135426-10-7; **34**, 5451-40-1; **35**, 7013-21-0; **36**, 135394-16-0; **37**, 135394-17-1; **38**, 135394-18-2; **39**, 135394-19-3; $PhNH_2$, 62-53-3; $2\text{-}FC_6H_4NH_2$, 348-54-9; $PhCH_2NH_2$, 100-46-9; $PhCH_2CH_2NH_2$, 64-04-0; $H_2NCH_2CHPh_2$, 3963-62-0; $H_2NCH_2CH_2C_6H_2(OMe)_3$, 135394-20-6; (*R*)-$PhCH_2CH(NH_2)CH_3$, 156-34-3; (*S*)-$PhCH_2CH(NH_2)CH_3$, 51-64-9; MeI, 74-88-4; $HC(OEt)_3$, 122-51-0; H_2NCHEt_2, 616-24-0; cyclobutylamine, 2516-34-9; cyclopentylamine, 1003-03-8; 1-methylcyclopentylamine, 40571-45-7; cyclohexylamine, 108-91-8; 2-(2-pyridyl)ethylamine, 2706-56-1; 2-(3-thienyl)ethylamine, 59311-67-0; adenine, 73-24-5; N^6-cyclopentyladenine, 103626-36-4; 2,3-dihydrofuran, 1191-99-7; 2-chloro-N^6-cyclopentyladenine, 135394-21-7; adenosine, 58-61-7; adenylate cyclase, 9012-42-4.

Interphenylene 7-Oxabicyclo[2.2.1]heptane Thromboxane A_2 Antagonists. Semicarbazone ω-Chains†

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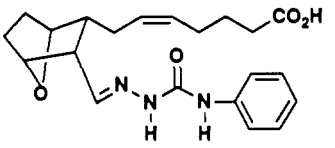
A series of chiral interphenylene 7-oxabicyclo[2.2.1]heptane semicarbazones **19–26** were prepared and evaluated for their in vitro thromboxane (TxA_2) antagonistic activity and in vivo duration of action. The potency of **19–26** was found to highly dependent on the substitution pattern of the interphenylene ring and decreased in the order ortho > meta ≫ para. SQ 35,091 (**25**), [1*S*-(1α,2α,3α,4α)]-2-[[3-[[[(phenylamino)carbonyl]hydrazono]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic acid, was identified as a potent and long-acting TxA_2 antagonist. In human platelet rich plasma SQ 35,091 inhibitied arachidonic acid (800 μM) and U-46,619 (10 μM) induced aggregation with I_{50} values of 3 and 12 nM, respectively. In contrast, no inhibition of ADP (20 μM) induced aggregation was observed at >1000 μM. Receptor binding studies with [^{3}H]-SQ 29,548 showed SQ 35,091 was a competitive antagonist with a K_d value of 1.0 ± 0.1 nM in human platelet membranes. In vivo SQ 35,091 (0.2 mg/kg po) showed extended protection (T_{50} = 16 h) from U-46,619 (2 mg/kg iv) induced death in mice. These compounds have for the first time demonstrated that a metabolically stable interphenylene α-sidechain can be introduced into a prostanoid-like series of TxA_2 antagonists with the maintainance of potent antagonistic activity.

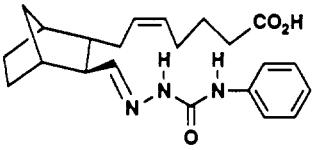
Introduction

Thromboxane A_2 (TxA_2)[1] is an extremely potent, short-lived endogenous mediator which induces both platelet activation and aggregation, and smooth muscle contraction. The biological activities of TxA_2 have implicated it as a contributor in the pathogenesis of thrombotic and vasospastic disorders.[2] However, in order to establish a definitive connection between TxA_2 and specific diseases it has been necessary to examine models in which the activities of TxA_2 can be experimentally elicited and/or suppressed. This has prompted the development of stable, selective TxA_2 agonists and antagonists as pharmacological tools. These compounds have demonstrated that TxA_2 mimics are able to elicit and TxA_2 antagonists are able to block a number of cardiovascular abnormalities and suggest that antagonists possessing suitable pharmacokinetic and pharmacodynamic properties have the important clinical potential to be developed as useful therapeutic agents.[2b,3]

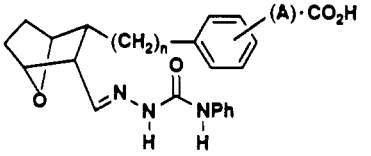
Nearly 10 years ago bicyclic semicarbazones SQ 27,825[4] and EP-045[5] were found to act as selective TxA_2 antagonists of moderate potency as measured by their ability to inhibit arachidonic acid induced platelet aggregation (AAIPA). As in the case of many prostaglandin analogues, both SQ 27,825 and EP-045 contain a metabolically labile 5(*Z*)-heptenoic acid side chain (α-chain) which is subject to in vivo β-oxidation. This process generally results in a rapid loss of antagonist activity and consequently limited in vivo duration of action.[6a,b] As part of a program to develop an orally active TxA_2 antagonist with an extended in vivo duration of action we have attempted to identify a metabolically stable surrogate for the 5(*Z*)-heptenoic acid side chain which is compatible with potent antagonist activity. Thus, we have prepared and evaluated a series of chiral 7-oxabicyclo[2.2.1]heptane analogues of SQ 27,825 (**1**) in which a metabolically stable interphenylene group



SQ 27,825



EP-045



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has replaced the olefin α-side chain.[6c] The synthesis of this series of antagonists is described and the effect of the

† Presented at the 200th American Chemical Society National Meeting, Washington, DC, August 26–31, 1990; paper MEDI 118.

(1) Hamberg, M.; Svensson, J.; Samuelsson, B. Thromboxanes: A New Group of Biologically Active Compounds Derived From Prostaglandin Endoperoxides. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 2994–2998.

(2) (a) Halushka, P. V.; Mais, D. E. Basic and Clinical Pharmacology of Thromboxane A_2. *Drugs of Today* **1989**, *25*(6), 383–393. (b) Smith, E. F., III. Thromboxane A_2 in Cardiovascular and Renal Disorders: Is There a Defined Role for Thromboxane Receptor Antagonists or Thromboxane Synthase Inhibitors? *Eicosanoids* **1989**, *2*, 199–212. (c) Ogletree, M. L. Overview of Physiological and Pathophysiological Effects of Thromboxane A_2. *Federation Proc.* **1987**, *46*(1), 133–138.

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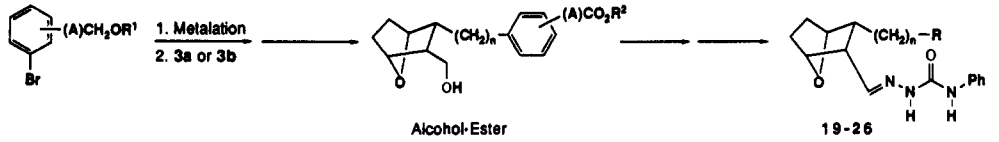
Table I. Synthesis of Interphenylene 7-Oxabicycloheptane Semicarbazones



no.	R	n	lactol **3a** or **3b** to intermediate alcohol–ester: method[a]	lactol **3a** or **3b** to intermediate alcohol–ester: overall % yield	alcohol–ester to semicarbazone: method[b]	alcohol–ester to semicarbazone: overall % yield[c]	formula[d]
19		2	A	34	A	77	$C_{24}H_{27}N_3O_4 \cdot 0.16H_2O$
20		1	B	23	A	81	$C_{23}H_{25}N_3O_4 \cdot 0.25H_2O$
21		2	C	58	B	55	$C_{24}H_{27}N_3O_4$
22		1	A	48	A	85	$C_{23}H_{25}N_3O_4$
23		1	D	32	A	55	$C_{23}H_{25}N_3O_5 \cdot 0.25H_2O$
24		1	D	8	A	81	$C_{23}H_{25}N_3O_5 \cdot 0.25H_2O$
25		1	A	40	A	39[e] (mp 177–178 °C)	$C_{24}H_{27}N_3O_4$
26		1	A, E	10	A	70	$C_{25}H_{29}N_3O_4 \cdot 0.60H_2O$

[a] Method A: (1) tBuLi/ether, −100 °C; (2) 10% Pd–C/H_2 (40 psi)/HOAc or 20% $Pd(OH)_2$–C/H_2 (1 atm)/HOAc; (3) Ac_2O/DMAP/pyr, 25 °C; (4) CrO_3/H_2SO_4/acetone, 0 °C; (5) aqueous NaOH/THF, 25 °C; (6) CH_2N_2/ether or HCl/MeOH, 0 °C. Method B: (1) tBuLi/ether, −100 °C; (2) 10% Pd–C/H_2 (40 psi)/HOAc; (3) Ac_2O/pyr; (4) Jones, 0 °C; (5) CH_2N_2/ether, 0 °C; (6) tBuOK/MeOH, 0 to 25 °C. Method C: (1) Mg/THF; (2) Ac_2O/py, 0 to 25 °C; (3) CrO_3/H_2SO_4/acetone, 25 °C; (4) CH_2N_2/ether; (5) 10% Pd–C/H_2 (1 atm)/$HClO_4$/MeOAc; (6) tBuOK/MeOH, 0 to 25 °C. Method D: (1) tBuLi/ether, −78 °C; (2) 10% Pd–C/H_2 (40 psi)/HOAc; (3) aqueous HF/CH_3CN, 25 °C for **23**; (4) NaH (1.1 equiv)/THF/DMF then $BrCH_2CO_2Et$, 25 °C; Method E: see Scheme III for homologation sequence. [b] Method A: (1) Dess–Martin periodinane/CH_2Cl_2, 25 °C; (2) 4-Phenylsemicarbazide/MeOH or EtOH, 25 °C; (3) LiOH/aqueous THF, 25 °C. Method B: PCC/NaOAc/Celite/CH_2Cl_2, 25 °C; (2) 4-Phenylsemicarbazide/EtOH, 25 °C; (3) LiOH/aqueous THF, 25 °C. [c] All products were isolated as stable, amorphous, hygroscopic solid white foams with the exception of **25** which was a recrystallized white solid. [d] Satisfactory C, H, and N combustion analyses (±0.4%) were obtained for **19–26**. [e] Recrystallized (anti isomer).

interphenylene substitution pattern and side-chain length on TxA_2 antagonistic activity have been determined.

