Synthesis and ^{13}C NMR Spectra of *cis*- and *trans*-{2-(Haloaryl)-2-[(1*H*-imidazol)-1-yl]methyl]}-1,3-dioxolane-4-methanols [1]

David R. Chapman and Ludwig Bauer*

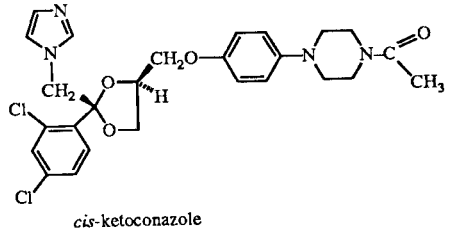
Department of Medicinal Chemistry, M/C 781, University of Illinois at Chicago, Chicago, Illinois 60680-6998

Received April 5, 1990

Syntheses and ^{13}C nmr spectra of a number of *cis* and *trans* 2-(haloaryl)-2-[(1*H*-imidazol-1-yl)methyl]-4-(hydroxymethyl)-1,3-dioxolanes are described. The haloaryl groups are 2,4-dichloro, 2,4-difluoro-, 4-chloro- and 4-bromophenyl. In these series, some of the *cis* compounds become available through crystalline bromo benzoates **5**. Separations of some *trans* isomers are achieved through fractional crystallizations of imidazolyl benzoate nitrates **6**. Stereochemical assignments are based primarily on one major ^{13}C chemical shift difference, namely that of C-4 of the 1,3-dioxolane ring, the chemical shift of the *trans* isomers being 1.0-2.5 ppm downfield from that of the *cis* isomers.

J. Heterocyclic Chem., **27**, 2053 (1990).

In order to synthesize some analogs of the oral antifungal agent ketoconazole [2], we required a number of pure *cis* and *trans* {2-(haloaryl)-2-[(1*H*-imidazol-1-yl)-methyl]-1,3-dioxolane}-4-methanols **7**, and the corresponding diastereomeric sulfonates **8**. The side chain of ketoconazole can be built up from **8** without introducing additional asymmetric centers.



cis-ketoconazole

This paper addresses some aspects of the syntheses and separations of pure diastereomeric dioxolanes, **2** to **8**, with haloaryl groups such as 2,4-dichloro-, 2,4-difluoro, 4-chloro- and 4-bromophenyl. While a number of pure *cis* isomers in these series have been well characterized, preparative methods of separation and physical data for the corresponding *trans* isomers are either very sparse, or missing. Excellent procedures have been developed for the isolation of *cis*-2-(2,4-dichlorophenyl)-2-[halomethyl or (1*H*-imidazolyl)methyl]-1,3-dioxolanes **4a-8a** which are pivotal intermediates for the synthesis of *cis*-ketoconazole [3-5]. This work elaborates on the relatively few experimental details available for the isolation and characterization of intermediates leading to *trans*-ketoconazole [3], and related haloaryldioxolanes. Although reliable ^{13}C nmr data identifying some of the *cis* and *trans* isomers have been reported recently [6], these investigators fail to provide additional experimental details on the separation of their diastereomers.

Ketalization of commercially available acetophenones (*e.g.*, **1**, **3**, or **12**) with glycerol provides dioxolanes which are precursors for **7** [3,7]. An attractive one-step synthesis of **7** from 1-aryl-2-(1*H*-imidazol-1-yl)ethanones **13** was explored but was associated with problems which are discussed below. Such starting materials **13** are available from the well-versed alkylation of imidazole by phenacyl halides **12** [8,9]. In our experiments, the formation of **13** is accompanied by quaternary salts **14**. These salts had been noticed before because reference is made to the fact that the use of ethanol as a solvent for the alkylation encourages the formation of **14** [8]. A more recent paper mentions that the use of aprotic solvents minimizes the formation of **14** [9]. But neither paper reports the isolation or physical data on these quaternary salts **14**. In three of the four reaction sequences in cold DMF, **14** was readily isolated and their structure proved by microanalyses and nmr spectra.

Although ketalization of **13** with a number of 1,2-diols proceeds well [7], problems arise when glycerol becomes the reagent. For one, *ortho*-halo substituted acetophenones react sluggishly, or not all [7]. To promote ketal formation, prior investigators added 1-butanol to increase the yields of 1,3-dioxolanes, but these were usually contaminated by all kinds of extraneous by-products, possibly butyl ethers and acetals, as evidenced by the presence of various and sundry nmr signals attributable to *O*-*n*-butyl groups. We found that by omitting 1-butanol, the 4-chloro and 4-bromo analogs of **13** reacted with glycerol to form good yields of **7**, but 2,4-dichloro and 2,4-difluoro analogs gave poor yields of **7**, in spite of longer reaction times or higher temperatures. But the real problem is that the diastereomers of **7**, which are the end of the reaction sequence, could not be separated.

We examined literature syntheses of **7** for stages at which intermediate *cis* and *trans* dioxolanes could be separated. One of the most general synthetic schemes (Chart 1) starts with the ketalization of a ring halo-substituted acetophenones **1** or phenacyl halides **3** with glycerol in either benzene or toluene, using 4-toluenesulfonic acid (TsOH) as catalyst, to furnish a mix-

Chart 1

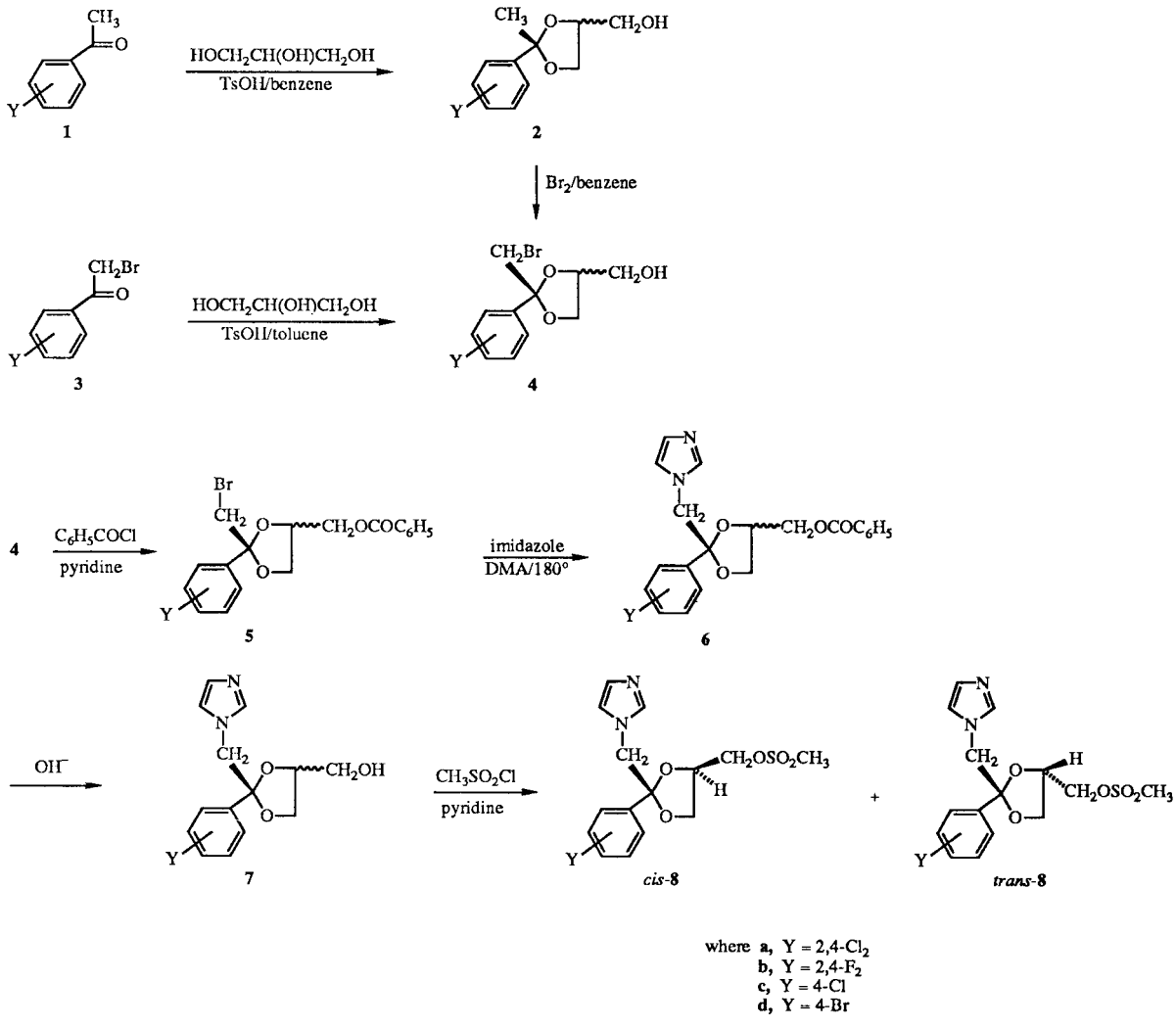
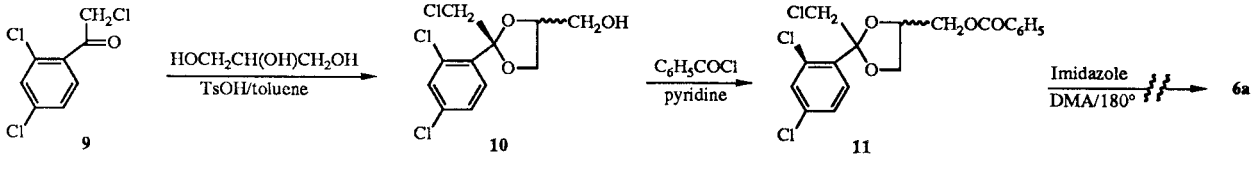


