

### **Research Article**

#### Carbocyclization of Carbohydrates to Hydroxylated Cycloalka(e)nes

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Abstract: Carbohydrates, inexpensive and rich in stereochemistry, are nature's gifts to the synthetic organic chemists. We have been conducting research on the carbocyclization of carbohydrates for many years, i.e. the conversion of simple, readily available monosaccharides into hydroxylated cycloalkanes and cycloalkenes with pharmaceutical potential. Several key reactions are presented in this Article to illustrate such facile transformation namely  $[\pi 4s + \pi 2s]$  cycloaddition - intramolecular nitrone-alkene and nitrile oxide-alkene cycloadditions, intramolecular direct aldol reaction and intramolecular Horner–Wadsworth–Emmons olefination. These protocols provide facile entries to 6 and 7-membered hydroxylated carbocycles in enantiomerically pure forms which then could be further elaborated into target molecules. Examples including calystegines, tropane alkaloid, cyclohexanyl and cyclohexenyl gabosines, cycloheptanones, valiolamine, validoxylamine G, pseudo-acarviosin, and a SGLT2 inhibitor are presented.

Keywords: carbohydrates, natural products, organic synthesis, pericyclic reactions, hydroxylated carbocycles

This review article describes our research efforts on finding a short, facile, and efficient way of transforming carbohydrates into hydroxylated carbocycles over a period of about 30 years. There are excellent reviews on the topic published elsewhere.<sup>1</sup>

The story begins when I was a postdoctoral fellow at Oxford working with Professor George Fleet in 1983. We were trying to synthesize shikimic acid from D-mannose using an intramolecular aldol condensation or a Wittig-type alkenation as the key step. Installing a phosphono-acetate moiety at the C-5 of the benzyl furanoside intermediate 1 to form the Wittig-Horner–Emmons precursor met with difficulty (Scheme 1).<sup>2</sup>

Simple  $S_N 2$  displacement reactions in carbohydrates are known to be sluggish/difficult due to the high concentration of oxygen functions (electron rich). Thus the derived standard electrophiles, 5-tosylate 2 and 5-iodide 3 were found to be inert towards substitution. We then attempted to use the 5-triflate 4 as a reactive leaving group (this was new at that time). Gratifyingly, the alkylation proceeded smoothly to give the Horner–Wadsworth–Emmons (HWE) alkenation precursor in a good yield. Subsequent unmasking the aldehyde function in 5 by hydrogenolysis afforded lactol 6 that was treated with base to give the cyclohexene motif, the protected shikimic acid 7. Acid catalysed removal of the blocking groups in 7 furnished shikimic acid in an excellent overall yield.<sup>2</sup>





Up to date, this intramolecular HWE alkenation is still one of the most powerful strategies for the carbocyclization of sugar molecules. A notable example of using this strategy was demonstrated by Fang and co-workers<sup>3</sup> to synthesize anti-viral agent Tamiflu<sup>®</sup> **12** and its more potent phosphonate analog **13** in a similar manner (Scheme 2).

\* Tamiflu® is a registered trademark of F. Hoffmann-La Roche, Ltd.

The reasons for researching on carbocyclization of carbohydrates are attributed to the fact that many biologically active molecules are hydroxylated cycloalkanes/alkenes. Carbohydrates are obvious starting materials that offer the most facile and economical way to approach these highly oxygenated carbocycles with defined stereochemistry. Some hydroxlated cyclohexanes and cyclohexene are listed in Figure 1. They display a wide plethora of bioactivities including antibiotic, antitumor, antiviral, glycosidase inhibitory activities.

Calystegines,<sup>4</sup> displayed specific glycosidase inhibition, are a group of bicyclic heterocycles which are in equilibrium with the open chain form, a hydroxylated gamma-amino cycloheptanone that are potentially accessible from carbohydrates (Figure 2).

Gabosines are a group of hydroxylated cyclohexanones/ cyclohexenones that display antibiotic, anticancer, and DNA binding properties (Figure 3).<sup>5</sup> All these compounds should in theory be approachable from sugars, but how could we effect the carbocyclization efficiently?







