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New synthetic methodology using organosulfur compounds

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Abstract– Electron-deficient 3-sulfur-substituted 2-pyrones are shown to cycloadd with high stereoselectivity to electron-rich vinylic ethers, vinylic thioethers, and 1,3-dioxoles under sufficiently mild conditions to allow isolation of the initial, bridged, bicyclic lactone adducts. These structurally and stereochemically rich bicycloadducts are easily converted into highly functionalized cyclohexenes as exemplified by high yield syntheses of chorismic acid, 4-epi-shikimic acid, and also 1α, 25-dihydroxyvitamin D_3.

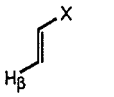
INTRODUCTION

During the past two decades, my research group at Johns Hopkins has been developing organosulfur chemistry in various ways. Highlights include the following topics: (1) development of mixed phenylthio(alkyl)cuprate reagents for selective transfer of alkyl groups in coupling and in conjugate addition reactions;[1] (2) study of organocuprate reactions with β-alkylthio-α, β-enones,[2] with α, β-ethylenic sulfones,[3] and with enantiomerically pure α-sulfinyl-α, β-enones[4] leading, for example, to highly enantiocontrolled total syntheses of natural estrone[4k] and natural β-vetivone;[4n] (3) selective oxidation of β-hydroxysulfides into β-ketosulfides on alumina surfaces;[5] (4) selective opening of epoxides by thiols adsorbed to alumina;[6] (5) mechanistic and synthetic study of sulfonate ester elimination reactions effected by chromatographic alumina;[7] (6) mechanistic study of organocopper substitution reactions with some unsaturated tosylate esters suggesting that cuprate substitutions can resemble solvolysis reactions in some cases;[8] (7) photochemical deoxygenation of aryl sulfoxides;[9] (8) generation and reaction of 1-(arylsulfinyl) alkenyllithium reagents as a means of preparing terminal allenes;[9] (9) stereocontrolled preparation of chiral, non-racemic E-1-alkenyl sulfoxides and reduction to the corresponding sulfides;[10] (10) development of a high-yield, one-flask procedure using (diethylamino)sulfur trifluoride (DAST) for replacement of an anomeric hydroxyl group by a fluorine atom;[11] (11) α-fluorination of β-keto sulfoxides;[12] and (12) an additive Pummerer rearrangement of vinylic sulfoxides using dichloroketene for asymmetric synthesis of (-) -methyl jasmonate.[13] In recent years, we have studied inverse-electron-demand Diels-Alder cycloadditions using electron-deficient 3-sulfur-substituted 2-pyrones and 2-pyridones, and this is the topic described in detail in the following discussion.

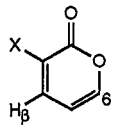
A sulfonyl group stabilizes an adjacent carbanionic center about as well as a carboxylate ester does.[14a] For example, the thermodynamic acidity of aliphatic sulfones (pKa≈23-25) is approximately the same as (or slightly higher than) that of aliphatic carboxylate esters, and the acidity of 1,1-bissulfonylmethane (pKa≈13) approximates that of malonate esters.[14] In sharp contrast, however, sulfinyl and especially sulfonyl groups are considerably more inductively electron withdrawing than carboxylate ester groups.[14] For example, the comparison shown here of data accumulated over the years in our laboratory

for ^{1}H NMR chemical shifts of the hydrogen atoms attached to the sp^2-carbon atoms of conjugated unsaturated sulfoxides, sulfones, and the corresponding carboxylate esters[15] indicate that H_β is more deshielded (i.e. lower δ values and therefore lower electron density) in the sulfoxides and especially in the sulfones than in the esters (Table I). NMR ^{13}C data support this conclusion also.

Table 1.