Chart 2

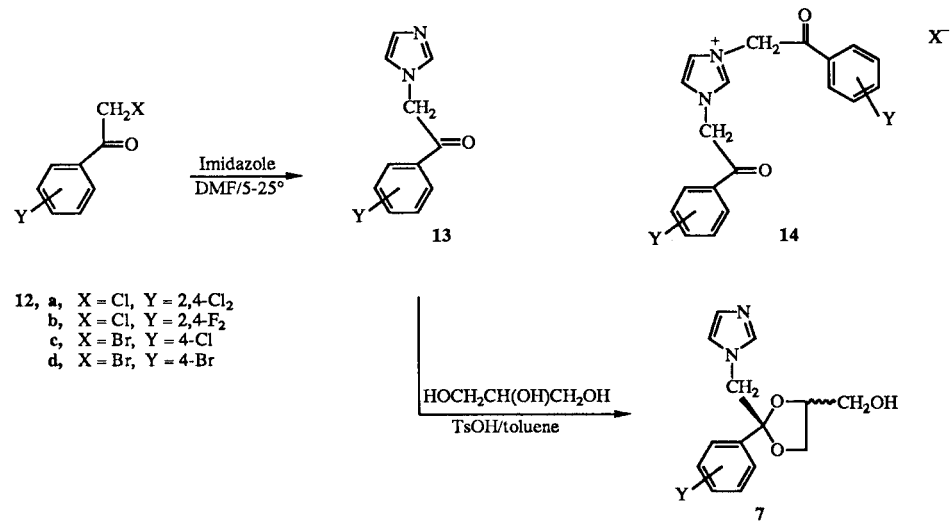


ture of *cis* and *trans* trisubstituted 1,3-dioxolanes, **2** or **4**, respectively. 1-Butanol was omitted and excellent yields of **2** (or **4**) were obtained. Benzene was retained as solvent only for those ketalizations which were followed by bromination in the same medium.

Conversion of **2** to **5** can be achieved in two ways. The literature method functionalizes the methyl group by bromination of **2** to form **4**, which need not be isolated, but can be benzoylated immediately to provide **5**. An alternate procedure was examined briefly in the 2,4-dichlorophenyl series: benzoylation of **2** first, followed by bromination also leads to **5**. This method proved to be more cumbersome since the benzoate of **2** needed to be purified, prior to bromination. A more facile synthesis of **5** consists of the ketalization of commercially available phenacyl bromides **3** to form **4**, which then eliminates the bromination step [7].

It should be noted that the products from the various ketalizations (of **1**, **3**, or **9**) with glycerol yield only the five-membered ketals, This is contrast to the reaction of benzaldehyde with glycerol which furnishes a mixture consisting approximately of equal amounts of *cis* and *trans*

Chart 3



2-phenyl-4-hydroxymethyl-1,3-dioxolanes, and *cis* and *trans* 2-phenyl-1,3-dioxan-5-ols [10]. It is conceivable that the methyl group (in acetophenone, compared to benzaldehyde) provides sufficient steric encumbrance to prevent the formation of the six-membered ketal and the formation of the five-membered ketals is thermodynamically favored. In most of the ketalizations reported here, the *cis* isomer is formed in slight excess (about, 60:40, *cis* to *trans*, by nmr). To substantiate that the thermodynamically favored product is formed, **3a** was boiled in toluene with new anhydrous 4-toluenesulfonic acid (24 hours) which did not change the nature of the diastereomeric mixture.

In the four series, *cis* and *trans* bromo alcohols **4**, no attempt was made to isolate or separate the isomers, but these were esterified immediately with benzoyl chloride to form **5**. In the 2,4-dichlorophenyl series, fortuitously, the *cis*-bromo benzoate **5a** crystallizes out in good yield when the crude reaction mixture is diluted with methanol [4] (but, not with ethanol, or many of the other common alcohols, or solvents). The mother liquor, now enriched with *trans*-**5a**, was chromatographed repeatedly but further separation of diastereomers was not achieved on either silica or alumina [11].

In three of the four series, a vital *trans* intermediate could be isolated in the next step of the sequence. Displacement of the bromo group of **5** by imidazole took place in boiling *N*,*N*-dimethylacetamide (165°, 48-72 hours) [3,7] to form **6**. The yield of **6** was not improved by using the imidazole anion instead of imidazole. Although the displacement took place under somewhat forcing conditions, it is still surprising that this substitution at a neopentyl carbon worked so well. When mixtures of *cis* and *trans* **6** were neutralized with nitric acid, some of the resultant nitrates of **6** could be fractionally crystallized.

One attractive alternate route was the conversion of the relatively inexpensive and commercially available 2,2',4'-trichloroacetophenone (**9**) to **6a**. Ketalization of **9** with glycerol, followed by benzoylation provided an excellent yield of **11**. Pure *cis*-isomer of **11** readily crystallized from the reaction mixture. However, many attempts to displace the chloro group in *cis*-**11** by imidazole to form *cis*-**6a**, failed. Unlike the bromo analogs, the chloro group on **11** was just inert to displacement, with or without added iodide ion, or silver fluoborate (to simulate a potential S_N1 type of displacement) [12], *cis*-**6a** being recovered in good yield Elevating the reaction temperature just caused destruction of some the starting material, but no product was obtained.

Hydrolysis of the benzoates **6** furnished alcohols **7** and subsequent acylations with methanesulfonyl chloride formed **8**, without problems. Alcohols **7a** also reacted readily with 4-toluenesulfonyl chloride to furnish the corresponding 4-toluenesulfonate. Nucleophilic displacements of the sulfonates by phenoxide ions from appropriate piperazinophenols leads to ketoconazole and analogs and these syntheses are the subject of the following paper [13].