Synthesis

Interphenylene 7-oxabicyclo[2.2.1]heptane semicarbazones were available through the intermediate alcohol–esters, as shown in Scheme I, by elaboration of known chiral 7-oxabicycloheptane tetrahydrofuranol **3a**. The analogues prepared along with the methods employed and yields obtained are summarized in Table I. The synthesis of tetrahydrofuranol **3a** by Diels–Alder methodology followed by resolution of **3a** has been described previously.[7]

Alcohol–Esters. The synthesis of alcohol–ester intermediate **7**, an example in which a single methylene spacer is present between the oxabicycloheptane ring and aryl ring ($n = 1$) is shown in Scheme II. The carboxyl side chain was introduced in the alcohol oxidation state (silyl protected) by transmetalation of aryl bromide **2**[8] (1.7 equiv *t*-BuLi/ether, −100 or −78 °C to 0 °C) followed by addition of lactol **3a** to a solution of the resulting aryllithium reagent (2.2 equiv, ether/THF, −78 to 0 °C). The diol addition product **4** was obtained as a mixture of alcohol diastereomers (~1:1) and was then subjected to catalytic hydrogenation to selectively remove the benzylic hydroxyl group. The reduction of the ortho-substituted analogues was substantially more difficult than the meta and para isomers and lower yields were obtained. In addition, it was noted that 20% $Pd(OH)_2$–C was a superior catalyst for the reduction of the ortho isomers while 10% Pd–C was effective for the meta and para analogues. In the case of **4**, reduction afforded a single product **5** in 55% yield with

(3) For recent reviews see: (a) Hall, S. E. Thromboxane A_2 Receptor Antagonists. *Med. Res. Rev.* **1991**, *11*, in press. (b) Cross, P. E.; Dickinson, R. P. Thromboxane Synthetase Inhibitors and Antagonists. In *Annual Reports in Medicinal Chemistry*, Bailey, D. M., Ed.; Academic Press, New York, 1987; Vol. 22, pp 95–105.

(4) (a) Nakane, M.; Reid, J. Unpublished results. (b) For the analogous semicarbazides, see: Ogletree, M. L.; Harris, D. N.; Greenberg, R.; Haslanger, M. F.; Nakane, M. Pharmacological Actions of SQ 29,548, A Novel Selective Thromboxane Antagonist. *J. Pharmacol. Exp. Ther.* **1985**, *234*(2), 435–441.

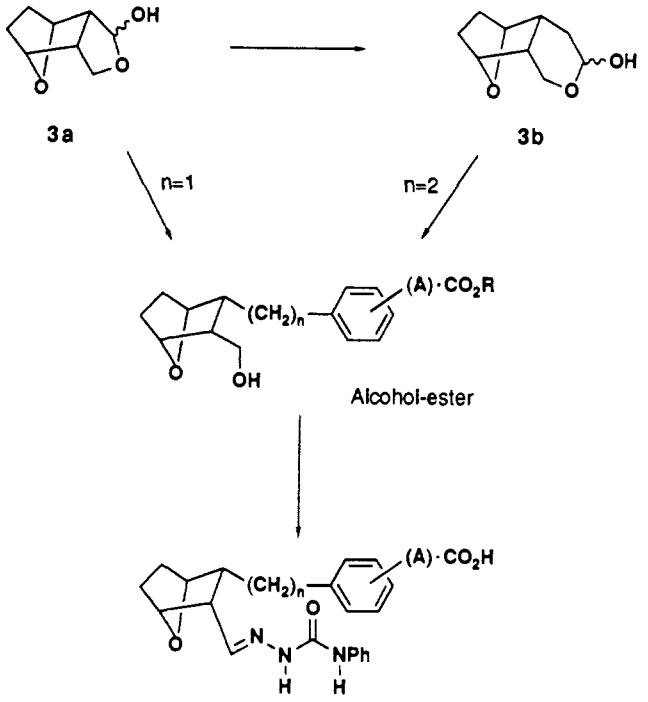
(5) See: US Patent 4,628,061, 1986, and EP82646, 1983.

(6) (a) Samuelsson, B.; Granstroem, E.; Green, K.; Hamberg, M. Metabolism of Prostaglandins. *Ann. NY Acad. Sci.* **1971**, *180*, 138–163. (b) Kunau, W.-H. Chemistry and Biochemistry of Unsaturated Fatty Acids. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*(2), 61–74. (c) Nelson, N. A.; Jackson, R. W.; Au, A. T.; Wynalda, D. J.; Nishizawa, E. E. Synthesis of *dl*-4,4,4-Trinor-3,7-Inter-m-Phenylene-3-Oxaprostaglandins Including One Which Inhibits Platelet Aggregation. *Prostaglandins* **1975**, *10*(5), 795–806.

(7) Das, J.; Haslanger, M. F.; Gougoutas, J. Z.; Malley, M. F. Synthesis of Optically Active 7-Oxabicyclo[2.2.1]heptanes and Assignment of Absolute Configuration. *Synthesis* **1987**, 1100–1103 and references cited therein.

(8) Aryl bromides employed for **19–22** were prepared from the corresponding commercially available bromophenylacetic acids. Aryl bromide **2** for the preparation of **25** and **26** was prepared from *o*-bromobenzaldehyde. The procedures are described in the Experimental Section.

Scheme I



cis-exo side-chain stereochemistry. The side-chain stereochemistry of **5** was established by ^{1}H NMR ($CDCl_3$) which showed characteristic doublets[9] for the cis-exo 7-oxabicycloheptane bridgehead protons at δ 4.24 (J = 5 Hz) and δ 4.55 (J = 5 Hz). Importantly, the cis-exo stereochemistry of tetrahydrofuranol **3a** was retained in **5** and there was no evidence for the formation of product with trans side-chain stereochemistry resulting from epimerization of the ring-opened lactol prior to aryllithium addition. In the case of **21**, an aryl Grignard reagent was successfully substituted for the aryllithium (method C, Table I). Alcohol **5** was elaborated to intermediate alcohol-ester **7** in a straightforward sequence involving protection of the alcohol (acetylation), treatment with excess Jones reagent (acetone, 0 °C) followed by deacetylation and esterification (method A, Table I). The overall yield of alcohol-ester **7** from alcohol **5** was 70–80%. Alternatively, the crude Jones oxidation product was initially esterified followed by removal of the acetate with potassium *tert*-butoxide in methanol (method B, Table I). The butanoic acid analogue **26** was prepared from alcohol-ester **10** by Arndt-Eistert homologation of **7** as shown in Scheme III. The analogues in which a two methylene spacer (n = 2) is present between the oxabicycloheptane ring and aryl ring were prepared from 7-oxabicycloheptane tetrahydropyranol **3b** in place of **3a** by a route analogous to that used for the synthesis of **7**. Tetrahydropyranol **3b** was available from tetrahydrofuranol **3a** by Wittig homologation (see experimental section). The interphenylenoxy analogues were available as depicted in Scheme IV. In particular, **23** was prepared via alcohol-ester **16** from silyl-protected *m*-bromophenol **12** by the previously described sequence involving transmetalation, lactol addition, and hydrogenolysis to afford alcohol **14**. Fluoride-induced desilylation of **14** followed by treatment of the resulting alcohol-phenol **15** with sodium hydride (1.1 equiv, THF) then ethyl bromoacetate gave the desired alcohol-ester **16** (method D, Table I). The ortho-substituted interphenylenoxy analogue **24** was prepared by a similar route from *o*-bromophenol by employing an *O*-benzyl protecting group in place of the silyl-protecting group.[10] The yield of addition product from **3** in this example was only 35%. The benzyl group was conveniently cleaved during hydrogenolysis of the benzylic alcohol.

Semicarbazones. The alcohol-esters were generally elaborated to the desired semicarbazones as exemplified for the conversion of **7** to **25** (Scheme V). Thus, oxidation of **7** to the corresponding aldehyde-ester with Dess-Martin periodinane[11] followed by sodium thiosulfate/sodium bicarbonate workup (method A, Table I) gave **17** in 80% crude yield. Generally, the yields using the Dess-Martin procedure were 80–100%. It was also possible to use pyridinium chlorochromate[12] with a small sacrifice in yield (method B, Table I). No epimerization of the aldehyde was observed by ^{1}H NMR when either procedure was used. The semicarbazone side chain (ω-chain) was introduced into the crude labile aldehyde-esters by treatment with 4-phenylsemicarbazide (1.1 equiv, methanol, 25 °C). The resulting semicarbazone **18** was obtained as a mixture of syn/anti isomers in 90–95% yield. Basic hydrolysis of ester **18** yielded the desired crude acid **25** which was recrystallized to afford crystalline *anti*-**25**. Semicarbazone **25** showed a single spot on TLC (silica gel, 1:9 CH_3OH/CH_2Cl_2) but equilibrated within several hours in $CDCl_3$ to a syn/anti mixture (TLC). Generally, the crude products were not recrystallized but isolated as stable, amorphous, hygroscopic, solid white foams and were a mixture of syn/anti isomers. The syn/anti ratio was dependent on the specific structure. In the case of **25** the equilibrium syn/anti ratio was determined as 30/70 by ^{1}H NMR ($CDCl_3$) and showed a characteristic companion pair of doublets at δ 4.47 and 4.58 (J = 5 Hz) for one of the oxabicycloheptane bridgehead protons of the syn and anti isomers, respectively; a characteristic upfield shifted imine proton at δ 6.60 (**d**, J = 8 Hz) for the minor syn isomer (the companion downfield imine proton resonance for the anti isomer is presumably obscured by the aromatic resonances) and characteristic downfield -NH- singlets at δ 7.76 and 8.29 (-NHPh-) and δ 9.83 and 10.54 (-NNH-) for the anti and syn isomers, respectively.

Structure-Activity and Discussion

In Vitro. Chiral interphenylene 7-oxabicycloheptane semicarbazones were evaluated for their ability to inhibit platelet aggregation of human platelet rich plasma in response to exogenous arachidonic acid (800 μM) and TxA_2 mimetic U-46,619 (10 μM).[13] The data are summarized in Table II and are expressed as I_{50} (μM) values, the

(9) See refs 23 and 24 in Hall et al. (Hall, S. E.; Han, W.-C.; Haslanger, M. F.; Harris, D. N.; Ogletree, M. L. 9,11-Epoxy-9-homo-14-oxaprosta-5-enoic Acid Derivatives. Novel Inhibitors of Fatty Acid Cyclooxygenase. *J. Med. Chem.* **1986**, *29*, 2335–2347).

