Synthesis of piperazine-2,5-diones related to bicyclomycin: 3-acetoxy-1,4-dibenzyl-3-[1-(2-methoxyethyl)- and 1-(2-hydroxyethyl)ethenyl]piperazine-2,5-dione. 1. Route via acyclic intermediates[1]

PETER YATES AND JOHN HAROLD HOARE

Lash Miller Chemical Laboratories, University of Toronto, Toronto, Ont., Canada M5S 1A1

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3-Acetoxy-1,4-dibenzyl-3-[1-(2-methoxyethyl)ethenyl]piperazine-2,5-dione (**32**) and its 2-hydroxyethyl analogue (**46**), which possess several of the structural features of the antibiotic bicyclomycin, have been synthesized by a route involving construction of the piperazine-2,5-dione ring at a late stage in the reaction sequence. Treatment of ethyl 3-(2-methoxyethyl)-3-methylglycidate with acetic anhydride and sulfuric acid gives ethyl 2-acetoxy-3-(2-methoxyethyl)-3-butenoate (**10**), which is converted to the corresponding carboxylic acid by ethanolysis, hydrolysis, and reacetylation. This, on conversion to its acid chloride and reaction with *N,N'*-dibenzylglycinamide, gives 2-acetoxy-*N*-benzyl-*N*-(2-benzylamino-2-oxoethyl)-3-(2methoxyethyl)-3-butenamide (**21**). Compound **21**, on hydrolysis and oxidation, gives the corresponding 2-oxo compound, which on treatment with magnesium isopropylcyclohexylamide followed by acetylation yields **32**. Demethylation of **21** with alkylthiotrimethylsilanes gives the corresponding 2-hydroxyethyl compound, whose tetrahydropyranyl ether on subjection to the above reaction sequence gives the 2-(tetrahydropyran-2-yloxy)ethyl analogue of **32**. This, on hydrolysis, gives a 3:1 mixture of compound **46** and a spiro compound formed by displacement of the acetoxyl group by the hydroxyl oxygen atom of **46**.

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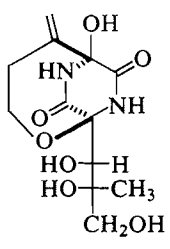
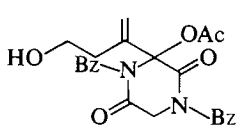
On a synthétisé l'acétoxy-3 dibenzyl-1,4 [(méthoxy-2 éthyl)-1 éthenyl]-3 pipérazinedione-2,5 (**32**) et son analogue hydroxy-2 éthyle (**46**) qui possède plusieurs caractéristiques structurales de l'antibiotique bicyclomycine. On a réalisé cette synthèse selon une méthode qui fait intervenir l'élaboration du cycle pipérazinedione-2,5 lors de la dernière étape d'une série de réactions. Le (méthoxy-2 éthyl)-3 méthyl-3 glycidate d'éthyle réagit avec l'anhydride acétique et l'acide sulfurique en donnant l'acétoxy-2 (méthoxy-2 éthyl)-3 butène-3 oate d'éthyle (**10**) que l'on transforme en acide carboxylique par une éthanolyse, suivie d'une hydrolyse et d'une réacétylation. L'acide transformé en son chlorure, réagit avec la *N,N'*-dibenzylglycinamide en donnant l'acétoxy-2 *N*-benzyl *N*-(benzylamino-2 oxo-2 éthyl)(méthoxy-2 éthyl)-3 butène-3 amide (**21**). Le composé **21**, par hydrolyse suivie d'une oxydation, donne le composé oxo correspondant qui, par une réaction avec l'isopropylcyclohexylamide de magnésium suivie d'une acétylation, conduit au dérivé **32**. La déméthylation du composé **21**, par les alkylthiotriméthylsilanes, donne le composé hydroxy-2 éthyle correspondant dont l'éther tétrahydropyrannyle, soumis à la même série de réactions décrite plus haut, conduit à l'analogue (tétrahydropyrannyl)-2 oxy)-2 éthyle du composé **32**. Ce dernier soumis à une hydrolyse donne un mélange 3:1 du composé **46** et d'un composé spiro formé par déplacement du groupe acétoxyle par l'atome d'oxygène du groupe hydroxyle du composé **46**.

[Traduit par le journal]

Bicyclomycin, an antibiotic produced by *Streptomyces sapporoensis* and *S. aizuensis* (2), is a member of the large class of naturally occurring piperazine-2,5-diones with the unusual structure **1** (3, 4). It has been found to be active against Gram-negative bacteria and does not cause cross resistance to the usual antibiotics; it has also been found to stimulate the growth of chickens and swine (5). There have been several recent synthetic approaches to bicyclomycin of considerable interest (4, 6–10). We have undertaken the synthesis of the 3-acetoxypiperazine-2,5-dione derivative **2** (Bz = benzyl), which we anticipated might serve as a structural prototype for closure to the bicyclic ring system of bicyclomycin. Although **2** lacks the trihydroxyisobutyl side chain of **1**, the work of Nakatsuka *et al.* (7) gives promise that this can be introduced at a later stage.

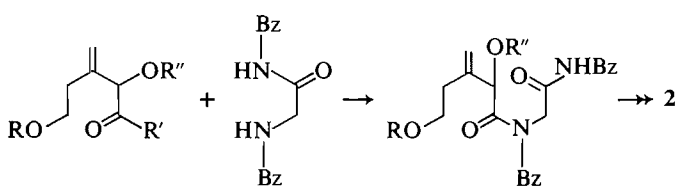


1



2

Two general types of synthetic strategy were envisioned for the construction of **2**: (*i*) *route via acyclic intermediates*: construction of an intermediate of type **3**, reaction of this with *N,N'*-dibenzylglycinamide (**4**) to form a diamide **5**, and closure to the piperazine-2,5-dione ring at a late stage in the synthetic sequence (Scheme 1), and (*ii*) *route via cyclic intermediates*: construction of the piperazine-2,5-dione ring at an early stage of the synthesis in the form of a 3-alkylidene derivative of type **6**, conversion to an epoxide of type **7**, and manipulation of this to introduce the desired functionality (Scheme 2). We report here on the successful application of the first approach.



3 **4** **5**

SCHEME 1

[1]For a preliminary account of part of this work, see ref. 1.

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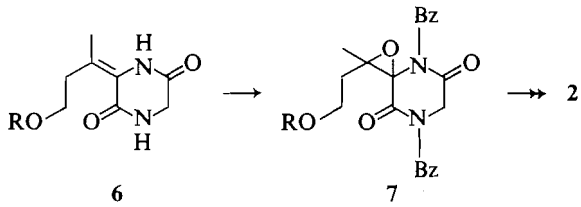
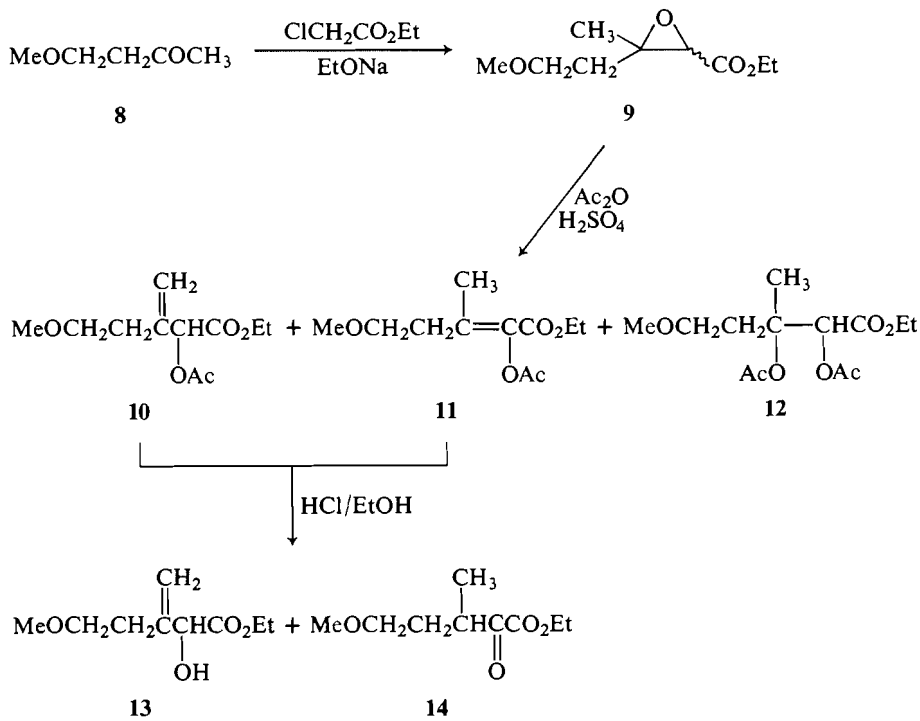