Identification of Diastereomers.

Proton nmr spectra of the diastereomers were obtained routinely and served as a check on the correct proton distribution within the framework of the expected spin-spin patterns. However, proton chemical shifts and coupling constants were not analyzed completely for all compounds due to the complexity of the spin systems. The well-separated signals in the ^{13}C nmr spectra lent themselves to chemical shift assignments. The ^{13}C nmr data was compatible with established chemical shifts for

Table 1

Carbon-13 Chemical Shifts of Compounds 2-11

Chemical shifts measured downfield from tetramethylsilane in deuteriochloroform

Compound	1,3-Dioxolane					Imidazoyl					Halo-substituted Ar						Benzoate Ar			
	C-2	C-4	C-5	2-CH_2	4-CH_2	C-2	C-4	C-5	C=O	CH_3	1	2	3	4	5	6	1	2	3	4
2a-*cis*	108.9	76.1	65.7	25.5	63.1	–	–	–	–	–	138.0	134.6	128.9	132.8	126.8	131.2	–	–	–	–
2a-*trans*	108.9	77.5	66.1	25.9	62.8	–	–	–	–	–	138.0	134.6	128.2	132.6	127.0	131.1	–	–	–	–
4a-*cis*	107.0	76.8	66.4	35.7	62.5	–	–	–	–	–	133.1	131.3	129.5	133.1	127.0	131.7	–	–	–	–
4a-*trans*	107.6	79.0	66.9	36.2	62.1	–	–	–	–	–	134.5	131.7	130.5	131.8	127.0	131.3	–	–	–	–
5a-*cis* [a]	108.0	74.5	67.7	35.4	64.1	–	–	–	166.4	–	135.4	133.2	129.4	133.0	126.9	131.1	131.3	129.4	128.2	133.2
5a-*trans* [a]	108.0	76.4	67.1	36.1	62.6	–	–	–	165.4	–	135.8	134.6	130.1	133.1	127.1	131.4	131.4	129.9	128.6	133.4
6a-*cis* [a]	108.1	74.3	67.1	51.5	63.9	138.5	128.5	120.9	166.1	–	135.9	134.2	129.6	132.9	127.2	131.3	131.3	129.6	128.5	133.3
6a-*trans*	108.2	75.9	66.9	52.3	62.6	138.7	128.3	120.9	166.1	–	135.6	133.2	129.5	133.1	127.1	131.2	131.2	129.4	128.3	133.2
7a-*cis* [a]	107.6	77.1	66.9	51.4	61.9	139.8	128.2	121.3	–	–	135.9	134.8	129.7	133.0	127.3	131.4	–	–	–	–
7a-*trans*	107.8	78.6	67.1	52.3	61.7	138.5	128.3	120.9	–	–	135.6	135.6	129.2	132.6	127.2	131.1	–	–	–	–
8a-*cis* [a]	108.4	73.9	67.6	51.0	66.4	138.8	128.3	121.1	–	37.5	136.1	133.9	129.4	132.9	127.3	131.4	–	–	–	–
8a-*trans*	108.5	75.0	67.0	52.0	66.6	138.5	128.7	120.6	–	37.3	135.8	130.9	129.3	132.6	127.2	131.0	–	–	–	–
10-*cis*	107.7	76.8	66.5	46.8	62.4	–	–	–	–	–	135.5	134.5	129.9	132.9	126.9	131.1	–	–	–	–
10-*trans*	108.1	78.8	67.0	47.4	62.0	–	–	–	–	–	135.4	135.3	129.6	132.5	126.9	130.9	–	–	–	–
11-*cis*	108.5	74.4	67.5	46.7	64.0	–	–	–	166.2	–	135.7	134.6	129.6	133.0	126.9	130.1	131.3	129.7	128.5	133.3
11-*trans*	108.4	76.3	67.2	47.7	62.7	–	–	–	165.8	–	135.7	132.8	129.4	131.1	126.8	129.6	130.9	129.3	128.1	133.0
4b-*cis*	106.1	77.1	66.7	36.3	62.3	–	–	–	–	–	122.0	163.5	105.0	160.2	111.0	129.4	–	–	–	–
4b-*trans*	107.0	78.8	67.3	36.8	62.1	–	–	–	–	–	123.1	163.5	104.8	160.2	111.0	129.1	–	–	–	–
5b-*cis*	107.0	74.8	67.7	35.9	64.0	–	–	–	166.1	–	122.0	163.5	104.9	160.0	110.8	129.5	130.5	129.7	128.4	133.2
5b-*trans*	107.1	76.3	67.5	37.0	62.9	–	–	–	159.9	–	123.0	163.5	104.7	160.0	111.0	129.1	130.1	129.4	128.2	133.1
6b-*cis*	107.1	74.5	67.3	52.4	63.9	138.6	128.3	120.9	166.0	–	122.0	163.6	105.1	160.0	111.1	129.2	129.6	129.6	128.4	133.3
6b-*cis* [b]	106.9	74.2	66.5	51.5	64.1	138.4	128.7	121.0	165.6	–	122.4	163.0	105.0	159.4	111.2	129.6	129.3	129.3	127.3	133.4
6b-*trans*	107.5	75.8	67.1	53.1	62.6	138.7	128.2	120.9	165.9	–	122.7	163.5	104.8	160.0	111.1	129.0	129.4	129.2	128.8	133.2
6b-*trans* [b]	107.1	75.5	66.7	52.1	62.7	138.5	127.9	120.9	165.3	–	123.3	162.9	104.7	159.8	111.0	129.0	129.3	129.0	128.4	133.1
6b-*cis* [c]	105.8	74.2	66.4	52.5	64.0	137.0	123.9	119.2	165.4	–	121.7	163.1	105.3	159.8	111.5	129.0	129.2	129.2	128.5	133.6
6b-*trans* [c]	106.2	75.8	66.2	53.4	62.5	136.9	123.8	119.5	165.2	–	122.4	163.0	105.1	159.7	111.5	129.2	129.0	129.0	128.5	133.4
7b-*cis*	106.7	77.3	66.9	52.1	61.9	138.9	128.2	121.2	–	–	122.1	163.8	105.1	161.2	111.2	129.2	–	–	–	–
7b-*trans*	106.9	78.5	67.5	53.0	61.4	138.3	127.9	120.8	–	–	123.1	163.3	104.5	159.9	110.9	128.8	–	–	–	–
8b-*cis*	107.0	73.7	67.4	51.3	66.0	138.3	127.9	120.7	–	36.9	121.1	163.2	104.6	159.7	110.8	128.6	–	–	–	–
8b-*trans*	107.3	74.8	67.1	52.5	66.4	138.2	128.3	120.5	–	36.9	122.1	163.2	104.5	159.7	110.9	128.4	–	–	–	–
4c-*cis*	106.9	76.6	66.2	37.6	62.6	–	–	–	–	–	134.9	127.4	128.5	137.5	–	–	–	–	–	–
4c-*trans*	107.6	79.0	67.1	38.4	62.1	–	–	–	–	–	134.7	127.0	128.6	138.7	–	–	–	–	–	–
5c-*cis* [a]	107.7	74.3	67.5	37.2	64.1	–	–	–	166.1	–	134.9	127.5	128.6	139.8	–	–	129.7	129.7	128.4	133.2
5c-*trans* [a]	108.0	76.6	67.4	38.7	63.0	–	–	–	166.1	–	134.8	127.4	128.2	138.7	–	–	130.9	129.5	128.3	133.2
6c-*cis*	108.2	74.4	67.2	54.0	64.1	138.6	128.5	120.8	166.0	–	134.7	127.0	128.7	138.6	–	–	129 .7	129.7	128.3	133.3
6c-*trans* [a]	108.5	76.0	66.9	54.7	62.8	138.6	128.3	120.8	166.0	–	134.9	127.1	128.7	138.7	–	–	129.7	129.7	128.3	133.3
7c-*cis*	107.6	77.0	66.5	53.6	62.1	138.8	128.6	121.0	–	–	135.1	127.2	128.0	137.9	–	–	–	–	–	–
7c-*trans*	108.0	79.2	67.3	54.7	62.0	138.8	128.3	120.9	–	–	135.0	126.8	128.3	138.7	–	–	–	–	–	–
8c-*cis*	108.0	73.9	67.8	53.5	66.2	138.2	128.8	121.4	–	37.2	135.1	125.9	127.1	136.8	–	–	–	–	–	–
8c-*trans*	108.1	75.2	67.2	54.6	66.8	138.1	128.7	121.1	–	37.3	135.2	126.2	126.9	137.7	–	–	–	–	–	–