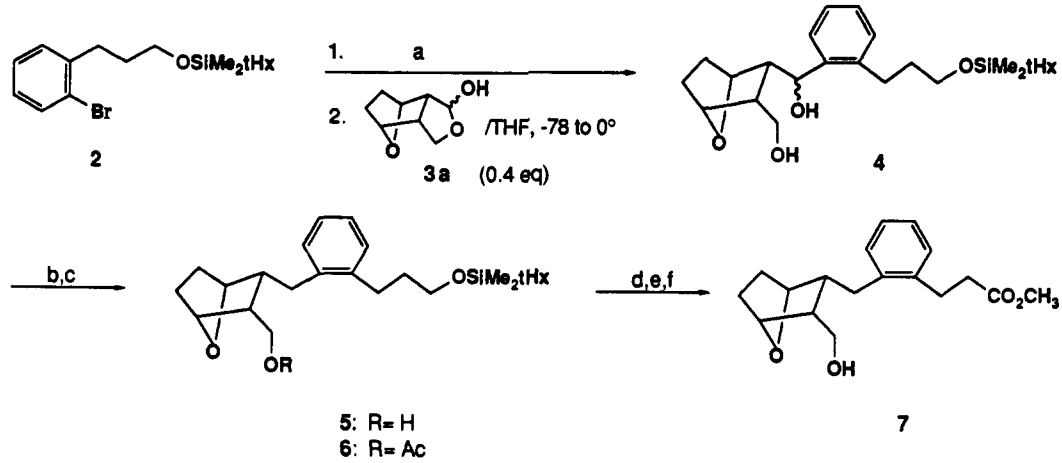
(10) It was necessary to employ a benzyl protecting group in the ortho case to circumvent observed O to C silyl migration in the *tert*-butyldimethylsilyl-protected ortho aryllithium reagent.

(11) Dess, D. B.; Martin, J. C. Readily Accessible 12-I-5 Oxidant for the Conversion of Primary and Secondary Alcohols to Aldehydes and Ketones. *J. Org. Chem.* **1983**, *48*, 4155–4156.

(12) (a) Corey, E. J.; Suggs, J. W. Pyridinium Chlorochromate. An Efficient Reagent for Oxidation of Primary and Secondary Alcohols to Carbonyl Compounds. *Tetrahedron Lett.* **1975**, 2647–2651. (b) Piancatelli, G.; Scettri, A.; D'Auria, M. Pyridinium Chlorochromate. A Versatile Oxidant in Organic Synthesis. *Synthesis* **1982**, 245–258.

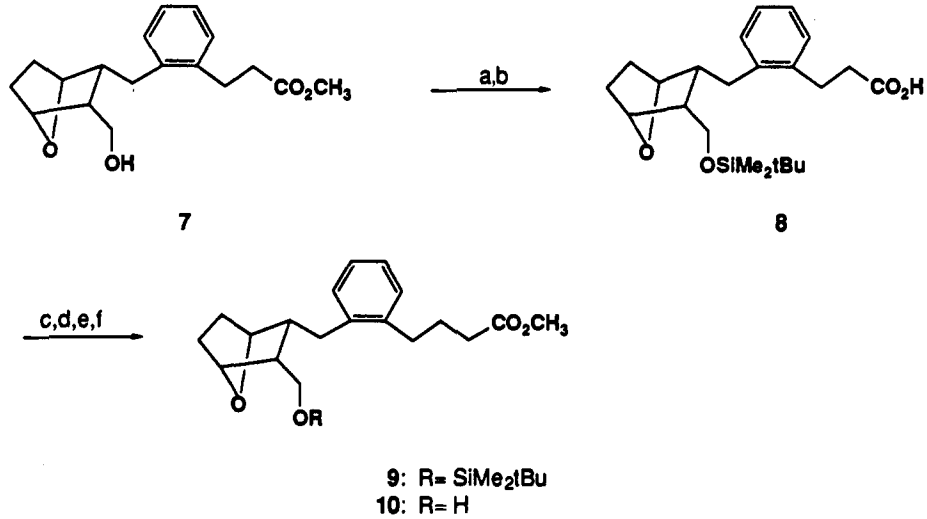
(13) As described in the following: Harris, D. N.; Phillips, M. B.; Michel, I. M.; Goldenberg, H. J.; Sprague, P. W.; Antonaccio, M. J. 9α-Homo-9,11-Epoxy-5,13-Prostadienoic Acid Analogs: Specific Stable Agonist (SQ 26,538) and Antagonist (SQ 26,536) of the Human Platelet Thromboxane Receptor. *Prostaglandins* **1981**, *22*, 295–307.

Scheme II[a]



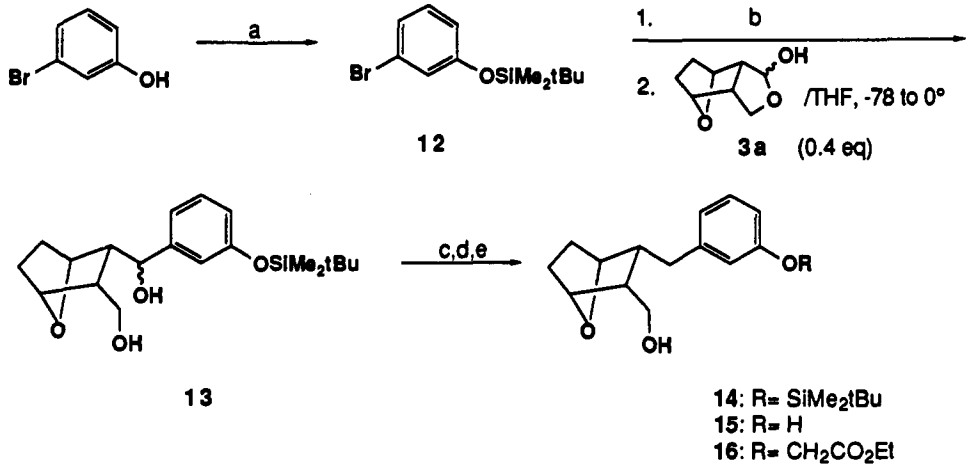
[a] (a) tBuLi (1.7 equiv)/ether, −100 to 0 °C, 97%; (b) 20% $Pd(OH)_2$–C/H_2 (1 atm)/HOAc, 55%; (c) Ac_2O/DMAP/py, 25 °C; (d) CrO_3/H_2SO_4/acetone, 0 °C; (e) aqueous NaOH/THF, 25 °C; (f) HCl/MeOH, 0 °C, 74% from **5**.

Scheme III[a]



[a] (a) $tBuMe_2SiCl$/DMAP/Et_3N/CH_2Cl_2, 25 °C; 99%; (b) LiOH/aqueous THF, 25 °C, 98%; (c) $(COCl)_2$/DMF/CH_2Cl_2, 25 °C; (d) excess CH_2N_2/ether, 0 °C; (e) Ag_2O/MeOH, 60 °C, 27% from **8**; (f) 48% aqueous HF/CH_3CN, 25 °C, 94%.

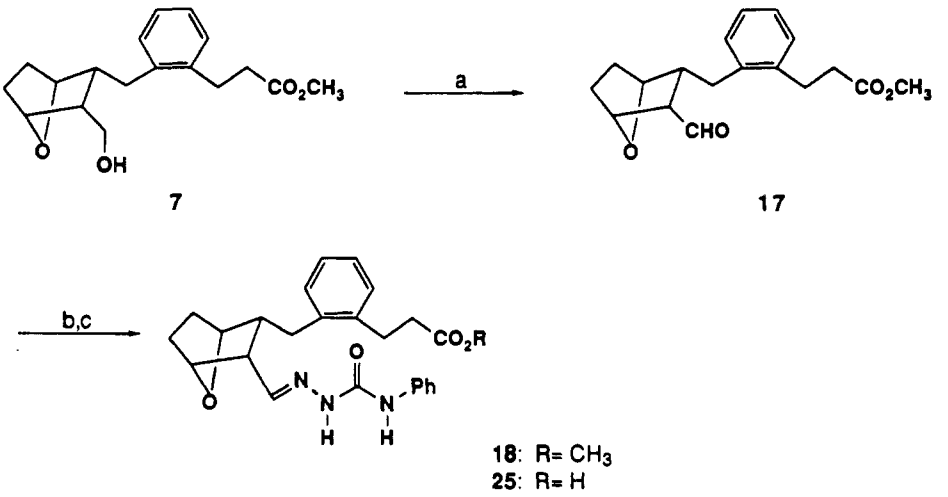
Scheme IV[a]



[a] (a) $tBuMe_2SiCl$/imidazole/DMF, 25 °C, 99%; (b) tBuLi (1.7 equiv)/ether, −78 to 0 °C, 90%; (c) 10% Pd–C/H_2 (40 psi)/HOAc, 70%; (d) 48% aqueous HF/CH_3CN, 25 °C, 98%; (e) NaH (1.1 equiv)/THF/DMF, 25 °C then $BrCH_2CO_2Et$, 52%.

concentration of antagonist required for 50% inhibition of platelet aggregation. In addition, all semicarbazones were evaluated for their ability to inhibit platelet aggregation in response to exogenous adenosine diphosphate (ADP, 20 μM) and exhibited I_{50} values greater than 1000 μM. Semicarbazones with reasonable platelet inhibitory activity, **21–26**, were also evaluated for their ability to inhibit the specific binding of [^{3}H]-SQ 29,548 to TxA_2

Scheme V[a]



[a] (a) Dess–Martin periodinane/CH_2Cl_2, 25 °C, 80%; (b) 4-Phenylsemicarbazide/MeOH, 25 °C, 92%; (c) LiOH/aqueous THF, 25 °C, 53%.