SCHEME 2

We commenced our preparation of compounds of type **3** with the synthesis of ethyl 2-hydroxy-3-(2-methoxyethyl)-3-butanoate (**13**) by the route shown in Scheme 3, based on an earlier synthesis of 2-hydroxy-3-methyl-3-butenoate by Vogel and Schinz (11). 4-Methoxy-2-butanone (**8**), prepared by addition of methanol to methyl vinyl ketone (12), was subjected to a Darzens reaction with ethyl chloroacetate and sodium ethoxide by the general procedure of Burness (13) to give the glycidic ester **9** as a mixture of *E* and *Z* isomers.[2] Treatment of **9** with acetic anhydride and sulfuric acid gave a mixture of the acetates **10**, **11**, and **12** from which the monoacetates **10** and **11** could readily be separated by distillation. The ^{1}H nmr spectrum of the mixture of monoacetates showed that very little of the acetate **15** was formed in the epoxide ring opening reaction; we attribute the regioselectivity of this reaction to the participation of the methoxyl group in the removal of a proton from the *C*-methyl group via a six-membered transition state (cf. **16**). Although it was possible in the ethyl 3,3-dimethylglycidate series (11) to convert the diacetate corresponding to **12** to the monoacetate corresponding to **10** by pyrolysis, this was not found to be possible in the case of the diacetate **12**. The mixture of monoacetates **10** and **11** was ethanolized with ethanolic hydrogen chloride giving a mixture of the unsaturated hydroxy ester **13** and the keto ester **14**, from which the latter could be removed by Girard's reagent T to give the desired compound **13**.

Although the secondary alcohol group of **13** would have at some stage to be oxidized to a ketonic group for the formation of **2**, we decided to convert **13** first to an amide, as indicated in Scheme 1. This was because we anticipated that oxidation of **13** to **17** might lead to complications in forming the amide bond both because of Michael-type addition to the α,β-unsaturated ketone system and the previously observed formation of pyrrolidones in reactions of pyruvic esters with amines (15). The hydroxy ester **13** was hydrolyzed with aqueous sodium hydroxide at room temperature to the hydroxy acid **18**, which was acetylated to give the acetoxy acid **19**, which was in turn converted to its acid chloride **20**. This was added to two equivalents of *N*,*N*′-dibenzylglycinamide (**4**), prepared by treatment



SCHEME 3

[2]In preliminary work we carried out model studies with ethyl 3,3-dimethylglycidate. This was initially prepared by the Darzens reaction of acetone with ethyl chloroacetate and potassium *tert*-butoxide (14); however, we found that under these conditions a mixture of the ethyl and *tert*-butyl esters of the glycidic acid was formed. This problem was avoided by the use of sodium ethoxide.

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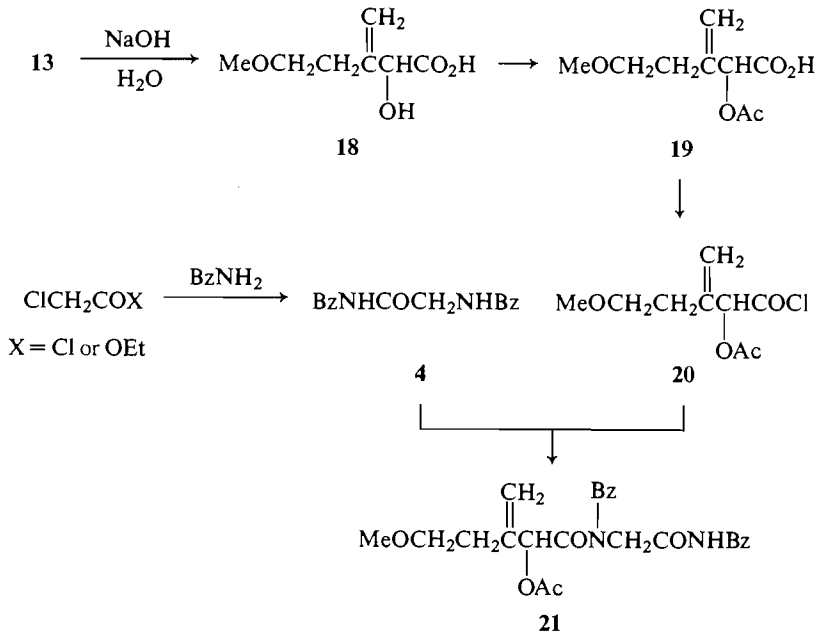
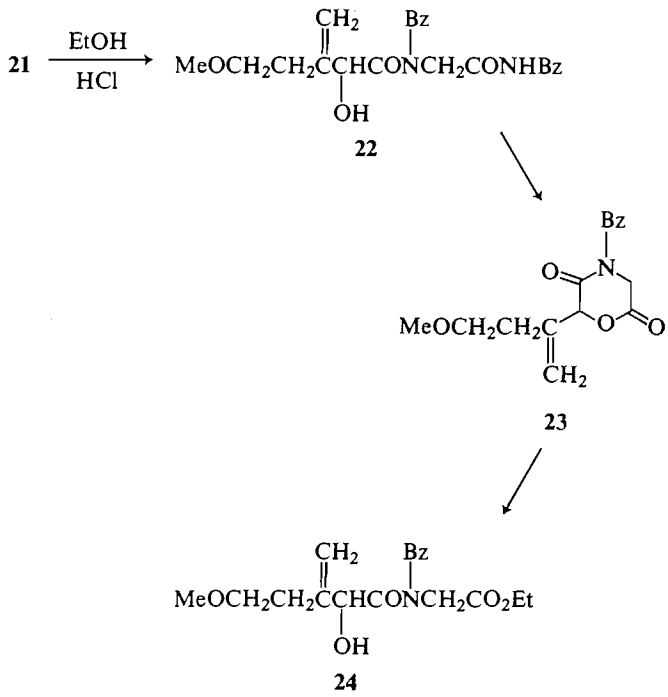


SCHEME 4

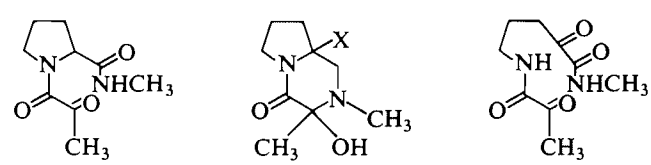


SCHEME 5

of benzylamine with chloroacetyl chloride or ethyl chloroacetate (16), giving the desired diamide **21** and the hydrochloride salt of **4** (Scheme 4). Rotational isomerism about one of the amide carbon–nitrogen bonds in **21** led to doubling of some of the signals in its ^{1}H nmr spectrum: the acetyl protons gave rise to two singlets at δ 2.17 and 2.23 ppm and the acetoxy methine proton to two singlets at δ 5.53 and 5.82 ppm.[3] Such effects of rotational isomerism together with effects due to the diastereotopic nature of the benzylic proton served to complicate the ^{1}H nmr spectra of many of the compounds related to **21** prepared in the present work.

It was now necessary to remove the acetyl group so that oxidation of the secondary alcohol to a ketonic group could be effected. An initial attempt to remove the acetyl group by treatment of **21** with ethanolic hydrogen chloride gave the ester **24**. This unusually facile amide cleavage is considered to involve the initial formation of the desired alcohol **22**, which by intramolecular displacement of benzylamine is converted to the lactone **23**, which in turn is ethanolyzed to **24** (Scheme 5). This complication was avoided by hydrolysis of **21** under basic conditions; reaction with sodium hydroxide in ethanol gave the alcohol **22** (Scheme 6). This was then oxidized with activated manganese dioxide to the ketone **25** whose formation was readily detected by ^{1}H nmr spectroscopy, in that its vinylic proton signals (δ 6.12 and 6.30 ppm) were shifted appreciably downfield relative to those of **21** (δ 5.17 ppm) and its precursors as a result of conjugation of the ethylenic double bond and the ketonic group.

The stage was now set for the closure of **25** to the corresponding piperazine-2,5-dione. It has previously been observed that oxo diamides such as **26** close spontaneously to piperazine-2,5-dione of type **27** and that the more entropically disfavored closure of the dioxo diamide **28** to the piperazinedione **29** could be effected by acid catalysis (17). However, attempts to bring about the closure of **25** at room or elevated



26 **27**, X = H; **29**, X = OH **28**

temperatures or under a variety of acidic conditions were unsuccessful. Treatment of **25** in benzene with lithium, sodium, or potassium hydride gave homogeneous reaction mixtures which gave only polymeric material on work-up. Success was

[3]Although each amide group may give rise to rotational isomers, it seems probable that the effects on the signals referred to originate from isomerism at the internal amide group.

