Monoaryl- and Bisaryldihydroxytropolones as Potent Inhibitors of Inositol Monophosphatase†

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The first successful preparation of mono- and disubstituted 3,7-dihydroxytropolone involves a four-step synthetic scheme. Thus, bromination of 3,7-dihydroxytropolone (**8**) followed by permethylation of the resultant products furnished gram quantities of intermediates **13**−**18**. Single or double Suzuki coupling reactions between these permethylated monobromo- and dibromodihydroxytropolone derivatives and a variety of boronic acids delivered the expected products whose deprotection yielded the desired compounds **1a**−**u** and **26a**−**n**, usually in fair to good yields. Tropolones **1** and **26** were found to be potent inhibitors of inositol monophosphatase with IC_{50} values in the low-micromolar range. The results are discussed in the context of the recently described novel mode of inhibition of the enzyme by 3,7-dihydroxytropolones.

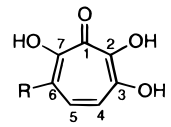
Introduction

Inositol monophosphatase (IMPase, EC 3.1.3.25) hydrolyzes all inositol monophosphates produced by the dephosphorylation of inositol polyphosphates in the phosphoinositide cycle or by the de novo synthesis from glucose-6-phosphate.[1] The past decade has witnessed an upsurge of interest in the enzyme following the discovery that it is inhibited by lithium at concentrations similar to those used in the treatment of manic depressive patients and the suggestion by Berridge that it might be the actual target of lithium therapy.[2] Lithium is remarkable as a drug in that it acts on the manic phase of the illness by normalizing the mood of patients rather than sedating them. It is perhaps the only drug for which clear prophylaxis has been demonstrated in the central nervous system.[3] However, despite the undisputable value of lithium as a drug, a number of issues detract from its utility.[4] It has a narrow therapeutic window, and various side effects ranging from mild to serious have been reported over the years. These include weight gain, tremor, and memory impairment, as well as kidney failure, decompensation of cardiac status, and transient leukocytosis. In addition, for reasons unclear at the present time, it takes between 7 and 10 days for lithium to exert its antimanic effect; as a result, other antipsychotic drugs are needed during that period of time. The narrow therapeutic window of lithium requires monitoring plasma drug concentration, a costly procedure. Hence, several laboratories have searched for other inhibitors of IMPase in the hope of developing a drug which would lack the spectrum of side effects associated with lithium therapy.[5]

The human enzyme has been cloned and expressed.[6] Several structures, determined by X-ray crystallography, have been published,[7] and numerous kinetic studies have been conducted, thus refining both the knowledge of the active site and the mechanistic features of substrate hydrolysis.[8] IMPase is a homodimer of 30-kDa subunits, each of them requiring at least two magnesium ions for activation.[8] The active site is rather large and potentially able to accommodate bulky molecules, a proposal that has been experimentally confirmed.[9] It is believed that hydrolysis of the phosphate occurs through the direct attack of a molecule of water via activation by a glutamic acid residue.[7b] An alternative mechanism of hydrolysis, involving in-line attack of another water molecule, has also been discussed.[8e]

Among the noncompetitive or competitive inhibitors of the enzyme reported in the literature, the most potent are the bisphosphonic acids.[5a] However, these compounds do not efficiently cross the blood−brain barrier, and their prodrugs are characterized by a very low bioavailability.[10]

We recently reported that 3,7-dihydroxytropolone (**1**, R = H) is the foremost representative of a new class of potent, competitive inhibitors of inositol monophosphatase.[11] These compounds interact with the active



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site in such a way that three oxygens of the seven-membered ring are effective chelators of the two magnesium ions. Modeling studies carried out on the structure of the enzyme−substrate complex showed that three contiguous oxygens of the ring superimpose perfectly with the ester oxygen of inositol monophosphate, the phosphate oxygen which chelates both metal ions M1 and M2, and a molecule of water believed to be the nucleophile responsible for the hydrolysis of the phosphate function (Figure 1). The finding that analogous six-membered rings were inactive demonstrates the uniqueness of hydroxytropolones as inhibitors of IMPase. Attempts to increase the potency of the parent dihydroxytropolone would require derivatizing it. The

† Dedicated to the memory of Dr. Zdenek Janousek.

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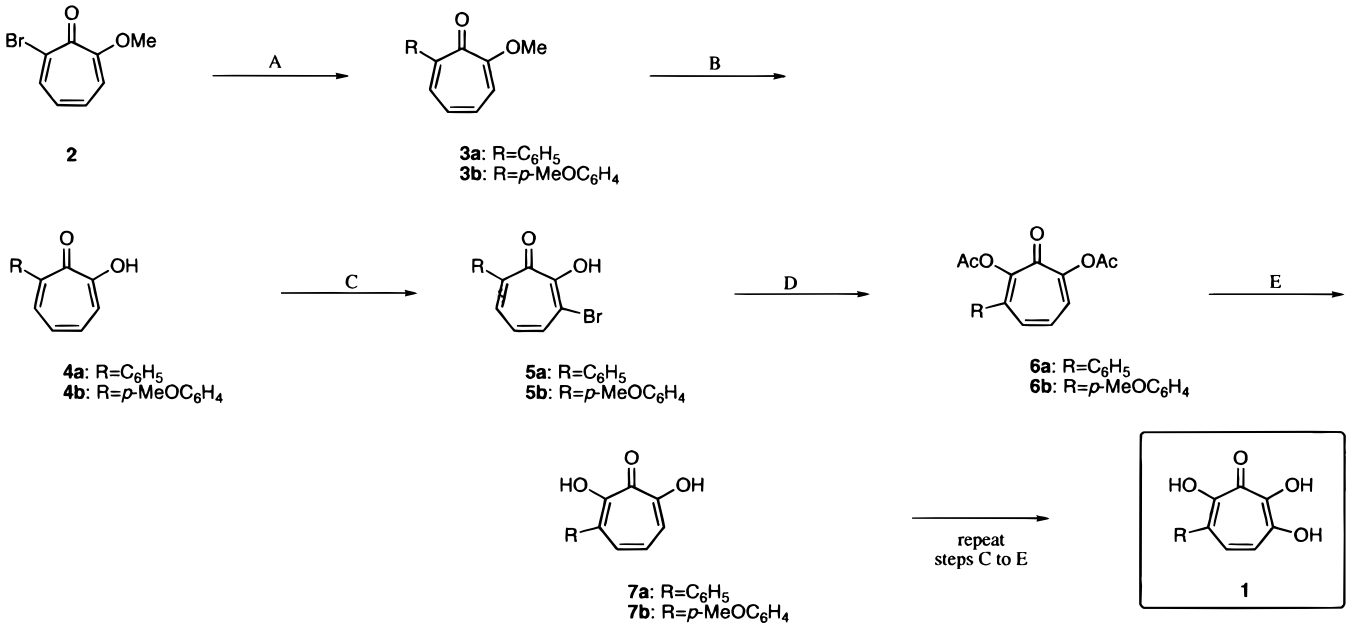
Scheme 1



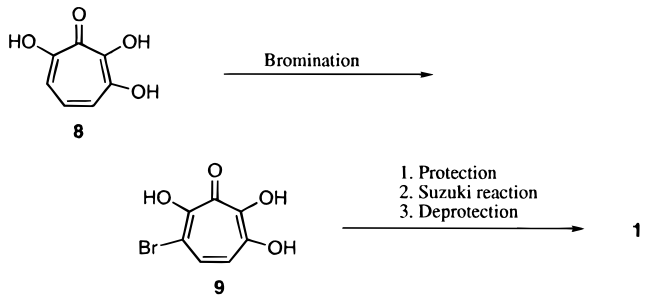
size of the active site of the enzyme is large enough to accommodate bulky groups, and additional interactions[5] with the amino acid residues can be expected. On the basis of modeling studies, we were especially interested in preparing and testing diverse functionalized aryldihydroxytropolones (**1**, R = aryl). In this paper, we describe the chemistry developed to prepare 4-mono- and 4,6-disubstituted 3,7-dihydroxytropolones and their activity as inhibitors of IMPase.

Chemistry

Work describing the use of **2** in Suzuki coupling reactions suggested it could be a convenient means to reach our target molecules.[12,16] This would be possible only if the additional hydroxyl groups can be efficiently introduced. Such a transformation is in principle possible through sequential bromination of the aryltropolone, acetolysis of the resultant bromo derivative using Takeshita's reagent (ATA; see below),[17] and hydrolysis of the subsequent polyacetate, as shown in Scheme 1 (steps C−E). Only one hydroxyl group at a time can be introduced since direct dibromination of tropolones is known to occur in α and γ positions.[18] Thus, six steps are needed to introduce the two hydroxyl groups.

The feasibility of this synthetic route was tested on the 7-phenyl and 7-(*p*-methoxyphenyl) derivatives **3a**,**b**.[16] Demethylation was achieved with HCl in methanol to give tropolones **4a** (86% yield) and **4b** (99% yield), respectively. Bromination using *N*-bromosuccinimide furnished a 4:1 to 3:2 mixture of the expected bromotropolones **5a**,**b** and the corresponding 3,5-dibromides. The desired monobromo derivatives were isolated in only 32% and 45% yield after chromatographic purification. Treatment with a 20:2:1 mixture of acetic anhydride/trifluoroacetic acid/acetic acid (ATA)[17] led to the isolation of diacetates **6a**,**b** (57% and 50% yield, respectively). Hydrolysis of the acetate functions in hot aqueous acetic acid produced the hydroxytropolones **7a**,**b** (51% and 39% yield, respectively). The low overall yield of the sequence (8% from **3a** to **7a** and 9% from **3b** to **7b**) coupled with the fact that a second, similar

Scheme 2

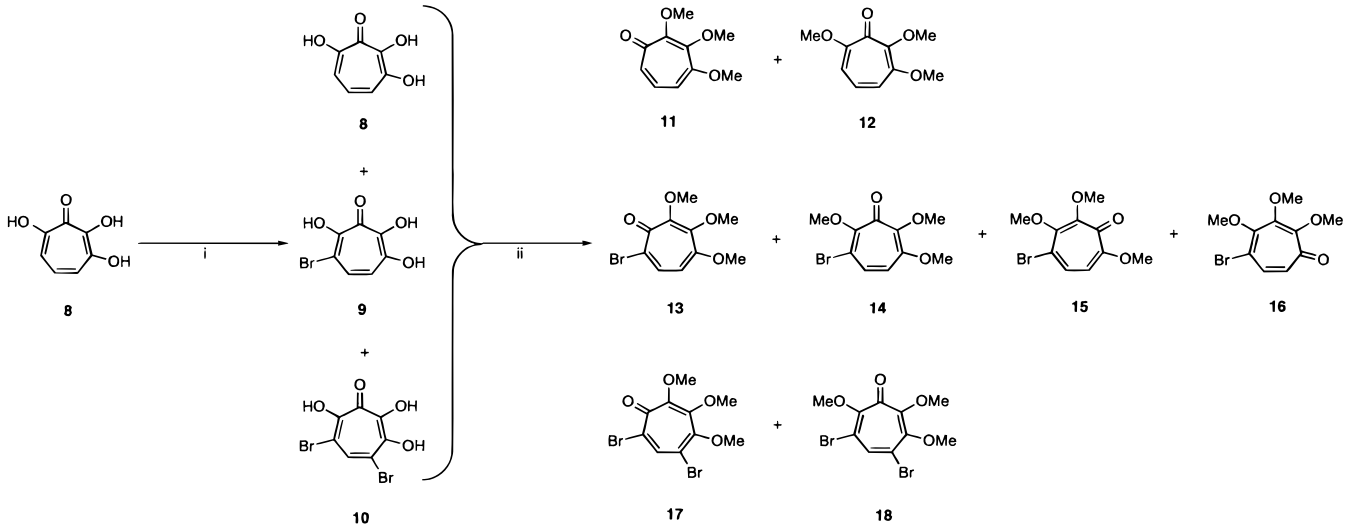


sequence of reactions was needed for the introduction of the fourth oxygen led us to consider an alternative route.

Thus, reversing the synthetic sequence (i.e., introducing the hydroxyl groups on the seven-membered ring *first* and carrying out the Suzuki coupling reaction *at the end*) would not only shorten the synthesis but also make the preparation more convergent (Scheme 2).[19] The known and readily available 3,7-dihydroxytropolone (**8**) was chosen as the ideal starting material for the sequence. This compound is easily prepared in three steps from commercially available tropolone by double bromination, acetolysis, and hydrolysis of the resultant triacetates.[11,17b,20]

Bromination of **8** proved to be more challenging than expected. It was soon discovered that the desired 4-bromo-3,7-dihydroxytropolone (**9**) was more reactive toward brominating agents than the starting material **8**, thus yielding significant amounts of dibromide **10**. Considerable effort was spent to find conditions which would maximize the amount of **9** at the expense of **10**. In the end it was found that slow addition (5.5 h) of an acetone solution of *N*-bromosuccinimide (NBS) to a cooled (−15 °C) solution of 3,7-dihydroxytropolone (**8**) in dry dimethylformamide (DMF) and stirring at the same temperature for an additional 16 h reproducibly led to a 47:43:10 mixture of unconsumed starting material **8**/monobromo derivative **9**/dibromo derivative **10** (Scheme 3).

Scheme 3[a]

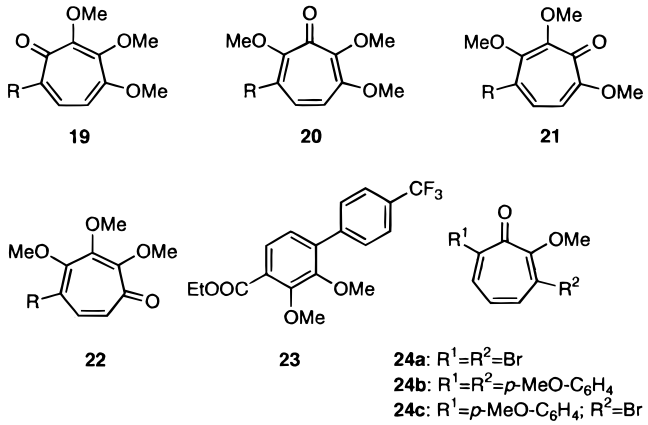


[a] (i) NBS (slow addition), −20 °C; (ii) CH_2N_2, 0 °C.

Permethylation of model 3,7-dihydroxytropolone (**8**) was next studied. Classical methylation reactions (e.g., using methyl iodide under basic conditions) led to unreproducible results and low yields of isolated permethylated products. On the other hand, reaction with freshly prepared diazomethane at 0 °C proceeded smoothly to produce the desired compounds (two isomers) in 89% isolated yield. Thus, reaction of the crude mixture from bromination as described above with excess diazomethane at 0 °C furnished, after workup, a mixture of permethylated isomeric trimethoxytropones **11** and **12**, bromotrimethoxytropones **13**−**16**, and dibromotrimethoxytropones **17** and **18** (Scheme 3).[21] Chromatographic separation led to the isolation of all eight products in the pure form. Trimethoxytropones **11** and **12** could be deprotected (vide infra) and recycled. This somewhat tedious procedure nevertheless permitted the preparation of the desired monobromo and dibromo compounds in gram quantities. Structural assignment of all eight isomers was achieved using ^1H and ^{13}C NMR in 1-D and 2-D modes at 500 and 125 MHz, respectively. Heteronuclear multiple quantum correlation (HMQC) and heteronuclear multiple bond correlation (HMBC) were run to establish direct and long-range $^{13}C-^1H$ connectivities.[22] These studies resulted in the unambiguous assignment of all isomers to the structures depicted in Scheme 3 and are exemplified by the monobromo derivatives **13** to **16**. Thus, the proton in the α position to the brominated carbon was always found at a lower field than the other proton, due to the combined effects of the Br and OMe substituents (or CO in structure **16**); in addition both were characterized by a geminal H−H coupling (^3J = 13 Hz). The patterns obtained from the HMBC spectra clearly indicated the geminal (^2J) and vicinal (^3J) couplings. For instance, the 2-D spectrum of compound **14** was the only one displaying no coupling pattern for carbon 1 (C=O); in addition it showed ^3J couplings for two C−OMe (carbons 2 and 7) and ^2J and ^3J couplings for the C−Br (carbon 6) and only one C−OMe (carbon 3). An analogous analysis was carried out for each compound.

