# グルカールボロン酸エステルを用いた新規 *C*-グルコシドの合成法の開発とその応用

２０１３年

坂槇　茂輝

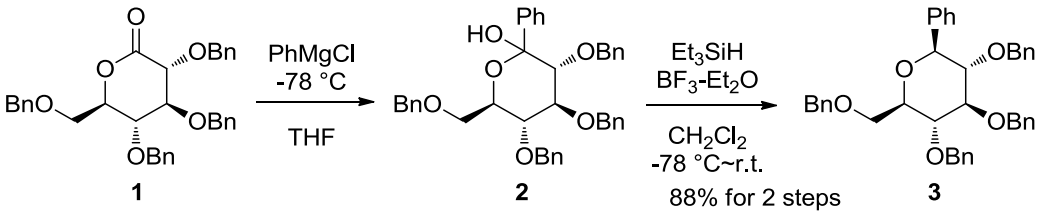
# 目次

# 第１章　緒言

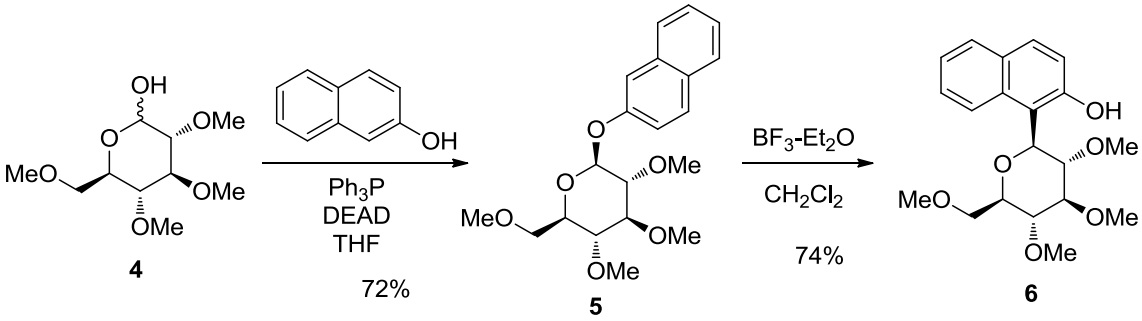
天然物である carthamin[1] や mangiferin[2]、bergenin[3,4] といった *C*-グルコシド誘導体は、近年、抗 HIV 活性や抗潰瘍作用、抗高脂血症といった、興味ある生理活性により注目を浴びている。加えて、*C*-グルコシドは *O*-グルコシドに比べて代謝的に安定であるため、創薬化学的な見地からも非常に興味深い化合物群である[5]。ゆえに、*C*-グルコシドの効率的な合成法は、有機合成化学および創薬化学にとって非常に大きなツールと考えられる[6-9]。

今までに報告されたアリール-β-*C*-グルコシド化の手法は、大別すると次に示す３つに分類される。

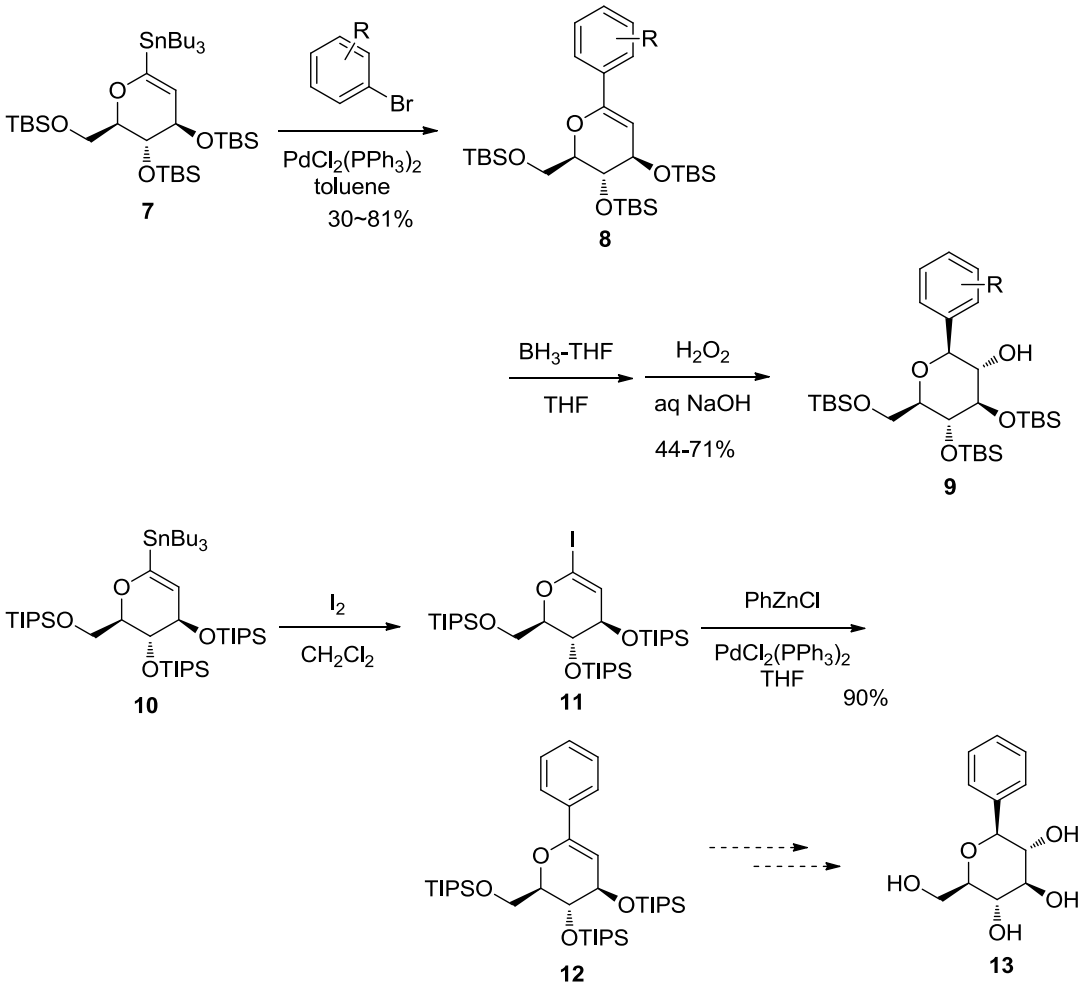
**Scheme 1. Reaction of Arylmetal with D-Gluconolactone and Reduction (Kraus *et al.*[10], 1988, Ellsworth *et al.*[11], 2003)**



**Scheme 2. *O*- to *C*- Glucosidic Bond Rearrangement (Fries-type Rearrangement) (Kometani *et al.*[12], 1988)**




**Scheme 3. Reaction via Palladium-catalyzed Coupling and Stereoselective hydroboration–oxidation (Friesen *et al.*, Dubois *et al.*,[13-15] 1990, Friesen *et al.*[16], 1991)**




各々の手法はいずれもアリール-β-*C*-グルコシドの合成に広く用いられている

が、それぞれ問題点がある。すなわち、グルコノラクトンにアリールメタルを反応させる方法 (Scheme 1) では、置換基の種類が限られ、エステル等、メタルと反応するような置換基のついた化合物には使えない。酸触媒による *O*-グルコシドから *C*-グルコシドへの転位（Fries 型転位）による方法 (Scheme 2) では、電子豊富な環にしか適用できず、汎用性に乏しいと考えられる。そして、パラジウム触媒カップリングを経由する方法 (Scheme 3) では、Stille 型反応のため猛毒のスズ化合物由来のグルカールを用いること、などである。

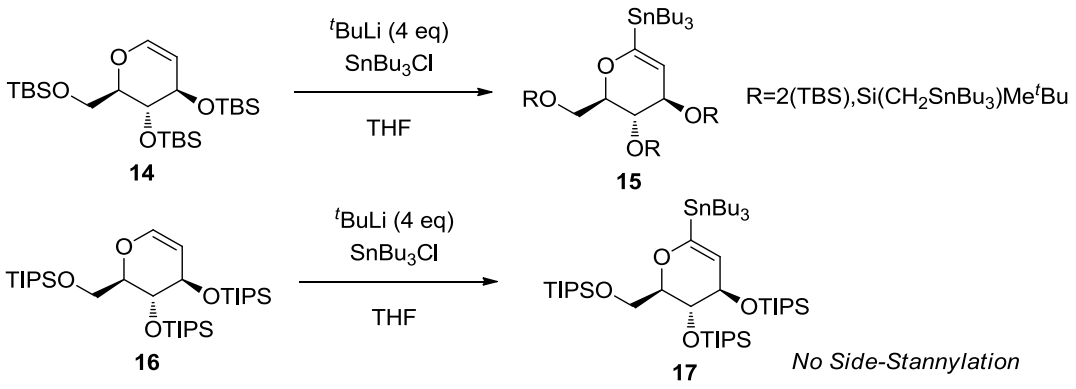
著者は、これらの中で、基質に対しての汎用性が期待できるため、三番目のグルカールに基づいたカップリングアプローチに着目し、スズの代わりに安定で毒性がなく、取り扱いが容易なボロン酸誘導体を用いた新たなアリール-*C*-グルコシド化の開発研究に着手することにした。

# 第２章　グルカールボロン酸誘導体基質の合成およびアリール-*C*-グリコシル化反応

## 第１節　トリス（トリイソプロピルシリル）グルカールボロン酸誘導体を用いた検討

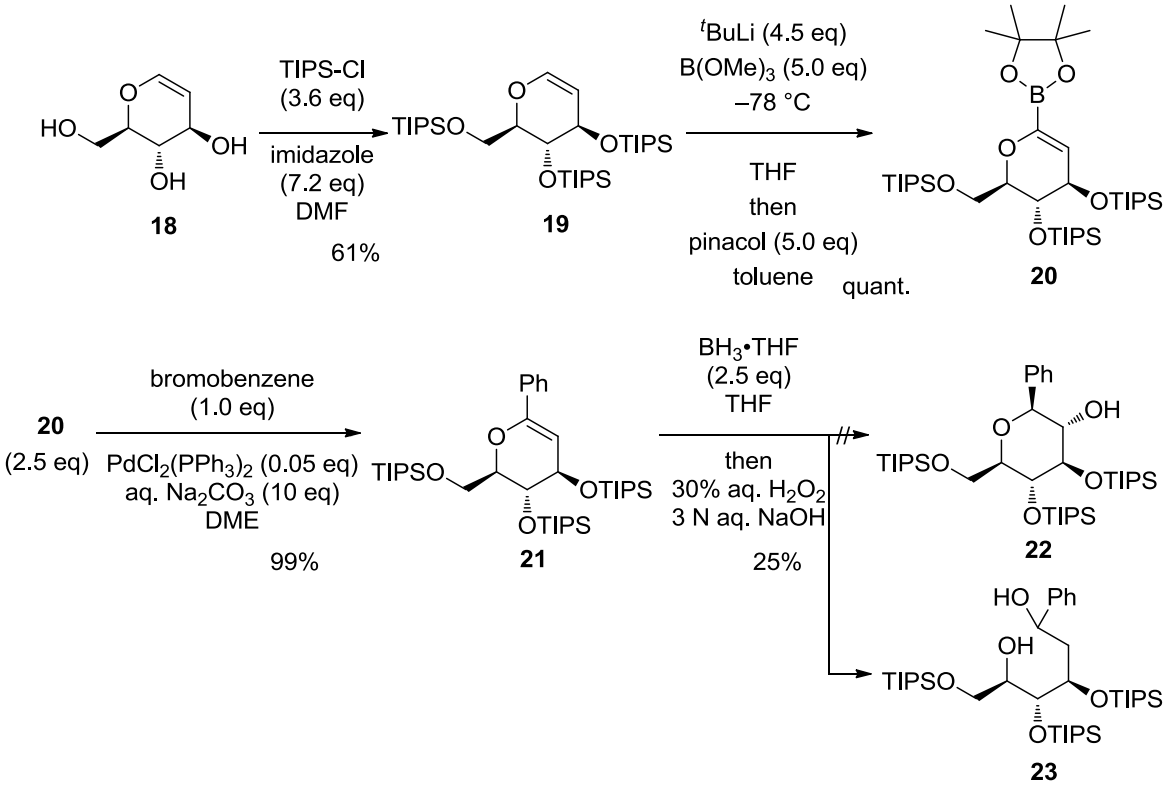
まず、基質に用いるグルカールボロン酸誘導体の合成を行った。保護基としては汎用性の高いシリル系保護基を用いることとした。シリル系保護基はいろいろ考えられるが、Scheme 4 に示すように、Friesen らはグルカールスズ体の合成の際、TBS 基を保護基に用いると、使用した *tert*-BuLi のために TBS 基の一部が脱プロトン化された後スズ化され、side-stannylation が同時に起こるのに反し、TIPS 基では side-stannylation は起こらず、問題なく反応が進行することを報告している [15,16]。それゆえ、我々は最初に、TIPS 基保護のグルカールボロン酸をデザインし合成した (Scheme 5)。

**Scheme 4. Side-stannylation Reaction**




市販のグルカール **18** に対して DMF 中、過剰量の TIPS-Cl とイミダゾールを作用させ、tri-TIPS 体 **19** を得た。ついで *tert*-BuLi によるリチオ化後にホウ酸トリメチルによりボロン酸を合成し、得られたボロン酸に対してピナコールを作用させることで安定なボロン酸ピナコールエステル **20** を油状物として得た。このグルカールボロン酸エステル **20** をブロモベンゼンとの鈴木カップリング反応に付すと、アリール-*C*-グルコシド **21** を定量的に与え、ここにスズ化合物に代わるパラジウム触媒カップリング反応による C-グルコシル化法を開発した。しかしながら、糖誘導体 **22** に導くべく、続くヒドロホウ素化とアルカリ条件下での過酸化水素による酸化反応 [17] による水酸基の導入を試みたが成功せず、低収率ながら得られたものは開環体 **23** のみであった。