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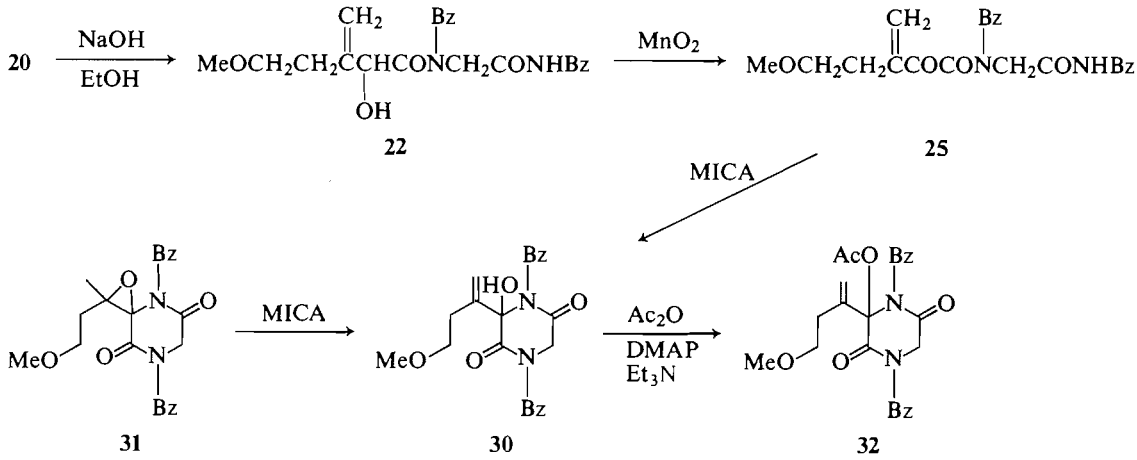
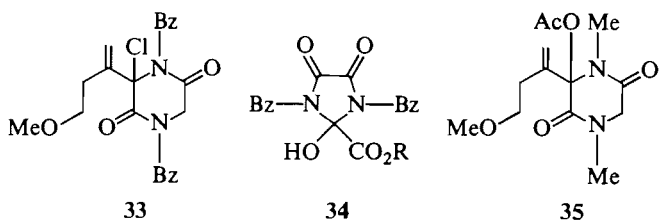


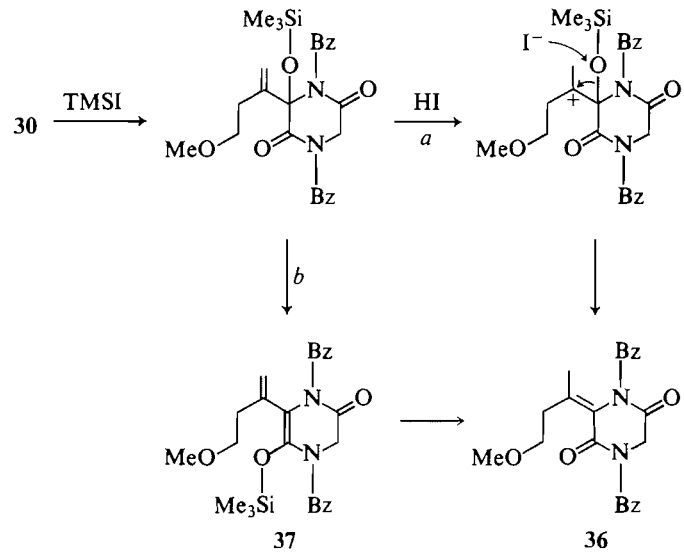
SCHEME 6

finally achieved by the use of magnesium isopropylcyclohexylamide (MICA), a reagent introduced by Corey *et al.* (18) for the conversion of epoxides to allylic alcohols, whose use for the present purpose was suggested to us by its successful application in the conversion of the epoxide **31** to **30** in our work on the synthesis of the latter via cyclic intermediates (19).

Since we had observed that the piperazine-2,5-dione **30** reverted in part to the acyclic precursor **25** on chromatography on silica (19), we decided to acetylate the hydroxyl group in order to prevent ring opening. Treatment with acetyl chloride gave a product that is considered to be the chloride **33** since it showed neither hydroxyl nor acetoxyl bands in its ir spectrum; attempted crystallization of **33** from aqueous acetone gave a mixture of **25** and **30**. Successful acetylation of **30** was accomplished with acetic anhydride and pyridine, or better with acetic anhydride, 4-(dimethylamino)pyridine (DMAP) and triethylamine (20), to give **32** (Scheme 6). Although the ir spectrum of **32** shows a normal acetoxyl band at 5.76 μm, the acetoxyl protons give rise to an abnormally high field signal in the ^{1}H nmr spectrum of **32** at δ 1.30 ppm. This is considered



to be due to shielding resulting from "folding over" of a benzyl group; such an effect has been observed before in the spectra of some 3-benzylpiperazine-2,5-diones (21) and we have observed an analogous effect in the case of the alkoxyl protons of a series of *N,N'*-dibenzyl-4,5-dioxoimidazoline-2-carboxylic acid esters (**34**) (22). In order to confirm that the very unusual position of the acetoxyl signal of **32** was due to shielding by a benzyl group (and not to a structural misassignment!), we synthesized **35**, the *N,N*-dimethyl analogue of **32**, by a route entirely analogous to that used for the synthesis of **32**. The ^{1}H nmr spectrum of **35** showed a normal acetoxyl proton signal at δ 2.15 ppm, confirming that the abnormal position of this signal in the spectrum of **32** is due to the presence of the benzyl groups. The ^{1}H nmr spectra of **35** and its precursors were simpler than those of **32** and its precursors because of the



SCHEME 7

absence of diastereotopic benzylic methylene proton signals, and served further to corroborate the structural assignments.

The eventual synthesis of the bicyclic system of bicyclomycin (**1**) will require bond formation between the oxygen atom of the methoxyl group in **32** and C-6 of the piperazinedione ring. Such bond formation would be expected to occur more readily if the oxygen atom were part of a hydroxyl rather than a methoxyl group. We therefore undertook the synthesis of the hydroxy analogue of **32**.

We initially attempted to prepare this from **32** by treatment with trimethylsilyl iodide (TMSI) (23). This gave none of the desired product. Since we suspected that the lability of the acetoxyl group of **32** was responsible (cf. the formation of **33** from **30** and acetyl chloride), we investigated the reaction of **30** with two equivalents of TMSI in an attempt both to silylate the hydroxyl group and cleave the methyl ether. Surprisingly, the product obtained was the (*E*)-alkylidenepiperazinedione **36** (19). One possible mechanism for this reaction is depicted by path *a* in Scheme 7. A related reaction has been reported in which TMSI reduces α-hydroxy ketones to the corresponding ketones (24); a mechanism analogous to one proposed for this reaction (path *b* in Scheme 7) would lead to **37**, which could be converted to **36** upon acidic work-up.

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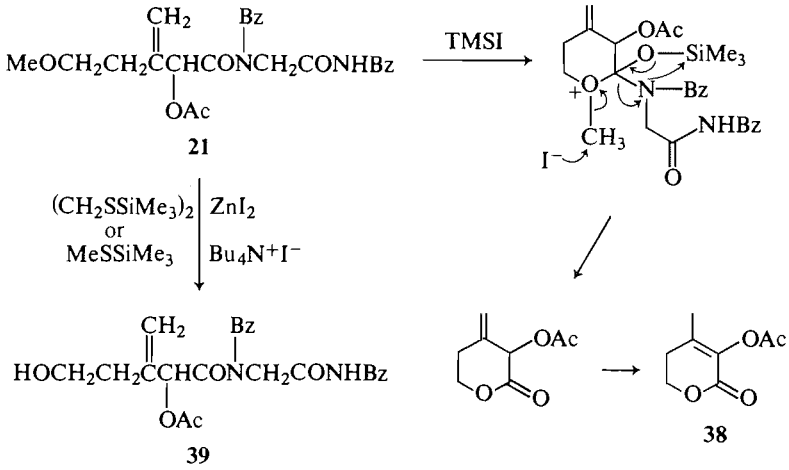
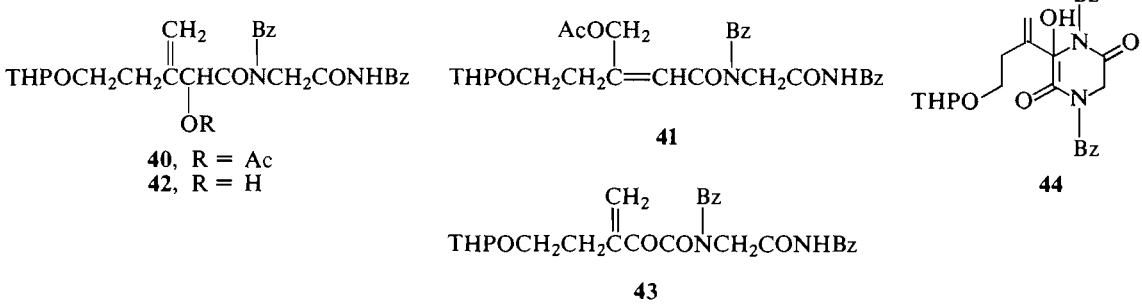


SCHEME 8

In view of these difficulties we decided to remove the *O*-methyl group at an earlier stage in the synthetic sequence. Treatment of **21** with TMSI or with TMSI generated *in situ* from trimethylsilyl chloride and sodium iodide (25) gave the *O*-acetyl derivative of 5,6-dihydro-3-hydroxy-4-methyl-2*H*-pyran-2-one (26), which could arise by the route shown in Scheme 8. Hydriodic acid generated *in situ* from *p*-toluenesulfonic acid and sodium iodide (27) failed to react with **21**. Treatment of **21** with aluminum trichloride and ethanethiol (28) gave sulfur-containing products in which the acetoxyl group had been lost. We finally investigated the use of the procedures recently introduced by Hanessian and Guindon for the cleavage of methyl ethers with thiotrimethylsilanes, zinc iodide, and tetrabutylammonium iodide (29). Compound **21** was resistant to phenylthiotrimethylsilane but was demethylated, albeit in low yield, by the use of the more reactive 1,2-ethanedithiobis(trimethylsilane) or methylthiotrimethylsilane to give the desired alcohol **39** (Scheme 8). Its formation was indicated by the appearance of a band at 2.95 μm in the ir spectrum of **39** and the absence of a methoxyl proton signal in its ^{1}H nmr spectrum.