Table 1 (continued)

Chemical shifts measured downfield from tetramethylsilane in deuteriochloroform

Compound	1,3-Dioxolane				1-Imidazoyl					Halo-substituted Ar						Benzoate Ar		
	C-2	C-4	C-5	2-CH_2	4-CH_2	C-2	C-4	C-5	C=O	CH_3	1	2	3	4	5	6	1	2	3	4
4d-*cis*	106.8	76.6	66.3	37.4	62.4	–	–	–	–	–	138.0	127.7	131.4	123.0	–	–	–	–	–	–
4d-*trans*	107.4	78.8	67.2	38.1	62.1	–	–	–	–	–	139.1	127.3	131.2	122.8	–	–	–	–	–	–
5d-*cis* [a]	107.8	74.3	67.5	37.2	64.1	–	–	–	166.1	–	138.4	127.9	131.5	123.0	–	–	131.1	129.7	128.4	133.6
5d-*trans* [a]	108.0	76.5	67.3	38.6	62.8	–	–	–	165.9	–	139.1	127.6	131.4	123.0	–	–	131.4	129.9	128.6	133.4
6d-*cis*	108.3	74.3	67.1	53.9	64.1	138.7	128.7	120.8	166.0	–	138.6	127.5	131.7	123.4	–	–	131.8	129.6	128.3	133.3
6d-*trans* [a]	108.4	75.9	66.9	54.6	62.7	138.7	128.3	120.9	166.0	–	138.6	127.3	131.6	123.3	–	–	131.6	129.4	128.3	133.3
7d-*cis*	107.7	77.0	66.5	53.6	62.1	138.5	128.1	121.1	–	–	138.8	127.6	131.7	123.3	–	–	–	–	–	–
7d-*trans*	107.9	78.7	67.2	54.7	61.9	138.4	128.3	120.9	–	–	139.4	127.7	131.6	123.1	–	–	–	–	–	–
8d-*cis*	108.6	73.9	67.8	53.4	66.3	138.7	128.5	121.2	–	37.5	137.7	127.5	131.9	128.5	–	–	–	–	–	–
8d-*trans*	108.7	75.1	67.2	54.4	66.9	138.6	128.3	120.7	–	37.4	138.5	127.2	131.6	123.6	–	–	–	–	–	–

[a] Identical to carbon-13 shifts reported by Suezawa *et al.* [Ref 6]. [b] The nmr spectrum taken in deuteriodimethyl sulfoxide. [c] The nmr spectrum of the nitrate in deuteriodimethyl sulfoxide.

Table 2

Carbon-13 Chemical Shift Differences of Compounds **2-11**

	1,3-Dioxolane Ring Carbons			Methylene C's on Ring	
trans-cis Isomers	DIF C-2	DIF C-4	DIF C-5	DIF 2-CH_2	DIF 4-CH_2
2a	0.0	1.4	0.4	0.4	-0.3
10	0.4	2.0	0.5	0.6	-0.4
4a	0.6	2.2	0.5	0.5	-0.4
4b	0.9	1.7	0.6	0.5	-0.2
4c	0.7	2.4	0.9	0.8	-0.5
4d	0.6	2.2	0.9	0.7	-0.3
11	-0.1	1.9	-0.3	1.0	-1.3
5a	0.0	1.9	-0.6	0.7	-1.5
5b	0.1	1.5	-0.2	1.1	-1.1
5c	0.3	2.3	-0.1	1.5	-1.1
5d	0.2	2.2	-0.2	1.4	-1.3
6a [a]	0.1	1.6	-0.2	0.8	-1.3
6b [a]	0.4	1.3	-0.2	0.7	-1.3
6b [b]	0.2	1.3	0.2	0.6	-1.4
6b [c]	0.4	1.6	-0.2	0.9	-1.5
6c [a]	0.3	1.6	-0.3	0.7	-1.3
6d [a]	0.1	1.6	-0.2	0.7	-1.4
7a	0.2	1.5	0.2	0.9	-0.2
7b	0.2	1.2	0.6	0.9	-0.5
7c	0.4	2.2	0.8	1.1	-0.1
7d	0.2	1.7	0.7	1.1	-0.2
8a	0.1	1.1	-0.6	1.0	0.2
8b	0.3	1.1	-0.3	1.2	0.4
8c	0.1	1.3	-0.6	1.1	0.6
8d	0.1	1.2	-0.6	1.0	0.6
Average		1.6		0.8	

[a] Taken as the free base. [b] Taken as the free base in deuteriodimethyl sulfoxide. [c] Taken as the nitrate in deuteriodimethyl sulfoxide.

various carbons, including those for phenyl, dioxolane and 1-substituted imidazole [14] rings. Furthermore, published ^{13}C chemical shifts [6] for some of the these *cis* and *trans* isomers correlated with our work and permitted us to use these chemical shifts as a diagnostic means to assign stereochemistry (Table 1). Assignments for individual *cis* and *trans* isomers is possible only provided that data for both isomers are available [6]. Unfortunately, ^{13}C chemical shift differences between the isomers are really quite small (Table 2). The most pronounced difference is for chiral C-4 of the dioxolane ring. The chemical shift of the *trans* isomers, **2** to **8**, is between 1.0 and 2.5 ppm further downfield than those of the corresponding *cis* isomers. The only other noticeable, and decidedly smaller chemical shift differences between the *trans* and *cis* isomers, were from the methylene carbon attached at C-2 of the dioxolane, being between 0.5 and 1.5 ppm for the compounds examined. The order of magnitude of chemical shift differences is relatively consistent within each series of similar compounds, as seen in the Tables. But, it must be stressed that pairs of diastereomers need to be available to permit unequivocal identification of the ^{13}C nmr signals for *cis* and *trans* isomers.