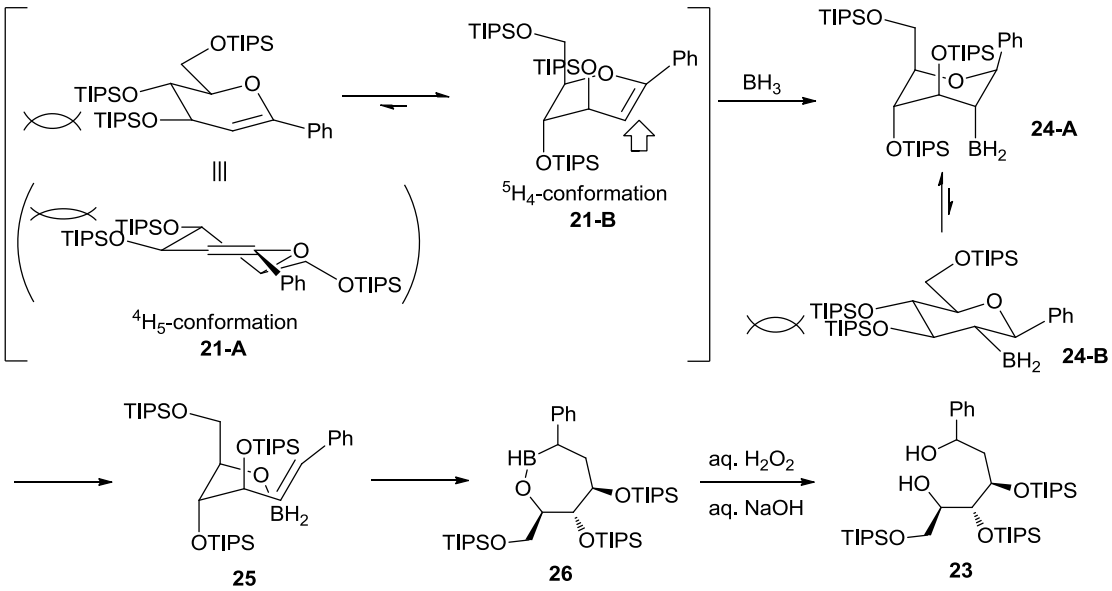
**Scheme 5. A Trial for the Preparation of Tri-TIPS-Protected β-D-glucoside 22**




この予想外の結果については、Figure 1 のように考察した。グルカールカップリング生成物 **21** には、$^{4}H_{5}$-conformation (**21-A**) と $^{5}H_{4}$-conformation (**21-B**) の２つのコンフォメーションが存在する。この場合、vinylogous anomeric effect により、$^{4}H_{5}$-conformation よりも $^{5}H_{4}$-conformation のほうが安定であることが知られている[18]。**21** のように、TIPS 基のようなかさ高い置換基がついたグルカールにおいては、TIPS 基同士の反発により $^{4}H_{5}$-conformation (**21-A**) がより取りにくくなっており、$^{5}H_{4}$-conformation (**21-B**) の形で存在していると考えられる[19]。それ故、ヒドロホウ素化がより立体的に空いている方向から起こり **24** を与えるが、**24** は

ピラン環の立体配座変換により **24-A** および **24-B** の２つのコンフォメーションを取りうると考えられる。しかしながら **24-B** では嵩高い TIPS 基同士の反発により、**24-A** が優勢に存在すると考えられ、その **24-A** からホウ素原子と環内の酸素原子との間で結合を生成し開環体 **25** を生成し、その後ホウ素原子が分子内ヒドロホウ素化を起こし７員環ボラサイクル **26** を経由して最終的に過酸化水素による酸化反応で **23** を与えたと推測される [20]。

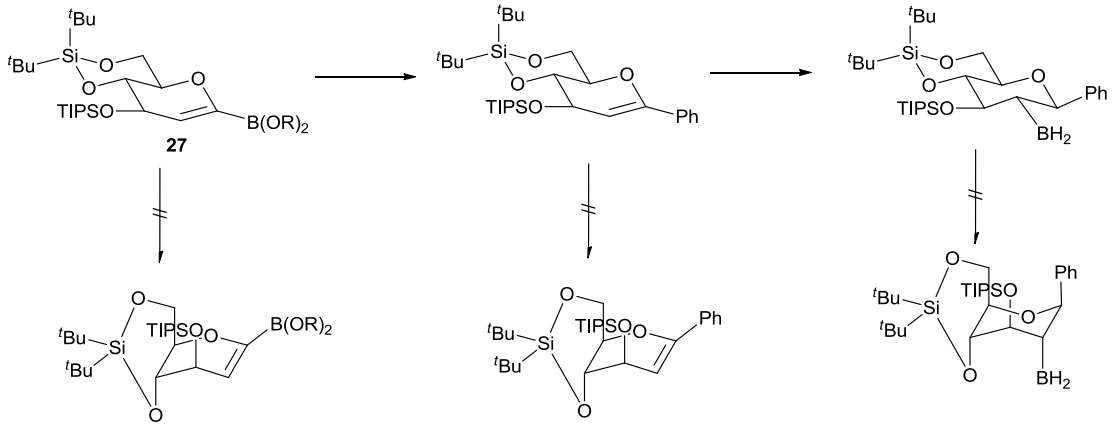
**Figure 1.　Plausible Mechanism for the Formation of 23 from 21**



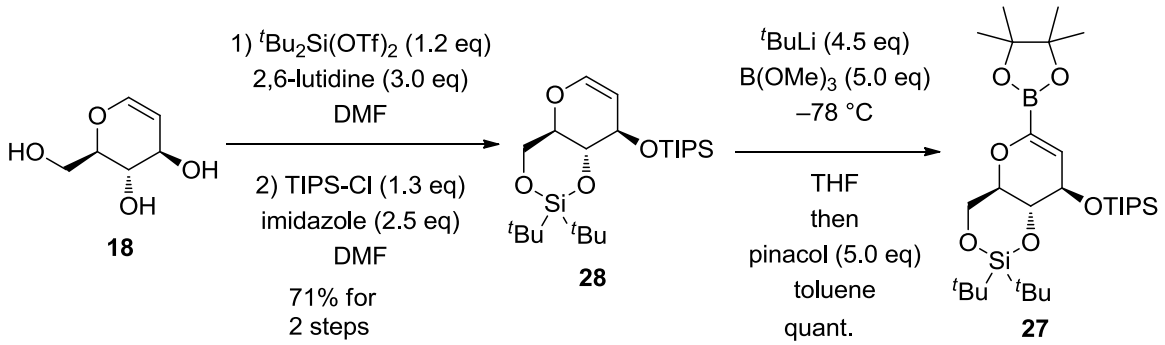
## 第２節　架橋シリル基保護グルカールボロン酸誘導体を用いた検討

第２章第１節に示した考察から、基質として Figure 1 の **21-A** から **21-B** の相互変換を起こさない、すなわちアキシャル―エカトリアル相互の配座変換を起こさないような基質として、ジ-*tert*-ブチルシリレン基で架橋したグルカールボロン酸誘導体 **27** をデザインした (Figure 2)。

**Figure 2**.　**Design of a bicyclic boronate 27**




**Scheme 6.　Synthesis of the Bicyclic Glucal Boronate 27**



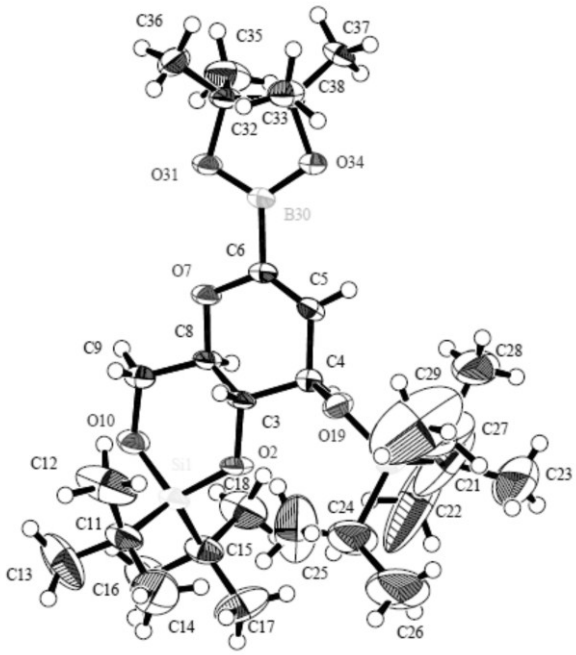


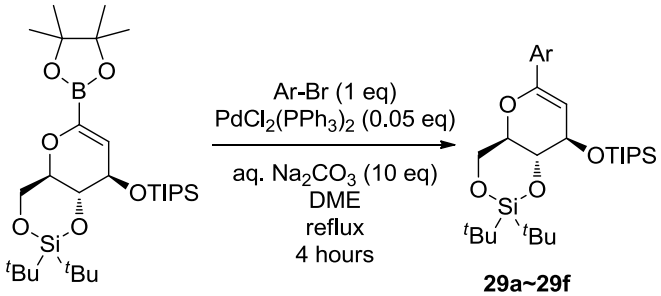

**Figure 3. ORTEP drawing of 27. The displacement ellipsoids are drawn at the 50% probability level.**

合成法を Scheme 6 に示す。まず文献に報告の通りの方法[21]で **28** を合成した。すなわち、市販の D-グルカール **18** から、*tert*-$Bu_2Si(OTf)_2$ を用いてグルカールの４位と６位に架橋シリル化を行い、その後残った水酸基をトリイソプロピルシリルクロリドで保護し **28** を得た。次いで *tert*-BuLi を用いてビニル位をリチオ化したのちにホウ酸トリメチルを反応させ、その後系内でピナコールによりピナコールエステルにすることにより目的とするグルカールボロン酸誘導体 **27** を得た。このものは粗体では粘性物であったが、さらなるゲルろ過精製により結晶化することに成功し、X線結晶構造解析にてその構造を確認した (Figure 3)。本結晶は、他のボロン酸エステルと同様、室温で少なくとも６か月間安定である

ことを確認した。

この **27** を用いて、ヘテロアリール体を含む各種アリールブロミドとの反応の scope and limitation を実施した。Table 1 に示すように、単純なフェニル基 (Entry 1) だけでなく、メトキシ基 (Entry 2) のような電子供与性、あるいはエステル基 (Entry 3,4) のような電子吸引性置換基を有したフェニル基、およびヘテロ環 (Entry 5,6) であっても容易にカップリング反応が進行し、**29a**~**29f** を定量的に生成することを認めた。得られたカップリング体については、キノリン誘導体 **29f** を除き、続く立体選択的ヒドロホウ素化反応と、塩基性下での酸化反応を行った。その結果、Table 2 に示すように収率は中程度であったが、いずれも目的とする保護アリール-*C*-グルコシド体 **30a**~**30e** であった。生成物の立体は、$^1$H NMR におけるアノマー位（１位）と２位との間のカップリング定数 ($J_{1,2} \approx 9.5$ Hz) からすべて $\beta$ 体であることを決定した。最後に、**30a**~**30e** のシリル基をテトラ-*n*-ブチルアンモニウムフルオリドで脱保護することによりアリール-*C*-グルコシド **31a**~**31e** を中～高収率で得た。

**Table 1. Suzuki Cross-Couplings of Glucal Boronate 27 with Aryl Bromides**




**27** (2.5 eq) **29a~29f**

[a] Isolated yield.

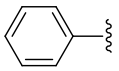
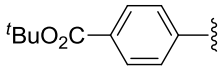
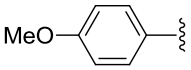
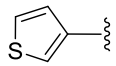
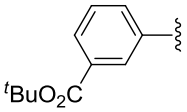
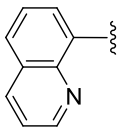
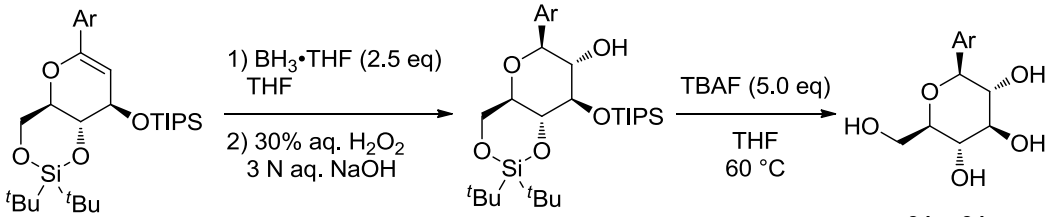
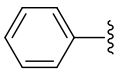
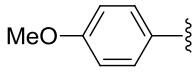
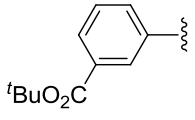
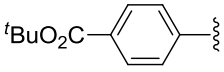
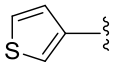
| entry | Ar | product | yield (%)[a] | entry | Ar | product | yield (%)[a] |
|---|---|---|---|---|---|---|---|
| 1 |  | **29a** | 99 | 4 |  | **29d** | 99 |
| 2 |  | **29b** | 99 | 5 |  | **29e** | 99 |
| 3 |  | **29c** | 99 | 6 |  | **29f** | 99 |

**Table 2. Stereoselective Synthesis of Aryl-β-*C*-glucosides 31**



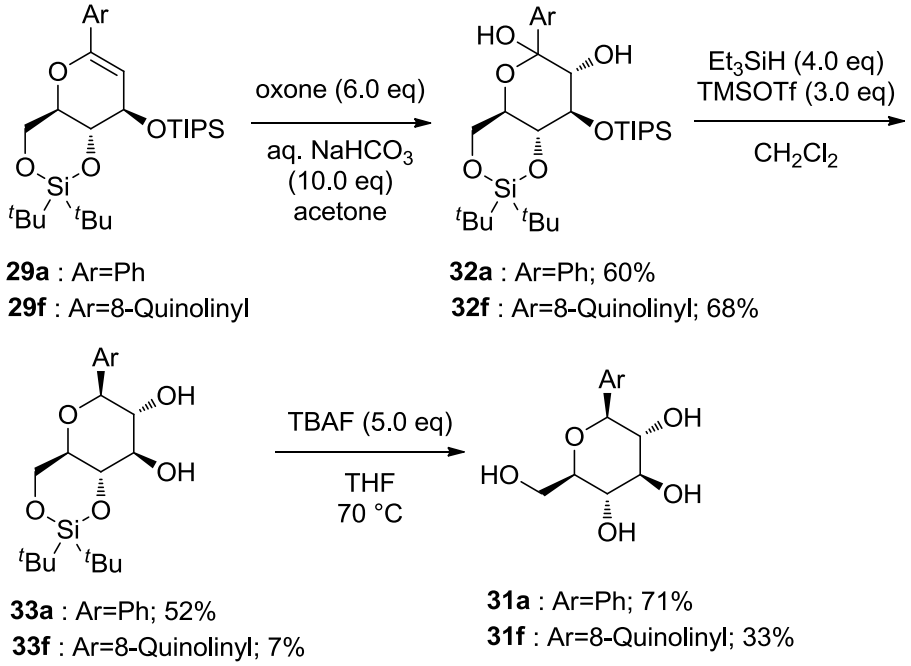

**29a~29e** **30a~30e** **31a~31e**

| entry | material | Ar | product | yield (%)[a] | product | yield (%)[a] |
|---|---|---|---|---|---|---|
| 1 | **29a** |  | **30a** | 58 | **31a** | 43[b] |
| 2 | **29b** |  | **30b** | 60 | **31b** | 52 |
| 3 | **29c** |  | **30c** | 52 | **31c** | 83 |
| 4 | **29d** |  | **30d** | 41 | **31d** | 90 |
| 5 | **29e** |  | **30e** | 49 | **31e** | 37 |

[a] Isolated yield. [b] Overall 25% yield from **30a**.