Table II. Pharmacological Evaluation of Interphenylene 7-Oxabicycloheptane Semicarbazones

	in vitro				in vivo duration of action:[c] T_{50}, h	
	I_{50}, μM[a]		K_d, nM:[b]	slope	10	0.2
no.	AAIPA	UIPA	platelet	factor	mg/kg po	mg/kg po
19	688					
20	310					
21	30	133	1070	1.03		
22	0.37	4.6	171	1.05	8.3	1.7
23	7.2	25	1196	0.98		
24	0.015	0.046	6.0	1.10		3.6
25	0.003	0.012	1.0	1.0		16.0
26	0.012	0.072	21.1	1.40		8.7
(1*S*)-SQ27,825	0.23	0.71	39.4	1.45		
GR32191	0.033	0.059	2.0	1.08	9.3	0.5
BM13.505	0.73	1.6	11.3	0.96	34.6	7.1

[a] Inhibition of arachidonic acid (800 μM) or U-46,619 (10 μM) induced platelet aggregation in human platelet rich plasma (PRP), see ref 13. [b] Determined by measurement of the inhibition of specific binding of [^{3}H]-SQ 29,548 in human platelet membranes, see ref 14. [c] Protection from U-46,619-induced (2.0 mg/kg iv) death in mice as a function of time, see ref 17.

receptors in human platelet membranes.[14] The data are expressed as dissociation constants (K_d, nM) calculated from their individual I_{50} values and slope factors. Importantly, the radioligand binding and platelet data show the same rank order of potency and establish that these antagonists are ligands for the TxA_2 receptor. The slope factors suggest that, with the exception of **26**, they act as competitive antagonists. In particular, semicarbazone **25** exhibited exceptionally high affinity for the TxA_2 receptor with a K_d value of 1.0 ± 0.01 nM. For comparative purposes, values were determined under identical conditions for several other TxA_2 antagonists, (1*S*)-SQ 27,825, GR 32191,[15] and BM13.505.[16]

The results in Table II clearly establish that an interphenylene carboxyl sidechain is not only compatible with potent TxA_2 antagonist activity in the 7-oxabicycloheptane semicarbazone series but can result in structures with *enhanced* potency when compared to analogues with the natural 5(*Z*)-heptenoic acid α-side chain. In particular, **25** and **26** were 75- and 19-fold more potent than (1*S*)-SQ 27,825, respectively, in their ability to inhibit AAIPA. The substitution pattern on the interphenylene phenyl ring appears to be particularly critical in determining potency as the para-substituted analogue **19** and the ortho-substituted analogue **25** differed in potency by more than 10000-fold. In general, it was found that the platelet activity decreases in the order ortho > meta ≫ para. The optimal α-chain length, although not as critical, appears to be dependent on the specific phenyl substitution pattern. In the limited number of examples examined (i.e. **21** and **22**), a spacing of a single methylene rather than two carbons between the phenyl ring and the oxabicycloheptane ring results in an increase in potency. In the ortho-

(14) As described in the following: Hedberg, A.; Hall, S. E.; Ogletree, M. L.; Harris, D. N.; Liu, E. C.-K. Characterization of [5,6-^{3}H]SQ 29,548 as a High Affinity Radioligand, Binding to Thromboxane A_2/Prostaglandin H_2-Receptors in Human Platelets. *J. Pharmacol. Exp. Ther.* **1988**, *245*(3), 786–792.

(15) (a) Humphrey, P. P. A.; Hallet, P.; Hornby, E. J.; Wallis, C. J.; Collington, E. W.; Lumley, P. Pathophysiological Actions of Thromboxane Receptor Blockade With GR32191. *Circulation (Supplement I)*, **1990**, *81*(1), I-42–I-52. (b) Hornby, E. J.; Foster, M. R.; McCabe, P. J.; Stratton, L. E. The Inhibitory Effect of GR32191, A Thromboxane Receptor Blocking Drug, on Human Platelet Aggregation, Adhesion and Secretion. *Thromb. Haemostasis* **1989**, *61*(3), 429–436. (c) Lumley, P.; White, B. P.; Humphrey, P. P. A. GR32191, A Highly Potent and Specific Thromboxane A_2 Receptor Blocking Drug on Platelets and Vascular and Airway Smooth Muscle *In Vitro*. *Br. J. Pharmacol.* **1989**, *97*, 783–794.

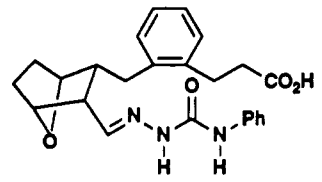
(16) (a) Stegmeier, K.; Pill, J.; Patscheke, H. A Selective and Potent TXA_2 Receptor Antagonist. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1986**, *332*, (supplement), R36. (b) Smith, E. F., III; McDonald, J. Protective Effects of the Thromboxane Receptor Antagonists BM13.177 and BM13.505 Against U-46619-Induced Sudden Death in Rats. *Pharmacology* **1988**, *36*(5), 340–347. (c) Review: Lefer, A. M. Daltroban (BM 13.505)· A Highly Specific, Potent Thromboxane Receptor Antagonist. *Drugs of The Future* **1988**, *13*(11), 999–1005.

substituted series, the interphenoxy analogue **24** retained excellent activity and was only 5-fold less potent than its carbon analogue **25**.

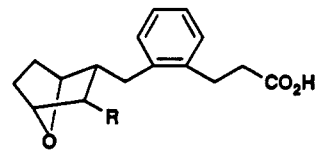
In Vivo. Interphenylene 7-oxabicycloheptane semicarbazones exhibiting potent antagonist activity in vitro were evaluated for their in vivo duration of action by their ability to inhibit U-46,619 induced lethality (2.0 mg/kg iv) in mice as a function of time.[17] The data are summarized in Table II and are expressed as a T_{50} (h) value, the calculated time for which one half of the population survived at a given single oral dose, either 10 mg/kg and/or 0.2 mg/kg. Both GR32191 and BM13.505 were also evaluated for comparison. Examination of the results establishes that the more potent semicarbazones **22**, **24**, **25**, and **26** are orally effective in providing protection from U-46,619 induced death. In particular, **25** exhibited exceptionally long duration (16 h) at a single oral dose of 0.2 mg/kg.

Conclusions

Interphenylene 7-oxabicyclo[2.2.1]heptane semicarbazones **19–26** have demonstrated for the first time that it is possible to introduce a metabolically stable interphenylene carboxyl side chain into a prostanoid-like series of TxA_2 antagonists and retain potent antagonistic activity. In the case of the 7-oxabicycloheptane semicarbazone (1*S*)-SQ 27,825, a remarkable 75-fold *increase* in potency was realized. SQ 35,091 (**25**) has been identified as an



25 (SQ 35,091)



27

exceptionally potent (AAIPA I_{50} = 3 nM and K_d = 1 nM) and orally active TXA_2 antagonist with a long duration of action in vivo. Most importantly, the interphenylene 7-oxabicycloheptane semicarbazone series of antagonists has defined the interphenylene substitution pattern and side-chain length necessary for maximal activity in this series and suggested a substructure **27** for the development of novel TxA_2 antagonists with modified ω-chains.

Experimental Section

^1H NMR spectra reported were measured at 270 MHz and ^{13}C NMR spectra were measured at 67.8 MHz on a JOEL FX-270 or GX-270 spectrometer unless noted otherwise. ^1H NMR (400 MHz) spectra were measured on a JOEL GX-400 spectrometer. Chemical shifts are reported in δ units and are relative to internal $(CH_3)_4Si$ assigned at δ 0.00 and/or $CHCl_3$ assigned at δ 7.24 or $CDCl_3$ assigned to δ 77.0; coupling constants (J) are given in hertz. Infrared spectra (IR) were recorded on a Perkin-Elmer Model 983 infrared spectrophotometer and were calibrated with the 1601 cm^{-1} polystyrene absorption. Mass spectra (MS) were measured with an Extranuclear Simulscan or Finnigan TSQ mass spectrometer in chemical ionization (CI) or electron impact (EI) mode. All compounds exhibited spectra consistent with their structure. Elemental combustion analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer. All final compounds (**19–26**) showed acceptable (±0.4%) elemental analysis. Melting points (mp) were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

All reactions excluding hydrogenations were conducted under an argon atmosphere. All reagents and starting materials were obtained from commercial sources and used without further purification unless indicated; tetrahydrofuran (THF) and ether were distilled under argon from benzophenone ketyl; CH_2Cl_2 was distilled under nitrogen from P_2O_5; triethylamine was distilled from calcium hydride. 4-Phenylsemicarbazide obtained from Aldrich was purified before use.[18] Flash chromatography[19] was performed by using Merck silica gel 60. Thin-layer chromatography (TLC) was performed by using E. Merck Kieselgel 60 F_{254} (0.25 mm) plates which were visualized with acidic aqueous ammonium molybdate/ceric sulfate stain and/or under UV_{254} illumination.

[4a*R*-(4aα,5β,8β,8aα)]-Octahydro-5,8-epoxy-1*H*-2-benzopyran-3-ol (3b). To a mixture of 277 g (808 mmol, Fluka) of (methoxymethyl)triphenylphosphonium chloride in 530 mL of dry THF cooled to 0 °C was added dropwise 350 mL (1.9 M in toluene, 670 mmol, Callery Chemicals) of potassium *tert*-amylate solution over 35 min, maintaining the reaction temperature below 5 °C. The reaction mixture was stirred for an additional 20 min then 50.0 g (321 mmol) of solid lactol **3a**[7] was added in portions over 10 min. The resulting mixture was stirred at 0 °C for 30 min then at room temperature for 1.5 h followed by addition of 35 mL of ice-cold acetaldehyde at 0 °C over 35 min. The reaction mixture was diluted with 500 mL of water and then the pH was adjusted to 7 by addition of 10% aqueous HCl solution. The solution was further diluted with 100 mL of water then extracted with seven 500-mL portions of ether. The combined ether extracts were dried ($MgSO_4$) and concentrated in vacuo to give a crude oil. The crude oil was suspended in 1 L of isopropyl ether (IPE) and stirred at room temperature for 24 h and then at 0 °C for 2 h. The solid precipitate which formed (triphenylphosphine oxide) was removed by filtration. The solid was rinsed with three 300-mL portions of IPE. The filtrate was concentrated in vacuo and the residue combined with 1 L of water then stirred for 2 h at room temperature. The product-containing aqueous layer was decanted from the solids which formed. The solids were washed two additional times with 250-mL portions of water. The combined aqueous decantants (1.5 L) were concentrated in vacuo to ~500 mL and allowed to stand at 0 °C for 2 days. The product-containing aqueous layer was decanted from an oily precipitate. The oil was stirred with 250 mL of water and then the aqueous layer again decanted. The water decantants were combined, concentrated in vacuo to ~500 mL, and then filtered through a 2 in. pad of Celite. The pad was rinsed with 30 mL of water. The product-containing filtrate was diluted with 560 mL of water, and cooled to 0 °C, and then 170 mL of concentrated HCl solution was slowly added. The reaction mixture was stirred at room temperature for 3 h, neutralized by slow addition of 184 g of solid $NaHCO_3$, and then filtered through a 3 in. pad of Celite. The filtrate was extracted with four 500-mL portions of hexane to remove lactol dimer then seven 1-L portions of EtOAc. The EtOAc extracts were combined, dried ($MgSO_4$), concentrated in vacuo, and then triturated with 400 mL of hexane. The white solid which formed was collected to afford 44 g (81%) of crude lactol **3b** which was used without further purification. Lactol **3b** was a mixture of α,β-alcohol epimers. IR (KBr): 3381, 3009, 2880, 1319, 1290, 1188, 1084, 1011 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.30–2.35 (m, 9 H), 3.47 (t, J = 9, 0.25 H), 3.55–3.90 (m, 3 H), 4.23 (m, 2.1 H), 5.09 (m, 0.75 H), 5.33 (dd, J = 3.6, 0.25 H). ^{13}C NMR ($CDCl_3$) δ 28.9, 29.2, 29.8, 30.0, 30.1, 35.2, 38.9, 43.0, 43.3, 59.9, 62.1, 78.2, 78.6, 81.0, 91.3, 91.6. MS(CI): m/z 153 (M + H − H_2O).

