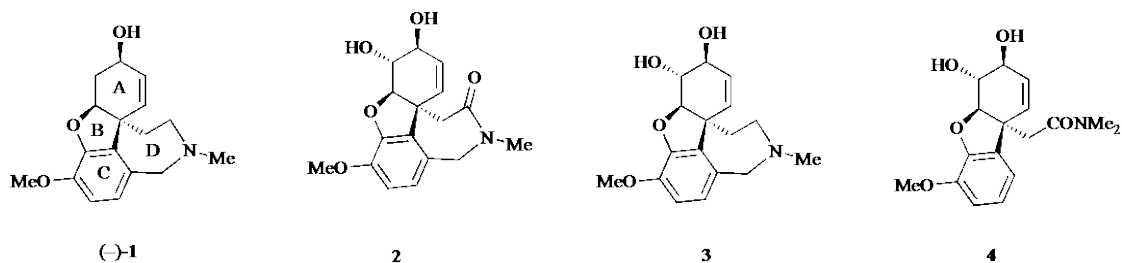


# Concise Routes to Derivatives and Analogues of (-)- and (+)-Galanthamine and an Assessment of their Capacities to Inhibit Acetylcholinesterase

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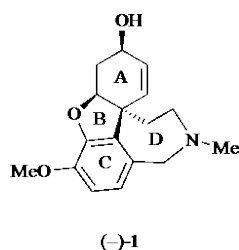


**ABSTRACT:** Concise syntheses of certain di- and mono-oxygenated derivatives (e.g. **2** and **3**, respectively) and analogues (e.g. **4** – a D-ring monoseco-analogue of **2**) of both the (-)- and (+)-enantiomeric forms of the alkaloid galanthamine [(**-**)-**1**] are reported. All have been assessed for their capacities to inhibit acetylcholinesterase but, in contrast to the predictions from docking studies, none binds strongly to this enzyme.

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## INTRODUCTION

The alkaloid (–)-galanthamine [(–)-**1**] has been isolated from a range of plant sources and is currently used in the clinic for the symptomatic treatment of mild to moderate forms of Alzheimer’s disease.<sup>1</sup> It exerts its beneficial effects by crossing the blood-brain barrier and then, in part at least, inhibiting acetylcholinesterase (AChE). It also acts as an allosteric modulator of the nicotinic acetylcholine receptor.<sup>1,2</sup> The non-natural enantiomer of compound **1**, viz. *ent*-**1** or (+)-galanthamine, has also been shown to accumulate in brain tissue but does so through non-specific binding.<sup>3</sup>



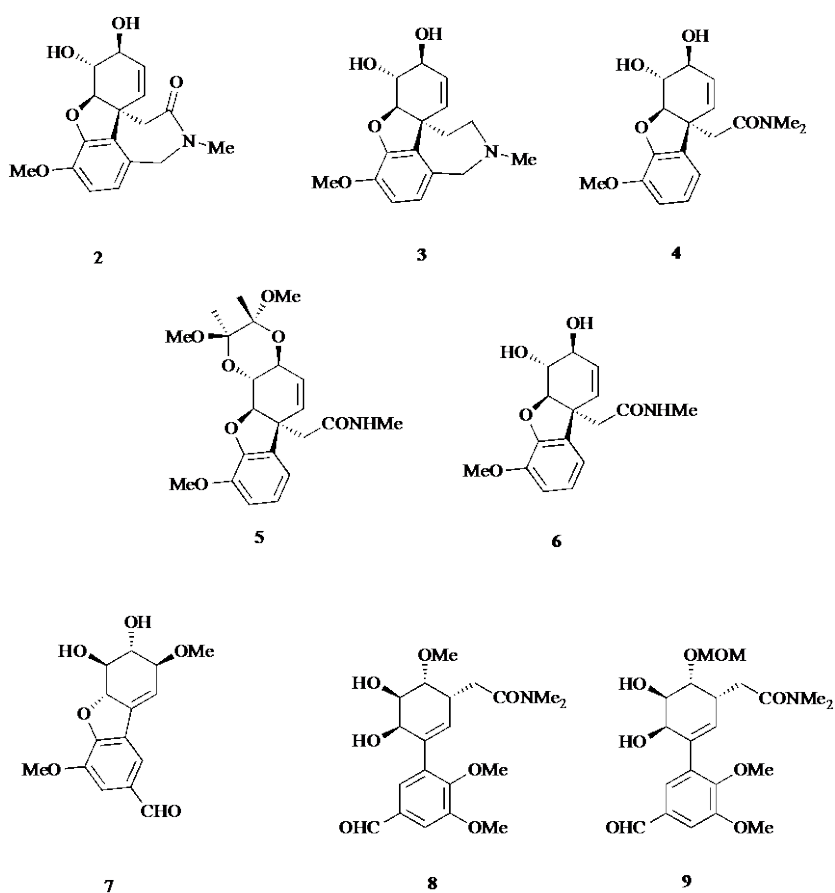
**Figure 1: The Structure of the Alkaloid (–)-Galanthamine**

Currently (–)-galanthamine is produced industrially by extraction from various plants sources, most notably the red spider lily (*Lycoris radiata*), the wild daffodil (*Narcissus pseudonarcissus*), the summer snowflake (*Leucojum aestivum*) and the Caucasian snowdrop (*Galanthus woronowii*).<sup>1</sup> However, both the increasing demands for the natural product and the erosion of habitat of at least some of the producing plants has prompted investigations into other methods for obtaining it or for identifying analogues with improved efficacy. As

part of such efforts, galanthamine has been the subject of a significant number of total synthesis studies with the first of these being reported by Barton and Kirby<sup>4</sup> and involving mimicking of the proposed biogenesis. Substantial refinements of this process have been reported in the interim<sup>5</sup> and one of these has formed the basis of a pilot-plant scale synthesis of the alkaloid<sup>5a</sup> although it is not clear if this is contributing significantly to the commercial production of the alkaloid. Magnus and co-workers have described<sup>6</sup> a related and highly effective approach. Intramolecular Heck reactions have provided another means for assembling the tetracyclic framework of galanthamine,<sup>7</sup> including those accomplished in an enantioselective manner, while various chirons (corresponding to the A-ring) have been employed for its assembly in either enantiomeric form.<sup>8,9a</sup> New routes to (-)-galanthamine continue to be reported,<sup>1e</sup> including approaches from our group.<sup>9</sup>

The identification and biological evaluation of analogues of galanthamine has been another focus of significant activity<sup>10</sup> that is now greatly assisted by data derived from the high-resolution X-ray analysis of the alkaloid bound to the active site of acetylcholinesterase.<sup>11</sup> Biomimetic diversity-oriented synthesis, sophisticated QSAR analyses, multicomponent-coupling chemistries as well as more conventional studies have all revealed active compounds.<sup>12</sup> The screening of natural products for relevant activities remains an ongoing area of investigation and has also resulted in the isolation of new inhibitors of the title enzyme.<sup>13</sup>

As part of an ongoing program to establish concise routes to the tetracyclic framework of galanthamine,<sup>1e,9</sup> we now report chemoenzymatic syntheses of two oxygenated derivatives, **2** and **3**, as well analogues **4-9** of the natural or (-)-form of the alkaloid (Figure 2).<sup>14</sup>



**Figure 2**

Syntheses of the enantiomers of the first five of these derivatives/analogues, *viz.* compounds *ent-2* to *ent-6*, are also described. As detailed below, and contrary to the predictions arising

from molecular docking studies, none of these is an effective inhibitor of acetylcholinesterase.

Our motivation for undertaking the studies described herein was that the introduction of additional functionalities within the galanthamine framework should increase water solubility and/or provide the means for conjugating the drug with various groups including peptide fragments<sup>10f</sup> or other entities (e.g. memantine)<sup>10d</sup> and thus allowing for the development of a multi-targeted therapeutic approach.<sup>10d</sup> In principle, then, the attachment of such moieties could provide new inhibitors (or even just prodrug forms<sup>10e</sup> of galanthamine) that are superior to existing therapies. As revealed below, the nature of our synthetic strategy is such that additionally oxygenated forms of the galanthamine A-ring were likely to be the most readily accessible. Accordingly, and since this region of alkaloid has not been “explored” previously, such derivatives became a major focus of the work detailed below.

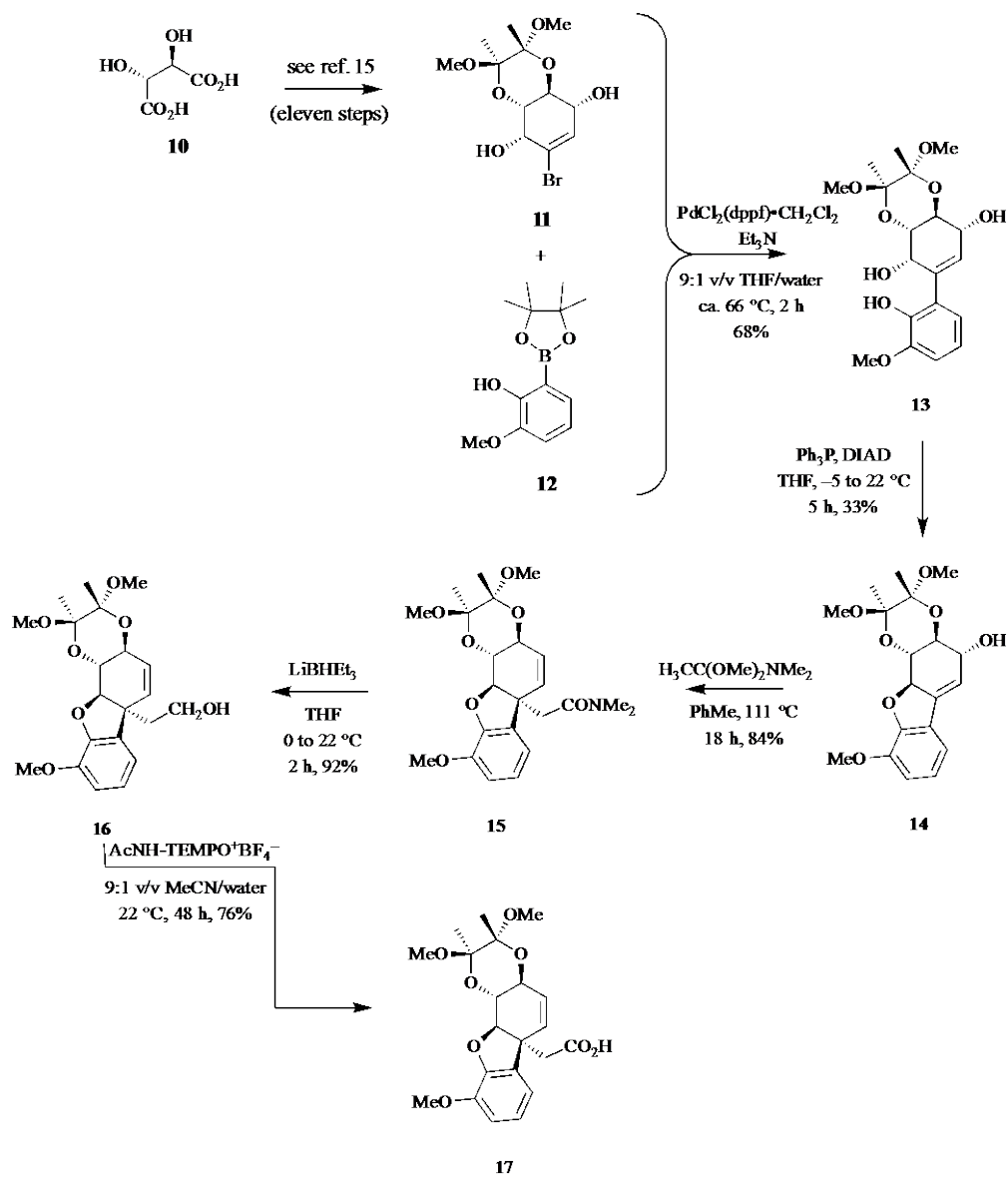
## RESULTS AND DISCUSSION

### *Chemical Synthesis Studies*

The reaction sequence used to assemble ABC-ring substructures of (–)-galanthamine is shown in Scheme 1 and employs the readily available *L*-tartaric acid (**10**) as starting material. Thus, as specified in a recent publication,<sup>15</sup> compound **10** can be converted over eleven steps involving reduction, Grignard addition and ring-closing metatheses as key transformations, into the 1,2-diacetal annulated bromocyclohexene **11**. Coupling of compound **11** with the readily available<sup>16</sup> aryl boronic acid ester **12** proceeded under conventional conditions to give

the anticipated arylated cyclohexene **13** (68%). Following protocols established during the course of our syntheses of the ribisins,<sup>17</sup> this last compound was engaged in an intramolecular Mitsunobu reaction using triphenylphosphine in conjunction with di-*iso*-propyl azodicarboxylate (DIAD) wherein the phenolic hydroxyl group served as the internal nucleophile and so affording the acid-sensitive isobenzofuran **14** (33%). As demonstrated through work in the enantiomeric series (see below), if appropriate account is taken of this acid-sensitivity then the Mitsunobu reaction can be a high yielding one. Despite concerns about the potential for competing isomerization of compound **14** to its more conjugated (fully aromatic) counterpart, on subjecting it to conditions previously employed for effecting the Eschenmoser-Claisen rearrangement of allylic alcohols<sup>18</sup> the amide **15** was produced in 84% yield. The structure of this compound followed not only from the derived NMR, IR and mass spectral data but also from a single-crystal X-ray analysis of its enantiomer (see below). Compound **15** embodies both the targeted ABC-ring substructure of (-)-galanthamine and the associated quaternary carbon. In anticipation of installing the final (D) ring of the title alkaloid the amide residue within compound **15** was reduced using LiBHET<sub>3</sub> and the 1°-alcohol **16** thereby obtained in 92% yield.

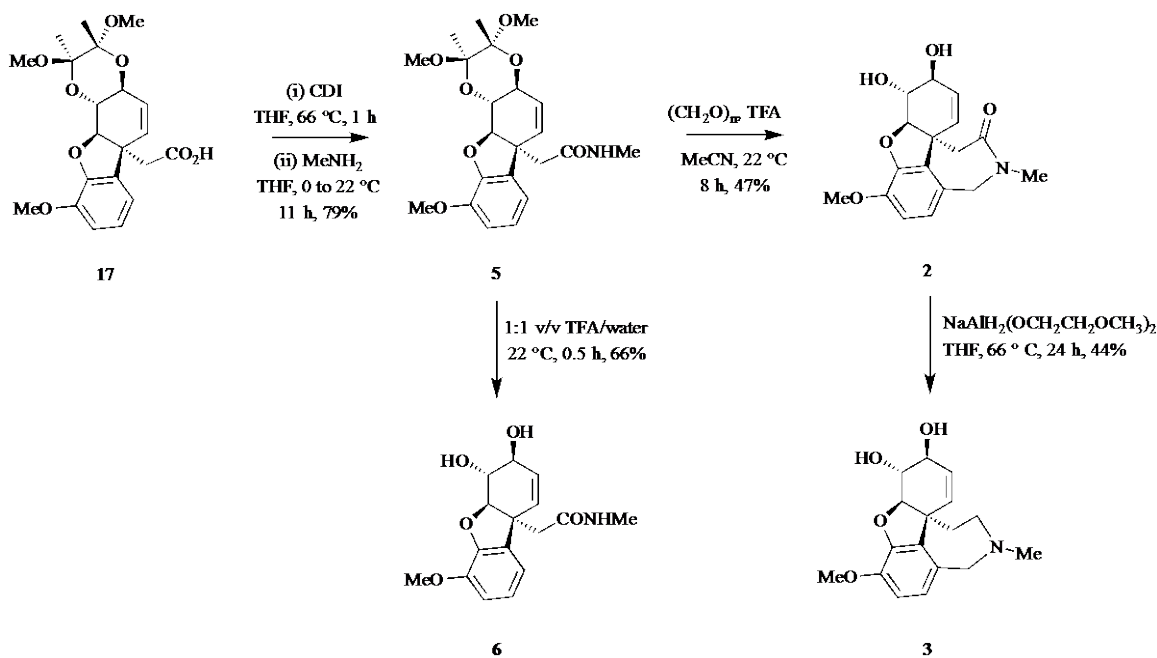
**Scheme 1: Synthesis of Key Acid 17 Embodying the ABC-ring Substructure and Associated Quaternary Carbon of (-)-Galanthamine**



Oxidation of compound **16** under conditions defined by Bobbitt and Bailey<sup>19</sup> then gave the acid **17** (76%) that represents the key precursor to the targeted galanthamine derivatives/analogues **2-6**.

The straightforward manipulations of acid **17** leading to the targeted (-)-galanthamine derivatives/analogues **2, 3, 5** and **6** are shown in Scheme 2. Thus, coupling of compound **17** and methylamine, using 1,1'-carbonyldiimidazole (CDI) for activation of the acid, afforded amide **5** (79%) and on exposure of the latter to modified Pictet-Spengler conditions,<sup>7c,20</sup> involving paraformaldehyde in the presence of trifluoroacetic acid (TFA), the tetracyclic lactam **2** (47%) was formed as a result of concomitant cleavage of the Ley acetal moiety.