Attempts to selectively monodebrominate the isomeric permethylated dibromo derivatives **17** and **18** using a variety of reagents did not succeed.[23]

The relative reactivity of all four isomeric monobromo derivatives **13**−**16** in the Suzuki coupling reaction was next studied in parallel experiments using *p*-(trifluoromethyl)phenylboronic acid. Isomers **13**−**15** displayed essentially identical behavior under standard conditions (10% $Pd[P(Ph)_3]_4$, toluene−ethanol, Na_2CO_3, 110 °C, 16 h), affording the desired products **19d**, **20c**, and **21b** (85−90% isolated yields). Isomer **16**, however, yielded



24a: $R^1=R^2$=Br
24b: $R^1=R^2$=*p*-MeO-C_6H_4
24c: R^1=*p*-MeO-C_6H_4; R^2=Br

the expected coupled product **22b** in much lower yield (37%) along with the biphenyl derivative **23** (9% yield), the result of a nucleophilic addition reaction of ethanol followed by ring contraction. In another analogous experiment, the ratio was reversed (26% yield of **23** and 5% yield of **22b**).[24] The structure of compound **23** was determined by the method used for tropones **11**−**18**, as described above. Carrying out the experiment in the absence of ethanol yielded the desired product **22b** in 83% yield. These experiments demonstrate that all four regioisomeric tropones **13**−**16** possess virtually identical reactivities in the Suzuki coupling reaction.

A number of coupling reactions between either the model compound **2**, or any of the four monobrominated compounds **13**−**16**, and diversely functionalized boronic acids, or boranes, were carried out using the standard conditions described above to produce the corresponding aryl derivatives **3**, **19**, **20**, **21**, or **22**. The yields were in most cases fair to good, thus demonstrating the flexibility of the synthetic method (Table 1).[25] It should be

Table 1. Yields of the Suzuki Coupling Reactions and of the Deprotection Step

starting material	Suzuki reaction product	R	yields (%)	deprotected product	R	yields (%)
2	**3a**	C_6H_5	94	**4a**	C_6H_5	86[a]
14	**20a**	C_6H_5	67	**1a**	C_6H_5	79
2	**3c**	C_6H_5-C_6H_4	78	**4c**	C_6H_5-C_6H_4	*b*
2	**3b**	*p*-MeO-C_6H_4	91	**4b**	*p*-MeO-C_6H_4	95[a]
13	**19a**	*p*-MeO-C_6H_4	50	**1b**	*p*-HO-C_6H_4	49
15	**21a**	*p*-MeO-C_6H_4	69	**1b**	*p*-HO-C_6H_4	*b*
2	**3d**	*p*-BnO-C_6H_4	70	**4d**	*p*-HO-C_6H_4	78
14	**20b**	*p*-BnO-C_6H_4	69	**1b**	*p*-HO-C_6H_4	95
13	**19b**	*o,m′*-$(MeO)_2$-C_6H_3	50	**1c**	*o,m*-$(HO)_2$-C_6H_3	40
13	**19c**	*o*-F-C_6H_4	62	**1d**	*o*-F-C_6H_4	88
16	**22a**	*m*-F_3C-C_6H_4	50	**1e**	*m*-F_3C-C_6H_4	70
13	**19d**	*p*-F_3C-C_6H_4	83	**1f**	*p*-F_3C-C_6H_4	*b*
14	**20c**	*p*-F_3C-C_6H_4	88	**1f**	*p*-F_3C-C_6H_4	80
15	**21b**	*p*-F_3C-C_6H_4	89	**1f**	*p*-F_3C-C_6H_4	*b*
16	**22b**	*p*-F_3C-C_6H_4	37[c]	**1f**	*p*-F_3C-C_6H_4	*b*
14	**20d**	*m,m*-$(F_3C)_2$-C_6H_3	64	**1g**	*m,m*-$(F_3C)_2$-C_6H_3	68
2	**3e**	*o*-OHC-C_6H_4	95	**4e**	*o*-OHC-C_6H_4	d
2	**3f**	*m*-OHC-C_6H_4	75	**4f**	*m*-OHC-C_6H_4	82
13	**19e**	*m*-OHC-C_6H_4	59	**1h**	*m*-OHC-C_6H_4	63
15	**21c**	*m*-OHC-C_6H_4	70	**1h**	*m*-OHC-C_6H_4	*b*
16	**22c**	*m*-OHC-C_6H_4	87	**1h**	*m*-OHC-C_6H_4	*b*
2	**3g**	*m*-NC-C_6H_4	76	**4g**	*m*-NC-C_6H_4	96
14	**20e**	*m*-NC-C_6H_4	57	**1i**	*m*-NC-C_6H_4	74
14	**20f**	*m*-MeCONH-C_6H_4	42	**1j**	*m*-MeCONH-C_6H_4	49
13	**19f**	*m*-BocNH-CH_2-C_6H_4	42	**1k**	*m*-NH_2-CH_2-C_6H_4	*d*
13	**19g**	*p*-[$(C_6H_5)_2C$═N═$(CH_2)_2$]-C_6H_4	28	**1l**	*p*-[H_2N-$(CH_2)_2$]-C_6H_4	82
14	**20g**	*m*-NO_2-C_6H_4	64	**1m**	*m*-NO_2-C_6H_4	52
14	**20h**	1-naphthyl	55	**1n**	1-naphthyl	82
14	**20i**	2-naphthyl	52	**1o**	2-naphthyl	98
14	**20j**	*m*-[5-(2-naphthyl)-2-oxadiazolyl]phenyl	38	**1p**	*m*-[5-(2-naphthyl)-2-oxadiazolyl]phenyl	92
2	**3h**	*m*-[7-(2-methoxy)troponyl]-C_6H_4	45	**4h**	*m*-[7-(2-methoxy)troponyl]-C_6H_4	*b*
13	**19h**	2-benzofuryl	46	**1q**	2-benzofuryl	63
13	**19i**	2-thienyl	19	**1r**	2-thienyl	81
13	**19j**	3-thienyl	88	**1s**	3-thienyl	58
2	**3i**	5-pyrimidyl	30	**4i**	5-pyrimidyl	85
14	**19k**	5-pyrimidyl	37	**1t**	5-pyrimidyl	25
2	**3j**	*n*-C_8H_{17}	38	**4j**	*n*-C_8H_{17}	*b*
14	**20k**	*t*-$BuMe_2SiO$-$(CH_2)_4$-	31	**1u**	HO-$(CH_2)_4$-	30
14	**20l**	*t*-Bu$(C_6H_5)_2SiO$-$(CH_2)_5$-	31	**1v**	HO-$(CH_2)_5$-	*d*

[a] HCl or MeONa in methanol (see Experimental Section). [b] Not carried out. [c] A byproduct was also isolated (see text). [d] Not successful.

noted that careful chromatographic purification at this stage is very important since the dihydroxytropolones produced in the next step proved to be very difficult to purify by any means (vide infra).

Introduction of only one aryl group (using *p*-methoxyboronic acid) on a dibromotropolone derivative (2-methoxy-3,7-dibromotropone, **24a**) was attempted but resulted instead in the isolation of the bisaryl derivative **24b** as the major product (30% yield), the desired monoaryl derivative **24c** being isolated in only 7% yield.

The deprotection step was worked out on a mixture of isomeric permethylated dihydroxytropolones **11** and **12**. It was found that treatment with an excess of trimethylsilyl iodide in dry acetonitrile at 80 °C, evaporation of the volatiles (including any HI that might have formed), and hydrolysis of the crude material thereby formed resulted in the isolation of the desired 3,7-dihydroxytropolone (**8**) in virtually quantitative yield.[26] These conditions were successfully used in most of the cases described in Table 1 and show the tolerance for many functional groups. The reported isolated yields are unoptimized. The deprotection step usually works well; however, the compounds produced are characterized by low solubility in most organic solvents or water and crystallization proved to be very difficult in many cases. As expected, compounds incorporating additional methoxy (**19a**,**b**), benzyloxy (**3d** and **20b**), or silyloxy (**20k**) groups underwent complete cleavage of all ether functions. Deprotection of the benzylidenimine moiety present in **19g** also occurred as expected, thereby delivering the amine. Compound **4e** (R = *o*-CHO-C_6H_4) was not observed, and the tricyclic product that would presumably form during the last step could not be isolated, or even detected.[27] Product **1k** (R = H_2NCH_2-C_6H_4) was formed but could not be purified.[28]

The aldehyde group of product **3f** was reacted with hydroxylamine and benzylhydroxylamine to give the expected oximes **3k** (R = *m*-HO-N═CH-C_6H_4) and **3l** (R = *m*-BnO-N═CH-C_6H_4) in excellent yields (93% and 96% yield, respectively). However, deprotection of the tropolonic methyl ether functions with TMSI simultaneously resulted in the transformation of the oxime into a nitrile group, thus producing product **4g** instead (72% and 77% isolated yield, respectively). Reaction between tropolone **4f** and hydroxylamine hydrochloride under basic conditions slowly converted the starting aldehyde into the corresponding oxime **4k** (R = *m*-HO-N═CH-C_6H_4) in quantitative yield. Application of this procedure to dihydrotropolone derivative **1h** also resulted in the formation of the desired oxime **1w** (R = *m*-HO-N═CH-C_6H_4) along with a byproduct. However purification was not readily achieved.

Reduction of aldehyde **3f** was achieved using sodium triacetoxyborohydride and yielded the desired alcohol **3m** (R = *m*-$HOCH_2$-C_6H_4) in 91% yield. Similar conditions applied to aldehydes **21c** and **22c** furnished the

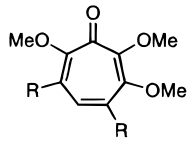
Table 2. Yields of the Double Suzuki Coupling Reactions and of the Deprotection Step

R	Suzuki reaction product	yield (%)	deprotected product	yield (%)
p-MeO-C_6H_4	**25a**	77	**26a**[a]	99
o-F-C_6H_4	**25b**	89	**26b**	53
m-F_3C-C_6H_4	**25c**	90	**26c**	30
p-F_3C-C_6H_4	**25d**	93	**26d**	76
m,m-$(F_3C)_2$-C_6H_3	**25e**	81	**26e**	86
m-OHC-C_6H_4	**25f**	71	**26f**	87
m-NC-C_6H_4	**25g**	68	**26g**	70
m-MeCONH-C_6H_4	**25h**	41	**26h**	27
m-NO_2-C_6H_4	**25i**	68	**26i**	35
1-naphthyl	**25j**	100	**26j**	79
2-naphthyl	**25k**	81	**26k**	76
m-[5-(2-naphthyl)-2-oxadiazolyl]phenyl	**25l**	45	**26l**	25
2-benzofuryl	**25m**	15	**26m**	73
3-thienyl	**25n**	60	**26n**	98

[a] R = *p*-HO-C_6H_4.

corresponding alcohols **21d** and **22d** (R = *m*-$HOCH_2$-C_6H_4) in 66% and 50% yield, respectively.

We next focused our attention on the possibility of carrying out a double Suzuki coupling reaction on the dibromo derivatives **17** and **18**, with the intention of producing 4,6-disubstituted-3,7-dihydroxytropolones (**26**). Dibromination of 3,7-dihydroxytropolone (**8**) could be achieved by using NBS in refluxing CCl_4. Several washings of the crude solid with water afforded 4,6-dibromo-3,7-dihydroxytropolone (**10**) with an overall yield of 75%. Permethylation was readily achieved using a slight excess of diazomethane to furnish a 1:4 mixture of compounds **17** and **18**, identical with the compounds isolated before (vide supra). Double Suzuki coupling reaction was performed on **18** using the same conditions as above, but with 2.2 equiv of boronic acid, and was found to deliver the expected bisaryl derivatives **25** in generally good isolated yields. It has to be noted



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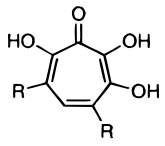

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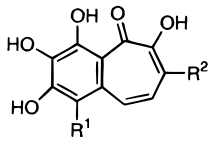
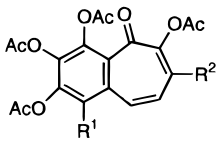


27a: R^1=R^2=H
27b: R^1=R^2=Br
27c: R^1=Br, R^2=OH
27d: R^1=H, R^2=OH



28a: R^1=R^2=Br
28b: R^1=Br,R^2=OAc

that compound **25j** was isolated as a 1:1 mixture of rotamers; this mixture was observed even at 353 K. Deprotection of compounds **25** was achieved in a similar manner and furnished the target bisaryldihydroxytropolones **26**. Here again, the two *p*-methoxy substituents (present in compound **25a**) underwent concomitant deprotection, leading to the isolation of the desired bis-(*p*-hydroxyphenyl) derivative **26a**. Results are compiled in Table 2.

Reports[29] that commercially available purpurogallin (**27a**) could be dibrominated to produce **27b** led us to consider it as a possible entry into the field of benzotropolones characterized by a polyhydroxylated seven-membered ring (of the type **27c**). In addition, the six-membered ring bromine would potentially be usable for further diversification via additional Suzuki coupling reactions. Thus, purpurogallin[30] was treated with 2 equiv of bromine in acetic acid to produce **27b** (55% isolated yield). Attempts to transform this material into the desired hydroxytropolone derivative **27c** using classical methodology (NaOH, copper, sodium β-naphthalenesulfonate in water) yielded only purpurogallin.[31] Treatment of **27b** with ATA at 100 °C for 24 h provided tetraacetate **28a** and pentaacetate **28b** in 20% and 43% isolated yield, respectively, thus leaving the six-membered ring bromine untouched. Here again, the structure of the compound was ascertained by using ^1H and ^{13}C NMR in 1-D and 2-D modes at 500 and 125 MHz, respectively. HMQC and HMBC were also run to establish direct and long-range $^{13}C-^1H$ connectivities.[22] However, hydrolysis of **28b** in a mixture of acetic acid and water at 100 °C furnished 3-hydroxypurpurogallin (**27d**) in 36% isolated yield, the result of concomitant acetate hydrolysis and brominolysis of **28b**.

Table 3. IC_{50} Values of Tropolone Derivatives as Inhibitors of IMPase[a]

product	IC_{50} (μM)	product	IC_{50} (μM)
L-690,330[a]	0.8	**1q**	7
8	10	**1r**	15
7a	200	**1s**	25
27d	>200	**1t**	10
10	10	**1u**	5
1a	20	**26a**	10
1b	10	**26b**	>200
1c	7	**26c**	>200
1d	65	**26d**	200
1e	10	**26e**	70
1f	130	**26f**	>100
1g	10	**26g**	30
1h	20	**26h**	65
1i	4	**26i**	20
1j	20	**26j**	>100
1l	90	**26k**	>100
1m	8	**26l**	>200
1n	20	**26m**	40
1o	>100	**26n**	35
1p	40		

[a] See ref 5a. Rates were determined in duplicate using six concentrations of compound in addition to a control without inhibitor and fitted by the equation $v = V_0/(1 + [I]/IC_{50})$ for competitive inhibition, where V_0 is the uninhibited rate and [I] is the concentration of inhibitor. Standard deviations for the fitted parameters were below 20%. IC_{50} values from separate experiments differed by less then 2-fold.