The alcohol **39** was converted to its tetrahydropyranyl derivative **40** by reaction with 2-(*tert*-butoxy)tetrahydropyran and hydrochloric acid in methylene chloride (30),[4] which was converted to the piperazine-2,5-dione **44** via the intermediates **42** and **43** by the same sequence of reactions that had been used in the conversion of the methyl ether **20** to the piperazine-2,5-dione **30**. Attempted acetylation of **44** suffered from extensive ring opening. However, it was found that the magnesium alk-



oxide formed as an intermediate in the cyclization of **43** to **44** with MICA could be acetylated directly with acetic anhydride to give the acetoxypiperazinedione **45**. The tetrahydropyranyl group of **45** was removed with acetic acid in aqueous tetrahydrofuran by the general procedure of Grieco *et al.* (31) to give a 3:1 mixture of the target compound **46** and the spiro compound **47** (Scheme 9), which were separated by chromatography. The ir spectrum of **46** showed a hydroxyl-stretching band at 2.90 μm and its ^{1}H nmr spectrum showed the absence of the multiplet at δ 1.6 ppm characteristic of the tetrahydropyranyl group. The spiro compound **47** showed only amide bands at 5.97 μm in the carbonyl-stretching region of its ir spectrum; in its ^{1}H nmr spectrum the vicinal methylene protons no longer gave rise to simple triplet signals as they did in the spectrum of **46** but gave rise to complex multiplets as a result of ring formation.

The acid-catalyzed conversion of **46** to **47** finds precedent in the chemistry of bicyclomycin (1) itself, which has been found (4) to undergo acid-catalyzed rearrangement to the diastereomeric spiro compounds **48** and **49** (Scheme 10).

Experimental

Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Unless otherwise specified, the ir spectra were recorded for $CHCl_3$ solutions and the ^{1}H and ^{13}C nmr spectra for $CDCl_3$ solutions. Mass spectra were recorded at 70 eV and peak positions (m/e) are followed by relative abundances in parentheses. Chromatographic separations were carried out by liquid column chromatography except where otherwise indicated. All R_f values were

[4]A minor product formed in this reaction is considered to be **41**, formed by allylic rearrangement.

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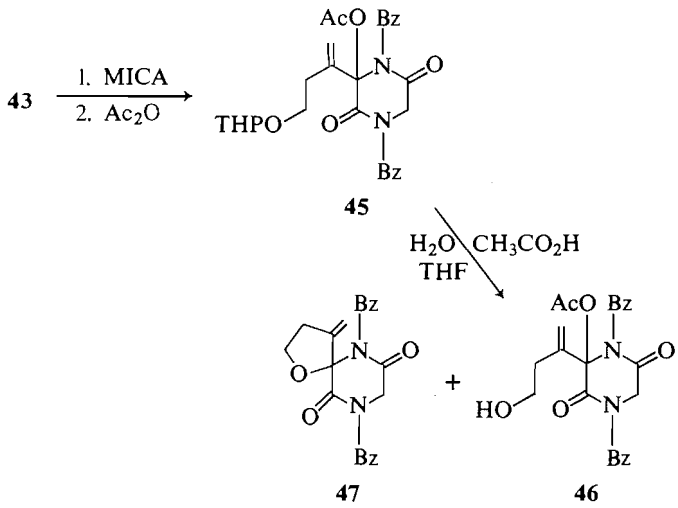
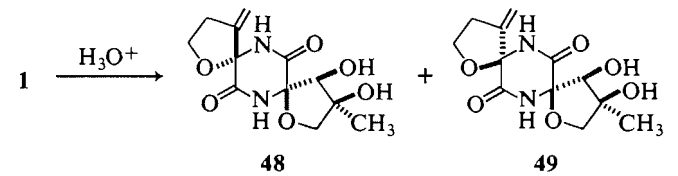


SCHEME 9



SCHEME 10

determined on analytical thin-layer chromatographic silica gel plates. Preparative thin-layer chromatography was carried out on 20 × 20 × 1-mm or 20 × 20 × 2-mm silica gel plates containing a fluorescent indicator. The bands were extracted with methanol and the residue obtained after filtration and evaporation was triturated with chloroform or dichloromethane; filtration and evaporation yielded the product; iodine or uv visualization was employed. Apparatus for the experiments that were carried out under nitrogen was flame dried immediately prior to use under a dry nitrogen flow. All organic extracts were dried over anhydrous $MgSO_4$ and evaporated by means of a rotary evaporator at water aspirator pressure.

Ethyl 3,3-dimethylglycidate

When a Darzens reaction was performed on acetone and ethyl chloroacetate with potassium *tert*-butoxide as base (14) a 1:1 mixture of ethyl and *tert*-butyl glycidates was obtained.

The procedure of Burness (13) was therefore used. Sodium ethoxide was prepared from sodium (3.61 g, 0.157 mol) and ethanol; removal of the ethanol *in vacuo* gave a solid (22.30 g) which was found to contain ~48% by weight sodium ethoxide by titration with potassium hydrogen phthalate. This solid was added portionwise with mechanical stirring to acetone (9.10 g, 0.157 mol), ethyl chloroacetate (28.85 g, 0.235 mol), and ether (125 mL) cooled to −10°C in an ice–salt bath under nitrogen. The temperature was kept below −5°C during addition of base. The mixture was then stirred in the ice–salt bath for 2 h; the ice–salt bath was removed and stirring was continued overnight at room temperature. A solution of acetic acid (2 mL) in water (48 mL) was added and the ether layer was separated. The aqueous layer was washed with ether (3 × 25 mL). The combined ether phases were dried, filtered, concentrated, and distilled at 88°C (20 Torr) to give 14.9 g (66%) of ethyl 3,3-dimethylglycidate; ir λ_{max}: 5.77 μm; ^{1}H nmr δ: 4.17 (q, J = 7 Hz, 2H), 3.25 (s, 1H), 1.38 (s, 3H), 1.35 (s, 3H), 1.27 (t, J = 7 Hz, 3H).

Reaction of ethyl 3,3-dimethylglycidate with acetic acid anhydride. Formation of ethyl 2-acetoxy-3-methyl-3-butenoate, ethyl 2-acetoxy-3-methyl-2-butenoate, and ethyl 2,3-diacetoxy-3-methylbutanoate

The procedure of Vogel and Schinz (11) was followed. Ethyl 3,3-dimethylglycidate (14.32 g, 99.5 mmol) was stirred at room temperature in freshly distilled acetic anhydride (13.4 mL). Concentrated H_2SO_4 (0.5 mL) was added with stirring and the mixture became hot. The solution was cooled on ice and after 10 min another 0.25 mL of concentrated H_2SO_4 was added. The mixture was stirred for 1 h at room temperature and 30 min at 100°C. The cooled mixture was dissolved in ether (50 mL) and the solution was washed with water (10 mL) and aqueous 10% $NaHCO_3$ (10 mL). The ether phase was dried, filtered, and concentrated. The residue was fractionally distilled. Ethyl 2-acetoxy-3-methyl-2-butenoate and ethyl 2-acetoxy-3-methyl-3-butenoate distilled at 90–95°C (10 Torr) and the diacetate, ethyl 2,3-diacetoxy-3-methylbutanoate, distilled at 98–103°C (10 Torr). The diacetate (ir λ_{max}: 5.76 μm; ^{1}H nmr δ: 5.40 (s), 4.33 (q, J = 7 Hz), 1.82 (s), 1.98 (s), 1.58 (s), 1.53 (s), 1.27 (t, J = 7 Hz)) was converted into the monoacetate mixture by pyrolysis with a Bunsen burner flame. The combined monoacetate mixture was redistilled at 95°C (10 Torr) to give ~10 g (59%) of ethyl 2-acetoxy-3-methyl-2-butenoate and ethyl 2-acetoxy-3-methyl-3-butenoate; ir λ_{max}: 5.75 μm; ^{1}H nmr δ: 5.32 (s), 5.0–5.2 (m), 4.17 (q, J = 7 Hz), 2.10 (s), 1.78 (s), 1.25 (t, J = 7 Hz).