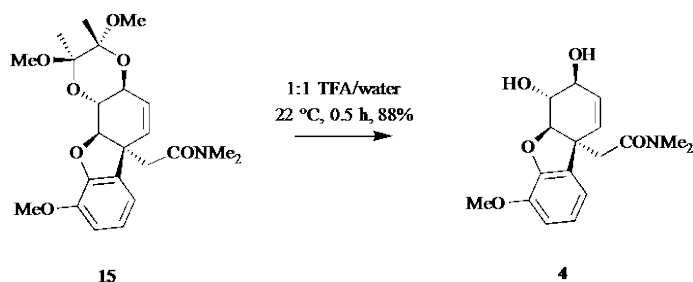
**Scheme 2: Conversion of Acid 17 into the (-)-Galanthamine Derivatives/Analogues 2, 3, 5 and 6**



On treatment with sodium bis(2-methoxyethoxy)aluminum dihydride, compound **2** was reduced to the azepine **3** (44%) while hydrolysis of the 1,2-diacetal residue within compound **5** using aqueous trifluoroacetic acid (TFA) afforded the diol **6** (66%). Compound **6** can be considered as a hybrid of the title alkaloid and the neurologically active natural product ribisin D.<sup>17,21</sup>

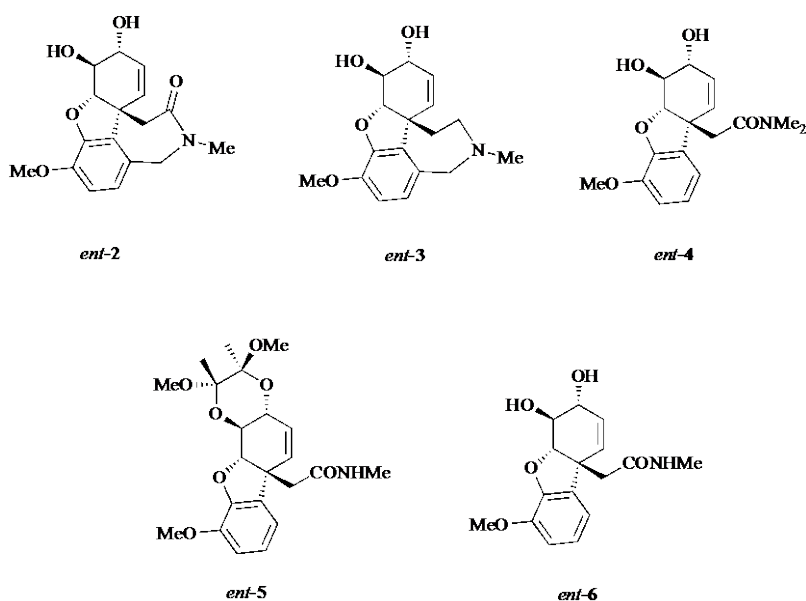
The synthesis of analogue **4**, a mono-seco derivative of 5*R*-hydroxy-(–)-galanthamine (**3**), simply involved (Scheme 3) acid-catalyzed hydrolysis of precursor **15** under conventional conditions. This reaction proceeded in 88% yield.

### Scheme 3: Hydrolysis of Biacetal **15** Leading to Analogue **4**



All of the spectral data obtained on the targeted compounds **2-6** were in complete accord with the assigned structures but final confirmation of that of the first (i.e. **2**) followed from a single crystal X-ray analysis of its enantiomer (see below).

In an effort to establish a more meaningful SAR profile for the abovementioned analogues, the enantiomerically-related derivatives/analogues *ent-2* to *ent-6* (Figure 2) were sought. While the routes defined above could simply be adapted for this purpose by starting with *D*- rather than *L*-taratric acid, we were able to establish a shorter pathway by starting with an enzymatically-derived chiron that is readily available in the required enantiomeric form (but less so in the opposite one required to prepare the derivatives/analogues just described).

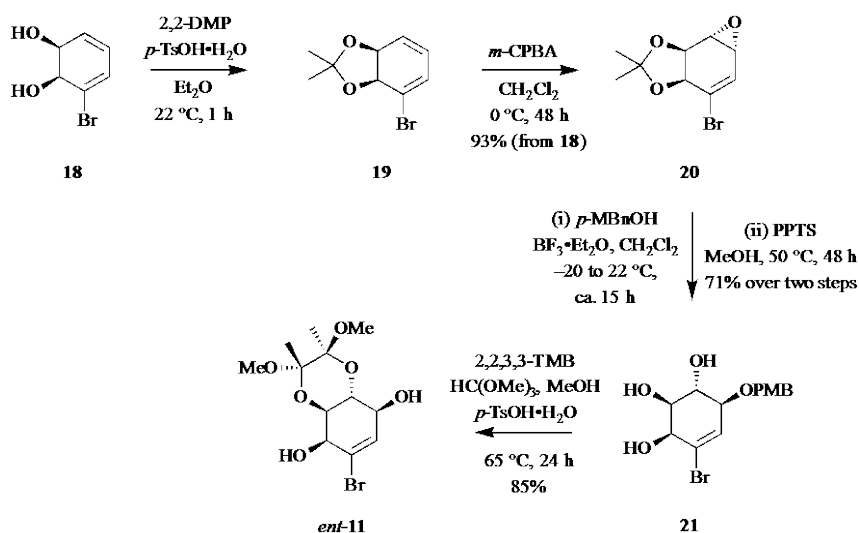


**Figure 3: The Enantiomeric Series of Derivatives/Analogues**

The synthesis of the enantiomeric series of compounds started, as shown in Scheme 4, with the enzymatically-derived and enantiomerically pure *cis*-1,2-dihydrocatechol **18**<sup>22</sup> that was converted into the corresponding and well-known<sup>23</sup> acetonide **19** under standard conditions. Immediate treatment of the last compound with *m*-chloroperbenzoic acid (*m*-CPBA) then

afforded, in a completely regio- and stereo-selective fashion, epoxide **20**<sup>23</sup> (93% from **18**). Reaction of compound **20** with a large excess of *p*-methoxybenzylalcohol (*p*-MBnOH) in the presence of boron trifluoride etherate (BF<sub>3</sub>•Et<sub>2</sub>O) resulted in selective nucleophilic opening of the epoxide ring at the allylic carbon<sup>24</sup> but the protected bromoconduritol thus formed was not isolated. Rather, it was simply allowed to react with methanol in the presence of pyridinium tosylate (PPTS) and thereby affording triol **21** (71%). Treatment of a methanolic solution of this last compound with 2,2,3,3-tetramethoxybutane (2,2,3,3-TMB) in the presence of *p*-toluenesulfonic acid monohydrate (*p*-TsOH•H<sub>2</sub>O) then resulted in the selective formation of the “Ley”-acetal<sup>25</sup> *ent*-**11** (85%) and so establishing an “enantiomeric overlap” with the synthetic sequence leading to the original sets of analogues.

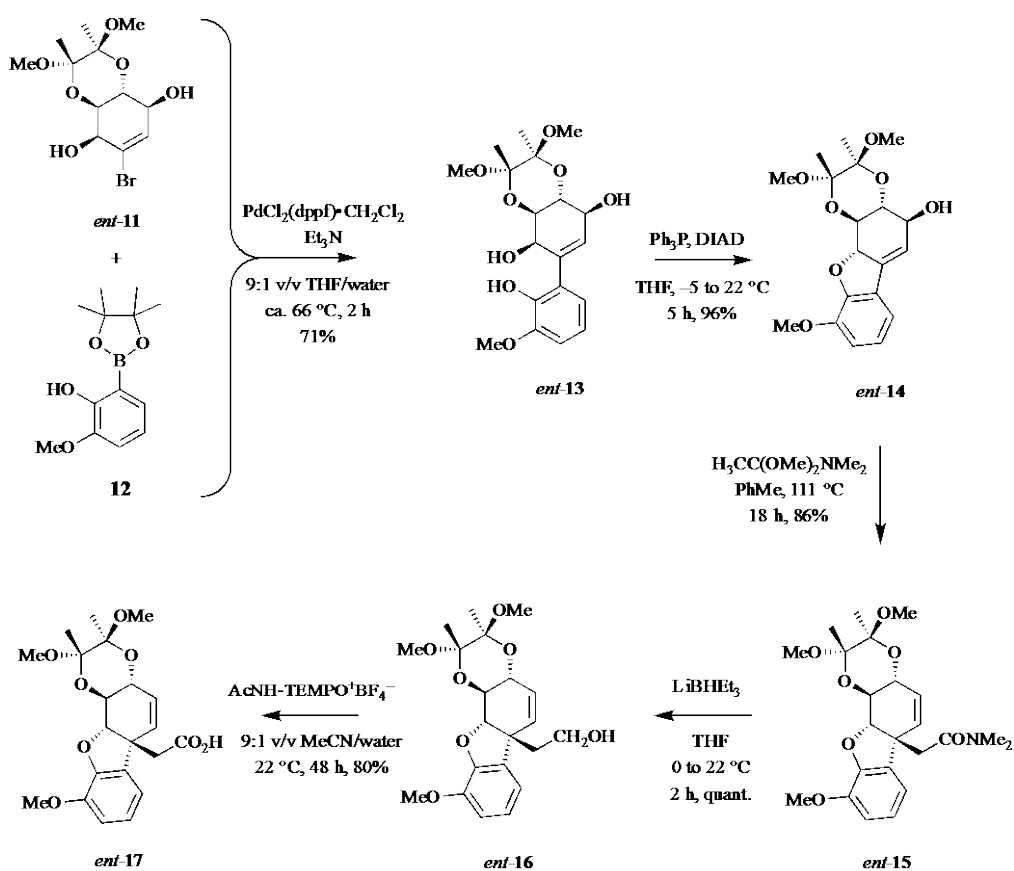
**Scheme 4: Synthesis of Bromoconduritol *ent*-11 from the Enzymatically-derived and Homochiral *cis*-1,2-Dihydrocatechol.**



During the conversion **21** → *ent*-**11** acetal formation is presumed to take place prior to cleavage of the PMB-ether unit since the reverse order of events would lead to an intermediate conduritol embodying two adjacent *trans*-diol moieties and the formation of two isomeric Ley-type acetals would therefore be expected. Indeed, when the tetra-ol derived from hydrolysis of compound **21** was subjected to reaction with 2,2,3,3-TMB in the presence of *p*-TsOH•H<sub>2</sub>O then a *ca.* 1:1 mixture of the two possible bis-acetals is formed.

As shown in Scheme 5, and as was the case in the enantiomeric series, compound *ent*-**11** could be engaged in a Suzuki-Miyaura cross-coupling reaction<sup>26</sup> with arylboronic acid ester **12** and so affording the anticipated product *ent*-**13** (71%) that participated in an intramolecular Mitsunobu reaction to give compound *ent*-**14** (96%). Allylic alcohol *ent*-**14** underwent an Eschenmoser-Claisen rearrangement reaction on thermolysis with the dimethyl acetal of *N,N*-dimethylacetamide in refluxing toluene and thereby affording *N,N*-dimethylamide *ent*-**15** (86%). The structure of this last compound was confirmed by a single-crystal X-ray analysis, details of which are provided in the Experimental Section and the Supporting Information (SI). Reduction of compound *ent*-**15** with lithium triethylborohydride and oxidation of the resulting 1°-alcohol, *ent*-**16** (quant.), using the Bobbitt/Bailey protocol,<sup>19</sup> then gave acid *ent*-**17** (80%).

**Scheme 5: Synthesis of Key Acid *ent-17* from Bromoconduritol *ent-11***

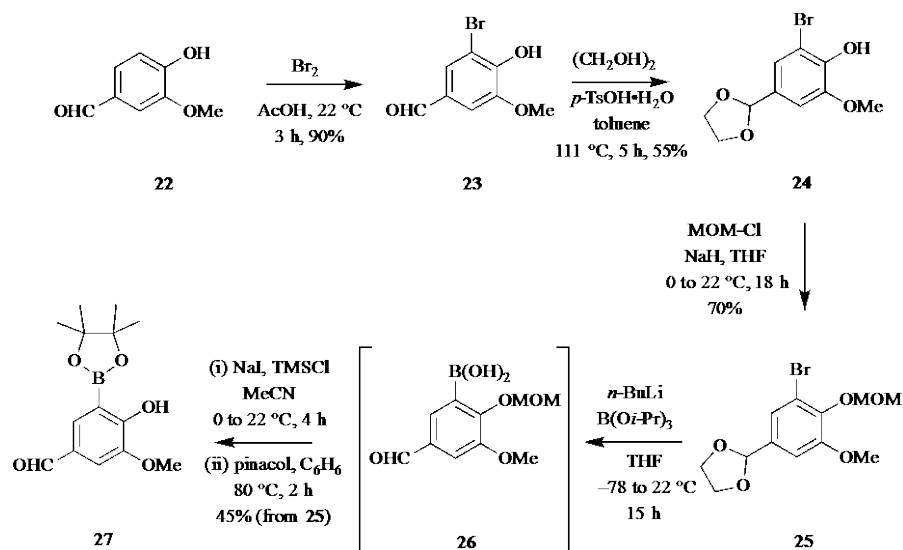


Following precisely the same reaction sequences as detailed above in Schemes 2 and 3, compound *ent-17* was converted into the target derivatives *ent-2* to *ent-6* (Figure 2) with the structure of the first of these being confirmed by single-crystal X-ray analysis. The mono-

seco analogue of compound *ent-2*, namely amide *ent-4*, was readily obtained in 77% yield by simply treating bis-acetal *ent-15* with aqueous trifluoroacetic acid (cf Scheme 3).

As part of an effort to develop galanthamine derivatives containing additional functionality in the aromatic C-ring, especially ones capable of conjugation with motifs that might bind to the so-called peripheral and anionic binding site of acetylcholinesterase,<sup>27</sup> we sought to exploit the synthetic chemistry detailed above for this purpose. As such, the relevant arylboronate acid ester (representing a synthon for the C-ring) was required and the route used to obtain this is shown in Scheme 6. Thus, vanillin (**22**) was converted, under established conditions, into its bromo-derivative **23**<sup>28</sup> (90%) and the aldehydic residue within the latter then protected as the corresponding ethylene acetal using standard conditions and so affording compound **24** in 55% yield. The readily derived MOM-ether, **25** (70%), of the last compound was subjected to a metallation/borylation protocol and the intermediate boronic acid **26** obtained on hydrolytic work up was reacted with sodium iodide/trimethylsilyl chloride (to cleave the MOM ether) and then pinacol and thus affording the hitherto unreported ester **27** (45% from **25**). The structure of this last compound was confirmed by single-crystal X-ray analysis (see Experimental Section and SI for details).

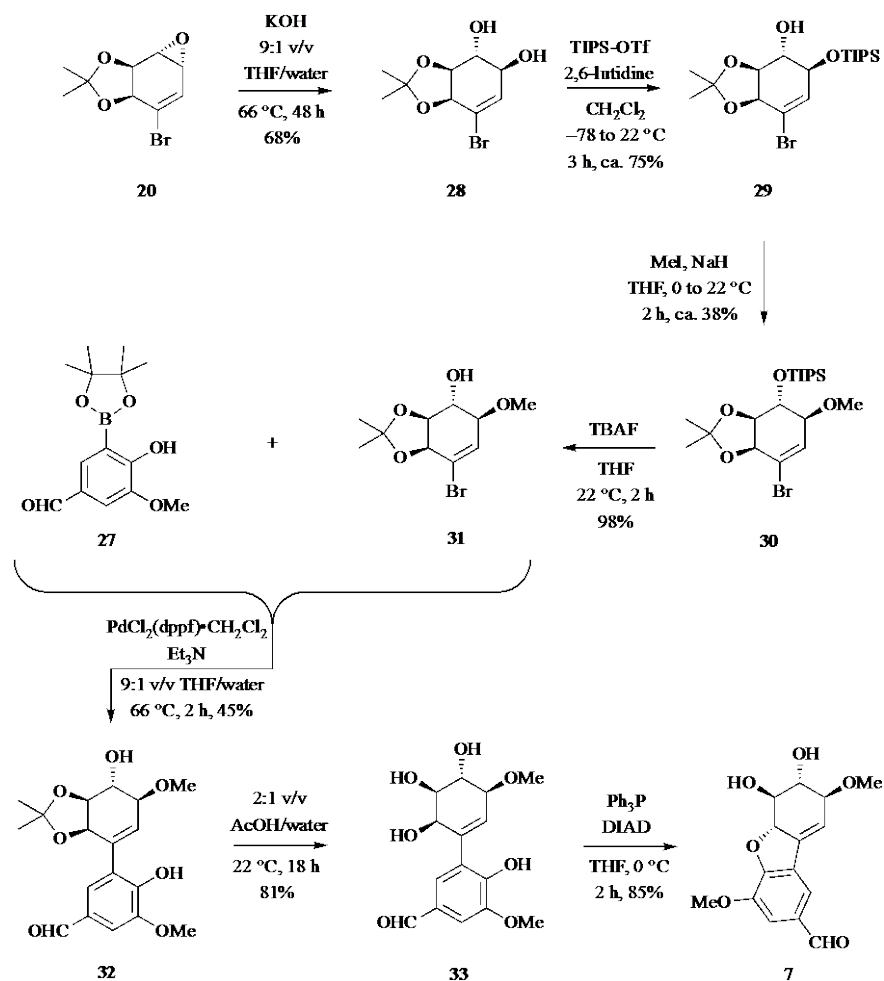
### **Scheme 6: Synthesis of Aryl Boronate Ester 27**



In the opening stages of attempts to exploit ester **27** in the production of galanthamine analogues related to those described above, the epoxide **19** (Scheme 7) was subject to hydrolytic cleavage and thus affording the previously reported<sup>29</sup> *trans*-diol **28** (68%). The allylic hydroxyl group of diol **28** was selectively protected through its reaction with tri-*iso*-propylsilyl trifluoromethanesulfonate (TIPS-OTf) in the presence of 2,6-lutidine and so producing the allylic ether **29** (88%).<sup>30</sup> The location of the TIPS group within this product was established using COSY experiments. On treating compound **29** with methyl iodide in the presence of sodium hydride the *bis*-ether **30** (49%), rather than the anticipated regioisomer, was obtained. Since the illustrated locations of the ether residues within compound **30** (that thwart the application of the anticipated Eschenmoser-Claisen rearrangement) were not appreciated until an X-ray analysis was carried out on a derivative, this was carried forward by first treating it with TBAF and thus affording the homoallylic alcohol **31** (98%). Compound **31** was engaged in a Suzuki-Miyaura cross-coupling reaction with ester **27** to give the arylated and crystalline cyclohexene **32** (45%), the illustrated structure of which was established by single-crystal X-ray analysis. Acid-catalyzed hydrolysis of the acetonide