Biological Activities

Table 3 summarizes the IC_{50} values for tropolone derivatives as inhibitors of IMPase. The bisphosphonic acid L-690,330, a known competitive inhibitor, was also tested and is included in the table as a reference compound. Its IC_{50} value of 0.8 μM agrees well with the published K_i of 0.33 μM.[5a] The parent compound, dihydroxytropolone (**8**), had an IC_{50} value of 10 μM and was previously shown to be a competitive inhibitor with respect to the substrate, inositol 1-phosphate, with a K_i value of 5 μM.[11] Some of the compounds listed in Table 3 were also tested for their mechanism of inhibition. These included **1e**,**f** as derivatives with meta and para substituents on the aromatic ring and **1m** and **26i** as examples for mono- versus bissubstituted dihydrox-

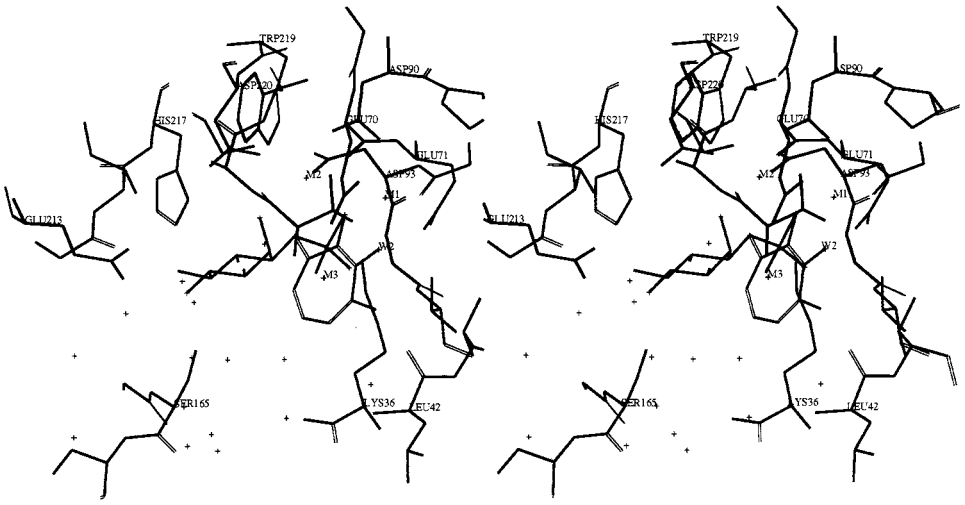


Figure 1. Stereoview of the active site of the inositol monophosphatase complex with Ca^{2+} and D-inositol 1-phosphate.[7d] M1, M2, and M3 are the positions of the three Ca^{2+} ions. W2 is the potential nucleophilic water molecule.[7b] Glu-70, Asp-90, Asp-93, and Asp-220 are metal ion ligands. In our model for the binding of 3,7-dihydroxytropolone, oxygen 2 (superimposed on a phosphate oxygen) chelates both M1 and M2, oxygen 1 (superimposed on the phosphoester oxygen) chelates M2, and oxygen 3, by displacing W2, chelates M1 and makes a hydrogen bond with Glu-70. A hydrogen bond between the fourth oxygen and Leu-42 also participates in the binding. The plane of the molecule was estimated to be around 70° from the mean plane of the inositol ring of D-Ins(1)P, thereby precluding the third metal ion (M3) from positioning itself in the active site.[11]

ytropolones. The rate of substrate hydrolysis was measured in a coupled spectrophotometric assay[8g] by varying the concentration of inositol 1-phosphate at different fixed concentrations of the inhibitor. Plots of 1/rate versus 1/[inositol 1-phosphate] always gave a series of straight lines that intersected in a common point on the *y*-axis, indicating competitive inhibition with respect to the substrate. Kinetic constants were determined using the equation for competitive inhibition and the computer program COMP.[32] The following K_i values were obtained: 5 ± 1 μM (**1e**), 40 ± 5 μM (**1f**), 10 ± 1 μM (**1m**), 20 ± 2 μM (**26i**). Equations for noncompetitive or uncompetitive inhibition could not be fitted to the experimental data. These results indicate that the derivatives of dihydroxytropolone described in this paper follow the same mechanism of inhibition as their parent compound, i.e., they compete with the substrate inositol 1-phosphate for binding to the active site of IMPase.

None of the derivatives synthesized displayed any significant improvement in affinity as compared to **8**. Some additional observations can be made. Aromatic side chains are easily accommodated as single substitutions, whereas in most cases some affinity is lost with the bissubstituted derivatives. This is not always true though; for example, **26a** is just as potent as **1b**, indicating that, in principle, the topology of the active site allows two aromatic side chains. However, at least for the symmetrical compounds of this work, there was no advantage of the bissubstituted over the monosubstituted derivatives. It should also be noted that in many cases of the **26** series, for example **26d** or **26l**, solubility problems were encountered above 100 mM. Another observation is related to the effect of substituents on the phenyl side chain. Substituents in the meta position (compounds **1e**,**h**,**i**,**m**) have no effect, whereas para substituents decrease the affinity, as in **1f**. We believe that this is a steric rather than an electronic effect, since the small hydroxyl group in **1b** does not change the efficacy of inhibition as compared to **1a**.

According to our model of dihydroxytropolone binding to IMPase, three contiguous oxygen atoms of the seven-membered ring chelate two active site Mg^{2+} ions (Figure 1).[11] The fourth oxygen makes an interaction with the main chain carbonyl group of Leu-42. If correct, this model predicts that substituents in position 4 of the cycle, as in our series of derivatives, point into a space that is occupied by inositol in enzyme−substrate complexes. We therefore anticipated that an increase in affinity may be achieved through the interaction of side chains in this position with Glu-213, a residue that contributes a factor of about 20 to the binding interaction with inositol 1-phosphate.[7c] In particular, a hydroxyphenyl side chain, as in **1b**, appeared to have about the right length to reach Glu-213 and form a hydrogen bond. The lack of any improvement in affinity as compared to **8** perhaps indicates that our original model may have to be modified. For example, since there are four contiguous oxygens, the seven-membered ring could be rotated by 51° without losing any interaction with the two magnesium ions. In this case, the side chain in position 4 of the ring would no longer point toward Glu-213. However, through this rotation the postulated interaction of the fourth oxygen atom in **8** with Leu-42 would be lost, and another explanation for the 8-fold increase in affinity of dihydroxytropolone as compared to monohydroxytropolone would be needed.[11]

It is not immediately apparent how the enzyme can accommodate a second aromatic side chain in the active site (as in **26a**). Our model predicts that an additional substituent in position 7 would interfere with a enzyme loop comprising amino acids 36−41. However, residues 30−40 were shown to be completely disordered in the crystal structure of the apoenzyme, indicating some flexibility in this area.[7c]

Conclusion

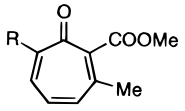
A short synthetic scheme has been worked out that allows for the first time an easy access to diversely functionalized mono- and disubstituted 3,7-dihydroxytropolones.[33,34] These compounds are inhibitors of IM-

Pase with moderate to good affinities. Clearly, more derivatives will be needed to more thoroughly explore the structure−activity relationship of these tropolones as inhibitors of this enzyme. In addition, a more detailed comprehension of the precise binding mode in the active site would be greatly helped by a high-resolution X-ray structure of an enzyme−inhibitor complex.

Experimental Section

Unless otherwise stated, materials were obtained from commercial sources and used without further purification. Tetrahydrofuran was distilled under nitrogen from sodium/benzophenone immediately prior to use. Diisopropylamine and triethylamine were distilled from calcium hydride and stored under nitrogen over 3-Å molecular sieves. Reactions involving LDA and TMSI were conducted under an inert atmosphere. Drying of the organic extract was carried out using $NaSO_4$. Chromatography was performed using Merck 60 (230−400 ASTM) silica gel according to the procedure published by Still (abbreviations for the elution solvents are as follows: H = heptane, C = methylene chloride, A = ethyl acetate, E = diethyl ether, T = toluene).[35] Unless otherwise stated, ^1H and ^{19}F NMR spectra were recorded in deuterated chloroform at 200 and 188 MHz, and proton-decoupled ^{13}C NMR spectra were recorded at 50 MHz; chemical shifts are expressed in ppm downfield from internal or external tetramethylsilane, hexafluorobenzene, and deuterated chloroform, respectively; coupling constants (J) are expressed in hertz (Hz). Low-resolution mass spectra were recorded using the positive or negative ion thermospray method, and high-resolution mass spectra were obtained from FAB methodology.

2-Carbomethoxy-3-methyl-7-methoxytropone (i).[13] Methyl iodide (170 mg, 1.2 mmol) was added to a mixture of 7-carboxy-6-methyltropolone (180 mg, 1 mmol) and cesium carbonate (359 mg, 1.1 mmol) in anhydrous DMF (5 mL) at room temperature. Stirring was continued overnight. The crude mixture was then concentrated, and the residue was subjected to a standard workup. Chromatography and elution with H/A (9:1) yielded the desired product as an amber oil (152 mg, 73% yield): ^1H NMR δ 2.31 (s, 3H), 3.90 (s, 6H), 6.62 (d, 1H, ^3J = 9.9), 6.75 (d, 1H, ^3J = 10.8), 6.96 (dd, 1H, ^3J = 9.9, 10.8); MS (TSP$^+$) 209 (MH^+).



i: R=OMe
ii: R=*t*-Butyl
iii: R= (*i*-Prop)$_2$N

2-Carbomethoxy-3-methyl-7-*tert*-butyltropone (ii).[12] To a solution of ester **i** (104 mg, 0.5 mmol) in dry THF (1 mL) cooled to −78 °C was added dropwise *tert*-butyllithium (294 μL of a 1.7 N solution in hexanes, 0.5 mmol). The dark-red solution was stirred at the same temperature for 0.5 h and quenched with water (40 μL). The solution was warmed, and a usual workup led to the isolation of a brown oil. Chromatographic separation using H/E (9:1) as eluent gave 26 mg (22%) of tropone **ii** and 22 mg of a byproduct of unidentified structure. **ii**: ^1H NMR (500 MHz) δ 1.30 (s, 9H), 2.26 (s, 3H), 3.85 (s, 3H), 6.69 (dd, 1H, ^3J = 1.3, 11.5), 6.80 (dd, 1H, ^3J = 7.9, 11.5), 7.06 (dd, 1H, ^3J = 1.3, 7.9); ^{13}C NMR (125 MHz) δ 18.98, 30.11, 37.83, 52.19, 128.69, 131.88, 135.35, 138.48, 141.39, 160.26, 168.19, 187.91; MS (TSP$^+$) 235 (MH^+), 252 (MNH_4^+).

2-Carbomethoxy-3-methyl-7-(diisopropylamino)-tropone (iii).[12] To a cooled (−78 °C) solution of LDA freshly prepared from diisopropylamine (50.6 mg, 70 μL, 0.5 mmol) in dry THF (1 mL) and *n*-butyllithium (312.5 μL of a 1.6 N solution in hexanes, 0.5 mmol) was added a solution of compound **i** (104 mg, 0.5 mmol) in THF (0.5 mL). Stirring of the resultant deep-red solution was continued for 30 min. Addition of water (40 μL), warming, and a usual workup furnished an orange oily residue which was subjected to chromatography. Elution (H/A = 4:1) afforded 22 mg of tropone **iii** (16% yield); this was followed by 28 mg (27%) of unconsumed starting material. **iii**: ^1H NMR (360 MHz) δ 1.34 (d, 12H, ^3J = 6.9), 2.29 (s, 3H), 3.83 (s, 3H), 4.11 (sept, 2H, ^3J = 6.8), 6.20 (d, 1H, ^3J = 10.7), 6.40 (d, 1H, ^3J = 10.4), 6.75 (t, 1H, ^3J = 10.5); ^{13}C NMR (125 MHz) δ 20.65, 22.97, 49.53, 51.98, 109.83, 123.51, 132.72, 143.61, 155.40, 169.21, 182.53.

Boronic Acids. General Procedure. To a vigorously stirred solution of the starting bromide (10 mmol) in THF (50 mL) cooled at −78 °C was added dropwise *n*-butyllithium (6.875 mL of a 1.6 N solution in hexanes). Stirring was continued for 15 min, and triisopropylborate (5.64 g, 6.92 mL, 30 mmol) was rapidly added. After 1 h of additional stirring at −78 °C, the mixture was warmed to room temperature and stirring was continued overnight. A usual workup and evaporation of the dried combined organic phases delivered the crude material which was subjected to purification when needed.

***p*-(Benzyloxy)phenylboronic Acid.** The crude material (2.28 g) was pure enough to be used in the next step (99% yield): ^1H NMR δ 5.18 (s, 2H), 7.12 (d, 2H, ^3J = 8.4), 7.32−7.54 (m, 5H), 8.20 (d, 2H, ^3J = 8.4); MS (TSP$^+$) 246 (MNH_4^+).

***o,m′*-Dimethoxyphenylboronic Acid.** The crude material was dissolved in diethyl ether (15 mL), and *n*-heptane (10 mL) was added. The resultant solution was placed in the cold for 16 h. Filtration gave the compound in 37% yield (651 mg): ^1H NMR δ 3.83 (s, 3H), 3.91 (s, 3H), 6.91 (d, 1H, ^3J = 9.4), 6.99 (dd, 1H, ^4J = 3.9, ^3J = 9.4), 7.42 (d, 1H, ^4J = 3.9).

***p*-[2-[(Diphenylmethylene)amino]ethyl]phenylboronic Acid.** Chromatography and elution (H/A = 1:1) delivered 1.09 g of the desired boronic acid (33% yield): ^1H NMR δ 3.07 (t, 2H, ^3J = 7.2), 3.69 (t, 2H, ^3J = 7.2), 6.89−7.68 (m, 12H), 7.98 (d, 2H, ^3J = 6.1).

***m*-[5-(2-Naphthyl)-2-oxadiazolyl]phenylboronic Acid.** Chromatography and sequential elution with H/A (1:1) and pure ethyl acetate led to the isolation of the boronic acid in 60% yield (1.90 g): ^1H NMR δ 7.17−8.30 (badly defined multiplet, 10H), 8.67 (s, 1H); MS (TSP$^+$) 317 (MH^+).

***m*-[[N-(*tert*-Butoxycarbonyl)amino]methyl]phenylboronic Acid.** Chromatography and elution (H/A = 3:2) gave the compound in 10% yield (250 mg): ^1H NMR δ 1.49 (s, 9H), 4.99 (d, 2H, ^3J = 9.7), 7.47 (t, 1H, ^3J = 7.2), 7.53 (d, 1H, ^3J = 7.3), 8.09 (s, 1H), 8.13 (d, 1H, ^3J = 7.3).

Bromination of Tropolones. 3-Bromo-7-phenyltropolone (5a). A mixture of starting tropolone **4a** (198 mg, 1 mmol), *N*-bromosuccinimide (178 mg, 1 mmol), and benzene (3 mL) was refluxed for 3 h. The solution was cooled and worked up. The crude orange solid was purified by crystallization in hot toluene (1 mL). After separation the crystals were washed with some *n*-pentane: yield, 89 mg (32%); ^1H NMR δ 6.88 (t, 1H, ^3J = 10.5), 7.42−7.62 (m, 6H), 8.10 (d, 1H, ^3J = 10.6); MS (TSP$^+$) 277, 279 (MH^+), 294, 296 (MNH_4^+). 3,5-Dibromo-7-phenyltropolone was also isolated as a byproduct of the reaction (32 mg, 9%): ^1H NMR δ 7.35−7.52 (m, 5H), 7.83 (d, 1H, ^4J = 2.0), 8.37 (d, 1H, ^4J = 2.0).

3-Bromo-7-(*p*-methoxyphenyl)tropolone (5b). The same procedure was used. A 10 mmol scale crude product purified by double crystallization from hot CCl_4 yielded 1.23 g (40%) of desired bromotropolone **5b**; this yield was raised to 45% when purification was achieved by chromatography (eluent: H/E/A = 700:300:5): ^1H NMR δ 3.86 (s, 3H), 6.87 (t, 1H, ^3J = 10.5), 6.99 (d, 2H, ^3J = 8.8), 7.46 (d, 2H, ^3J = 8.8), 7.54 (d, 1H, ^3J = 10.8), 8.05 (d, 1H, ^3J = 10.8); MS (TSP$^+$) 307, 309 (MH^+), 324, 326 (MNH_4^+).

3,5-Dibromo-7-(*p*-methoxyphenyl)tropolone was also isolated in 10% yield (385 mg): ^1H NMR δ 3.86 (s, 3H), 6.99 (d, 2H, ^3J = 8.7), 7.46 (d, 2H, ^3J = 8.7), 7.86 (d, 1H, ^4J = 1.9), 8.34 (d, 1H, ^4J = 1.9); MS (TSP$^+$) 385, 387, 389 (MH^+).

1,7-Dibromo-2,3,4,6-tetrahydroxy-5*H*-benzocycloheptadien-5-one (27b). A solution of bromine (1.6 g, 0.515 mL) in acetic acid (5 mL) was added dropwise at room temperature to a solution of purpurogallin (**27a**) (1.10 g, 5 mmol) in acetic acid (35 mL). The mixture was stirred at the same temperature for 10 days and filtered. The solid was washed with CH_2Cl_2 and recrystallized from acetone (three crops): yield, 1.046

g (55%); ^{1}H NMR δ 7.25 (d, 1H, ^3J = 13.0), 7.85 (d, 1H, ^3J = 13.0); MS (TSP$^-$) 375, 377, 379 (M − H), 297, 299 (M − H − Br).