Ethyl 2-hydroxy-3-methyl-3-butenoate

A solution of the mixture of ethyl 2-acetoxy-3-methyl-2-butenoate and ethyl 2-acetoxy-3-methyl-3-butenoate (7.11 g) in 4% HCl in ethanol (14 mL) was boiled under reflux for 1.5 h. After cooling, solid $NaHCO_3$ was added to neutralize the solution which was then filtered, concentrated, and distilled at 71–74°C (12 Torr) to give a quantitative yield of the ethanolyzed material. This mixture (4.56 g), methanol (20 mL), acetic acid (2.1 mL), and Girard reagent T (2.0 g) were boiled under reflux for 0.5 h. The cooled solution was dissolved in methylene chloride (50 mL) and the solution was washed with water (10 mL). The aqueous phase was washed several times with methylene chloride. The combined methylene chloride phases were dried, filtered, and concentrated. The residue was distilled at 68–69°C (10 Torr) to give ethyl 2-hydroxy-3-methyl-3-butenoate (3.53 g, 70%); ir λ_{max}: 2.98, 5.78 μm; ^{1}H nmr δ: 4.8–5.1 (m, 2H), 4.48 (s, 1H), 4.18 (q, J = 7 Hz, 2H), 3.28 (s, 1H), 1.73 (m, 3H)0, 1.27 (t, J = 7 Hz, 3H).

Ethyl 3-(2-methoxyethyl)-3-methylglycidate (9)

4-Methoxy-2-butanone (**8**) was prepared in 60% yield by addition of methanol to methyl vinyl ketone (12).

Ketone **8** (50.7 g, 0.497 mol) was subjected to a Darzens reaction with ethyl chloroacetate (97.3 g, 0.794 mol) and sodium ethoxide (48% by weight NaOEt; 70.7 g, 0.499 mol) in ether (425 mL) in analogous fashion to the preparation of ethyl 3,3-dimethylglycidate. Ethyl 3-(2-methoxyethyl)-3-methylglycidate (**9**) was obtained as a mixture of *cis* and *trans* isomers, bp 93–98°C (0.35 Torr), in 78% yield; ir λ_{max}: 5.62, 8.95 μm; ^{1}H nmr δ: 4.20 (q, J = 7 Hz, 2H), 3.72 and 3.33 (2 s, 1H), 3.45 (t, J = 6 Hz, 2H), 3.28 and 3.25 (2 s, 3H), 1.90 and 1.87 (2 t, J = 6 Hz, 2H), 1.42 and 1.37 (2 s, 3H), 1.28 (t, J = 7 Hz, 3H); m/e: 188 (0.2), 173 (2), 157 (5), 115 (45), 45 (100). *Anal.* calcd. for $C_9H_{16}O_4$: C 57.43, H 8.57; found: C 57.01, H 8.47.

Ethyl 2-hydroxy-3-(2-methoxyethyl)-3-butenoate (13)

Ethyl 3-(2-methoxyethyl)-3-methylglycidate (**9**) (43.54 g, 0.231 mol) was treated with acetic anhydride (34 mL) by an analogous procedure to that used for the opening of the epoxide ring of ethyl 3,3-dimethylglycidate except that only 15 drops of concentrated H_2SO_4 were used and the mixture was heated on a steam bath for ~8 h. The work-up was the same as before.

Ethyl *cis*- and *trans*-2-acetoxy-5-methoxy-3-methyl-2-pentenoate (**11**) and ethyl 2-acetoxy-3-(2-methoxyethyl)-3-butenoate (**10**) were fractionally distilled at 66–68°C (0.01 Torr) in 45% yield from ethyl 2,3-diacetoxy-5-methoxy-3-methylpentanoate (**12**), which could not be distilled without decomposition. Pyrolysis of the diacetate **12** resulted in decomposition with loss of methanol.

A solution of monoacetate mixture **10** and **11** (32.60 g, 0.142 mol) in 4% HCl in ethanol was boiled under reflux for 1.5 h and worked up in analogous fashion to the work-up of ethyl 2-hydroxy-3-methyl-3-butenoate. A quantitative yield of crude ethanolyzed mixture was

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obtained. A solution of this mixture (30.75 g, 0.163 mol) and Girard's reagent T (20.0 g, 0.119 mol) in methanol (115 mL) and acetic acid (13 mL) was boiled under reflux for 0.5 h and worked up as before. The residue was distilled at 55–65°C (0.005 Torr) to give **13** in 65% yield; ir λ_{max}: 2.90, 5.76 μm; ^{1}H nmr δ: 5.13 (s, 1H), 4.98 (m, 1H), 4.62 (br s, 1H), 4.25 (q, J = 7 Hz, 2H), 3.82 (br s, 1H), 3.46 (t, J = 6 Hz, 2H), 3.37 (s, 3H), 2.33 (t, J = 6 Hz, 2H), 1.28 (t, J = 7 Hz, 3H); *m/e*: 189 (2), 188 (0.3), 171 (3), 156 (11), 115 (27), 83 (100). *Accurate Mass* calcd. for $C_9H_{16}O_4$: 188.1049; found: 188.1057.

*2-Acetoxy-3-(2-methoxyethyl)-3-butenoyl chloride (**20**)*

Ethyl 2-hydroxy-3-(2-methoxyethyl)-3-butenoate (**13**) (35.45 g, 0.188 mol) in aqueous 25% NaOH (125 mL) was stirred for 4 days at room temperature. The basic solution assumed a dark red-brown color during this time. It was then cooled in an ice bath and acidified with concentrated hydrochloric acid. The light yellow aqueous solution was saturated with sodium chloride and the resulting solution was extracted several times with methylene chloride. The combined methylene chloride phases were dried, filtered, and concentrated giving a quantitative yield of crude 2-hydroxy-3-(2-methoxyethyl)-3-butenoic acid (**18**) as a viscous yellow syrup; ir λ_{max}: 3–4, 5.64, 5.81 μm; ^{1}H nmr δ: 7.67 (bs, 2H), 5.23 (s, 1H), 5.07 (br s, 1H), 4.60 (s, 1H), 3.52 (t, J = 7 Hz, 2H), 3.32 (s, 3H), 2.35 (t, J = 6 Hz, 2H).

Compound **18** (10.0 g, 62 mmol) was dissolved in methylene chloride (50 mL) and acetyl chloride (7.35 mL, 104 mmol) was added. The mixture was stirred at room temperature for 12 h and concentrated. The residue was dissolved in saturated aqueous $NaHCO_3$ with stirring. This solution was acidified with 3 *N* hydrochloric acid and extracted several times with methylene chloride. The combined methylene chloride phases were dried, filtered, and concentrated giving 10.1 g (80%) of 2-acetoxy-3-(2-methoxyethyl)-3-butenoic acid (**19**) as a viscous syrup; ir λ_{max}: 5.79 μm; ^{1}H nmr δ: 10.32 (s, 1H), 5.40 (s, 1H), 5.31 (s, 1H), 5.15 (br s, 1H), 3.57 (t, J = 6 Hz, 2H), 3.32 (s, 3H), 2.43 (t, J = 6 Hz, 2H), 2.13 (s, 3H).

A solution of **19** (456 mg, 2.40 mmol) and oxalyl chloride (1.42 mL, 16.5 mmol) in methylene chloride (5 mL) was stirred at room temperature for 12 h. The reaction mixture was concentrated under high vacuum and the residue was distilled at 54°C (0.015 Torr) giving 2-acetoxy-3-(2-methoxyethyl)-3-butenoyl chloride (**20**) (318 mg, 60%) as a clear, colorless liquid; ir λ_{max}: 5.60, 5.74 μm; ^{1}H nmr δ: 5.55 (s, 1H), 5.38 (s, 1H), 5.30 (m, 1H), 3.57 (t, J = 6 Hz, 2H), 3.35 (s, 3H), 2.45 (t, J = 6 Hz, 2H), 2.20 (s, 3H).