Preparation of Aryl Bromides for 19–25. [2-(4-Bromophenyl)ethoxy]dimethyl(1,1,2-trimethylpropyl)silane (28).

(17) As described in the following: Kohler, C.; Wooding, W.; Ellenbogen, L. Intravenous Arachidonate in the Mouse: A Model for the Evaluation of Antithrombotic Drugs. *Thromb. Res.* **1976**, *9*, 67–80.

(18) Wheeler, A. S. *Organic Syntheses*, 2nd ed.; Gilman, H., Blatt, A. H., Eds.; Wiley: New York, 1941; Collect. Vol. I, pp 450–451.

(19) Still, W. C.; Kahn, M.; Mitra, A. J. Rapid Chromatographic Technique for Preparative Separation with Moderate Resolution. *J. Org. Chem.* **1978**, *43*(14), 2923–2925.

To a solution of 52.7 g (245 mmol) of 4-bromophenylacetic acid in 200 mL of dry THF was added dropwise at 0 °C a solution of 275 mL (1 M in THF, 275 mmol) of borane/THF. The resulting solution was stirred at 0 °C for 30 min and then at room temperature for 2 h. The reaction mixture was recooled to 0 °C, quenched by slow addition of 50 mL of water, and then concentrated in vacuo. The residue was dissolved in 1.2 L of ether, washed with three 250-mL portions of saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated in vacuo to afford the intermediate alcohol as an oil. To a solution of the crude alcohol, 0.75 g (6.1 mmol) of 4-dimethylaminopyridine, and 52 mL (370 mmol) of triethylamine in 200 mL of dry CH_2Cl_2 at 0 °C was added dropwise 52 mL (260 mmol) of dimethylthexylsilyl chloride over 10 min. The reaction mixture was warmed to room temperature, stirred for 30 h, and then diluted with 700 mL of hexane. The resulting slurry was filtered and the solids rinsed with 300 mL of hexane. The filtrate was concentrated in vacuo and the residue was dissolved in 1 L of ether and then washed with three 300-mL portions of 0.3 N aqueous HCl solution and 200 mL of saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated in vacuo to give an oil. The crude product was purified by bulb-to-bulb distillation (120 °C/~1 mm) to afford 71.9 g (83%) of **28** as a colorless oil. ^1H NMR ($CDCl_3$): 0.00 (s, 6 H), 0.82 (overlapping s and d, 12 H), 1.68 (m, 1 H), 2.74 (t, J = 8, 2 H), 3.74 (t, J = 8, 2 H), 7.05 (d, J = 8, 2 H), 7.36 (d, J = 8, 2 H). ^{13}C NMR ($CDCl_3$): δ -3.49, 18.5, 20.3, 25.2, 34.2, 38.9, 63.8, 119.9, 130.9, 131.2, 138.5.

[2-(3-Bromophenyl)ethoxy]dimethyl(1,1,2-trimethylpropyl)silane (29). Prepared from 3-bromophenylacetic acid as a colorless oil in 87% yield as described above.

1-Bromo-3-[(*tert*-butyldimethylsilyl)oxy]benzene (12). A solution of 11.5 g (66.5 mmol) of *m*-bromophenol, 6.80 g (100 mmol) of imidazole and 10.3 g (68.3 mmol) of chloro-*tert*-butyldimethylsilane in 75 mL of sieve-dried dimethylformamide was stirred at room temperature for 18 h and then partitioned between 250 mL of cold 1 M aqueous HCl solution and 150 mL of hexane. The organic layer was separated and the aqueous layer extracted with an additional 100 mL of hexane. The organic extracts were combined, washed with 100 mL of saturated aqueous $NaHCO_3$ solution and then 100 mL of water, dried ($MgSO_4$), and concentrated in vacuo to afford 18.8 g (99%) of 12 as a colorless oil. IR (film): 2955, 2932, 2859, 1589, 1474, 1269, 932 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.00 (s, 6 H), 0.78 (s, 9 H), 6.56 (m, 1 H), 6.80 (br s, 1 H), 6.88 (d, J = 6, 2 H). ^{13}C NMR ($CDCl_3$) δ -4.5, 18.1, 25.6, 118.8, 122.4, 123.5, 124.4, 130.4, 156.5. MS(EI): m/z 288, 286 ($M^{\cdot+}$).

[3-(2-Bromophenyl)propoxy]dimethyl(1,1,2-trimethylpropyl)silane (2). To a stirred suspension of 46.8 g (140 mmol) of methyl (triphenylphosphoranylidene)acetate in 250 mL of dry THF at room temperature was added dropwise 25.0 g (135 mmol) of 2-bromobenzaldehyde, over 30 min. The reaction was mildly exothermic and became homogeneous. The resulting solution was stirred for 18 h and then concentrated in vacuo to give an oily solid. This material was slurried with 250 mL of hexane and then filtered to remove solid triphenylphosphine oxide. The filtrate was concentrated in vacuo and the resulting oil was passed through a pad of silica gel (Merck silica, 9.5 × 2.0 cm, 1:4 EtOAc/petroleum ether elution). The eluent was concentrated in vacuo to give an oil. The crude oil was purified by bulb-to-bulb distillation (125–135 °C, ~0.5 mm) to afford 32.0 g (98%) of 3-(2-bromophenyl)propenoic acid ethyl ester (**30**) as a pale yellow liquid.

A mixture of 14.0 g (58.1 mmol) of **30** and 750 mg of 5% rhodium on alumina catalyst in 150 mL of methanol was stirred under an atmosphere of hydrogen (balloon) for 3 h (until the starting material was consumed by TLC). The reaction mixture was passed through a 0.4 μM polycarbonate membrane and the filtrate was concentrated in vacuo to give an orange oil. The oil was dissolved in 100 mL of ether and then washed with 50 mL of saturated $NaHCO_3$ solution and 50 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to afford 13.7 g (97%) of 3-(2-bromophenyl)propanoic acid ethyl ester (**31**) as a pale yellow liquid.

To a solution of 13.6 g (56.0 mmol) of **31** in 75 mL of dry toluene cooled to -78 °C was added 118 mL (1.0 M in toluene, 118 mmol) of diisobutylaluminum hydride solution. The reaction was stirred at -78 °C for 2 h then warmed to 0 °C for 2 h. The resulting solution was quenched by very slow addition of 10 mL of 6 N HCl and then more rapid addition of 100 mL of 6 N HCl. The reaction was stirred for an additional 10 min and then added to 50 mL of ether, and the organic layer was separated. The organic layer was washed with two 100-mL portions of 1 N HCl, 100 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to afford 12.0 g (100%) of 3-(2-bromophenyl)propanol (**32**) as a colorless oil.

To a solution of 12.0 g (55.8 mmol) of **32**, 15.3 g (55.8 mmol) of dimethylthexylsilyl chloride and 8.6 mL (62 mmol) of triethylamine in 100 mL of dry CH_2Cl_2 was added 200 mg (1.6 mmol) of 4-(dimethylamino)pyridine. The reaction mixture was stirred at room temperature for 4 h and then 100 mL of hexane was added and the resulting slurry filtered to remove triethylamine hydrochloride. The filtrate was concentrated in vacuo and the resulting oil purified by flash chromatography (12 × 9 cm, 1:19 ether/hexane) to afford 23.2 g (92%) of **2** as a colorless oil. IR (neat): 2955, 2865, 1469, 1100, 830, 776, 748 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.00 (s, 6 H), 0.77, 0.80, 0.82 (overlapping s and d, 12 H), 1.55 (m, 1 H), 1.73 (m, 2 H), 2.70 (crude t, J = 8, 2 H), 3.54 (t, J = 7), 6.94 (m, 1 H), 7.12 (m, 2 H), 7.41 (d, J = 8, 1 H). ^{13}C NMR ($CDCl_3$) δ -3.37, 18.6, 20.4, 25.1, 32.7, 32.8, 34.27, 62.1, 124.5, 127.3, 127.4, 130.4, 132.7, 141.6. MS(CI): m/z 359,357 (M + H), 273,271.

Preparation of Alcohol-Esters for 19–26. [1*S*-1α,2α,3α,4α]-4-[2-[3-(Hydroxymethyl)-7-oxabicyclo[2.2.1]-hept-2-yl]ethyl]benzeneacetic Acid, Methyl Ester (33), Alcohol-Ester for 19. Prepared from bromide **28** and lactol **3b** by method A (see below) in 34% overall yield.

[1*S*-1α,2α,3α,4α]-4-[[3-(Hydroxymethyl)-7-oxabicyclo-[2.2.1]hept-2-yl]methyl]benzeneacetic Acid, Methyl Ester (38), Alcohol-Ester for 20 (Method B). To a solution of 10.0 g (29.1 mmol) of aryl bromide **28** in 60 mL of dry ether cooled to -78 °C was added dropwise 30 mL (1.7 M in pentane, 51 mmol) of *tert*-butyllithium solution over 10 min. The reaction mixture was stirred at -78 °C for 30 min then at 0 °C for 15 min. The resulting solution was recooled to -78 °C, 20 mL of dry THF was introduced, and then a solution of 1.87 g (12 mmol) of lactol **3a** in 20 mL of dry THF was added. The reaction mixture was stirred at -78 °C for 10 min then at 0 °C for 30 min followed by quenching with 5 mL of H_2O. The resulting mixture was partitioned between 150 mL of ether and 200 mL of H_2O. The organic phase was separated, washed with 200 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to give an oil. The crude material was purified by flash chromatography (25 × 5 cm, 1:9 ether/petroleum ether and then 1:1 EtOAc/petroleum ether) to afford 4.40 g (87%) of diol **34** as a colorless oil. R_f (silica gel, 1:1 ethyl acetate/petroleum ether) = 0.20; the R_f of **3a** was 0.08 under the same conditions.

