Registry No. 1 (free base), 60503-05-1; 1·H_2SO_4, 83997-16-4; 2 (free base), 105806-65-3; 2·H_2SO_4, 126721-07-1; 3, 69201-89-4; 4, 63358-25-8; 5, 17460-56-9; 6, 105806-76-6; 7, 51219-18-2; 8, 51219-20-6; 9, 81344-50-5; 10, 61635-50-5; 11, 105806-73-3; 12, 77433-27-3; 13, 105806-74-4; 14, 126644-60-8; Z-D-Phe-OH, 2448-45-5; H-Pro-OH, 147-85-3; MeI, 74-88-4; BOC-Arg-OH·HCl, 35897-34-8; Z-Cl, 501-53-1; Z-D-MePhe-Pro-OH, 105806-75-5; thrombin, 9002-04-4.

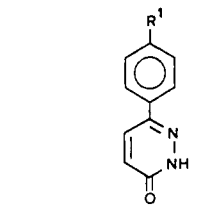
1,4-Bis(3-oxo-2,3-dihydropyridazin-6-yl)benzene Analogues: Potent Phosphodiesterase Inhibitors and Inodilators

William J. Coates, H. Douglas Prain, Martin L. Reeves, and Brian H. Warrington*

Smith Kline & French Research Ltd., The Frythe, Welwyn, Hertfordshire AL6 9AR, U.K. *Received July 10, 1989*

1,4-Bis(3-oxo-2,3-dihydropyridazin-6-yl)benzene and a series of related bis(azinone) compounds were synthesized. These novel compounds were evaluated for inhibition of the low K_m, cAMP-selective, cGMP-inhibited phosphodiesterase (PDE III) derived from cat heart and hemodynamic activity in the ganglion- and β-blocked anesthetized cat. The most potent PDE III inhibitor of the series was 6-[4-(5-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl)-phenyl]pyridazin-3(2*H*)-one (IC_{50} = 0.07 μM), which also retained the greatest inotrope and vasodilator (inodilator) potency (ED_{50} for first derivative of left ventricular pressure (dLVP/dt(max)) = 0.02 μmol/kg, ED_{15} for 15% fall in perfusion pressure = 0.01 μmol/kg). The structure–activity relationships observed within the bis(azinone) series were consistent with those reported for formally analogous 6-(4-substituted-phenyl)pyridazin-3(2*H*)-one-based PDE III-inhibiting inodilators with less-extended phenyl substituents (see e.g. Sircar et al. *J. Med. Chem.* **1987**, *30*, 1955, Moos et al. *J. Med. Chem.* **1987**, *30*, 1963). PDE III inhibitory potency is associated with overall planar topology of the phenylpyridazinone moiety and the presence of two critically separated electronegative centers. A methyl group at the 5-position of a dihydropyridazinone ring leads to enhanced potency. However, the generally higher levels of PDE III inhibitory potency shown by compounds in the bis(azinone) series relative to earlier 6-(4-substituted-phenyl)pyridazin-3(2*H*)-one derivatives appears to derive from a closer to optimal separation of two interacting points in the inhibitor molecule achieved through the more extended bis(azinone) structure. Correlation between the pharmacological and PDE III inhibitory activities of compounds in the bis(azinone) series provides additional evidence for PDE III being an important mediator of inodilator action.

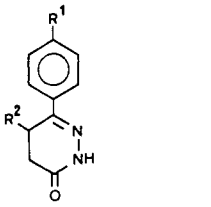
The inotropic and vasodilator (inodilator) properties of substituted 6-phenylpyridazin-3(2*H*)-ones and 4,5-dihydro-6-phenylpyridazin-3(2*H*)-ones are well-recognized.[1-14] Activity is retained by the phenylpyridazinone derivatives **1** and **2** where R^1 is a small, heteroatom-containing substituent and compounds in which R^1 is acetamido (e.g. **1a**, **2a**,**b**) or 1H-imidazol-1-yl (e.g. **1b**, **2c**,**d**) are particularly potent. There is substantial evidence that the inodilator activity of 6-(4-substituted)phenylpyridazin-3(2*H*)-ones is strongly associated with their ability to inhibit the low K_m, cAMP-selective, cGMP-inhibited cyclic nu-



1

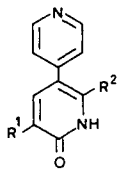
a) R^1 = NHAc

b) R^1 = 1H-imidazol-1-yl



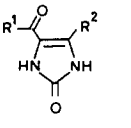
2

	R^1	R^2	
a)	NHAc	H	
b)	NHAc	CH_3	
c)	1H-imidazol-1-yl	H	(CI-914)
d)	1H-imidazol-1-yl	CH_3	(CI-930)



3

	R^1	R^2	
a)	NH_2	H	(amrinone)
b)	CN	CH_3	(milrinone)



4

	R^1	R^2	
a)	4-(SCH_3)-phenyl	CH_3	(enoximone)
b)	3-pyridyl	C_2H_5	(piroximone)

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Table I. Structure[a] and Biological Properties of Compounds in This Study

