex m), 6.47 (2 H, s), 5.28 (1 H, m), 5.00 (1 H, br t, *J* 4.0), 3.90 (6 H, s, 2 × OMe), 3.85 (3 H, s, OMe), 3.53 (3 H, s, OMe) and 3.00–1.67 (8 H, complex m); δ_C(15 MHz) 184.6, 165.2, 153.1, 151.4, 136.5, 136.2, 133.1, 130.0, 129.5, 128.3, 111.3, 105.9, 68.9, 60.8, 56.1, 55.0, 42.7, 38.8, 37.4, 31.4, 29.1 and 20.9; *m/z* (%) 546 (2) and 544 (2) (M^+), 465 (6) [(M − Br)$^+$], 343 (7) [(M − Br − $C_6H_5CO_2H$)$^+$] and 181 (100) {$[(CH_3O)_3C_7H_4]^+$}.

(1RS,6RS,7SR)-7-[(1'RS)-1'-*Benzoyloxy*-3'-(3'',4'',5''-*trimethoxyphenyl*)*propyl*]-7-*bromo*-3-*methoxybicyclo*[4.1.0]*hept*-3-*en*-2-*one* **23b**.—Methylation of α-hydroxy enone **22b** (48 mg, 0.09 mmol) using dimethyl sulfate (0.37 cm^3, 3.95 mmol) and potassium carbonate (0.37 g, 2.71 mmol) in acetone (2.5 cm^3) was carried out as described above. Subjection of the crude reaction product to PLC (7:3 dichloromethane–diethyl ether elution) afforded a single major and chromophoric band (R_f 0.25), which upon extraction gave the *title α-methoxy enone* **23b** (35.1 mg, 71%) as a pale yellow oil (Found: M^+, 544.1083); ν_{max}(NaCl)/cm^{-1} 2955, 1715, 1672, 1630, 1590, 1502, 1450, 1415, 1260, 1230, 1120 and 705; δ_H(60 MHz) 8.27–7.92 (2 H, complex m), 7.65–7.32 (3 H, complex m), 6.22 (2 H, s), 5.52 (1 H, br t, *J* 4.0), 5.15 (1 H, m), 3.83 (6 H, s, 2 × OMe), 3.77 (3 H, s, OMe), 3.47 (3 H, s, OMe) and 2.98–1.62 (8 H, complex m); δ_C(15 MHz) 185.3, 165.5, 152.9, 149.9, 136.0, 135.8, 133.5, 129.9, 129.6, 128.6, 114.2, 105.3, 70.2, 60.7, 55.9, 55.0, 43.2, 38.6, 35.4, 31.4, 30.0 and 21.4; *m/z* (%) 546 (4) and 544 (4) (M^+), 465 (5) [(M − Br)$^+$], 343 (5) [(M − Br − $C_6H_5CO_2H$)$^+$] and 181 (100) {$[(CH_3O)_3C_7H_4]^+$}.

(RS)-6-[1'-*Benzoyloxy*-3'-(3'',4'',5''-*trimethoxyphenyl*)*propyl*]-2-*methoxycyclohepta*-2,4,6-*trienone* **24**.—DBU (1.3 cm^3, 8.71 mmol) was slowly added to a magnetically stirred solution of the α-methoxy enone **23a** (0.48 g, 0.85 mmol) in dry benzene (25 cm^3) maintained at ambient temperature. The dark brown reaction mixture was stirred for a further 1 h, then was diluted with HCl (50 cm^3 of a 2 mol dm^{-3} aqueous solution) and dichloromethane (100 cm^3). The separated aqueous phase was extracted with dichloromethane (2 × 50 cm^3) and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield a dark brown oil.

Subjection of the crude reaction product to PLC (7:3 dichloromethane–diethyl ether elution) afforded a single major and chromophoric band (R_f 0.25), which upon extraction gave the *title troponoid* **24** (0.37 g, 85%) as a pale yellow oil (Found: M^+, 464.1831. $C_{27}H_{28}O_7$ requires M, 464.1835); ν_{max}(NaCl)/cm^{-1} 2950, 2850, 1718, 1628, 1592, 1505, 1260, 1220, 1120 and 710; δ_H(60 MHz) 8.10 (2 H, m), 7.65–6.51 (7 H, complex m), 6.36 (2 H, s), 5.71 (1 H, m), 3.92 (3 H, s, OMe), 3.84 (9 H, s, 3 × OMe) and 3.01–2.00 (4 H, complex m); δ_C(15 MHz) 179.7, 165.4, 165.3, 153.2, 149.5, 136.3, 136.0, 133.9, 133.5, 132.6, 129.7, 129.5, 128.5, 126.8, 112.0, 105.2, 77.3, 60.8, 56.3, 56.0, 37.6 and 32.2; *m/z* (%) 464 (15) (M^+), 359 (7) [$(M - C_6H_5CO)^+$], 342 (28), [$(M - C_6H_5CO_2H)^+$], 314 (13) [$(M - C_6H_5CO_2H - CO)^+$], 181 (54) {$[(CH_3O)_3C_7H_4]^+$}, 105 (100) [$(C_6H_5CO)^+$] and 77 (48) [$(C_6H_5)^+$]; λ_{max}(MeOH)/nm 320 (4.1), 233 (4.9) and 208 (4.9).

An exactly analogous procedure starting with α-methoxy enone **23b** afforded troponoid **24** in 80% yield.

(RS)-6-[1′-*Hydroxy*-3′-(3″,4″,5″-*trimethoxyphenyl*)*propyl*]-2-*methoxycyclohepta*-2,4,6-*trienone* **25**.—Anhydrous potassium carbonate (0.11 g, 0.80 mmol) was added to a magnetically stirred solution of compound **24** (0.30 g, 0.65 mmol) in dry methanol (20 cm^3) maintained at room temperature. The reaction mixture was stirred for 2.5 h before being neutralised with HCl (50 cm^3 of a 1 mol dm^{-3} aqueous solution) and diluted with dichloromethane (50 cm^3). The separated aqueous phase was extracted with dichloromethane (2 × 100 cm^3) and the combined organic phases then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a yellowish oil. Subjection of the crude reaction product to PLC (7:3 dichloromethane–diethyl ether elution) afforded two major and chromophoric bands, R_f 0.35 and 0.6.