Bromination of 3,7-Dihydroxytropolone. In a four-neck, 1-L flask equipped with a mechanical stirrer, a thermometer and an addition funnel designed for slow addition were added 3,7-dihydroxytropolone[11,17b] (6.16 g, 40 mmol) and anhydrous DMF (400 mL) under argon. The solution was cooled to −15 °C by using an acetone bath and a cryostat. *N*-Bromosuccinimide (7.12 g, 40 mmol) was dissolved in acetone (400 mL), and the resultant solution was placed in the addition funnel. This solution was then added dropwise over a period of time of 5.5−6 h, and stirring was continued overnight at the same temperature. This produced a red-brown solution which was evaporated under reduced pressure (DMF was removed by using an oil pump) until a dark, oily solid was obtained (18.91 g). Water (520 mL) was added to this residue, and the mixture was stirred for 20 h. Filtration and drying of the precipitate yielded 6.1 g of creamy powder whose ^{1}H NMR indicated a 47:43:10 mixture of **9**/**8**/**10**.

4-Bromo-3,7-dihydroxytropolone (9): ^{1}H NMR (CD_3OD) δ 6.82 (d, 1H, ^3J = 12.2), 7.57 (d, 1H, ^3J = 12.2).

4,6-Dibromo-3,7-dihydroxytropolone (10): ^{1}H NMR (CD_3-OD) δ 8.24 (s, 1H).

Compound **10** was also obtained in the pure form by direct bisbromination of 3,7-dihydroxytropolone. Thus refluxing for 6 h a mixture of *N*-bromosuccinimide (178 mg, 1 mmol) and 3,7-dihydroxytropolone (75 mg, 0.5 mmol) in benzene (2 mL) and evaporating the solvent left a crude, creamy solid which was stirred in water (4 mL) for 2 h to give the pure compound (72 mg). Evaporation of the filtrate and repetition of the process with 2 mL of water yielded another crop (50 mg): total yield, 122 mg (78%); MS (TSP$^-$) 309, 311, 313 (M − H). Anal. ($C_7H_4Br_2O_4$) C, H.

ATA Reactions. General Procedure. The required starting material (1 mmol) was dissolved in a 20:2:1 mixture of acetic anhydride/trifluoroacetic acid/acetic acid (ATA;[17] 4 mL) and heated at 90 °C for the requisite time. The mixture was then allowed to cool to room temperature and worked up. Chromatographic purification of the crude material led to the isolation of the desired product.

3-Phenyl-2,7-diacetoxytropone (6a): heating time, 16 h; eluent, H/A (3:2); yield, 170 mg (57%); ^{1}H NMR δ 2.10 (s, 3H), 2.37 (s, 3H), 6.99−7.45 (m, 8H); MS (TSP$^+$) 299 (MH$^+$), 256 (MH$^+$ − Ac).

3-(*p*-Methoxyphenyl)-2,7-diacetoxytropone (6b): heating time, 4.5 h; eluent, H/E (7:3); yield, 164 mg (50%); ^{1}H NMR δ 2.14 (s, 3H), 2.37 (s, 3H), 3.85 (s, 3H), 6.90−7.33 (m, 7H); MS (TSP$^+$) 329 (MH$^+$), 346 (MNH$_4^+$). Further elution gave 2-acetoxy-7-bromo-3-(*p*-methoxyphenyl)tropone as a byproduct (14 mg, 4% yield): ^{1}H NMR δ 2.22 (s, 3H), 3.85 (s, 3H), 6.83 (t, 1H, ^3J = 10.5), 6.94 (d, 2H, ^3J = 8.9), 7.22 (d, 1H, ^3J = 10.6), 7.31 (d, 2H, ^3J = 8.7), 7.92 (d, 1H, ^3J = 10.1); MS (TSP$^+$) 349, 351 (MH$^+$).

1-Bromo-2,3,4,6,7-pentaacetoxy-5*H*-benzocycloheptadien-5-one (28b) and 1,7-Dibromo-2,3,4,6-tetraacetoxy-5*H*-benzocycloheptadien-5-one (28a): heating time, 24 h; eluent, H/A (3:2); yield **28b**, 231 mg (44%); ^{1}H NMR δ 2.26 (s, 3H), 2.29 (s, 3H), 2.30 (s, 6H), 2.38 (s, 3H), 6.56 (d, 1H, ^3J = 13.0), 7.70 (d, 1H, ^3J = 13.0); ^{13}C NMR δ 20.04, 20.05, 20.35, 20.55, 118.1, 124.4, 130.2, 130.5, 131.6, 138.4, 140.2, 142.2, 143.7, 144.7, 166.2, 166.7, 167.7, 180.7; MS (TSP$^+$) 542, 544 (MNH$_4^+$). More elution delivered **28a** (109 mg, 20% yield): ^{1}H NMR δ 2.28 (s, 3H), 2.30 (s, 3H), 2.32 (s, 3H), 2.38 (s, 3H), 6.91 (d, 1H, ^3J = 12.8), 7.48 (d, 1H, ^3J = 12.8); MS (TSP$^+$) 562, 564, 566 (MNH$_4^+$).

Hydrolysis of Polyacetate Compounds. 3-Phenyl-7-hydroxytropolone (7a). The bisacetate **6a** (298 mg, 1 mmol) was dissolved in a 2:1 mixture of acetic acid/water, heated at 100 °C for 8 h, cooled, and evaporated. Crystallization from hot CCl_4 gave the product in 26% yield (56 mg): ^{1}H NMR δ 7.16−7.30 (m, 2H), 7.42−7.57 (m, 5H); MS (TSP$^+$) 215 (MH$^+$), 232 (MNH$_4^+$). Anal. ($C_{13}H_{10}O_3$) C, H.

3-(*p*-Methoxyphenyl)-7-hydroxytropolone (7b). A solution of tropone **6b** (65 mg, 0.2 mmol) in methanol (0.6 mL) and 0.4 mL of a 1 M solution of sodium methanolate in methanol was stirred for 40 h at room temperature. The pH was raised to 7 by adding 1 N HCl, the mixture was evaporated, and dry THF (6 mL) was added to the residue. Filtration and addition of CH_2Cl_2 (1.5 mL) induced a precipitate which was filtered to give 95 mg of the pure compound (39% yield): ^{1}H NMR δ 3.82 (s, 3H), 5.83 (d, 1H, ^3J = 12.4), 6.94 (d, 2H, ^3J = 9.0), 7.03 (t, 1H, ^3J = 11.7), 7.45 (d, 2H, ^3J = 8.9), 7.97 (d, 1H, ^3J = 12.1); MS (TSP$^+$) 245 (MH$^+$).

2,3,4,6,7-Pentahydroxy-5*H*-benzocycloheptadien-5-one (27d). The procedure was the same as for compound **8a**. The crude material was sublimed at 160−215 °C: 0.01 mbar (yield, 85 mg (36%)); ^{1}H NMR δ 6.71 (d, 1H, ^3J = 12.4), 6.80 (s, 1H), 7.25 (d, 1H, ^3J = 12.4); MS (TSP$^+$) 237 (MH$^+$). Anal. ($C_{11}H_8O_6$·0.25H_2O) C, H.

Permethylation of the 9/8/10 Mixture. The **9**/**8**/**10** mixture (5 g) was dissolved in dry tetrahydrofuran (700 mL) and the solution was cooled to 0 °C. Freshly prepared diazomethane (CAUTION) (320 mL of a 0.4 M solution in ether, 4 equiv) was added slowly, and the mixture was stirred overnight at 0 °C. Excess diazomethane was cautiously destroyed by adding acetic acid (2 mL), and the solution was warmed and evaporated. This was run several times (total amount of starting **9**/**8**/**10** mixture: 17.59 g), and a total of 23.76 g was obtained. Purification of the residue was achieved by chromatography on silical gel and elution with solvents of increasing polarities. Thus heptane/ethyl acetate (8:2) delivered dibromo derivatives **17** and **18**; this was followed by mono bromoderivatives **16**, **14**, **13**, and **15** by increasing the amount of ethyl acetate (6:4 to 1:4). Compounds **11** and **12** were isolated using pure ethyl acetate and a 9:1 mixture of ethyl acetate/methanol, respectively. Further purification is sometimes achieved by performing a second chromatography and using a mixture of ethyl acetate and methylene chloride as eluent.

5,7-Dibromo-2,3,4-trimethoxytropone (17): 200 mg; ^{1}H NMR (500 MHz) δ 3.90 (s, 3H), 3.92 (s, 3H), 3.97 (s, 3H), 7.93 (s, 1H); ^{13}C NMR (125 MHz) δ 60.5, 60.9, 61.8, 123.4, 124.0, 133.9, 154.1, 156.1, 160.3, 173.3; MS (TSP$^+$) 355, 357, 359 (MH$^+$).

4,6-Dibromo-2,3,7-trimethoxytropone (18): 1.928 g; ^{1}H NMR (500 MHz) δ 3.87 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 8.37 (s, 1H); ^{13}C NMR (125 MHz) δ 60.3, 61.0, 62.0, 116.0, 133.7, 139.5, 154.7, 157.1, 163.1, 174.3; MS (TSP$^+$) 355, 357, 359 (MH$^+$).

7-Bromo-2,3,4-trimethoxytropone (13): 2.081 g; ^{1}H NMR (500 MHz) δ 3.86 (s, 3H), 3.88 (s, 3H), 3.94 (s, 3H), 6.77 (d, 1H, ^3J = 13.2), 7.38 (d, 1H, ^3J = 13.2); ^{13}C NMR (125 MHz) δ 60.5, 60.9, 61.8, 119.2, 134.0, 137.1, 155.2, 157.0, 158.7, 180.3; MS (TSP$^+$) 275, 277 (MH$^+$).

6-Bromo-2,3,7-trimethoxytropone (14): 2.668 g; ^{1}H NMR (500 MHz) δ 3.90 (s, 3H), 3.93 (s, 3H), 3.98 (s, 3H), 6.68 (d, 1H, ^3J = 12.9), 7.28 (d, 1H, ^3J = 12.9); ^{13}C NMR (125 MHz) δ 56.4, 59.5, 59.8, 120.6, 124.2, 132.2, 153.7, 157.5, 162.1, 173.5; MS (TSP$^+$) 275, 277 (MH$^+$).

4-Bromo-2,3,7-trimethoxytropone (15): 1.75 g; ^{1}H NMR (500 MHz) δ 3.86 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 6.13 (d, 1H, ^3J = 11.0), 7.92 (d, 1H, ^3J = 11.1); ^{13}C NMR (125 MHz) δ 56.4, 60.2, 61.5, 104.1, 131.2, 136.0, 153.2, 157.5, 160.7, 174.3; MS (TSP$^+$) 275, 277 (MH$^+$).

5-Bromo-2,3,4-trimethoxytropone (16): 1.974 g; ^{1}H NMR (500 MHz) δ 3.89 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 6.45 (d, 1H, ^3J = 11.1), 7.50 (d, 1H, ^3J = 11.1); ^{13}C NMR (125 MHz) δ 56.5, 59.9, 61.2, 109.6, 122.9, 130.1, 156.3, 156.5, 163.0, 173.8; MS (TSP$^+$) 275, 277 (MH$^+$).

2,3,4-Trimethoxytropone (11): 5.40 g; ^{1}H NMR (500 MHz) δ 3.83 (s, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 6.26 (d, 1H, ^3J = 11.6), 6.86 (d, 1H, ^3J = 12.1), 7.00 (dd, 1H, ^3J = 11.6, 12.1); ^{13}C NMR (125 MHz) δ 56.2, 59.5, 61.2, 106.0, 131.7, 133.1, 153.9, 159.6, 160.5, 180.9; MS (TSP$^+$) 197 (MH$^+$).

2,3,7-Trimethoxytropone (12): 3.47 g; ^{1}H NMR (500 MHz) δ 3.84 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 6.61 (d, 1H, ^3J = 9.3), 6.84 (d, 1H, ^3J = 10.9), 6.93 (dd, 1H, ^3J = 9.3, 10.9); ^{13}C NMR (125 MHz) δ 56.4, 57.9, 59.4, 109.6, 118.3, 127.9, 153.1, 160.0, 164.8, 173.7; MS (TSP$^+$) 197 (MH$^+$).

3,7-Dibromo-2-methoxytropone (24a). To a slurry of the 3,7-dibromotropolone (1.87 g, 6.7 mmol) in THF (28 mL) at 0

°C was added slowly a freshly prepared solution of diazomethane (CAUTION) (56 mL of a 0.4 M solution in diethyl ether, 18.09 mmol), and stirring was continued overnight at room temperature. Acetic acid (2 mL) was added slowly to the stirring mixture cooled at 0 °C. Evaporation of the volatiles, chromatography of the residue, and elution (H/A = 9:1) delivered the desired compound (296 mg, 15% yield): ^{1}H NMR δ 4.01 (s, 3H), 6.49 (dd, 1H, ^3J = 9.4, 11.7), 7.52 (d, 1H, ^3J = 11.7), 8.03 (d, 1H, ^3J = 9.4); MS (TSP$^+$) 293, 295, 297 (MH^+), 310, 312, 314 (MNH_4^+).

Permethylation of 3,7-Dihydroxytropolone. The same procedure was applied to 3,7-dihydroxytropolone using an excess (6 equiv) of diazomethane solution (CAUTION). A 55:45 mixture of isomeric trimethoxytropones **11** and **12** was obtained and purified by chromatography using pure ethyl acetate as eluent (yield: 89%).

Suzuki Coupling Reaction. General Procedure for the Monosubstituted Tropones. In a flask flushed with argon were placed the requisite isomer of permethylated monobromotropolone derivative (**2, 13**, **14**, **15**, or **16**; 110 mg, 0.4 mmol), toluene (8 mL), and palladium tetrakistriphenylphosphine (46 mg, 0.04 mmol, 0.1 equiv). A 2 M aqueous solution of sodium carbonate (0.4 mL, 0.8 mmol, 2 equiv) and the boronic acid (0.44 mmol, 1.1 equiv) dissolved[36] in absolute ethanol (0.4 mL) were then sequentially added, and the mixture was heated at 100 °C for 16 h. Evaporation of the volatiles left a residue which was purified by chromatography on silica gel. Elution gave the desired products in yields described in Table 1. The eluents and the isolated masses are given first.

7-Phenyl-2-methoxytropone (3a): E; 80 mg; ^{1}H NMR δ 3.95 (s, 3H), 6.74 (d, 1H, ^3J = 9.4), 6.83−6.94 (m, 1H), 6.99−7.10 (m, 1H), 7.29−7.90 (m, 6H); MS (TSP$^+$) 213 (MH^+).

7-(*p*-Methoxyphenyl)-2-methoxytropone (3b): E; 88 mg; ^{1}H NMR δ 3.83 (s, 3H), 3.94 (s, 3H), 6.73 (d, 1H, ^3J = 9.4), 6.81−7.06 (m, 4H), 7.41−7.47 (m, 3H); MS (TSP$^+$) 243 (MH^+).

7-(*p*-Phenylphenyl)-2-methoxytropone (3c): H/A = 1:1; 90 mg; ^{1}H NMR δ 3.96 (s, 3H), 6.77 (d, 1H, ^3J = 9.6), 6.88−6.98 (m, 1H), 7.03−7.11 (m, 1H), 7.40−7.73 (m, 10H); MS (TSP$^+$) 289 (MH^+), 311 (MNa^+).

7-[*p*-(Benzyloxy)phenyl]-2-methoxytropone (3d): H/A = 1:9, then pure A; 89 mg; ^{1}H NMR δ 3.94 (s, 3H), 5.11 (s, 2H), 6.98−7.46 (m, 12H), 7.59 (dd, 1H, ^4J = 1.2, ^3J = 8.1).

7-(*o*-Formylphenyl)-2-methoxytropone (3e): H/A = 4:1; 91 mg; ^{1}H NMR δ 3.96 (s, 3H), 6.84 (d, 1H, ^3J = 9.7), 6.88−6.98 (m, 1H), 7.11−7.22 (m, 1H), 7.26 (dd, 1H, ^4J = 1.4, ^3J = 7.5), 7.42 (dd, 1H, ^4J = 1.1, ^3J = 8.7), 7.45−7.69 (m, 2H), 7.95 (dd, 1H, ^4J = 1.5, ^3J = 7.6), 9.81 (s, 1H).