structure = A - X - B

	A	X	B	% yield	mp, °C	recrystn solvent	lit mp, °C	ref	formula[b]	inhibn of PDE III, IC_{50},[c] μmol/kg	anaesthetized cat: inotropic ED_{50},[d-f] μmol/kg	anaesthetized cat: vasodilator ED_{15},[g,e] μmol/kg
5	PZ	1,4-benzene	PZ	19[h]	>250	AcOH/HCl			$C_{14}H_{10}N_4O_2 \cdot 0.1H_2O$	0.33 (0.07)	0.04 (4)	0.06
6	PZ	1,3-benzene	PZ	22[i]	>250	reprecip[j]			$C_{14}H_{10}N_2O_2 \cdot 0.4H_2O$	3.9 (0.55)	3.16 (3)	3.23
7	PZ	2,5-thiophene	PZ	7[k]	>250	reprecip[l]			$C_{12}H_8N_4O_2S$	0.49 (0.09)	0.73 (2)	0.38
8	PZ	4,4'-biphenyl	PZ	22[m]	>250	AcOH/PrOH			$C_{20}H_{14}N_4O_2 \cdot 0.1H_2O$	>100		
9	DHPZ	1,4-benzene	DHPZ	6[h]	>250	Me_2CO			$C_{14}H_{14}N_2O_2 \cdot 0.1H_2O$	0.64 (0.07)	0.55 (3)	0.12
10	MDHPZ	1,4-benzene	MDHPZ	30[n]	>250	reprecip[j]			$C_{16}H_{18}N_4O_2$	0.11 (0.02)	0.06 (3)	0.04
11	MPZ	1,4-benzene	MPZ	72[o]	>250	reprecip[j]			$C_{16}H_{14}N_4O_2 \cdot 0.1H_2O$	37.5 (6.9)		
12	PZ	1,4-benzene	MDHPZ	2[p]	>250	reprecip[q]			$C_{15}H_{14}N_4O_2$	0.07 (0.01)	0.02 (4)	0.01
13	THIADZ	1,4-benzene	THIADZ	19[r]	302-3	MeOH			$C_{14}H_{14}N_4O_2S_2$	0.08 (0.01)	0.13 (2)	0.09
25	$NHCOCH_3$	1,4-benzene	MDHPZ		234-5	aq DMSO	235-6	1	$C_{13}H_{15}N_3O_2$	0.9 (0.16)	0.03 (4)	0.08
26	1-imidazolyl	1,4-benzene	MDHPZ		199-200	EtOH	197-8	12	$C_{14}H_{14}N_4O$	0.42 (0.06)	0.18 (2)	0.09
27	$CONH_2$	1,4-benzene	MDHPZ		216-8	MeOH	216-8	2	$C_{12}H_{13}N_3O_2$	2.23 (0.28)	0.07 (2)	0.1
28	NH_2	1,4-benzene	MDHPZ		272-6	EtOH/Et_2O	195-7	1	$C_{11}H_{13}N_3O \cdot HCl$	37 (12.9)	1.7 (4)	0.5
29	$NHCOCH_3$	1,4-benzene	DHPZ		252-4	H_2O	252	11	$C_{12}H_{13}N_3O_2 \cdot 0.25H_2O$	7.13 (1.7)	0.19 (2)	0.20
30	1-imidazolyl	1,4-benzene	DHPZ		218	EtOH	206-7	12	$C_{13}H_{12}N_4O$	3.72 (0.08)	0.64 (2/3)	0.42
31	NH_2	1,4-benzene	DHPZ		249-52	EtOH/Et_2O	251-2	11	$C_{19}H_{11}N_3O \cdot HCl$	61.7 (19.5)	4.43 (4)	1.4
32	OCH_3	1,4-benzene	DHPZ		150-1	EtOH	150-1	43	$C_{11}H_{12}N_2O_2$	12.7 (6.1)		
33	$NHCOCH_3$	1,4-benzene	PZ		302-5	DMF		44	$C_{12}H_{11}N_3O_2$	6.38 (2.02)		
34	NH_2	1,4-benzene	PZ		288-93	EtOH/Et_2O		44	$C_{10}H_9N_3O$	22.8 (5.2)		

[a] For details of abbreviations used see Scheme I. [b] All compounds analyzed for C, H, and N were within 0.4% of the calculated formula values. [c] Concentration required to inhibit enzyme activity by 50%. Values are means ± SEM shown in parentheses (n = 3–5). [d] Dose producing 50% increase in dLVP/dt(max) from control values. [e] Calculated from dose–response curves and expressed as an arithmetic mean of two or more separate experiments. [f] Arbitrary duration is given in parentheses and is based on the time taken for dLVP/dt to return to control values under standard assay conditions following a dose = ED_{50}. Values are 4, >1 h; 3, >0.5 h; 2, >0.25 h; 1, <0.25 h. The shape of the dose–response curves may vary. [g] Dose producing 15% decrease in autoperfused hindquarters perfusion pressure. [h] From 1,4-diacetylbenzene. [i] From 1,3-diacetylbenzene. [j] Dissolved in 2 N NaOH, acidified with AcOH to pH 5. [k] From 2,5-diacetylthiophene. [l] Dissolved in methanolic KOH, acidified with AcOH to pH 5. [m] From 4,4'-diacetylbiphenyl. [n] From 1,4-dipropionylbenzene. [o] From 10. [p] From 4-n-propylacetophenone. [q] Dissolved in 2 N NaOH, acidified with aqueous NH_4Cl to pH 11. [r] From 1,4-bis(2-bromopropionyl)benzene.

cleotide phosphodiesterase (PDE III),[15-25] one of several isoenzymic forms of PDE which vary in their substrate specificity, kinetic characterization, and cellular location.[26]

Several attempts[8,27,28] have been made to identify common spatial and electronic features in phenylpyridazinone derivatives and other inodilating, PDE III inhibitors such as amrinone (**3a**), milrinone (**3b**), enoximone (**4a**), and piroximone (**4b**) and relate these to analogous elements of cAMP structure potentially involved in interactions with the PDE III enzyme. These studies have led to suggestions that in compounds **1**–**4** the negative electrostatic field associated with the ring amide function mimics the cAMP cyclic phosphate charge and makes the major contribution to binding, and a heteroatom center in a phenyl substituent or pyridyl ring acts as a functional equivalent of a binding feature of the adenine fragment of the anti conformer of cAMP (probably either the N(1) or N(3) lone pair). In addition, when present in the molecule, an appropriately located small alkyl group, such as the methyl group (R^2) in dihydropyridazinones **2b** and **2d**, pyridinone **3b**, and imidazolone **4a** or the ethyl group (R^2) in **4b**, may make a further contribution to binding by means of highly regiospecific interaction.[8,27,28] In a search for potent and long-lasting inotropes, we have identified novel 6-phenylpyridazinone-based compounds in which the contribution made by the phenyl substituent to overall binding to PDE III substantially exceeds that seen in known compounds of high affinity such as **1** and **2**, where R^1 is an acetamido or 1-imidazolyl[9] substituent. We report here the synthesis of the congeneric bis(pyridazinone) compounds **5**–**13**, whose structures are shown in a codified form in Table I.

Chemistry

As shown in Scheme I, 1,4-diacetylbenzene,[29] 1,3-diacetylbenzene,[30] 2,5-diacetylthiophene,[31] and 4,4'-diacetylbiphenyl[32] were each treated with glyoxylic acid,

(15) In an alternative classification system, this enzyme would be described as type IV (see Cyclic Nucleotide Phosphodiesterases: Nomenclature Recommendation in *Advances in Cyclic Nucleotide and Protein Phosphorylation Research*; Strada, S. J., and Thompson, W. J., Eds.; Raven Press: New York, 1984; Vol. 16, p vi). However, the present classification allows distinction between the low K_m, cAMP-specific, cGMP-inhibited phosphodiesterase and the cAMP-specific enzyme which is inhibited by rolipram [4-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone]. See also ref 26.