A mixture of 4.30 g (10.2 mmol) of diol **34** and 3.4 g of 10% palladium on carbon catalyst in 50 mL of glacial acetic acid was shaken under hydrogen (40 psi) in a Parr apparatus for 20 h. The reaction mixture was then filtered and the filtrate concentrated in vacuo to give an oil. The oil was partitioned between 75 mL of EtOAc and 75 mL of 1 M aqueous NaOH solution. The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo to give a colorless oil. The crude material was purified by flash chromatography (25 × 5 cm, 1:1 EtOAc/petroleum ether) to afford 3.10 g (75%) of **35** as a colorless oil. R_f (silica gel, 1:1 ethyl acetate/petroleum ether) = 0.34.

A solution of 2.60 g (6.44 mmol) of alcohol **35** and 25 mg (0.20 mmol) of 4-(dimethylamino)pyridine in 10 mL of 1:1 pyridine/acetic anhydride was stirred at room temperature for 30 min. The solvent was removed in vacuo and the residue partitioned between 50 mL of ether and 50 mL of 1 M aqueous HCl solution. The organic phase was separated, washed with 50 mL of 1 M aqueous NaOH solution, dried ($MgSO_4$), and concentrated in vacuo to give 2.83 g (99%) of acetate **36** as a colorless oil. R_f (silica gel, 1:2 ethyl acetate/petroleum ether) = 0.69; the R_f of **35** was 0.16 under the same conditions.

To a solution of 2.80 g (6.28 mmol) of acetate **36** in 50 mL of reagent acetone cooled to 0 °C was added 6 mL of Jones reagent.[20] The reaction mixture was stirred at 0 °C for 1 h then quenched

(20) See Djerassi procedure in Fieser and Fieser: Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, pp 142–144.

with 3 mL of isopropyl alcohol. After 30 min the resulting green slurry was filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was partitioned between 50 mL of EtOAc and 50 mL of water. The organic layer was separated and the aqueous layer extracted with an additional 25 mL of EtOAc. The organic extracts were combined, dried ($MgSO_4$), and then at 0 °C treated with excess ethereal diazomethane.[21] After 5 min the excess diazomethane was quenched with several drops of glacial HOAc and the solution concentrated in vacuo to give an oil. The crude material was purified by flash chromatography (20 × 5 cm, 1:3 EtOAc/petroleum ether) to yield 1.40 g (67%) of acetate–ester **37** as a colorless oil. R_f (silica gel, 1:2 ethyl acetate/petroleum ether) = 0.34; the R_f of **36** was 0.64 under the same conditions.

To a solution of 1.35 g (4.07 mmol) of **37** in 35 mL of dry methanol cooled to 0 °C was added 500 mg (4.46 mmol) of potassium *tert*-butoxide. The reaction mixture was warmed to room temperature, stirred for 1 h, and then concentrated in vacuo. The residue was partitioned between 50 mL of EtOAc and 50 mL of 1 M aqueous HCl. The aqueous layer was separated and extracted with an additional 25 mL of EtOAc. The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo and the crude material purified by flash chromatography (12 × 5 cm, 3:2 EtOAc/petroleum ether) to give 635 mg (54%) of alcohol–ester **38** as white solid. IR (KBr): 3440, 2951, 1734, 1435, 1261, 1146, 1016 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.30–2.85 (m, 5 H), 2.09 (m, 1 H), 2.22 (m, 1 H), 2.52 (dd, J = 11, 14, 1 H), 2.77 (dd, J = 5, 14, 1 H), 3.60 (s, 2 H), 3.70 (3 H s with overlapping 2 H m, 5 H total), 4.22 (d, J = 5, 1 H), 4.54 (d, J = 5, 1 H), 7.15 (d, J = 8, 2 H), 7.21 (d, J = 8, 2 H). ^{13}C NMR ($CDCl_3$) δ 29.3, 29.7, 33.7, 40.7, 47.5, 49.1, 52.0, 61.8, 79.4, 79.6, 129.0, 129.3, 131.5, 140.3, 172.2. MS(CI): m/z 291 (M + H), 273, 255, 213, 195.

[1*S*-1α,2α,3α,4α]-3-[2-[3-(Hydroxymethyl)-7-oxabicyclo-[2.2.1]hept-2-yl]ethyl]benzeneacetic Acid, Methyl Ester (43), Alcohol–Ester for 21 (Method C). To a mixture of 5.77 g (237 mmol) of magnesium turnings and a small crystal of iodine in 70 mL of dry THF at 50 °C was added ~5% of a solution of 20.7 g (60.3 mmol) of bromide **29** in 120 mL of THF. The reaction was stirred until the iodine color dissipated then the remaining bromide solution was added dropwise over 40 min followed by continued heating at 50 °C for 1.5 h. The resulting solution of Grignard reagent was cooled to 0 °C and a solution of 3.00 g (17.9 mmol) of lactol **3b** in 75 mL of THF was added over 20 min. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 3 h. The resulting solution was cooled to 0 °C, quenched by slow addition of 50 mL of methanol, and then filtered to remove excess magnesium. The filtrate was concentrated in vacuo and the residue partitioned between 100 mL of saturated aqueous NH_4Cl solution and 150 mL of EtOAc. The aqueous layer was separated and extracted with two- 150-mL portions of EtOAc. The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo. The crude material was purified by flash chromatography (3:97 CH_3OH/CH_2Cl_2) to afford 7.52 g (97%) of diol **39** as an oil. R_f (silica gel, 6:94 CH_3OH/CH_2Cl_2) = 0.63, 0.66.

To a solution of 7.39 g (17.1 mmol) of diol **39** in 7.5 mL of pyridine at 0 °C was added 4.8 mL of acetic anhydride. The reaction mixture was stirred for 1 h and then warmed to room temperature for 16 h. The resulting solution was added to 400 mL of ether and washed with three 100-mL portions of 1 N aqueous HCl solution, dried ($MgSO_4$), and concentrated in vacuo to give the crude diacetate **40**. A solution of the crude diacetate in 100 mL of acetone at room temperature was treated with Jones reagent[20] until an orange color persisted then stirred for 1 h. The reaction mixture was quenched with 2-propanol and filtered. The filtrate was concentrated in vacuo and the residue partitioned between 150 mL of water and 150 mL of EtOAc. The aqueous layer was separated and extracted with two 150-mL portions of EtOAc. The organic extracts were combined, washed with two 50-mL portions of water, dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in 100 mL of ether and treated with excess ethereal diazomethane.[21] After 1 h the excess diazomethane was quenched with glacial HOAc and the solution concentrated in vacuo to give an oil. The crude oil was purified by flash chromatography (200 g silica, 1:2 then 1:1 ether/hexane) to give 5.50 g (83%) of ester **41** as an oil. R_f (silica gel, 1:1 ether/hexane) = 0.20.

A mixture of 5.40 g (13.9 mmol) of ester **41** and 540 mg of 10% palladium on carbon catalyst in 100 mL of methyl acetate containing 2.5 mL of 70% aqueous $HClO_4$ was stirred under an atmosphere of hydrogen (balloon) for 4 h. The mixture was filtered through a pad of Celite which was rinsed with three 50-mL portions of EtOAc. The filtrate was concentrated in vacuo to one half volume and then washed with two 30-mL portions of saturated aqueous NH_4Cl solution and 50 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography (200 g silica, 1:2 then 1:1 ether/hexane) to afford 3.62 g (75%) of acetate–ester **42** as an oil. R_f (silica gel, 2:98 CH_3OH/CH_2Cl_2) = 0.48.

To a solution of 3.62 g (10.5 mmol) of acetate–ester **42** in 100 mL of CH_3OH at 0 °C was added 1.29 g (11.5 mmol) of potassium *tert*-butoxide. The reaction mixture was stirred for 15 min then warmed to room temperature and stirred for 1.75 h. The resulting solution was partitioned between 100 mL of 0.1 N aqueous NaOH solution and 100 mL of ether. The aqueous layer was separated and extracted with two 100-mL portions of ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to give 3.06 g (97%) of alcohol–ester **43** as an oil. R_f (silica gel, 4:96 CH_3OH/CH_2Cl_2) = 0.54. IR (neat): 3440, 2975, 1735, 1607, 1589, 1437, 1261, 1153 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.25–2.05 (m, 10 H), 2.50 (m, 1 H), 2.70 (m, 1 H), 3.55 (m, 2 H), 3.58 (s, 3 H), 4.35 (d, J = 5, 1 H), 4.49 (d, J = 5, 1 H), 6.95–7.30 (m, 4 H). ^{13}C NMR ($CDCl_3$) δ 29.1, 29.7, 35.4, 41.0, 45.8, 49.0, 51.9, 61.5, 79.0, 80.0, 126.7, 127.1, 128.5, 129.3, 133.9, 142.3, 172.0. MS(CI): m/z 305 (M + H).

[1*S*-1α,2α,3α,4α]-3-[[3-(Hydroxymethyl)-7-oxabicyclo-[2.2.1]hept-2-yl]methyl]benzeneacetic Acid, Methyl Ester (44), Alcohol–Ester for 22. Prepared from bromide **29** and lactol **3a** by method A in 48% overall yield.