7-(*m*-Formylphenyl)-2-methoxytropone (3f): H/A = 7:3, then pure A; 72 mg; ^{1}H NMR δ 3.98 (s, 3H), 6.80 (d, 1H, ^3J = 9.6), 6.88−6.98 (m, 1H), 7.07−7.18 (m, 1H), 7.48−7.60 (m, 2H), 7.77 (dt, 1H, ^4J = 1.5, ^3J = 7.8), 7.88 (dt, 1H, ^4J = 1.3, ^3J = 7.5), 7.98 (t, 1H, ^4J = 1.6), 10.04 (s, 1H); MS (TSP$^+$) 241 (MH^+).

7-(*m*-Cyanophenyl)-2-methoxytropone (3g): C/E = 9:1; 72 mg; ^{1}H NMR δ 3.99 (s, 3H), 6.82 (d, 1H, ^3J = 10.6), 6.89−6.99 (m, 1H), 7.10−7.21 (m, 1H), 7.41−7.54 (m, 2H), 7.61−7.77 (m, 3H), (CD_3CN) 3.93 (s, 3H), 6.90−7.00 (m, 2H), 7.19 (dd, 1H, ^3J = 8.7, 10.6), 7.45−7.58 (m, 2H), 7.63−7.71 (m, 2H), 7.77 (s, 1H); MS (TSP$^+$) 238 (MH^+), 255 (MNH_4^+).

7-[*m*-[7-(2-Methoxytropolonyl)]phenyl]-2-methoxytropone (3h): C/A = 1:1, the M/A = 1:9; 62 mg; ^{1}H NMR δ 3.95 (s, 6H), 6.76 (d, 2H, ^3J = 9.4), 6.84−6.94 (m, 2H), 6.99−7.11 (m, 2H), 7.40−7.51 (m, 3H), 7.55−7.60 (m, 3H); MS (TSP$^+$) 347 (MH^+), 364 (MNH_4^+).

7-(5-Pyrimidyl)-2-methoxytropone (3i): M/A = 1:9; 26 mg; ^{1}H NMR δ 4.00 (s, 3H), 6.85 (d, 1H, ^3J = 9.7), 6.93−7.04 (m, 1H), 7.15−7.26 (m, 1H), 7.48 (dd, 1H, ^4J = 1.0, ^3J = 8.9), 8.87 (s, 2H), 9.18 (s, 1H); MS (TSP$^+$) 215 (MH^+).

7-*n*-Octyl-2-methoxytropone (3j): H/A = 1:1; 38 mg; ^{1}H NMR δ 0.86 (t, 3H, ^3J = 6.9), 1.18−1.90 (m, 12H), 2.74 (t, 2H, ^3J = 7.6), 3.91 (s, 3H), 6.70 (d, 1H, ^3J = 9.6), 6.72−6.83 (m, 1H), 6.93−7.00 (m, 1H), 7.34 (d, 1H, ^3J = 8.8); MS (TSP$^+$) 249 (MH^+).

7-(*p*-Methoxyphenyl)-2,3,4-trimethoxytropone (19a): H/A = 1:1; 60 mg; ^{1}H NMR δ 3.73 (s, 3H), 3.86 (s, 3H), 3.96 (s, 3H), 3.99 (s, 3H), 6.86−7.02 (m, 4H), 7.27−7.34 (m, 2H).

7-(*o,m′*-Dimethoxyphenyl)-2,3,4-trimethoxytropone (19b): H/A = 3:7; 66 mg; ^{1}H NMR δ 3.72 (s, 3H), 3.79 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 3.95 (s, 3H), 6.28 (d, 1H, ^3J = 10.4), 6.81−6.86 (m, 3H), 7.18 (d, 1H, ^3J = 10.3), (CD_3CN) 3.68 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 3.87 (s, 6H), 6.48 (d, 1H, ^3J = 10.6), 6.84−6.94 (m, 3H), 7.20 (d, 1H, ^3J = 10.8).

7-(*o*-Fluorophenyl)-2,3,4-trimethoxytropone (19c): H/A = 9:1; 61 mg; ^{1}H NMR δ 3.94 (s, 6H), 3.98 (s, 3H), 6.33 (d, 1H, ^3J = 10.5), 7.16−7.36 (m, 5H); ^{19}F NMR δ 49.01−49.13 (m, 1F); MS (TSP$^+$) 249 (MH^+).

7-[*p*-(Trifluoromethyl)phenyl]-2,3,4-trimethoxytropone (19d): H/A = 7:3; 113 mg; ^{1}H NMR δ 3.92 (s, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 6.34 (d, 1H, ^3J = 10.7), 7.26 (d, 1H, ^3J = 10.7), 7.56 (d, 2H, ^3J = 8.5), 7.64 (d, 2H, ^3J = 8.5); ^{19}F NMR δ 99.17 (s, 3F); MS (TSP$^+$) 341 (MH^+).

7-(*m*-Formylphenyl)-2,3,4-trimethoxytropone (19e): H/A = 3:2; 71 mg; ^{1}H NMR δ 3.93 (s, 3H), 3.94 (s, 6H), 6.36 (d, 1H, ^3J = 10.8), 7.31 (d, 1H, ^3J = 10.6), 7.56 (t, 1H, ^3J = 7.7), 7.74−7.88 (m, 2H), 7.96−7.98 (m, 1H), 10.04 (s, 1H), (CD_3CN) 3.83 (s, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 6.49 (d, 1H, ^3J = 10.8), 7.35 (d, 1H, ^3J = 10.7), 7.58 (t, 1H, ^3J = 7.6), 7.73 (d, 1H, ^3J = 7.6), 7.85 (d, 1H, ^3J = 7.6), 7.95 (s, 1H), 10.02 (s, 1H); MS (TSP$^+$) 301 (MH^+).

7-[*m*-[[*N*-(*tert*-Butoxycarbonyl)amino]methyl]phenyl]-2,3,4-trimethoxytropone (19f): H/A = 7:3; 67 mg; ^{1}H NMR δ 1.46 (s, 9H), 3.92 (s, 6H), 3.93 (s, 3H), 4.35 (d, 2H, ^3J = 7.8), 6.33 (d, 1H, ^3J = 8.7), 7.23−7.40 (m, 5H), (CD_3CN) 1.42 (s, 9H), 3.82 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 4.24 (d, 2H, ^3J = 6.2), 6.45 (d, 1H, ^3J = 10.4), 7.20−7.36 (m, 5H); MS (TSP$^+$) 402 (MH^+), 419 (MNH_4^+).

7-[*p*-[2-[(Diphenylmethylene)amino]ethyl]phenyl]-2,3,4-trimethoxytropone (19g): H/A = 2:3; 53 mg; ^{1}H NMR δ 3.04 (t, 2H, ^3J = 7.6), 3.67 (t, 2H, ^3J = 7.6), 3.92 (s, 6H), 3.94 (s, 3H), 6.32 (d, 1H, ^3J = 10.9), 7.00−7.65 (m, 15H), (CD_3CN) 2.98 (t, 2H, ^3J = 6.8), 3.59 (t, 2H, ^3J = 6.8), 3.81 (s, 3H), 3.82 (s, 3H), 3.86 (s, 3H), 6.43 (d, 1H, ^3J = 11.2), 6.95−7.02 (m, 2H), 7.14 (d, 2H, ^3J = 7.2), 7.24−7.62 (m, 11H); MS (TSP$^+$) 480 (MH^+).

7-(2-Benzofuryl)-2,3,4-trimethoxytropone (19h): H/A = 1:1; 57 mg; ^{1}H NMR δ 3.90 (s, 3H), 3.93 (s, 3H), 3.98 (s, 3H), 6.47 (d, 1H, ^3J = 11.2), 7.18−7.34 (m, 2H), 7.46 (d, 1H, ^3J = 7.8), 7.63 (d, 1H, ^3J = 7.1), 8.02 (s, 1H), 8.19 (d, 1H, ^3J = 11.1); MS (TSP$^+$) 313 (MH^+), 330 (MNH_4^+).

7-(2-Thienyl)-2,3,4-trimethoxytropone (19i): H/A = 1:1; 21 mg; ^{1}H NMR δ 3.92 (s, 3H), 3.97 (s, 3H), 3.98 (s, 3H), 6.47 (d, 1H, ^3J = 11.1), 7.13 (dd, 1H, ^3J = 4.2, 5.6), 7.47 (dd, 1H, ^4J = 2.8, ^3J = 5.6), 7.54 (dd, 1H, ^4J = 2.8, ^3J = 4.2), 7.82 (d, 1H, ^3J = 11.1), (CD_3CN) 3.83 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 6.59 (d, 1H, ^3J = 11.2), 6.94 (dd, 1H, ^3J = 4.4, 6.1), 7.15 (dd, 1H, ^4J = 1.2, ^3J = 6.1), 7.52 (dd, 1H, ^4J = 1.2, ^3J = 4.4), 7.60 (d, 1H, ^3J = 11.2).

7-(3-Thienyl)-2,3,4-trimethoxytropone (19j): H/A = 1:1; 98 mg; ^{1}H NMR δ 3.87 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 6.32 (d, 1H, ^3J = 10.7), 7.28−7.48 (m, 3H), 7.83 (s, 1H), (CD_3CN) 3.83 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 6.44 (d, 1H, ^3J = 10.6), 7.37−7.44 (m, 2H), 7.53 (d, 1H, ^3J = 10.6), 7.85−7.89 (m, 1H); MS (TSP$^+$) 279 (MH^+).

6-(5-Pyrimidyl)-2,3,7-trimethoxytropone (19k): pure A, then M/A = 5:95; 40 mg; ^{1}H NMR δ 3.91 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 6.38 (d, 1H, ^3J = 10.6), 7.26 (d, 1H, ^3J = 10.6), 8.85 (s, 2H), 9.15 (s, 1H); MS (TSP$^+$) 275 (MH^+).

6-Phenyl-2,3,7-trimethoxytropone (20a): H/A = 3:2; 73 mg; ^{1}H NMR δ 3.74 (s, 3H), 3.97 (s, 3H), 3.99 (s, 3H), 6.95 (s, 2H), 7.31−7.48 (m, 5H), (CD_3CN) 3.69 (s, 3H), 3.83 (s, 3H), 3.94 (s, 3H), 6.94 (d, 1H, ^3J = 12.4), 7.06 (d, 1H, ^3J = 12.5), 7.30−7.46 (m, 5H); MS (TSP$^+$) 273 (MH^+).

6-[*p*-(Benzyloxy)phenyl]-2,3,7-trimethoxytropone (20b): H/A = 1:1; 104 mg; ^{1}H NMR δ 3.76 (s, 3H), 3.98 (s, 6H), 4.00 (s, 3H), 5.13 (s, 2H), 6.91 (d, 1H, ^3J = 12.6), 6.99 (d, 1H, ^3J = 12.5), 7.04 (d, 2H, ^3J = 8.4), 7.30−7.51 (m, 7H), (CD_3CN) 3.68 (s, 3H), 3.82 (s, 6H), 3.92 (s, 3H), 5.13 (s, 2H), 6.89−7.09 (m, 4H), 7.39 (d, 2H, ^3J = 8.8), 7.36−7.55 (m, 5H).

6-[*p*-(Trifluoromethyl)phenyl]-2,3,7-trimethoxytropone (20c): H/A = 2:3; 119 mg; ^{1}H NMR δ 3.92 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 6.35 (d, 1H, ^3J = 10.6), 7.26 (d, 1H, ^3J = 10.6), 7.56 (d, 2H, ^3J = 8.4), 7.65 (d, 2H, ^3J = 8.4), (CD_3-

CN) 3.83 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 6.46 (d, 1H, ^3J = 10.6), 7.31 (d, 1H, ^3J = 10.4), 7.58 (d, 2H, ^3J = 8.4), 7.68 (d, 2H, ^3J = 8.4); ^{19}F NMR δ 99.15 (s, 3F); MS (TSP$^+$) 341 (MH$^+$).

6-[*m*,*m*-Bis(trifluoromethyl)phenyl]-2,3,7-trimethoxytropone (20d). A first chromatography was run (H/A = 3:2) to give a slightly impure material which was subjected to a second chomatography (T/A = 7:3): 104 mg; ^{1}H NMR δ 3.83 (s, 3H), 3.87 (s, 3H), 3.92 (s, 3H), 6.50 (d, 1H, ^3J = 11.2), 7.41 (d, 1H, ^3J = 11.2), 7.96 (s, 1H), 8.03 (s, 2H), (CD$_3$CN) 3.95 (s, 3H), 3.98 (s, 6H), 6.41 (d, 1H, ^3J = 10.8), 7.30 (d, 1H, ^3J = 10.8), 7.84 (s, 1H), 7.94 (s, 2H); ^{19}F NMR δ 99.17 (s, 6F).

6-(*m*-Cyanophenyl)-2,3,7-trimethoxytropone (20e): C/E = 4:1; 68 mg; ^{1}H NMR δ 3.80 (s, 3H), 3.99 (s, 3H), 4.02 (s, 3H), 6.85 (d, 1H, ^3J = 12.6), 6.98 (d, 1H, ^3J = 12.6), 7.51−7.71 (m, 4H), (CD$_3$CN) 3.71 (s, 3H), 3.85 (s, 3H), 3.94 (s, 3H), 6.88 (d, 1H, ^3J = 12.6), 7.06 (d, 1H, ^3J = 12.6), 7.53−7.72 (m, 4H); MS (TSP$^+$) 298 (MH$^+$).

6-(*m*-Acetamidophenyl)-2,3,7-trimethoxytropone (20f): A/M = 95:5; 55 mg; ^{1}H NMR δ 2.19 (s, 3H), 3.71 (s, 3H), 3.94 (s, 3H), 3.98 (s, 3H), 6.92 (s, 2H), 7.02 (d, 1H, ^3J = 7.6), 7.33 (t, 1H, ^3J = 7.6), 7.54 (s, 1H), 7.56 (d, 1H, ^3J = 7.6), (CD$_3$CN) 2.07 (s, 3H), 3.68 (s, 3H), 3.82 (s, 3H), 3.91 (s, 3H), 6.89 (d, 1H, ^3J = 12.5), 6.98 (d, 1H, ^3J = 8.3), 7.02 (d, 1H, ^3J = 12.5), 7.35 (t, 1H, ^3J = 8.3), 7.51−7.55 (m, 2H).

6-(*m*-Nitrophenyl)-2,3,7-trimethoxytropone (20g): H/A = 3:2; 81 mg; ^{1}H NMR δ 3.81 (s, 3H), 3.98 (s, 3H), 4.01 (s, 3H), 6.87 (d, 1H, ^3J = 12.5), 6.98 (d, 1H, ^3J = 12.5), 7.56−7.73 (m, 2H), 8.22−8.26 (m, 2H), (CD$_3$CN) 3.73 (s, 3H), 3.84 (s, 3H), 3.95 (s, 3H), 6.93 (d, 1H, ^3J = 12.6), 7.10 (d, 1H, ^3J = 12.6), 7.60−7.77 (m, 2H), 8.17−8.26 (m, 2H); MS (ES$^+$) 318 (MH$^+$).

6-(1-Naphthyl)-2,3,7-trimethoxytropone (20h): H/A = 2:3; 71 mg; ^{1}H NMR δ 3.65 (s, 3H), 4.04 (s, 6H), 6.89 (d, 1H, ^3J = 12.6), 6.98 (d, 1H, ^3J = 12.6), 7.32 (dd, 1H, ^4J = 1.0, ^3J = 7.0), 7.39−7.60 (m, 4H), 7.87−7.95 (m, 2H).

6-(2-Naphthyl)-2,3,7-trimethoxytropone (20i): H/A = 3:7; 67 mg; ^{1}H NMR δ 3.76 (s, 3H), 3.99 (s, 3H), 4.00 (s, 3H), 6.94 (d, 1H, ^3J = 12.6), 7.06 (d, 1H, ^3J = 12.6), 7.46−7.55 (m, 3H), 7.80−7.91 (m, 4H), (CD$_3$CN) 3.68 (s, 3H), 3.84 (s, 3H), 3.92 (s, 3H), 7.00 (s, 2H), 7.39−7.53 (m, 3H), 7.78 (s, 1H), 7.83−7.92 (m, 3H).

6-[*m*-[5-(2-Naphthyl)-2-oxadiazolyl]phenyl]-2,3,7-trimethoxytropone (20j): H/A = 1:4, then pure A; 71 mg; ^{1}H NMR δ 3.82 (s, 3H), 4.02 (s, 3H), 4.04 (s, 3H), 7.02 (s, 2H), 7.55−7.68 (m, 4H), 7.90−8.03 (m, 3H), 8.19−8.26 (m, 3H), 8.66 (s, 1H), (CD$_3$CN) 3.78 (s, 3H), 3.89 (s, 3H), 3.98 (s, 3H), 6.99 (d, 1H, ^3J = 12.2), 7.12 (d, 1H, ^3J = 12.2), 7.55−8.26 (m, 10H), 8.73 (s, 1H); MS (TSP$^+$) 467 (MH$^+$).