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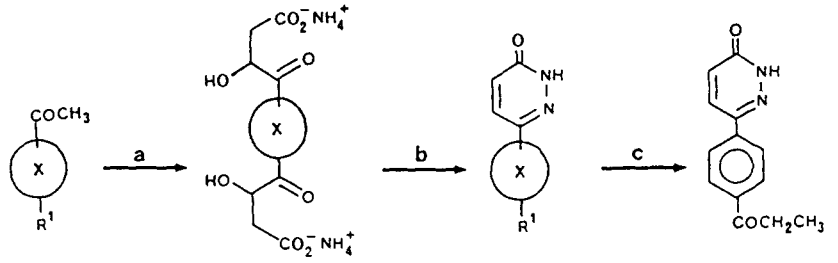
Scheme I[a]



R^1	Ring system (X)	14
$COCH_3$	1,4-benzene	
$COCH_3$	1,3-benzene	
$COCH_3$	2,5-thiophene	
$COCH_3$	4,4'-biphenyl	
$CH_2CH_2CH_3$	1,4-benzene	

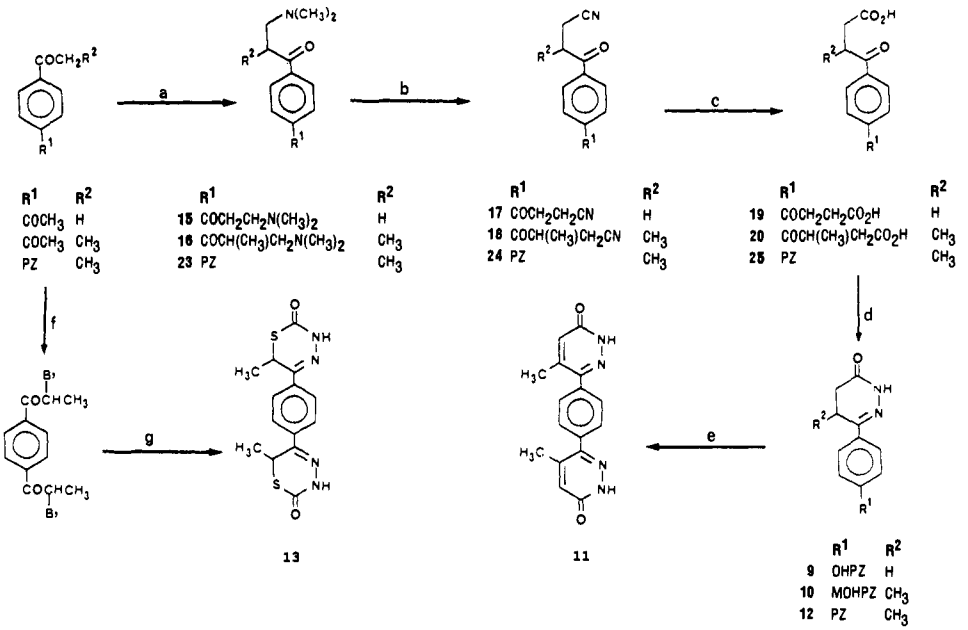
R^1	Ring system (X)	22
5 PZ	1,4-benzene	
6 PZ	1,3-benzene	
7 PZ	2,5-thiophene	
8 PZ	4,4'-biphenyl	
21 $CH_2CH_2CH_3$	1,4-benzene	

PZ: R=H
MPZ: R=CH_3

DHPZ: X=CH_2 R=H
MDHPZ: X=CH_2 R=CH_3
THIADZ: X=S R=CH_3

[a] Reagents: (a) (i) $OHCCO_2H{\cdot}H_2O$, (ii) NH_4OH; (b) $N_2H_4{\cdot}H_2O$; (c) CrO_3/Ac_2O.

Scheme II[a,b]



R^1	R^2
$COCH_3$	H
$COCH_3$	CH_3
PZ	CH_3

R^1	R^2
15 $COCH_2CH_2N(CH_3)_2$	H
16 $COCH(CH_3)CH_2N(CH_3)_2$	CH_3
23 PZ	CH_3

R^1	R^2
17 $COCH_2CH_2CN$	H
18 $COCH(CH_3)CH_2CN$	CH_3
24 PZ	CH_3

R^1	R^2
19 $COCH_2CH_2CO_2H$	H
20 $COCH(CH_3)CH_2CO_2H$	CH_3
25 PZ	CH_3

13

11

R^1	R^2
9 OHPZ	H
10 MOHPZ	CH_3
12 PZ	CH_3

[a] Reagents: (a) $HCHO/NHMe_2$; (b) KCN/MeOH; (c) cHCl; (d) $N_2H_4{\cdot}H_2O$; (e) sodium 3-nitrobenzenesulfonate/NaOH; (f) Br_2/AcOH; (g) $CH_3OCSNHNH_2$. [b] For abbreviations, see Scheme I.

followed by ammonia, to give solutions of the corresponding bis(2-hydroxy-4-oxobutanoate) compounds **14**.[33] Without isolation of these intermediates, the solutions were treated with hydrazine at reflux temperature to give bis(pyridazinone) compounds **5–8**.

For the synthesis of **9** and **10** (Scheme II), 1,4-diacetylbenzene and 1,4-dipropionylbenzene[34] were each converted into their respective Mannich bases **15** and **16** in a manner similar to that described by McEvoy and Allen.[35] Compounds **15** and **16** underwent elimination–addition with cyanide to give the dinitriles **17** and **18**, respectively, which on hydrolysis gave the corresponding diacids **19** and **20**. Cyclocondensation of compounds **19** and **20** with hydrazine hydrate gave bis(pyridazinone) compounds **9** and **10**, respectively. Oxidation of compound **10** using sodium *m*-nitrobenzenesulfonate[11] gave the compound **11**.