[1*S*-1α,2α,3α,4α]-3-[[3-(Hydroxymethyl)-7-oxabicyclo-[2.2.1]hept-2-yl]methyl]phenoxy]acetic Acid, Ethyl Ester (16), Alcohol–Ester for 23 (Method D). To a solution of 18.7 g (65.1 mmol) of bromide **12** in 100 mL of dry ether cooled to −78 °C was added dropwise 46 mL (1.7 M in pentane, 78 mmol) of *tert*-butyllithium solution over ~30 min. The reaction mixture was stirred at −78 °C for 30 min then at 0 °C for 15 min. The resulting anion solution was recooled to −78 °C and then added dropwise was a solution of 3.60 g (23.1 mmol) of lactol **3a** in 15 mL of THF. The reaction mixture was warmed to 0 °C and after 1 h quenched with 5 mL of water. The resulting mixture was added to 100 mL of water, the organic phase was separated, washed with 100 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to give an oil. The crude oil was purified by flash chromatography (10 × 10 cm, 1:4 EtOAc/petroleum ether then EtOAc) to afford 7.54 g (90%) of diol **13** as a colorless glass. R_f (silica gel, ethyl acetate) = 0.38; the R_f of **3a** was 0.24 under the same conditions.

A mixture of 7.50 g (20.6 mmol) of diol **13** and 5.0 g of 10% palladium on carbon catalyst in 100 mL of glacial HOAc was shaken on a Parr apparatus under an atmosphere of hydrogen (40 psi) for 20 h. TLC indicated the reaction was 70% complete. The mixture was passed through a 0.4 μM polycarbonate filter to remove the catalyst. To the filtrate was added 5.0 g of fresh catalyst and hydrogenation repeated as above. The resulting mixture was refiltered and the filtrate concentrated in vacuo to give a solid. The crude material was purified by flash chromatography (10 × 10 cm, 1:1 EtOAc/petroleum ether) to afford 5.05 g (70%) of alcohol **14** as a white solid, mp 106–110 °C. R_f (silica gel, ethyl acetate) = 0.48; the R_f of **13** was 0.40 under the same conditions.

To a solution of 1.51 g (4.34 mmol) of **14** in 30 mL of CH_3CN was added 1.5 mL of 48% aqueous HF solution. The reaction mixture was stirred at room temperature for 4 h and then added to 100 mL of water and extracted with two 50-mL portions of EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford 1.00 g (98%) of alcohol–phenol

(21) Prepared from *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine as described in Fieser and Fieser: Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, pp 191–195.

15 as a colorless oil. R_f (silica gel, ethyl acetate) = 0.35; the R_f of 14 was 0.47 under the same conditions.

The oil was removed from 200 mg (60% in oil, 5.0 mmol) of sodium hydride dispersion by three washes with petroleum ether then 5 mL of dry THF was added followed by a small drop of water. To the resulting mixture was added dropwise at room temperature a solution of 980 mg (4.19 mmol) of 15 in 10 mL of THF. The reaction mixture was stirred for 1 h and then 3 mL of sieve-dried DMF was introduced to aid in solubilizing the anion. To the resulting homogeneous solution was added 0.60 mL (5.4 mmol) of ethyl bromoacetate and stirred for 2 h. The reaction mixture was added to 50 mL of 1 M aqueous HCl solution and extracted with two 35-mL portions of EtOAc. The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to give an oil. The crude oil was purified by flash chromatography (20 × 5.0 cm, 3:1 EtOAc/petroleum ether) to afford 695 mg (52%) of alcohol–ester 16 as an oil. IR: (neat) 3426 (broad), 2981, 1756, 1586, 1203, 1019 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30 (t, J = 7, 3 H), 1.35–1.83 (m, 5 H), 2.09 (m, 1 H), 2.21 (m, 1 H), 2.49 (dd, J = 11, 14, 1 H), 2.76 (dd, J = 5, 14, 1 H), 3.77 (overlapping m, 2 H), 4.21 (d, J = 5, 1 H), 4.27 (q, J = 7, 2 H), 4.54 (d, J = 5, 1 H), 4.61 (s, 2 H), 6.85 (m, 2 H), 6.83 (d, J = 8, 1 H), 7.20 (dd, J = 8, 8, 1 H). ^{13}C NMR ($CDCl_3$) δ 14.1, 29.3, 29.7, 34.1, 47.4, 49.1, 61.3, 61.8, 65.4, 79.4, 79.7, 111.8, 115.5, 122.3, 129.5, 143.3, 158.0, 168.9. MS(CI): m/z 321 (M + H), 235.

[1*S*-1α,2α,3α,4α]-[3-[[3-(Hydroxymethyl)-7-oxabicyclo-[2.2.1]hept-2-yl]methyl]phenoxy]acetic Acid, Ethyl Ester (45), Alcohol–Ester for 24. Prepared from *O*-benzyl-*o*-bromophenol and lactol **3a** by method D (aqueous HF silyl cleavage step omitted) in 8% overall yield.

[1*S*-1α,2α,3α,4α]-2-[[3-(Hydroxymethyl)-7-oxabicyclo-[2.2.1]hept-2-yl]methyl]benzenepropanoic Acid, Methyl Ester (7), Alcohol–Ester for 25 (Method A). To a solution of 5.00 g (14.0 mmol) of bromide **2** in 30 mL of dry ether cooled to −100 °C was added dropwise 15 mL (1.7 M in pentane, 25 mmol) of *tert*-butyllithium solution over 15 min. The reaction mixture was stirred at −100 °C for 15 min then at 0 °C for 15 min. The resulting pale yellow anion solution was recooled to −78 °C and then 30 mL of dry THF was introduced followed by the rapid addition of a solution of 875 mg (5.61 mmol) of lactol **3a** in 10 mL of THF. The reaction mixture was warmed to 0 °C, stirred for 1 h, quenched with 5 mL of water, and then partitioned between 100 mL of water and 25 mL of EtOAc. The organic layer was separated, and the aqueous layer was extracted with an additional 25 mL of EtOAc. The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to give an oil. The crude oil was purified by flash chromatography (12 × 5.0 cm, 1:4 EtOAc/petroleum ether and then 4:1 EtOAc/petroleum ether) to afford 2.35 g (97%) of diol **4** as a colorless oil. R_f (silica gel, ethyl acetate) = 0.53; the R_f of **3a** was 0.24 under the same conditions.

A mixture of 1.90 g (4.38 mmol) of **4** and 1.9 g of 20% palladium hydroxide on carbon catalyst in 60 mL of glacial HOAc was stirred rapidly under an atmosphere of hydrogen (balloon) for 5 h. The reaction mixture was filtered through a 0.4 μM polycarbonate membrane and the filtrate was concentrated in vacuo (room temperature bath). The residue was partitioned between 50 mL of water and 50 mL of EtOAc. The organic layer was separated, washed with 50 mL of 1 M aqueous NaOH solution, dried ($MgSO_4$), and concentrated in vacuo to give an oil. The crude material was purified by flash chromatography (12 × 5.0 cm, 1:2 EtOAc/petroleum ether) to afford 1.03 g (55%) of alcohol **5** as a colorless oil. R_f (silica gel, 1:1 ethyl acetate/petroleum ether) = 0.50; the R_f of **4** was 0.34 under the same conditions. In addition, 573 mg (30%) of starting material **4** (as a single diastereomer) was recovered.

A solution of 1.00 g (2.39 mmol) of **5** and 50 mg (0.41 mmol) of 4-(dimethylamino)pyridine in 6 mL of 1:1 dry pyridine/acetic anhydride was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo and the residue partitioned between 25 mL of EtOAc and 20 mL of 1 M aqueous HCl solution. The organic layer was separated, washed with 20 mL of 1 M aqueous NaOH and then 20 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to afford crude acetate **6** as an oil. R_f (silica gel, 1:1 ethyl acetate/petroleum ether) = 0.72; the R_f of **5** was 0.40 under the same conditions.

To a solution of the crude acetate **6** in 15 mL of reagent acetone cooled to 0 °C was added rapidly 3.3 mL of Jones reagent.[20] The reaction mixture was stirred for 2 h, quenched by addition of 1 mL of 2-propanol and stirred for an additional 30 min. The resulting green slurry was filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue partitioned between 25 mL of ether and 25 mL of water. The organic layer was separated and concentrated in vacuo to give the crude acetate–acid as an oil.

A solution of the crude acetate–acid in 15 mL of 2:1 1 M aqueous NaOH/THF was stirred at room temperature for 30 min. The reaction mixture was cooled in an ice bath, quenched by addition of 15 mL of 1 M aqueous HCl solution then extracted with two 25-mL portions of ether. The ether extracts were combined, washed with 25 mL of brine, and concentrated in vacuo to give the crude alcohol–acid as an oil.

A solution of the crude alcohol–acid in 10 mL of acidic CH_3OH (prepared by addition of 0.5 mL of acetyl chloride to 10 mL of dry CH_3OH at 0 °C) was stirred at 0 °C for 2 h then concentrated in vacuo. The resulting oil was purified by flash chromatography (15 × 3.0 cm, EtOAc) to afford 526 mg (74% from **5**) of alcohol–ester **7** as a colorless oil. Crystallization (ether/hexane) of a small sample gave **7** as colorless prisms, mp 100–101 °C. IR (KBr): 3404, 2978, 2953, 2882, 1732, 1435, 1371, 1296, 1190, 1170 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.27–1.85 (m, 4 H), 2.15 (m, 3 H), 2.58 (m, 3 H), 2.82 (dd, J = 4, 14, 1 H), 3.67 (s, 3 H), 3.74 (m, 2 H), 4.24 (d, J = 5, 1 H), 4.53 (d, J = 5, 1 H), 7.17 (m, 4 H). ^{13}C NMR ($CDCl_3$) δ 27.6, 29.5, 30.4, 35.0, 46.9, 49.1, 51.7, 61.8, 79.5, 126.4, 126.5, 128.9, 129.6, 138.5, 139.2, 173.4. MS(CI): m/z 305 (M + H).

[1*S*-1α,2α,3α,4α]-2-[[3-(Hydroxymethyl)-7-oxabicyclo-[2.2.1]hept-2-yl]methyl]benzenebutanoic Acid, Methyl Ester (10), Alcohol–Ester for 26 (Method E). To a solution of 2.00 g (6.58 mmol) of alcohol–ester **7** in 15 mL of dry CH_2Cl_2 was added at room temperature 1.2 mL (8.6 mmol) of triethylamine, 1.09 g (7.24 mmol) of *tert*-butylchlorodimethylsilane and 80 mg (0.66 mmol) of 4-(dimethylamino)pyridine. The reaction mixture was stirred for 4 h and then diluted with 50 mL of ether and the resulting slurry filtered. The filtrate was washed with 25 mL of 1 M aqueous HCl solution and then 25 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to give 2.73 g (99%) of the crude silyl ether as a colorless oil. R_f (silica gel, 1:1 ethyl acetate/hexane) = 0.67; the R_f of **7** was 0.14 under the same conditions. A solution of the silyl ether and 1.1 g (26 mmol) of lithium hydroxide monohydrate in 18 mL of 2:1 THF/water was stirred rapidly at room temperature for 7 h. The reaction mixture was concentrated in vacuo and the residue partitioned between 50 mL of ice-cold EtOAc and 50 mL of ice-cold 1 M aqueous HCl solution. The organic layer was separated, washed with 25 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to give an oil. The crude oil was further dried by azeotroping with ~20 mL of toluene to afford 2.60 g (98% from **7**) of acid **8** as a colorless oil. R_f (silica gel, 1:1 ethyl acetate/hexane) = 0.07 (streaks); the R_f of the starting ester was 0.67 under the same conditions.