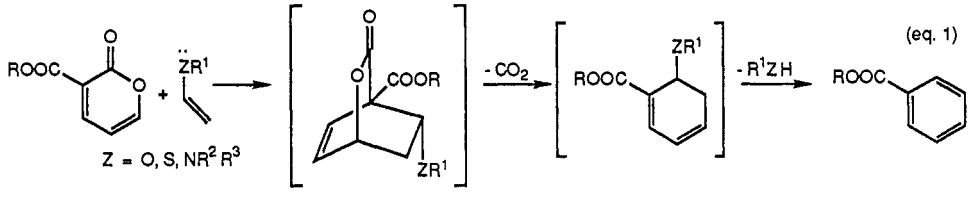


X	δH_β
MeOOC	5.82
PhOS	5.90
PhO_2S	6.03



X	δH_β	δC_6
H	7.3	151.7
MeOOC	7.7	156.5
TolOS	8.1	——
$TolO_2S$	8.4	157.1

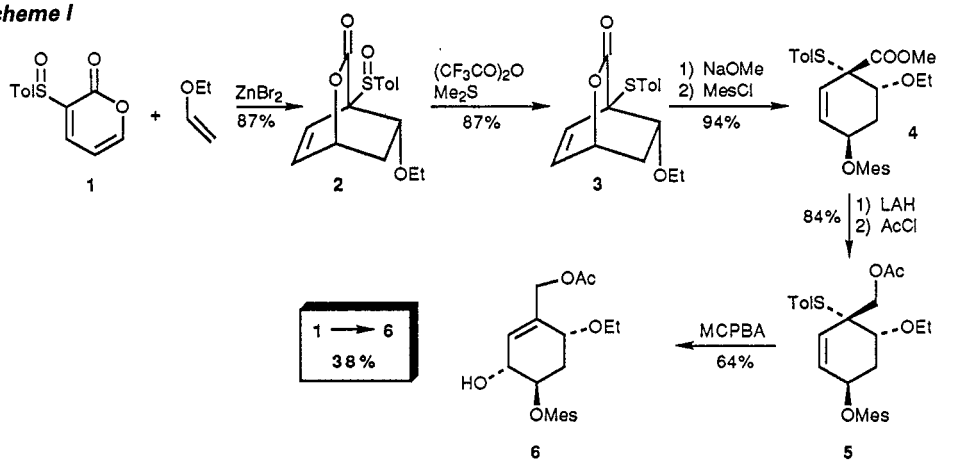
We have used this information in designing new synthetic methodology for inverse-electron-demand Diels-Alder cycloadditions using electron-deficient 2-pyrones and 2-pyridones. 3-Alkoxycarbonyl-2-pyrones enter into inverse-electron-demand 2+4-cycloadditions with electron-rich olefins, but in most instances the temperatures required for cycloadditions are so high (typically >150°C) that in situ extrusion of CO_2 from the lactone bridge of the initial cycloadducts occurs spontaneously, often forming aromatic products (eq. 1).[16] Indeed such cycloadditions-cycloreversions have been used intentionally to convert 2-pyrones into a variety of aromatic target compounds.[17] 3-Sulfinyl-2-pyrones and especially 3-sulfonyl-2-pyrones, being more electron-deficient dienes than the corresponding 3-alkoxycarbonyl-2-pyrones, seemed to us to be excellent candidates for Diels-Alder reaction with electron-rich olefins leading to isolable, bridged, bicyclic lactone (i.e. non-aromatic) adducts. Such rigid, highly functionalized cycloadducts carrying considerable structural and stereochemical information would be versatile building blocks for elaboration into various classes of interesting and/or useful complex target compounds. A description of our research in this area follows.