なお、**29f** のような、窒素原子を有した化合物のヒドロホウ素化―酸化反応は非常に汚くなり、目的物を得ることができなかった。そこで、酸化剤としてオキソンを用いる反応を検討した (Scheme 7)。まず、モデル基質として無置換フェニル体 **29a** を選択し、アセトン中、オキソンと炭酸水素ナトリウム水溶液で処理したところ、ジヒドロキシ体 **32a** を 60%の収率、約 10 : 1 の anomeric mixture として得た。これをシラン還元に付すと、TIPS 基も脱離するが、完全にアノマー位の立体が β 体に制御された架橋シリル化アリール-*C*-グルコシド **33a** が 52%で得られてきた。最後に TBAF で架橋シリル基を脱保護し、目的の *C*-グルコシド **31a** に導いた。その通算収率は 33%であった。次いで本ルートをキノリン誘導体 **29-f** に適用し、*C*-グルコシド **31f** への変換を実施した。すると、シラン還元 (7%) と脱架橋シリル化反応 (33%) の収率は低いながらも目的のアリール-*C*-グルコシド **31f** を得ることができた。

**Scheme 7. Alternative Synthesis of β-*C*-glucosides 31a and 31f from Arylglucals 29a and 29f Using Oxone**

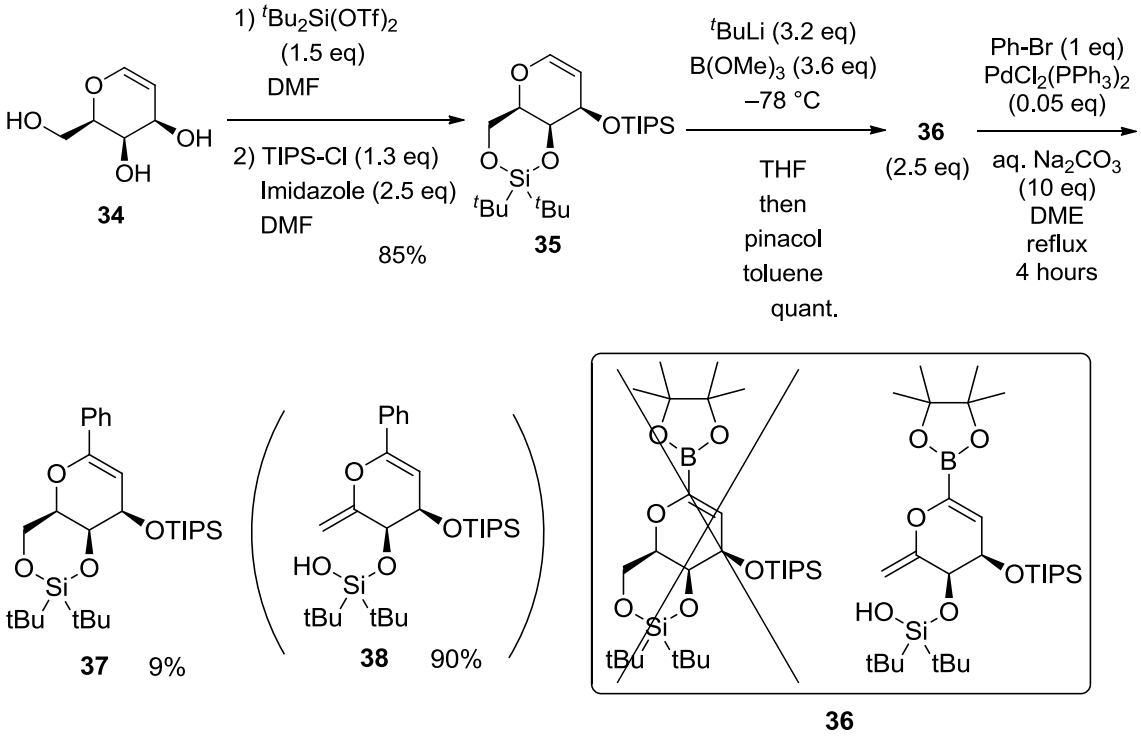



以上のように、著者は、安全で取扱の容易なグルカールボロン酸エステル **27** を用いて、汎用性の高いアリール-β-*C*-グルコシドの合成法を見出すことに成功した。

# 第３章　*C*-ガラクトシド合成の検討

第２章第２節において著者が開発した手法の糖部位の適用範囲を探るため、グルコース誘導体以外にガラクトース誘導体にも応用できるか検討することにした。すなわち、D-グルカールの代わりに D-ガラクタールを用いてボロン酸エステルを合成、その後アリールハライドとのカップリング反応にて *C*-ガラクトシドを合成するというものである。

**Scheme 8. Synthetic Approach of *C*-Galactoside.**



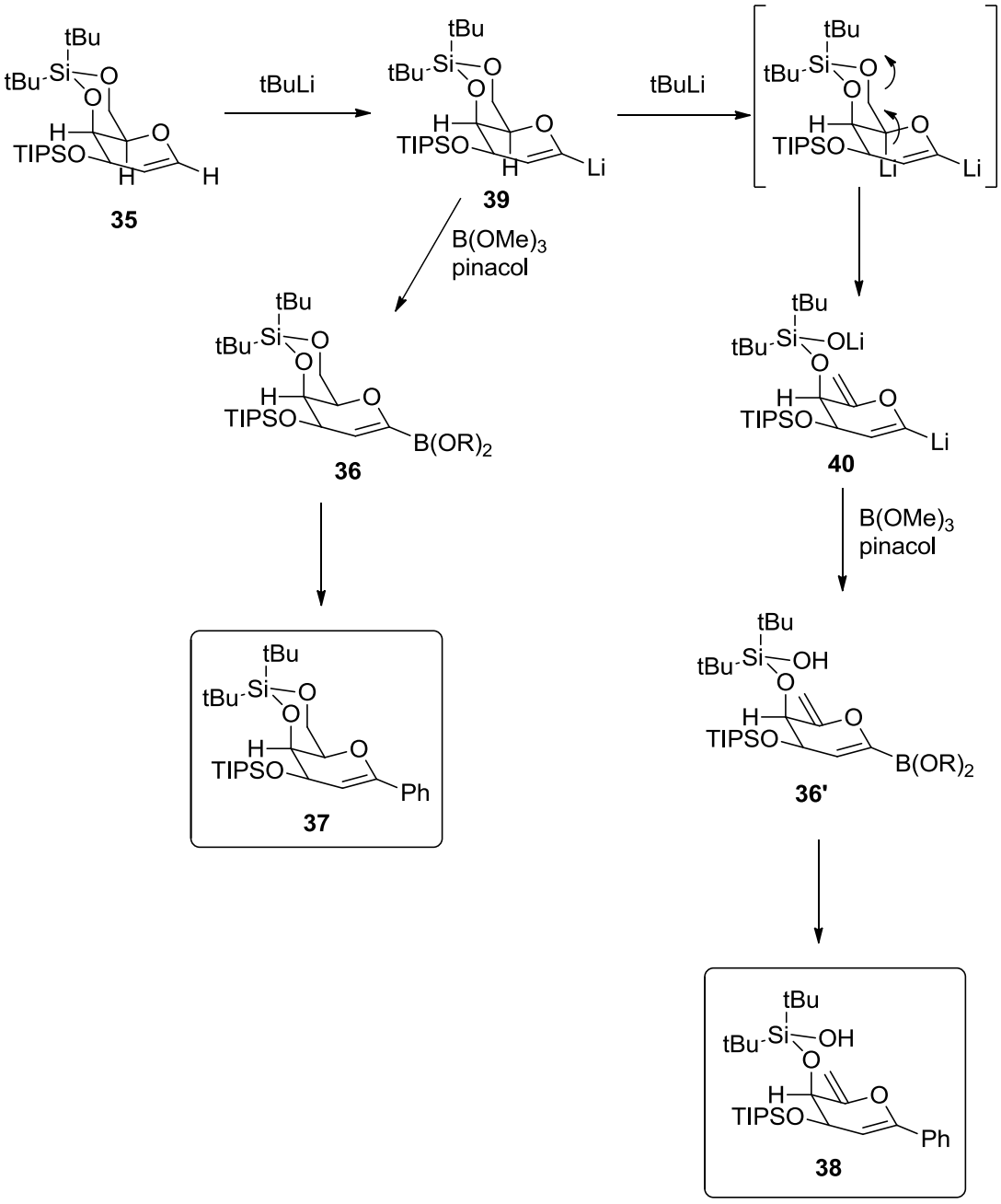

Scheme 8 に示すように、市販の D-ガラクタール **34** を出発原料とし、まず架橋シリル基で保護したのち[22]、残りの水酸基を TIPS 基で保護した D-ガラクタール

**35** を合成した。その後、*tert*-BuLi でオレフィン部位をリチオ化し、ホウ酸エステルと反応させてピナコール処理を行い、ガラクタールボロン酸 **36** を合成した。まず、ガラクタールを用いてもグルカールの際と同様に反応が進行するかどうかを見極めるため、本化合物はそのまま精製せずにカップリング反応を行った。すると得られたものは所望のカップリング体 **37** がメインではなく、オレフィン体 **38** がメインである分離不可能な混合物であり、その比は NMR からおよそ **37** : **38** = 1 : 10 であった。

副生成物 **38** の生成理由については次のように考察した (Scheme 9)。まず、過剰の *tert*-BuLi でオレフィン部がリチオ化されて **39** を生成した後、架橋シリル基の部分の５位のプロトンがさらに引き抜かれ **40** が生成、その後トリメチルホウ酸とピナコールで処理されて **36'** が得られ、これがブロモベンゼンとの鈴木カップリングにより **38** を生成したと考えられる。グルカールの場合には、まったく同じ、あるいはそれ以上の *tert*-BuLi の当量数で反応を実施しても、**38** のような生成物は全く得られておらず、その理由としてガラクタールの場合はグルカールと比べて５位が立体的に空いている結果、脱プロトン化が起こりやすくなっている、などの理由が考えられるが、詳細は不明である。

本結果より、ガラクタールからの *C*-ガラクトシド誘導体についてはこれ以上の合成検討を中止した。

**Scheme 9. Plausible Mechanism of the formation of 39.**

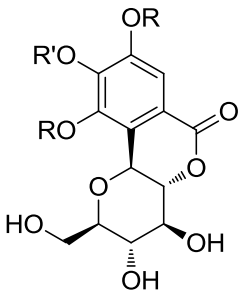


# 第４章　Bergenin 誘導体(Tri-*O*-methylnorbergenin)合成への応用

著者が開発したアリール-β-*C*-グルコシドの新規合成法は、操作が比較的簡便であること、短工程であること、立体選択性が高いことがあげられるため、様々な天然物への応用が可能である。

Bergenin 誘導体 (Figure 4) は、*Ardisia japonica* など様々な植物から単離され[4]、またその生理活性も抗 HIV 活性[4]、抗潰瘍作用[23]、脂質低下作用[24]などがあることが報告されている。

**Figure 4. Bergenin Derivatives**




R=H, R'=Me: Bergenin (**41**)

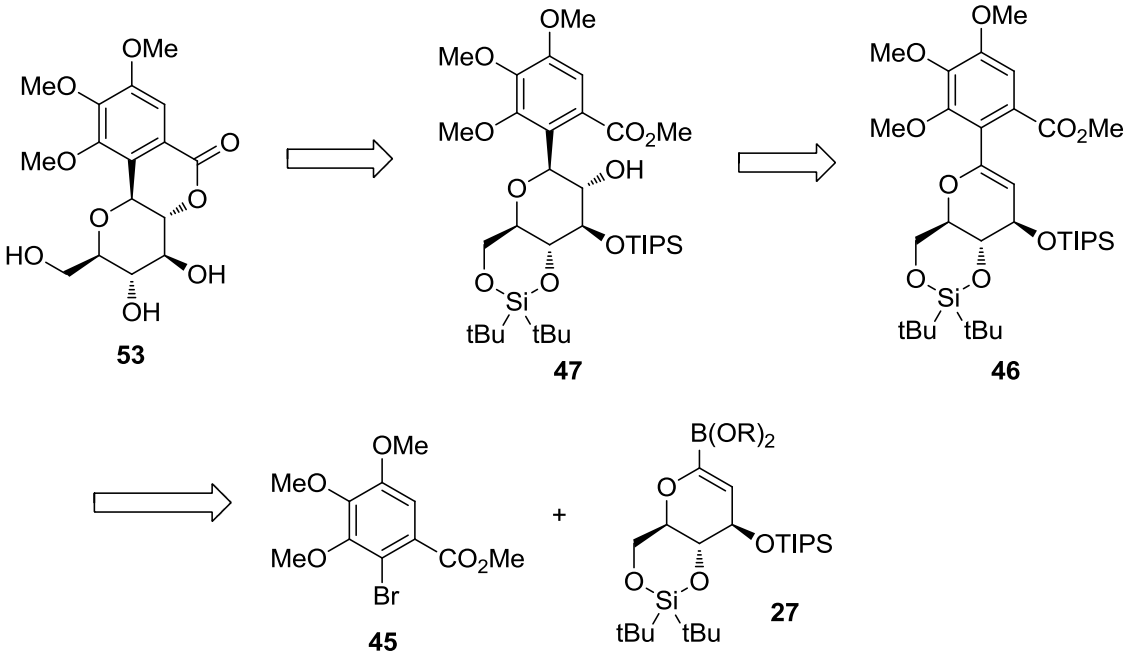
R=R'=Me: Tri-*O*-methylnorbergenin (**42**)
also called 8,10-*O*-methylbergenin

R=R'=H: Norbergenin (**43**)