Table 3
Microanalytical Data

		Analysis Calcd. Found C%	H%	N%
5c-*cis & trans*	$C_{18}H_{19}ClN_2O_4 \cdot 0.33H_2O$	51.76	4.02	–
		51.73	3.89	–
6b-*cis*	$C_{21}H_{18}F_2N_2O_4 \cdot HNO_3$	54.43	4.13	9.07
		53.91	4.12	9.51
6b-*trans*	$C_{21}H_{18}F_2N_2O_4 \cdot HNO_3$	54.43	4.13	9.07
		54.24	4.25	9.31
6c-*cis & trans*	$C_{21}H_{19}ClN_2O_4 \cdot HNO_3$	54.61	4.36	9.10
		54.60	4.44	9.08
6d-*cis*	$C_{21}H_{19}BrN_2O_4 \cdot HNO_3$	49.81	3.98	8.30
		49.65	4.07	8.28
6d-*trans*	$C_{21}H_{19}BrN_2O_4 \cdot HNO_3$	49.81	3.98	8.30
		50.03	4.07	8.05
7a-*cis*	$C_{14}H_{14}Cl_2N_2O_3$	51.08	4.28	8.51
		51.05	4.13	8.46
7a-*trans*	$C_{14}H_{14}Cl_2N_2O_3$	51.08	4.28	8.51
		50.86	4.11	8.30
7b-*cis*	$C_{14}H_{14}F_2N_2O_3$	56.75	4.76	9.46
		56.73	4.81	9.43
7b-*trans*	$C_{14}H_{14}F_2N_2O_3$	56.75	4.76	9.46
		56.71	4.76	9.64
7c-*cis & trans*	$C_{14}H_{15}ClN_2O_3$	57.05	5.13	9.51
		57.14	5.13	9.54
7d-*cis*	$C_{14}H_{15}BrN_2O_3$	49.60	4.45	8.26
		50.02	4.42	8.26
7d-*trans*	$C_{14}H_{15}BrN_2O_3$	49.60	4.45	8.26
		49.53	4.46	8.19
8a(Tos)-*cis* [a]	$C_{21}H_{20}Cl_2N_2O_5S \cdot 0.33H_2O$	51.53	4.25	5.72
		51.46	4.02	5.89
8a-*cis*	$C_{15}H_{16}Cl_2N_2O_5S$	44.24	3.95	6.87
		44.16	3.90	6.78
8a-*trans*	$C_{15}H_{16}Cl_2N_2O_5S$	44.24	3.95	6.87
		44.43	3.88	6.81
8b-*cis* [b]	$C_{15}H_{16}F_2N_2O_5S \cdot 0.33CH_2Cl_2$	45.72	4.17	6.97
		45.50	4.29	7.37
8b-*trans* [b]	$C_{15}H_{16}F_2N_2O_5S \cdot 0.25CH_2Cl_2$	46.31	4.20	7.08
		46.22	4.27	7.13
8c-*cis & trans* [b]	$C_{15}H_{17}ClN_2O_5S \cdot 0.33CH_2Cl_2$	45.90	4.44	6.98
		45.67	4.46	6.89
8d-*cis*	$C_{15}H_{17}BrN_2O_5S$	43.18	4.10	6.71
		43.24	4.07	6.66
11-*cis*	$C_{18}H_{15}Cl_3O_4$	53.82	3.76	–
		53.98	3.78	–
11-*trans*	$C_{18}H_{15}Cl_3O_4$	53.82	3.76	–
		53.79	3.67	–
13b	$C_{11}H_8F_2N_2O$	59.45	3.65	12.60
		59.39	3.57	12.41
14a	$C_{19}H_{13}Cl_5N_2O_2 \cdot 0.25H_2O$	46.80	2.79	5.74
		46.65	2.60	5.77
14c	$C_{19}H_{15}BrCl_2N_2O_2 \cdot 0.5H_2O$	49.28	3.45	6.05
		49.29	3.08	6.20
14d	$C_{19}H_{15}Br_3N_2O_2$	42.03	2.78	5.16
		41.95	2.69	5.65

[a] The 4-toluenesulfonate instead of the methanesulfonate. [b] The amount of methylene choride adhering to the analytical sample was corroborated by integration of the methylene signal in the proton nmr spectrum.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^1H and ^{13}C nmr spectra (at 75.4 MHz) were recorded in deuteriochloroform (unless stated otherwise) using a Varian XL-300 spectrometer; some ^{13}C nmr spectra were obtained on a Nicolet NIC-360 NB spectrometer (at 90.8 MHz). Chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane and signals are described as s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet and br is used to describe broad signals. When complex spins systems of the AA'XX' type are described, the chemical shifts reported are those at the center of the two sets of complex multiplets. Proton and carbon to fluorine coupling constants are not reported. The ^{13}C nmr chemical shifts are compiled in Table 1. The ratios of *cis* and *trans* diastereomers were estimated from the relative heights of ^{13}C nmr signals attributable to C-4 and C-5 ring carbons, as well as from the methylene carbons attached at C-2 and C-4 of these 1,3-dioxolanes. The ^{13}C chemical shift differences for pertinent carbons are presented in Table 2. Elemental analyses were performed by Midwest Microlab, Indianapolis, IN and are in Table 3.

All research chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI unless specified otherwise, and were used as supplied. Pyridine, *N,N*-dimethylacetamide (DMA), *N,N*-dimethylformamide (DMF) and deuteriodimethyl sulfoxide were stored over 4Å molecular sieves once the container had been opened. Chloroform, toluene and benzene were ACS grade and were purchased from Scientific Supply Co. Petroleum ether refers to that fraction boiling between 30-60°. Evaporation or removal of solvents, *in vacuo*, implies their distillation by means of a rotary flash evaporator at the water pump (20-30 Torr) at about 40°, unless specified otherwise. All analytical samples were dried at room temperature in a vacuum desiccator. Thin layer chromatography was performed on Aldrich silica gel coated polyester plates with a 254 nm fluorescent indicator. Column chromatography was performed on Aldrich grade 60 (230-400 mesh) silica gel unless noted otherwise. Flash chromatography was carried out according to published procedures [15].

Method A. Synthesis of **13** and **14**. 1-(2,4-Dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone (**13a**).

To a cold (0-5°) stirred solution of imidazole (30.0 g, 0.44 mole) in DMF (70 ml) was added 2,2',4'-trichloroacetophenone (**12a**, 20.0 g, 0.090 mole), in several portions. After 2 hours, the stirred mixture was allowed to warm the room temperature and poured into water (400 ml). After 12 hours, the orange gelatinous precipitate which had developed, was filtered, washed with water and extracted with chloroform (150 ml). The insoluble salt **14a** was filtered off.

The chloroform extract was evaporated, *in vacuo*, to provide an orange solid which was recrystallized twice from methanol to yield colorless crystals of **13a** (5.3 g, 23%), mp 84-85°; lit [9] mp 76.5-78.5°; lit [8] reports the hydrochloride mp 169-170°; ^1H nmr: δ 5.34 (s, 2H, CH_2), imidazole proton signals as singlets at 7.50 (H-2), 6.94 (H-4), 7.10 (H-5), phenyl proton signals, 7.37-7.59 (m); ^{13}C nmr: δ 55.4 (CH_2), imidazole carbons, 138.0 (C-2), 129.7 (C-4), 119.1 (C-5), phenyl carbons, 120.0, 127.9, 130.7, 131.0, 132.5,

139.2, and 193.7 (C=O).

The chloroform-insoluble quarternary salt **14a** (1.55 g, 4.3%) was washed with chloroform, mp 226°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 6.15 (CH_2), imidazole proton signals at 9.30 (H-2), 7.86 (H-4, H-5), phenyl proton signals, 7.72-8.18 (m); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 57.3, (CH_2), imidazole carbons at 138.6 or 138.0 (C-2), 123.6 (C-4, C-5), phenyl carbons, 127.8, 130.8, 132.2, 132.6, 138.0 or 138.6, and 191.1 (C=O).

1-(2,4-Difluorophenyl)-2-(1*H*-imidazol-1-yl)ethanone (**13b**).

This compound was prepared, as above, starting from 2-chloro-2',4'-fluoroacetophenone (**12b**, 14.3 g, 0.075 mole). The chloroform extract was decolorized with silica gel (50 g), and after removal of the solvent yielded a pale yellow solid, (7.7 g, 46%) mp 125-127°; ^{1}H nmr: δ 5.29, 5.30, 5.30 (narrow d, CH_2), imidazole proton signals as singlets at 7.49 (H-2), 6.92 (H-4), 7.12 (H-5), phenyl proton signals, 6.93-7.05, 8.05 (m's); ^{13}C nmr: δ 55.4 (CH_2), imidazole carbons at 138.0 (C-2), 129.5 (C-4), 120.1 (C-5), phenyl carbons, 104.9, 112.4, 118.5, 133.1, 163.0, 167.0, and 188.8 (C=O).