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For the preparation of the unsymmetrically substituted compound **12**, the acyl function of 4-propylacetophenone[36] was elaborated according to Scheme I to give pyridazinone **21**. Compound **21** was then oxidized with chromium trioxide to give propionylphenylpyridazinone **22**, which was then converted (Scheme II) by way of Mannich base **23**, nitrile **24**, and carboxylic acid **25** into compound **12**. As shown in Scheme II, bis(1,3,4-thiadiazinone) compound **13** was synthesized by treatment of the symmetrical dibromo derivative of 1,4-dipropionylbenzene[37] with (methoxythiocarbonyl)hydrazine.[38] For purposes of comparison, a series of known compounds (Table I, **25–34**) were prepared by standard methods as exemplified in the literature references given in Table I.

Results and Discussion

The inotropic and vasodilator (inodilator) properties of the 6-phenylpyridazinone derivatives **1** and **2** are well-known[5-9,12] and substantial evidence[17-25] has been amassed that their pharmacological effects arise largely from their ability to inhibit the low K_m, cAMP-selective, cGMP-inhibited phosphodiesterase (PDE III). Correlation of the in vivo inotropic potency and in vitro PDE III inhibitory activity of a range of 6-phenylpyridazinone derivatives with imidazole-based substituents at the 4-position of the phenyl ring[7] and of a more structurally diverse series of inotropes[12] has been demonstrated.

In our work, the PDE III inhibitory potency of a large number of phenylpyridazinone-based compounds, measured by the concentration required to cause 50% inhibition of the enzyme (IC_{50}), has been used as a convenient predictor of inodilator activity. Examination of the data generated showed that while PDE III inhibitory properties were retained by compounds with a small substituent (e.g. amino or methoxy) containing a heteroatom connected directly to the 4-position of the phenyl ring, compounds with an extended 4-substituent that placed a heteroatom further from the ring (e.g. acetamido, 1-imidazolyl, and carboxamido) frequently showed relatively greater inhibitory potency. This characteristic difference in the levels of PDE III affinity associated with the two structural classes of substituent is exemplified by the PDE III inhibitory data given in Table I for compounds **25–34**. Comparison of **25**, **26**, and **27** with **28**; **29** and **30** with **31** and **32**; and **33** with **34** shows that the affinity of the compounds with an extended substituent (i.e. **25–27**, **29**, **30**, and **33**) always exceeds that of otherwise comparable compounds with a substituent containing a single heteroatom attached directly to the phenyl ring (i.e. **28**, **31**, **32**, **34**). In most comparisons the difference in affinity exceeds 1 order of magnitude. In addition, it was noted that within the group with extended substituents, compounds with particularly high PDE III affinity were characterized by a capacity, in their preferred conformation,[39] to invoke a lone pair binding option at a position approximately in the same plane as the phenylpyridazinone moiety about 4.15 Å from the phenyl 4-position and within 20° of an extended 1,4-benzene ring axis.[40] On the basis of these findings, 6-(4-substituted-phenyl)pyridazin-3(2*H*)-one analogues in which the phenyl 4-substituent was a pyridazinone were targeted for synthesis as, potentially, a lone pair could be invoked in these compounds at either a similar position or one slightly further from the phenyl ring.

On preparation, bis(azinone) compounds **5**, **9**, and **12** were found to show IC_{50} values for PDE III inhibition of 0.33, 0.64, and 0.07 μM, respectively, and exceeded the potency of known, high-affinity compounds such as the comparable acetamido compounds **33**, **29**, and **25** by approximately 1 order of magnitude. In addition, in our assays compounds **9** and **12** were also about 5-fold more potent as PDE III inhibitors than the clinically evaluated imidazolyl compounds CI-914 (**2c**) and CI-930 (**2d**). When one pyridazinone moiety (shown as fragment A in Table I) in the bis(azinone) compounds **5** and **9–12** was considered to be formally the phenyl substituent of a 6-(4-substituted-phenyl)pyridazin-3(2*H*)-one derivative and to be less important than the other pyridazinone fragment in determining PDE III affinity, consistency with previously described structure–affinity relationships in the phenylpyridazinone series could be recognized. Thus, in good agreement with the relative levels of affinity seen for analogous pyridazinone derivatives in the 6-[4-(1*H*-imidazol-1-yl)phenyl]pyridazinone series,[7] the inhibitory potency of compound **11**, containing a 2,3-dihydro-5-methyl-3-oxopyridazin-6-yl moiety, was exceeded approximately 10-fold by that of the approximately equipotent derivatives **5** and **9**, which contain 2,3-dihydro-3-oxopyridazin-6-yl and 3-oxo-2,3,4,5-tetrahydropyridazin-6-yl groups, respectively, while a level of potency up to 10 times greater than that of **5** and **9** was retained by compounds **10** and **12**, which have a 5-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl moiety. It was therefore concluded that the presence of a pyridazinone group as a phenyl substituent had not significantly altered the binding characteristics of the residual phenylpyridazinone moiety which was essentially similar in the 6-[4-(1*H*-imidazol-1-yl)phenyl]pyridazinone and bis(azinone) series. The higher inhibitory potency of the bis(azinones) therefore arose from the ability of a pyridazinone substituent in a 6-(4-substituted-phenyl)pyridazin-3(2*H*)-one derivative make a contribution to overall binding which was larger than that of either an acetamido or (1*H*-imidazol-1-yl) group. As the PDE III affinity of **12** differed only marginally from that of compound **10**, it could also be concluded that, as phenyl substituents, the 2,3-dihydro-3-oxopyridazin-6-yl and 5-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl moieties were approximately equal in their ability to confer PDE III affinity and that the modes of binding at each end of a bis(azinone) molecule were different.

The approximately linear bis(thiadiazinone) analogue **13**, which in models closely overlays compounds **10** and **12**, shows a level of PDE III inhibitory potency closely similar to those of these compounds. Due to differences in the structure of their central rings, 1,3-disubstitued benzene **6** and 2,5-disubstituted thiophene **7** were significantly different in their topology from compounds **5** and **9–13**. Both of these angular molecules showed a separation of their carbonyl end groups which was less than that of compound **5** but greater than the distance between the carbonyl functions of (acetamidophenyl)pyridazinone **33**. Their IC_{50} values also lay between those of compounds **5** and **33**. This result suggested that one of the roles[41] of the central region of the bis(azinone) compounds **5–7** and **9–12** may be to act as a spacer to maintain an appropriate