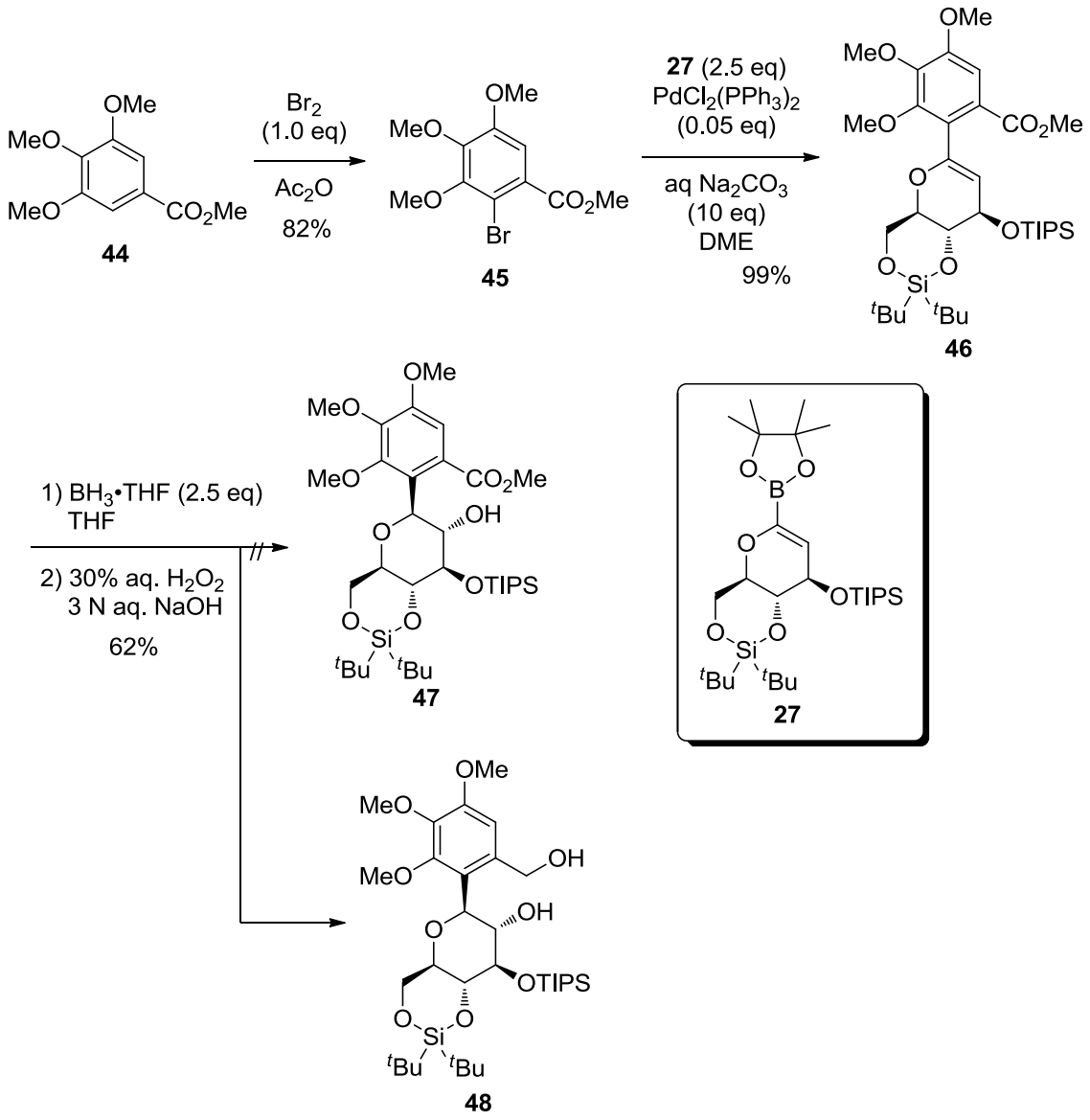
その中で、bergenin 誘導体である tri-*O*-methylnorbergenin (**42**) は、Fries 型転位反応を用いた方法[25]よりすでに報告されている。そこで著者も、この Tri-*O*-methylnorbergenin を標的化合物に選び、より短工程で合成ができるかどうか検討することとした。これが成功すれば、Fries 型転位では合成できない様々

な置換基をベンゼン環上に持つ bergenin 誘導体が容易に合成できることになり、非常に有用な方法になりうる。その逆合成ルートを Scheme 10 に示す。

**Scheme 10. Retrosynthesis of Tri-O-methylnorbergenin (42).**



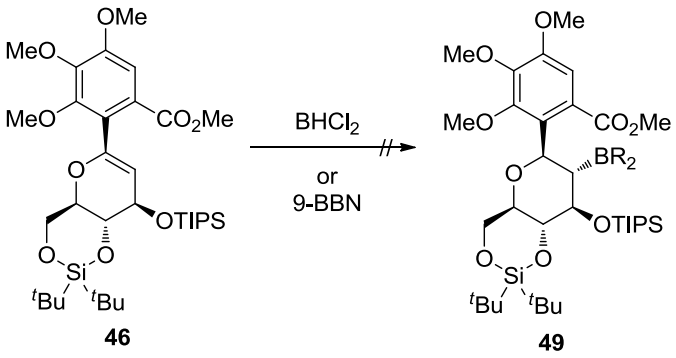
**Scheme 11. Synthesis of Tri-*O*-methylnorbergenin (1)**




実際の合成は Scheme 11 に示すように実施した。すなわち、没食子酸エステル **44** をブロモ化し **45** を得、その後著者が考案したグルカールボロン酸誘導体 **27** との鈴木カップリング反応により、カップリング体 **46** を良好な収率で得た。続いて立体選択的なヒドロホウ素化反応と酸化反応を行い水酸基を導入しようと

したが、得られたものは所望の **47** ではなく、エステル基が還元されたベンジルアルコール体 **48** で、その収率は 62%であった。本反応においてエステル基まで還元された原因として、ヒドロホウ素化反応でのオレフィン反応部位近傍のエステル基が存在するため、という仮説を立てた。そこでヒドロホウ素化反応の際に還元剤が残らない、すなわち過剰のハイドライドがない試薬（9-BBN や $BHCl_2$ 等）によりこの副反応を回避させようと考えた。しかしながら、これら試薬を用いた場合には目的物は得られず、ほぼ原料回収に終わった (Scheme 12)。

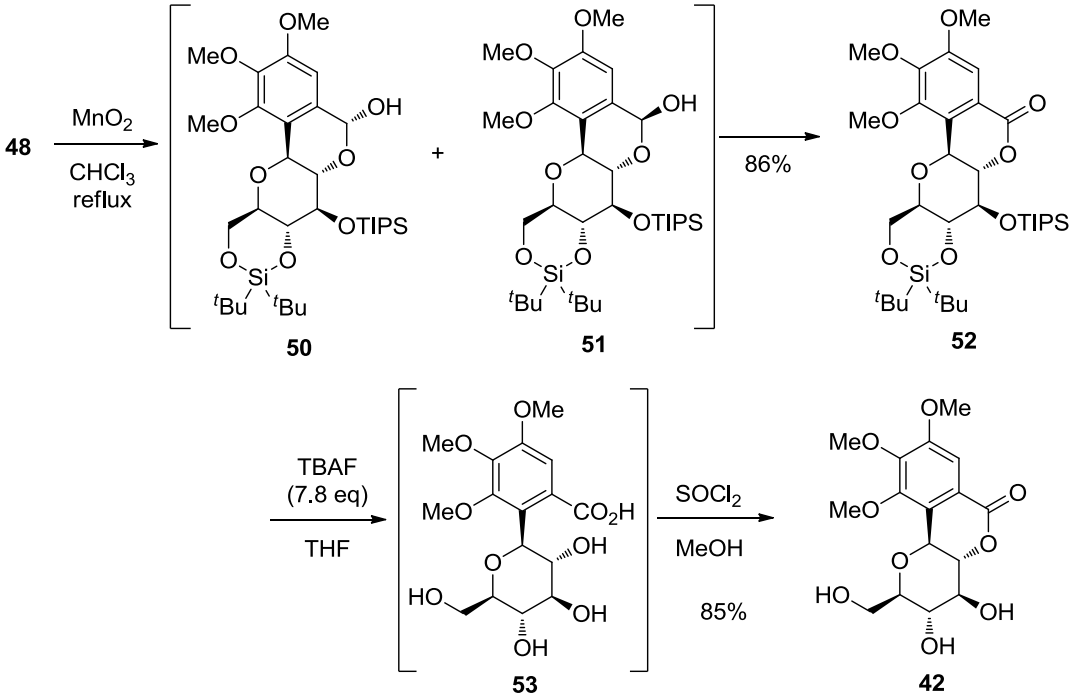
**Scheme 12. Hydroboration using non-reducible reagent.**




そこで、これ以上の検討は中止し、得られたベンジルアルコール **48** の再酸化によりカルボン酸に誘導後、エステルを生成させることとし、まず二酸化マンガンを用いて反応を行った (Scheme 13)。すると、予想したラクトール体 **50**、**51** 以外に、さらに酸化が進んだラクトン体 **52** の合計３種類の化合物を生成するこ

とを認めた。

**Scheme 13. Synthesis of Tri-*O*-methylnorbergenin (2)**




このことは、時間をかければ所望のラクトン体 **52** に収束することを意味しており、事実、２日間反応させたところ、86%の収率で目的とするラクトン体 **52** を得ることができた。

最後に、天然物 **42** に導くべく、TBAF で保護基の除去を試みたところ、TBAF の塩基性のためか、ラクトン環まで開環したカルボン酸体 **53** が得られた。そこで、$SOCl_2$ で処理し、酸クロライド生成と同時にラクトン形成を行うことで、所望の bergenin 誘導体 **42** の合成を完了した。

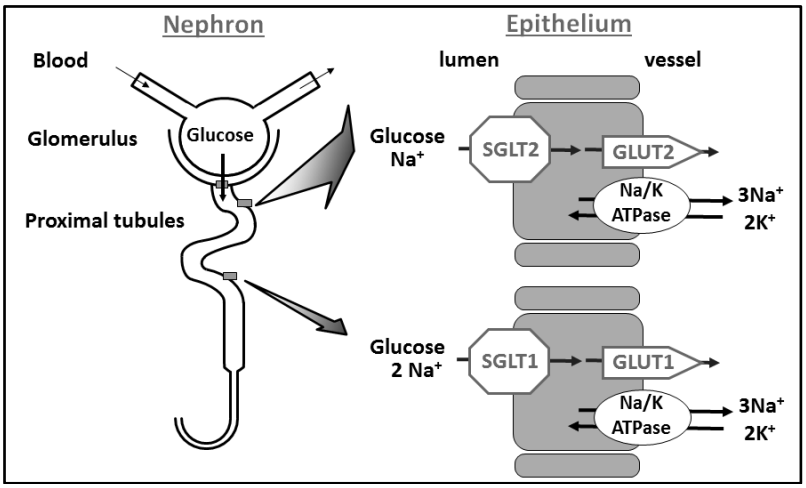
ここで得られたラクトン体 **42** のスペクトルデータは、文献報告のスペクトルデータと完全に一致した。その没食子酸エステル **44** からの通算収率は 45%で、既存の Fries 型転位を用いた方法 (33%) に比べ収率が向上した[25]。前述のように、既存の方法では *O*-グルコシドから *C*-グルコシドへの Fries 型転位反応を行うため、*C*-グルコシド結合の隣の位置に酸素官能基を有する必要があり、適用できる置換ベンゼン体が非常に限られる。一方、著者が開発した方法ではベンゼン環上の置換基の寛容性が広いため、種々の bergenin 誘導体の合成が可能になり、その汎用性が大いに期待されるものとなった。

# 第５章　SGLT2 阻害剤への応用

近年、食生活の欧米化に伴い、２型糖尿病患者が増加してきている。糖尿病治療薬としては、現在までに、様々な種類の治療薬が開発されているが、その中でも、インスリンに依存しない薬剤は低血糖を引き起こしにくいため、広く用いられている。

腎臓では、血中グルコースが糸球体により濾過されるが、その大部分は、近位尿細管の起始部に存在するナトリウム依存性グルコース共輸送体（SGLT2）により再吸収される (Figure 5)。一部は同じく近位尿細管の遠位部に存在する SGLT1 によっても再吸収される。SGLT2 は腎臓の尿細管にほぼ局在して存在するが、SGLT1 は尿細管以外に消化管や心筋などにも存在することが報告されているため [26]、SGLT2 を阻害することにより、他の臓器に影響することなく血中へのグルコースの再吸収を抑えられると考えられる。このことから、SGLT2 阻害剤はインスリンに依存しない新しい糖尿病治療薬としての可能性を秘めている [27]。

**Figure 5. Action of Sodium-Glucose Cotransporter (SGLT)**

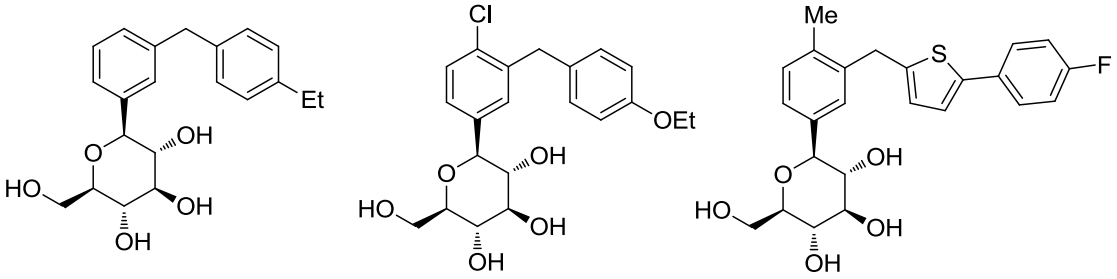



近年になって、いくつかの SGLT2 阻害剤が開発されてきており、いくつかは承認取得、あるいは臨床試験を実施中である。その構造上の特徴としては、D-グルコースがアグリコンと *O*-あるいは *C*-グルコシド結合をしている [28,29]。その中でも、アリール-*C*-グルコシド誘導体は **54** や **55** (dapagliflozin) に代表される化合物が Bristol Myers Squibbs (BMS) 社 [30] から、**56** に代表される化合物が我々のグループである田辺三菱製薬 [5] から報告されている (Figure 6)。その構造的特徴は、アリール環がさらにメチレンを介して別のアリール環で置換された、２つ以上のアリール環が存在することである。今回我々は、更なる SGLT2 阻害剤の開発を目的として、著者が開発した前述の新規 *C*-グルコシド合成法を利用した新たな化合物の合成を試みた。