Extraction of the more mobile band afforded (RS)-6-[1′-*methoxy*-3′-(3″,4″,5″-*trimethoxyphenyl*)*propyl*]-2-*methoxycyclohepta*-2,4,6-*trienone* (28.5 mg, 12%) as a pale yellow oil (Found: M^+, 374.1721. $C_{21}H_{26}O_6$ requires M, 374.1730); ν_{max}(NaCl)/cm^{-1} 2940, 2840, 1625, 1588, 1555, 1504, 1455, 1240, 1120 and 725; δ_H(60 MHz) 7.29–6.55 (4 H, complex m), 6.36 (2 H, s), 4.12–3.58 (1 H, complex m), 3.94 (3 H, s, OMe), 3.85 (6 H, s, 2 × OMe), 3.82 (3 H, s, OMe), 3.25 (3 H, s, OMe), 2.88–2.41 (2 H, complex m) and 2.18–1.64 (2 H, complex m); δ_C(15 MHz) 180.1, 164.6, 153.1, 141.5, 137.2, 136.9, 136.1, 135.5, 130.2, 112.0, 105.2, 84.6, 60.8, 56.7, 56.2, 56.0, 39.1 and 32.2; *m/z* (%) 374 (46) (M^+), 193 (57), 182 (92) and 151 (100); λ_{max}(MeOH)/nm 320 (3.8), 228 (4.3) and 206 (4.5).

Extraction of the less mobile band afforded (RS)-6-[1′-*hydroxy*-3′-(3″,4″,5″-*trimethoxyphenyl*)*propyl*]-2-*methoxycyclohepta*-2,4,6-*trienone* **25** (183 mg, 79%) as a pale yellow oil (Found: M^+, 360.1583. $C_{20}H_{24}O_6$ requires M, 360.1573); ν_{max}(NaCl)/cm^{-1} 3400, 2955, 2850, 1625, 1590, 1560, 1505, 1445, 1240 and 1120; δ_H(60 MHz) 7.45–6.51 (4 H, complex m), 6.36 (2 H, s), 4.53 (1 H, br t, *J* 6.0), 3.86 (3 H, s, OMe), 3.82 (6 H, s, 2 × OMe), 3.79 (3 H, s, OMe), 3.42 (1 H, s), 2.86–2.42 (2 H, complex m) and 2.22–1.62 (2 H, complex m); δ_C 180.1, 164.4, 153.1, 144.6, 137.0, 136.8, 136.1, 136.0, 129.4, 112.6, 105.2, 75.1, 60.8, 56.2, 56.1, 40.0 and 32.4; *m/z* (%) 360 (37) (M^+), 332 (5) [$(M - CO)^+$] and 182 (100); λ_{max}(MeOH)/nm 320 (3.9), 226 (4.4) and 206 (4.5).

6-[1′-*Oxo*-3′-(3″,4″,5″-*trimethoxyphenyl*)*propyl*]-2-*methoxycyclohepta*-2,4,6-*trienone* **26**.—DMSO (93 mm^3, 1.30 mmol) was added to a magnetically stirred solution of oxalyl dichloride (57 mm^3, 0.65 mmol) in dichloromethane (5.0 cm^3) maintained at −60 °C under argon. After 10 min a solution of the alcohol **25** (195 mg, 0.54 mmol) in dichloromethane (3.0 cm^3) was added in one portion to the reaction mixture. The solution thus obtained was stirred at −60 °C for 20 min, then triethylamine (380 mm^3, 2.71 mmol) was added and the mixture was stirred while being allowed to warm to room temperature. The resulting solution was diluted with HCl (20 cm^3 of a 2 mol dm^{-3} aqueous solution) and extracted with dichloromethane (3 × 20 cm^3). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a bright yellow oil. Subjection of this material to PLC (1:1 dichloromethane–diethyl ether elution) afforded a single major and chromophoric band (R_f 0.3), which upon extraction yielded the *title ketone* **26** (187 mg, 96%) as a lemon-yellow oil (Found: M^+, 358.1419. $C_{20}H_{22}O_6$ requires M, 358.1416); ν_{max}(NaCl)/cm^{-1} 2950, 1690, 1620, 1590, 1500, 1465, 1275, 1218, 1120 and 1000; δ_H(60 MHz) 7.70 (1 H, br s), 7.53–6.63 (3 H, complex m), 6.45 (2 H, s), 3.98 (3 H, s, OMe), 3.88 (6 H, s, 2 × OMe), 3.85 (3 H, s, OMe) and 3.60–2.63 (4 H, complex m); δ_C(15 MHz) 201.1, 180.3, 165.7, 153.2, 143.0, 136.5, 136.3, 136.1, 132.6, 125.3, 113.2, 105.4, 60.8, 56.4, 56.1, 40.8 and 30.6; *m/z* (%) 358 (46) (M^+), 330 (22) [$(M - CO)^+$], 315 (19) [$(M - CO - CH_3)^+$], 195 (62) and 181 (100) {$[(CH_3O)_3C_7H_4]^+$}; λ_{max}(MeOH)/nm 370 (3.6), 313 (3.8), 241 (4.4) and 205 (4.6).

6-[1′-(*Methoxyimino*)-3′-(3″,4″,5″-*trimethoxyphenyl*)*propyl*]-2-*methoxycyclohepta*-2,4,6-*trienone* **27**.—Methoxylamine hydrochloride[19] (10 mg, 0.12 mmol) was added to a magnetically stirred solution of ketone **26** (38.1 mg, 0.11 mmol) in dry pyridine (0.2 cm^3) maintained at room temperature. The resulting orange reaction mixture was stirred at room temperature for 1.5 h before being neutralised with cold HCl (10 cm^3 of a 2 mol dm^{-3} aqueous solution) and extracted with dichloromethane (3 × 20 cm^3). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield an orange oil. Subjection of this material to PLC (1:1 dichloromethane–diethyl ether elution) provided two major bands, R_f 0.3 and 0.7.