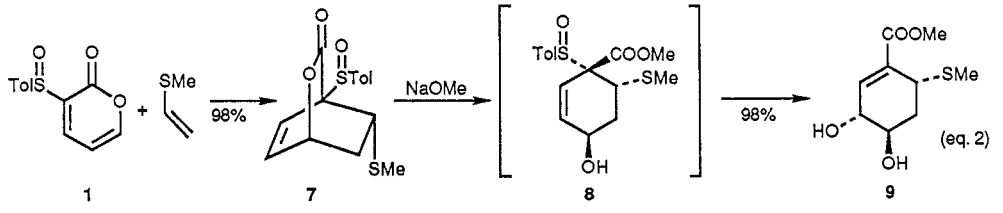
RESULTS AND DISCUSSION

Pyrone sulfoxide **1**,[18] prepared in 5 steps from commercially available 5,6-dihydro-2-pyrone,[18] reacted with ethyl vinyl ether in the presence of zinc dibromide at room temperature for 3 days to form bicyclic lactone sulfoxide **2** as a 10:1 endo/exo mixture in very high yield. Methanolysis of the lactone bridge under a variety of conditions leading to a cyclohexenyl allylic sulfoxide failed to produce acceptable yields of an allylic alcohol via a [2,3]-sigmatropic rearrangement. Therefore an indirect path was explored. Reduction of bicyclic sulfoxide **2** to bicyclic sulfide **3** proceeded smoothly.[19] Methanolysis and mesitoylation gave polysubstituted cyclohexene **4** cleanly and in high yield. Reduction of the methyl ester and acetylation produced protected allylic sulfide **5**. Sulfide→ sulfoxide oxidation with *m*-chloroperbenzoic acid and spontaneous [2,3]-sigmatropic rearrangement gave allylic alcohol **6** (Scheme I). The overall yield of allylic alcohol **6** in eight steps from pyrone sulfoxide **1** was 38%. *This regiospecifically tetrasubstituted, stereospecifically trioxygenated cyclohexene represents a complex, versatile synthon in which four hydroxyl groups are present in different forms, (i.e., free OH, ether, acetate ester, and mesitoate ester), and therefore these four oxygen functionalities can be manipulated independently.*

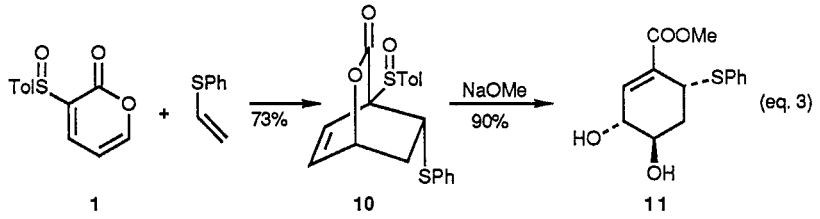
Scheme I



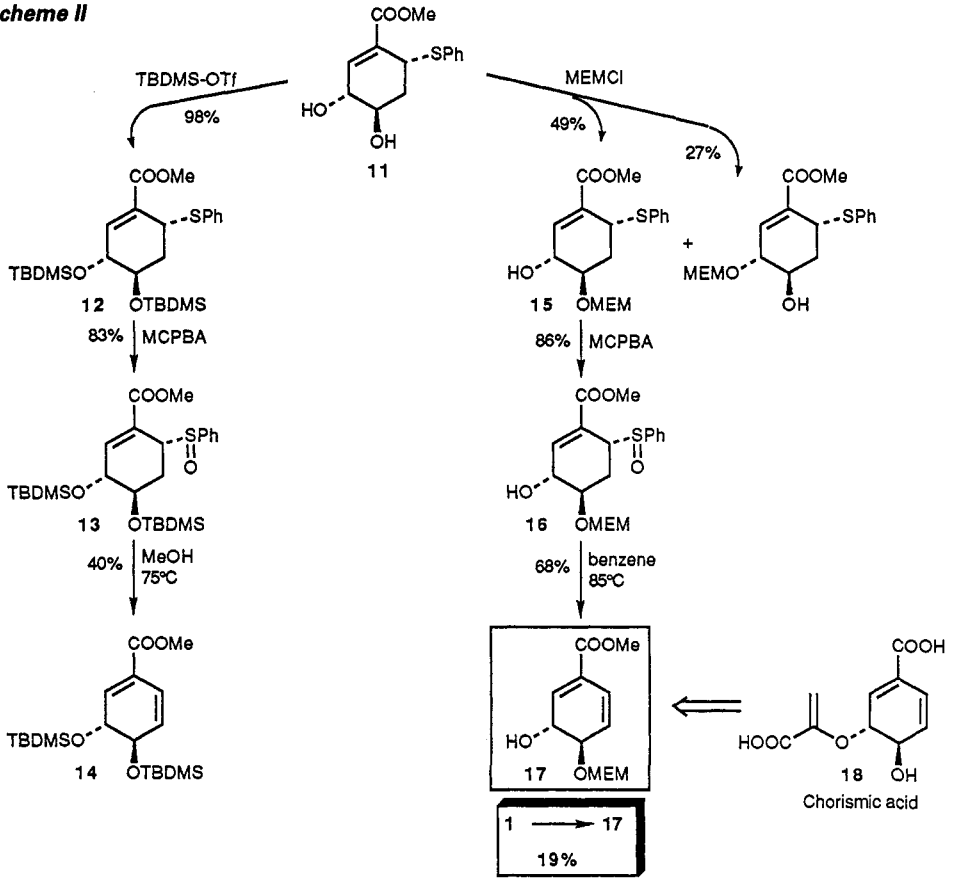
Medium and high pressures usually facilitate reactions with negative volumes of activation such as Diels–Alder cycloadditions.[20] Although pyrone sulfoxide **1** failed to react with methyl or phenyl vinyl *thio*ethers in the presence of zinc dibromide at room temperature, highly successful room temperature 2+4 cycloaddition occurred at 6.8 Kbar, as illustrated by eq 2, with methyl vinyl thioether.[21] Only the *endo*-methylthio cycloadduct **7** was produced. Methanolysis of the bridged bicyclic lactone sulfoxide **7** produced in situ allylic sulfoxide **8**, which spontaneously underwent an efficient [2,3]-sigmatropic rearrangement to polysubstituted cyclohexene *trans*-diol **9** in only two steps and in 96% overall yield from pyrone sulfoxide **1**. *This two-step high yield procedure represents an effective conversion of an aromatic α-pyrone into a non-aromatic, regiospecifically tetrasubstituted, stereospecifically trans-dihydroxylated cyclohexene.*