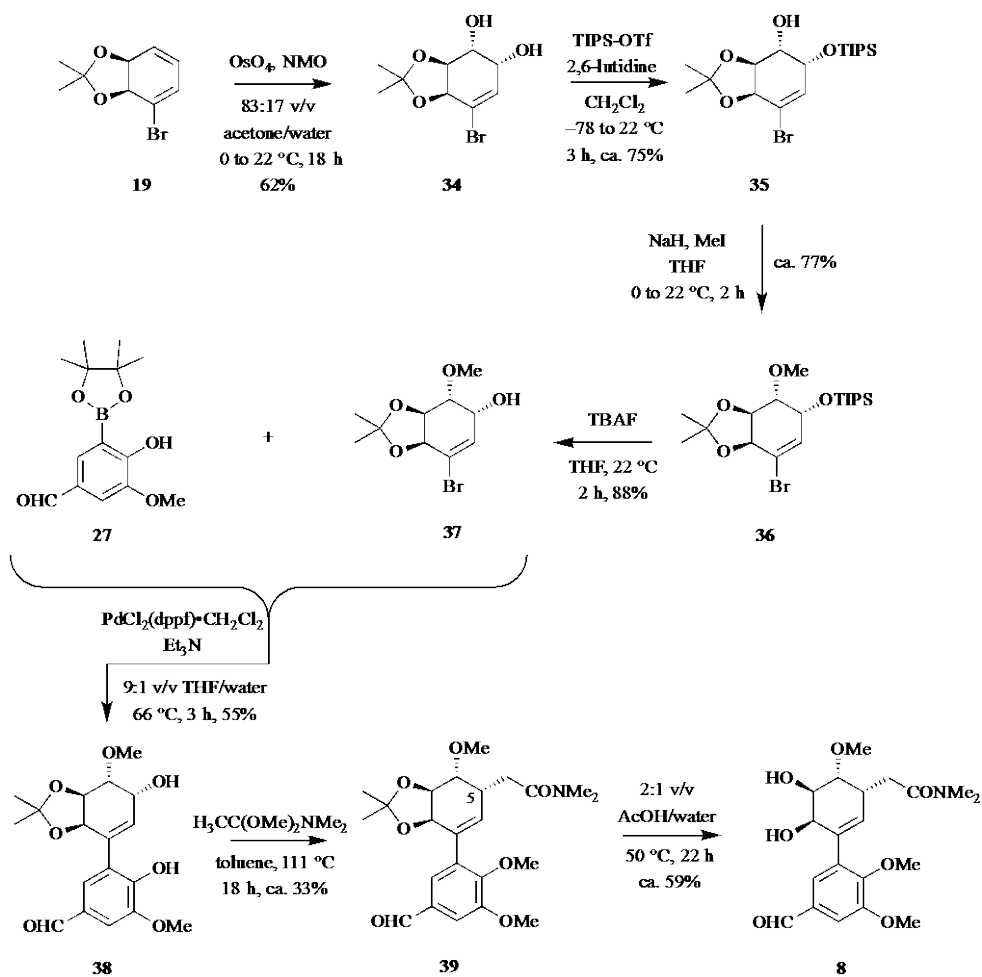
residue within the last compound gave triol **33** (81%). Even though the position of the methoxy group within compound **33** precluded the application of the type of EC-rearrangement used earlier, it was subjected to an intramolecular Mitsunobu reaction so as to produce a system, namely compound **7** (85%), that embodies the ABC-ring ensemble associated with (-)-galanthamine.

#### Scheme 7: Synthesis of Analogue 7



The synthesis of analogue **8** is shown in Scheme 8 and involved, as the initial step, the regio- and diastereo-selective *cis*-dihydroxylation of the diene **19**. Selective silylation of the allylic hydroxyl group within the resulting and previously reported<sup>17b,31</sup> diol **34** (62%) was readily achieved using TIPS-OTf in the presence of 2,6-lutidine and the product ether **35** (88%) subjected to *O*-methylation using methyl iodide/base.

**Scheme 8: Synthesis of Analogue 8**

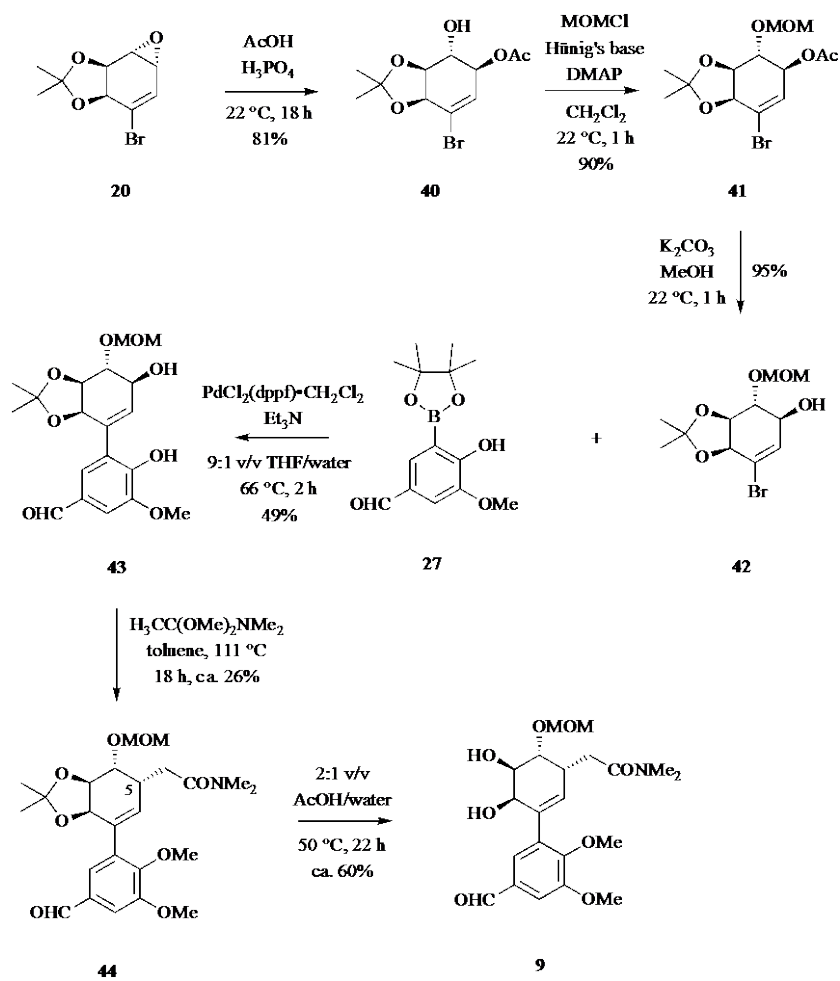


Treatment of the product *bis*-ether **36** (92%) with TBAF resulted in cleavage of the *O*-TIPS bond and formation of the alcohol **37** (88%) that could be cross-coupled with boronate ester **27** under Suzuki-Miyaura conditions and so affording the anticipated product **38** (55%). Contrary to expectations, however, the allylic alcohol residue within compound **38** failed to engage in an Eschenmoser-Claisen rearrangement on treatment with *N,N*-dimethylacetamide dimethyl acetal. Rather, the replacement of the associated allylic hydroxyl group with a *N,N*-dimethylacetamide residue took place to give, in a stereoselective manner and after

accompanying *O*-methylation of the phenolic hydroxyl group, amide **39** (40%). This was contaminated by small amounts (7%) of its chromatographically inseparable C5-epimer. “Thwarted E-C rearrangements” of this type have been reported previously<sup>32</sup> and in this instance the process may be driven by electron-rich arene residue facilitating ionization of the intermediate mixed acetal with the ensuing and extensively stabilized cation then undergoing nucleophilic capture by 1-methoxy-*N,N*-dimethylethen-1-amine that is itself generated through thermal cracking of the starting dimethyl acetal. The basic structure of product **39** follows from the observation that the diastereotopic methylene hydrogens of the acetamide side-chain both show vicinal couplings to the adjacent allylic hydrogen. The illustrated configuration of the C5 acetamide residue is assigned on the basis that this would be introduced preferentially, during the course of the abovementioned nucleophilic capture process, from that face of the intermediate cation opposite to the sterically demanding and nearby acetonide residue. Hydrolysis of this acetonide residue within compound **33** under standard conditions then gave analogue **8** in 69% yield.

The synthesis of the final galanthamine analogue **9** followed a very similar route to that used in preparing congener **8**. The reaction sequence involved is shown in Scheme 9. Thus, reaction of epoxide **19** with acetic acid in the presence of a mineral acid gave the previously reported *trans*-diol mono-acetate **40**<sup>9a</sup> (81%), the free hydroxyl of which was protected as the corresponding MOM-ether using standard protocols and thus affording compound **41**<sup>9a</sup> in 91% yield.

### Scheme 9: Synthesis of Analogue 9



Cleavage of the acetate unit with the last compound could be effected under conventional conditions and the resulting allylic alcohol **42**<sup>9a</sup> (95%) then cross-coupled with boronate ester **27** in the usual manner and so giving product **43** (49%). As was the case with congener **32** (Scheme 8), on subjecting compound **43** to conditions often used to effect the EC-rearrangement this substrate also engaged in both an allylic substitution reaction and *O*-methylation of the phenolic hydroxyl of the precursor. As consequence a

chromatographically inseparable and 3:1 mixture of amide **44** and its  $\beta$ -epimer (35% combined yield) was formed. The salient spectral features of compound **44** resembled those of congener **33**. Hydrolysis of the mixture of acetonide **44** and its C5-epimer under conventional conditions then gave, after chromatographic purification, diol **9** (69%) that, like the other galanthamine derivatives/analogues, was subjected to molecular docking studies and evaluation as a potential inhibitor of acetylcholinesterase. Details are presented in the following section.

### **Biological Evaluation and Molecular Docking Studies**

The abovementioned derivatives/analogues of (-)- and (+)-galanthamine were each evaluated for their ability to inhibit AChE using a modified method involving addition of DMSO so as to ensure dissolution of these otherwise rather insoluble compounds.<sup>33</sup> The inhibitory effect of DMSO itself on the AChE was taken into account by subtracting a control measurement for obtaining the IC<sub>50</sub> values of the tested materials. A summary of the inhibition data thus obtained is shown in Table 1. These assays reveal that only one of the compounds, namely derivative **3**, showed a measureable IC<sub>50</sub> value (of 420  $\mu$ M) compared to the positive control (-)-galanthamine [(-)-**1**] which had an IC<sub>50</sub> value of 0.9  $\mu$ M. Clearly, then, and regardless of the absolute stereochemistries of the systems involved, none of the above-mentioned derivatives/analogues is a strong inhibitor of AChE.

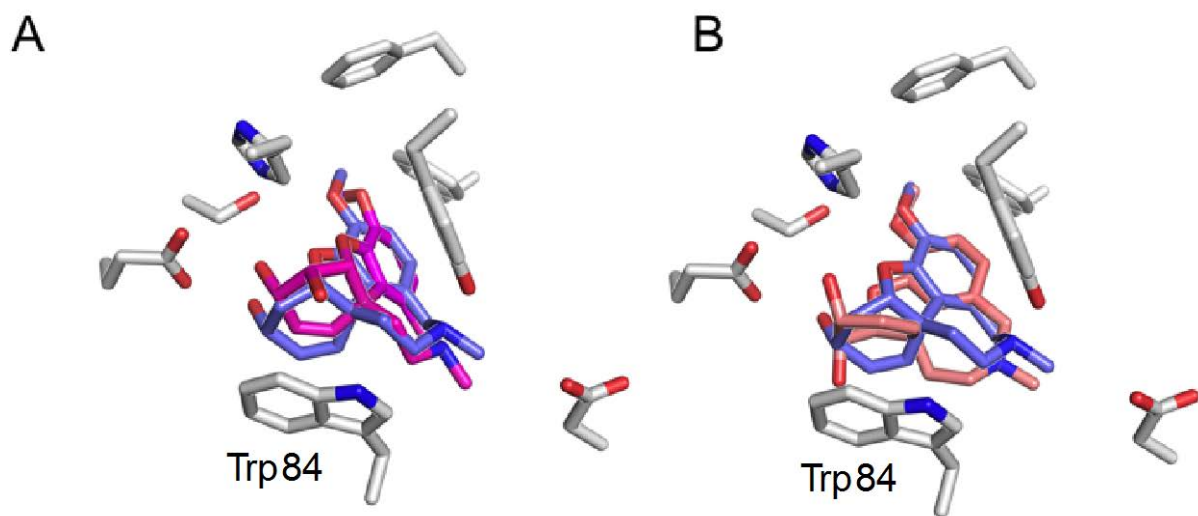
**Table 1:** Outcomes of Evaluating Galanthamine Derivatives and Analogues as Inhibitors of AChE and the Calculated Docking Binding Energies (BEs) of Them.

Entry	Compound	IC <sub>50</sub> ( $\mu$ M)	Docking BE (kcal)
1	<b>2</b>	>500	-8.9
2	<i>ent-2</i>	>500	-9.6
3	<b>3</b>	420 $\pm$ 57	-8.4
4	<i>ent-3</i>	>500	-9.5
5	<b>4</b>	>500	-6.0
6	<i>ent-4</i>	>500	-9.1
7	<b>5</b>	>500	-
8	<i>ent-5</i>	>500	-
9	<b>6</b>	>500	-6.3
10	<i>ent-6</i>	>500	-9.2
11	<b>7</b>	>500	-7.8
12	<b>8</b>	>500	-
13	<b>9</b>	>500	-
14	<b>1</b> (+ve control)	0.9 $\pm$ 0.2	-10.2

Analysis of these inhibition data was undertaken through molecular docking simulations and using the structure of (-)-galanthamine bound to human AChE.<sup>34</sup> Crystallographic studies have revealed that (-)-galanthamine binds into the active site of AChE with the tetrahydroazepine or D-ring assuming a boat-like conformation and the associated *N*-methyl group in a pseudo-equatorial orientation spanning the acyl and choline-binding sites.<sup>35</sup> Docking simulations, using AUTODOCK, matched the solved structure (see Figure 4A) with the key interactions between AChE and (-)-galanthamine being evident and so suggesting that docking simulations of this type can provide the correct orientation of binding for the compounds. Surprisingly, with the exception of compounds **5** and *ent-5*, **8** and **9** - for which no bound structures could be obtained (in the case of the first two of these compounds this may be a consequence of their significantly greater size), the derivatives all had significant docking binding energies, albeit weaker than (-)-galanthamine (see right-hand column, Table 1). This highlights some of the known limitations in the prediction of binding affinity by docking programs.<sup>36-38</sup> The docking studies do, however, reveal the likely structural basis for

the reduced affinity of these analogues. For example, the configuration of compound **3** matches the orientation of (–)-galanthamine, except that the additional (C5) hydroxyl moiety is positioned towards tryptophan 84 and so produces a distortion in the shape of the A-ring. This most likely results in destabilization of the  $\pi$ - $\pi$  stacking interaction between the indole ring of Trp84 and this ring (A)<sup>39</sup> with this loss of interaction impairing the compound's capacity to inhibit AChE.

**Figure 4.** Overlap of (–)-Galanthamine (**1**) (blue) and the Docked Derivatives **3** (A, purple) and *ent*-**3** (B, peach) in the Active Site of AChE



The (+)-enantiomer, *ent*-**3**, of compound **3** also has a hydroxyl positioned towards Trp84, again disrupting the stabilizing cyclohexene-indole interactions, although on this occasion it is the same hydroxyl moiety that is present in galanthamine, potentially explaining, in part at least, why (+)-galanthamine derivatives are not potent inhibitors of AChE.

## CONCLUSIONS

The synthetic chemistry studies detailed above have established that the ABC-ring system of galanthamine is readily obtained through the Suzuki-Miyaura cross-coupling of *o*-hydroxyarylboronates with conduritols incorporating a brominated double-bond and then engaging the products of such processes in an intramolecular Mitsunobu reaction. Furthermore, most of the polyhydroxylated tetrahydrodibenzofurans arising from such a reaction sequence engage in a thermally promoted Eschenmoser-Claisen type rearrangement reaction on treatment with *N,N*-dimethylacetamide dimethyl acetal in refluxing toluene. The angularly-substituted tetrahydrodibenzofurans thus formed, which embody the quaternary carbon center associated with the title alkaloid and represent mono-seco analogues of the same, can then be elaborated, using Pictet-Spengler chemistry, to give oxygenated derivatives of galanthamine, certain variants of which have recently been isolated from Chinese medicinal plants.<sup>40</sup> Interestingly, these new natural products were also poor inhibitors of AChE.

The biological evaluation of the galanthamine derivatives and analogues obtained by the pathways described above reveals the finely tuned nature of the interactions of the parent alkaloid with the target enzyme AChE. In particular, structurally “modest” changes to the galanthamine framework, as embodied in the oxygenated derivatives **2**, *ent*-**2**, **3** and *ent*-**3**, can completely disrupt binding and such that the compounds are rendered inactive. These studies have also revealed that the computational prediction of the likely binding affinity of galanthamine analogues to AChE is fraught.