Extraction of the more mobile band afforded the *bis*-N-*methoxyimine* **28** (4.1 mg, 9%) as a bright orange oil (Found: M^+, 416.1956. $C_{22}H_{28}N_2O_6$ requires M, 416.1947); ν_{max}(NaCl)/cm^{-1} 2950, 1600, 1504, 1456, 1420, 1228, 1210, 1120, 1045 and 892; δ_H(60 Mz) 7.23–5.63 (6 H, complex m), 4.02 (3 H, s, OMe), 3.95 (3 H, s, OMe), 3.88 (12 H, s, 4 × OMe) and 3.00–2.53 (4 H, complex m); *m/z* (%) 416 (19) (M^+), 385 (13) [$(M - OCH_3)^+$] and 181 (100) {$[(CH_3O)_3C_7H_4]^+$}; λ_{max}(MeOH)/nm 324 (3.5) and 294 (3.5).

Extraction of the less mobile band yielded the *title* N-*methoxyimine* **27** (34.7 mg, 85%) (a 3:2 mixture of geometric isomers as determined by ^{13}C NMR analysis) as a pale yellow oil (Found: M^+, 387.1675. $C_{21}H_{25}NO_6$ requires M, 387.1682); ν_{max}(NaCl)/cm^{-1} 2960, 1625, 1595, 1505, 1470, 1224, 1115 and 1050; δ_H(60 MHz) 7.35 (1 H, br s), 7.32–6.43 (3 H, complex m), 6.40 (2 H, s), 4.03 (3 H, s, OMe), 3.97 (3 H, s, OMe), 3.87 (6 H, s, 2 × OMe), 3.83 (3 H, s, OMe) and 3.33–2.53 (4 H, complex m); δ_C(15 MHz) 179.8, 179.7, 165.1, 164.8, 158.5, 157.6, 153.1 (two signals superimposed), 143.9, 143.6, 136.5, 136.2 (two signals superimposed), 136.0, 134.9 (two signals superimposed), 132.0, 131.2, 128.1, 127.2, 112.1 (two signals superimposed), 105.3 (two signals superimposed), 62.6, 62.0, 60.8 (two signals superimposed), 56.4, 56.3, 56.1 (two signals superimposed), 36.6, 32.9, 32.5 and 28.3; *m/z* (%) 387 (6) (M^+), 356 (15) [$(M - OCH_3)^+$] and 181 (100) {$[(CH_3O)_3C_7H_4]^+$}; λ_{max}(MeOH)/nm 352 (3.6) and 280 (3.9).

(RS)-6-[1′-*Mesyloxy*-3′-(3″,4″,5″-*trimethoxyphenyl*)*propyl*]-2-*methoxycyclohepta*-2,4,6-*trienone* **29**.—Freshly distilled methanesulfonyl chloride (85 mm^3, 1.1 mmol) was added dropwise to a magnetically stirred solution of the alcohol **25** (360 mg, 1.0 mmol) and triethylamine (210 mm^3, 1.5 mmol) in dry dichloromethane (12 cm^3) maintained at 0–5 °C under argon. The reaction mixture was stirred at this temperature for 20 min

before being diluted with ice–water (10 cm^3) and dichloromethane (10 cm^3). The separated aqueous phase was extracted with dichloromethane (2 × 10 cm^3) and the combined phases were washed sequentially with cold hydrochloric acid (1 × 20 cm^3 of a 10% aqueous solution), $NaHCO_3$ (1 × 20 cm^3 of a saturated aqueous solution) and brine (1 × 20 cm^3), then were dried (Na_2SO_4), filtered, and concentrated under reduced pressure (at 0–5 °C) to afford the crude (*RS*)-6-[1′-mesyloxy-3′-(3″,4″,5″-trimethoxyphenyl)propyl]-2-methoxycyclohepta-2,4,6-trienone **29** (~420 mg, >95%) as a pale yellow oil, δ_H(60 MHz) 7.23–6.43 (4 H, complex m), 6.33 (2 H, s), 5.25 (1 H, br t, *J* 6.0), 3.92 (3 H, s, OMe), 3.83 (6 H, s, 2 × OMe), 3.80 (3 H, s, OMe), 2.90 (3 H, s, OSO_2Me) and 2.87–1.67 (4 H, complex m) (R_f 0.1, 7:3 dichloromethane–diethyl ether elution). This material was employed without further purification in the next step.

(RS)-6-[1′-*Azido*-3′-(3″,4″,5″-*trimethoxyphenyl*)*propyl*]-2-*methoxycyclohepta*-2,4,6-*trienone* **30**.—Sodium azide (0.072 g, 1.11 mmol) and 18-crown-6 (0.030 g, 0.11 mmol) were added in rapid succession to a magnetically stirred solution of crude mesyl ester **29** (420 mg, 0.96 mmol) in dry THF (4.0 cm^3). The resulting mixture was stirred at ambient temperature for 16 h before being diluted with water (20 cm^3) and dichloromethane (50 cm^3). The separated aqueous phase was extracted with dichloromethane (2 × 50 cm^3) and the combined organic phases were washed with $NaHCO_3$ (1 × 20 cm^3 of a saturated aqueous solution), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield a yellow oil. Subjection of this material to PLC (3:2 dichloromethane–diethyl ether elution) afforded a single major and chromophoric band (R_f 0.35), which upon extraction gave the *title azide* **30** (0.185 g, 86%) as a pale yellow oil (Found: M^+, 385.1630. $C_{20}H_{23}N_3O_5$ requires M, 385.1638); ν_{max}(NaCl)/cm^{-1} 2950, 2850, 2110, 1625, 1590, 1560, 1505, 1460, 1220, 1120 and 1005; δ_H(60 MHz) 7.33–6.48 (4 H, complex m), 6.36 (2 H, s), 4.26 (1 H, br t, *J* 7.0), 3.97 (3 H, s, OMe), 3.87 (6 H, s, 2 × OMe), 3.84 (3 H, s, OMe), 2.87–2.43 (2 H, complex m) and 2.27–1.74 (2 H, complex m); δ_C(15 MHz) 179.6, 165.2, 153.3, 148.2, 136.4, 135.7, 132.9, 126.5, 111.9, 105.2, 68.3, 60.8, 56.3, 56.1, 37.5 and 32.5 (one signal obscured/overlapping); *m/z* (%) 385 (15) (M^+), 357 (31) [(M − CO)$^+$], 342 (45) [(M − HN_3)$^+$], 314 (21) [(M − CO − HN_3)$^+$] and 181 (100) {[$(CH_3O)_3C_7H_4$]$^+$}; λ_{max}(MeOH)/nm 321 (3.8), 231 (4.3) and 206 (4.6).