Phenyl vinyl thioether also underwent highly diastereoselective but somewhat longer room temperature, 6.8 kbar, 2+4 cycloaddition with pyrone sulfoxide **1** (eq 3). Only the *endo*-phenylthio adduct **10** was formed. Methanolysis was followed in situ by spontaneous [2,3]-sigmatropic rearrangement to form (phenylthio)cyclohexene *trans*-diol **11** in 66% overall yield from pyrone sulfoxide **1**. All attempts failed to derivatize the secondary hydroxyl group liberated by methanolysis of the lactone *before* [2,3]-sigmatropic rearrangement. Having used the sulfinyl group in pyrone sulfoxide **1** as a precursor to the allylic hydroxyl group in *trans*-diol **11**, we now wanted to use the phenylthio group from the phenyl vinyl thioether as a precursor to a regiospecifically placed carbon–carbon double bond with the aim of preparing a chorismic acid intermediate; sulfide→ sulfoxide oxidation followed by pyrolysis was thought to meet these requirements, but first protection of the diol functionality was carried out.



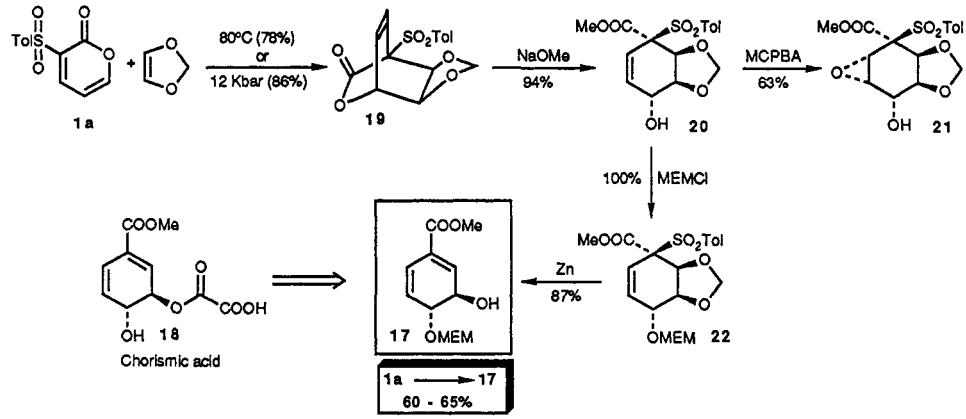
Scheme II



Silylation proceeded without difficulty to produce bis-silyl ether **12** (Scheme II). Peracid oxidation led cleanly to sulfoxide **13**, which was pyrolyzed in methanol at 75° C to form cyclohexadiene *trans*-diol derivative **14**. Selective monoprotection of the homoallylic hydroxyl group in *trans*-diol **11** led to MEM ether derivative **15**, which was oxidized into sulfoxide **16**. Pyrolysis of this cyclohexadienyl sulfoxide in methanol at 75° C led to monoprotected cyclohexadiene *trans*-diol **17**, previously converted into chorismic acid (**18**),[22] a key intermediate in the shikimate biosynthetic pathway that bacteria and lower plants use to convert carbohydrates into aromatic compounds.[23] Preparation of diol **17** in only five steps and in 19% overall yield from pyrone sulfoxide **1** represents a short formal total synthesis of racemic chorismic acid.[24] Attempts to prepare enantiomerically pure pyrone sulfoxide **1** were not very promising.[24]