## EXPERIMENTAL SECTION

**General Protocols.** Unless otherwise specified, proton ( $^1\text{H}$ ) and carbon ( $^{13}\text{C}$ ) NMR spectra were recorded at room temperature in base-filtered  $\text{CDCl}_3$  on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. The signal due to residual  $\text{CHCl}_3$  appearing at  $\delta_{\text{H}}$  7.26 and the central resonance of the  $\text{CDCl}_3$  “triplet” appearing at  $\delta_{\text{C}}$  77.0 were used to reference  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, respectively.  $^1\text{H}$  NMR data are recorded as follows: chemical shift ( $\delta$ ) [multiplicity, coupling constant(s)  $J$  (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. Infrared spectra ( $\text{cm}^{-1}$ ) were recorded on a FTIR Spectrometer. Samples were analyzed as thin films or finely divided solids. Low-resolution ESI mass spectra were recorded on a single quadrupole mass spectrometer interfaced with a liquid chromatograph, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F<sub>254</sub> plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid:ceric sulfate:sulfuric acid (conc.):water (37.5 g : 7.5 g : 37.5 g : 720 mL), potassium permanganate:potassium carbonate:5% w/v aq. sodium hydroxide solution:water (3 g : 20 g : 5 mL : 300 mL), *p*-anisaldehyde or vanillin:sulfuric acid (conc.):ethanol (15 g : 2.5 mL : 250 mL). Flash chromatographic separations were carried out following protocols defined by Still *et al.*<sup>41</sup> with silica gel 60 (40–63  $\mu\text{m}$ ) as the stationary phase and using the AR- or HPLC-grade solvents indicated. The melting points of solids

purified by such means were recorded directly (ie after they had crystallized from the concentrated chromatographic fractions). Starting materials, reagents, drying agents and other inorganic salts were generally commercially available and used as supplied. THF, methanol and CH<sub>2</sub>Cl<sub>2</sub> were dried using a solvent purification system that is based upon a technology originally described by Grubbs *et al.*<sup>42</sup>

**Specific Chemical Transformations. (2*R*,3*R*,4*aS*,5*S*,8*R*,8*aS*)-6-(2-Hydroxy-3-methoxy-phenyl)-2,3-dimethoxy-2,3-dimethyl-2,3,4*a*,5,8,8*a*-hexahydrobenzo[*b*][1,4]dioxine-5,8-diol (13) and Enantiomer *ent*-13.** A magnetically stirred solution of *bis*-acetal **11**<sup>15</sup> (805 mg, 2.37 mmol), ester **12** (720 mg, 2.88 mmol) and triethylamine (3 mL) in THF/water (20 mL of a 9:1 v/v mixture) was subject to sonication under an atmosphere of nitrogen for 0.5 h. PdCl<sub>2</sub>dppf•CH<sub>2</sub>Cl<sub>2</sub> (140 mg, 0.191 mmol) was then added and the ensuing mixture heated under reflux for 2 h before being cooled and quenched with phosphate buffer (5 mL of a 1 M aqueous solution at pH 7). The mixture thus obtained was cooled to 0 °C, treated with methanol/30% aq. hydrogen peroxide (10 mL of a 1:1 v/v mixture) and then allowed to warm to room temperature over 1 h. The resulting mixture was diluted with water (50 mL) and extracted with ethyl acetate (5 × 20 mL). The combined organic phases were washed with brine (2 × 20 mL) before being dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The ensuing thick, orange oil was triturated with diethyl ether (5 × 2 mL) and the resulting yellow solid subject to flash column chromatography (silica, 4:15:1 v/v ethyl acetate/hexane/methanol → 12:7:1 v/v ethyl acetate/hexane/methanol gradient elution). Concentration of the appropriate fractions (*R*<sub>f</sub> = 0.3 in 10:9:1 v/v/v ethyl acetate/hexane/methanol) afforded phenol **13** (618 mg, 68%) as a white powder, m.p. = 202–210 °C, [ $\alpha$ ]<sub>D</sub><sup>20</sup> = –93.8 (*c* = 0.1, methanol). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  6.89 (dd, *J* = 7.5 and 1.8 Hz,

1H), 6.83–6.73 (complex m, 2H), 5.76 (d,  $J = 2.5$  Hz, 1H), 4.60 (d,  $J = 3.7$  Hz, 1H), 4.23 (dd,  $J = 8.0$  and  $2.5$  Hz, 1H), 4.09 (dd,  $J = 11.0$  and  $8.0$  Hz, 1H), 3.85 (s, 3H), 3.69 (dd,  $J = 11.0$  and  $3.7$  Hz, 1H), 3.34 (s, 3H), 3.28 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H) (signals due to hydroxyl protons not observed);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  149.0, 145.0, 138.9, 132.9, 128.6, 123.6, 120.3, 112.2, 100.7, 100.3, 71.4, 70.7, 69.7, 69.0, 56.6, 48.3, 48.2, 18.1(5), 18.1(0); IR  $\nu_{\text{max}}$  3456, 3283, 2941, 1589, 1468, 1218, 1129, 1119, 914, 594  $\text{cm}^{-1}$ ; MS (ESI, +ve)  $m/z$  788  $[(2\text{M} + \text{Na})^+, 80\%]$ , 405  $[(\text{M} + \text{Na})^+, 100]$ ; HRMS (ESI, +ve)  $m/z$   $(\text{M} + \text{Na})^+$  calcd for  $\text{C}_{19}\text{H}_{26}\text{NaO}_8$  405.1525, found 405.1526.

Compound *ent*-**13** was prepared in an analogous fashion from *ent*-**11** (2.04 g, 5.34 mmol) to give 1.60 g (71%) of product,  $[\alpha]_{\text{D}}^{20} = +86.4$  ( $c = 0.1$ , methanol). All the other spectral data acquired on this material were identical with those reported above for compound **13**.

**(2R,3R,4aS,5R,11aR,11bS)-2,3,10-Trimethoxy-2,3-dimethyl-2,3,4a,5,11a,11b-hexahydrobenzo[*b*][1,4]dioxino[2,3-*g*]benzofuran-5-ol (14) and Enantiomer *ent*-14.** A magnetically stirred solution of phenol **13** (605 mg, 1.58 mmol) and  $\text{PPh}_3$  (456 mg, 1.74 mmol) in THF (70 mL) maintained at  $-5$  °C was treated, dropwise over 0.5 h, with di-*iso*-propyl azodicarboxylate (364  $\mu\text{L}$ , 1.74 mmol). The resulting solution was stirred at  $-5$  °C for 4 h then allowed to warm to room temperature over 1 h before being concentrated under reduced pressure. The orange oil thus obtained was subjected to two successive flash chromatographic separations (silica, hexane  $\rightarrow$  1:1 v/v ethyl acetate/hexane gradient elution) and concentration of appropriate fractions ( $R_f = 0.7$ , 2:1 v/v ethyl acetate/hexane) afforded allylic alcohol **14** (193 mg, 33%) as a white foam,  $[\alpha]_{\text{D}}^{20} = -157$  ( $c = 0.6$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.99 (dd,  $J = 7.5$  and  $1.2$  Hz, 1H), 6.89 (apparent t,  $J = 7.5$  Hz, 1H),

6.82 (dd,  $J = 8.1$  and  $1.2$  Hz, 1H), 5.81 (m, 1H), 5.14 (dt,  $J = 9.0$  and  $3.6$  Hz, 1H), 4.67–4.61 (complex m, 1H), 4.04 (dd,  $J = 10.5$  and  $9.0$  Hz, 1H), 3.93 (dd,  $J = 10.5$  and  $7.7$  Hz, 1H), 3.88 (s, 3H), 3.34 (s, 6H), 2.34 (d,  $J = 4.8$  Hz, 1H), 1.36(3) (s, 3H), 1.35(9) (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  151.6, 145.4, 139.1, 125.7, 122.1, 116.2, 113.6, 113.5, 99.2, 98.9, 84.0, 74.1, 71.3, 70.1, 56.0, 48.4, 48.0, 17.7, 17.6; IR  $\nu_{\text{max}}$  3486, 2959, 2897, 1614, 1597, 1494, 1445, 1133, 1114, 1098, 1035, 1015, 786  $\text{cm}^{-1}$ ; MS (ESI, +ve)  $m/z$  752 [(2M + Na) $^+$ , 25%], 387 [(M + Na) $^+$ , 100%]; HRMS (ESI, +ve)  $m/z$  (M + Na) $^+$  calcd for  $\text{C}_{19}\text{H}_{24}\text{NaO}_7$  387.1420, found 387.1423.

Compound *ent*-**14** was prepared in an analogous fashion from *ent*-**13** (345 mg, 0.90 mmol) to give 314 mg (96%) of product,  $[\alpha]_{\text{D}}^{20} = +102$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ). All the other spectral data acquired on this material were identical with those reported above for compound **14**.

***N,N*-Dimethyl-2-((2*R*,3*R*,4*aS*,6*aS*,11*aR*,11*bR*)-2,3,10-trimethoxy-2,3-dimethyl-2,3,11*a*,11*b*-tetrahydrobenzo[*b*][1,4]dioxino[2,3-*g*]benzofuran-6*a*(4*aH*)-yl)acetamide (15) and Enantiomer *ent*-15.** A magnetically stirred solution of allylic alcohol **14** (180 mg, 0.494 mmol) in toluene (20 mL) maintained at 22 °C was treated with *N,N*-dimethylacetamide dimethyl acetal (900  $\mu\text{L}$ , 4.9 mmol) and the resulting solution heated under reflux for 18 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained was triturated with diethyl ether. The resulting waxy solid was subjected to flash chromatography (silica, 20:79:1 v/v ethyl acetate/hexane/methanol  $\rightarrow$  60:39:1 v/v ethyl acetate/hexane/methanol gradient elution) and concentration of appropriate fractions ( $R_f = 0.2$  in 2:1 v/v ethyl acetate/hexane) afforded amide **15** (178 mg 84%) as a white foam,  $[\alpha]_{\text{D}}^{20} = -89.9$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.83 (m, 1H),

6.75 (d,  $J = 7.8$  Hz, 1H), 6.72 (d,  $J = 7.6$  Hz, 1H), 6.02 (dd,  $J = 10.0$  and  $2.7$  Hz, 1H), 5.74 (dd,  $J = 10.0$  and  $2.0$  Hz, 1H), 5.04 (d,  $J = 9.6$  Hz, 1H), 4.55 (dt,  $J = 9.6$  and  $2.0$  Hz, 1H), 3.85 (s, 3H), 3.76 (t,  $J = 9.6$  Hz, 1H), 3.30 (s, 3H), 3.16 (s, 3H), 2.89 (s, 3H), 2.78 (s, 3H), 2.71 (d,  $J = 15.8$  Hz, 1H), 2.61 (d,  $J = 15.8$  Hz, 1H), 1.34 (s, 3H), 1.28 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  169.0, 145.6(4), 145.5(6), 134.2, 128.9, 126.9, 121.5, 115.3, 112.0, 99.8, 87.1, 70.5, 65.9, 56.1, 51.0, 48.1, 47.4, 42.5, 37.3, 35.3, 17.7(4), 17.7(0) (one signal obscured or overlapping); IR  $\nu_{\text{max}}$  2954, 2889, 1651, 1491, 1459, 1380, 1276, 1115, 1061, 1000, 954, 739  $\text{cm}^{-1}$ ; MS (ESI, +ve)  $m/z$  456 [(M + Na) $^+$ , 100%], 201 (35); HRMS (ESI, +ve)  $m/z$  (M + Na) $^+$  calcd for  $\text{C}_{23}\text{H}_{31}\text{NNaO}_7$  456.1998, found 456.2000.

Compound *ent*-**15** was prepared in an analogous fashion from *ent*-**14** (234 mg, 0.64 mmol) to give 238 mg (86%) of product as a white foam. A small sample was crystallised (diethyl ether/methanol/hexane) to give a white, crystalline solid, mp = 160–165 °C (decomposition),  $[\alpha]_{\text{D}}^{20} = +87.1$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ). All the other spectral data acquired on this material were identical with those reported above for compound **15**.

**2-((2*R*,3*R*,4*aS*,6*aS*,11*aR*,11*bR*)-2,3,10-Trimethoxy-2,3-dimethyl-2,3,11*a*,11*b*-tetrahydrobenzo[*b*][1,4]dioxino[2,3-*g*]benzofuran-6*a*(4*aH*)-yl)ethan-1-ol (16) and Enantiomer *ent*-**16**.** A magnetically stirred solution of amide **15** (146 mg, 0.337 mmol) in THF (17 mL) maintained at 0 °C was treated, dropwise, with lithium triethylborohydride (1.7 mL of a 1 M solution in THF, 1.7 mmol). The resulting mixture was warmed to room temperature over 2 h, re-cooled to 0 °C, quenched with methanol (2 mL) and then treated with silica (200 mg of flash chromatographic grade material) before being subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane  $\rightarrow$  1:1 v/v ethyl acetate/hexane gradient elution). Concentration of relevant fractions ( $R_f = 0.6$ , 2:1 v/v ethyl acetate/hexane) afforded

compound **16** (122 mg, 92%) as a white foam,  $[\alpha]_D^{20} = -131.9$  ( $c = 1.8$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.84 (apparent t,  $J = 7.8$  Hz, 1H), 6.74 (m, 1H), 6.69 (dd,  $J = 7.5$  and 1.2 Hz, 1H), 5.91 (broad d,  $J = 10.0$  Hz, 1H), 5.70 (broad d,  $J = 10.0$  Hz, 1H), 4.89 (d,  $J = 9.6$  Hz, 1H), 4.31 (ddd,  $J = 9.6$ , 2.7 and 1.5 Hz, 1H), 3.84 (s, 3H), 3.72 (t,  $J = 9.6$  Hz, 1H), 3.67–3.57 (complex m, 2H), 3.28 (s, 3H), 3.17 (s, 3H), 1.96 (dt,  $J = 13.7$  and 6.7 Hz, 1H), 1.85 (dt,  $J = 13.7$  and 6.4 Hz, 1H), 1.40 (broad singlet, 1H), 1.34 (s, 3H), 1.28 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  145.7, 145.4, 133.6, 130.1, 126.4, 121.8, 114.9, 112.0, 99.9, 99.7, 86.9, 70.8, 65.4, 59.3, 56.1, 51.7, 48.0, 47.5, 43.5, 17.7, 17.6; IR  $\nu_{\text{max}}$  3508, 2948, 2837, 1619, 1588, 1491, 1459, 1281, 1130, 1116, 1036, 753, 736  $\text{cm}^{-1}$ ; MS (ESI, +ve)  $m/z$  415  $[(\text{M} + \text{Na})^+]$ , 100%]; HRMS (ESI, +ve)  $m/z$   $(\text{M} + \text{Na})^+$  calcd for  $\text{C}_{21}\text{H}_{28}\text{NaO}_7$  415.1733, found 415.1733.

Compound *ent*-**16** was prepared in an analogous fashion from *ent*-**15** (177 mg, 0.408 mmol) to give 160 mg (quantitative) of product,  $[\alpha]_D^{20} = +108$  ( $c = 0.9$ ,  $\text{CHCl}_3$ ). All the other spectral data acquired on this material were identical with those reported above for compound **16**.

**2-((2R,3R,4aS,6aS,11aR,11bR)-2,3,10-Trimethoxy-2,3-dimethyl-2,3,11a,11b-tetrahydrobenzo[b][1,4]dioxino[2,3-g]benzofuran-6a(4aH)-yl)acetic acid (17) and Enantiomer *ent*-17.** A magnetically stirred solution of alcohol **16** (122 mg, 0.310 mmol) in acetonitrile/water (9:1 v/v, 2.3 mL) maintained at room temperature was treated, in one portion, with 4-(acetylamino)-2,2,6,6-tetramethyl-1-oxo-piperidinium tetrafluoroborate (280 mg, 0.93 mmol). The resulting dark-brown solution was stirred at 22 °C for 48 h (by which time it was a pale-yellow color) then poured into water (3 mL) and extracted with diethyl ether ( $5 \times 4$  mL). The combined organic extracts were washed with HCl ( $2 \times 1$  mL of a 1 M aqueous solution) and brine ( $2 \times 5$  mL) before being dried ( $\text{Na}_2\text{SO}_4$ ), filtered and

concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, CH<sub>2</sub>Cl<sub>2</sub> → 1:19 v/v methanol/CH<sub>2</sub>Cl<sub>2</sub> gradient elution) and concentration of appropriate fractions ( $R_f = 0.2$  in 1:19 v/v methanol/CH<sub>2</sub>Cl<sub>2</sub>) afforded acid **17** (96 mg, 76%) as a clear, colorless gum,  $[\alpha]_D^{20} = -88.5$  ( $c = 0.6$ , CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.85 (m, 1H), 6.76 (d,  $J = 7.4$  Hz, 1H), 6.74 (d,  $J = 7.4$  Hz, 1H), 5.96 (dd,  $J = 10.0$  and 2.6 Hz, 1H), 5.77 (d,  $J = 10.0$  Hz, 1H), 5.17 (d,  $J = 9.7$  Hz, 1H), 4.40 (d,  $J = 9.7$  Hz, 1H), 3.85 (s, 3H), 3.75 (t,  $J = 9.7$  Hz, 1H), 3.29 (s, 3H), 3.17 (s, 3H), 2.76 (d,  $J = 15.6$  Hz, 1H), 2.63 (d,  $J = 15.6$  Hz, 1H), 1.36 (s, 3H), 1.28 (s, 3H) (signal due to carboxylic acid group proton not observed); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  174.8, 145.6, 132.9, 128.1, 127.9, 121.9, 115.0, 112.3, 99.9, 99.8, 86.0, 70.5, 65.5, 56.1, 50.9, 48.0, 47.5, 44.0, 17.7 (signals due to two carbons obscured or overlapping); IR  $\nu_{max}$  2950, 1710, 1712, 1619, 1491, 1459, 1284, 1128, 1116, 1034, 960, 732 cm<sup>-1</sup>; MS (ESI, +ve)  $m/z$  429 [(M + Na)<sup>+</sup>, 100%]; HRMS (ESI, +ve)  $m/z$  (M + Na)<sup>+</sup> calcd for C<sub>21</sub>H<sub>26</sub>NaO<sub>8</sub> 429.1525, found 429.1524.

Compound *ent*-**17** was prepared in an analogous fashion from *ent*-**16** (150 mg, 0.382 mmol) to give 115 mg (80%) of product,  $[\alpha]_D^{20} = +95.7$  ( $c = 1.2$ , CHCl<sub>3</sub>). All the other spectral data acquired on this material were identical with those reported above for compound **17**.