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Table II. Correlation Data for Compounds **5–7, 9, 10, 12, 13,** and **25–31**

coefficients for equation $\log A = m \log B + C$				statistical data			
A	B	m	C	r^2	s	F	n
All Compounds							
IC_{50}	ED_{50}	0.88	0.61	0.49	0.66	13.3	14
IC_{50}	ED_{15}	1.09	0.93	0.55	0.62	16.9	14
ED_{50}	ED_{15}	1.08	0.23	0.84	0.31	66.1	14
Bis(azinone) Compounds (**5–7, 9, 10, 12, 13**)							
IC_{50}	ED_{50}	0.68	−0.2	0.69	0.34	14.6	7
IC_{50}	ED_{15}	0.70	0.13	0.76	0.30	19.9	7
ED_{50}	ED_{15}	0.94	0.14	0.87	0.28	41.4	7
Compounds **25–31**							
IC_{50}	ED_{50}	0.87	1.10	0.64	0.48	11.7	7
IC_{50}	ED_{15}	1.54	1.64	0.78	0.38	21.9	7
ED_{50}	ED_{15}	1.56	0.48	0.89	0.26	48.7	7

distance between the interacting end groups. Notably, when end-group separation was increased, in 4,4′-substituted biphenyl **8**, little evidence of PDE III inhibition was detected.

Selected compounds (Table I; **5–7, 9, 10, 12, 13, 25–31**) were studied in ganglion and β-blocked, anesthetized cats. Following a bolus intravenous injection of the test compound, the maximum value of the first derivative of left ventricular pressure, dLVP/dt(max), was measured as an index of contractility and inotropic activity was quantitatively assessed as the dose (ED_{50}) required to cause a 50% increase in this parameter. An attempt was made to assess the duration of inotropic action by use of an arbitrary scale based on the time taken for dLVP/dt to return to control values. During the course of these experiments, autoperfused hindquarters perfusion pressure, heart rate, and left intraventricular pressure were also monitored. Changes in heart rate and left intraventricular pressure were minimal in these experiments and no values are given here. Vasodilator activity was assessed by the dose (ED_{15}) required to cause a 15% fall in perfusion pressure. Values for ED_{50}, ED_{15}, and duration of action are given in Table I. Compound **12**, which showed the highest PDE III inhibitory potency (IC_{50} = 0.07 μM), was also the most potent inotrope (ED_{50} = 0.02 μmol/kg) and vasodilator (ED_{15} = 0.01 μmol/kg). The biological data were examined for evidence of correlation between IC_{50}, ED_{50}, and ED_{15} values. The results are shown in Table II. The level of correlation between IC_{50} for the inhibition of PDE III and ED_{50} for dLVP/dt for all of the pharmacologically assayed compounds in Table I was comparable but slightly lower than that obtained in a study of 6-[4-(1*H*-imidazol-1-yl)-phenyl]pyridazin-3(2*H*)-one derivatives using a dog model.[7] A similar correlation coefficient (r^2 = 0.55) was obtained for regression of IC_{50} for PDE III inhibition with ED_{15} for vasodilation. In addition, ED_{50} and ED_{15} were themselves highly correlated. These results provide further evidence for a casual relationship between PDE III inhibition and inotropic and vasodilator effects. A slightly improved correlation between the parameters could be obtained when bis(azinone) compounds **5–7, 9, 10, 12,** and **13** and the more simply substituted compounds **25–31** were regressed separately, probably reflecting a small difference in the pharmacodynamic behavior of the two groups of compounds rather than any fundamental difference in mechanism. No correlation could be detected between "duration" and any other biological parameter.

Conclusions

The 1,4-bis(3-oxopyridazin-6-yl)benzenes **5** and **9–12** are formally analogous to known potent PDE III inhibiting 6-(4-substituted-phenyl)pyridazin-3(2*H*)-one derivatives and provided the effects of saturation and 5-methylation in one of the pyridazinone moieties of compounds **5** and **9–12** are considered to be relatively unimportant in determining PDE III affinity, the structure–affinity relationships of 1,4-bis(2,3-dihydro-3-oxopyridazin-6-yl)-benzene derivatives can be reconciled, in both sense and magnitude, with earlier findings.[7]

Bis(azinones) **5** and **9–12** are distinguished from earlier 6-(4-substituted-phenyl)pyridazin-3(2*H*)-ones such as the acteamido and 1*H*-imidazol-1-yl compounds **1** and **2** by their characteristically greater PDE III inhibitory potency. Generally, the distance separating the polar end groups of 6-(4-substituted-phenyl)pyridazin-3(2*H*)-one-based PDE III inhibitors (i.e. the ring amide function of the pyridazinone and a polar feature in the phenyl 4-substituent) appears to be an important factor in determining PDE III inhibitory potency. The enhanced level of affinity associated with a pyridazinone derivative as a phenyl 4-substituent relative to less extended phenyl substituents such as acetamido and 1*H*-imidazol-1-yl probably arises from its ability to place an enzyme-binding entity (probably a ring amide lone pair) at a closer to optimal position to the remainder of the molecule. Structural variations of the pyridazinone substituent and the central ring region of bis(azinones) appear to be subordinate to polar end group separation in determining PDE III affinity as compounds **10** and **12** and bis(azinones) with altered central structure (i.e. **6** and **7**) retain levels of PDE III inhibitory potency in line with their end-group separations.

The presence of two relatively polar pyridazinone groups in the bis(azinones) does not compromise cell penetration; those bis(azinones) which have high PDE III affinity are potent inotropes and vasodilators. Also notable is the fact that the level and duration of inotropic and vasodilator potency achieved by compounds with a chiral center such as the acetamido compound **2c** or CI-930 **2d** are exceeded by nonchiral bis(azinone) **5**, which can be readily synthesized by a one-pot process from a commercially available material.

Experimental Section

Melting points were determined on a Büchii capillary melting point apparatus and are uncorrected. Analytical samples were homogeneous by TLC performed on silica gel plates with chloroform and methanol (9:1) as eluant. Elemental analyses (C, H, N, and, when present, Cl and S) of new compounds were within 0.4% of the theoretical values. NMR spectra were determined on Bruker AM 250 or AM 360 spectrometers and IR spectra were recorded on a Perkin-Elmer Model 298 instrument. All structural assignments were consistent with IR and NMR spectra.