(RS)-N-[1-(4′-*Methoxy*-3′-*oxocyclohepta*-1′,4′,6′-*trienyl*)-3-(3″,4″,5″-*trimethoxyphenyl*)*propyl*]*acetamide* **6**.—Azide **30** (0.84 g, 2.18 mmol) was dissolved in methanol (32 cm^3) containing 10% palladium on charcoal (0.28 g). The magnetically stirred reaction mixture was maintained under hydrogen (1 atm) for 2.5 h, after which time the catalyst was removed by filtration through a Celite pad. The pad was washed with dichloromethane (200 cm^3) and the combined filtrates were concentrated under reduced pressure to yield a brownish oil. The crude aminotropolone **31** was dissolved in dry pyridine (12 cm^3) then was treated, at room temperature, with freshly distilled acetic anhydride (7.6 cm^3). The reaction mixture was immediately concentrated under reduced pressure to give a dark brown oil. Subjection of the residue to PLC (acetone elution) afforded a single major and chromophoric band (R_f 0.3) which, upon extraction, gave the title compound **6**[11] (672 mg, 77%) as a nearly colourless oil (Found: M^+, 401.1833. $C_{22}H_{27}NO_6$ requires M, 401.1838); ν_{max}(NaCl)/cm^{-1} 3300, 2950, 2855, 1650, 1625, 1595, 1560, 1505, 1465, 1225, 1125, 1005 and 730; δ_H(400 MHz) 7.27 (1 H, br s, 2′-H), 7.07 (1 H, t, $J_{6',7'} = J_{6',5'} = 10.0$, 6′-H), 6.83 (1 H, dd, $J_{7',6'}$ 10.4, $J_{7',2'}$ 1.4, 7′-H), 6.75 (1 H, br d, $J_{NH,1}$ 8.0, NHCO), 6.70 (1 H, d, $J_{5',6'}$ 10.0, 5′-H), 6.37 (2 H, s), 4.80 (1 H, m), 3.93 (3 H, s, OMe), 3.83 (6 H, s, 2 × OMe), 3.82 (3 H, s, OMe), 2.64 (2 H, m), 2.02 (2 H, m) and 1.99 (3 H, s, Ac); δ_C(15 MHz; CD_3OD) 181.3, 172.7, 166.2, 155.4, 154.3, 138.1, 137.3, 134.8, 134.4, 129.9, 114.9, 106.7, 61.0, 57.5, 56.8, 56.5, 38.3, 33.9 and 22.6; *m/z* (%) 401 (21) (M^+), 358 (5) [(M − $COCH_3$)$^+$], 342 (38) [(M − CH_3CONH_2)$^+$], 220 (25), 207 (91), 181 (77) {[$(CH_3O)_3C_7H_4$]$^+$} and 43 (100) [$(CH_3CO)^+$]; λ_{max}(MeOH)/nm 321 (4.2), 234 (4.8) and 208 (4.9).

1-[(3a′RS,5a′RS,6′SR,6a′SR,6b′SR)-6′-*Bromo*-2′,2′-*dimethyl*-3a′H-*hexahydrocyclopropa*[e][1,3]*benzodioxol*-6′-*yl*]-3-(3″,4″,5″-*trimethoxyphenyl*)*propan*-1-*one* **32**.—Oxidation of the alcohol **19** (2.0 g, 4.25 mmol) using the same conditions as employed for the conversion of alcohol **21** into ketone **22** (but using 1.8 mol equiv. of TFAA, 2.3 mol equiv. of DMSO, and 4.0 mol equiv. of triethylamine) afforded a yellow oil on work-up. Subjection of this material to PLC (9:1 dichloromethane–diethyl ether elution) afforded a single major band (R_f 0.5), which upon extraction gave the *title ketone* **32** (1.70 g, 82%) as a clear oil (Found: M^+, 468.1152. $C_{22}H_{29}{}^{79}BrO_6$ requires M, 468.1148); ν_{max}(NaCl)/cm^{-1} 3000, 2952, 2850, 1700, 1590, 1508, 1460, 1420, 1235, 1125, 1050 and 870; δ_H(60 MHz) 6.40 (2 H, s), 4.68 (1 H, d, *J* 6.0), 4.28–3.91 (1 H, complex m), 3.86 (6 H, s, 2 × OMe), 3.81 (3 H, s, OMe), 3.57–2.54 (4 H, complex m), 2.09 (3 H, m), 1.64–0.77 (3 H, complex m), 1.45 (3 H, s, Me) and 1.35 (3 H, s, Me); δ_C(15 MHz) 204.0, 153.1, 136.3 (two peaks superimposed), 107.6, 105.4, 73.2, 68.9, 60.8, 56.1, 44.2, 38.6, 33.0, 30.9, 30.3, 28.0, 25.7, 25.0 and 16.0; *m/z* (%) 470 (11) and 468 (11) (M^+), 331 (7) {[M − Br − $(CH_3)_2CO$]$^+$}, 181 (100) {[$(CH_3O)_3C_7H_4$]$^+$} and 43 (28) [$(CH_3CO)^+$].

1-{(1′RS,2′SR,3′RS,6′RS,7′SR)-7′-*Bromo*-2′,3′-*dihydroxybicyclo*[4.1.0]*heptan*-7′-*yl*}-3-(3″,4″,5″-*trimethoxyphenyl*)*propan*-1-*one* **33**.—Hydrolysis of acetonide **32** (0.22 g, 0.47 mmol), using the same conditions as employed for the conversion of compound **20** into diol **21** but with a reaction time of 7 h, gave the *keto diol* **33** (0.19 g, 95%) as a nearly colourless oil, ν_{max}(NaCl)/cm^{-1} 3450, 2950, 2850, 1700, 1590, 1505, 1455, 1420, 1230, 1123 and 725; δ_H 6.41 (2 H, s), 4.24–2.47 (7 H, complex m), 3.86 (6 H, s, 2 × OMe), 3.81 (3 H, s, OMe) and 2.30–0.84 (7 H, complex m); *m/z* (%) 430 (4) and 428 (4) (M^+), 348 (1) [(M − HBr)$^+$] and 181 (100) {[$(CH_3O)_3C_7H_4$]$^+$}. This material was of sufficient purity for use in the next step.