***N*-Methyl-2-((2*R*,3*R*,4*aS*,6*aS*,11*aR*,11*bR*)-2,3,10-trimethoxy-2,3-dimethyl-2,3,11*a*,11*b*-tetrahydrobenzo[*b*][1,4]dioxino[2,3-*g*]benzofuran-6*a*(4*aH*)-*yl*)acetamide (5) and Enantiomer *ent*-5.** A magnetically stirred solution of acid **17** (93 mg, 0.23 mmol) in THF (12 mL) maintained at room temperature was treated with 1,1'-carbonyldiimidazole (49 mg, 0.30 mmol). The resulting solution was heated under reflux for 1 h before being cooled to room temperature and then placed in an ice-bath at 0 °C. Methylamine (700  $\mu$ L of a 2M

solution in THF, 1.4 mmol) was then added dropwise and the ensuing solution maintained at 0 °C for 3 h before being warmed to 22 °C and stirred at this temperature for another 8 h. After this time the reaction mixture was diluted with ethyl acetate (40 mL) and washed with NH<sub>4</sub>Cl (3 × 15 mL of a saturated aqueous solution). The combined aqueous phases were extracted with ethyl acetate (3 × 10 mL) and the combined organic phases washed with brine (2 × 10 mL) before being dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:15:1 v/v ethyl acetate/hexane/methanol → 8:11:1 v/v ethyl acetate/hexane/methanol gradient elution) and concentration of appropriate fractions ( $R_f = 0.3$  in 10:9:1 v/v ethyl acetate/hexane/methanol) gave amide **5** (76 mg, 79%) as a clear, colorless oil,  $[\alpha]_D^{20} = -102.1$  ( $c = 1.2$ , CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.81 (m, 1H), 6.72 (dd,  $J = 8.0$  and 1.2 Hz, 1H), 6.68 (dd,  $J = 7.5$  and 1.2 Hz, 1H), 6.09 (dd,  $J = 10.0$  and 2.6 Hz, 1H), 5.72 (dd,  $J = 10.0$  and 1.5 Hz, 1H), 5.36 (broad q,  $J = 4.8$  Hz, 1H), 4.97 (d,  $J = 9.7$  Hz, 1H), 4.37 (ddd,  $J = 9.7$ , 2.6 and 1.5 Hz, 1H), 3.81 (s, 3H), 3.71 (t,  $J = 9.7$  Hz, 1H), 3.27 (s, 3H), 3.13 (s, 3H), 2.71 (d,  $J = 4.8$  Hz, 3H), 2.51 (d,  $J = 14.0$  Hz, 1H), 2.42 (d,  $J = 14.0$  Hz, 1H), 1.32 (s, 3H), 1.26 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 169.5, 145.5, 133.4, 128.7, 126.9, 121.6, 115.2, 112.1, 99.8, 99.7, 86.9, 70.3, 65.5, 56.0, 51.2, 48.0, 47.4, 46.8, 26.2, 17.7, 17.6 (signal due to one carbon obscured or overlapping); IR  $\nu_{\max}$  3317, 2952, 2921, 1646, 1548, 1491, 1457, 1377, 1197, 1114, 1034, 999, 955, 735 cm<sup>-1</sup>; MS (ESI, +ve)  $m/z$  442 [(M + Na)<sup>+</sup>, 100%]; HRMS (ESI, +ve)  $m/z$  (M + Na)<sup>+</sup> calcd for C<sub>22</sub>H<sub>29</sub>NNaO<sub>7</sub> 442.1842, found 442.1842.

Compound *ent*-**5** was prepared in an analogous fashion from *ent*-**17** (115 mg, 0.28 mmol) to give 91 mg (79%) of product,  $[\alpha]_D^{20} = +89.1$  ( $c = 1.3$ , CHCl<sub>3</sub>). All the other spectral data acquired on this material were identical with those reported above for

compound **5**.

**2-((5aR,6R,7S,9aS)-6,7-Dihydroxy-4-methoxy-6,7-dihydrodibenzo[*b,d*]furan-9a(5aH)-yl)-N-methylacetamide (6) and Enantiomer *ent*-6.** A round-bottomed flask charged with a magnetic stirrer bar and amide **5** (16.7 mg, 0.04 mmol) was treated sequentially with water (250  $\mu$ L) and trifluoroacetic acid (250  $\mu$ L) and the ensuing mixture stirred at 22 °C for 0.5 h then the volatiles were removed under reduced pressure. The residue thus obtained was subject to flash chromatography (silica, 5:4:1 v/v ethyl acetate/hexane/methanol) and concentration of appropriate fractions ( $R_f = 0.3$  in 8:1:1 v/v ethyl acetate/hexane/methanol) afforded diol **6** (8.1 mg, 66%) as a white foam,  $[\alpha]_D^{20} = -11$  ( $c = 0.4$ , methanol).  $^1\text{H NMR}$  [400 MHz,  $(\text{CD}_3)_2\text{CO}$ ]  $\delta$  7.04 (broad s, 1H), 6.84–6.74 (complex m, 3H), 6.00 (dd,  $J = 10.1$  and 2.3 Hz, 1H), 5.67 (dd,  $J = 10.1$  and 1.5 Hz, 1H), 5.25 (d,  $J = 8.7$  Hz, 1H), 4.75 (broad s, 1H), 4.22 (partially obscured and broad s, 1H), 4.18 (d,  $J = 8.7$  Hz, 1H), 3.82 (s, 3H), 3.40 (t,  $J = 8.7$  Hz, 1H), 2.63 (d,  $J = 4.6$  Hz, 3H), 2.48 (d,  $J = 13.9$  Hz, 1H), 2.41 (d,  $J = 13.9$  Hz, 1H);  $^{13}\text{C NMR}$  [100 MHz,  $(\text{CD}_3)_2\text{CO}$ ]  $\delta$  170.7, 146.9, 146.2, 135.5, 131.6, 128.5, 122.1, 116.1, 113.3, 90.4, 75.8, 69.9, 56.4, 51.6, 46.8, 25.9; IR  $\nu_{\text{max}}$  3315, 2943, 1642, 1491, 1272, 1199, 1179, 1132, 1064, 945, 723  $\text{cm}^{-1}$ ; MS (ESI, +ve)  $m/z$  634 [ $(2\text{M} + \text{Na})^+$ , 40], 328 [ $(\text{M} + \text{Na})^+$ , 100]; HRMS (ESI, +ve)  $m/z$   $(\text{M} + \text{Na})^+$  calcd for  $\text{C}_{16}\text{H}_{19}\text{NNaO}_5$  328.1161, found 328.1158.

Compound *ent*-**6** was prepared in an analogous fashion from *ent*-**5** (16.7 mg, 0.04 mmol) to give 11.8 mg (97%) of product,  $[\alpha]_D^{20} +16.7$  ( $c = 1.0$ , methanol). All the other spectral data acquired on this material were identical with those reported above for compound **6**.

**(4a*R*,5*R*,6*S*,8a*S*)-5,6-Dihydroxy-3-methoxy-11-methyl-4a,5,11,12-tetrahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-10(9*H*)-one (2) and Enantiomer *ent*-2.** A magnetically stirred solution of amide **5** (56 mg, 0.133 mmol) in acetonitrile (14 mL) was treated, sequentially, with paraformaldehyde (20 mg, 0.67 mmol) and trifluoroacetic acid (63  $\mu$ L, 0.82 mmol). The resulting solution was stirred at room temperature for 8 h then quenched with phosphate buffer (15 mL of a 1 M aqueous solution at pH 7) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  10 mL). The combined organic extracts were washed with brine (1  $\times$  5 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>) before being filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:15:1 v/v ethyl acetate/hexane/methanol  $\rightarrow$  8:1:1 v/v ethyl acetate/hexane/methanol gradient elution) and concentration of the appropriate fractions ( $R_f$  = 0.4 in 8:1:1 v/v ethyl acetate/hexane/methanol) afforded lactam **2** (19.7 mg, 47%) as a white, amorphous solid,  $[\alpha]_D^{20} = -139$  ( $c = 0.4$ , methanol). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.71 (apparent s, 2H), 5.97 (dd,  $J = 10.2$  and 4.7 Hz, 1H), 5.58 (d,  $J = 10.2$  Hz, 1H), 4.78–4.73 (complex m, 1H), 4.67–4.63 (complex m, 1H), 4.53 (d,  $J = 16.0$  Hz, 1H), 4.32 (d,  $J = 16.0$  Hz, 1H), 4.12 (m, 1H), 3.85 (s, 3H), 3.18 (d,  $J = 14.2$  Hz, 1H), 3.07 (d,  $J = 14.2$  Hz, 1H), 3.04 (s, 3H) (signals due to hydroxyl group protons not observed); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  171.8, 145.9, 144.8, 131.9, 128.7, 125.7, 125.1, 120.4, 111.9, 88.4, 68.5, 67.0, 56.1, 52.1, 43.2, 42.3, 35.9; IR  $\nu_{\max}$  3357, 2924, 1623, 1508, 1438, 1280, 1101, 1070, 1031, 971, 880, 793 cm<sup>-1</sup>; MS (ESI, +ve)  $m/z$  657 [(2M + Na)<sup>+</sup>, 40%], 340 [(M + Na)<sup>+</sup>, 100]; HRMS (ESI, +ve)  $m/z$  (M + Na)<sup>+</sup> calcd for C<sub>17</sub>H<sub>19</sub>NNaO<sub>5</sub> 340.1161, found 340.1159.

Compound *ent*-**2** was prepared in an analogous fashion from *ent*-**5** (20 mg, 0.048

mmol) to give 9.5 mg (63%) of product as a white, amorphous solid. A small sample was recrystallised (diethyl ether) to give a white, crystalline solid, mp = 135–140 °C,  $[\alpha]_{\text{D}}^{20} = +127$  ( $c = 0.4$ , methanol). All the other spectral data acquired on this material were identical with those reported above for compound **2**.

**(4aR,5R,6S,8aS)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6H-benzo[2,3]-benzofuro[4,3-cd]azepine-5,6-diol (3) and Enantiomer ent-3.** A magnetically stirred solution of lactam **2** (9.5 mg, 0.03 mmol) in THF (5 mL) maintained at room temperature was treated with  $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$  (60  $\mu\text{L}$  of a 60% w/v solution in toluene, 0.184 mmol) and the ensuing mixture heated under reflux for 24 h after which time it was cooled to 0 °C (ice-bath), quenched with potassium sodium tartrate (2 mL of a saturated aqueous solution), diluted with water (10 mL) then extracted with  $\text{CHCl}_3$  ( $3 \times 5$  mL). The combined organic extracts were washed with brine ( $1 \times 2$  mL) before being dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:19 v/v  $\text{NH}_3$  saturated methanol/ $\text{CHCl}_3 \rightarrow 1:9$  v/v  $\text{NH}_3$  saturated methanol/ $\text{CHCl}_3$  gradient elution) and concentration of appropriate fractions ( $R_f = 0.2$  in 1:9 v/v  $\text{NH}_3$  saturated methanol/ $\text{CHCl}_3$ ) afforded amine **3** (4.0 mg, 44%) as a white, amorphous solid,  $[\alpha]_{\text{D}}^{20} = -86.6$  ( $c = 0.3$ ,  $\text{CDCl}_3$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.66 (d,  $J = 8.2$  Hz, 1H), 6.63 (d,  $J = 8.2$  Hz, 1H), 6.23 (d,  $J = 10.2$  Hz, 1H), 5.93 (dd,  $J = 10.2$  and 3.8 Hz, 1H), 4.57 (d,  $J = 4.6$  Hz, 1H), 4.30 (m, 1H), 4.19–4.09 (complex m, 2H), 3.84 (s, 3H), 3.63 (m, 1H), 3.27 (m, 1H), 2.98 (broad d,  $J = 14.8$  Hz, 1H), 2.34 (s, 3H), 2.18 (m, 1H), 1.81 (dd,  $J = 13.4$  and 2.2 Hz, 1H) (signals due to hydroxyl group protons not observed);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  145.4, 144.0, 132.3, 129.1, 128.1, 126.6, 122.4, 111.1, 90.9, 72.4, 67.6, 60.1, 55.9, 54.2, 49.8, 42.0, 36.0; IR  $\nu_{\text{max}}$  3345, 2921, 1626, 1596, 1507, 1439, 1282, 1041, 948,

793, 726  $\text{cm}^{-1}$ ; MS (ESI, +ve)  $m/z$  629  $[(2M + \text{Na})^+, 30\%]$ , 326  $[(M + \text{Na})^+, 100]$ , 304  $[(M + \text{H})^+, 7]$ ; HRMS (ESI, +ve)  $m/z$   $(M + \text{H})^+$  calcd for  $\text{C}_{17}\text{H}_{22}\text{NO}_4$  304.1549, found 304.1544.

Compound *ent-3* was prepared in an analogous fashion from *ent-2* (9.5 mg, 0.030 mmol) to give 4.0 mg (44%) of product,  $[\alpha]_{\text{D}}^{20} +60.5$  ( $c = 0.4$ ,  $\text{CDCl}_3$ ). All the other spectral data acquired on this material were identical with those reported above for compound **3**.

**2-((5aR,6R,7S,9aS)-6,7-Dihydroxy-4-methoxy-6,7-dihydrodibenzo[*b,d*]furan-9a-(5aH)-yl)-*N,N*-dimethylacetamide (4) and Enantiomer *ent-4*.** Amide **15** (15 mg, 0.035 mmol) was treated trifluoroacetic acid/water (200  $\mu\text{L}$  mixture) and the resulting mixture stirred at 22 °C for 0.5 h then the volatiles were removed under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:19 v/v methanol/ $\text{CH}_2\text{Cl}_2$ ) and concentration of the relevant fractions ( $R_f = 0.1$ ) afforded diol **4** (9.8 mg, 88%) as a clear, colorless oil,  $[\alpha]_{\text{D}}^{20} = +5.7$  ( $c = 0.9$ ,  $\text{CH}_3\text{OH}$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.86 (m, 1H), 6.78–6.73 (complex m, 2H), 5.98 (d,  $J = 9.9$  Hz, 1H), 5.83 (d,  $J = 9.9$  Hz, 1H), 5.01 (d,  $J = 7.5$  Hz, 1H), 4.45 (broad s, 1H), 3.85 (s, 3H), 3.71 (m, 1H), 2.88 (s, 3H), 2.81 (s, 3H), 2.79 (m, 1H), 2.58 (d,  $J = 15.8$  Hz, 1H) (signals due to hydroxyl protons not observed);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  169.7, 145.5, 145.3, 134.1, 129.4, 128.5, 122.0, 115.4, 111.9, 90.5, 74.4, 69.2, 56.1, 50.1, 42.7, 37.5, 35.6; IR  $\nu_{\text{max}}$  3389, 2927, 1616, 1489, 1457, 1402, 1271, 1093, 1058, 941, 749, 731  $\text{cm}^{-1}$ ; MS (ESI, +ve)  $m/z$  661  $[(2M + \text{Na})^+, 40\%]$ , 342  $[(M + \text{Na})^+, 100]$ ; HRMS (ESI, +ve)  $m/z$   $(M + \text{Na})^+$  calcd for  $\text{C}_{17}\text{H}_{21}\text{NNaO}_5$  342.1317, found 342.1311.

Compound *ent-4* was prepared in an analogous fashion from *ent-15* (23.7 mg, 0.055 mmol) to give 13.4 mg (77%) of product,  $[\alpha]_{\text{D}}^{20} -8.2$  ( $c = 1.3$ , methanol). All the other spectral data acquired on this material were identical with those reported above for

compound **4**.

**(1S,2S,3S,6S)-4-Bromo-6-((4-methoxybenzyl)oxy)cyclohex-4-ene-1,2,3-triol (21).**

**Step i:** BF<sub>3</sub>•OEt<sub>2</sub> (100 ~~mg~~) was added dropwise over 0.25 h, to a magnetically stirred solution of epoxide **20**<sup>23</sup> (2.00 g, 8.09 mmol) and *p*-methoxybenzyl alcohol (23.8 g, 175 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (80 mL) maintained at -20 °C. The resulting solution was allowed to warm to -10 °C over 2 h after which time a second aliquot of BF<sub>3</sub>•OEt<sub>2</sub> (150 ~~mg~~) was added dropwise over 0.25 h. The reaction mixture thus formed was warmed to 22 °C over 12 h then quenched with phosphate buffer (3 mL of a 1 M aqueous solution at pH 7) and the solvent then removed under reduced pressure. The residue thus obtained, which was comprised of a mixture of the desired PMB-ether and *p*-methoxybenzyl alcohol, was submitted directly to *step ii* as detailed immediately below.