General Preparation of the Bis(3-oxo-2,3-dihydropyridazin-6-yl) Compounds 5–8. The appropriate dialkanoyl compound (50 mmol) and glyoxylic acid monohydrate (13.81 g, 150 mmol) were stirred at 110 °C for 20 min and the semisolid mixture obtained was cooled, treated with aqueous ammonia to pH 10, and filtered. The filtrate was treated with hydrazine hydrate (10 mL), refluxed for 1 h, and the precipitated solid was collected and recrystallized to give the corresponding bis(3-oxo-2,3-dihydropyridazin-6-yl) compounds **5–8**.

1,4-Bis(3-oxo-2,3,4,5-tetrahydropyridazin-6-yl)benzene (9). A mixture of 1,4-diacetylbenzene[29] (8.1 g, 50 mmol), paraformaldehyde (4.0 g, 44 mmol), dimethylammonium chloride (10.6 g, 130 mmol), and concentrated HCl (0.2 mL) in ethanol (50 mL) was stirred and refluxed for 3 h. The pale yellow solution obtained was poured into dry acetone (200 mL) and the crude product was collected. Recrystallization gave 1,4-bis[3-(dimethylamino)-1-propionyl]benzene dihydrochloride (**15**; 12.3 g, 70%); mp 205 °C dec (from ethanol/acetone). Anal. ($C_{16}H_{24}N_2O_2 \cdot 2HCl$) C, H, N, Cl.

Potassium cyanide (5.5 g, 84 mmol) in water (30 mL) was added dropwise to a stirred solution of **15** (7.00 g, 20 mmol) in water

(70 mL) containing acetic acid (2.5 mL). When addition was complete the mixture was heated at 80 °C for 3 h. The crude precipitate was collected and washed with water to give 1,4-bis(3-cyano-1-propionyl)benzene (17; 3.52 g, 72% from 15); mp 162–5 °C. Anal. ($C_{14}H_{12}N_2O_2$) C, H, N.

A suspension of 17 (2.0 g, 8.3 mmol) in 1:1 acetic acid and concentrated HCl (150 mL) was refluxed for 2 h. The solution was evaporated to dryness and triturated with water to give 1.7 g of crude 1,4-bis(3-carboxy-1-propionyl)benzene (19). Without further purification 19 (1.54 g) was suspended in water (40 mL) and refluxed with hydrazine hydrate (0.8 mL; 16.5 mmol) for 4 h. The precipitated solid was collected, washed with water, and recrystallized to give compound 9 (0.25 g, 12% from 17); mp >250 °C (from acetone). Anal. ($C_{14}H_{14}N_4O_2 \cdot 0.1H_2O$) C, H, N.

1,4-Bis(5-methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl)benzene (10). In the manner described for the preparation of compound 9, 1,4-dipropionylbenzene[34] was converted in approximately 73% yield into 1,4-bis[3-(dimethylamino)-2-methylpropionyl]benzene dihydrochloride (16; mp 148–51 °C) which, without further purification, was converted into 1,4-bis(3-cyano-2-methylpropionyl)benzene (18; 67%, mp 142–5 °C (from H_2O)). Anal. ($C_{16}H_{16}N_2O_2 \cdot 0.1H_2O$) C, H, N. Dinitrile 17 was hydrolyzed to the corresponding dicarboxylic acid 20, which was treated with hydrazine to give compound 10 as a mixture of stereoisomers (30%, mp >300 °C). Anal. ($C_{16}H_{18}N_4O_2$) C, H, N.

1,4-Bis(5-methyl-3-oxo-2,3-dihydropyridazin-6-yl)benzene (11). A mixture of 10 (1.41 g, 4.7 mmol), sodium *m*-nitrobenzenesulphonate (2.20 g, 9.7 mmol), and sodium hydroxide (1 g, 25 mmol) in water (100 mL) was stirred under reflux until a clear solution was obtained. Heating was continued for 1 h, then the mixture was cooled and filtered. The filtrate was treated with aqueous $NaHCO_3$ to pH 10 and the precipitated solid was filtered off. The crude product was redissolved in dilute aqueous NaOH solution and the solution was adjusted with saturated aqueous ammonium chloride to give pH 11 and afford 11 (1.02 g, 72%), mp >250 °C. Anal. ($C_{16}H_{14}N_4O_2 \cdot 0.1H_2O$) C, H, N.

6-[4-(5-Methyl-3-oxo-2,3,4,5-tetrahydropyridazin-6-yl)phenyl]pyridazin-3(2*H*)-one (12). A mixture of 4-propylacetophenone[36] (20.2 g, 124 mmol) and glyoxylic acid monohydrate (11.5 g, 125 mmol) was stirred and heated at 110 °C for 3 h. The semisolid obtained was dissolved in aqueous ammonia and the filtered solution was treated with hydrazine hydrate (6.5 mL, 13 mmol) and stirred under reflux for 4 h to afford 6-(4-propylphenyl)pyridazin-3(2*H*)-one (21; 11.96 g, 42%); mp 180–2 °C. Anal. ($C_{13}H_{14}N_2O$) C, H, N.

A cooled solution of 21 (5.11 g, 22 mmol) in acetic anhydride (25 mL) containing concentrated sulfuric acid (5 mL) was treated dropwise with a solution of chromium trioxide (6.5 g, 65 mmol)) in acetic anhydride (29 mL). The reaction mixture was stirred at room temperature for 16 h and then poured onto crushed ice (250 mL) to afford 6-(4-propionylphenyl)pyridazin-3(2*H*)-one (22, 0.78 g, 14.4%); mp 205–5 °C. Anal. ($C_{13}H_{12}N_2O_2$) C, H, N.

In a manner similar to the preparation of 9, 2.28 g of compound 22 was treated with formaldehyde and dimethylammonium chloride to afford 2.12 g of 6-[4-[3-(dimethylamino)-2-methylpropionyl]phenyl]pyridazin-3(2*H*)-one hydrochloride (23) which, without further purification, was treated with potassium cyanide to give 6-[4-(3-cyano-2-methylpropionyl)phenyl]pyridazin-3-(2*H*)-one (24); mp 196–201 °C. Crude 24 was hydrolyzed to the corresponding carboxylic acid 25, which was treated directly with hydrazine hydrate to afford compound 12 (0.84 g, 32%); mp >250 °C. Anal. ($C_{15}H_{14}N_4O_2$) C, H, N.