1-(4-Chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone (**13c**).

This compound (10.6 g, 77%) was obtained as a pale orange solid from 2-bromo-4'-chloroacetophenone (**12c**, 14.5 g, 0.062 mole), as described above, mp 158-159°, lit [8] mp 160-161°; ^{1}H nmr: δ 5.36 (s, 2H, CH_2), imidazole proton signals as singlets at 7.50 (H-2), 6.92 (H-4), 7.11 (H-5), phenyl proton signals, 7.48-7.91 (m); ^{13}C nmr: δ 52.3 (CH_2), imidazole carbons at 138.0 (C-2), either 129.2, or 129.3 or 124.6 (C-4), 120.2 (C-5), phenyl carbons, 124.6 or 129.2 or 129.3, 132.3, 140.9, and 191.8 (C=O).

The by-product **14c** (1.39 g, 10%), was separated from **13c**, as described above, mp 253-254°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 6.20 (CH_2), imidazole proton signals at 9.11 (H-2), 7.82 (H-4, H-5), phenyl proton signals, 7.76-8.09 (m), ^{13}C nmr (deuteriodimethyl sulfoxide): δ 55.6, (CH_2), imidazole carbons at 138.5 or 139.3 (C-2), 123.7 (C-4, C-5), phenyl carbons, 129.2, 130.0, 132.5, 139.3 or 138.5, 190.4 (C=O).

1-(4-Bromophenyl)-2-(1*H*-imidazol-1-yl)ethanone (**13d**).

This compound (16.8 g, 88%) was prepared from **12d** (20.0 g, 0.07 mole) as a colorless powder, mp 163-164°, lit [8] mp 167-168°; ^{1}H nmr: δ 5.36 (s, 2H, CH_2), imidazole proton signals as singlets at 7.50 (H-2), 6.93 (H-4), 7.13 (H-5), phenyl proton signals, 7.65-7.84 (m); ^{13}C nmr: δ 52.3 (CH_2), imidazole carbons at 138.2 (C-2), either 129.3, or 129.7, (C-4), 120.1 (C-5), phenyl carbons, 129.7 or 129.3, 132.4, 132.7, 190.6 (C=O).

The by-product, **14d** (2.2 g, 11%), was isolated, mp 288-290°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 6.14 (CH_2), imidazole proton signals at 9.06 (H-2), 7.78 (H-4, H-5), phenyl proton signals, 7.87-8.02 (m); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 55.5, (CH_2), imidazole carbons at 13 138.0 (C-5), phenyl carbons, 128.6, 130.0, 132.0, 132.8, and 190.0 (C=O).

Method B-1. Synthesis of 2-Aryl-2-(halomethyl)-(1,3-dioxolan-4-yl)-methyl Benzoates **5** Starting from an Acetophenone.

In this method, **1** is ketalized, followed by bromination and then benzoylation and is illustrated for the synthesis of *cis*- and *trans*-[2-(bromomethyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl]methyl benzoate (**5a**). The ketalization step was modified. 1-Butanol, which had been added as an indispensable coreagent in prior preparations [4], was omitted, with no detriment to yield. A solution of 2,4-dichloroacetophenone (**1a**, 100 g, 0.53 mole), glycerol (58 g, 0.63 mole) and 4-toluenesulfonic acid monohydriate (3.0 g) was boiled in benzene (400 ml) with azeotropic removal of water by periodic changes of solvent (14 hours). To monitor the progress of the reaction, at various stages a small aliquot of the reaction mixture was withdrawn, washed with saturated aqueous sodium bicarbonate solution and solvents evaporated to provide a viscous oil which was checked (^{13}C nmr) for the progress of the reaction in terms of the formation of *cis* and *trans* **2a**. At the end of the prescribed period, no attempt was made to further purify or separate the isomers of **2a**, but rather the reaction sequence was continued, as follows.

The benzene solution was cooled (40°) and bromine (98 g, 0.63 mole) was added dropwise (1.5 hours). After stirring the mixture an additional 0.5 hour, solvents were removed, *in vacuo*. The residue was dissolved in methylene chloride (200 ml), washed with 6 N sodium hydroxide (100 ml), then with brine (50 ml) and dried with magnesium sulfate. Evaporation of the methylene chloride solution, *in vacuo*, left a yellow oil, shown by ^{13}C nmr to be a mixture of *cis*- and *trans*-**4a** (60:40), which was used in the next step without further purification.

To a stirred cold (below 5°) solution of crude alcohols **4a** in pyridine (350 ml) was added dropwise, benzoyl chloride (77.0 g, 0.55 mole) over 1 hour. The mixture was allowed to warm to room temperature and stirred for a further 2 hours, then diluted with an equal volume of water and the resultant bulky cream solid extracted into chloroform (3 x 200 ml). The organic extracts were washed with 6*N* hydrochloric acid (2 x 150 ml). After drying with magnesium sulfate, the chloroform extract was evaporated, *in vacuo*, to furnish a viscous red oil. Upon addition of methanol (200 ml), a copious colorless solid precipitated which was filtered off after several hours and washed with cold methanol. From the mother liquor, a second batch of *cis*-**5a** deposited, after 24 hours. The combined batches were recrystallized from ethanol to yield *cis*-**5a** (134 g, 57%, from **1a**), mp 116-117° lit [4] mp 118.3°.

The mother liquor was evaporated, *in vacuo*, and the red residual oil was chromatographed on silica gel (300 g) and fractions eluted with chloroform-methanol (10:1). The major fraction (R_f = 0.9) was isolated as a yellow oil (67.0 g, 28%). The ^{13}C nmr spectrum indicated that the product was a mixture of approximately 20% *cis* and 80% *trans*-**5a**. Thin layer chromatography showed that the two isomers had almost identical retention times. No further enrichment of the *trans* isomer was possible by these chromatographic methods.

cis- And *trans*-[2-(Bromomethyl)-2-(2,4-difluorophenyl)-1,3-dioxolan-4-yl]methyl Benzoate (**5b**).

The two isomers were synthesized using Method B-1. Starting with 10.0 g (0.064 mole) of 2',4'-fluoroacetophenone (**1b**), there was obtained 17.5 g (89%) of *cis* and *trans*-**4b**, as a pale yellow oil. Benzoylation gave *cis*- and *trans*-**5b** (24.0 g, 89% from **1b**) of as a pale red oil (60:40) by ^{13}C nmr from which neither the *cis* nor *trans* isomer crystallized upon addition of methanol. This mixture was used without further purification for the alkylation of imidazole (Method C).

Method B-2. Synthesis of **5** from 1-Aryl-2-haloethanones.

The starting ketones for these reactions were phenacyl halides and 1-butanol was again omitted from these ketalizations. An example is provided. A solution of 2,2',4'-trichloroacetophenone (**9**, 50.0 g, 0.224 mole), glycerol (24.7 g, 0.286 mole) and

4-toluenesulfonic acid (2.0 g, catalyst) in toluene (250 ml) was refluxed for 48 hours with azeotropic removal of water, and worked up as in method B-1. Crude *cis* and *trans* **10** were dissolved in pyridine (300 ml, cooled below 5°) and treated with benzoyl chloride (44.2 g, 0.35 mole), as outlined in Method B-1. The chloroform extract containing crude **11** was evaporated, *in vacuo*, to yield a red viscous oil which was dissolved in methanol (400 ml). After 3 days, the copious precipitate was collected by filtration, washed with methanol, dried and recrystallized from absolute ethanol to yield *cis*-**11** as a white powder (30.0 g, 33% from **9**), mp 114-116°.