Towards that end, we have been investigating the following strategies for the carbocyclization of sugars:

- 1. Carbocyclization of Carbohydrates *via* an Intramolecular Nitrone-Alkene Cycloaddition (INAC)
- Carbocyclization of Carbohydrates *via* an Intramolecular Nitrile Oxide-Alkene Cycloaddition (INOAC)
- 3. Carbocyclization of Carbohydrates *via* an Intramolecular Direct Aldol Addition of Sugar Diketone
- 4. Carbocyclization of Carbohydrates *via* an Intramolecular Horner-Wadsworth-Emmons (HWE) Olefination

From 1984, I started my independent research career at the University of Manchester and began to investigate the construction of carbocycles using an INAC reaction as the key step.

## **1.** Carbocyclization of Carbohydrates *via* an Intramolecular Nitrone-Alkene Cycloaddition (INAC)

2,3-O-Isopropylidene D-ribose 23 underwent a chelation controlled Grignard vinylation to give triol 24 (Scheme 3). Glycol cleavage oxidation of the vicinal diol in 24 affoded lactol 25 which on heating with *N*-methyl hydroxylamine furnished a hydroxylated cyclopentane 27 smoothly. This is an extremely short approach towards 5-membered carbocycles and its application to the syntheses of carbocyclic nucleosides should have received more attention.<sup>6</sup>

On the other hand, chelation controlled vinylation of diacetone mannose 28 gave allyl alcohol 29 stereoselectively which was protected as benzyl ether 30 (Scheme 4). Regioselective mild acid hydrolysis of the terminal acetonide was feasible as the *O*-8 was the least hindered and therefore protonated first. The resultant diol 31 was oxidatively cleaved to afford aldehyde 32 which was reacted with *N*-methyl hydroxylamine to give nitrone 33. INAC occurred smoothly on heating to give cyclohexane 34 in good yield. In both cases, the new C–N bond is *anti* to the *O*-2 stereochemistry and the ring fusion is *cis*.<sup>6</sup>







We had more interests in this INAC reaction because we reasoned that it could be controlled to provide 7-membered carbocycles. When a sugar molecule was elaborated to have a terminal alkene, on reaction with *N*-alkyl hydroxylamine, there would be two possible modes of INAC cyclization, the *exo* or the *endo* mode (Scheme 5), which leads to either a fused or a bridged isoxazolidine, respectively.<sup>7</sup> To be specific, a hept-6-enose would provide either a fused bicyclo[4.3.0] system, i.e. a cyclohexane skeleton from an *exo*-mode or a bridged bicyclo[4.2.1] system, i.e. a cycloheptane skeleton from an *endo*-mode INAC cyclization. We were particularly intrigued by the potential formation of 7-membered carbocycles as there are few synthetic strategies towards cycloheptanes whereas the synthetic methods for the construction of 5- and 6-membered carbocycles are plentiful.

We realised that the formation of a cyclohexane skeleton *via* the *exo*-mode of cyclization of hept-6-enose is the usual regioselectivity outcome with conventional protecting groups like benzyl ether, silyl ether, acetonide, and esters *etc*. For examples, nitrone **35** and **36**, both with a *cis*-diol acetonide protecting group gave cyclohexane rings in high yields (Scheme 6).<sup>8</sup> The stereochemistry of 4-OH apparently had no effect on the regioselectivity.

We reasoned that the mode of cyclization might be controlled by the blocking groups as they affect the orbital overlap between the nitrone and the alkene. Thus we investigated the effect of *trans*-diacetal blocking group on the regioselectivity of hept-6-enose. Epimeric nitrones **37** and **38** were readily prepared from D-arabinose involving glycosidation with benzyl alcohol, diacetalisation, debenzylation, Grignard









allylation, glycol cleavage oxidation and reaction with N-methyl hydroxylamine. Interestingly, nitrones 37 and 38 with a transdiacetal blocking group (the diol moiety is trans) afforded endomode of cyclization products 41, 44, 45, i.e., cycloheptane rings, for the first time (Scheme 7). Another notable feature of this reaction is that a trans-fused bicyclo[4.3.0] system, i.e. cyclohexane 40 and 43 were formed. The lower yield of cis-fused 42 and higher yield of trans-fused 43 is probably attributed to the 1,3 diaxial interaction between 4-OH and the 6-hydroxymethyl in 42, this steric interaction is absent in the cis-cycloadduct 39. The rigidity of the diacetal ring requires 2-O and 3-O in the trans-diequatorial dispositions, thus 4-OH and the 6-hydroxymethyl in 42 must be axial.8