(1RS,2RS,5SR,7SR,8SR)-1-*Bromo*-8-*hydroxy*-8-[2′-(3″,4″,5″-*trimethoxyphenyl*)*ethyl*]*tricyclo*[3.2.1.0^{2,7}]*octane*-3,4-*dione* **35a** *and* (1RS,2RS,5SR,7SR,8RS)-1-*Bromo*-8-*hydroxy*-8-[1′-(3″,4″,5″-*trimethoxyphenyl*)*ethyl*]*tricyclo*[3.2.1.0^{2,7}]*octane*-3,4-*dione* **35b**.—Oxidation of the diol **33** (0.19 g, 0.43 mmol), using the same procedure as employed for the conversion of diols **21** into α-hydroxy enones **22**, provided a yellow oil on work-up. Subjection of this material to PLC (9:1 dichloromethane–diethyl ether elution) yielded a single major and chromophoric band (R_f 0.4), which upon extraction afforded a 5:3 mixture* of epimeric γ-hydroxy diketones **35** (165 mg, 90%) as a yellow solid. Subjection of this material to flash chromatography (9:1 dichloromethane–diethyl ether elution) provided two fractions, A and B (R_f 0.6 and 0.4 respectively).

Concentration of fraction A afforded a yellow solid, which was recrystallised (hexane–chloroform) to give stereochemically pure γ-*hydroxy diketone* **35** (38 mg, 21%) as fine, pale yellow needles, double m.p. 90–95 and 113.5–115 °C (Found: M^+, 424.0510; C, 53.4; H, 4.9%. $C_{19}H_{21}{}^{79}BrO_6$ requires M, 424.0522; C, 53.7; H, 5.0%); ν_{max}(KBr)/cm^{-1} 3460, 2930, 2830, 1710, 1590, 1505, 1455, 1415, 1230, 1120 and 995; δ_H(60 MHz)

* This ratio, which was determined by ^1H NMR analysis, varied considerably between runs.

6.60 (2 H, s), 3.88 (6 H, s, 2 × OMe), 3.85 (3 H, s, OMe) and 3.18–1.69 (10 H, complex m); δ_C(15 MHz) 203.2, 198.2, 153.0, 136.5, 136.1, 106.3, 75.0, 60.8, 59.1, 56.1, 44.4, 40.3, 38.8, 35.0, 31.6 and 17.2; *m/z* (%) 426 (24) and 424 (24) (M^+) and 181 (100) $\{[(CH_3O)_3C_7H_4]^+\}$; λ_{max}(MeOH)/nm 264 (2.8), 227infl (3.8) and 210 (4.2).

Concentration of fraction B afforded a ~5:1 mixture of the epimeric γ-hydroxy diketones **35** (103 mg, 56%) as a yellow solid. Recrystallisation (from aq. MeOH) gave a second stereochemically pure *γ-hydroxy diketone* **35** as fine, pale yellow needles, m.p. ≥190 °C (decomp.) (Found: C, 53.4; H, 4.8; Br, 18.5. $C_{19}H_{21}BrO_6$ requires C, 53.7; H, 5.0; Br, 18.8%); ν_{max}(KBr)/cm^{-1} 3500, 2960, 1745, 1705, 1590, 1505, 1455, 1420, 1235, 1120 and 1002; δ_H(60 MHz; C_5D_5N) 6.60 (2 H, s), 3.92 (3 H, s, OMe), 3.72 (6 H, s, 2 × OMe), 3.44 (1 H, m) and 3.27–1.81 (9 H, complex m); δ_C(15 MHz; C_5D_5N) 193.2, 187.8, 154.0, 137.9, 106.2, 84.6, 60.5, 56.0, 53.0, 52.1, 40.6, 36.4, 30.7 and 27.9 (two peaks obscured/overlapping); *m/z* (%) 426 (44) and 424 (44) (M^+) and 181 (100) $\{[(CH_3O)_3C_7H_4]^+\}$; λ_{max}(MeOH)/nm 266infl (3.3), 222infl (4.1) and 209 (4.5).

2-Methoxy-6-[3′-(3″,4″,5″-trimethoxyphenyl)propyl]cyclohepta-2,4,5-trienone **38**.—Sodium borohydride was added in portions to a magnetically stirred solution of diphenyl diselenide (243 mg, 0.78 mmol) in absolute methanol (4.0 cm^3) maintained under argon at room temperature. The addition of sodium borohydride was continued until the yellow colour due to the diphenyl diselenide had been discharged. The resulting solution of sodium phenylselenide was cooled to 0 °C and a solution of mesyl ester **29** (214 mg, 0.49 mmol) in absolute methanol (4.0 cm^3) was added dropwise over a period of *ca.* 10 min. The resulting yellow solution was warmed to room temperature before being diluted with $NaHCO_3$ (20 cm^3 of a saturated aqueous solution). The aqueous phase was extracted with dichloromethane (3 × 20 cm^3) and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a yellow oil. Subjection of this material to PLC (development with dichloromethane–diethyl ether–methanol, 50 cm^3 : 50 cm^3 : 8 drops, two sweeps) afforded four major bands.

Extraction of the most mobile band (R_f 1.0) afforded diphenyl diselenide (0.153 g, 63% recovery) as a yellow solid and identical in all respects with an authentic sample.

Extraction of the second band (R_f 0.5) yielded (RS)-*2-methoxy-6-[1′-phenylseleno-3′-(3″,4″,5″-trimethoxyphenyl)propyl]cyclohepta-2,4,6-trienone* **37** (11 mg, 5%) as a pale yellow oil (Found: M^+, 500.1090. $C_{26}H_{28}O_5{}^{80}Se$ requires M, 500.1101). δ_H(60 MHz) 7.25 (5 H, br s), 6.33 (4 H, m), 6.28 (2 H, s), 3.90 (3 H, s, OMe), 3.83 (10 H, s) and 3.02–1.93 (4 H, complex m); δ_C(15 MHz) 179.2, 164.7, 153.2, 150.9, 136.4, 136.0, 135.6, 135.5, 131.6, 129.1, 128.9, 128.6, 127.8, 111.5, 105.3, 60.8, 56.1 (two signals superimposed), 51.5, 36.2 and 34.5; *m/z* (%) 500 (2) and 498 (1) (M^+), 343 (30) $[(M - PhSe)^+]$ and 181 (100) $\{[(CH_3O)_3C_7H_4]^+\}$.