6-[4-[(*tert*-Butyldimethylsilyl)oxy]butyl]-2,3,7-trimethoxytropone (20k): H/A = 7:3; 47 mg; ^{1}H NMR δ 0.46 (s, 6H), 0.89 (s, 9H), 1.58−1.68 (m, 4H), 2.65 (t, 2H, ^3J = 7.2), 3.63 (t, 2H, ^3J = 5.5), 3.91 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 6.84 (s, 2H); (CD$_3$CN) 0.45 (s, 6H), 0.91 (s, 9H), 1.50−1.68 (m, 4H), 2.51−2.58 (m, 2H), 3.53−3.59 (m, 2H), 3.79 (s, 3H), 3.84 (s, 3H), 3.89 (s, 3H), 6.90 (d, 1H, ^3J = 10.9), 6.97 (d, 1H, ^3J = 10.9); MS (TSP$^+$) 269 (MH$^+$ − *t*-BuMe$_2$Si).

6-[5-[(*tert*-Butyldiphenylsilyl)oxy]pentyl]-2,3,7-trimethoxytropone (20l): C/A = 9:1; 64 mg; ^{1}H NMR δ 1.39 (s, 9H), 1.40−1.66 (m, 6H), 2.61 (t, 2H, ^3J = 7.5), 3.66 (t, 2H, ^3J = 6.3), 3.90 (s, 3H), 3.91 (s, 3H), 3.93 (s, 3H), 6.81 (s, 2H), 7.35−7.42 (m, 6H), 7.64−7.67 (m, 4H); (CD$_3$CN) 1.03 (s, 9H), 1.42−1.63 (m, 6H), 2.61 (t, 2H, ^3J = 7.5), 3.69 (t, 2H, ^3J = 6.2), 3.79 (s, 3H), 3.81 (s, 3H), 3.87 (s, 3H), 6.85 (d, 1H, ^3J = 12.5), 6.93 (d, 1H, ^3J = 12.5), 7.38−7.46 (m, 6H), 7.66−7.70 (m, 4H); MS (TSP$^+$) 521 (MH$^+$).

4-(*p*-Methoxyphenyl)-2,3,7-trimethoxytropone (21a): H/A = 1:1; 83 mg; ^{1}H NMR δ 3.85 (s, 3H), 3.92 (s, 6H), 3.94 (s, 3H), 6.34 (d, 1H, J = 10.6), 6.94 (d, 2H, ^3J = 8.6), 7.27 (d, 1H, ^3J = 10.6), 7.44 (d, 2H, ^3J = 8.7), (CD$_3$CN) 3.68 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 3.93 (s, 3H), 6.95 (d, 1H, ^3J = 12.6), 6.99 (d, 2H, ^3J = 8.8), 7.04 (d, 1H, ^3J = 12.6), 7.29 (d, 2H, ^3J = 8.8); MS (TSP$^+$) 303 (MH$^+$).

4-[*p*-(Trifluoromethyl)phenyl]-2,3,7-trimethoxytropone (21b): H/A = 7:3; 121 mg; ^{1}H NMR δ 3.65 (s, 3H), 3.94 (s, 3H), 3.98 (s, 3H), 6.72 (d, 1H, ^3J = 10.6), 6.93 (d, 1H, ^3J = 10.6), 7.47 (d, 2H, ^3J = 8.2), 7.67 (d, 2H, ^3J = 8.2); ^{19}F NMR δ 99.22 (s, 3F); MS (TSP$^+$) 341 (MH$^+$).

4-(*m*-Formylphenyl)-2,3,7-trimethoxytropone (21c): H/A = 1:1, then pure A; 71 mg; ^{1}H NMR δ 3.64 (s, 3H), 3.94 (s, 3H), 3.98 (s, 3H), 6.74 (d, 1H, ^3J = 10.6), 6.98 (d, 1H, ^3J = 10.6), 7.55−7.67 (m, 2H), 7.88−7.93 (m, 2H), 10.07 (s, 1H).

5-[*m*-(Trifluoromethyl)phenyl]-2,3,4-trimethoxytropone (22a): H/A = 7:3; 68 mg; ^{1}H NMR δ 3.57 (s, 3H), 3.95 (s, 3H), 4.02 (s, 3H), 7.02 (d, 1H, ^3J = 9.4), 7.10 (d, 1H, ^3J = 9.4), 7.53−7.67 (m, 4H), (CD$_3$CN) 3.53 (s, 3H), 3.88 (s, 3H), 3.91 (s, 3H), 6.89 (d, 1H, ^3J = 12.7), 7.141 (d, 1H, ^3J = 12.7), 7.61−7.71 (m, 4H); ^{19}F NMR δ 99.14 (s, 3F); MS (TSP$^+$) 341 (MH$^+$).

5-[*p*-(Trifluoromethyl)phenyl]-2,3,4-trimethoxytropone (22b): H/A = 7:3; 50 mg; ^{1}H NMR δ 3.57 (s, 3H), 3.95 (s, 3H), 4.03 (s, 3H), 7.05 (s, 2H), 7.48 (d, 2H, ^3J = 8.2), 7.69 (d, 2H, ^3J = 8.2); ^{19}F NMR δ 99.14 (s, 3F); MS (TSP$^+$) 341 (MH$^+$).

Ethyl 4-[*p*-(trifluoromethyl)phenyl]-2,3-dimethoxybenzoate (23): eluted first as a byproduct of the reaction (13 mg, 9% yield); ^{1}H NMR δ 1.42 (t, 3H, ^3J = 7.10), 3.66 (s, 3H), 4.00 (s, 3H), 4.41 (q, 2H, ^3J = 7.1), 7.13 (d, 1H, ^3J = 8.2), 7.59 (d, 1H, ^3J = 8.2), 7.60−7.72 (m, 4H); ^{13}C NMR δ 14.3, 60.9, 61.2, 61.7, 123.9, 125.1, 125.2, 125.4, 126.5, 129.5, 138.6, 141.0, 151.6, 153.7, 165.8; ^{19}F NMR δ 99.20 (s, 3F); MS (TSP$^+$) 355 (MH$^+$).

5-(*m*-Formylphenyl)-2,3,4-trimethoxytropone (22c): H/A = 7:3; 104 mg; ^{1}H NMR δ 3.56 (s, 3H), 3.95 (s, 3H), 4.03 (s, 3H), 7.03 (d, 1H, ^3J = 12.7), 7.11 (d, 1H, ^3J = 12.7), 7.51−7.72 (m, 2H), 7.88−7.93 (m, 2H), 10.07 (s, 1H).

Preparation of Oximes. Oxime of 7-(*m*-Formylphenyl)-2-methoxytropone (3k). To a suspension of aldehyde **3f** (50 mg, 0.22 mmol) in ethanol (2 mL) were sequentially added pyridine (70 mg, 72 μL, 0.88 mmol) and a solution of hydroxylamine hydrochloride (15.3 mg, 0.24 mmol) in ethanol (1 mL). The mixture was stirred for 48 h and evaporated. Methylene chloride (5 mL) was added to the residue, and the organic phase was washed with water (3 × 5 mL) and dried. Chromatography using ethyl acetate as eluent furnished the pure oxime in 93% yield (52 mg): ^{1}H NMR δ 3.94 (s, 3H), 6.82 (d, 1H, ^3J = 9.5), 6.85−6.95 (m, 1H), 7.05−7.15 (m, 1H), 7.28−7.48 (m, 4H), 7.59 (s, 1H), 8.09 (s, 1H); MS (TSP$^+$) 256 (MH$^+$).

Benzyloxime of 7-(*m*-Formylphenyl)-2-methoxytropone (3l). The same procedure was used with *N*-benzylhydroxylamine (15.3 mg, 0.24 mmol): yield, 96% (73 mg): ^{1}H NMR δ 3.98 (s, 3H), 5.24 (s, 2H), 6.77 (d, 1H, ^3J = 9.5), 6.86−6.96 (m, 1H), 7.03−7.12 (m, 1H), 7.28−7.62 (m, 9H), 7.71 (s, 1H), 8.18 (s, 1H); MS (TSP$^+$) 346 (MH$^+$).

Reduction of Aldehydes 4f, 22c, and 23b. General Procedure. The requisite aldehyde (0.3 mmol) was dissolved in benzene (3 mL), and sodium triacetoxyborohydride (127 mg, 0.6 mmol) was added. The mixture was then refluxed for 1 h, cooled, and evaporated. Chromatography of the residue and elution with ethyl acetate furnished the desired alcohol.

7-[*m*-(Hydroxymethyl)phenyl]-2-methoxytropone (3m): 66 mg, 91% yield; ^{1}H NMR δ 3.96 (s, 3H), 4.70 (s, 2H), 6.77 (d, 1H, ^3J = 9.5), 6.85−6.95 (m, 2H), 7.02−7.13 (m, 1H), 7.34−7.50 (m, 5H); MS (TSP$^+$) 243 (MH$^+$).

4-[*m*-(Hydroxymethyl)phenyl]-2,3,7-trimethoxytropone (21d): 60 mg, 66% yield; ^{1}H NMR δ 3.62 (s, 3H), 3.91 (s, 3H), 3.95 (s, 3H), 4.77 (s, 2H), 6.70 (d, 1H, ^3J = 10.7), 6.96 (d, 1H, ^3J = 10.7), 7.25−7.41 (m, 4H), (CD$_3$CN) 3.57 (s, 3H), 3.83 (s, 3H), 3.88 (s, 3H), 4.65 (s, 2H), 6.82 (d, 1H, ^3J = 10.5), 6.95 (d, 1H, ^3J = 10.5), 7.22−7.40 (m, 4H).

5-[*m*-(Hydroxymethyl)phenyl]-2,3,4-trimethoxytropone (22d): 45 mg, 50% yield; ^{1}H NMR δ 3.55 (s, 3H), 3.93 (s, 3H), 4.00 (s, 3H), 4.76 (s, 2H), 7.00 (d, 1H, ^3J = 12.7), 7.12 (d, 1H, ^3J = 12.7), 7.25−7.47 (m, 4H), (CD$_3$CN) 3.53 (s, 3H), 3.88 (s, 3H), 3.93 (s, 3H), 4.66 (s, 2H), 6.90 (d, 1H, ^3J = 12.7), 7.11 (d, 1H, ^3J = 12.7), 7.23−7.47 (m, 4H); MS (TSP$^+$) 303 (MH$^+$).

Attempted Single Suzuki Reaction on 3,7-Dibromo-2-Methoxytropone. In a flask flushed with argon were placed 3,7-dibromo-2-methoxytropone (**24a**) (100 mg, 0.34 mmol), THF (22 mL), and palladium tetrakistriphenylphosphine (39 mg, 0.034 mmol, 0.1 equiv). A 1.8 M aqueous solution of potassium hydroxide (0.75 mL, 1.36 mmol, 4 equiv) and *p*-methoxyphenylboronic acid (73 mg, 0.48 mmol, 1.4 equiv)

were then sequentially added, and the mixture was stirred at room temperature for 16 h. Evaporation of the volatiles left a residue which was purified by chromatography on silica gel to give **3-bromo-7-(*p*-methoxyphenyl)-2-methoxytropone (24c):** eluent, H/E = 4:1; yield, 8 mg (7%); ^{1}H NMR δ 3.84 (s, 3H), 3.96 (s, 3H), 6.67 (dd, 1H, ^3J = 9.0, 11.6), 6.94 (d, 2H, ^3J = 8.8), 7.27−7.39 (m, 2H), 7.46 (d, 2H, ^3J = 8.8); MS (TSP$^+$) 321, 323 (MH^+), 338, 340 (MNH_4^+). More elution furnished **3,7-bis(*p*-methoxyphenyl)-2-methoxytropone (24b):** yield, 35 mg (30%); ^{1}H NMR δ 3.70 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 6.84−7.06 (m, 6H), 7.33−7.40 (m, 3H), 7.53 (d, 2H, ^3J = 8.8); MS (TSP$^+$) 349 (MH^+), 366 (MNH_4^+).

Double Suzuki Coupling Reaction. The procedure followed for the preparation of bisaryldihydroxytropolones is the same as the one for the monosubstituted derivatives on a 0.2-mmol scale (dibromotropolone derivative **18**), but with 2.2 equiv of boronic acid (0.44 mmol) and 4 equiv of sodium carbonate (0.2 mL, 0.4 mmol). Yields are given in Table 2. The eluents and isolated masses are given first.

4,6-Bis(*p*-methoxyphenyl)-2,3,7-trimethoxytropone (25a): H/A = 1:1; 63 mg; ^{1}H NMR δ 3.65 (s, 3H), 3.78 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 4.02 (s, 3H), 6.90−7.01 (m, 5H), 7.28−7.38 (m, 4H), (CD_3CN) 3.56 (s, 3H), 3.70 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 3.90 (s, 3H), 6.87−6.99 (m, 5H), 7.27−7.32 (m, 4H); MS (TSP$^+$) 409 (MH^+).

4,6-Bis(*o*-fluorophenyl)-2,3,7-trimethoxytropone (25b): H/A = 7:3; 68 mg; ^{1}H NMR δ 3.67 (s, 3H), 3.80 (s, 3H), 3.94 (s, 3H), 6.85 (s, 1H), 7.09−7.46 (m, 8H); ^{19}F NMR δ 48.78−48.90 (br s, 1F), 49.13−49.26 (br s, 1F); MS (TSP$^+$) 385 (MH^+).

4,6-Bis[*m*-(trifluoromethyl)phenyl]-2,3,7-trimethoxytropone (25c): H/A = 7:3; 87 mg; ^{1}H NMR δ 3.70 (s, 3H), 3.83 (s, 3H), 4.03 (s, 3H), 6.88 (s, 1H), 7.53−7.63 (m, 8H), (CD_3CN) 3.63 (s, 3H), 3.76 (s, 3H), 3.94 (s, 3H), 6.89 (s, 1H), 7.57−7.70 (m, 8H); ^{19}F NMR δ 99.35 (s, 3F), 99.38 (s, 3F); MS (TSP$^+$) 485 (MH^+).

4,6-Bis[*p*-(trifluoromethyl)phenyl]-2,3,7-trimethoxytropone (25d): H/A = 7:3; 90 mg; ^{1}H NMR δ 3.68 (s, 3H), 3.81 (s, 3H), 4.02 (s, 3H), 6.84 (s, 1H), 7.46 (d, 4H, ^3J = 8.1), 7.62−7.70 (m, 4H), (CD_3CN) 3.63 (s, 3H), 3.76 (s, 3H), 3.94 (s, 3H), 6.85 (s, 1H), 7.54 (d, 4H, ^3J = 8.2), 7.66−7.78 (m, 4H); ^{19}F NMR δ 99.09 (s, 3F), 99.11 (s, 3F); MS (TSP$^+$) 485 (MH^+).

4,6-Bis[*m*,*m*-bis(trifluoromethyl)phenyl]-2,3,7-trimethoxytropone (25e): pure C, then C/A = 99:1; 100 mg; ^{1}H NMR δ 3.75 (s, 3H), 3.88 (s, 3H), 4.05 (s, 3H), 6.79 (s, 1H), 7.82 (s, 4H), 7.92 (s, 2H); ^{19}F NMR δ 99.14 (s, 6F), 99.17 (s, 6F).

4,6-Bis(*m*-formylphenyl)-2,3,7-trimethoxytropone (25f): H/A = 1:1; 57 mg; ^{1}H NMR δ 3.66 (s, 3H), 3.81 (s, 3H), 4.02 (s, 3H), 6.89 (s, 1H), 7.54−7.66 (m, 4H), 7.86−7.90 (m, 4H), 10.04 (s, 1H), 10.05 (s, 1H); MS (TSP$^+$) 405 (MH^+).

4,6-Bis(*m*-cyanophenyl)-2,3,7-trimethoxytropone (25g): H/A = 4:1; 54 mg; ^{1}H NMR δ 3.68 (s, 3H), 3.83 (s, 3H), 4.03 (s, 3H), 6.76 (s, 1H), 7.47−7.69 (m, 8H); MS (TSP$^+$) 399 (MH^+).