We reasoned that cycloheptane ring might be more accommodating than 6-membered rings as far as ring strain is concerned. We therefore went on to study the effect of an acetonide with a trans-diol blocking group on the regioselectivity of nitrone cycloaddition of hept-6-enose (Scheme 8). Nitrones 46 and 47 with an acetonide of trans-2,3-diol provided endo-cycloadducts 48 and 49 as the major products for the first time.9

Hept-6-enose nitrones 50 and 51 with a 3,4-transacetonide were even more remarkable as only the endo-mode cycloheptanes were harvested in good yields (Scheme 9).10





Scheme 8. INAC of hept-6-enoses with a 2,3-trans-acetonide





We were wondering if the stereochemistry of the C-2/C-5 hydroxyl groups might affect the regioselectivity of the INAC reactions. We thus constructed a hept-6-enose nitrone **60** with only a 3,4-*trans*-acetonide from L-tartaric acid using standard reactions (Scheme 10). Only a cycloheptane ring **61** was obtained, thereby confirming that the *endo*-mode of cyclization was controlled by the *trans*-acetonide ring.<sup>11</sup>

Since we have established that 7-membered cycloheptanes can be accessed *via* a *trans*-acetonide directed *endo*-selective INAC reactions of hept-6-enoses, we set out to synthesize calystegine analogs. In this way, D-xylose was transformed into cycloheptanes **63**, **64**, **65** with a 3,4-*trans*-acetonide (Scheme 11). Debenzoylation afforded the corresponding alcohols in which **66** and **68** were oxidized to the same ketone **69**. Acidic deacetonation of **69** followed by global hydrogenolysis furnished (S)-3-hydroxy-calystegine B<sub>5</sub> **71**.<sup>10</sup> We found that *tert*-butanol was a good solvent for hydrogenolysis of a *N*-benzyl group as no side products from *N*-alkylation was possible.





On the other hand, D-ribose was converted into aldehyde **72** which underwent *trans*-acetonide directed *endo*-selective INAC reaction to give cycloheptane **73** in an excellent yield (Scheme 12). Acid hydrolysis of the acetonide ring produced

the diol **74** which underwent steric controlled regio-selective oxidation of the less hindered alcohol to give ketone **75**. Hydrogenolysis of the N–O bond afforded a B-type calystegine **76**.<sup>10</sup>





Then we investigated this *endo*-selective INAC approach towards syntheses of tropane alkaloid **90** and analogs.

### (A) Strategy towards tropane alkaloid 1: INAC of a Nitrone with a 2,3-*cis*-Isopropylidene as Blocking Group and an $\alpha$ , $\beta$ -Unsaturated Ester as Dipolarophile

Since the alkene moiety in 77 is an electrophilic alkene whereas the alkenes used in our INAC cyclization mode studies were simple nucleophilic alkenes, we were hoping that the electrophilic alkene of the enoate group in 77 might cause an *endo*-selective INAC reaction attributable to HOMO-LUMO reasons (Scheme 13). This proposal was supported by a precedent<sup>12</sup> that in the intermolecular nitrone-alkene cycloaddition of  $\alpha$ , $\beta$ -unsaturated ester **82**, and nitrone **81**, the new C–O was installed on the  $\beta$ -carbon in cycloadducts **83** and in **84** (Scheme 14). If this were applied to our INAC case, the *endo*-mode cyclization would have taken place. We were excited with this precedent and therefore proceeded with the synthesis.

To our disappointment, the INAC of nitrone **85** produced only *exo*-mode cycloadducts **86** and **87**, 6-membered carbocycles. Hence it appears that steric control is more important than electronic control for the regioselectivity (*exo* versus *endo*) of INAC reactions of hept-6-enoses (Scheme 15).<sup>11</sup>

## (B) Strategy towards tropane alkaloid 2: INAC of a Nitrone with a 3,4-*trans*-Isopropylidene as Blocking Group and an $\alpha$ , $\beta$ -Unsaturated Ester as Dipolarophile

Since we had shown that 3,4-*trans*-acetonide would direct an *endo*-selective mode of cyclization, we devised a synthetic route towards tropane alkaloid **90** based on this key step as summarised in Scheme 16.