*2-Acetoxy-*N*-benzyl-*N*-(2-benzylamino-2-oxoethyl)-3-(2-methoxyethyl)-3-butenamide (**21**)*

Acid chloride **20** (2.38 g, 10.8 mmol) in methylene chloride (50 mL) was stirred at room temperature while *N*,*N*′-dibenzylglycinamide (**4**) (16) (5.47 g, 21.5 mmol) in methylene chloride (10 mL) was added dropwise. After addition was complete, the mixture was stirred for 20 min. The *N*,*N*′-dibenzylglycinamide hydrochloride that had formed was filtered. The filtrate was washed with aqueous 10% $NaHCO_3$ (10 mL), aqueous 6 *N* hydrochloric acid (10 mL), and water (20 mL). The methylene chloride solution was dried, filtered, and concentrated to give a quantitative yield of 2-acetoxy-*N*-benzyl-*N*-(2-benzylamino-2-oxoethyl)-3-(2-methoxyethyl)-3-butenamide (**21**) as a pale yellow gum which resisted crystallization; ir λ_{max}: 2.99, 5.69, 5.95 μm; ^{1}H nmr δ: 7.17 (m, 11H), 5.82 (s, 0.5H), 5.53 (s, 0.5H), 5.0–5.3 (m, 2H), 3.7–4.8 (m, 6H), 3.42 (t, J = 6 Hz, 2H), 3.15 (s, 3H), 2.37 (t, J = 6 Hz, 2H), 2.33 (s, 1.5H), 2.17 (s, 1.5H); ^{13}C nmr δ: 171.4 (s), 171.0 (s), 168.9 (s), 168.0 (s), 167.4 (s), 139.6 (s), 139.5 (s), 138.2 (s), 136.0 (s), 135.3 (s), 127.2–128.9 (d), 119.2 (t), 119.1 (s), 74.6 (d), 71.3 (t), 71.2 (t), 58.5 (q), 52.1 (t), 50.3 (t), 49.4 (t), 43.4 (t), 43.3 (t), 32.9 (t), 20.6 (q); *m/e*: 438 (2), 379 (12), 91 (100). *Accurate Mass* calcd. for $C_{25}H_{30}N_2O_5$: 438.2155; found: 438.2215.

N-*Benzyl*-N-*(2-benzylamino-2-oxoethyl)-2-hydroxy-3-(2-methoxyethyl)-3-butenamide (**22**)*

A solution of compound **21** (1.796 g, 4.10 mmol) and NaOH (170 mg, 4.25 mmol) in ethanol (20 mL) was stirred for 8 h at room temperature. The ethanol solution was concentrated and the residue was dissolved in methylene chloride (20 mL). The solution was washed with water (5 mL), dried, filtered, and concentrated, giving a quantitative yield of **22** as a clear yellow gum; ir λ_{max}: 3, 5.95, 6.04 μm; ^{1}H nmr δ: 7.13 (m, 11H), 4.8–5.2 (m, 2H), 3.6–4.8 (m, 8H), 3.40 (t, J = 6 Hz, 2H), 3.17 (s, 3H), 2.30 (t, J = 6 Hz, 2H); *m/e*: 396 (1), 379 (2), 288 (4), 257 (6), 106 (31), 91 (100). *Accurate Mass* calcd. for $C_{23}H_{27}N_2O_3$ (M − OH): 379.2022; found: 379.2048.

N-*Benzyl*-N-*(2-benzylamino-2-oxoethyl)-3-(2-methoxyethyl)-2-oxo-3-butenamide (**25**)*

Compound **22** (4.37 g, 11.0 mmol) and activated manganese dioxide (32) (25 g) in methylene chloride or chloroform (170 mL) was stirred at room temperature for 14 h. The mixture was filtered through Celite and the solid was washed with hot chloroform (3 × 50 mL). The combined filtrates were concentrated leaving a quantitative yield of **25** as a pale yellow gum; ir λ_{max}: 2.98, 5.96, 6.09 μm; ^{1}H nmr δ: 7.17 (m, 11H), 6.30 (s, 1H), 6.12 (s, 1H), 3.6–4.7 (m, 6H), 3.42 (t, J = 6 Hz, 2H), 3.17 (s, 3H), 2.53 (t, J = 6 Hz, 2H); ^{13}C nmr δ: 193.6 (s), 193.4 (s), 168.2 (s), 167.4 (s), 167.1 (s), 142.6 (s), 142.2 (s), 138.0 (t), 137.8 (t), 135.4 (s), 134.6 (s), 134.2 (s), 128.9–126.7 (d), 70.7 (t), 58.4 (q), 52.5 (t), 46.5 (t), 43.4 (t), 29.5 (t); *m/e*: 394 (6), 349 (1), 303 (3), 281 (8), 253 (21), 246 (6), 91 (100). *Accurate Mass* calcd. for $C_{23}H_{26}N_2O_4$: 394.1893; found: 394.1909.

*Cyclization of **25**. Formation of 1,4-dibenzyl-3-hydroxy-3-[1-(2-methoxyethyl)ethenyl]piperazine-2,5-dione (**30**)*

A solution of magnesium isopropylcyclohexylamide (MICA) (18) in dry tetrahydrofuran (15 mL) was prepared from magnesium turnings (35 mg, 1.4 mmol), methyl bromide, and isopropylcyclohexylamine (0.5 mL, 3 mmol). Compound **25** (353 mg, 0.894 mmol) in dry tetrahydrofuran (4 mL) was syringed slowly dropwise into the stirred MICA solution at room temperature over a period of 2.5–3 h. The mixture was stirred for 18 h at room temperature and then cooled in an ice bath. Aqueous 2 *M* KH_2PO_4 (5 mL) was added to the cooled mixture. The acidified mixture was washed with methylene chloride (3 × 15 mL). The combined methylene chloride extracts were washed with water (10 mL), dried, filtered, and concentrated giving crude piperazine-2,5-dione **30** as a pale yellow gum (350 mg); ir λ_{max}: 2.98, 6.02 μm; ^{1}H nmr δ: 7.23 (m, 10H), 5.07 (m, 3H), 4.0–5.0 (m, 6H), 3.43 (t, J = 6 Hz, 2H), 3.30 (s, 3H), 2.33 (m, 2H).

Attempted crystallization of this product from combinations of chloroform, ether, ethyl acetate, and hexanes or cyclohexane was unsuccessful. Attempted crystallization from acetone–water resulted in its reversion to **25**.[5]

*3-Acetoxy-1,4-dibenzyl-3-[1-(2-methoxyethyl)ethenyl]piperazine-2,5-dione (**32**)*

Compound **30** (678 mg, 1.72 mmol) was treated with 4-dimethylaminopyridine (9 mg), acetic anhydride (2 mL), and triethylamine (2 mL) for 4 h at room temperature. The mixture was concentrated *in vacuo* and the residue was dissolved in methylene chloride (15 mL). The solution was washed with 3 *M* hydrochloric acid (5 mL) and water (5 mL), dried, filtered, and concentrated. The residue was chomatographed on silica with 20% ethyl acetate – chloroform as eluent. The product (R_f = 0.6) was eluted and the fraction concentrated to give the acetylated product **32** (359 mg, 48%) as a pale yellow gum which resisted crystallization; ir λ_{max}: 5.76, 5.98 μm; ^{1}H nmr δ: 7.20 (s, 5H), 7.15 (s, 5H), 5.60 (s, 1H), 5.40 (s, 1H), 3.7–5.3 (m, 6H), 3.50 (t, J = 6 Hz, 2H), 3.30 (s, 3H), 2.28 (t, J = 6 Hz, 2H), 1.30 (s, 3H); *m/e*: 436 (6), 393 (3), 378 (30), 113 (29), 91 (100). *Accurate Mass* calcd. for $C_{25}H_{28}N_2O_5$: 436.1998; found: 436.1995.

*3-Acetoxy-3-[1-(2-methoxyethyl)ethenyl]-1,4-dimethylpiperazine-2,5-dione (**35**)*

The following reaction sequence was carried out in analogous fash-

[5]Although neither **30** nor its precursors could be obtained in crystalline form, its spectra corresponded with those of **30** obtained by treatment of **31** with MICA; **31** and several of its precursors have been obtained in crystalline form and characterized by combustion elemental analysis (19).

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ion to the preparation of compound **32** and its precursors.

Acid chloride **19** (1.14 g, 5.17 mmol) in methylene chloride (50 mL) was treated with *N*,*N*′-dimethylglycinamide (33) (1.08 g, 10.6 mmol) in methylene chloride (5 mL) to give 2-acetoxy-3-(2-methoxyethyl)-*N*-methyl-*N*-(2-methylamino-2-oxoethyl)-3-butenamide as a yellow gum (1.32 g, 89%); ir λ_{max}: 2.95, 5.71, 5.93 μm; ^{1}H nmr δ: 7.03 (br s, 0.3H), 6.57 (br s, 0.7H), 5.63 (s, 0.7H), 5.47 (s, 0.3H), 5.27 (m, 2H), 4.12 (s, 1H), 3.92 (s, 1H), 3.53 (t, J = 6 Hz, 2H), 3.33 (s, 3H), 3.11 (s, 2H), 2.98 (s, 1H), 2.80 (s, 2H), 2.73 (s, 1H), 2.43 (t, J = 6 Hz, 2H), 2.17 (s, 3H).