先に我々のグループが報告した化合物は、BMS 社が開発した化合物の末端ベンゼン環をヘテロ環に変換したものであった [5]。そこで今回は、糖部分に直結

した中心ベンゼン環をヘテロ環に変換し、そのヘテロ環と 4-エチルベンジル基が置換した化合物をデザインした。

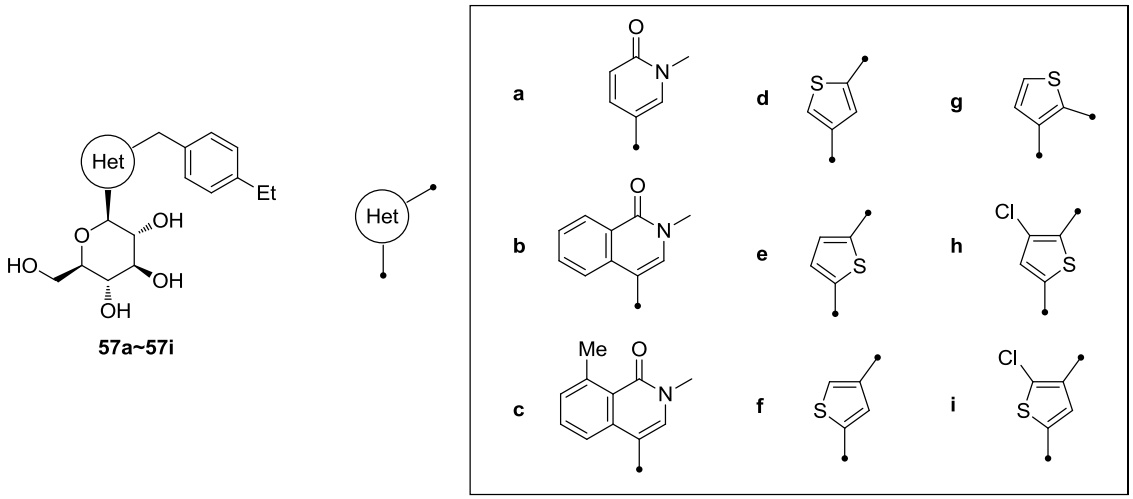
**Figure 6. SGLT Inhibitors (*C*-glucosides)**




すでに我々が行った最初の検討結果より、中心環がピラゾールなど、複数のヘテロ原子を含有する塩基性ヘテロ環で置換されたものは hSGLT2 阻害活性が全く見られないということが判明していた[31]。そのため、我々はよりベンゼン環に類似したヘテロ環として、ピリドン、イソキノリノン、およびチオフェン環を選択した。

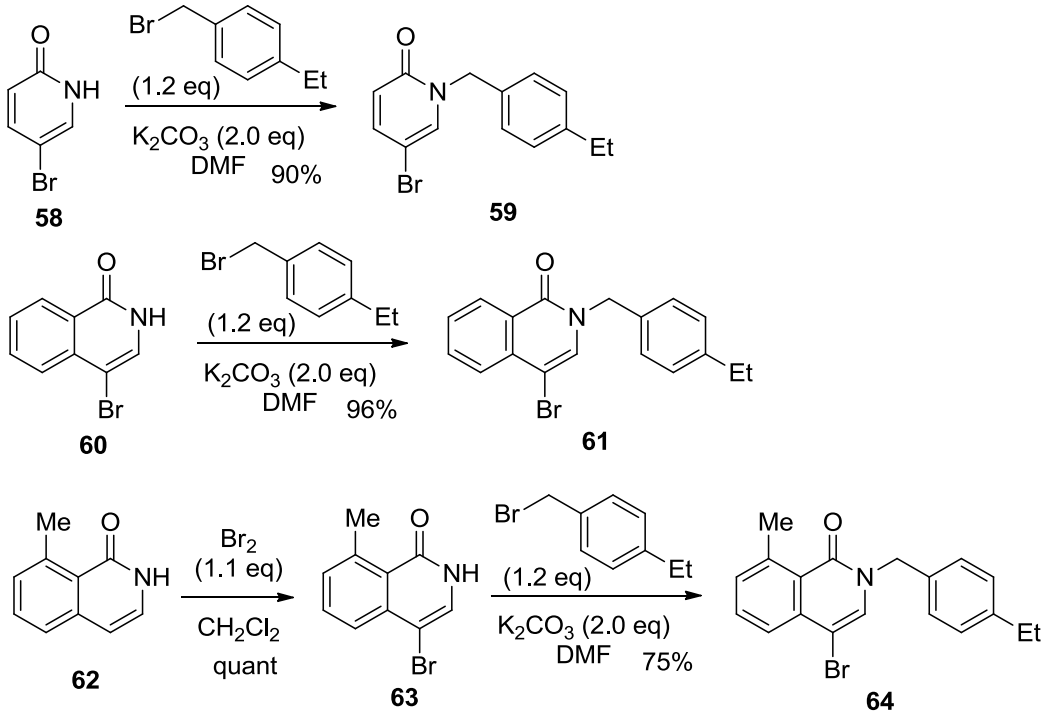
デザインした 4-エチルベンジル化ヘテロアリール-*C*-グルコシド **57a~57i** を Figure 7 に示す。そのアグリコン部として必要なヘテロアリールブロミドのうち、ピリドン環とイソキノリノン環を持つものは Scheme 14 に示すように合成した。

**Figure 7. Targeted Heteroaryl-*C*-glucosides**

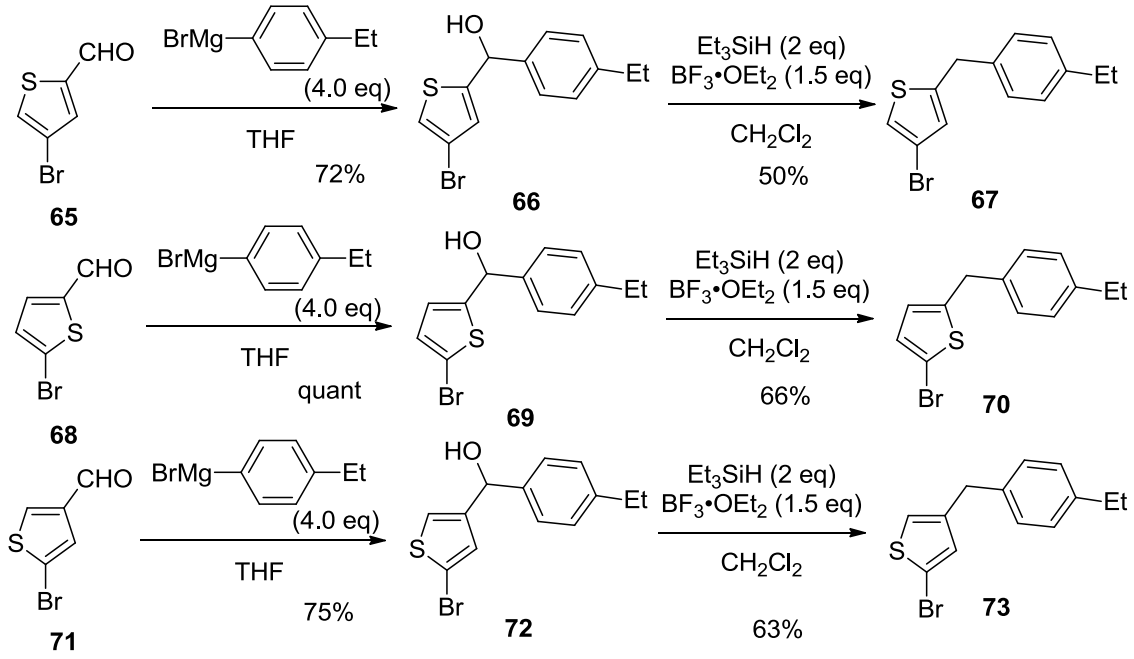


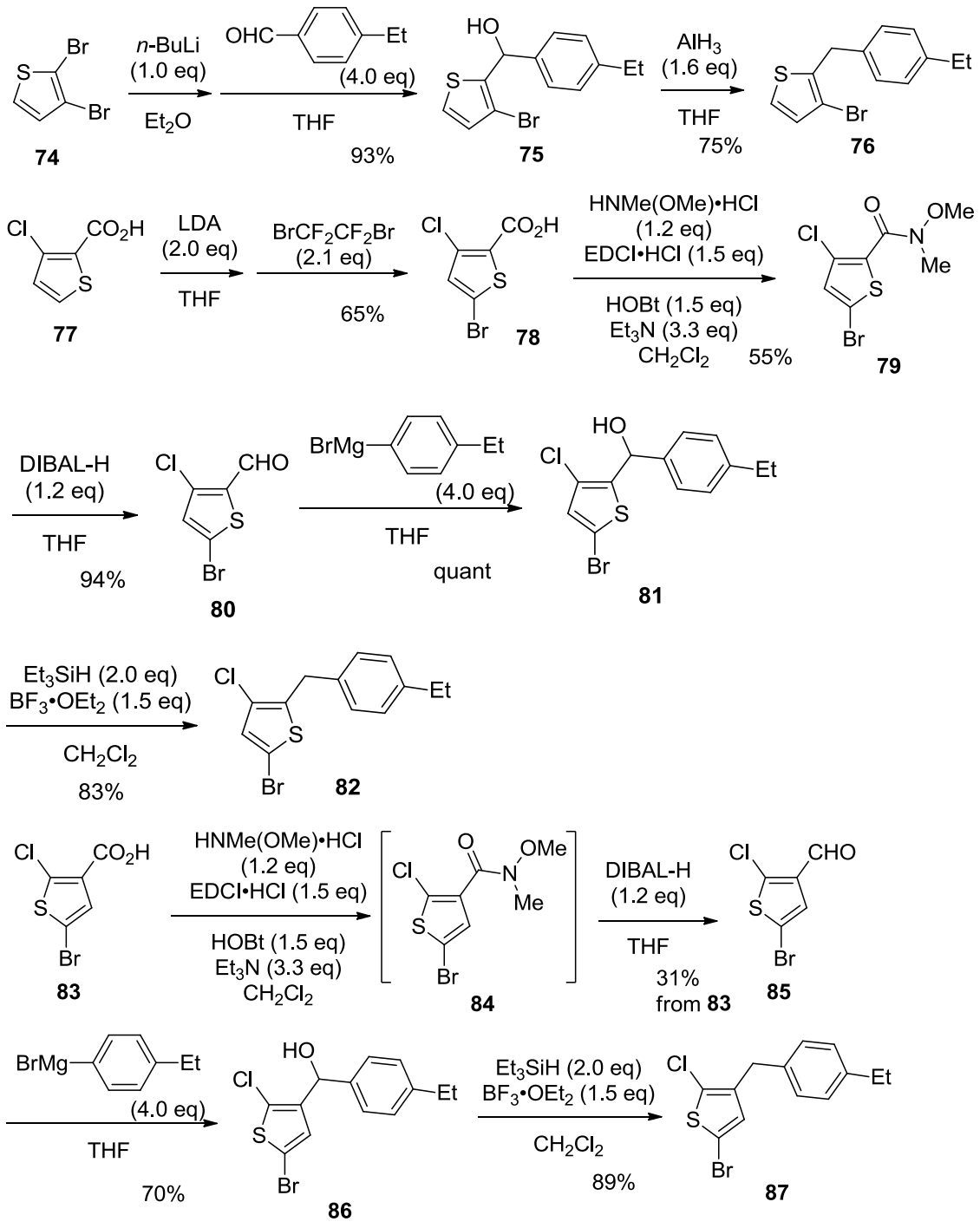

対応する 4-ブロモピリドン **58**、ならびに 4-ブロモイソキノリノン **60**、**63** を、炭酸カリウム存在下 DMF 中 4-エチルベンジルブロミドと加熱することによりアルキル化を行い、*N*-ベンジルヘテロアリールブロミド **59**、**61**、**64** をそれぞれ得た。アルキル化における N-選択性は、得られたアグリコンの NMR での nOe 測定および IR スペクトルでのカルボニル基の吸収ピーク値(1654~1662 $cm^{-1}$)により決定した。なお、4-ブロモ-8-メチルイソキノリノン **63** については、市販のイソキノリノン **62** をブロモ化することにより合成した。

**Scheme 14. Synthesis of Pyridone and Isoquinolinone Aglycons.**




**Scheme 15. Synthesis of Thiophene Aglycons (1).**





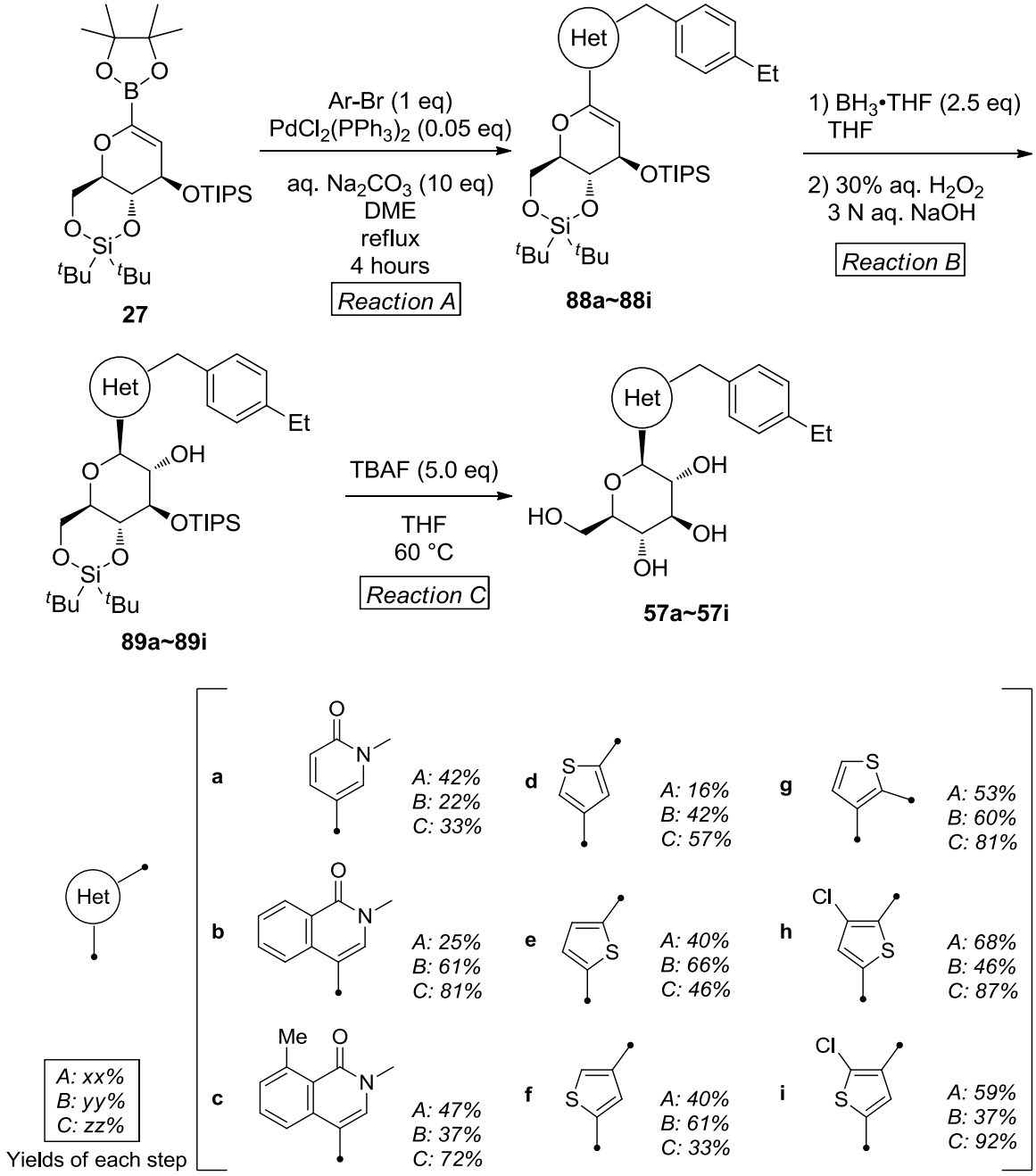

ついでチオフェン環を持った 4-エチルベンジルチオフェンブロミド誘導体 6 種 (**67**, **70**, **73**, **76**, **82**, **87**) の合成を行った (Scheme 15)。このうち、4-ブロモ-2-