Extraction of the third band (R_f 0.4) afforded the *title compound* **38** (142 mg, 85%) as a nearly colourless oil (Found: M^+, 344.1620. $C_{20}H_{24}O_5$ requires M, 344.1624); ν_{max}(NaCl)/cm^{-1} 2960, 1628, 1595, 1505, 1464, 1420, 1220, 1122 and 1005; δ_H(60 MHz) 7.12 (1 H, br s), 7.03–6.38 (3 H, m), 6.35 (2 H, s), 3.92 (3 H, s, OMe), 3.87 (6 H, s, 2 × OMe), 3.83 (3 H, s, OMe), 2.92–2.35 (4 H, complex m) and 2.32–1.45 (2 H, complex m); δ_C(15 MHz) 179.6, 164.9, 153.1, 151.7, 137.2, 136.4, 136.2, 131.5, 130.6, 111.5, 105.2, 60.8, 56.2, 56.1, 40.1, 35.5 and 32.3; *m/z* (%) 344 (24) (M^+), 329 (7) $[(M - CH_3)^+]$, 313 (8) $[(M - CH_3O)^+]$, 301 (5) $[(M - CH_3 - CO)^+]$ and 194 (100); λ_{max}(MeOH)/nm 322 (3.4), 236 (4.0) and 207 (4.1).

Extraction of the least mobile band (R_f 0.12) provided the alcohol **25** (3 mg, 2%) as a nearly colourless oil and which was identical in all respects with that obtained earlier.

Attempted Oxidative Coupling of Secocolchicinoid **38**.—(i) *Using thallium tristrifluoroacetate.* Thallium(III) oxide (11 mg, 2.41 × 10^{-5} mol) was added to a magnetically stirred solution of compound **38** (15 mg, 4.36 × 10^{-5} mol) in TFA (0.34 cm^3) maintained at 0 °C. The reaction mixture was brought to room temperature and was stirred at this temperature for 15 min. The resulting orange-brown solution was then diluted with ethyl acetate (20 cm^3) and washed with $NaHCO_3$ (2 × 10 cm^3 of a saturated aqueous solution). The organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield a yellow oil (~15 mg) which would not redissolve in any organic solvent. No further attempt was made to characterise this material.

(ii) *Using vanadium trifluoride oxide.* A solution of compound **38** (0.135 g, 0.39 mmol) in dichloromethane (17 cm^3) was added dropwise to a magnetically stirred solution of vanadium trifluoride oxide (0.151 g, 1.22 mmol) in a mixture of dichloromethane (4.9 cm^3) and TFA (2.6 cm^3) maintained at −46 °C under argon. The resulting rust-red mixture was stirred at −46 °C for a further 2.5 h before being warmed to room temperature and was then quenched with aq. citric acid (0.6 g in 4.0 cm^3). The reaction mixture was then basified with 5% aq. ammonium hydroxide and extracted with dichloromethane (3 × 100 cm^3). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield an orange foam (0.130 g). Subjection of this material to PLC (4:1 benzene–diethylamine elution, two sweeps) gave a single major chromophoric band (R_f 0.5), which upon extraction afforded a yellow oil (0.104 g). This material, which was a mixture of compounds as determined by ^{1}H NMR analysis, was subjected to semi-preparative HPLC [C_{18} μ-Bondapak column (Waters P/N 84176); 40:7:3 water–methanol–acetonitrile elution; flow rate 2.5 cm^3 min^{-1}; sample concentration 100 mg/0.5 cm^3; sample volume 20 mm^3; detector wavelength 350 nm].

The first band eluted (t_R 9.69 min) afforded 6-[3-{2-hydroxy-3,4-dimethoxy-6-[3-(4-methoxy-3-oxocyclohepta-1,4,6-trienyl)propyl]phenyl}-3-(3,4,5-trimethoxyphenyl)propyl]-2-methoxycyclohepta-2,4,6-trienone **42** (36.8 mg, 27%) as a pale yellow oil, ν_{max}(NaCl)/cm^{-1} 3440, 2980, 1628, 1595, 1570, 1475, 1398, 1220, 1120 and 730; δ_H(400 MHz) 7.24 (1 H, s), 7.02–6.84 (3 H, complex m), 6.71–6.63 (4 H, complex m), 6.58 (2 H, s), 6.40 (1 H, s), 4.69 (1 H, dd, *J* 9.0 and 4.0), 3.93 (6 H, s, 2 × OMe), 3.88 (3 H, s, OMe), 3.87 (3 H, s, OMe), 3.65 (3 H, s, OMe), 3.62(4) (3 H, s, OMe), 3.62(0) (3 H, s, OMe), 2.85–2.79 (1 H, complex m), 2.74–2.70 (1 H, complex m), 2.35 (2 H, br t, *J* 7.0), 2.25 (2 H, m), 2.17–2.11 (1 H, complex m), 2.09–2.01 (1 H, complex m) and 1.65–1.60 (2 H, complex m) (OH not observed); δ_C(100 MHz) 179.2, 179.0, 164.4, 157.6, 157.0, 152.3, 151.9, 151.8, 151.6, 146.3, 139.8, 136.1, 135.8, 131.4, 131.2, 131.1, 130.8, 120.3, 112.7, 111.6, 111.4, 107.6, 101.6, 100.5, 73.4, 60.7, 60.6, 56.3, 56.2, 55.8, 55.7, 40.7, 40.1, 37.5, 33.4 and 31.6; *m/z* (FAB) 673 $[(MH)^+]$; λ_{max}(MeOH)/nm 317 (3.9), 222 (4.5) and 208 (4.5).