Capitalising from our studies that 3,4-*trans*-acetonide would produce cycloheptane ring on INAC reactions of hept-6enoses, we proceeded to prepare the nitrone **97** from ribose.<sup>13</sup> The known allyl alcohol **91** was readily obtained from D-ribose *via* a steric-controlled allylation (Scheme 17). Thermodynamic acetonation of **91** formed the 7,8-*O*-isopropylidene first as the primary 8-alcohol was the most reactive of all. Then an acetonide was formed between *O*-4,5 instead of *O*-5,6 because the substituents on the acetonide ring **92** were *trans* to each other. The diacetonide **92** was then transformed into diol **95** without incident. Glycol cleavage oxidation of **95** with silica supported NaIO<sub>4</sub> furnished aldehyde **96** smoothly. This solid-phase NaIO<sub>4</sub> reagent<sup>14</sup> is highly recommended as the operation is very simple and the aldehyde harvested is usually un-hydrated. INAC reaction of **97** did produce the desired cycloheptane derivative **98** as the major product.<sup>13</sup>

As the cycloheptane skeleton was installed correctly, cycloadduct **98** was converted into natural tropane alkaloid **90** and its analogs **100–104** as shown in Figure 4.<sup>13</sup>







#### 2. Carbocyclization of Carbohydrates *via* an Intramolecular Nitrile Oxide-Alkene Cycloaddition (INOAC)

The use of chloramine-T in the conversion of ene-sugar oxime into a nitrile oxide and its subsequent INOAC reaction is known.<sup>15</sup> This cycloaddition shown in Scheme 18 can only be *exo*-mode as the *endo*-mode of cyclization would produce an impossible C=N bond at the bridge head position (Bredt's rule).<sup>16</sup>

Common chemicals for the transformation of oxime into nitrile oxide include NaOC1, NaOC1/NEt<sub>3</sub> and *N*-chorosuccinimde/NEt<sub>3</sub>.<sup>16</sup> Under the basic conditions,

the free hydroxyl group in nitrile oxide **105** would attack the nitrile carbon to give oximolactone **106** and failed to produce a carbocycle. The hydroxy groups of the sugar have to be protected in order to achieve satisfactory yields. Thus, providing a mildly acidic environment for the INOAC reactions is crucial in achieving a fruitful carbocyclization without the formation of oximolactone.

We found that adding flash chromatography silica gel to "buffer" the reaction medium dramatically increased the yield of the chloramine-T mediated INOAC reaction from 62 to 94% (Scheme 20).<sup>17</sup>









Towards the construction of 5-membered carbocycles, similar improvement in reaction yields were observed and examples are shown in Scheme 21. It is interesting to note that other acidic conditions attempted including the addition of acetic acid, benzoic acid, acetate buffer or phosphate buffer did not cause the INOAC to occur.

The silica gel mediated INOAC reactions were compatible with substrates containing unprotected hydroxyl groups, thus reducing masking/unmasking steps and rendering a synthesis shorter.<sup>17</sup>

We have applied this methodology to the construction of gabosine O and F.<sup>18</sup> Mannose was transformed readily into oxime **114** with a free hydroxyl group (Scheme 22). INOAC of **114** occurred smoothly to give a 6-membered carbocycle **115** which was hydrogenolysed, dehydrated, and then hydrogenated from the less hindered side to form ketone **118**. Acidic hydrolysis of the acetonide in **118** yielded the target molecule gabosine O.<sup>18</sup>

On the other hand, L-arabinose was transformed into oxime **119** with a free hydroxyl group. INOAC reaction of **120** furnished the 6-membered carbocycle in an excellent yield with the new C–C bond equatorially installed. Standard conversion afforded the target molecule gabosine F (Scheme 23).









# **3.** Carbocyclization of Carbohydrates *via* an Intramolecular Direct Aldol Addition of Sugar Diketone

First of all, we started our investigation on D-glucose since voglibose 18 and valiolamine 19 are obvious synthetic targets. Glycosidation of D-glucose with allyl alcohol and then

diacetalization produced 2,3- **124** and 3,4-diacetals **123** which were readily separable upon acetonation to the 4,6-acetonide **126**.<sup>19</sup> Palladium catalysed deallylation of glycoside **126** gave lactol **127** which underwent Grignard methyl addition followed by PDC oxidation afforded the 2,6-diketone **129**. Intramolecular aldol addition reactions of **129** were carried out under various basic conditions and the best results are shown in Table 1.





The stereo-selective formation of a particular aldol product can be controlled by either L-proline, strong or weak amine base. It is noteworthy that all the direct aldol reactions are not reversible. The resistance towards a retro-aldol reaction is probably attributable to steric reasons.