To a solution of 2.60 g (6.43 mmol) of acid **8** in 30 mL of toluene was added at room temperature a drop of DMF then dropwise over 10 min a solution of 0.70 mL (7.9 mmol) of oxalyl chloride in 5 mL of toluene. The reaction mixture was stirred until gas evolution ceased, ~30 min, then concentrated in vacuo. In order to remove residual oxalyl chloride 20 mL of toluene was added to the crude material and the resulting solution concentrated in vacuo. This procedure was repeated to give the crude acid chloride as a yellow oil. To a solution of the crude acid chloride in 30 mL of dry ether cooled in an ice bath was added excess ethereal diazomethane (prepared from 5.0 g of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine[21]), stirred for 30 min, and then carefully concentrated in vacuo to give the crude diazoketone as a bright yellow oil. R_f (silica gel, 1:1 ethyl acetate/hexane) = 0.62. To a solution of the crude diazoketone in 50 mL of CH_3OH heated to 60 °C was added at 10-min intervals three 500-mg portions (2.2 mmol, 6.6 mmol total) of Ag_2O. The dark reaction mixture was stirred for 30 min and then cooled and filtered through a pad of Celite. The filtrate was concentrated in vacuo to give a dark oil. The crude material was purified by flash chromatography (25 × 5.0 cm, 1:10 EtOAc/hexane) isolating the early eluting product fractions to afford 753 mg (27%) of homologated ester **9** as a

colorless oil. R_f (silica gel, 1:2 ethyl acetate/hexane) = 0.60; the R_f of the diazoketone was 0.40 under the same conditions. The ^{1}H NMR of this material indicated ~1–2% of methyl propionate impurity. An additional 289 mg (10%) of impure ester **9** (containing >2% of methyl propionate impurity) was obtained by isolating the later eluting fractions.

To a solution of 750 mg (1.74 mmol) of **9** in 4 mL of CH_3CN was added at room temperature 0.20 mL of 48% aqueous HF solution. The reaction mixture was stirred for 1 h and then added slowly was 25 mL of saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with two 20-mL portions of ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to afford 520 mg (94%) of alcohol–ester **10** as a colorless oil. ^{1}H NMR: ($CDCl_3$) δ 1.25–2.25 (m, 9 H), 2.38 (t, J = 7, 2 H), 2.56 (dd, J = 11, 14, 1 H), 2.67 (m, 1 H), 2.80 (dd, J = 4, 14, 1 H), 3.67 (s, 3 H), 3.75 (m, 2 H), 4.22 (d, J = 5, 1 H), 4.52 (d, J = 5, 1 H), 7.16 (s, 4 H). ^{13}C NMR ($CDCl_3$): δ 26.2, 29.6, 30.4, 32.0, 33.6, 47.1, 49.3, 51.6, 61.9, 79.5, 126.2, 129.4, 129.5, 139.3, 174.0.

Typical Procedure for Conversion of Alcohol–Esters to Semicarbazones. Preparation of [1*S*-1α,2α,3α,4α]-2-[[3-[[[(Phenylamino)carbonyl]hydrazono]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic Acid (25) from 7 (Method A). To a mixture of 424 mg (1.00 mmol) of Dess–Martin periodinane[11] in 5 mL of dry CH_2Cl_2 at room temperature was added in one portion a solution of the 200 mg (0.66 mmol) of alcohol–ester **7** in 1 mL of CH_2Cl_2. The reaction mixture was stirred for 15 min and then diluted with 25 mL of ether followed by 25 mL of saturated aqueous $NaHCO_3$ solution containing 1.1 g (7.0 mmol) of sodium thiosulfate. The two-phase mixture was stirred rapidly for 15 min and then the clear organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo to afford 160 mg (80%) of the crude aldehyde–ester **17** as an oil which was used without further purification. IR (film): 2951, 1736, 1719, 1437, 1171 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.30–1.90 (m, 4 H), 2.45–2.75 (m, 6 H), 2.96 (t, J = 8, 2 H), 3.67 (s, 3 H), 4.35 (d, J = 5, 1 H), 4.85 (d, J = 5, 1 H), 7.17 (s, 4 H), 9.69 (d, J = 4, 1 H). ^{13}C NMR ($CDCl_3$) δ 27.5, 28.9, 29.5, 32.3, 34.8, 49.1, 51.7, 58.8, 77.2, 78.3, 126.6, 126.8, 129.0, 129.5, 137.9, 138.5, 173.1, 203.0. MS(CI): m/z 303 (M + H).

To a solution of 150 mg (0.50 mmol) of aldehyde–ester **17** in 3 mL of CH_3OH was added at room temperature 90 mg (0.60 mmol) of 4-phenylsemicarbazide. The reaction mixture was stirred for 40 h then concentrated in vacuo to give a foam. The crude material was purified by flash chromatography (12 × 3.0 cm, 1:1 EtOAc/hexane) to afford 200 mg (92%) of semicarbazone **18** as a pale yellow foam. The 270-MHz ^{1}H NMR showed **18** as an ~4:1 anti/syn mixture.

A solution of 190 mg (0.44 mmol) of ester **18** and 37 mg (0.88 mmol) of lithium hydroxide monohydrate in 6 mL of 2:1 THF/water was stirred rapidly at room temperature for 3 h. The resulting solution was acidified (pH = 2) by addition of 1.0 mL of 1 M aqueous HCl solution and then partitioned between 20 mL of EtOAc and 20 mL of water. The organic layer was separated, washed with 20 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to give **25** as a pale yellow foam. TLC analysis (silica gel, 1:9 CH_3OH/CH_2Cl_2) showed the syn/anti isomers at R_f = 0.47 and 0.40. The crude mixture was purified by crystallization (EtOAc/hexane) to afford 98 mg (53%) of *anti*-**25** as small white flakes, mp 177–178 °C. TLC analysis (silica gel, 1:9 CH_3OH/CH_2Cl_2) showed only the anti isomer. IR (KBr): 3435, 2978, 1686, 1537, 1449 cm^{-1}. 400-MHz ^{1}H NMR ($CDCl_3$) of 70:30 anti/syn mixture δ 1.00–1.90 (m, 4 H), 2.20–3.10 (m, 8 H), 4.36 (d, J = 5, 1 H), 4.47 (d, J = 5, 0.7 H, anti isomer), 4.58 (d, J = 5, 0.3 H, syn isomer), 6.60 (d, J = 8, 0.3 H syn imine), 6.95–7.60 (m, 10 H), 7.76 (s, 0.7 H, anti –NHPh–), 8.29 (s, 0.3 H, syn –NHPh–), 9.83 (s, 0.7 H, anti –NNH–), 10.54 (s, 0.3 H, syn –NNH–). ^{13}C NMR ($CDCl_3$) of 70:30 anti/syn mixture δ 27.1, 27.8, 29.2, 29.3, 29.7, 31.9, 34.1, 34.6, 34.9, 46.3, 48.5, 48.7, 50.4, 78.0, 79.9, 80.2, 119.7, 119.9, 123.5, 123.7, 126.2, 126.4, 126.5, 126.9, 128.4, 128.5, 128.9, 129.0, 131.2, 137.6, 137.7, 138.1, 138.4, 138.7, 138.9, 145.8, 146.1, 154.7, 155.5, 177.1, 178.1. MS(CI): m/z 422 (M + H). Anal. ($C_{24}H_{27}N_3O_4$) C, H, N. Semicarbazones **19–24** and **26** were not recrystallized but isolated as crude foams.

[1*S*-1α,2α,3α,4α]-4-[2-[3-[[[(Phenylamino)carbonyl]hydrazono]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]ethyl]benzeneacetic Acid (19). Prepared as a solid white foam from **33** in 77% yield by method A.

[1*S*-1α,2α,3α,4α]-4-[[3-[[[(Phenylamino)carbonyl]hydrazono]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzeneacetic Acid (20). Prepared as a solid white foam from **38** in 81% yield by method A.

[1*S*-1α,2α,3α,4α]-3-[2-[3-[[[(Phenylamino)carbonyl]hydrazono]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]ethyl]benzeneacetic Acid (21) (Method B). To a slurry of 2.00 g (9.28 mmol) of pyridinium chlorochromate,[12] 2.00 g of oven-dried Celite, and 200 mg (2.44 mmol) of NaOAc in 20 mL of CH_2Cl_2 was added a solution of 0.92 g (3.0 mmol) of **43** in 13 mL of CH_2Cl_2. The reaction mixture was stirred for 110 min and then diluted with 125 mL of ether, stirred an additional 5 min, and filtered through a 2 in. pad of Florisil (ether elution, 150 mL). The filtrate was concentrated in vacuo to afford 0.69 g (75%) of crude aldehyde **46**. Crude **46** was converted to **21** as described above (method A) and isolated as a crude solid white foam in 55% overall yield.

[1*S*-1α,2α,3α,4α]-3-[[3-[[[(Phenylamino)carbonyl]hydrazono]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzeneacetic Acid (22). Prepared as a solid white foam from **44** in 85% yield by method A.

[1*S*-1α,2α,3α,4α]-[2-[[3-[[[(Phenylamino)carbonyl]hydrazono]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]phenoxy]acetic Acid (23). Prepared as a solid white foam from **16** in 55% yield by method A.

[1*S*-1α,2α,3α,4α]-[2-[[3-[[[(Phenylamino)carbonyl]hydrazono]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]phenoxy]acetic Acid (24). Prepared as a solid white foam from **45** in 81% yield by method A.

[1*S*-1α,2α,3α,4α]-2-[[3-[[[(Phenylamino)carbonyl]hydrazono]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenebutanoic Acid (26). Prepared as a solid white foam from **10** in 70% yield by method A.

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