1,4-Bis(2,3-dihydro-6-methyl-2-oxo-6*H*-thiadiazin-5-yl)benzene (13). A mixture of 1,4-bis(2-bromopropionyl)benzene[37] (2.64 g, 7.6 mmol) and (methoxythiocarbonyl)hydrazine[37] (2.41 g, 23 mmol) in acetonitrile (50 mL) was heated under reflux for 3 h. The solid which separated on cooling was collected and recrystallized from methanol to give compound 13 (0.4 g, 19%, mp 302–3 °C) as a mixture of stereoisomers.

Inhibition of Phosphodiesterases. Three peaks of cyclic nucleotide phosphodiesterase activity [PDE (peak I), PDE (peak II) and PDE (peak III)] from cat heart were separated by chromatography on DEAE-Sepharose CL-6B [(diethylamino)ethyl]-cellulose with a bead size of 45–165 μm) by a procedure essentially similar to that described by Reeves et al. for the separation of phosphodiesterase activity from guinea pig heart.[41] The high-speed supernatant from a cat heart homogenate tissue (2 g) in 20 mL of 20 mM PIPES [piperazine-*N*,*N*¹-bis(2-ethanesulfonic acid)], 50 mM sodium acetate, pH 6.5) was applied to a 15 × 1.5 cm column of DEAE-Sepharose equilibrated with the homogenization buffer. The PDE activities were eluted with a gradient of 0.05–1 M Na acetate in 20 mM PIPES. There were three major peaks which had the following characteristics. PDE (peak I) had high affinity for cyclic AMP and cyclic GMP and was characterized by an activation by Ca^{2+}/calmodulin complex. PDE (peak II) demonstrated relatively high affinity for cAMP and was not affected by Ca^{2+}/calmodulin complex. This activity was characterized as being potently inhibited by rolipram (4-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone).[26] PDE (peak III) had high affinity for cAMP. It could also hydrolyze cGMP though the preferred substrate was cAMP. cGMP was a potent inhibitor of the hydrolysis of cAMP. The activity was also insensitive to Ca^{2+}/calmodulin activation. The enzymes were assayed by incubation at 37 °C for 4–30 min in 50 mM Tris, 5 mM $MgCl_2$, pH 7.5, with ^{3}H-labeled cyclic nucleotide (4×10^5 disintegrations min^{-1}) and ^{14}C-labeled nucleotide 5′-monophosphate (3×10^3 disintegrations min^{-1}). The assay was stopped by boiling, and the ^{3}H-labeled 5′-monophosphate product was separated from substrate on boronate columns.[42] The reaction mixture was diluted with 0.5 mL of 100 mM HEPES [*N*-(2-hydroxyethyl)-piperazine-*N*¹-2-ethanesulfonic acid], 100 mM NaCl, pH 8.5, and applied to the column. The column was extensively washed with the same buffer, and the 5′-nucleotide was eluted with 6 mL of 0.25 M acetic acid. The recovery of product as judged by ^{14}C-recovery was approximately 80%. All assays were linear with time of incubation and concentration of enzyme over the range used in these experiments.

IC_{50} values (the concentration of inhibitor required for 50% inhibition of activity) were obtained for PDE (peak III) by incubation of the enzyme at 1 μM cAMP and a range of inhibitor concentrations from $0.1 \times IC_{50}$ to $100 \times IC_{50}$.

Anesthetized Cat Screen. Cats of either sex, weighing between 1.9 and 2.5 kg, were anesthetized with sodium pentobarbitone (Sagatal) 60 mg/kg ip. The trachea was cannulated to maintain a free passage of air. Blood pressure was recorded from a brachial artery, with a Bell and Howell Type 4-422 pressure transducer connected through a pressure preamplifier to a recorder. The blood pressure signal was also used to trigger a heart-rate meter. A brachial vein was cannulated for administration of drugs. The abdomen was opened and the descending aorta, caudal to the renal arteries, was cleared of surrounding tissue, and the inferior mesenteric artery was tied off. Prior to cannulation the preparation was left for $^3/_4$ h to allow small, broken vessels to seal and then 500 units/kg iv of heparin was administered to prevent blood clotting in the extracorporeal system. The descending aorta was cannulated toward the heart to receive blood and away from the heart toward the hindquarters to return blood by means of a Watson-Marlow peristaltic pump. The hindquarters were perfused at a constant flow rate, such that the pressure closely matched the mean systemic blood pressure, allowing calculation of hindquarters vascular resistance.

Left ventricular pressure was recorded via a polythene cannula introduced down the right carotid artery and manipulated through the semilunar valves into the left ventricle. The pressure signal was electronically differentiated to give a continuous linear record of dLVP/d*t*(max), which was taken as an index of contractility.

All animals were pretreated with 5 mg/kg pempidine (a ganglion blocking agent) to prevent reflex activity and produce a stable preparation with a lowered heart rate, blood pressure, and contractile state, which was sensitive to isoprenaline given in a range of doses from 0.01 to 0.1 μg/kg iv, and any cat not responding with an increase in contractility of at least 100% was rejected. Propranolol, a β-adrenoreceptor antagonist, was then given at a dose 1 mg/kg iv plus 3–4 mg/kg sc. When the preparation was stable, the test compound was given as a bolus in-

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travenous injection and the time course of the response was followed for at least 1 h.

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Registry No. 5, 107549-65-5; 6, 107549-69-9; 7, 126725-00-6; 8, 126725-01-7; 9, 107549-66-6; (*R**,*R**)-10, 126725-02-8; (*R**,*S**)-10, 126725-06-2; 11, 107549-68-8; 12, 107549-70-2; (*R**,*R**)-13, 126725-03-9; (*R**,*S**)-13, 126725-07-3; 15·2HCl, 21702-05-6; 16·2HCl, 107549-76-8; 17, 34555-41-4; 18, 107549-77-9; 19, 107549-74-6; 20, 126725-04-0; 21, 107549-80-4; 22, 107549-81-5; 23·HCl, 126725-05-1; 24, 107549-83-7; 25, 36725-27-6; 26, 86798-59-6; 27, 52240-83-2; 28·HCl, 126725-08-4; 29, 21394-91-2; 30, 84243-58-3; 31·HCl, 54557-93-6; 32, 1017-06-7; 33, 54558-04-2; 34, 24912-35-4; 35, 107549-84-8; 4-AcC_6H_4Ac, 1009-61-6; 3-AcC_6H_4Ac, 6781-42-6; 4-AcC_6H_4-4-C_6H_4Ac, 787-69-9; $OHCCO_2H$, 298-12-4; 4-$H_3CCH_2COC_6H_4COCH_2CH_3$, 17558-64-4; 4-$AcC_6H_4(CH_2)_2CH_3$, 2932-65-2; 4-$H_3CCHBrCOC_6H_4COCHBrCH_3$, 7709-84-4; $H_2NNHC(S)OCH_3$, 19692-07-0; 2,5-diacetylthiophene, 4927-10-0.