4,6-Bis(*m*-acetamidophenyl)-2,3,7-trimethoxytropone (25h): H/A = 1:1; 38 mg; ^{1}H NMR δ 2.15 (s, 3H), 3.59 (s, 3H), 3.70 (s, 3H), 3.92 (s, 3H), 6.88 (s, 1H), 6.98 (d, 2H, J = 7.5), 7.18−7.26 (m, 2H), 7.38−7.62 (m, 4H).

4,6-Bis(*m*-nitrophenyl)-2,3,7-trimethoxytropone (25i): H/A = 3:2; 59 mg; ^{1}H NMR δ 3.72 (s, 3H), 3.86 (s, 3H), 4.03 (s, 3H), 6.85 (s, 1H), 7.54−7.72 (m, 4H), 8.22−8.27 (m, 4H), (CD_3CN) 3.63 (s, 3H), 3.76 (s, 3H), 3.94 (s, 3H), 6.87 (s, 1H), 7.52−7.78 (m, 4H), 8.12 (d, 2H, ^3J = 7.6), 8.18 (s, 2H); MS (TSP$^+$) 439 (MH^+).

4,6-Di(1-naphthyl)-2,3,7-trimethoxytropone (25j): H/A = 7:3; 89 mg; isolated as a 1:1 mixture of rotamers; ^{1}H NMR δ 3.63 (s, 3H), 3.76 (s, 3H), 4.12 (s, 3H), 7.00 and 7.03 (s, 1H), 7.37−7.90 (m, 14H).

4,6-Di(2-naphthyl)-2,3,7-trimethoxytropone (25k): H/A = 7:3; 73 mg; ^{1}H NMR δ 3.68 (s, 3H), 3.84 (s, 3H), 4.10 (s, 3H), 7.27 (s, 1H), 7.45−7.60 (m, 6H), 7.70−7.94 (m, 8H).

4,6-Bis[*m*-[5-(2-naphthyl)-2-oxadiazolyl]phenyl]-2,3,7-trimethoxytropone (25l): H/A = 1:1; 66 mg; ^{1}H NMR δ 3.78 (s, 3H), 3.90 (s, 3H), 4.11 (s, 3H), 7.09 (s, 1H), 7.45−7.72 (m, 8H), 7.88−8.03 (m, 6H), 8.19−8.28 (m, 6H), 8.66 (s, 2H); MS (TSP$^+$) 737 (MH^+).

4,6-Di(2-benzofuryl)-2,3,7-trimethoxytropone (25m): H/A = 7:3; 13 mg; ^{1}H NMR δ 3.98 (s, 3H), 4.06 (s, 3H), 4.13 (s, 3H), 7.25−7.48 (m, 5H), 7.58−7.74 (m, 5H), 8.64 (s, 1H), (CD_3CN) 3.88 (s, 3H), 3.99 (s, 3H), 4.03 (s, 3H), 7.33−7.44 (m, 5H), 7.56−7.72 (m, 5H), 8.65 (s, 1H); MS (TSP$^+$) 429 (MH^+).

4,6-Di(3-thienyl)-2,3,7-trimethoxytropone (25n): H/A = 3:2; 43 mg; ^{1}H NMR δ 3.69 (s, 3H), 3.82 (s, 3H), 4.01 (s, 3H), 7.20−7.51 (m, 7H), (CD_3CN) 3.63 (s, 3H), 3.78 (s, 3H), 3.92 (s, 3H), 7.19−7.33 (m, 3H), 7.40−7.58 (m, 4H); MS (TSP$^+$) 361 (MH^+).

Deprotection Reactions under Acidic Conditions. 7-Phenyltropolone (4a). The starting methoxytropone **3a** (2.12 g, 10 mmol) was dissolved in methanol (30 mL), and concentrated aqueous HCl (30 mL) was added. The resultant solution was refluxed for 6 h and allowed to cool slowly. The pure product crystallized out overnight in 86% yield (1.70 g): ^{1}H NMR δ 7.02−7.12 (m, 1H), 7.31−7.54 (m, 7H), 7.58 (d, 1H, ^3J = 10.2); MS (TSP$^+$) 199 (MH^+), 216 (MNH_4^+).

7-(*p*-Methoxyphenyl)tropolone (4b). Application of the same procedure to **3b** led to the isolation of the corresponding tropolone **4b** in 95% yield (2.17 g): ^{1}H NMR δ 3.86 (s, 3H), 6.96−7.03 (m, 2H), 7.20 (t, 1H, ^3J = 9.5), 7.42−7.52 (m, 3H), 7.65−7.73 (m, 2H); MS (TSP$^+$) 229 (MH^+).

Deprotection Reactions with TMSI. General Procedure. The permethylated monosubstituted or disubstituted tropolone (0.15 mmol) was dissolved in dry acetonitrile (5 mL), and TMSI (freshly distilled over copper wire, 120 mg, 85 μL, 0.6 mmol, 4 equiv for the monosubstituted tropolone derivatives and twice this amount for the disubstituted tropolones derivatives) was added via syringe (as reaction times may vary from one compound to another it may be advisable to conduct the experiment in an NMR tube, thereby allowing the monitoring of the reaction by ^{1}H NMR spectroscopy). The mixture was then heated at 80 °C for a period of time ranging from 15 min to 3 h. Evaporation left an oily residue. Toluene (4 mL) was added and evaporated. This step was repeated twice to ensure complete removal of any excess TMSI and any hydriodic acid that might have formed. The oily residue was dissolved in acetonitrile, and water was then added to hydrolyze the silyloxy functions. After 2 h at room temperature the solution was evaporated, and the above treatment with toluene was applied (3 × 4 mL) to give a solid. This was dissolved in ethyl acetate (40 mL) and washed rapidly with a saturated $Na_2S_2O_3$ aqueous solution (10 mL). The organic phase was washed with water (2 × 10 mL), dried over sodium sulfate, and evaporated to furnish the tropolones in yields reported in Table 3.

3,7-Dihydroxytropolone (8): obtained quantitatively as a creamy powder, identical in every respect with an authentic sample.

7-(*p*-Hydroxyphenyl)tropolone (4d): 25 mg; ^{1}H NMR (CD_3OD) δ 6.84 (d, 2H, ^3J = 8.6), 7.20−7.57 (m, 5H), 7.75 (d, 1H, ^3J = 10.0); MS (TSP$^+$) 215 (MH^+), 232 (MNH_4^+).

7-(*m*-Formylphenyl)tropolone (4f): 28 mg; ^{1}H NMR δ 7.08−7.21 (m, 1H), 7.40−7.49 (m, 2H), 7.60−7.70 (m, 2H), 7.83 (d, 1H, ^3J = 7.8), 7.94 (d, 1H, ^3J = 7.6), 8.05 (s, 1H), 10.08 (s, 1H); MS (TSP$^+$) 227 (MH^+), 244 (MNH_4^+). This compound, when left in deuterated methanol, slowly transformed into the hemiketal: ^{1}H NMR (CD_3OD) δ 5.41 (s, 1H), 7.19 (t, 1H, ^3J = 10.1), 7.40−7.57 (m, 6H), 7.66 (d, 1H, ^3J = 10.0).

7-(*m*-Cyanophenyl)tropolone (4g): 32 mg; ^{1}H NMR δ 7.11−7.22 (m, 1H), 7.46−7.49 (m, 2H), 7.55−7.63 (m, 2H), 7.72 (d, 1H, ^3J = 7.7), 7.79 (d, 1H, ^3J = 7.8), 7.84 (s, 1H); ^{13}C NMR (90 MHz) δ 112.61, 118.57, 120.99, 127.51, 129.09, 131.73, 132.97, 133.81, 137.36, 137.53, 140.28, 141.06, 169.80, 171.98; IR (KBr) ν: 3204 (OH), 2227 (CN), 1598 (CO) cm^{-1}; MS (TSP$^+$) 241 (MNH_4^+).

The same compound was isolated from the reaction between TMSI and oximes **3k**,**l** using the above procedure, in 72% yield (24 mg) and 77% yield (25 mg), respectively.

7-(5-Pyrimidyl)tropolone (4i). This was carried out on a 0.112-mmol scale. The general procedure was followed up to the hydrolysis step. After evaporation of the volatile and treatment with toluene as above, the crude solid material was dissolved in 10 mL of water and 6 mL of methanol. To this stirring solution was slowly added a solution of silver nitrate

(18.7 mg, 0.112 mmol) in water (10 mL), and stirring was continued for 15 min. Filtration through a Millipore membrane and evaporation yielded 19 mg of the desired tropolone as a yellow powder (85% yield): ^{1}H NMR (CD_3OD) δ 7.20 (td, 1H, ^4J = 1.4, ^3J = 9.7), 7.38−7.58 (m, 2H), 7.75 (d, 1H, ^3J = 9.1), 8.97 (s, 2H), 9.14 (s, 1H); MS (TSP^+) 201 (MH^+).

6-Phenyl-3,7-dihydroxytropolone (1a): 27 mg; ^{1}H NMR (CD_3OD) δ 7.07 (d, 1H, ^3J = 11.8), 7.15 (d, 1H, ^3J = 11.8), 7.31−7.48 (m, 5H); ^{13}C NMR (CD_3OD) δ 119.62, 128.61, 129.07, 130.44, 131.68, 132.82, 141.49, 151.73, 155.94, 158.07, 163.29; MS (TSP^-) 229 (MH^-). Anal. ($C_{13}H_{10}O_4$) C, H.

6-(*p*-Hydroxyphenyl)-3,7-dihydroxytropolone (1b): 18 mg from **19a** and 35 mg from **20b**; ^{1}H NMR (CD_3OD) δ 6.83 (d, 2H, ^3J = 8.4), 7.05 (d, 1H, ^3J = 11.9), 7.15 (d, 1H, ^3J = 11.9), 7.31 (d, 2H, ^3J = 8.3); MS (TSP^+) 247 (MH^+). Anal. ($C_{13}H_{10}O_5 \cdot H_2O$) C, H.

6-(*o,m′*-Dihydroxyphenyl)-3,7-dihydroxytropolone (1c): 16 mg; ^{1}H NMR (CD_3OD) δ 6.60−6.76 (m, 3H), 7.01 (d, 1H, ^3J = 10.8), 7.12 (d, 1H, ^3J = 10.8); MS (TSP^+) 263 (MH^+). Anal. ($C_{13}H_{10}O_6 \cdot 0.33H_2O$) C, H.

6-(*o*-Fluorophenyl)-3,7-dihydroxytropolone (1d): 35 mg; ^{1}H NMR (CD_3OD) δ 7.05 (s, 2H), 7.08−7.42 (m, 4H); ^{19}F NMR (CD_3OD) δ 49.1−49.3 (m, 1F); MS (TSP^+) 271 (MH^+). Anal. ($C_{13}H_9O_4F$) C, H.

6-[*m*-(Trifluoromethyl)phenyl]-3,7-dihydroxytropolone (1e): 31 mg; ^{1}H NMR (CD_3OD) δ 7.12 (s, 2H), 7.57−7.77 (m, 4H); ^{19}F NMR (CD_3OD) δ 101.80 (s, 3F); MS (TSP^+) 299 (MH^+), 316 (MNH_4^+). Anal. ($C_{14}H_9O_4F_3$) C, H.

6-[*p*-(Trifluoromethyl)phenyl]-3,7-dihydroxytropolone (1f): 36 mg from **20c**; ^{1}H NMR (CD_3OD) δ 7.06 (d, 1H, ^3J = 11.6), 7.17 (d, 1H, ^3J = 11.6), 7.64 (d, 2H, ^3J = 8.4), 7.72 (d, 2H, ^3J = 8.4); ^{19}F NMR (CD_3OD) δ 101.00 (s, 3F); MS (TSP^+) 299 (MH^+), 316 (MNH_4^+). Anal. ($C_{14}H_9O_4F_3 \cdot 0.25H_2O$) C, H.

6-[*m,m*-Bis(trifluoromethyl)phenyl]-3,7-dihydroxytropolone (1g): 37 mg; ^{1}H NMR (CD_3OD) δ 7.08 (d, 1H, ^3J = 12.2), 7.17 (d, 1H, ^3J = 12.2), 7.96 (s, 1H), 8.06 (s, 2H); ^{19}F NMR (CD_3OD) δ 101.77 (s, 6F); MS (TSP^+) 367 (MH^+). Anal. ($C_{15}H_8O_4F_6$) C, H.

6-(*m*-Formylphenyl)-3,7-dihydroxytropolone (1h): 21 mg; ^{1}H NMR (CD_3OD) δ 7.09 (d, 1H, ^3J = 11.6), 7.17 (d, 1H, ^3J = 11.6), 7.64 (t, 1H, ^3J = 7.7), 7.79 (d, 1H, ^3J = 7.8), 7.92 (d, 1H, ^3J = 7.5), 8.01 (s, 1H), 10.04 (s, 1H); MS (TSP^+) 259 (MH^+), 276 (MNH_4^+). Anal. ($C_{14}H_{10}O_5$) C, H. This compound, when left in deuterated methanol, slowly transformed into the hemiketal: ^{1}H NMR (CD_3OD) δ 5.43 (s, 1H), 7.12−7.52 (m, 6H).

6-(*m*-Cyanophenyl)-3,7-dihydroxytropolone (1i): 28 mg; ^{1}H NMR (CD_3OD) δ 7.10 (s, 2H), 7.60 (t, 1H, ^3J = 7.7), 7.72 (d, 1H, ^3J = 7.8), 7.76 (d, 1H, ^3J = 7.8), 7.84 (s, 1H); MS (TSP^-) 255 (MH^-). Anal. ($C_{14}H_9NO_4 \cdot 0.25H_2O$) C, H, N.

6-(*m*-Acetamidophenyl)-3,7-dihydroxytropolone (1j): 21 mg; ^{1}H NMR (CD_3OD) δ 2.12 (s, 3H), 7.03 (d, 1H, ^3J = 11.7), 7.13 (d, 1H, ^3J = 11.7), 7.18 (d, 1H, ^3J = 8.2), 7.37 (t, 1H, ^3J = 8.3), 7.58 (d, 1H, ^3J = 8.3), 7.63 (s, 1H); MS (TSP^+) 288 (MH^+), 305 (MNH_4^+). Anal. ($C_{15}H_{13}NO_5 \cdot 0.33H_2O$) C, H; N: calcd, 4.72; found, 3.93.

6-[*p*-(2-Aminoethyl)phenyl]-3,7-dihydroxytropolone (1l): 33 mg; ^{1}H NMR (CD_3OD) δ 3.00 (t, 2H, ^3J = 7.8), 3.23 (t, 2H, ^3J = 7.8), 7.06 (d, 1H, ^3J = 11.8), 7.13 (d, 1H, ^3J = 11.8), 7.34 (d, 2H, ^3J = 8.2), 7.46 (d, 2H, ^3J = 8.2); MS (TSP^-) 272 (MH^-); HR-MS (FAB) calcd for $C_{15}H_{16}NO_4$ 274.1079, found 271.1091. Anal. ($C_{15}H_{15}NO_4 \cdot HI \cdot 1.5H_2O$) H, N; C: calcd, 42.07; found, 41.28.

6-(*m*-Nitrophenyl)-3,7-dihydroxytropolone (1m): 21 mg; ^{1}H NMR (CD_3OD) δ 7.12 (d, 1H, ^3J = 11.6), 7.19 (d, 1H, ^3J = 11.6), 7.72 (t, 1H, ^3J = 7.9), 7.91 (d, 1H, ^3J = 7.6), 8.27 (d, 1H, ^3J = 8.4), 8.37 (s, 1H); MS (TSP^-) 274 (MH^-); HR-MS (FAB) calcd for $C_{13}H_{10}NO_6$ 276.0508, found 276.0504.

6-[(1-Naphthyl)phenyl]-3,7-dihydroxytropolone (1n): 34 mg; ^{1}H NMR (CD_3OD) δ 7.03 (d, 1H, ^3J = 12.2), 7.12 (d, 1H, ^3J = 12.2), 7.29−7.58 (m, 5H), 7.85−7.94 (m, 2H); MS (TSP^+) 281 (MH^+). Anal. ($C_{17}H_{12}O_4 \cdot 1.33H_2O$) C, H.