The methanol filtrate was concentrated to an oil and flash chromatographed on silica gel using chloroform as eluent. The major fraction (which showed no separation of tlc, Rf 0.9) was collected and the solvent removed to yield a pale yellow oil which, on the basis of ^{13}C nmr was identified as a mixture of *cis*- and *trans*-**11** (20:80).

Synthesis of *cis*- and *trans*-2-[(bromomethyl)-2-(4-chlorophenyl)-1,3-dioxolan-4-yl]methyl benzoate (**5c**) started with 2-bromo-4'-chloroacetophenone (**3c**, 40 g, 0.17 mole) and the reaction mixture was worked up as in method B-1, furnish a mixture of *cis*-and *trans*-**4c** (49.5 g, 95%) as a pale yellow oil. Benzoylation of **4c** with benzoyl chloride (23.9 g, 0.17 mole) gave a 60:40 mixture of *cis*- and *trans*-**5c** (54.9 g, 78% from **3c**), as an off-white solid, after chromatography on silica gel (500 g, eluted with chloroform), mp 68-73°.

cis And *trans*-[2-(Bromomethyl)-2-(4-bromophenyl)-1,3-dioxolan-4-yl]methyl Benzoate (**5d**).

These two isomers were synthesized (Method B-1) from 2,4-'-dibromoacetophenone (**3d**, 83.0 g, 0.29 mole). After chromatography on silica gel (800 g), elution with chloroform afforded a yellow oil (119 g, 88% from **3d**, Rf = 0.75) which crystallized slowly on standing to a yellow solid, mp = 68-71°, and is a 60:40 mixture of *cis* and *trans* **5d**.

Method B-2. Synthesis of **7** from the Ketalization of 1-Aryl-2-(1*H*-imidazol-1-yl)ethanones **13**.

The ketalization of **13** with glycerol in the presence of 1-butanol had been reported [3]. An example, but omitting 1-butanol, is provided. A mixture of 1-(4-chlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone (**13c**, 5.0 g, 0.023 mole), glycerol (2.3 g, 0.025 mole) and 4-toluenesulfonic acid in toluene (150 ml) was refluxed for 24 hours with azeotropic removal of water. After cooling, toluene was removed, *in vacuo*, the residue neutralized with saturated aqueous sodium bicarbonate solution and extracted with methylene chloride (2 x 75 ml). The extracts were washed with brine (50 ml), dried with magnesium sulfate, and evaporated to dryness, *in vacuo*. The residue was triturated with ether and a 60:40 mixture of *cis* and *trans* (**7c**, 5.91 g, 88%) was filtered off, mp 106-110°.

Similarly, **13d** (5.0 g, 0.019 mole) was converted to a mixture of *cis*- and *trans*-**7d** (60:40), mp 109-114°.

Method C. {2-Aryl-2-[(1-*H*-imidazolyl)methyl]-(1,3-dioxolan-4-yl)}-methyl Benzoate Nitrates (**6**·Nitrates).

Either the pure *cis* or pure *trans* isomer of **5**, or mixtures thereof, can be converted to **6**. The literature procedure [4] was adapted to convert *cis*-**5a** to *cis*-**6a**. A solution of *cis*-**5a** (40.0 g, 0.089 mmole) and imidazole (18.0 g, 0.28 mmole) in DMA (50 ml) was refluxed for 4 days, (protected from moisture by a calcium chloride drying tube). The deep red solution was cooled, diluted with water (100 ml) and extracted with ether (5 x 50 ml). The combined ether fractions were washed with brine and dried (magnesium sulfate). To this orange solution was added dropwise a slight excess of concentrated nitric acid, with swirling. An orange oil formed which adhered to the bottom and sides of the flask. After decanting solvents, the oil was dissolved in 2-propanol, and the resultant orange solution was layered with an equal volume of ether. A crystalline solid which developed slowly as ether diffused into the alcohol, was filtered (*cis*-**6a**·nitrate, 23.0 g, 52%) and dried, mp 171-172°, lit [4] mp, 172°.

The ether solution (which had been decanted from the nitrate) was evaporated to dryness, *in vacuo*, and the yellow gummy solid triturated with methanol to yield 8.7 g (22%) of colorless starting material (*cis*-**5a**, mp 116-117°, nmr).

To isolate *trans*-**6a** the following procedure was adopted: A solution of the chromatographically purified mixture of *cis* and *trans* **5a** (20:80), described above, (67.0 g, 0.15 mole) and imidazole (30 g, 0.45 mole) were reacted in DMA (400 ml), and worked up, as above. The free base in ether (250 ml) was treated with a slight excess of concentrated nitric acid to give a greasy precipitate. Ether was decanted off and the solid triturated with 2-propanol to yield a colorless solid, in an orange solution. The solid was filtered, washed with 2-propanol, then ether and was dried. The product proved to be pure *trans* **6a** (23.8 g, 40% of the total *trans* isomer present initially), mp 169-170°.

cis And *trans*-{2-(2,4-Difluorophenyl)-2-[1*H*-imidazol-1-yl]methyl-(1,3-dioxolan-4-yl)}methyl Benzoate Nitrate (**6b**).

These two isomers were prepared using essentially, Method C. A 60:40 mixture of *cis* and *trans*-**5b** (prepared above, by Method B-1, 24.0 g, 0.058 mole) and imidazole (20.0 g, 0.24 mole) in DMA (200 ml) was refluxed 5 days, cooled and poured into water (500 ml). The product was extracted into ether (5 x 75 ml). Addition of nitric acid gave an pale orange solid. Ether was decanted and the residue boiled with 2-propanol. Upon cooling there was isolated *trans*-**6b** nitrate (3.71 g, 13%), mp 198-200°. Evaporation of the 2-propanol solution provided a gummy solid which was triturated with methylene chloride to give *cis*-**6b** (3.9 g, 14%), mp 140-142°.

cis And *trans*-{2-(4-bromophenyl)-2-[1*H*-imidazol-1-yl]methyl-(1,3-dioxolan-4-yl)}methyl benzoate (**6d**) nitrates were isolated as follows. A solution of *cis*- and *trans*-**5d** (12.9 g, 0.028 mole) and imidazole (7.7 g, 0.113 mole) in DMA (150 ml) was refluxed for 4 days and worked up as described in Method C. After the addition of a slight excess of concentrated nitric acid to the ether solution of **6d** a semi-crystalline precipitate was obtained. Ether was decanted off and the residue triturated with 2-propanol. The solid was boiled briefly with 2-propanol. Upon cooling, the colorless solid was collected by filtration, dried and identified as the *trans*-**6d**·nitrate (2.3 g, 16%), mp 168-171°.

The initial 2-propanol filtrate was layered with ether, and upon standing, pure *cis*-**6d**· nitrate (5.3 g, 37%) was deposited as a colorless crystalline solid, mp 170°.

Attempts to separate *cis*- and *trans*-{2-(4-chlorophenyl)-2-[1*H*-imidazol-1-yl]methyl-(1,3-dioxolan-4-yl)}methyl benzoate nitrate (**6**) proved unsuccessful. Starting with a mixture of *cis*- and *trans*-**5c** (30.0 g, 0.072 mole), there was obtained **6c**·nitrate (14.5 g, 43%) as a crystalline colorless solid which recrystallized from 2-propanol, mp 146-150°, but proved to be a 60:40 mixture of the *cis* and *trans* isomers which could not be separated by this method.

Method D. Hydrolysis of Benzoates **6** to **7**.