ベンジル体 **67**、2-ブロモ-5-ベンジル体 **70**、2-ブロモ-4-ベンジル体 **73** については、対応するブロモチオフェンアルデヒドと 4-エチルフェニルマグネシウムブロミドとのカップリング反応により合成したカルビノール **66**, **69**, **72** の水酸基をトリエチルシランと $BF_3$･$Et_2O$ の組み合わせによる加水素分解還元により合成した。3-ブロモ-2-ベンジル体 **76** については、まず 2,3-ジブロモチオフェン **74** の２位選択的なハロゲンーリチウム交換反応 [32] とそれに続く 4-エチルベンズアルデヒドとの反応によりカルビノール **75** を合成した。その水酸基を塩化アルミニウムと水素化リチウムアルミニウムの組み合わせ [32] で生成する水素化アルミニウムにより還元を実施することにより、中程度の収率で得た。クロロ基を有した 5-ブロモ-3-クロロ-2-ベンジルチオフェン体 **82** および 5-ブロモ-2-クロロ-3-ベンジルチオフェン体 **87** については、前者では対応するクロロチオフェンカルボン酸の 2-ブロモ化を必要としたが、ブロモクロロチオフェンカルボン酸のカルボキシル基のアルデヒドへの変換、4-エチルマグネシウムブロミドとのカップリング反応、生じた水酸基のトリエチルシラン-$BF_3$･$Et_2O$ 系での還元を順次行うことにより合成した。

以上合成したアグリコン９種 **(59**, **61**, **64**, **67**, **70**, **73**, **76**, **82**, **87)** と著者が見出したグルカールボロン酸 **27** とのパラジウム触媒による鈴木カップリング反応により **88a~88i** を得た。それに続く立体選択的なヒドロホウ素化反応とアルカリ条

件下での過酸化水素による酸化反応により **89a~89i** を得た。これらのアノマー位の立体配置は、NMR のカップリング定数により β 配置であると決定した($J_{1,2}$ ≈ 9.5 Hz)。最後に、シリル保護基を TBAF で処理することでヘテロアリール-*C*-グルコシド **57a~57i** を得た (Scheme 16)。

**Scheme 16. Synthesis of Heteroaryl-*C*-Glucosides 57a~57i.**



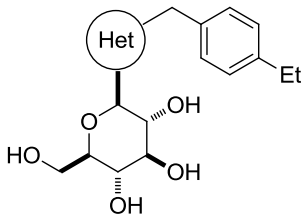

合成したヘテロアリール-*C*-グルコシド **57a~57i** に関して、in vitro の系であるヒト SGLT2 (hSGLT2) の阻害活性と、in vivo の系である雄 Sprague–Dawley

(SD) ラット 200g あたり 24 時間での尿中グルコース排泄量 (rUGE) の測定を実施した。それらの結果を Table 3 に示す。比較のため中心部がベンゼン環である BMS 社化合物 (**54**) についての結果も載せた。ピリドン、あるいはイソキノリノン環に変換した **57a~57c** の hSGLT2 の阻害活性はそれぞれ $IC_{50}$ = 363 nM, 11.6 nM, 98.6 nM と、対照化合物 **54** ($IC_{50}$ = 5.1 nM) より減弱した (Entry 1~3)。

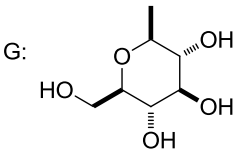
チオフェン誘導体のうち、3,5- (Entry 4)、2,5- (Entry 5)、および 2,4- (Entry 6) 二置換チオフェン誘導体については、それらの SGLT2 阻害活性はそれぞれ $IC_{50}$ = 23.6 nM、19.1 nM、76.0 nM と弱いながらも活性を示した。また、ラット尿中グルコース排泄量についても対照化合物 **54** (1485 mg/day) より弱いものの、活性は認められた (Entries 4~6) (それぞれ 580 ng/day、782 mg/day、826 mg/day)。一方、2,3-二置換チオフェン誘導体 **57g** については、その hSGLT2 阻害活性 $IC_{50}$ = 2559 nM と、ほとんど認められなかった (Entry 7)。これらのことより、これら二置換チオフェン誘導体では、グルコースとエチルベンゼン環が適切な位置に配置されていることが、hSGLT2 阻害活性の発現に重要であることが示唆された。

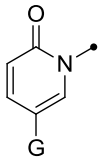
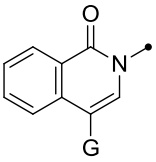
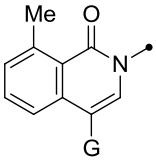
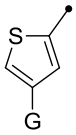
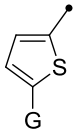
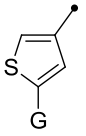
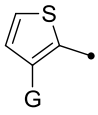
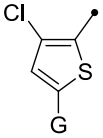
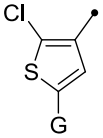
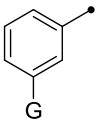
さらに、置換基効果を見るために、まずクロロ基を有する三置換チオフェン誘導体の評価を行った (Entry 8, 9)。4-クロロ-5-ベンジル体 **57h** では、その hSGLT2 阻害活性は $IC_{50}$ が 64.0 nM であり、クロロ基を持たない二置換チオフェン体 **57e** の阻害活性（$IC_{50}$ = 19.1 nM）のほぼ三分の一程度に活性は減弱した

**Table 3. SAR exploration of heteroaryl-*C*-glucosides.**




**57a-57i**
Het: Heteroaromatic

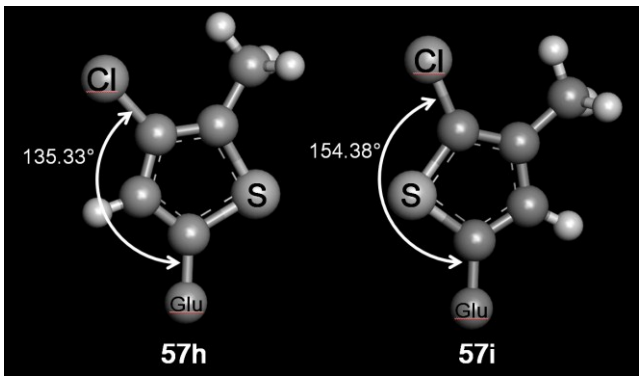



| Entry | Cpd. | Het | hSGLT2 $IC_{50}$ (nM) | rUGE (mg/day) |
|---|---|---|---|---|
| 1 | **57a** |  | 363 | NT |
| 2 | **57b** |  | 11.6 | NT |
| 3 | **57c** |  | 98.6 | NT |
| 4 | **57d** |  | 23.6 | 580 |
| 5 | **57e** |  | 19.1 | 782 |
| 6 | **57f** |  | 76.0 | 826 |
| 7 | **57g** |  | 2559 | NT |
| 8 | **57h** |  | 64.0 | 615 |
| 9 | **57i** |  | 4.0 | 1381 |
| 10 | **54** |  | 5.1 | 1485 |

(Entry 8 vs 5)。一方、その置換パターンが逆の 5-クロロ-4-ベンジル体 **57i** の hSGLT2 阻害活性は $IC_{50}$ = 4.0 nM と、対照化合物とほぼ同等の強い阻害活性を示し、クロロ基を持たない二置換体 **57f** の阻害活性（$IC_{50}$ = 76.0 nM）の２０倍であった (Entry 9 vs 7)。この結果は、**57h** および **57i** におけるクロロ基とグルコー

ス部位との間の角度の違いに起因するものと推察された。事実、**57h** におけるクロロ基とグルコース部分の角度は 135.33°、**57i** においては 154.38°と計算された (Figure 8)。筆者は、**57h** のクロロ基は阻害活性には影響を与えないが、**57i** のクロロ基は望みの方向に置換されているがゆえに阻害活性が向上したと推察した。また、これら三置換チオフェン誘導体についてのラット 200 g あたりの尿中グルコース排泄量について測定を行ったところ、4-クロロ-5-ベンジル体 **57h** は 615 mg/day、5-クロロ-4-ベンジル体 **57i** は 1381 mg/day であり、特に後者は対照化合物 **54** に匹敵する活性を示した。**57i** のクロロ基の変換により、さらなる活性向上が期待できる。

**Figure 8. Calculated angle of chlorine and glucose moiety.**




以上の検討より、ピリドン環を持った誘導体では in vitro での阻害活性が消失するが、イソキノリノン環誘導体に関しては、in vitro 阻害活性が認められる

ものの、8 位にメチル基を置換すると阻害活性が減弱した。一方で、チオフェン環誘導体では良好な hSGLT2 阻害活性を有し、ラットでの尿中グルコース排泄量も認められた。特に 5-クロロ-4-ベンジル体 **57i** は hSGLT2 阻害活性、ラット尿中グルコース排泄量ともに対照化合物として用いた 3-ベンジルベンゼン体 **54** と同等であることを見出し、新規な SGLT2 阻害薬となりうる可能性が示唆された。

# 第６章　結語

著者は、以上述べたように、今までに知られている毒性のスズ誘導体ではなく、毒性がなく長期間安定なグルカールボロン酸エステルを考案し、これを用いてパラジウム触媒による鈴木カップリングを経由した、汎用性の高いアリール-β-*C*-グルコシドの合成法を確立した。

また、今回著者が開発したグルカールボロン酸エステルを用いて、天然物である bergenin 誘導体の効率的合成、および近年、２型糖尿病治療薬として注目されている SGLT2 阻害薬の合成に応用した。今後、本手法がアリール-β-*C*-グルコシドの合成に広く利用されることを大いに期待したい。

## 謝辞

本研究を遂行するに当たり、終始ご指導ご鞭撻を頂きました千葉大学薬学部石川勉教授に感謝申し上げます。また、本研究は田辺三菱製薬(株)にて実施したものであり、本研究の機会を与えていただいた代表取締役社長　土屋裕弘博士、取締役研究本部長　加賀邦明氏、創薬化学第二研究所所長　上野裕明博士、創薬化学第一研究所第一部部長　安田公助博士、創薬化学第二研究所マネージャー　有友啓一博士に深く感謝いたします。

また、本研究の遂行に際して有益なご助言をいただいた野村純宏博士、川西英治博士をはじめとする合成部門の諸兄に御礼申し上げます。

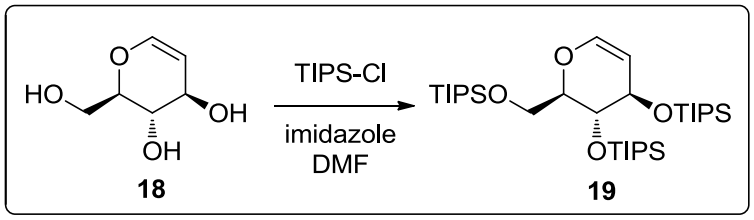
さらに、薬理試験を実施していただいた植田喜一郎博士をはじめとする薬理第二研究所代謝グループ、およびX線解析をはじめとする各種分析を行っていただきました創薬化学第一、第二研究所分析部門の諸兄に感謝いたします。

## 実験の部

All reactions were carried out under inert gas or with $CaCl_2$ tube and reaction mixtures were stirred magnetically. All reagents and solvents were purchased from commercial suppliers and used without further purification unless otherwise noted. Reaction products were monitored by TLC using 0.25 mm E. Merck silica gel plates (60 F254) and were visualized using UV light or 5% phosphomolybdic acid in 95% EtOH. NMR spectra were collected on JEOL JNM-ECX400P and Varian UNITY INOVA500 spectrometers. Chemical shifts were given in parts per million (ppm) downfield from internal reference tetramethylsilane standard; coupling constants (*J* value) were given in hertz (Hz). Infrared spectra were measured on Perkin-Elmer PARAGON1000. APCI- and ESI-MS spectra were obtained on Finnigan MAT SSQ7000C or ThermoQuest LCQ Advantage eluting with 10 mM $AcONH_4$ / MeOH. GC-MS spectra were measured on Shimadzu GCMS-QP2010. All compounds were found to be >95% pure by HPLC analysis unless otherwise noted.

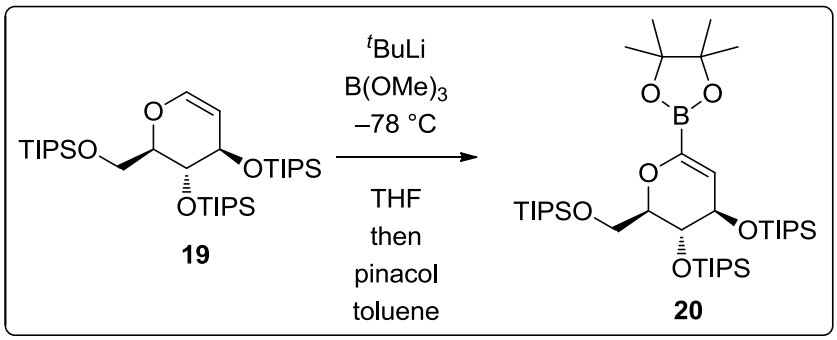
## 第２章第１節に関する実験の部

**1,5-Anhydro-2-deoxy-3,4,6-tris-*O*-triisopropylsilyl-D-arabino-hex-1-enitol (19)**[33]



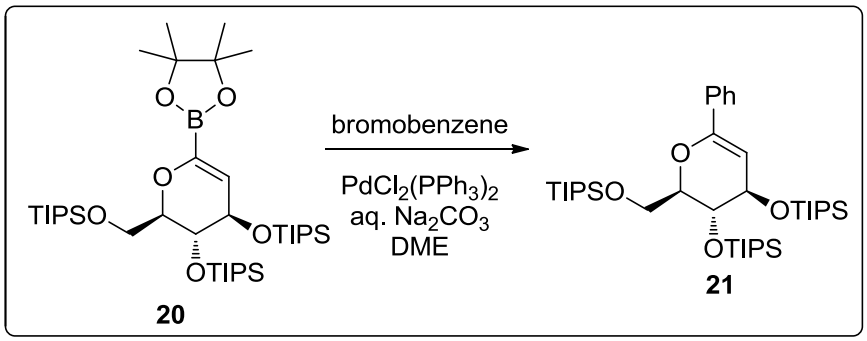

To a solution of D-glucal **18** (8.40 g, 57.5 mmol) in DMF (250 mL) was added imidazole (28.0 g, 414 mmol), then TIPS-Cl (44.4 mL, 207 mmol) was added dropwise at room temperature. After being stirred at 60 °C for 48 hr, the mixture was concentrated. The residual oil was dissolved in ether, washed with water and brine, dried over sodium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by silica gel column chromatography (10% – 20% $CHCl_3$ in hexane) to give **19** (24.4 g, 69%) as a colorless oil. $^1$H NMR ($CDCl_3$, 300 MHz) δ 6.35 (d, *J* = 6.3 Hz, 1H), 4.80 (ddd, *J* = 1.8 Hz, 5.0 Hz, 6.5 Hz, 1H), 4.23 (ddt, *J* = 1.9 Hz, 3.9 Hz, 5.9 Hz, 1H), 4.06 (m, 2H), 3.95 (dt, *J* = 1.9 Hz, 5.2 Hz, 1H), 3.82 (dd, *J* = 3.8 Hz, 11.3 Hz, 1H), 1.03 – 1.11 (m, 63H). MS (APCI, *m/z*) 632 $[M + NH_4]^+$.