The preparation of mannose diketone **135** was executed in a similar manner (Scheme 25). Disappointingly, all strong and weak basic conditions failed to generate an aldol product with the exception of L-proline, which provided aldol 136 as the sole cyclohexanone in 60% yield.<sup>19</sup>

We have also investigated an intramolecular direct aldolization of 2,7-diketones, in search for a synthetic avenue towards hydroxylated cycloheptanones. The 2,7-diketones were prepared from D-ribose or D-mannose using standard reactions and the results are summarized in Scheme 26.<sup>20</sup>





Application of the versatile intramolecular direct aldolization strategy to synthesis was demonstrated by the following examples.

#### 3a. Synthesis of Valiolamine and Voglibose (AO128)

D-Glucose was transformed smoothly into aldol 131 as stated above. Oximation of the ketone moiety in 131 followed by hydrogenation/hydrogenolysis furnished amine 142. Acidic removal of the acetals in 142 provided vailolamine 19 which, reportedly, could be converted into the anti-diabetic agent voglibose (AO128) 18 (Scheme 27).19

#### 3b. Synthesis of Pseudo-Acarviosin

Methyl acarviosin 143 was obtained from the natural antidiabetic agent, acarbose, by acidic methanolysis (Figure 5). As methyl acarviosin is a stronger  $\alpha$ -amylase inhibitor, we wanted to replace the sugar moiety in 143 with a cyclohexane to render the compound more stability in acid conditions. In search for an improved anti-diabetic drug, we proceeded to synthesize pseudo-acarviosin 144 for biological screening.

Retrosythesis of pseudo-acarviosin 144 via a palladium catalysed allylic substitution would give two fragments, an allylic chloride 145 and a cyclohexanyl amine 146. Chloride 145 would be accessed from D-glucose via a direct aldol strategy while the amine 146 should be approached from L-arabinose through an INAC reaction.21







The palladium-catalysed coupling plan is the result of a massive experimentation. We attempted a great many coupling reaction conditions between different partners, amine with mesylate, ketone, allylic epoxide, allyic cyclic sulphite, or allylic acetate.<sup>22</sup> As most of the electrophiles are unstable under the conditions and elimination is the major side-reaction, none of the coupling reactions gave the desired product except for using allylic chloride as the coupling partner shown in Scheme 29.<sup>23</sup>

Since the coupling conditions were established, we started to construct the two coupling partners **145** and **146**. D-Glucose was converted into aldol **130** as said earlier.<sup>19</sup> Elimination of the alcohol in **130** followed by reduction of the ketone group in **147** produced allylic alcohol **148** which was separated from its epimer *via* an acetylation and deacetylation protocol. The isolated **148** was then transformed into the allylic chloride **145** by standard reactions (Scheme 30).







On the other hand, the amine coupling partner 146 was assembled from L-arabinose *via* an INAC reaction of a protected hept-6-enose 151 as the key step (Scheme 31).<sup>21</sup> The major *exo*-cycloadduct 154 with a *trans*-ring fusion was formed with the correct stereochemistry. It is noteworthy that the *trans*-fused *exo*-cycloadduct could only be harvested with the nitrone containing a *trans*-diacetal blocking group. The cycloadduct 154 was transformed readily into the cyclohexyl amine 146 using standard reactions with a good overall yield.

With the coupling partners in our hand, palladium catalysed allylic substitution of chloride **145** with amine **146** proceeded with retention of configuration to give the protected allylic amine **161** (Scheme 32). Hydrolysis gave the target molecule pseudo-acarviosin **144** which was shown to be a stronger sucrose and glucoamylase inhibitor than acarbose.<sup>21</sup>

#### 3c. Synthesis of Validoxylamine G

Capitalising on the palladium-catalysed allylic substitution reaction, the silyl ether **162** of the afore-prepared amine **142** and allylic chloride **145** (both are direct aldol products from D-glucose) were coupled together to form pseudo-glycosyl amine **163** which on complete acidic deprotection afforded validoxylamine G **164** in a good yield (Scheme 33).<sup>19</sup>







#### 3d. Synthesis of Gabosines

A number of gabosines were easily assembled from D-glucose *via* the direct aldol strategy. Only a few of them are illustrated here.<sup>24,25</sup> Thus the aforesaid enone **147** was regioand stereo-selectively reduced to the  $\alpha$ -allylic alcohol **165** in an excellent yield (Scheme 34). Functional group manipulation of **165** with standard reactions then furnished gabosine A, D, and E without incident.<sup>25</sup>