The second band eluted (t_R 13.8 min) yielded 6-(3-{3,4-dimethoxy-6-[3-(4-methoxy-3-oxocyclohepta-1,4,6-trienyl)-1-(3,4,5-trimethoxyphenyl)propylidene]-5-oxocyclohexa-1,3-dienyl}propyl)-2-methoxycyclohepta-2,4,6-trienone **43** (17.5 mg, 14%) as a yellow oil, ν_{max}(NaCl)/cm^{-1} 2995, 1673, 1622, 1590, 1570, 1470, 1395, 1215, 1115 and 705; δ_H(400 MHz) 7.15 (2 H, s), 7.23–6.82 (5 H, complex m), 6.69–6.51 (3 H, m), 6.59 (1 H, s), 3.94 (3 H, s, OMe), 3.91 (3 H, s, OMe), 3.89 (3 H, s, OMe), 3.87 (3 H, s, OMe), 3.75 (6 H, s, 2 × OMe), 3.62 (3 H, s, OMe), 3.41 (2 H, br t, *J* 8.0), 3.05 (2 H, br t, *J* 7.0), 2.35 (2 H, br t, *J* 7.0), 2.26 (2 H, br t, *J* 8.0) and 1.64 (2 H, br p, *J* 7.0); δ_C(100 MHz) 196.9, 179.2, 179.0, 164.6, 164.4, 157.7, 152.5, 151.5, 151.1, 150.9, 139.9, 136.7, 136.0 (two signals superimposed), 135.6, 131.6, 131.0, 130.7, 130.4, 120.0, 119.3, 111.5, 111.3, 107.7, 103.4, 60.8, 60.7, 56.3, 56.2, 56.0, 55.9, 40.5, 39.5, 34.7, 33.1 and 31.9; *m/z* (FAB)

671 [(MH)$^+$]; λ_{max}(MeOH)/nm 317 (3.9), 243 (4.4) and 207 (4.4).

The third band eluted (t_R 16.7 min) provided 2-methoxy-6-(3-{3,4,5-trimethoxy-2-[3-(4-methoxy-3-oxocyclohepta-1,4,6-trienyl)-1-(3,4,5-trimethoxyphenyl)propyl]phenyl}propyl)cyclohepta-2,4,6-trienone **41** (13 mg, 11%) as a pale yellow oil, ν_{max}(NaCl)/cm^{-1} 2900, 1625, 1595, 1575, 1472, 1219, 1115, 1090 and 728; δ_H(400 MHz) 7.21 (1 H, s), 7.02 (1 H, s), 7.00–6.78 (3 H, complex m), 6.66–6.55 (7 H, complex m), 4.12 (1 H, m), 3.93 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.89 (6 H, s, 2 × OMe), 3.72 (6 H, s, 2 × OMe), 3.64 (3 H, s, OMe), 3.29 (3 H, s, OMe), 2.77–2.70 (1 H, complex m), 2.68–2.64 (1 H, complex m), 2.32 (3 H, br t, *J* 9.0), 2.17–2.13 (1 H, complex m), 2.02–1.98 (1 H, complex m) and 1.66 (2 H, m); δ_C(100 MHz) 179.2, 179.1, 164.5, 164.4, 157.8, 157.7, 152.1, 151.9, 151.5, 151.4, 142.6, 139.9, 136.2, 135.9, 131.3, 131.0, 130.6, 130.4, 120.4, 113.4, 111.4, 111.2, 107.5, 101.8, 101.6, 83.1, 60.8, 60.7, 57.0, 56.3, 56.2, 55.9, 55.8, 40.8, 39.4, 37.3, 33.6 and 31.7 (two signals obscured/overlapping); *m/z* (FAB) 687 [(MH)$^+$]; λ_{max}(MeOH)/nm 322 (3.8), 238 (4.5) and 206 (4.7).

Oxidation of Dimeric Phenol **42**.—Reaction of compound **42** under the Swern conditions employed earlier for the conversion of the alcohol **25** into ketone **26** (but with a ten-fold excess of oxidant) gave an orange oil on work-up. Subjection of this material to semi-preparative HPLC [C_{18} μ-Bondapak column (Waters P/N 84176); 40:7:3 water–methanol–acetonitrile elution; flow rate 2.5 cm^3 min^{-1}; sample concentration 100 mg/0.5 cm^3; sample volume 20 mm^3; detector wavelength 350 nm] afforded dimeric quinone methide **43** (7 mg, 47%) as a yellow oil. This material was identical, in all respects, with that obtained earlier.

(3aα,5aβ,6aβ,6bα)-5a,6,6-*Tribromo*-2,2-*dimethyl*-3aH-*hexahydrocyclopropa*[e][1,3]*benzodioxole* **50**.—A solution of bromoalkene **49** (3.00 g, 13.0 mmol) in benzene (10 cm^3) was treated with phenyl(tribromomethyl)mercury (14.0 g, 26.0 mmol) and the resulting suspension was stirred vigorously under nitrogen at reflux for 75 min. The reaction mixture was then cooled to 0 °C, treated with hexane (60 cm^3), and kept at −20 °C for 24 h. The resulting thick precipitate was filtered off through a glass frit and the filtrate was concentrated under reduced pressure. The retained solids were suspended in hexane (50 cm^3) and the suspension was stirred vigorously at room temperature for 16 h, then was filtered, combined with the original filtrate, and concentrated to give a yellow oil. Subjection of this material to MPLC (1:1 hexane–dichloromethane elution) gave two major fractions, A and B (R_f 0.45 and 0.2 respectively).

Concentration of fraction A gave a light yellow solid which, upon recrystallisation (methanol), afforded the *title cyclopropane* **50** (2.26 g, 47% at 91% conversion) as needles, m.p. 59–60 °C (Found: C, 29.9; H, 3.3; Br, 59.1. $C_{10}H_{13}Br_3O_2$ requires C, 29.7; H, 3.2; Br, 59.2%); ν_{max}(KBr)/cm^{-1} 2980, 2935, 1449, 1437, 1379, 1369, 1248, 1215, 1060 and 879; δ_H(400 MHz) 4.19 (1 H, d, *J* 5.6, 6b-H), 4.05 (1 H, m, 3a-H), 2.80 (1 H, ddd, *J* 15.6, 6.6 and 5.6, 5-H), 2.29 (1 H, ddd, *J* 15.6, 8.6 and 3.9, 5-H), 2.24 (1 H, s, 6a-H), 1.88 (1 H, m, 4-H), 1.75 (1 H, m, 4-H), 1.49 (3 H, s, Me) and 1.37 (3 H, s, Me); δ_C(100 MHz) 108.7, 72.2, 71.6, 41.6, 40.7, 37.0, 31.3, 27.6, 26.0 and 25.3; *m/z* (%) 393 (1), 391 (3), 389 (3) and 387 (1) [(M − CH_3)$^+$], 327 (2), 325 (4) and 323 (2) [(M − Br)$^+$], 269 (20), 267 (41) and 265 (22) {[M − Br − $(CH_3)_2CO$]$^+$} and 43 (100) [$(CH_3CO)^+$].