**(1,5-Anhydro-2-deoxy-3,4,6-tris-*O*-triisopropylsilyl-D-arabino-hex-1-enitolyl)benzene (21)**



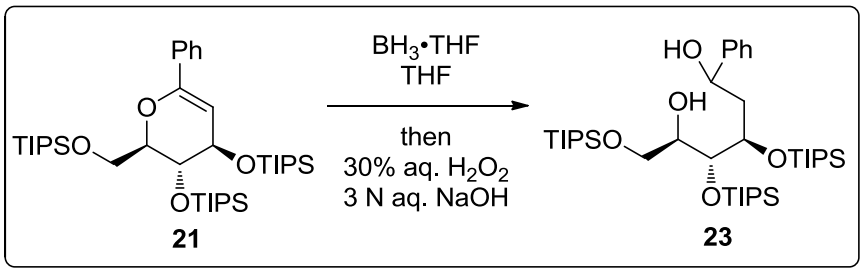

To a solution of **19** (21.28 g, 34.6 mmol) in THF (160 mL) was added *tert*-butyllithium (1.50 M, 103 mL, 155 mmol) at –78 °C dropwise, then stirred at 0 °C for 1 hour. To a mixture was added trimethyl borate (19.4 mL, 174 mmol) at –78 °C, then stirred at 0 °C for 15 minutes and gradually warmed to room temperature and stirred for 1 hour. The mixture was quenched by $H_2O$, then the mixture was extracted with ether, washed with brine, dried over sodium sulfate, filtered, the filtrate was

evaporated under reduced pressure to give crude boronic acid as a colorless viscous oil. To a solution of boronic acid in toluene (250 mL) was added pinacol (4.91 g, 41.6 mmol), then the mixture was stirred at room temperature for overnight. The reaction mixture was washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure to afford quantitative yield of glucal boronic acid ester **20** (27.4 g) as a colorless viscous oil.




To a mixture of boronic acid ester **20** (7.92 g, 10.7 mmol) and bromobenzene (785 mg, 5 mmol) in DME (50 mL) was added dichlorobis(triphenylphosphine)palladium (175 mg, 0.25 mmol) and 2 M aq $Na_2CO_3$ (12.5 mL, 25 mmol), then the mixture was refluxed for 3 hours. The mixture was cooled to ambient temperature and diluted with AcOEt, then washed with water, brine, dried over sodium sulfate, and filtered. After the filtrate was concentrated, the crude material was purified by silica gel column chromatography (hexane) to give **21** (3.62 g, 99%) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.64 (m, 2H), 7.28 – 7.34 (m, 3H), 5.34 (dd, *J* = 1.5 Hz, 5.4 Hz, 1H), 4.46 (m, 1H), 4.18 (td, *J* = 1.9 Hz, 5.2 Hz, 1H), 4.14 (m, 1H), 4.10 (m, 1H), 3.91 (dd, *J* = 4.4 Hz, 11.3 Hz, 1H), 1.00 – 1.10 (m, 63H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.3, 136.4, 128.2, 127.9, 125.4, 96.7, 81.3, 70.1, 66.8, 62.0, 18.2, 18.2, 18.1, 18.1, 18.0, 18.0, 12.6, 12.5, 12.1. MS (APCI, *m/z*) 691 $[M + H]^+$. IR (neat, $cm^{-1}$) 1944, 2867, 1652, 1464, 1060. Anal. calcd for $C_{39}H_{74}O_4Si_3$ C: 67.76, H: 10.79; found C: 67.86, H: 11.03. $[\alpha]_D^{25} = -10.0°$ (c, 0.2, $CHCl_3$).

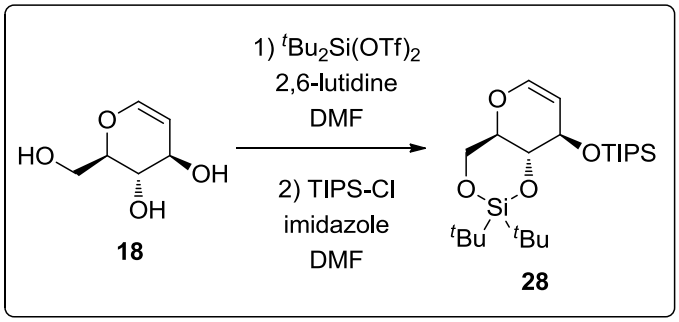
**2-deoxy-1-*C*-phenyl-3,4,6-tris-*O*-(triisopropylsilyl)-D-arabino-hexitol (23)**



To a solution of compound **21** (640 mg, 0.926 mmol) in THF (10 mL) was added borane-tetrahydrofuran complex (1.0 M in THF, 2.30 mL, 2.3 mmol) dropwise at 0 °C. After being stirred at 0 °C for overnight, the mixture was added 30% aqueous hydrogen peroxide (5 mL) and 3 N aqueous sodium hydroxide (5 mL), and stirred at 0 °C for 4 hours. The reaction mixture was extracted with $Et_2O$, washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated and dried, then the crude material was purified by silica gel column chromatography (0% – 5% AcOEt in hexane) to give compound **23** (167 mg, 25%) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.36 (m, 5H), 5.01 (td, *J* = 2.4 Hz, 9.8 Hz, 1H), 4.40 (td, *J* = 3.6 Hz, 6.6 Hz, 1H), 4.15 (t, *J* = 3.9 Hz, 1H), 4.01 (dtd, *J* = 2.1 Hz, 4.5 Hz, 6.5 Hz, 1H), 3.84 – 3.86 (m, 2H), 3.23 (d, *J* = 1.9 Hz, 1H), 2.66 (d, *J* = 2.5 Hz, 1H), 2.29 (ddd, *J* = 3.0 Hz, 6.9 Hz, 14.3 Hz, 1H), 1.94 (ddd, *J* = 6.3 Hz, 10.0 Hz, 14.2 Hz, 1H), 1.01 – 1.18 (m, 63H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 145.0, 128.4, 127.3, 125.7, 74.8, 74.1, 73.8, 72.4, 65.7, 42.5, 18.2, 18.2, 18.0, 12.9, 12.9, 12.0. MS (APCI, *m/z*) 711.5 $[M + H]^+$. IR (KBr, $cm^{-1}$) 3419, 2944, 2892, 1463. HRMS (ESI, *m/z*) calcd for $C_{10}H_{14}NaO_5S$ $[M + H]^+$ 711.5235, found 711.5259. $[\alpha]_D^{25}$ = +13.3° (c, 0.15, $CHCl_3$).

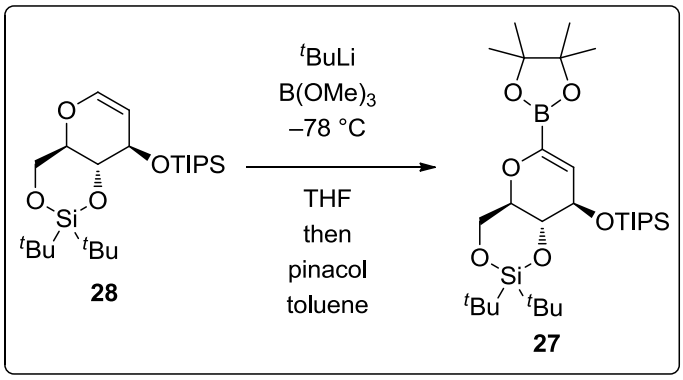
## 第２章第２節に関する実験の部

**(4a*R*,8*R*,8a*R*)-2,2-di-*tert*-butyl-8-[(triisopropylsilyl)oxy]-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasiline (28)**[21]




To a solution of D-glucal (50.0 g, 342 mmol) in DMF (615 mL) was added 2,6-lutidine (120 mL, 1026 mmol) dropwise at –50 °C. After being stirred at –50 °C for 1 hr, the mixture was added di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (181 mL, 411 mmol) dropwise and stirred at this temperature for overnight. Water (730 mL) was added and the mixture was extracted with hexane – ether (1 : 1), washed with 5% aq. citric acid, saturated aq. $NaHCO_3$, water, and brine, dried over sodium sulfate, and filtered. After the filtrate was concentrated, the crude material was purified by silica gel column chromatography (10% AcOEt in hexane) to give bridged-silyl alcohol (80.00 g) as a colorless solid. To a solution of above bridged-silyl alcohol (79.60 g, 278 mmol) in DMF (2.67 L) was added imidazole (47.3 g, 695 mmol), then TIPS-Cl (77.3 mL, 361 mmol) was added dropwise at room temperature. After being stirred at 50 °C for 19 hr, the mixture was concentrated. The residual oil was dissolved in hexane – ether (1 : 1), washed with water and brine, dried over sodium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by silica gel column chromatography (hexane) to give **28** (102 g, 71% from **18**) as a colorless solid. $^1$H NMR ($CDCl_3$, 300 MHz) δ 6.22 (dd, *J* = 1.1 Hz, 6.2 Hz, 1H), 4.67 (dd, *J* = 2.0 Hz, 6.0 Hz, 1H), 4.42 (dt, *J* = 1.8 Hz, 6.9 Hz, 1H), 4.15 (dd, *J* = 4.8 Hz, 10.1 Hz, 1H), 4.00 (dd, *J* = 6.8 Hz, 10.3 Hz, 1H), 3.95 (t, *J* = 10.3 Hz, 1H), 3.81 (dt, 4.6 Hz, 10.1 Hz, 1H), 1.08 – 1.13 (m, 21H), 1.06 (s, 9H), 0.99 (s, 9H). MS (APCI, *m/z*) 460 $[M + NH_4]^+$. IR (nujol, $cm^{-1}$) 1651. Mp. 49 – 50 °C.

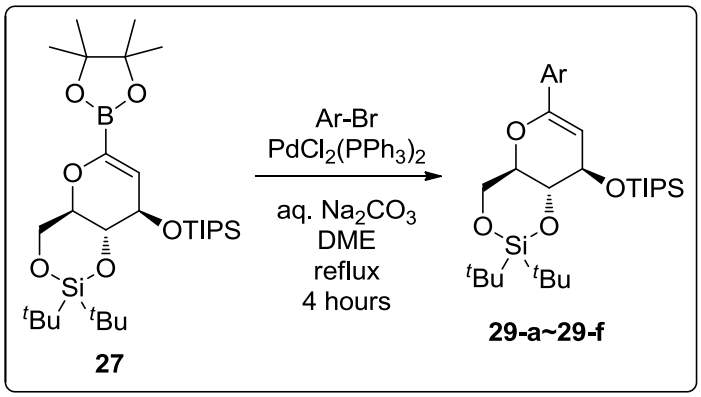
**1,5-Anhydro-2-deoxy-4,6-*O*-di-(*tert*-butyl)silanediyl-3-*O*-triisopropylsilyl-D-arabino-hex-1-enitolylboronic acid pinacol ester** (**27**)




To a solution of **28** (6.63 g, 15.0 mmol) in THF (70 mL) was added *tert*-butyllithium (1.42 M, 47.0 mL, 70.5 mmol) at –78 °C dropwise, then stirred at 0 °C for 1 hour. To a mixture was added trimethyl borate (8.4 mL, 75.3 mmol) at – 78 °C, then stirred at 0 °C for 15 minutes and gradually warmed to room temperature and stirred for 1 hour. The mixture was quenched by $H_2O$, then the mixture was extracted with ether, washed with brine, dried over sodium sulfate, filtered, the filtrate was evaporated under reduced pressure to give crude boronic acid as a colorless viscous oil. To a solution of boronic acid in toluene (70 mL) was added pinacol (2.12 g, 17.9 mmol), then the mixture was stirred at room temperature for overnight. The reaction mixture was washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure to afford quantitative yield of glucal boronic acid ester **27** (11.03 g) as a colorless viscous oil which was used without further purification.

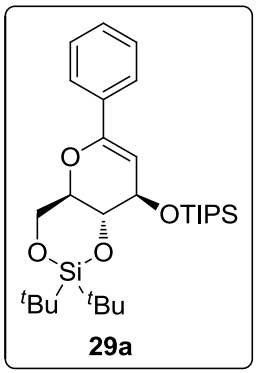
An analytical sample was prepared by purification using preparative HPLC and recrystallization from MeOH to afford pure glucal boronic acid ester **27** as a colorless fine needle. $^1$H NMR ($CDCl_3$, 400 MHz) δ 5.45 (d, $J$ = 2.2 Hz, 1H), 4.44 (dd, $J$ = 2.2 Hz, 7.2 Hz, 1H), 4.26 (dd, $J$ = 5.0 Hz, 10.5 Hz, 1H), 4.02 (m, 1H), 3.99 (dd, $J$ = 3.0 Hz, 7.4 Hz, 1H), 3.77 (td, $J$ = 5.0 Hz, 10.5 Hz, 1H), 1.27 (s, 12H), 1.10-1.16 (m, 21H), 1.05 (s, 9H), 0.98 (s, 9H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 148.9 (br), 119.3, 84.3, 77.3, 73.0, 71.4, 66.3, 27.5, 27.0, 24.6, 22.7, 19.8, 18.2, 12.6. MS(CI, *m/z*) 569 $[M + H]^+$. IR (KBr, $cm^{-1}$) 2941, 2864, 1643, 1471, 1418, 1373, 1109. Anal. calcd for $C_{29}H_{57}BO_6Si_2$ C: 61.24, H: 10.10, B: 1.90; found C: 61.12, H: 10.02, B: 1.70. Mp. 169 – 171 °C. $[\alpha]_D^{25} = -32.0°$ (c, 0.2, $CHCl_3$).