A solution of this product (1.03 g, 3.60 mmol) and sodium hydroxide (174 mg, 4.35 mmol) in ethanol (20 mL) was stirred for 10 h at room temperature to give 2-hydroxy-3-(2-methoxyethyl)-*N*-methyl-*N*-(2-methylamino-2-oxoethyl)-3-butenamide as a water-soluble yellow gum; ir λ_{max}: 3.02, 6.05 μm; ^{1}H nmr δ: 6.28 (br s, 1H), 5.12 (m, 2H), 4.73 (bs, 1H), 3.8–4.5 (m, 3H), 3.48 (t, J = 6 Hz, 2H), 3.28 (s, 3H), 3.00 (s, 3H), 2.74 (d, J = 4 Hz, 3H), 2.30 (t, J = 6 Hz, 2H).

This alcohol (571 mg, 2.34 mmol) and activated manganese dioxide (4.5 g) in methylene chloride (30 mL) were stirred at room temperature for 11 h to give 3-(2-methoxyethyl)-*N*-methyl-*N*-(2-methylamino-2-oxoethyl)-2-oxo-3-butenamide as a pale yellow gum (435 mg, 77%); ir λ_{max}: 3.01, 5.98, 6.02 μm; ^{1}H nmr δ: 6.90 (br s, 1H), 6.30 (m, 2H), 4.05 (m, 2H), 3.50 (t, J = 6 Hz, 2H), 3.30 (s, 3H), 3.00 and 2.93 (2 s, 3H), 2.77 (d, J = 4 Hz, 3H), 2.62 (t, J = Hz, 2H).

A solution of this product (435 mg, 1.80 mmol) in tetrahydrofuran (2 mL) was syringed into a solution of MICA prepared from magnesium turnings (63 mg, 2.6 mmol), methyl bromide, and isopropylcyclohexylamine (0.5 mL), in dry tetrahydrofuran (12 mL). The mixture was stirred overnight at room temperature and treated with 3 *M* hydrochloric acid (5 mL) to give 3-hydroxy-3-[1-(2-methoxyethyl)ethenyl]-1,4-dimethylpiperazine-2,5-dione as a pale yellow gum (403 mg, 93%), which was ether insoluble and resisted crystallization; ir λ_{max}: 6.04 μm; ^{1}H nmr δ: 5.23 (br s, 1H), 5.17 (m, 2H), 3.97 (m, 2H), 3.47 (t, J = 6 Hz, 2H), 3.30 (s, 3H), 2.98 (s, 3H), 2.90 (s, 3H), 2.27 (t, J = 6 Hz, 2H).

The hydroxy piperazinedione (40.3 mg, 1.66 mmol) was acetylated in a solution of acetic anhydride (2 mL), triethylamine (2 mL), and a few crystals of 4-dimethylaminopyridine. The mixture was stirred for 18 h at room temperature to give a gummy residue which was chromatographed on silica with 10% methanol – ethyl acetate as eluent. The product (R_f = 0.5), 3-acetoxy-3-[1-(2-methoxyethyl)ethenyl]-1,4-dimethylpiperazine-2,5-dione (**35**), was a pale yellow gum (311 mg, 66%), which resisted crystallization in a variety of solvents; ir λ_{max}: 5.79, 6.01 μm; ^{1}H nmr δ: 5.57 (s, 1H), 5.27 (m, 1H), 4.03 (s, 2H), 3.48 (t, J = 6 Hz, 2H), 3.32 (s, 3H), 2.92 (s, 3H), 2.75 (s, 3H), 2.27 (t, J = 6 Hz, 2H), 2.15 (s, 3H); *m*/*e*: 284 (12), 225 (100), 192 (19), 180 (14). *Accurate Mass* calcd. for $C_{13}H_{20}N_2O_5$: 284.1372; found: 284.1346.

*Reaction of **30** with trimethylsilyl iodide. Formation of (E)-1,4-dibenzyl-3-(4-methoxy-2-butylidene)piperazine-2,5-dione (**36**)*

Piperazine-2,5-dione **30** (91 mg, 0.21 mmol) was dissolved in $CHCl_3$ in an nmr tube and trimethylsilyl iodide (TMSI) (66 μL, 0.46 mmol) was added. The solution turned dark red-brown on addition of the TMSI. The reaction was followed by ^{1}H nmr spectroscopy for 19 h at room temperature. The contents of the nmr tube were dissolved in methylene chloride (15 mL) and the solution was washed with saturated aqueous Na_2SO_3 (5 mL), 3 *N* hydrochloric acid (5 mL), aqueous 10% $NaHCO_3$, and water (5 mL). The methylene chloride solution was dried, filtered, and concentrated. The residue was chromatographed on a 1-mm preparative silica gel plate with 20% ethyl acetate – chloroform as eluent. The band (R_f = 0.3) was eluted with methanol–chloroform, and the fraction concentrated, giving a gum (64 mg) whose ^{1}H nmr spectrum was identical with that of (*E*)-1,4-dibenzyl-3-(4-methoxybut-2-ylidene)piperazine-2,5-dione (**36**) (19).

*Reaction of **20** with trimethylsilyl iodide. Formation of 3-acetoxy-5,6-dihydro-4-methyl-2H-pyran-2-one (**38**)*

(*i*) Compound **20** (100 mg, 0.229 mol), TMSI (65 μL, 0.48 mmol), and $NaHCO_3$ (100 mg, 1.19 mmol) in methylene chloride (2 mL) were stirred for 18 h at room temperature. The mixture was washed with saturated aqueous Na_2SO_3 (1 mL), 3 *N* hydrochloric acid (1 mL), aqueous 10% $NaHCO_3$ (1 mL), and water (1 mL), dried, filtered, and concentrated. The residue was chromatographed on a 1-mm preparative silica gel plate with 20% ethyl acetate – chloroform as eluent. The strongly fluorescent band (R_f = 0.46) was eluted with methanol–chloroform giving **38** (26) (30 mg, 77%) as a yellow oil; ir λ_{max}: 5.65, 7.78 μm; ^{1}H nmr δ: 5.20 (t, J = 6 Hz, 2H), 2.53 (t, J = 6 Hz, 2H), 2.25 (s, 3H), 1.88 (s, 3H).

Compound **20** gave the same product on treatment with one equivalent of TMSI.

(*ii*) Reaction of **20** (114 mg, 0.260 mmol) with sodium iodide (83 mg, 0.55 mmol) and trimethylsilyl chloride (66 μL, 0.52 mmol) in acetonitrile (2 mL) for 10 h at room temperature gave a mixture of **38** and unconsumed **20** after work-up as in (*i*).

(*iii*) Reaction of **20** (152 mg, 0.347 mmol) with zinc iodide (761 mg, 2.39 mmol) and TMSI (0.35 mL, 2.46 mmol) in methylene chloride (2 mL) for 5 min at room temperature gave a mixture of **38** and unconsumed **20** after work-up as in (*i*).

*2-Acetoxy-*N*-benzyl-3-(2-hydroxyethyl)-*N*-(2-benzylamino-2-oxoethyl)-3-butenamide (**39**)*

The general procedure of Hanessian and Guindon (29) for the cleavage of methyl ethers with thiotrimethylsilanes in the presence of tetrabutylammonium iodide and zinc iodide was employed.

(*i*) A solution of **21** (185 mg, 0.422 mmol), zinc iodide (purified by washing with carbon tetrachloride; 0.65 g, 2.0 mmol), tetra-*n*-butylammonium iodide (0.47 g, 1.3 mmol), and phenylthiotrimethylsilane (34) (0.72 g, 4.0 mmol) in 1,2-dichloroethane (8 mL) was heated with stirring at 73–75°C for 20 h. Work-up with aqueous 10% $NaHCO_3$ returned only **21**.

(*ii*) A solution of **21** (125 mg, 0.285 mmol), zinc iodide (273 mg, 0.855 mmol), tetra-*n*-butylammonium iodide (167 mg, 0.428 mmol), and 1,2-ethanedithiobis(trimethylsilane) (34) (407 mg, 1.71 mmol) in 1,2-dichloroethane (5 mL) was heated with stirring at 80°C for 13 h. The mixture was cooled, washed with aqueous 10% $NaHCO_3$, dried, filtered, and concentrated. The residue was loaded on a silica gel plug with chloroform. After removal of sulfur-containing compounds by elution with chloroform, the product was eluted with ethyl acetate. Concentration of the ethyl acetate solution gave a 35% yield of **39**.

(*iii*) A similar reaction of **21** with a 2:5:1.5:1 molar ratio of 1,2-ethanedithiobis(trimethylsilane), zinc iodide, tetrabutylammonium iodide, and **21** for 3 h at 75°C gave dihydropyrone **38** and unconsumed **21** after work-up with aqueous 10% $NaHCO_3$.