Concentration of fraction B gave the starting alkene **49** (260 mg, 9% recovery), identical in all respects with an authentic sample.

6-[3′-(2″-*Iodo*-3″,4″,5″-*trimethoxyphenyl*)*propyl*]-2-*methoxycyclohepta*-2,4,6-*trienone* **54**.—Molecular iodine (25 mg, 9.88 × 10^{-5} mol), then silver trifluoroacetate (50 mg, 0.23 mmol), were added to a magnetically stirred solution of compound **38** (34 mg, 9.88 × 10^{-5} mol) in dry chloroform (3.0 cm^3) at room temperature. The reaction mixture was stirred at room temperature for *ca.* 10 min until the iodine colour had been completely discharged. After this time the silver salts were removed by filtration through a pad of anhydrous sodium hydrogen carbonate and anhydrous sodium sulfate. The residual solids were washed with dichloromethane (2 × 20 cm^3) and the combined filtrates were concentrated under reduced pressure to give a yellow oil. Subjection of this material to PLC (45:45:10 dichloromethane–diethyl ether–methanol elution) afforded a single major and chromophoric band (R_f 0.4), which on extraction gave the *title compound* **54** (42 mg, 91%) as a nearly colourless oil (Found: M$^+$, 470.0595. $C_{20}H_{23}IO_5$ requires M, 470.0592); ν_{max}(NaCl)/cm^{-1} 2950, 1627, 1590, 1570, 1472, 1220, 1100, 1000 and 728; δ_H(60 MHz; C_6D_6) 7.40–6.30 (5 H, complex m), 3.95 (3 H, s, OMe), 3.80 (9 H, s, 3 × OMe), 3.00–2.40 (4 H, complex m) and 2.20–1.60 (2 H, complex m); δ_C(15 MHz) 179.6, 164.9, 153.6, 153.1, 151.5, 140.4, 139.9, 136.4, 131.5, 130.7, 111.5, 108.7, 87.9, 60.9, 60.7, 56.2, 40.5, 40.4 and 31.3 (one signal obscured/overlapping); *m/z* (%) 470 (7) (M$^+$), 343 (93) [(M − I)$^+$], 194 (80) and 181 {[$(CH_3O)_3C_7H_4$]$^+$}; λ_{max}(MeOH)/nm 321 (4.1), 234 (4.8) and 210 (4.9).

Attempts to Effect Intramolecular Heck Reaction of 6-[3′-(2″-*Iodo*-3″,4″,5″-*trimethoxyphenyl*)*propyl*]-2-*methoxycyclohepta*-2,4,6-*trienone* **54**.—(i) *Using* Pd^0 *with sodium hydrogen carbonate as base and methanol as solvent.* Palladium(II) acetate (0.5 mg, 2.2 × 10^{-6} mol) followed by sodium hydrogen carbonate (20 mg, 0.24 mmol) were added to a solution of the iodoarene **54** (47 mg, 0.10 mmol) and triphenylphosphine (67 mg, 0.25 mmol) in methanol (2.0 cm^3). The reaction mixture was heated under reflux for 16 h, then was cooled to room temperature and diluted with water (10 cm^3) and dichloromethane (20 cm^3). The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 20 cm^3). The combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield a brown oil. Subjection of this material to PLC (45:45:10 dichloromethane–diethyl ether–methanol elution) afforded a single major and chromophoric band (R_f 0.4), which upon extraction afforded 2-methoxy-6-[3′-(3″,4″,5″-trimethoxyphenyl)propyl]cyclohepta-2,4,6-trienone **38** (34.7 mg, 100%) as a pale yellow oil. This material was identical in all respects with that obtained earlier.

(ii) *Using* Pd^0 *with triethylamine as base and acetonitrile as solvent.* Palladium(II) acetate (0.4 mg, 1.8 × 10^{-6} mol) was added to a solution of the iodoarene **54** (40 mg, 8.5 × 10^{-5} mol) and triethylamine (15 mm^3, 0.11 mmol) in dry acetonitrile (1.0 cm^3). The reaction mixture was refluxed under argon for 24 h. The resulting dark brown solution was subjected to PLC (45:45:10 dichloromethane–diethyl ether–methanol elution) to afford a single major and chromophoric band (R_f 0.4), which upon extraction afforded the starting iodoarene **54** (18 mg, 45% recovery).

Attempted Radical Cyclisation of 6-[3′-(2″-*Iodo*-3″,4″,5″-*trimethoxyphenyl*)*propyl*]-2-*methoxycyclohepta*-2,4,6-*trienone* **54** *using* Bu_3SnH.—Tributyltin hydride (6 mm^3, 2.34 × 10^{-5} mol) was added to a solution of iodoarene **54** (10 mg, 2.13 × 10^{-5} mol) and α,α′-azoisobutyronitrile (AIBN) (0.2 mg) in C_6D_6 (0.4 cm^3) contained in a 5 mm NMR tube. The solution was then thoroughly degassed and placed in an oil-bath (~64 °C) under argon. The resulting yellow solution was maintained at ~64 °C with the periodic addition of further AIBN (0.2 mg/3 h) until the consumption of the starting material was complete (as determined by ^{1}H NMR analysis). The reaction mixture was

then subjected to PLC (45:45:10 dichloromethane–diethyl ether–methanol elution) and, after extraction of the major chromophoric band (R_f 0.4), 2-methoxy-6-[3′-(3″,4″,5″-trimethoxyphenyl)propyl]cyclohepta-2,4,6-trienone **38** (5 mg, 68%) was obtained. This material was identical in all respects with that obtained earlier.

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