The literature procedure [4] was followed but additional time was needed to complete the hydrolysis, which was monitored by tlc, until the ester had disappeared. To a suspension of *cis*-**6a** (2.0 g, 4.03 mmoles) in 1,4-dioxane (15 ml) was added 6*N* sodium hydroxide solution (6 ml), and the mixture was refluxed for 1.5 hours, until tlc indicated complete hydrolysis. After cooling, the mixture was diluted with water (50 ml) and the resultant oil was extracted into chloroform. The organic phase was washed with brine, dried (magnesium sulfate) and the solvent evaporated, *in vacuo*, to yield *cis*-**7a** (1.3 g, 98%) as an off-white solid, mp 131-133°, lit [4] mp, 140°.

trans-2-(2,4-Dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolane-4-methanol (*trans*-**7a**).

Using Method D, and starting with *trans*-**6a** (18.5 g, 0.036 mole), there was obtained *trans*-**7a** (10.7 g, 87%) as a pale yellow crystalline solid, mp 99-101°. This compound has been reported in a patent, being made from **4a** and imidazole, mp 129° [4].

cis And *trans*-2-(2,4-Difluorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolane-4-methanol (**7b**).

From *cis*-**6b**·nitrate (3.5 g, 7.6 mmoles), and using Method D, there was obtained *cis*-**7b** (2.1 g, 94%) as a colorless solid, mp 141-142°.

Similarly, *trans*-**6b**·nitrate (3.7 g, 7.7 mmoles) yielded *trans*-**7b** (2.08 g, 92%), as a colorless solid, mp 98-100°.

cis- And *trans*-2-(4-Chlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolane-4-methanol (**7c**).

Using Method D, a mixture of *cis* and *trans* **6c**·nitrate (4.0 g, 8.7 mmoles) was hydrolysed to afford a 60:40 mixture of *cis*- and *trans*-**7c** (2.5 g, 98%), as an off-white solid, mp 123-128°.

cis- And *trans*-2-(4-Bromophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolane-4-methanol (**7d**).

cis-**6d**·Nitrate (5.3 g, 10.5 mmoles) was hydrolyzed to furnish *cis*-**7d** (1.96 g, 55%) as a cream-colored solid, mp 130-132°.

Similarly, *trans*-**6d**·nitrate (2.23 g, 4.4 mmoles) was transformed to *trans*-**7d** (1.5 g, 100%), colorless solid, mp 142-143°.

General Method E. Formation of Sulfonates **8**.

This method is illustrated for the formation of *trans*-{2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl}methyl methanesulfonate (*trans*-**8a**): To a cooled (0-5°) solution of *trans*-**7a** (5.0 g, 15.0 mmoles) in dry pyridine (25 ml) was added dropwise methanesulfonyl chloride (1.9 g, 17.0 mmoles) in 15 minutes. After standing 18 hours, the reaction mixture solidified. The mixture was diluted with water (50 ml) and extracted with methylene chloride (3 x 50 ml). The extract was washed with brine, dried with magnesium sulfate, and solvents evaporated, *in vacuo*. Upon drying, *in vacuo*, there was obtained a beige solid which was dissolved in hot benzene. After separating a small amount of oil, the solvent was removed to furnish the product (5.25 g, 85%), mp 101-103°.

Other methanesulfonates were obtained in this manner: *cis*-**8a** was recrystallized from benzene to produce a yellow solid, mp 86-88°, lit [4] mp 111.7°; ^{1}H and ^{13}C nmr spectra agreed with the structure and the sample gave a satisfactory microanalysis.

From *cis*-**7b** (1.0 g, 3.4 mmoles), there was formed *cis*-**8b** (1.1 g, 87%), as a yellow oil which failed to crystallize.

Similarly, *trans*-**7b** was transformed to *trans*-**8b** in 68% yield and was isolated as a pale yellow oil which defied crystallization.

cis- And *trans*-**8c** were obtained from a mixture of *cis*- and *trans*-**7c** in 51%, as a colorless oil following chromatography on silica gel (methylene chloride/ethanol 9:1; Rf = 0.75). This compound analyzed for 0.33 mole of methylene chloride, the presence of which was confirmed by ^{1}H nmr spectroscopy (a characteristic singlet for the solvent was observed at 5.3 ppm).

From *cis*-**7d** (2.0 g, 5.8 mmoles) there was prepared *cis*-**8d** (1.73 g, 70%) as a colorless solid, mp 85-87°, after two recrystallizations from benzene.

From *trans*-**7d** there was formed *trans*-**8d** (60%), as a colorless gum.

cis-{2-(2,4-Dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,-3-dioxolan-4-yl}methyl 4-toluenesulfonate was prepared by adding 4-toluenesulfonyl chloride (3.2 g, 0.017 mole) in pyridine (15 ml) to an ice-cold stirred solution of *cis*-**7a** in pyridine (5.0 g, 0.015 mole in 20 ml). After 1 hour, the mixture was permitted to stand at room temperature for 18 hours, poured into water, extracted by chloroform. The extract was washed with water, dried and solvents removed, *in vacuo*, to provide an oil which was diluted with toluene (50 ml). The insoluble solid proved to be unreacted **8a**. Upon removal of toluene, *in vacuo*, the residue (6.4 g, 80%) slowly crystallized, mp 100-103°.

REFERENCES AND NOTES

[1] We gratefully acknowledge support for this work by Research Contract (NO1-HD-8-2900) from NICHHD.

[2] For reviews, consult [a] A. K. Saksena, V. M. Girjavallabhan, A. A. Cooper and D. Loebenberg, *Ann. Rep. Med. Chem.*, **24**, 111 (1989); [b] D. Berg and M. Plempel, Editors, Sterol Biosynthesis Inhibitors, VCH Publishers, New York, NY 1988.

[3] J. Heeres, US Patent 4,101,666, July 18, 1978.

[4] J. Heeres, L. J. J. Backx, J. H. Mostmans and J. Van Cutsem, *J. Med. Chem.*, **22**, 1003 (1979).

[5] J. Heeres, L. J. J. Backx and J. H. Mostmans, US Patent 4,358,449, Nov. 9, 1982.

[6] H. Suezawa, M. Hirota, K. Yamamoto, I. Takeuchi and Y. Hamada, *Bull. Chem. Soc. Japan.*, **57**, 883 (1984).

[7] J. Heeres and J. Van Cutsem, *J. Med. Chem.*, **24**, 1360, (1981).

[8] E. F. Godefroi, J. Heeres, J. van Cutsem and P. A. J. Janssen, *J. Med. Chem.*, **12**, 784 (1969).

[9] G. Mixich and K. Thiele, Arzneim. Forsch, **29**, 1510 (1979).

[10] H. S. Hill, M. S. Whelen and H. Hibbert, *J. Am. Chem. Soc.*, **50**, 2235 (1928); [b] N. Baggett, J. S. Brimacombe, A. B. Foster, M. Stacey and D. H. Whiffen, *J. Chem. Soc.*, 2574 (1960), and unreported work in our Laboratory.

[11] There is reference to the isolation of *trans*-**5a** by hplc [Ref 3a], but details are not provided.

[12] P. DeShong, J. A. Cipollina and N. K. Lowmaster, *J. Org. Chem.*, **53**, 1356 (1988).

[13] D. R. Chapman, L. Bauer, D. P. Waller and L. J. D. Zaneveld, *J. Heterocyclic Chem.*, **27**, 2063 1990).

[14] M. Begtrup. J. Elguero, R. Faure, P. Camps, C. Estopá, D. Ilavsky, A. Fruchier, C. Marzin, and J. de Mendoza, *Magn. Reson. Chem.*, **26**, 134 (1988).

[15] W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).