### 4. Carbocyclization of Carbohydrates *via* an Intramolecular Horner–Wadsworth–Emmons (HWE) Olefination

Intramolecular HWE olefination was introduced at the beginning of this article, interestingly, it is perhaps still the best strategy for a short and efficient carbocyclization of carbohydrate. Towards this end, we globally protected D-gluconolactone with 2-methoxypropene as mixed acetals **166** (Scheme 35).<sup>26</sup> Addition of methyl phosphonate carbanion followed by oxidation of the alcohol in **167** caused intramolecular HWE alkenation to proceed concomitantly to give the protected cyclohexanone **169** in just 3 steps from the free sugar! Acidic removal of the acetals afforded gabosine I **170** and regioselective acetylation at the primary alcohol provided gabosine G **171**. The relatively labile mixed acetal blocking groups were problematic, but we have circumvented this obstacle with ethoxymethyl (EOM) protecting group.<sup>27</sup> Since EOM protected cyclohexanone **172** could also be synthesized readily from D-gluconolactone (Scheme 36), application of this route to the syntheses of streptol and other gabosines were accomplished.<sup>27,28</sup> Exploiting this facile carbocyclization strategy, we embarked on the construction of sodium-dependent glucose cotransporter 2 (SGLT2) inhibitors.

Sergliflozin is a potent SGLT2 inhibitor, but was abandoned for further investigation because phenyl glycosides are prone to hydrolysis and therefore not suitable for development into useful medicine. Replacing the sugar moiety in sergliflozin with a pseudo-sugar unit would provide a stable "glycoside" **173** as the "glycosidic bond" is now an ether linkage (Figure 6).<sup>29</sup>

The synthetic avenue towards pseudo glucopyranoside **173** is shown in Scheme 37. Regio- and stereo-selective reduction of **172** gave  $\alpha$ -alcohol **174** which was activated and displaced with chloride to  $\beta$ -chloride **175**. Palladium catalysed allylic substitution of the allylic chloride **175** with phenolic alcohol **176** proceeded with retention of configuration to form allylic ether **177** in an excellent yield. Catalytic hydrogenation followed by acid removal of the EOM groups afforded the target molecule **173** which is a potent and selective SGLT2 inhibitor. Other analogs have also been made on extending this carbocyclization strategy.<sup>30,31</sup>



Scheme 36. Synthesis of stable EOM blocked cyclohexanone 172







#### Conclusion

In this Article, transformation of carbohydrates into highly oxygenated cycloalkanes and cycloalkenes has been described using four synthetic strategies, namely intramolecular nitronealkene and nitrile oxide-alkene cycloadditions, direct aldol addition, and Horner-Wadsworth-Emmons (HWE) olefination. The latter strategy probably offers the most facile and efficient avenue to the pseudo-D-glucopyranose motif to date. The carbocyclized intermediates could then elaborated into various target molecules containing hydroxyl/amine functional groups of defined stereochemistry. Considering the low cost, availability in large quantities, and rich stereochemistry of sugar molecules, carbohydrates are perhaps the ideal starting materials for the construction of heavily oxygenated natural products or molecules with pharmaceutical implication. Research towards the syntheses of carbocyclic nucleosides should have received more attention.

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Professor Tony K. M. Shing obtained his first degree from the University of Hong Kong, his M.Sc. (analytical chemistry), Ph.D. (carbohydrate chemistry) and D.Sc. (organic synthesis) degrees from the University of London. After postdoctoral work at McGill University and Oxford University, Prof. Shing began his independent career at the University of Manchester England, as a New Blood Lecturer in 1984. He was visiting Associate Professor at the University of California, Irvine, before returning to Hong Kong

in 1990. He joined the Department of Chemistry at the Chinese University of Hong Kong (CUHK) as a Lecturer, was promoted to Senior Lecturer in 1993, and to full Professor in 1996. In 2016 August, he retired from CUHK and joined Sophia University as an Invited Visiting Professor. Professor Shing moved to Keio University in October last year and is now a full Professor at the Department of Chemistry. He is also the Chairman of the Hong Kong Section of the Royal Society of Chemistry. His research interest is on the syntheses of organic molecules with chemotherapeutic potential, namely anti-cancer, anti-viral, or anti-diabetic activity.