6-[(2-Naphthyl)phenyl]-3,7-dihydroxytropolone (1o): 41 mg; ^{1}H NMR δ ($CD_3OD/CDCl_3$): 7.10 (d, 1H, ^3J = 12.2), 7.24 (d, 1H, ^3J = 12.2), 7.44−7.52 (m, 2H), 7.59 (d, 1H, ^3J = 8.2), 7.82−7.92 (m, 4H); MS (TSP^+) 281 (MH^+). Anal. ($C_{17}H_{12}O_4$) C, H.

6-[*m*-[5-(2-Naphthyl)-2-oxadiazolyl]phenyl]-3,7-dihydroxytropolone (1p): 58 mg; ^{1}H NMR (CD_3OD) δ 7.13 (d, 1H, ^3J = 11.9), 7.19 (d, 1H, ^3J = 11.9), 7.50−7.69 (m, 4H), 7.84−7.98 (m, 3H), 8.12−8.23 (m, 2H), 8.24 (s, 1H), 8.59 (s, 1H); MS (TSP^+) 425 (MH^+). Anal. ($C_{25}H_{16}N_2O_5 \cdot 0.5H_2O$) C, H; N: calcd, 6.46; found, 5.90.

6-(2-Benzofuryl)-3,7-dihydroxytropolone (1q): 25 mg; ^{1}H NMR (DMSO-d_6) δ 7.01 (d, 1H, ^3J = 12.2), 7.22−7.37 (m, 2H), 7.61 (d, 1H, ^3J = 8.3), 7.72 (d, 1H, ^3J = 8.4), 7.78 (s, 1H), 7.96 (d, 1H, ^3J = 12.2); HR-MS (FAB) calcd for $C_{15}H_{11}O_5$ 271.0605, found 271.0606. Anal. ($C_{15}H_{10}O_5 \cdot 2.5H_2O$) C; H: calcd, 4.79; found, 4.04.

6-(2-Thienyl)-3,7-dihydroxytropolone (1r): 28 mg; ^{1}H NMR (DMSO-d_6) δ 6.93 (d, 1H, ^3J = 12.2), 7.17 (t, 1H, ^3J = 5.5), 7.62−7.82 (m, 3H); MS (TSP^+) 237 (MH^+); HR-MS (FAB) calcd for $C_{11}H_9O_4S$ 237.0221, found 237.0219.

6-(3-Thienyl)-3,7-dihydroxytropolone (1s): 20 mg; ^{1}H NMR (360 MHz/DMSO-d_6) δ 6.96 (d, 1H, ^3J = 12.0), 7.29 (d, 1H, ^3J = 12.0), 7.44 (d, 1H, ^3J = 4.9), 7.58 (dd, 1H, ^3J = 3.0, 4.9), 7.82 (d, 1H, ^3J = 3.0); MS (TSP^+) 237 (MH^+). Anal. ($C_{11}H_8O_4S$) C, H.

6-(5-Pyrimidyl)-3,7-dihydroxytropolone (1t): 29 mg; procedure was the same as for compound **5i**; ^{1}H NMR (DMSO-d_6) δ 7.02 (d, 1H, ^3J = 11.6), 7.17 (d, 1H, ^3J = 11.6), 8.90 (s, 2H), 9.17 (s, 1H); MS (TSP^+) 233 (MH^+); HR-MS (FAB) calcd for $C_{11}H_9N_2O_4$ 233.0562, found 233.0567.

6-(4-Hydroxybutyl)-3,7-dihydroxytropolone (1u): 10 mg; ^{1}H NMR (CD_3OD) δ 1.55−1.78 (m, 4H), 2.80 (t, 2H, ^3J = 7.5), 3.58 (t, 2H, ^3J = 6.3), 6.99 (d, 1H, ^3J = 11.7), 7.09 (d, 1H, ^3J = 11.7); MS (TSP^+) 209 ($MH^+ - H_2O$), 227 (MH^+); HR-MS (FAB) calcd for $C_{11}H_9N_2O_4$ 227.0919, found 227.0916.

4,6-Bis(*p*-hydroxyphenyl)-3,7-dihydroxytropolone (26a): 50 mg; after treatment with sodium thiosulfate, the product was washed with diethyl ether; ^{1}H NMR (CD_3OD) δ 6.82 (d, 4H, ^3J = 8.9), 7.17 (s, 1H), 7.30 (d, 4H, ^3J = 8.9); MS (TSP^+) 339 (MH^+). Anal. ($C_{19}H_{14}O_6 \cdot 0.5Et_2O \cdot H_2O$) C, H.

4,6-Bis[*o*-(fluoromethyl)phenyl]-3,7-dihydroxytropolone (26b): 27 mg; ^{1}H NMR δ 7.13−7.26 (m, 6H), 7.34−7.44 (m, 3H); ^{19}F NMR δ 48.34 (br s, 2F); MS (TSP^+) 343 (MH^+). Anal. ($C_{19}H_{12}O_4F_2 \cdot 0.25H_2O$) C, H.

4,6-Bis[*m*-(trifluoromethyl)phenyl]-3,7-dihydroxytropolone (26c): 20 mg; ^{1}H NMR (360 MHz/DMSO-d_6) δ 7.04 (s, 1H), 7.64 (t, 2H, ^3J = 8.6), 7.72 (d, 2H, ^3J = 8.6), 7.78 (d, 2H, ^3J = 8.6), 7.84 (s, 2H); ^{19}F NMR (338 MHz/DMSO-d_6) δ 101.71 (s, 6F); MS (TSP^+) 443 (MH^+). Anal. ($C_{21}H_{12}O_4F_6 \cdot 0.25H_2O$) C, H.

4,6-Bis[*p*-(trifluoromethyl)phenyl]-3,7-dihydroxytropolone (26d): 50 mg; ^{1}H NMR (360 MHz/DMSO-d_6) δ 7.09 (s, 1H), 7.68−7.74 (m, 8H); ^{19}F NMR (338 MHz/DMSO-d_6) δ 101.75 (s, 6F); MS (TSP^+) 443 (MH^+); HR-MS (FAB) calcd for $C_{21}H_{13}O_4F_6$ 443.0718, found 443.0705.

4,6-Bis[*m,m*-bis(trifluoromethyl)phenyl]-3,7-dihydroxytropolone (26e): 74 mg; ^{1}H NMR δ 7.19 (s, 1H), 7.7 (s, 2H), 7.96 (s, 4H); ^{19}F NMR δ 99.07 (s, 12F); MS (TSP^+) 579 (MH^+). Anal. ($C_{23}H_{10}O_4F_{12}$) C, H.

4,6-Bis(*m*-formylphenyl)-3,7-dihydroxytropolone (26f): 47 mg; one of the aldehyde functions was found to have transformed into a hemiketal; ^{1}H NMR δ 5.44 (s, 1H), 7.23−7.30 (m, 1H), 7.44−7.48 (m, 3H), 7.57 (s, 1H), 7.62−7.66 (m, 1H), 7.77 (d, 1H, ^3J = 7.9), 7.92 (d, 1H, ^3J = 7.6), 7.99 (s, 1H), 10.08 (s, 1H); MS (TSP^+) 363 (MH^+), 380 (MNH_4^+). Anal. ($C_{21}H_{16}O_7 \cdot 0.75H_2O$) C, H.

4,6-Bis(*m*-cyanophenyl)-3,7-dihydroxytropolone (26g): 37 mg; ^{1}H NMR (DMSO-d_6) δ 7.03 (s, 1H), 7.61 (t, 2H, ^3J = 7.6), 7.78−7.88 (m, 4H), 7.97 (s, 2H); MS (TSP^+) 357 (MH^+), 374 (MNH_4^+). Anal. ($C_{21}H_{12}N_2O_4 \cdot 0.5H_2O$) C, H, N.

4,6-Bis(*m*-acetamidophenyl)-3,7-dihydroxytropolone (26h): 17 mg; ^{1}H NMR (CD_3OD) δ 2.12 (s, 3H), 6.82 (d, 4H, ^3J = 8.9), 7.17 (s, 1H), 7.30 (d, 4H, ^3J = 8.9); MS (TSP^+) 421 (MH^+), 438 (MNH_4^+); HR-MS (FAB) calcd for $C_{23}H_{21}N_2O_6$ 421.1400, found 421.1402. Anal. ($C_{23}H_{20}N_2O_6 \cdot 2.5H_2O$) C, N; H: calcd, 5.46; found, 4.83.

4,6-Bis(*m*-nitrophenyl)-3,7-dihydroxytropolone (26i): 21 mg; ^{1}H NMR (DMSO-d_6) δ 7.10 (s, 1H), 7.70 (t, 2H, ^3J =

7.6), 7.94 (d, 4H, ^3J = 7.8), 8.21 (d, 2H, ^3J = 7.4), 8.31 (s, 2H); MS (TSP$^-$) 395 (MH^-); HR-MS (FAB) calcd for $C_{19}H_{13}N_2O_8$ 397.0672, found 397.0667. Anal. ($C_{19}H_{13}N_2O_8 \cdot 0.75H_2O$) C; H: calcd, 3.32; found, 2.83.

4,6-Di(1-naphthyl)-3,7-dihydroxytropolone (26j): 48 mg; isolated as a 1:1 mixture of rotamers; ^{1}H NMR δ 6.93 and 6.98 (s, 1H), 7.48−7.70 (m, 10H), 7.88−7.99 (m, 4H); MS (TSP$^+$) 407 (MH^+); HR-MS (FAB) calcd for $C_{27}H_{19}O_4$ 407.1277, found 407.1283. Anal. ($C_{27}H_{18}O_4 \cdot 2H_2O$) C; H: calcd, 5.01; found, 4.24.

4,6-Di(2-naphthyl)-3,7-dihydroxytropolone (26k): 46 mg; ^{1}H NMR δ 7.48−7.60 (m, 6H), 7.68 (d, 2H, ^3J = 8.3), 7.85−7.99 (m, 7H); MS (TSP$^+$) 407 (MH^+). Anal. ($C_{27}H_{18}O_4$) C, H.

4,6-Bis[*m*-[5-(2-naphthyl)-2-oxadiazolyl]phenyl]-3,7-dihydroxytropolone (26l): 26 mg; ^{1}H NMR (DMSO-d_6) δ 7.17 (s, 1H), 7.57−7.82 (m, 9H), 7.99−8.22 (m, 9H), 8.31 (s, 2H), 8.80 (s, 2H). Anal. ($C_{43}H_{26}N_4O_6 \cdot H_2O$) C, H; N: calcd, 7.86; found, 7.05.

4,6-Di(2-benzofuryl)-3,7-dihydroxytropolone (26m): 42 mg; ^{1}H NMR (CD_3OD) δ 7.20−7.40 (m, 4H), 7.61−7.69 (m, 4H), 7.78 (s, 2H), 9.20 (s, 1H); MS (TSP$^+$) 387 (MH^+); HR-MS (FAB) calcd for $C_{23}H_{15}O_6$ 387.0868, found 387.0875. Anal. ($C_{23}H_{14}O_6 \cdot 1.25H_2O$) C, H.

4,6-Di(3-thienyl)-3,7-dihydroxytropolone (26n): 46 mg; ^{1}H NMR δ 7.40−7.48 (m, 4H), 7.55−7.65 (m, 2H), 7.68 (s, 1H); MS (TSP$^+$) 319 (MH^+); HR-MS (FAB) calcd for $C_{15}H_{11}O_4S_2$ 319.0098, found 319.0087. Anal. Calcd for $C_{15}H_{10}O_4S_2$: C, 56.59; H, 3.17. Found: C, 57.18; H, 3.69.

Oxime of 7-(*m*-Formylphenyl)tropolone (3k). The procedure used for the preparation of oximes **3k**,**l** was followed using aldehyde **4f** (50 mg, 0.22 mmol), pyridine (70 mg, 72 μL, 0.88 mmol), and hydroxylamine hydrochloride (15.3 mg, 0.24 mmol) in ethanol. Evaporation of the organic extract furnished 52 mg of the pure oxime **3k** (98% yield): ^{1}H NMR δ 7.03−7.48 (dt, 1H, ^4J = 2.0, ^3J = 10.4), 7.49 (m, 4H), 7.58−7.66 (m, 3H), 8.13 (s, 1H); MS (TSP$^+$) 242 (MH^+), 259 (MNH_4^+).

Inhibition of IMPase by Tropolone Derivatives. The human recombinant enzyme was produced in *Escherichia coli* and purified to homogeneity as previously described.[8f,g] IC_{50} values were determined at 37 °C in 50 mM TrisCl, 250 mM KCl, pH 7.5, using a radiochemical assay with 0.2 mM DL-*myo*-inositol 1-phosphate ($2 \times K_m$), 0.2 μCi/μmol D-[^{3}H]inositol 1-phosphate, 2 mM $MgCl_2$, and varying concentrations of inhibitor.[37] K_i values were determined at 37 °C and pH 7.5 by measuring the release of inorganic phosphate in a coupled spectrophotometric assay.[8f,g] The concentrations of substrate were varied between 0.05 and 0.5 mM at different fixed concentrations of inhibitor with 0.5 mM $MgCl_2$. For all experiments the amount of enzyme was adjusted so that no more than 10% of the substrate was utilized during the reaction.

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(12) Methyltropone **i** was first briefly considered for derivatization because of the possibility of bromination of the methyl group.[13] However a variety of conditions led only to the bromine being introduced on the cycle. On the other hand, reactions between **i** and *tert*-butyllithium or freshly prepared lithium diisopropylamide (LDA) provided products **ii** and **iii** in low yields (see Experimental Section), resulting from substitution of the seven-membered ring methoxy group (as demonstrated by ^{1}H and ^{13}C NMR experiments in 1-D and 2-D modes at 500 and 125 MHz). Moreover attempts to substitute the bromine atom of 7-bromo-2-methoxytropone (**3**) with alcohols under basic or acidic conditions gave either untractable mixtures or, again, compounds arising from replacement of the methoxy group (low yields).[15]

(13) 2-Carbomethoxy-3-methyl-7-methoxytropone was obtained by methylation of 6-methyl-7-carboxytropolone, a byproduct of the preparation of 6-carboxymethyl-7-carboxytropolone;[14] see Experimental Section.

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(19) Preparation of boronic acids was needed in several cases.
(20) An improved procedure for the preparation of 3,7-dibromotropolone was worked out.[11]
(21) Permethylated mono- and dibromodihydroxytropolones display a tendency to react with excess diazomethane to form pyrazolotropolone derivatives; precedents for this kind of reactivity have been reported in the past.[18]
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(23) These included treatment with *tert*-butyllithium, tributyltin hydride, and tris(trimethylsilyl)silane.
(24) The two experiments were carried out by the same person using the same experimental procedure; the results thus demonstrate, in this precise case, the extreme sensitivity of the reaction to minute variations in experimental conditions. This is the only example of ring contraction observed in this study; it is of note that it is also the only example of a reaction between isomer **16** and a boronic acid substituted in the para position by an electron-withdrawing substituent. The results may be indicative of an activation of the tropolone ring by the *p*-(trifluoromethyl)-phenyl group toward nucleophilic species.
(25) The direct introduction of a nucleophile on the tropolone ring resulted in the substitution of a methoxy substituent, leaving the bromine untouched; S. R. Piettre, C. Schelcher, unpublished results.
(26) Treatment of permethylated dihydroxytropolones with TMSI at room temperature resulted in the rapid cleavage of two of the three ether functions; removal of the third methoxy group was much slower (20% unconsumed after 24 h at room temperature) and required heating.
(27) This speculative hemiketal would result from the interaction between the tropolonic oxygen adjacent to the *o*-CHO-phenyl and the aldehyde group; no aldehyde signal could be observed by ^{1}H NMR spectroscopy.
(28) Deprotection of the permethylated tropolone derivative resulted in the formation of the desired amino compound (as shown by ^{1}H NMR spectroscopy); however, this material was highly impure, and efforts to purify it did not succeed. The methods used to attempt purification include classical chromatography or HPLC on silica gel (reverse-phase), cellulose, and resins as well as crystallization in various solvents.
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(33) Only 10 compounds encompassing the 3,7-dihydroxytropolonic unit have been reported so far in the literature, among which are the parent compound **8**, 3,5,7-trihydroxytropolone, and the natural products puberulonic acid and puberulic acid.
(34) It should be noted that the results described in this paper are adaptable to solid-phase synthesis; Piettre, S. R.; Baltzer, S. A New Approach to the Solid-Phase Suzuki Reaction. *Tetrahedron Lett.* **1997**, *38*, 1197−2000.
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(38) Modeling experiments were carried out as described in ref 11.

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