**Step ii:** A magnetically stirred solution of the material obtained from *step i* in methanol (160 mL) was treated with pyridinium *p*-toluenesulfonate (2.03 g, 8.09 mmol) and the mixture so formed heated at 50 °C for 48 h after which time it was cooled to 22 °C then treated with NaHCO<sub>3</sub> (500 mg) and the solvent removed under reduced pressure. The residue thus obtained was treated with ethyl acetate (200 mL) then water (100 mL) and the separated aqueous layer extracted with ethyl acetate (4 × 50 mL). The combined organic phases were washed with brine (1 × 30 mL) then dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The resulting yellow oil was subject to flash column chromatography (silica, CH<sub>2</sub>Cl<sub>2</sub> → 1:19 v/v methanol/CH<sub>2</sub>Cl<sub>2</sub> gradient elution) and concentration of appropriate fractions (*R*<sub>f</sub> = 0.2 in 1:19 v/v methanol/CH<sub>2</sub>Cl<sub>2</sub>) afforded triol **21** (1.98 g, 71% from **20**), as a white foam, [α]<sub>D</sub><sup>20</sup> = +132.1 (*c* 1.1, CHCl<sub>3</sub>). <sup>1</sup>H NMR [400

MHz, (CD<sub>3</sub>)<sub>2</sub>CO]  $\delta$  7.32 (d,  $J$  = 8.8 Hz, 2H), 6.89 (d,  $J$  = 8.8 Hz, 2H), 6.14 (d,  $J$  = 2.4 Hz, 1H), 4.67 (s, 2H), 4.58 (d,  $J$  = 5.1 Hz, 1H), 4.27–4.20 (complex m, 2H), 4.03 (broad s, 1H), 3.86 (dd,  $J$  = 7.4 and 2.0 Hz, 1H), 3.82 (broad d,  $J$  = 9.7 Hz, 1H), 3.78 (s, 3H), 3.54 (m, 1H); <sup>13</sup>C NMR [100 MHz, (CD<sub>3</sub>)<sub>2</sub>CO]  $\delta$  160.2, 132.8, 131.8, 130.2, 124.8, 114.4, 80.8, 74.1, 72.3(2), 72.2(5), 71.8, 55.5; IR (KBr)  $\nu_{\text{max}}$  3437, 2918, 2848, 1732, 1449, 1368, 1241, 1072, 1026 cm<sup>-1</sup>; MS (ESI, +ve)  $m/z$  369 and 367 [(M + Na)<sup>+</sup>, 100 and 98%]; HRMS (ESI, +ve)  $m/z$  (M + Na)<sup>+</sup> calcd for C<sub>14</sub>H<sub>17</sub><sup>79</sup>Br NaO<sub>5</sub> 367.0155, found 367.0157.

**(2*S*,3*S*,4*aR*,5*S*,8*S*,8*aR*)-6-Bromo-2,3-dimethoxy-2,3-dimethyl-2,3,4*a*,5,8,8*a*-hexahydrobenzo[*b*][1,4]dioxine-5,8-diol (*ent*-**11**).** A magnetically stirred solution of the triol **21** (2.57 g, 7.44 mmol), 2,2,3,3-tetramethoxybutane (1.91 g, 10.7 mmol) and trimethyl orthoformate (3.40 mL, 31.1 mmol) in dry methanol (50 mL) was treated with *p*-TsOH•H<sub>2</sub>O (73 mg, 5 mol%). The resulting mixture was heated under reflux for 24 h, cooled to 22 °C, treated with NaHCO<sub>3</sub> (2.00 g) and the solvent removed under reduced pressure. The residue thus obtained was treated with ethyl acetate (100 mL) then NaHCO<sub>3</sub> (30 mL of a saturated aqueous solution). The separated organic phase was washed with NaHCO<sub>3</sub> (1 x 30 mL of a saturated aqueous solution) and water (1 x 30 mL) then the combined aqueous layers extracted with ethyl acetate (3 x 30 mL). The combined organic phases were washed with brine (2 x 20 mL) then dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The resulting thick, orange oil was subjected to flash column chromatography (silica, 1:20 v/v methanol/CH<sub>2</sub>Cl<sub>2</sub> elution) and concentration of appropriate fractions ( $R_f$  = 0.3) afforded bis-acetal *ent*-**11** (2.14 g, 85%) as a white foam,  $[\alpha]_{\text{D}}^{20} = +72.6$  ( $c$  = 1.1, CHCl<sub>3</sub>) {lit.<sup>15</sup> (for **11**),  $[\alpha]_{\text{D}}^{20} = -76.5$  ( $c$  = 1.0, CHCl<sub>3</sub>)}. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  6.05 (d,  $J$  = 2.5 Hz, 1H), 4.22 (d,  $J$  = 4.1 Hz, 1H), 4.06 (dd,  $J$  = 7.9 and 2.5 Hz, 1H), 3.87 (dd,  $J$  = 11.1 and 7.9 Hz,

1H), 3.63 (dd,  $J = 11.1$  and  $4.1$  Hz, 1H), 3.30 (s, 3H), 3.25 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H) (signals due to hydroxyl group protons not observed);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  135.2, 124.0, 100.8, 100.2, 73.1, 71.8, 69.8, 69.2, 48.3, 48.2, 18.1, 18.0; IR (KBr)  $\nu_{\text{max}}$  3160, 2940, 1636, 1454, 1375, 1136, 1077, 1031, 980, 915  $\text{cm}^{-1}$ ; MS (ESI, +ve)  $m/z$  363 and 361 [(M + Na)<sup>+</sup>, 95 and 100%]; HRMS (ESI, +ve) (M+Na)<sup>+</sup> calcd for  $\text{C}_{12}\text{H}_{19}^{79}\text{BrNaO}_6$  361.0263, found 361.0263.

**3-Bromo-4-hydroxy-5-methoxybenzaldehyde (23).** A magnetically stirred solution of vanillin (**22**) (4.00 g, 26.3 mmol) in acetic acid (10 mL) was treated with molecular bromine (1.34 mL, 0.03 mol) and the ensuing mixture stirred at 22 °C for 3 h and during which time a precipitate appeared. The reaction mixture was quenched with water (30 mL) and the precipitate was filtered off, washed with water (1 × 50 mL) then methanol (1 × 20 mL) before being dried under vacuum to afford compound **23**<sup>28</sup> (5.40 g, 90%) as a white, crystalline solid, mp = 164 °C (lit.<sup>28</sup> mp = 160-162 °C).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  9.79 (s, 1H), 7.64 (d,  $J = 1.7$  Hz, 1H), 7.36 (d,  $J = 1.7$  Hz, 1H), 6.52 (s, 1H), 3.99 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  189.6, 148.9, 147.7, 130.1, 130.0, 108.2, 108.0, 56.6; IR  $\nu_{\text{max}}$  3305, 2980, 1674, 1590, 1463, 1290, 1157, 1047, 680  $\text{cm}^{-1}$ ; MS (ESI, +ve)  $m/z$  255 and 253 [(M+Na)<sup>+</sup>, 100 and 99%]; HRMS (ESI, +ve) (M+Na)<sup>+</sup> calcd for  $\text{C}_8\text{H}_7^{79}\text{BrNaO}_3$  252.9476, found 252.9479.

**2-Bromo-4-(1,3-dioxolan-2-yl)-6-methoxyphenol (24).** Compound **23** (5.00 g, 21.8 mmol), toluene (120 mL), *p*-TsOH·H<sub>2</sub>O (39 mg, 0.21 mmol) and ethylene glycol (3.60 mL, 65.2 mmol) were placed in a round-bottom flask fitted with a Dean-Stark trap and condenser. The ensuing mixture was heated under reflux for 5 h before being cooled, quenched with  $\text{NaHCO}_3$  (100 mL of a saturated solution) and extracted with ethyl acetate (1 × 100 mL). The

organic phase was dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure and the light-yellow oil thus obtained subjected flash chromatography (silica, 5:1 v/v hexane/ethyl acetate elution). Concentration of the relevant fractions ( $R_f = 0.4$  in 1:9 v/v ethyl acetate/hexane) gave compound **24** (3.30 g, 55%) as a light-yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.24 (d,  $J = 1.5$  Hz, 1H), 6.94 (d,  $J = 1.5$  Hz, 1H), 5.97 (s, 1H), 5.71 (s, 1H), 4.14–4.11 (complex m, 2H), 4.04–3.98 (complex m, 2H), 3.92 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  147.2, 143.8, 130.7, 123.2, 108.0, 107.9, 102.9, 65.2, 56.4; IR  $\nu_{\text{max}}$  3358, 2963, 2887, 1684, 1603, 1589, 1503, 1466, 1426, 1280, 1181, 1090, 1044  $\text{cm}^{-1}$ ; MS (ESI, +ve)  $m/z$  299 and 297 [(M+Na) $^+$ , 92 and 100%] 277 and 275 [(M+H) $^+$ , 45 and 40]; HRMS (ESI, +ve) (M+H) $^+$  calcd for  $\text{C}_{10}\text{H}_{12}^{79}\text{BrNaO}_4$  274.9919, found 274.9921.

**2-(3-Bromo-5-methoxy-4-(methoxymethoxy)phenyl)-1,3-dioxolane (25).** A magnetically stirred mixture of phenol **24** (3.23 g, 11.79 mmol) in dry THF (30 mL) maintained at 0 °C was treated with NaH (564 mg of a 60% suspension in oil, 14.2 mmol). After 0.5 h the reaction mixture was treated with chloromethyl methyl ether (980  $\mu\text{L}$ , 12.9 mmol) and then stirred at 22 °C for 18 h before being quenched with water (100 mL, CAUTION: possibility of evolution of hydrogen gas). The separated aqueous layer was extracted with diethyl ether (3  $\times$  30 mL) and the combined organic phases were washed with brine (1  $\times$  30 mL) then dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and gave, after concentration of the relevant fractions ( $R_f = 0.5$  in 1:3 v/v ethyl acetate/hexane), bromide **25** (2.65 g, 70%) as a clear, colorless oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7.28 (d,  $J = 1.9$  Hz, 1H), 6.98 (d,  $J = 1.9$  Hz, 1H), 5.74 (s, 1H), 5.17 (s, 2H), 4.13–4.01 (complex m, 4H), 3.86 (s, 3H), 3.64 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$

153.3, 143.9, 135.1, 123.1, 117.6, 109.6, 102.6, 98.6, 65.3, 58.0, 56.1; IR  $\nu_{\max}$  2941, 2891, 2839, 1696, 1570, 1484, 1463, 1416, 1384, 1274, 1157, 1081, 1043, 942, 854  $\text{cm}^{-1}$ ; MS (EI, 70 eV)  $m/z$  320 and 318 ( $M^+$ , 99 and 100%), 289 and 287 (55 and 53), 239 (85), 166 (25); HRMS (EI, 70 eV)  $M^+$  calcd for  $\text{C}_{12}\text{H}_{15}^{79}\text{BrO}_5$  318.0103, found 318.0104.

**4-Hydroxy-3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (27).** *Step i.* A magnetically stirred mixture of bromide **25** (1.30 g, 4.15 mmol) in dry THF (15 mL) maintained at  $-78\text{ }^\circ\text{C}$  was treated with *n*-BuLi (3.1 mL of a 1.6 M solution in THF, 5.0 mmol). After 1 h the reaction mixture was treated with tri-*iso*-propyl borate (1.9 mL, 8.3 mmol) and then stirred at  $22\text{ }^\circ\text{C}$  for 15 h before being quenched with HCl (10 mL of a 10% w/v aqueous solution). The separated aqueous layer was extracted with ethyl acetate ( $3 \times 50\text{ mL}$ ) and the combined organic phases were washed with brine ( $1 \times 50\text{ mL}$ ) before being dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated under reduced pressure. The residue thus obtained, and which is presumed to contain boronic acid **26**, was subjected directly to *step ii* of the reaction sequence.

*Step ii.* A magnetically stirred mixture of the product obtained from *step i* in dry acetonitrile (40 mL) maintained at  $0\text{ }^\circ\text{C}$  was treated with sodium iodide (0.62 g, 14.5 mmol) and chlorotrimethylsilane (530  $\mu\text{L}$ , 14.5 mmol). The resulting solution was warmed to  $22\text{ }^\circ\text{C}$  over 4 h then treated with  $\text{Na}_2\text{S}_2\text{O}_3$  (20 mL of a saturated aqueous solution). The separated aqueous layer was extracted with ethyl acetate ( $3 \times 20\text{ mL}$ ) and the combined organic phases were washed with brine ( $1 \times 20\text{ mL}$ ) before being dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated under reduced pressure. The residue thus obtained was immediately subjected to *step iii* of the reaction sequence.

*Step iii.* A magnetically stirred suspension of the product obtained from *step ii* in benzene (30 mL) was treated with pinacol (990 mg, 8.40 mmol) and the solution thus obtained heated under reflux for 2 h in an apparatus fitted with a Dean–Stark trap and a condenser. The cooled reaction mixture was treated with water (20 mL) and the separated aqueous layer extracted with ethyl acetate (3 × 20 mL). The combined organic phases were then washed with brine (1 × 50 mL) before being dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 2:3 v/v diethyl ether/hexane elution) to afford, after concentration of the relevant fractions (*R<sub>f</sub>* = 0.4), boronic ester **27** (520 mg, 45% from **25**) as a white, crystalline solid, mp = 73 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.82 (s, 1H), 8.33 (s, 1H), 7.72 (d, *J* = 1.9 Hz, 1H), 7.49 (d, *J* = 1.9 Hz, 1H), 3.93 (s, 3H), 1.38 (s, 12H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 190.9, 158.6, 148.3, 133.8, 129.6, 111.7, 85.1, 56.0, 24.8; IR *v*<sub>max</sub> 3407, 2992, 2931, 2830, 2797, 2714, 1683, 1620, 1587, 1467, 1388, 1372, 1298, 1256, 1140, 1056, 980, 846, 674 cm<sup>-1</sup>; MS (EI, 70 eV) *m/z* 278 (M<sup>+</sup>, 38%), 221 (100), 178 (51), 177 (30); HRMS (EI, 70 eV) M<sup>+</sup> calcd for C<sub>14</sub>H<sub>19</sub>BO<sub>5</sub> 278.1326, found 278.1326.

**(3a*S*,4*S*,5*S*,7a*S*)-7-Bromo-2,2-dimethyl-5-((tri-*iso*-propylsilyl)oxy)-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-ol (29).** Tri-*iso*-propylsilyl trifluoromethanesulfonate (1.95 mL, 7.3 mmol) was added, dropwise, to a magnetically stirred solution of compound **28**<sup>29</sup> (1.40 g, 5.3 mmol) and 2,6-lutidine (2.5 mL, 21.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) maintained at -78 °C under a nitrogen atmosphere. The ensuing mixture was allowed to warm to 22 °C over 3 h then treated with NH<sub>4</sub>Cl (60 mL of a saturated aqueous solution). The separated aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (1 × 20 mL) and the combined organic phases were dried (MgSO<sub>4</sub>), filtered, and concentrated under reduced pressure. The resulting light yellow-oil

was subjected to flash chromatography (silica, 3:100 v/v ethyl acetate/hexane elution) and gave, after concentration of the appropriate fractions ( $R_f = 0.3$  in 0.5:2.5:5.5 v/v/v ethyl acetate/ $\text{CH}_2\text{Cl}_2$ /hexane), a ca. 6:1 mixture of compound **29** and its regioisomeric silyl ether (1.95 g, 88% combined yield) as a light-yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.42 (s, 1H), 4.66 (d,  $J = 6.6$  Hz, 1H), 4.17 (m, 1H), 4.11 (m, 1H), 3.55 (t,  $J = 8.7$  Hz, 1H), 2.45 (s, 1H), 1.54 (s, 3H), 1.40 (s, 3H), 1.15–1.04 (complex m, 21H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  144.5, 110.2, 92.2, 79.3, 77.0, 74.5, 73.6, 28.0, 25.7, 18.0(1), 17.9(9), 12.4; IR  $\nu_{\text{max}}$  3469, 2943, 2893, 2866, 1635, 1463, 1382, 1248, 1070, 1019, 997, 882, 866, 828  $\text{cm}^{-1}$ ; MS (ESI, +ve)  $m/z$  445 and 443 [ $(\text{M}+\text{Na})^+$ , 100 and 97%]; HRMS (ESI, +ve)  $(\text{M}+\text{Na})^+$  calcd for  $\text{C}_{18}\text{H}_{33}^{79}\text{BrNaO}_4\text{Si}$  443.1229, found 443.1232.

**(((3a*R*,4*R*,5*S*,7a*S*)-7-Bromo-5-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo [*d*][1,3]-dioxol-4-yl)oxy)tri-*iso*-propylsilane (30).** Sodium hydride (342 mg of a 60% dispersion in mineral oil, 8.6 mmol) was added to a magnetically stirred solution of a ca. 6:1 mixture of compound **29** and its regioisomer (1.20 g, 2.9 mmol) and iodomethane (391  $\mu\text{L}$ , 6.3 mmol) in dry THF (20 mL) maintained at 0 °C under a nitrogen atmosphere. Stirring was continued for 2 h at 22 °C then the reaction mixture was treated with ice/water (70 mL) (CAUTION: possibility of hydrogen evolution). The separated aqueous phase was extracted with ethyl acetate (1  $\times$  30 mL) and the combined organic phases were then dried ( $\text{MgSO}_4$ ), filtered, and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 1:50 v/v ethyl acetate/hexane elution) to give, after concentration of the appropriate fractions ( $R_f = 0.4$  in 0.5:2.5:5.5 v/v/v ethyl acetate/ $\text{CH}_2\text{Cl}_2$ /hexane), a ca. 5:1 mixture of compound **30** and its regioisomer (612 mg, 49% combined yield) as a yellowish oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (major regioisomer) 6.16 (m, 1H),

4.63 (m, 1H), 4.47 (m, 1H), 4.36 (m, 1H), 3.86 (m, 1H), 3.41 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.12–0.95 (complex m, 21H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  [major regioisomer] 129.4, 122.3, 110.0, 77.3, 77.2(3), 77.2(2), 69.9, 57.3, 27.5, 26.2, 18.0(2), 17.9(5), 12.5; IR  $\nu_{\text{max}}$  2939, 2892, 2866, 1645, 1463, 1381, 1234, 1163, 1078, 1039, 1011, 941, 882, 815, 680  $\text{cm}^{-1}$ ; MS (ESI, +ve)  $m/z$  459 and 457 [(M+Na) $^+$ , 98 and 96%], 355 (100), 347 and 345 (67 and 65); HRMS (ESI, +ve) (M+Na) $^+$  calcd for  $\text{C}_{19}\text{H}_{35}^{79}\text{BrNaO}_4\text{Si}$  457.1386, found 457.1389.