9,11-Epoxy-9-homoprosta-5-enoic Acid Analogues as Thromboxane A_2 Receptor Antagonists

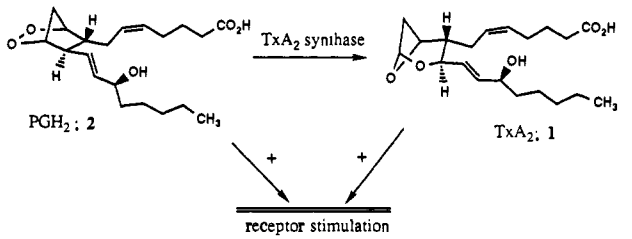
Jagabandhu Das,* Steven E. Hall,* Masami Nakane,† Martin F. Haslanger,‡ Joyce A. Reid, Dianne Garber, Vu Chi Truc, Don N. Harris, Anders Hedberg, and Martin L. Ogletree

Departments of Chemistry and Pharmacology, The Squibb Institute for Medical Research, P.O. Box 4000, Princeton, New Jersey 08543-4000. *Received October 6, 1989*

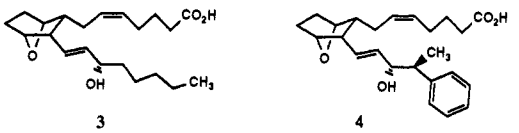
A novel bicyclic prostaglandin analogue, (1*S*)-[1α,2α(*Z*),3α(1*E*,3*S**,4*R**),4α]-7-[3-(3-hydroxy-4-phenyl-1-pentenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid (**4**), was found to be a potent and selective thromboxane A_2 (TxA_2) receptor antagonist. Alcohol **4** was the only member in a series of allylic alcohols which did not display direct contractile activity in the rat stomach strip model. Alcohol **4** was effective in the inhibition of (a) arachidonic acid induced platelet aggregation of human platelet-rich plasma (I_{50} = 0.65 ± 0.1 μM); (b) 11,9-epoxymethano-PGH_2 induced contraction of guinea pig trachea (pA_2 = 8.0 ± 0.2) or rat aorta (pA_2 = 8.1 ± 0.2); and (c) arachidonic acid induced bronchoconstriction in the anesthetized guinea pig (1 mg/kg iv). A radioiodinated analogue of **4** bound in a specific and saturable manner to human platelet membranes with a K_d = 2.3 ± 0.9 nM. Modification of the α-chain, in an attempt to minimize in vivo metabolism, resulted in TxA_2 receptor antagonists of reduced in vitro potency.

The pursuit of pharmacological agents that modulate the synthesis or actions of thromboxane A_2 (TxA_2, **1**)[1] has been an area of intense effort over the past decade.[2] TxA_2, as well as its biosynthetic precursor PGH_2 (**2**), are potent stimulators of platelet aggregation and mediate vascular and pulmonary smooth muscle contraction (Scheme I). Earlier studies[3] from these laboratories have described a series of 7-oxabicyclo[2.2.1]heptane analogues related to **3** which were found to antagonize TxA_2 at the receptor level. These analogues were TxA_2 receptor antagonists in the platelet preparations but displayed direct contractile activity in smooth muscle preparations. In addition, **3** was not specific in that it inhibited platelet aggregation by both TxA_2 and non-TxA_2 dependent mechanisms. In this report, we describe the modification of the ω-chain terminus which led to a highly selective TxA_2 receptor antagonist, **4** (Scheme II). Alteration of the α-chain in an attempt to limit in vivo degradation of **4** by β-oxidation led to TxA_2 receptor antagonists of reduced potency.

Scheme I

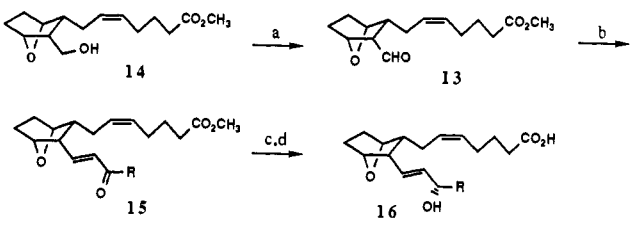


Scheme II



3 4

Scheme III[a]



14 13 15 16

[a] (a) PCC, Celite, NaOAc, CH_2Cl_2, 23 °C; (b) $(H_3CO)_2POCH_2COR$, NaH, DME, 23 °C; (c) $NaBH_4$, $CeCl_3$, CH_3OH, 0 °C; (d) LiOH, H_2O, THF, 23 °C.

Chemistry

Allylic alcohols **4–12** (Table I), which possess the natural 5(*Z*)-heptenoic acid α-chain, were prepared by using the straightforward sequence outlined in Scheme III. These analogues derived from the common precursor, aldehyde **13**, which was previously synthesized from alcohol ester **14** via a Collins oxidation[3a] but was more conveniently prepared with pyridinium chlorochromate. Aldehyde **13** was extremely sensitive to epimerization during the Horner–Emmons condensation but this side reaction could be prevented as long as complete consumption of the NaH had occurred.[4] A more convenient procedure employed the $LiCl/R_3N$ methodology described by Masamune and Roush.[5] In addition to the lack of epimerization, the latter method afforded less of the *cis*-enone isomers. Reduction[6] using $NaBH_4/CeCl_3$ followed by hydrolysis afforded the target allylic alcohols. Separation of the C(15) alcohol

† Present address: Pfizer Central Research, Nagoya, Japan.
‡ Present address: Schering-Plough, Pharmaceutical Research Division, Bloomfield, NJ.

(1) Hamberg, M.; Svensson, J.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 2994. For the total synthesis of TxA_2 and its characterization, see: (b) Bhagwat, S. S.; Hamann, P. R.; Still, W. C. *J. Am. Chem. Soc.* **1985**, *107*, 6372. (c) Bhagwat, S. S.; Hamann, P. R.; Still, W. C.; Bunting, S.; Fitzpatrick, F. A. *Nature (London)* **1985**, *315*, 511.

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