(*iv*) A solution of **21** (8.27 g, 18.9 mmol), zinc iodide (15.84 g, 49.65 mmol), methylthiotrimethylsilane (12.44 g, 103 mmol), and tetra-*n*-butylammonium iodide (1.22 g, 3.30 mmol) in 1,2-dichloroethane (155 mL) was heated at 80°C for 1.5 h. During this time the solution became yellow. The solution was cooled, washed with 3 *N* hydrochloric acid (50 mL), dried, filtered, and concentrated. The residue was dissolved in chloroform and ether was added slowly to precipitate tetra-*n*-butylammonium iodide as white crystals. The solution was filtered and concentrated and the residue was chromatographed on silica with ethyl acetate as eluent. The first materials eluted were sulfur-containing compounds; **39** was then eluted (R_f = 0.4) and obtained as a viscous yellow gum which assumed a dark green color after being pumped on under high vacuum overnight (3.02 g, 38%); ir λ_{max}: 2.93, 5.74, 5.96 μm; ^{1}H nmr δ: 7.22 (m, 11H), 5.72 and 5.48 (2 s, 1H), 2.8–4.8 (m, 11H), 2.83 (t, J = 6 Hz, 2H), 2.07, 1.95 (s, 3H). Its spectra indicated that this was a cleaner product than that obtained by procedure (*ii*).

*2-Acetoxy-*N*-benzyl-*N*-(2-benzylamino-2-oxoethyl)-3-[2-(tetrahydropyran-2-yloxy)ethyl]-3-butenamide (**40**) and 3-acetoxymethyl-*N*-benzyl-*N*-(2-benzylamino-2-oxoethyl)-5-(tetrahydropyran-2-yloxy)-2-pentenamide (**41**)*

A mixture of crude **39** (3.02 g, 7.11 mmol) and tetrahydropyran-2-yl *tert*-butyl ether (15 mL) in methylene chloride (5 mL) and three drops of concentrated hydrochloric acid was stirred for 18 h at room temperature. Solid $NaHCO_3$ and $MgSO_4$ were added and the mixture

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was filtered after stirring for a few min. The filtrate was concentrated under high vacuum and the residue was chromatographed on silica with 1:1 ethyl acetate – cyclohexane as eluent. A fraction (R_f = 0.4) was eluted after elution of residual tetrahydropyran-2-yl *tert*-butyl ether which was found to contain two components whose R_f values were very similar in a variety of solvent systems. It was re-chromatographed twice on silica with an increasing proportion of ethyl acetate (20%, 40%, 60%) in the ethyl acetate – cyclohexane eluent. The minor component (211 mg, 6%) with a slightly higher R_f was obtained as an orange gum and is considered to be **41**; ir λ_{max}: 5.75, 6.03 μm; ^{1}H nmr δ: 7.30 (m, 11H), 6.15, 5.38 (m, 1H), 3.2–5.4 (m, 13H), 2.50 (t, J = 6 Hz, 2H), 2.03, 1.95 (s, 3H), 1.13–1.80 (m, 6H); *m/e*: 449, 423, 394, 364, 255 (29), 253 (19), 91 (100).

Compound **40** was eluted last as a yellow gum (2.80 g, 77%), ir λ_{max}: 2.98, 5.71, 5.92 μm; ^{1}H nmr δ: 7.28 (m, 11H), 5.80 (s, 0.7H), 5.18 (s, 0.3H), 5.0–5.4 (m, 2H), 3.1–4.8 (m, 11H), 2.42 (t, J = 6 Hz, 2H), 2.10 (s, 1H), 2.03 (s, 2H), 1.0–1.8 (m, 6H); *m/e*: 423 (6), 364 (10), 120 (20), 106 (31), 91 (100). *Accurate Mass* calcd. for $C_{24}H_{27}N_2O_5$ (M − C_5H_9O): 423.1920; found: 423.1927.

N-*Benzyl*-N-*(2-benzylamino-2-oxoethyl)-2-hydroxy-3-[2-(tetrahydropyran-2-yloxy)ethyl]-3-butenamide (42)*

Compound **40** (2.53 g, 4.99 mmol) and sodium hydroxide (203 mg, 5.10 mmol) in absolute ethanol (50 mL) were stirred for 8 h at room temperature. An analogous work-up to that used in the preparation of **24** gave a quantitative yield of **42** as a viscous yellow gum; ir λ_{max}: 2.91, 5.98, 6.05 μm; ^{1}H nmr δ: 7.17 (m, 11H), 3.1–5.2 (m, 15H), 2.37 (m, 2H), 1.13–1.80 (m, 6H).

N-*Benzyl*-N-*(2-benzylamino-2-oxoethyl)-2-oxo-3-[2-(tetrahydropyran-2-yloxy)ethyl]-3-butenamide (43)*

Compound **42** (2.33 g, 4.99 mmol) was oxidized with activated manganese dioxide (15 g) in chloroform (150 mL) for 18 h at room temperature and worked up as in the case of **25** to give a quantitative yield of **43** as a pale yellow gum; ir λ_{max}: 2.97, 5.96, 6.08 μm; ^{1}H nmr δ: 7.27 (m, 10H), 6.73 (br s, 1H), 6.42 (m, 2H), 3.1–4.8 (m, 11H), 2.60 (t, J = 6 Hz, 2H), 1.1–1.8 (m, 6H); *m/e*: 380 (2), 363 (18), 272 (13), 181 (23), 91 (100). *Accurate Mass* calcd. for $C_{22}H_{24}N_2O_4$ (M − C_5H_8O): 380.1736; found: 380.1714.

3-Acetoxy-1,4-dibenzyl-3-[1-(2-(tetrahydropyran-2-yloxy)ethyl)-ethenyl]piperazine-2,5-dione (45)

A solution of MICA was prepared from magnesium (86 mg, 3.6 mmol), methyl bromide, and isopropylcyclohexylamine (0.6 mL) in dry tetrahydrofuran (60 mL) as in the previous cases. Compound **43** (1.274 g, 2.741 mmol) in dry tetrahydrofuran (10 mL) was syringed dropwise into the MICA solution at room temperature under nitrogen over a period of 3 h. The mixture was stirred for 15 h at room temperature during which time it turned cloudy. Acetic anhydride (0.80 mL, 8.5 mmol) was syringed into the reaction flask and the mixture was stirred for an additional 5 h at room temperature. The solution was poured into water (20 mL) and the aqueous solution was extracted with chloroform (4 × 25 mL). The combined chloroform extracts were dried, filtered, concentrated, and pumped on for 1 h under high vacuum. The residue was chromatographed on silica with 60% ethyl acetate – cyclohexane as eluent. Compound **45** was eluted first (R_f = 0.57), the next fraction (R_f = 0.43) was acetylated isopropylcyclohexylamine, and the final fraction (R_f = 0.36) contained uncharacterized polymeric products. Compound **45** was obtained as a pale yellow gum (878 mg, 63%); ir λ_{max}: 5.76, 5.99 μm; ^{1}H nmr δ: 7.27 (s, 5H), 7.23 (s, 5H), 5.70 (s, 1H), 5.47 (s, 1H), 3.3–5.4 (m, 11H), 2.33 (t, J = 6 Hz, 2H), 1.4–1.8 (m, 6H), 1.33 (s, 3H); *m/e*: 506 (1), 422 (7), 363 (11), 271 (8), 106 (24), 91 (93), 84 (100). *Accurate Mass* calcd. for $C_{29}H_{34}N_2O_6$: 506.2417; found: 506.2411.

3-Acetoxy-1,4-dibenzyl-3-(3-hydroxy-1-methylenepropyl)piperazine-2,5-dione (46) and 6,9-dibenzyl-4-methyleneoxa-6,9-diazaspiro-[4.5]decane-7,10-dione (47)

A solution of **45** (878 mg, 1.73 mmol) in acetic acid (15 mL), water (6 mL), and tetrahydrofuran (3 mL) was stirred for ~15 h at room temperature. The solvent was removed *in vacuo* and the residue was chromatographed on silica with 60% ethyl acetate – cyclohexane as eluent. The initial fraction (R_f = 0.57) returned unconsumed **45** (25 mg). The second fraction (R_f = 0.45) gave **47** (153 mg, 21%), which was crystallized from ethanol–water, mp 93–95°C; ir λ_{max}: 5.97 μm; ^{1}H nmr δ: 7.25 (m, 10H), 5.25 (m, 1H), 4.95 (m, 1H), 3.9–4.8 (m, 8H), 2.87 (m, 2H); *m/e*: 362 (15), 271 (12), 229 (9), 124 (11), 91 (100). *Accurate Mass* calcd. for $C_{22}H_{22}N_2O_3$: 362.1630; found: 362.1643.

The final fraction (R_f = 0.27) gave **46** as a colorless gum (425 mg, 58%); ir λ_{max}: 2.90, 5.70, 5.95 μm; ^{1}H nmr δ: 7.28 (s, 5H), 7.23 (s, 5H), 5.67 (s, 1H), 5.47 (s, 1H), 3.6–5.4 (m, 8H), 2.93 (br s, 1H), 2.33 (t, J = 6 Hz, 2H), 1.30 (s, 3H); *m/e*: 363 (3), 272 (3), 230 (2), 91 (22), 83 (100). *Accurate Mass* calcd. for $C_{22}H_{23}N_2O_3$ (M − $C_2H_3O_2$): 363.1709; found: 363.1704.

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