**(3a*S*,4*R*,5*S*,7a*S*)-7-Bromo-5-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-ol (31).** A magnetically stirred solution of a ca. 5:1 mixture of compound **30** and its regioisomer (600 mg, 1.4 mmol) in THF (10 ml) maintained at 22 °C under a nitrogen atmosphere was treated with tetra-*n*-butylammonium fluoride (2 mL of 1.0 M solution in THF, 2.0 mmol). After 2 h the reaction mixture was concentrated under reduced pressure and the residue so-formed subjected to flash chromatography (silica, 1:2 v/v ethyl acetate/hexane elution) to provide, after concentration of the appropriate fractions ( $R_f = 0.4$  in 4:2.5:5.5 v/v/v ethyl acetate/ $\text{CH}_2\text{Cl}_2$ /hexane), compound **31** (377 mg, 98%) as a light-yellow oil,  $[\alpha]_{\text{D}}^{20} = -15.7$  ( $c = 2.4$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.28 (s, 1H), 4.68 (d,  $J = 6.5$  Hz, 1H), 4.15 (m, 1H), 3.66 (m, 2H), 3.48 (s, 3H), 2.64 (broad s, 1H), 1.55 (s, 3H), 1.42 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  132.2, 118.8, 111.0, 80.3, 77.5, 77.2, 72.5, 57.5, 28.1, 25.9; IR  $\nu_{\text{max}}$  3453, 2987, 2934, 2826, 1646, 1457, 1381, 1217, 1164, 1074, 869  $\text{cm}^{-1}$ ; MS (EI, 70 eV)  $m/z$  280 and 278 ( $\text{M}^+$ , both 3%), 265 and 263 (both 35%), 101 (100); HRMS (EI, 70 eV)  $\text{M}^+$  calcd for  $\text{C}_{10}\text{H}_{15}^{79}\text{BrO}_4$  278.0154, found 278.0148.

**4-Hydroxy-3-((3a*R*,6*S*,7*R*,7a*S*)-7-hydroxy-6-methoxy-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl)-5-methoxybenzaldehyde (32).** A magnetically stirred solution of compound **31** (150 mg, 0.54 mmol), ester **27** (180 mg, 0.65 mmol),

PdCl<sub>2</sub>dppf•CH<sub>2</sub>Cl<sub>2</sub> (31.5 mg, 0.04 mmol), and triethylamine (3 mL) in THF/water (18 mL of a 9:1 v/v mixture) was purged with nitrogen for 0.5 h and then heated under reflux for 2 h before being cooled, poured into water (50 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (1 × 40 mL) then dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions (*R<sub>f</sub>* = 0.5 in 1:3 v/v ethyl acetate/hexane) afforded phenol **32** (85 mg, 45%) as a white, crystalline solid, mp = 129 °C, [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +16.0 (*c* = 0.2, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.83 (s, 1H), 7.45 (d, *J* = 1.8 Hz, 1H), 7.39 (d, *J* = 1.8 Hz, 1H), 7.09 (s, 1H), 6.19 (d, *J* = 1.3 Hz, 1H), 5.17 (d, *J* = 6.4 Hz, 1H), 4.27 (dd, *J* = 8.9 and 6.4 Hz, 1H), 3.98 (s, 3H), 3.86 (m, 1H), 3.79 (m, 1H), 3.54 (s, 3H), 2.71 (broad s, 1H), 1.53 (s, 3H), 1.40 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  190.9, 149.2, 147.7, 132.3, 131.7, 129.2, 128.2, 125.1, 110.7, 108.4, 79.9, 77.7, 73.9, 72.9, 57.5, 56.4, 28.2, 26.0; IR  $\nu_{\max}$  3400, 2986, 2935, 2830, 1681, 1588, 1488, 1455, 1432, 1373, 1301, 1254, 1217, 1148, 1067, 990, 863, 732 cm<sup>-1</sup>; MS (EI, 70 eV) *m/z* 350 (M<sup>+</sup>, 5%), 292 (53), 260 (55), 232 (100), 231 (72), 218 (53), 203 (39), 189 (33); HRMS (EI, 70 eV) M<sup>+</sup> calcd for C<sub>18</sub>H<sub>22</sub>O<sub>7</sub> 350.1366, found 350.1369.

**(2'R,3'R,4'S,5'S)-2',3',4',6-Tetrahydroxy-5,5'-dimethoxy-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-carbaldehyde (33)**. Compound **32** (60 mg, 0.17 mmol) was treated with acetic acid/water (10 mL of a 2:1 v/v mixture) and the resulting mixture stirred at 22 °C for 18 h then cooled and concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 1:8:1 v/v/v methanol/ethyl acetate/hexane elution) gave, after concentration of the appropriate fractions (*R<sub>f</sub>* = 0.4), compound **33** (43 mg, 81%) as a white powder, mp = 191 °C, [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +7.5 (*c* = 0.1, CHCl<sub>3</sub>). <sup>1</sup>H NMR [400 MHz,

(CD<sub>3</sub>)<sub>2</sub>CO]  $\delta$  9.83 (s, 1H), 7.45 (d,  $J = 1.9$  Hz, 1H), 7.39 (d,  $J = 1.9$  Hz, 1H), 6.03 (d,  $J = 2.5$  Hz, 1H), 4.63 (d,  $J = 3.8$  Hz, 1H), 3.97 (m, 1H), 3.92 (s, 3H), 3.84 (dd,  $J = 7.6$  and 2.5 Hz, 1H), 3.62 (dd,  $J = 10.3$  and 3.8 Hz, 1H) 3.49 (s, 3H), 2.83 (broad s, 3H) (signal due to a hydroxyl group proton not observed); <sup>13</sup>C NMR [100 MHz, (CD<sub>3</sub>)<sub>2</sub>CO]  $\delta$  191.3, 151.3, 149.5, 137.4, 132.1, 129.9, 128.6, 128.4, 110.1, 82.9, 72.7, 71.8, 70.2, 57.6, 56.6; IR  $\nu_{\max}$  3346, 2926, 2839, 2821, 1678, 1586, 1454, 1429, 1383, 1298, 1257, 1145, 1106, 1070, 943, 858, 696 cm<sup>-1</sup>; MS (ESI, +ve)  $m/z$  643 [(2M+Na)<sup>+</sup>, 35%], 333 [(M+Na)<sup>+</sup>, 100]; HRMS (ESI, +ve) (M+Na)<sup>+</sup> calcd for C<sub>15</sub>H<sub>18</sub>NaO<sub>7</sub> 333.0950, found 333.0952.

**(5a*S*,6*S*,7*S*,8*S*)-6,7-Dihydroxy-4,8-dimethoxy-5a,6,7,8-tetrahydrobenzo[*b,d*]-furan-2-carbaldehyde (7).** A magnetically stirred solution of phenol **33** (40 mg, 0.13 mmol) in THF (12 mL) was treated with Ph<sub>3</sub>P (40 mg, 0.15 mmol) then cooled to 0 °C and treated, dropwise, with a solution of di-*iso*-propyl azodicarboxylate (25  $\mu$ L, 0.13 mmol) in THF (1 mL). The reaction mixture thus obtained was stirred at 0 °C for 2 h then concentrated under reduced pressure and the ensuing light-yellow oil subjected to flash chromatography (silica, 3:97 v/v methanol/CH<sub>2</sub>Cl<sub>2</sub> elution). Concentration of the relevant fractions ( $R_f = 0.4$  in 0.5:9.5 v/v methanol/CH<sub>2</sub>Cl<sub>2</sub>) afforded benzofuran **7** (32 mg, 85%) as a clear, light-yellow oil,  $[\alpha]_D^{20} = +92.0$  ( $c = 0.2$ , CHCl<sub>3</sub>). <sup>1</sup>H NMR [400 MHz, (CD<sub>3</sub>)<sub>2</sub>CO]  $\delta$  9.87 (s, 1H), 7.69 (d,  $J = 1.5$  Hz, 1H), 7.44 (d,  $J = 1.5$  Hz, 1H), 6.19 (t,  $J = 3.6$  Hz, 1H), 5.09 (m, 1H), 4.94 (s, 1H), 4.48 (broad s, 1H), 4.09 (m, 1H), 3.95 (s, 3H), 3.81–3.77 (complex m, 2H), 3.49 (s, 3H); <sup>13</sup>C NMR [100 MHz, (CD<sub>3</sub>)<sub>2</sub>CO]  $\delta$  191.1, 157.6, 146.9, 138.0, 133.1, 127.7, 118.2, 117.6, 114.0, 89.1, 83.8, 77.3, 75.6, 57.5, 56.6; IR  $\nu_{\max}$  3339, 2926, 2892, 2853, 2823, 1686, 1604, 1590, 1437, 1337, 1313, 1185, 1119, 1092, 1069, 997, 920, 721, 694 cm<sup>-1</sup>; MS (ESI, +ve)  $m/z$  607

[(2M+Na)<sup>+</sup>, 40%], 315 [(M+Na)<sup>+</sup>, 100], 293 (23), 195 (30); HRMS (ESI, +ve) (M+Na)<sup>+</sup> calcd for C<sub>15</sub>H<sub>16</sub>NaO<sub>6</sub> 315.0845, found 315.0847.

**(3a*S*,4*S*,5*R*,7a*S*)-7-Bromo-2,2-dimethyl-5-((tri-*iso*-propylsilyl)oxy)-3a,4,5,7a-tetra -hydrobenzo[*d*][1,3]dioxol-4-ol (35).** Tri-*iso*-propylsilyl trifluoromethanesulfonate (620  $\mu$ L, 2.3 mmol) was added, dropwise, to a magnetically stirred solution of compound **34**<sup>31</sup> (500 mg, 1.9 mmol) and 2,6-lutidine (880  $\mu$ L, 7.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) maintained at -78 °C under a nitrogen atmosphere. The ensuing mixture was allowed to warm to 22 °C over 3 h then treated with NH<sub>4</sub>Cl (30 mL of a saturated aqueous solution). The separated aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (1  $\times$  10 mL) and the combined organic phases were dried (MgSO<sub>4</sub>), filtered, and concentrated under reduced pressure. The resulting light yellow-oil was subjected to flash chromatography (silica, 3:100 v/v ethyl acetate/hexane elution) and gave, after concentration of the appropriate fractions (*R*<sub>f</sub> = 0.3 in 0.5:2.5:5.5 v/v/v ethyl acetate /CH<sub>2</sub>Cl<sub>2</sub>/hexane), a ca. 6:1 mixture of ether **35** and its regioisomer (700 mg, 88% combined yield) as a light-yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  (major regioisomer) 6.00 (m, 1H), 4.62 (dd, *J* = 5.2 and 1.5 Hz, 1H), 4.49 (m, 2H), 4.24 (m, 1H), 2.67 (d, *J* = 1.5 Hz, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 1.12–0.99 (complex m, 21H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  (major regioisomer) 130.8, 123.5, 110.0, 75.9, 75.7, 69.3, 68.3, 27.5, 26.2, 17.9(4), 17.9(3), 12.2; IR  $\nu_{\max}$  3560, 2943, 2893, 2867, 1645, 1463, 1382, 1370, 1340, 1236, 1080, 1055, 882, 863, 682 cm<sup>-1</sup>; MS (EI, 70 eV) *m/z* 423 and 421 [(M+ H)<sup>+</sup>, 10 and 9%], 407 and 405 [(M-CH<sub>3</sub>)<sup>+</sup>, 7 and 6], 321 and 319 (100 and 97); HRMS (EI, 70 eV) (M-CH<sub>3</sub>)<sup>+</sup> calcd for C<sub>17</sub>H<sub>30</sub><sup>79</sup>BrO<sub>4</sub>Si 405.1097, found 405.1096.

**(((3a*S*,4*S*,5*R*,7a*S*)-7-bromo-4-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo-*d*][1,3]diox-ol-5-yl)oxy)tri-*iso*-propylsilane (36).** Sodium hydride (172 mg of a 60%

dispersion in mineral oil, 4.3 mmol) was added to a magnetically stirred solution of a ca. 6:1 mixture of compound **35** and its regioisomer (600 mg, 1.4 mmol) and iodomethane (267  $\mu\text{L}$ , 4.3 mmol) in dry THF (15 mL) maintained at 0 °C under a nitrogen atmosphere. Stirring was continued for 2 h at 22 °C then the reaction mixture was treated with ice/water (30 mL) (CAUTION: possibility of evolution of hydrogen gas). The separated aqueous phase was extracted with ethyl acetate (1  $\times$  15 mL) and the combined organic phases were then dried ( $\text{MgSO}_4$ ), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 1:50 v/v ethyl acetate/hexane elution) to give, after concentration of the appropriate fractions ( $R_f = 0.4$  in 0.5:2.5:5.5 v/v/v ethyl acetate/ $\text{CH}_2\text{Cl}_2$ /hexane), a ca. 5:1 mixture of compound **36** and its regioisomer (570 mg, 92% combined yield) as a clear, colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (major regioisomer) 6.15 (d,  $J = 3.0$  Hz, 1H), 4.62 (m, 1H), 4.56 (m, 1H), 4.44 (t,  $J = 5.4$  Hz, 1H), 3.70 (m, 1H), 3.54 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H), 1.10–0.98 (complex m, 21H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (major regioisomer) 133.1, 122.2, 109.9, 80.3, 76.9, 75.1, 68.2, 59.7, 27.5, 26.0, 17.9(8), 17.9(6), 12.2; IR  $\nu_{\text{max}}$  2941, 2887, 2865, 1649, 1460, 1383, 1335, 1241, 1197, 1138, 1121, 1079, 1040, 956, 880, 858, 680  $\text{cm}^{-1}$ ; MS (ESI, +ve)  $m/z$  459 and 457 [(M+Na) $^+$ , 83 and 81%], 437 and 435 (88 and 86), 205 and 203 (97 and 100); HRMS (ESI, +ve) (M+Na) $^+$  calcd for  $\text{C}_{19}\text{H}_{35}^{79}\text{BrNaO}_4\text{Si}$  457.1386, found 457.1375.

**(3aS,4R,5R,7aS)-7-Bromo-4-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo-[d][1,3]-dioxol-5-ol (37)**. A magnetically stirred solution of a ca. 5:1 mixture of compound **36** and its regioisomer (600 mg, 1.4 mmol) in THF (10 ml) maintained at 22 °C under a nitrogen atmosphere was treated with tetra-*n*-butylammonium fluoride (2 mL of 1.0 M solution in THF, 4.1 mmol). After 2 h the reaction mixture was concentrated under reduced

pressure and the residue so-formed subjected to flash chromatography (silica, 1:2 v/v ethyl acetate/hexane elution). Concentration of the relevant fractions ( $R_f = 0.4$  in 4:2.5:5.5 v/v/v ethyl acetate/ $\text{CH}_2\text{Cl}_2$ /hexane) gave compound **37** (338 mg, 88%) as a white powder, mp = 61 °C,  $[\alpha]_D^{20} = +15.3$  ( $c = 0.6$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.15 (d,  $J = 3.0$  Hz, 1H), 4.59 (m, 1H), 4.53 (t,  $J = 5.1$  Hz, 1H), 4.33 (complex m, 1H), 3.76 (t,  $J = 4.4$  Hz, 1H), 3.54 (s, 3H), 2.55 (broad s, 1H), 1.42 (s, 3H), 1.40 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  132.0, 123.2, 110.3, 78.7, 76.2, 73.9, 66.3, 59.2, 27.6, 26.2; IR  $\nu_{\text{max}}$  3453, 2987, 2935, 2900, 2831, 1646, 1457, 1381, 1372, 1231, 1109, 1077, 1041, 964, 868  $\text{cm}^{-1}$ ; MS (EI, 70 eV) (EI, 70 eV) 280 and 278 ( $\text{M}^+$ , both 1%), 265 and 263 (74 and 76%), 177 and 175 (13 and 15), 124 (28), 115 (100); HRMS  $\text{M}^+$  calcd for  $\text{C}_{10}\text{H}_{15}^{79}\text{BrO}_4$  278.0154, found 278.0153.

**4-Hydroxy-3-((3a*R*,6*R*,7*R*,7a*R*)-6-hydroxy-7-methoxy-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl)-5-methoxybenzaldehyde (38).** A magnetically stirred solution of compound **37** (116 mg, 0.42 mmol), boronate ester **27** (139 mg, 0.50 mmol),  $\text{PdCl}_2\text{dppf}\cdot\text{CH}_2\text{Cl}_2$  (25 mg, 0.03 mmol) and triethylamine (2 mL) in THF/water (15 mL of a 9:1 v/v mixture) was purged with nitrogen for 0.5 h and then heated under reflux for 3 h before being cooled, poured into water (40 mL) and extracted with ethyl acetate ( $3 \times 20$  mL). The combined organic phases were washed with brine ( $1 \times 30$  mL) then dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions ( $R_f = 0.5$  in 1:3 v/v ethyl acetate/hexane) gave phenol **38** (80 mg, 55%) as a light-yellow oil,  $[\alpha]_D^{20} = +7.0$  ( $c = 0.2$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.82 (s, 1H), 7.39 (d,  $J = 1.5$  Hz, 1H), 7.37 (d,  $J = 1.5$  Hz, 1H), 6.10 (d,  $J = 3.3$  Hz, 1H), 5.15 (d,  $J = 5.8$  Hz, 1H), 4.64 (t,  $J = 5.5$  Hz, 1H), 4.52 (m, 1H), 3.96 (s, 3H), 3.79 (t,  $J = 4.6$  Hz, 1H), 3.59 (s,

3H), 2.65 (broad d,  $J = 8.3$  Hz, 1H), 1.46 (s, 3H), 1.40 (s, 3H) (signal due to hydroxyl group proton not observed);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  190.8, 149.4, 147.9, 134.8, 132.0, 129.2, 128.3, 125.9, 109.8, 108.4, 79.7, 73.6, 73.3, 65.0, 59.1, 56.3, 27.6, 25.9; IR  $\nu_{\text{max}}$  3368, 2985, 2936, 1681, 1588, 1456, 1432, 1297, 1149, 1120, 1071, 913, 873  $\text{cm}^{-1}$ ; MS (EI, 70 eV)  $m/z$  350 ( $\text{M}^+$ , 4%), 274 (41), 115 (100); HRMS (EI, 70 eV)  $\text{M}^+$  calcd for  $\text{C}_{18}\text{H}_{22}\text{O}_7$  350.1366, found 350.1370.