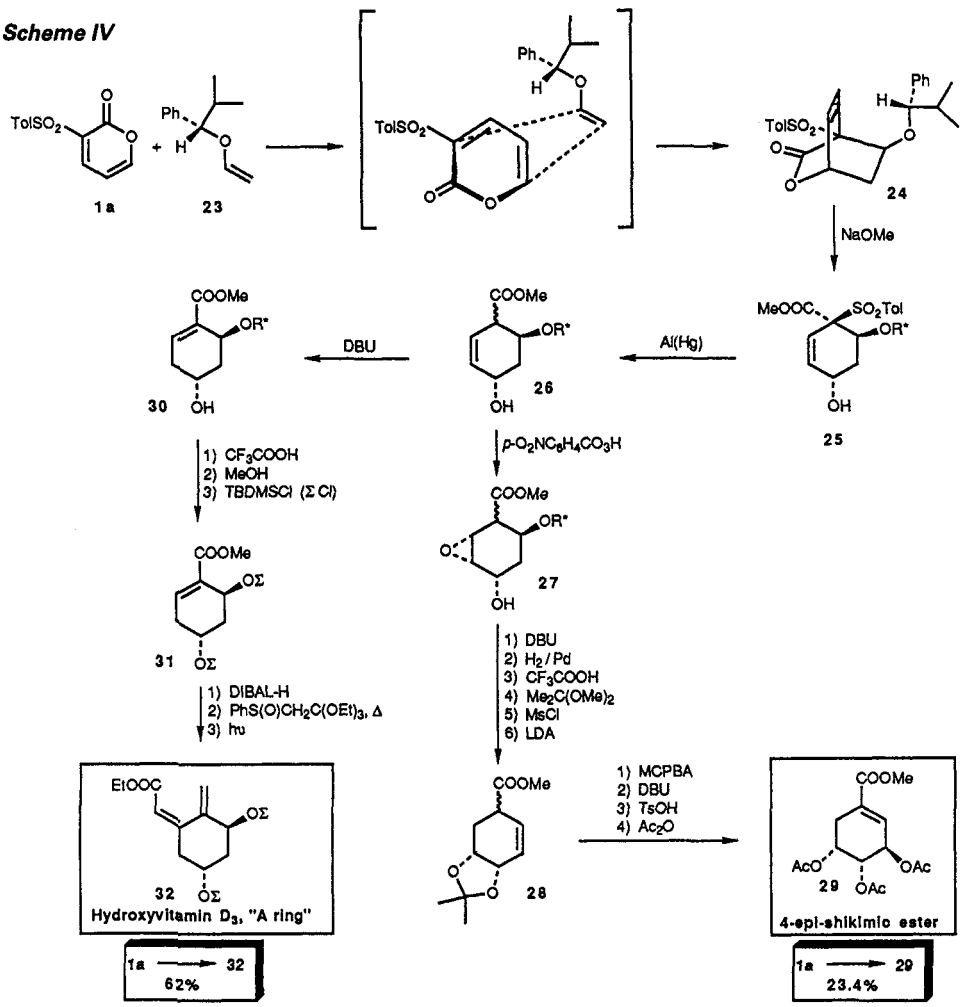
We have recently developed an even more efficient route to chorismic acid involving either thermal or high pressure inverse-electron-demand 2+4-cycloaddition between electron-deficient pyrone sulfone **1a** and electron-rich 1,3-dioxole (Scheme III). The higher electron-deficiency of 3-sulfonyl-2-pyrone **1a** compared to that of the corresponding pyrone sulfoxide **1** was required for successful cycloaddition with 1,3-dioxoles. The rigid, bridged, bicyclic lactone **19** produced in this way was easily methanolyzed into the corresponding six-membered carbocycle **20** in which every ring carbon atom is functionalized. To illustrate some of the rich potential of such systems for further chemical modification, stereocontrolled epoxidation *cis* to the directing allylic hydroxyl group produced 1, 2, 3, 4, 5-*pentaoxygenated* cyclohexane pseudosugar **21**. Protection of alcohol **20** formed the corresponding MEM-ether **22**. Reductive cleavage of the ring sulfonyl linkage then caused spontaneous unzipping of the neighboring dioxolane unit to yield cyclohexadiene mono-protected *trans*-diol **17** that has previously been converted into (±)-chorismic acid. This overall sequence (Scheme III), proceeding in 60–65% overall yield and in only 4 steps from the pyrone sulfone, represents the shortest synthetic approach to racemic chorismic acid on record.[25]