**2-((3a*S*,4*R*,5*R*,7a*R*)-7-(5-Formyl-2,3-dimethoxyphenyl)-4-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-yl)-*N,N*-dimethylacetamide (39).** A magnetic-ally stirred solution of compound **38** (60 mg, 0.17 mmol) in toluene (10 mL) was treated with *N,N*-dimethylacetamide dimethyl acetal (126  $\mu\text{L}$ , 0.87 mmol) and the ensuing mixture heated under reflux for 18 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, 4:1 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions ( $R_f = 0.3$  in 5:1 v/v ethyl acetate/hexane) then gave a ca. 5:1 mixture of amide **39** and its  $\square$ epimer (30 mg, 40% combined yield) as a clear, colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (major epimer) 9.87 (s, 1H), 7.39–7.36 (complex m, 2H), 6.01 (d,  $J = 4.6$  Hz, 1H), 5.20 (d,  $J = 6.7$  Hz, 1H), 4.41 (t,  $J = 6.7$  Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.65–3.59 (complex m, 1H), 3.48 (s, 3H), 3.34 (m, 1H), 3.01 (s, 3H), 2.94 (s, 3H), 2.73 (dd,  $J = 15.9$  and 5.1 Hz, 1H), 2.27 (dd,  $J = 15.9$  and 9.4 Hz, 1H), 1.44 (s, 3H), 1.35 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (major epimer) 191.2, 171.3, 153.3, 152.1, 134.6, 133.9, 133.1, 132.3, 127.5, 109.6, 109.0, 79.7, 74.4, 73.6, 60.8, 58.1, 56.0, 37.3, 35.5, 33.7, 33.4, 27.9, 25.7; IR  $\nu_{\text{max}}$  2982, 2932, 2857, 2831, 1691, 1646, 1578, 1458, 1421, 1384, 1240, 1142, 1034, 1002, 913, 863, 733  $\text{cm}^{-1}$ ; MS (ESI, +ve)  $m/z$  456

[(M+Na)<sup>+</sup>, 78%], 434 (100), 376 (21); HRMS (ESI, +ve) (M+Na)<sup>+</sup> calcd for C<sub>23</sub>H<sub>31</sub>NNaO<sub>7</sub> 456.1998, found 456.1996.

**2-((3*R*,4*R*,5*R*,6*R*)-5'-Formyl-5,6-dihydroxy-2',3',4-trimethoxy-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-*N,N*-dimethylacetamide (8).** A ca. 5:1 mixture of compound **39** and its β-epimer (16 mg, 0.04 mmol) was treated with acetic acid/water (10 mL of a 2:1 v/v mixture) and the resulting solution heated at 50 °C for 22 h then cooled to 22 °C and concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 1:8:1 v/v methanol/ethyl acetate/hexane elution) gave, after concentration of the appropriate fractions (*R<sub>f</sub>* = 0.4 in 1:9 v/v methanol/ethyl acetate), a ca. 6:1 mixture of compound **8** and its β-epimer (10 mg, 69% combined yield) as a light-yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (major epimer) 9.87 (s, 1H), 7.39 (complex m, 2H), 5.99 (m, 1H), 4.71 (m, 1H), 4.01 (dd, *J* = 9.2 and 4.0 Hz, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.80 (m, 1H), 3.50 (m, 1H), 3.46 (s, 3H), 3.02 (s, 3H), 2.95 (s, 3H), 2.85 (broad s, 1H), 2.74 (dd, *J* = 15.9 and 5.0 Hz, 1H), 2.20 (dd, *J* = 15.9 and 9.0 Hz, 1H) (signal due to a hydroxyl group proton not observed); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ (major epimer) 191.1, 171.4, 153.2, 151.7, 135.1, 134.9, 133.3, 132.4, 127.5, 109.8, 77.7, 69.0, 68.5, 61.0, 57.9, 56.0, 37.3, 35.6, 34.3, 32.4; IR *v*<sub>max</sub> 3395, 2957, 2935, 2828, 1688, 1627, 1463, 1420, 1387, 1260, 1128, 1105, 1089, 797 cm<sup>-1</sup>; MS (ESI, +ve) *m/z* 787 [(2M+H)<sup>+</sup>, 30%], 416 [(M+Na)<sup>+</sup>, 100], 394 (92), 376 (20); HRMS (ESI, +ve) (M+Na)<sup>+</sup> calcd for C<sub>20</sub>H<sub>27</sub>NNaO<sub>7</sub> 416.1685, found 416.1685.

**4-Hydroxy-3-((3*aR*,6*S*,7*R*,7*aR*)-6-hydroxy-7-(methoxymethoxy)-2,2-dimethyl-3*a*,6,7,7*a*-tetrahydrobenzo[d][1,3]dioxol-4-yl)-5-methoxybenzaldehyde (43).** A magnetic-ally stirred solution of compound **42**<sup>9a</sup> (100 mg, 0.33 mmol), boronate ester **27** (108 mg,

0.39 mmol), PdCl<sub>2</sub>dppf•CH<sub>2</sub>Cl<sub>2</sub> (19 mg, 0.02 mmol) and triethylamine (3 mL) in THF/water (18 mL of a 9:1 v/v mixture) was purged with nitrogen for 0.5 h and then heated under reflux for 2 h before being cooled, poured into water (50 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (1 × 40 mL) then dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions (*R<sub>f</sub>* = 0.3 in 1:3 v/v ethyl acetate/hexane) then gave phenol **43** (60 mg, 49%) as a light-yellow oil, [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +18.4 (*c* = 0.9, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.82 (s, 1H), 7.46 (d, *J* = 1.6 Hz, 1H), 7.39 (d, *J* = 1.6 Hz, 1H), 7.07 (s, 1H), 6.16 (d, *J* = 2.2 Hz, 1H), 5.21 (d, *J* = 6.2 Hz, 1H), 4.90 (d, *J* = 6.8 Hz, 1H), 4.86 (d, *J* = 6.8 Hz, 1H), 4.36 (dd, *J* = 8.4 and 6.2 Hz, 1H), 4.27 (broad d, *J* = 8.1 Hz, 1H), 4.08 (d, *J* = 3.3 Hz, 1H), 3.97 (s, 3H), 3.67 (m, 1H), 3.50 (s, 3H), 1.51 (s, 3H), 1.40 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  190.8, 149.2, 147.6, 133.6, 131.8, 129.2, 128.5, 125.0, 110.5, 108.1, 98.0, 83.2, 76.5, 74.0, 69.4, 56.4, 55.9, 28.2, 26.0; IR  $\nu_{\text{max}}$  3370, 2985, 2948, 2936, 1683, 1588, 1488, 1456, 1432, 1372, 1300, 1250, 1217, 1149, 1105, 1058, 1037, 996, 866, 732 cm<sup>-1</sup>; MS (EI, +ve) *m/z* 380 (M<sup>+</sup>, 2%), 362 (12), 260 (59), 259 (54), 231 (100), 218 (48); HRMS (EI, +ve) M<sup>+</sup> calcd for C<sub>19</sub>H<sub>24</sub>O<sub>8</sub> 380.1471, found 380.1478.

**2-((3a*S*,4*R*,5*R*,7a*R*)-7-(5-Formyl-2,3-dimethoxyphenyl)-4-(methoxymethoxy)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-yl)-*N,N*-dimethylacetamide (44).** A magnetically stirred solution of compound **43** (33 mg, 0.09 mmol) in toluene (10 mL) was treated with *N,N*-dimethylacetamide dimethyl acetal (64  $\mu$ L, 0.44 mmol) and the ensuing mixture heated under reflux for 18 h. The cooled reaction mixture was concentrated under reduced pressure and subsection of the ensuing residue to flash chromatography (silica,

9.5:0.5 v/v ethyl acetate /hexane elution) gave, after concentration of the appropriate fractions ( $R_f = 0.4$  in ethyl acetate), a ca. 3:1 mixture of amide **44** and its  $\beta$ -epimer (14 mg, 35% combined yield) as a clear, colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (major epimer) 9.87 (s, 1H), 7.38 (m, 2H), 5.98 (d,  $J = 4.3$  Hz, 1H), 5.22 (d,  $J = 6.0$  Hz, 1H), 4.77 (m, 2H), 4.46 (t,  $J = 6.5$  Hz, 1H), 4.04 (dd,  $J = 6.9$  and 4.5 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.43 (s, 3H), 3.30 (m, 1H), 3.01 (s, 3H), 2.94 (s, 3H), 2.75 (dd,  $J = 15.8$  and 5.1 Hz, 1H), 2.33 (dd,  $J = 15.8$  and 9.5 Hz, 1H), 1.44 (s, 3H), 1.35 (s, 3H);  $^{13}\text{C}$  NMR (mixture of epimers) (100 MHz,  $\text{CDCl}_3$ )  $\delta$  191.3, 171.2, 153.3, 152.0, 134.6, 134.0, 133.0, 132.3, 129.3, 127.7, 113.8, 109.6, 109.2, 100.0, 96.5, 76.2, 75.0, 74.1, 73.8, 60.8, 56.0, 55.7, 37.2, 35.5, 34.2, 33.8, 28.0, 27.9, 26.0; IR  $\nu_{\text{max}}$  2982, 2933, 2843, 1692, 1647, 1579, 1455, 1384, 1243, 1145, 1070, 1037, 918, 863  $\text{cm}^{-1}$ ; MS (ESI, +ve)  $m/z$  486  $[(\text{M}+\text{Na})^+, 100\%]$ , 464 (3), 60 (10); HRMS (ESI, +ve)  $(\text{M}+\text{Na})^+$  calcd for  $\text{C}_{24}\text{H}_{33}\text{NNaO}_8$  486.2104, found 486.2105.

**2-((3R,4R,5R,6R)-5'-Formyl-5,6-dihydroxy-2',3'-dimethoxy-4-(methoxymethoxy)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-N,N-dimethylacetamide (9).** Compound **44** (8 mg, 0.02 mmol) was treated with acetic acid/water (10 mL of a 2:1 v/v mixture) and the resulting solution heated at 50 °C for 22 h then cooled and concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 1:8:1 v/v methanol/ethyl acetate/hexane elution) gave, after concentration of the appropriate fractions ( $R_f = 0.4$  in 1:9 v/v methanol/ethyl acetate), a ca. 6.5:1 mixture of compound **9** and its  $\beta$ -epimer (5 mg, 69%) as a light-yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (major epimer) 9.87 (s, 1H), 7.38 (m, 2H), 5.97 (d,  $J = 4.4$  Hz, 1H), 4.76–4.71 (complex m, 3H), 4.14 (dd,  $J = 9.1$  and 5.7 Hz, 1H), 4.01 (m, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.45 (s, 3H), 3.34 (broad s, 1H), 3.02 (s, 3H), 2.94 (s, 3H), 2.84 (dd,  $J = 15.9$  and 5.2 Hz, 1H), 2.25 (dd,  $J = 15.9$  and 8.9 Hz,

1H) (signal due to hydroxyl group protons not observed);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (major epimer) 191.2, 171.4, 153.2, 151.7, 135.2, 135.0, 133.3, 132.5, 127.4, 109.8, 97.5, 76.9, 69.2, 68.9, 61.0, 56.0(1), 55.9(6), 37.3, 35.8, 35.6, 33.2; IR  $\nu_{\text{max}}$  3384, 2919, 2848, 1688, 1630, 1579, 1463, 1419, 1387, 1329, 1292, 1245, 1147, 1130, 1037, 917, 862  $\text{cm}^{-1}$ ; MS (ESI, +ve)  $m/z$  446  $[(\text{M}+\text{Na})^+]$ , 68%, 424 (100); HRMS (ESI, +ve)  $(\text{M}+\text{Na})^+$  calcd for  $\text{C}_{21}\text{H}_{29}\text{NNaO}_8$  446.1791, found 446.1780.

**Crystallographic Studies.** *Crystallographic Data.*

Compound *ent-2*.  $\text{C}_{17}\text{H}_{19}\text{NO}_5$ ,  $M = 317.34$ ,  $T = 150$  K, orthorhombic, space group  $P2_12_12_1$ ,  $Z = 4$ ,  $a = 6.58612(5)$  Å,  $b = 9.28140(8)$  Å,  $c = 23.3001(2)$  Å;  $V = 1424.30(2)$  Å<sup>3</sup>,  $D_x = 1.480$  g  $\text{cm}^{-3}$ , 2794 unique data ( $2\theta_{\text{max}} = 144.6^\circ$ ),  $R = 0.027$  [for 2725 reflections with  $I > 2.0\sigma(I)$ ];  $R_w = 0.072$  (all data),  $S = 1.01$ .

Compound *ent-15*.  $\text{C}_{23}\text{H}_{31}\text{NO}_7$ ,  $M = 433.50$ ,  $T = 150$  K, monoclinic, space group  $P2_1$ ,  $Z = 2$ ,  $a = 10.14845(9)$  Å,  $b = 10.61199(7)$  Å,  $c = 10.80864(10)$  Å;  $\beta = 106.8796(9)^\circ$ ;  $V = 1113.89(2)$  Å<sup>3</sup>,  $D_x = 1.292$  g  $\text{cm}^{-3}$ , 3907 unique data ( $2\theta_{\text{max}} = 144.8^\circ$ ),  $R = 0.026$  [for 3843 reflections with  $I > 2.0\sigma(I)$ ];  $R_w = 0.067$  (all data),  $S = 1.03$ .

Compound **27**.  $\text{C}_{14}\text{H}_{19}\text{BO}_5$ ,  $M = 278.11$ ,  $T = 150$  K, orthorhombic, space group  $Pbam$ ,  $Z = 8$ ,  $a = 23.0535(6)$  Å,  $b = 18.2756(6)$  Å,  $c = 6.8183(2)$  Å;  $V = 2872.66(15)$  Å<sup>3</sup>,  $D_x = 1.286$  g  $\text{cm}^{-3}$ , 3098 unique data ( $2\theta_{\text{max}} = 145.2^\circ$ ),  $R = 0.084$  [for 2982 reflections with  $I > 2.0\sigma(I)$ ];  $R_w = 0.191$  (all data),  $S = 1.06$ .

Compound **32**.  $\text{C}_{18}\text{H}_{22}\text{O}_7$ ,  $M = 359.38$ ,  $T = 150$  K, monoclinic, space group  $P2_1$ ,  $Z = 4$ ,  $a = 7.3153(1)$  Å,  $b = 31.4358(3)$  Å,  $c = 7.8245(1)$  Å;  $\beta = 94.8743(8)^\circ$ ;  $V = 1792.83(4)$  Å<sup>3</sup>,  $D_x = 1.331$  g  $\text{cm}^{-3}$ , 7018 unique data ( $2\theta_{\text{max}} = 145^\circ$ ),  $R = 0.030$  [for 6919 reflections with  $I > 2.0\sigma(I)$ ];  $R_w = 0.080$  (all data),  $S = 0.99$ .

*Structure Determination.* Diffraction images for compounds *ent-2*, *ent-15*, **27** and **32** were all measured on a diffractometer (Mo K  $\alpha$  radiation,  $\lambda = 0.71073 \text{ \AA}$ ) fitted with an area detector and the data extracted using the DENZO/Scalepack package.<sup>43</sup> The structure solutions for all four compounds were solved by direct methods (SIR92)<sup>44</sup> then refined using the CRYSTALS program package.<sup>45</sup> Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1517512, 1517513, 1517514 and 1517515). These data can be obtained free-of-charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

#### **AChE Inhibition Testing.**

The galanthamine derivatives/analogues described above were tested for inhibition against AChE as described by Sangnoi et al.<sup>33,46</sup> Thus, the compounds were dissolved in DMSO and made up to concentrations ranging from 5 mM to 3.05  $\mu\text{M}$  by serial dilution with DMSO. 2.5  $\mu\text{L}$  of a solution each compound was added to a solution of 5,5'-dithiobis-(2-nitrobenzoic acid) (125  $\mu\text{L}$  of a 1.5 mM aqueous solution), tris(hydroxymethyl)aminomethane buffer (72.5  $\mu\text{L}$  of a 15 mM solution at pH 8.0) and acetylthiocholine iodide (25  $\mu\text{L}$  of a 150  $\mu\text{M}$  aqueous solution) in water. Enzyme activity was followed after the addition of AChE (25  $\mu\text{L}$  of 0.03  $\mu\text{M}$  solution of *Electrophorus electricus*, Type V-S, EC 3.1.1.7) by measuring the absorption at 412 nm using a microplate spectrophotometer. Assays were repeated in triplicates and the hydrolysis rate calculated during the data from the absorptions observed over the first two minutes. Standard, commercially available graphic software was used to calculate the tabulated  $\text{IC}_{50}$  values.

## **Molecular Docking Studies.**

The three-dimensional coordinates of each compound were generated with the PRODRG server (<http://davapc1.bioch.dundee.ac.uk/cgi-bin/prodrg>).<sup>47</sup> Galanthamine and the above-mentioned derivatives/analogues were docked into the structure of human acetylcholinesterase (**4EY6**) using Autodock Vina v1.1.2 after removal of galanthamine from the active site gorge.<sup>48</sup>

## **ASSOCIATED CONTENT**

### **\* Supporting Information**

Data derived from the single-crystal X-ray analyses and CIFs of compounds *ent-2*, *ent-15*, **27** and **32** (CCDC Nos. 1517512, 1517513, 1517514 and 1517515, respectively); <sup>1</sup>H and <sup>13</sup>C NMR spectra of compounds **2-9**, *ent-11*, **13-17**, **21**, **23**, **24**, **25**, **27**, **29-33**, **35-39**, **43** and **44**.

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### **Notes**

The authors declare no competing financial interest.

## **ACKNOWLEDGMENTS**

We thank the Australian Research Council and the Institute of Advanced Studies for

financial support. JNB and NJF are the grateful recipients of Australian Post-graduate Awards while EST thanks the Islamic Development Bank for support.

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