Scheme III



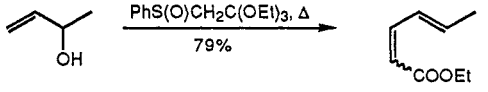
Perhaps most significant among our recent results is the discovery that pyrone sulfone **1a** cycloadds to some chiral, non-racemic vinyl ethers with outstanding levels of asymmetric induction. For example, cycloaddition with vinyl ether (S)-**23** gave bridged bicyclic lactone **24** on gram-scale as an 11.5:1.0 ratio of diastereomers at room temperature,[26] and at -45°C in the presence of an aluminum catalyst vinyl ether (S)-**23** gave lactone **24** on gram-scale as a 49:1 ratio of diastereomers in excellent yield (Scheme IV).[27] This stereochemical result is noteworthy not only because of its extraordinary level of absolute stereocontrol but also because the inducing chiral center is not bound rigidly to (i.e. no restricted rotation about) the reaction center.

Scheme IV



This chemical outcome is noteworthy because it provides a convenient, mild and short synthesis of highly functionalized cyclohexenes on preparatively useful scale and in extremely high enantiomeric purity. We have illustrated some of the considerable potential of this methodology by applying it also to asymmetric synthesis of 4-epi-shikimic acid ester,[26] an intermediate used to prepare (-)-chorismic acid, and to asymmetric synthesis of hormonally active 1α, 25-dihydroxyvitamin D_3 (Scheme IV).[27]

Key features in the asymmetric synthesis of shikimic ester **29** (Scheme IV) include the following: (1) peroxidation of allylic alcohol **26** with 40:1 selectivity for formation of the *cis*-epoxy alcohol **27**, and (2) peroxidation of protected allylic alcohol **28** with at least 60:1 selectivity for formation of the corresponding *trans*-epoxy alcohol. Key features in the asymmetric synthesis of the dihydroxyvitamin D_3 A-ring **32** (Scheme IV) include the following: (1) trifluoroacetolysis of allylic benzylic ether **30** chemospecifically at the benzylic linkage, and (2) one-flask, tandem Claisen rearrangement-sulfoxide pyrolysis using a new sulfinyl orthoester to form directly chiral, non-racemic dienoate ester **32** that has been converted previously into natural 1α, 25-dihydroxyvitamin D_3. Initial results suggest some generality for the tandem Claisen rearrangement-sulfoxide pyrolysis to convert allylic alcohols directly in one reaction vessel into 2-carbon extended dienoate esters (see eq. 4).[27] It is especially noteworthy that 4-epi-shikimic acid ester **29** was prepared from pyrone sulfone **1a** *via* Scheme IV in 14 steps, in 23.4% overall yield, and in at least 98% enantiomeric purity. Likewise, the A-ring synthon **32** of hormonally active 1α, 25-dihydroxyvitamin D_3 was prepared via Scheme IV in 9 steps, in 62% overall yield, and in virtually complete enantiomeric purity.



(eq. 4)

CONCLUSION

In conclusion, the strong inductively electron-withdrawing character of sulfinyl and especially of sulfonyl groups allows such 3-sulfur-substituted 2-pyrones to enter into sufficiently mild 2+4-cycloadditions with electron-rich dienophiles so that the initial, *non-aromatic*, bicyclic, lactone adducts can be isolated in excellent yields. When a chiral, non-racemic dienophile is used in the presence of an aluminum Lewis acid catalyst, a cycloadduct is obtained in extremely high diastereomeric purity. These cycloadducts are versatile synthons and chirons for elaboration into a multitude of useful and/or interesting complex target compounds. We are actively pursuing such endeavors.

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