**Typical Experimental procedure for the synthesis of 1-arylglucal derivative (29a~29f)**



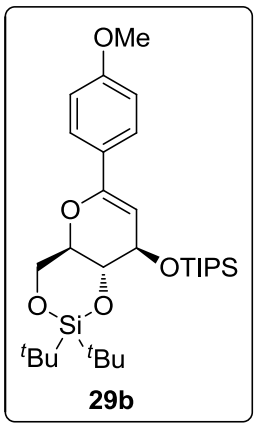

To a mixture of boronic acid ester **27** (2.5 mmol) and aryl bromide (1 mmol) in DME (20 mL) was added dichlorobis(triphenylphosphine)palladium (0.05 mmol) and 2 M aq $Na_2CO_3$ (5 mL), then the mixture was refluxed for 4 hours. The mixture was cooled to ambient temperature and diluted with AcOEt, then washed with water, brine, dried over sodium sulfate, and filtered. After the filtrate was concentrated, the crude material was purified by silica gel column chromatography to give compounds **29a**~**29f**.

**(1,5-Anhydro-2-deoxy-4,6-*O*-di-(*tert*-butyl)silanediyl-3-*O*-triisopropylsilyl-D-arabino-hex-1-enitolyl)benzene** (**29a**).




Following the general method described above, the title compound **29a** was isolated in 99% yield as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.52 (m, 2H), 7.28 – 7.36 (m, 3H), 5.23 (d, *J* = 2.5 Hz, 1H), 4.59 (dd, *J* = 2.5 Hz, 1H), 4.32 (dd, *J* = 5.0 Hz, 10.2 Hz, 1H), 4.10 (*J* = 7.5 Hz, 10.5 Hz, 1H), 4.00 (dd, *J* =5.0 Hz, 10.2 Hz, 1H), 1.08 (s, 9H), 1.01 (s, 9H), 0.95-1.20 (m, 21H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 151.0, 134.2, 128.6, 128.2, 125.1, 101.3, 77.5, 73.0, 71.8, 66.2, 27.5, 27.0, 22.8, 19.9, 18.2, 18.2, 12.5. MS (APCI, *m/z*) 519 $[M + H]^+$. IR (nujol, $cm^{-1}$) 2925, 2859, 1652, 1463, 1110. mp. 91 – 94 °C. HRMS (ESI, *m/z*) calcd for $C_{29}H_{51}O_4Si_2$ $[M + H]^+$ 519.3326, found 519.3290. $[\alpha]_D^{25} = -26.0°$ (c, 0.2, $CHCl_3$).

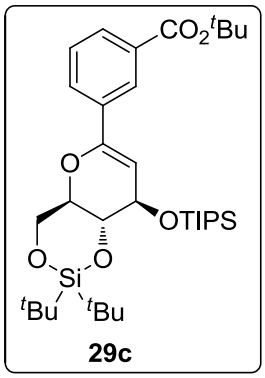
**(1,5-Anhydro-2-deoxy-4,6-*O*-di-(*tert*-butyl)silanediyl-3-*O*-triisopropylsilyl-D-arabino-hex-1-enitolyl)-4-methoxybenzene** (**29b**).



**29b**

Following the general method described above, the title compound **29b** was isolated in 99% yield as a colorless amorphous powder. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 5.11 (d, *J* = 2.4 Hz, 1H), 4.57 (dd, *J* =2.4 Hz, 6.8 Hz, 1H), 4.30 (dd, *J* = 5.0 Hz, 10.5 Hz, 1H), 4.10 (m, 1H), 4.08 (m, 1H), 3.98 (dd, *J* = 5.1 Hz, 10.5 Hz, 1H), 3.80 (s, 3H), 1.08 (s, 9H), 1.01 (s, 9H), 0.82 – 1.30 (m, 21H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.0, 150.9, 130.5, 126.5, 113.6, 99.7, 77.7, 72.9, 71.9, 66.2, 55.3, 27.5, 27.0, 22.8, 20.0, 18.2, 18.2, 12.5. IR (KBr, $cm^{-1}$) 2891, 2862, 1653, 1611, 1513, 1252, 1113. MS (APCI, *m/z*) 549 $[M + H]^+$. HRMS (ESI, *m/z*) calcd for $C_{30}H_{53}O_5Si_2$ $[M + H]^+$ 549.3432, found 549.3431. $[\alpha]_D^{25} = -20.0°$ (c, 0.2, $CHCl_3$).

**3-(1,5-Anhydro-2-deoxy-4,6-*O*-di-(*tert*-butyl)silanediyl-3-*O*-triisopropylsilyl-D-arabino-hex-1-enitolyl)benzoic acid *tert*-butyl ester** (**29c**).

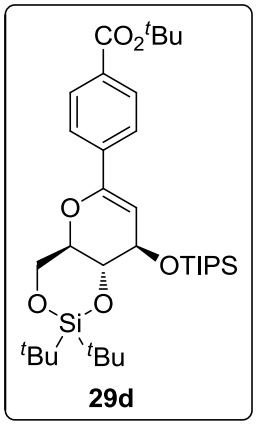


**29c**

Following the general method described above, the title compound **29c** was isolated in 99% yield as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.13 (t, *J* = 1.4 Hz, 1H), 7.92 (td, *J* = 1.5 Hz, 7.8 Hz, 1H), 7.66 (td, *J* = 1.2 Hz, 7.8 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 5.29 (d, *J* = 2.4Hz, 1H), 4.60 (dd, *J* = 2.4 Hz, 6.6 Hz, 1H), 4.33 (dd, *J* = 4.6 Hz, 10.8 Hz, 1H), 4.12 (d, *J* = 10.2 Hz, 1H), 4.09 (dd, *J* = 3.1 Hz, 10.2 Hz, 1H), 4.02 (dd, *J*

= 4.6 Hz, 10.5 Hz, 1H), 1.59 (s, 9H), 1.13-1.18 (m, 21H), 1.09 (s, 9H), 1.02 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.4, 150.3, 134.3, 132.1, 129.5, 128.9, 128.1, 126.2, 101.9, 81.1, 77.5, 73.1, 71.7, 66.1, 28.2, 27.5, 27.0, 22.8, 19.9, 18.3, 18.2, 12.5. MS (APCI, *m/z*) 619 $[M + H]^+$. HRMS (ESI, *m/z*) calcd for $C_{34}H_{59}O_6Si_2$ $[M + H]^+$ 619.3850, found 619.3860. $[\alpha]_D^{25} = -24.0°$ (c, 0.2, $CHCl_3$).

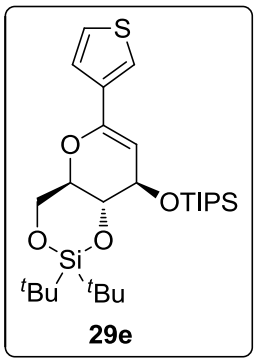
**4-(1,5-Anhydro-2-deoxy-4,6-*O*-di-(*tert*-butyl)silanediyl-3-*O*-triisopropylsilyl-D-arabino-hex-1-enitolyl)benzoic acid *tert*-butyl ester (29d).**



**29d**

Following the general method described above, the title compound **29d** was isolated in 99% yield as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 5.33 (d, *J* = 2.4 Hz, 1H), 4.60 (dd, *J* = 2.5 Hz, 6.7 Hz, 1H), 4.32 (dd, *J* = 4.9 Hz, 10.2 Hz, 1H), 4.11 (dd, *J* = 6.8 Hz, 10.3 Hz, 1H), 4.11 (app t, *J* = 10.3 Hz, 1H), 4.01 (dd, *J* = 4.2 Hz, 10.0 Hz, 1H), 1.59 (s, 9H), 1.12 – 1.15 (m, 21H), 1.09 (s, 9H), 1.01 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.4, 150.3, 137.9, 131.9, 129.4, 124.7, 103.1, 81.1, 77.4, 73.1, 71.7, 66.1, 28.2, 27.5, 27.0, 22.8, 19.9, 18.2, 18.2, 12.5. MS (APCI, *m/z*) 619 $[M + H]^+$. Anal. calcd for $C_{34}H_{58}O_6Si_2$ C: 65.97, H: 9.44; found C: 65.71, H: 9.62. $[\alpha]_D^{25} = -11.0°$ (c, 0.2, $CHCl_3$).

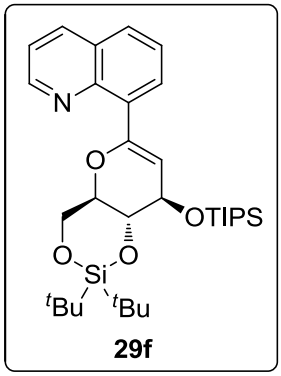
**3-(1,5-Anhydro-2-deoxy-4,6-*O*-di-(*tert*-butyl)silanediyl-3-*O*-triisopropylsilyl-D-arabino-hex-1-enitolyl)thiophene (29e).**




**29e**

Following the general method described above, the title compound **29e** was isolated in 99% yield as a colorless oil. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 1.0 Hz, 3.1 Hz, 1H), 7.23 – 7.30 (m, 1H), 7.14 (dd, *J* = 1.2 Hz, 5.2 Hz, 1H), 5.12 (d, *J* = 2.2 Hz, 1H), 4.56 (dd, *J* = 2.4 Hz, 6.8 Hz, 1H), 4.30 (dd, *J* = 4.9 Hz, 10.5 Hz, 1H), 4.05 – 4.11 (m, 2H), 3.94-4.00 (m, 1H), 1.12 – 1.16 (m, 21H), 1.08 (s, 9H), 1.01 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 147.8, 136.3, 125.7, 124.8, 121.8, 101.1, 77.5, 72.9, 71.6, 66.1, 27.5, 27.0, 22.8, 19.9, 18.2, 17.7, 12.5. MS (APCI, *m/z*) 525 $[M + H]^+$. IR (neat, $cm^{-1}$) 2941, 2891, 2863, 1657, 1470. Anal. calcd for $C_{27}H_{48}O_4SSi_2$ C: 61.78, H: 9.22; found C: 62.06, H: 9.52.

**8-(1,5-Anhydro-2-deoxy-4,6-*O*-di-(*tert*-butyl)silanediyl-3-*O*-triisopropylsilyl-D-arabino-hex-1-enitolyl)quinoline** (**29f**).

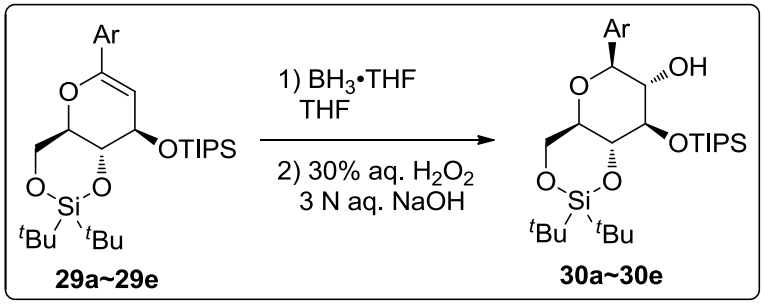



**29f**

Following the general method described above, the title compound **29f** was isolated in 99% yield as a colorless solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.94 (dd, *J* = 2.0 Hz, 4.1 Hz, 1H), 8.14 (dd, *J* = 8.2 Hz, 1.8 Hz, 1H), 7.91 (dd, *J* = 7.3 Hz, 1.5 Hz, 1H), 7.76 (dd, *J* = 1.5 Hz, 8.2 Hz, 1H), 7.51 (dd, *J* = 7.3 Hz, 8.2 Hz, 1H), 7.40 (dd, *J* = 4.2 Hz, 8.2 Hz, 1H), 6.11 (d, *J* = 2.4 Hz, 1H), 4.76 (dd, *J* = 2.3 Hz, 6.8 Hz, 1H), 4.32 (dd, *J* = 4.4 Hz, 9.6 Hz, 1H), 4.26 (dd, *J* = 6.9 Hz, 10.2 Hz, 1H), 4.20 (td, *J* = 10.0 Hz, 4.3 Hz, 1H), 4.11 (app t, *J* = 9.7 Hz, 1H), 1.14 – 1.26 (m, 21H), 1.10 (s, 9H), 1.03 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 145.0, 148.9, 145.8, 136.3, 132.9, 128.9, 128.7, 128.5, 125.9,

120.9, 108.8, 77.7, 73.1, 72.1, 66.3, 27.5, 27.0, 22.8, 19.9, 18.2, 12.5. mp. 89 – 92 °C. MS (APCI, *m/z*) 570 $[M + H]^+$. IR (neat + $CHCl_3$, $cm^{-1}$) 1470, 1387, 1163, 1127, 1109, 1065. HRMS (ESI, *m/z*) calcd for $C_{32}H_{51}NNaO_4Si_2$ $[M + Na]^+$ 592.3254, found 592.3255. $[\alpha]_D^{25} = 0.0°$ (c, 0.2, $CHCl_3$).

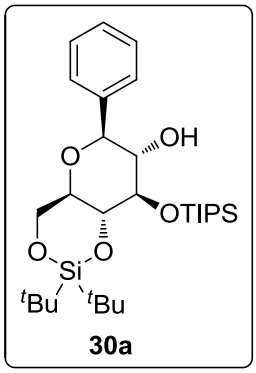
**Typical Experimental procedure for the synthesis of β-D-glucopyranosyl derivative (30a~30e)**




**29a~29e** **30a~30e**

To a solution of compound **29a**~**29e** (1 mmol) in THF (5.8 mL) was added borane-tetrahydrofuran complex (1.0 M in THF, (2.5 mmol)) dropwise at 0 °C. After being stirred at 0 °C for overnight, the mixture was added 30% aqueous hydrogen peroxide (3.3 mL) and 3 N aqueous sodium hydroxide (3.3 mL), and stirred at 0 °C for 4 hours. The reaction mixture was extracted with $Et_2O$, washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated and dried, then the crude material was purified by silica gel column chromatography to give compounds **30a**~**30e**.

**(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-di-*tert*-butyl-6-phenyl-8-[(triisopropylsilyl)oxy]hexahydropyrano[3,2-d][1,3,2]dioxasilin-7-ol** (**30a**).

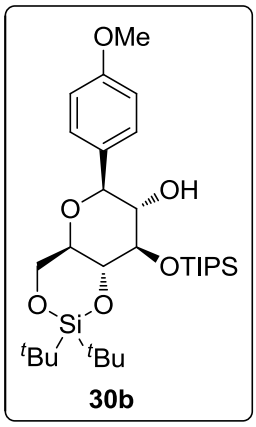



**30a**

Following the general method described above, the title compound **30a** was isolated in 58% yield as a colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.39 (m, 5H), 4.23 (d, *J* = 9.7 Hz, 1H), 4.19 (dd, *J* = 5.1 Hz, 10.2 Hz, 1H), 3.91 (t, *J* = 8.3 Hz, 1H),

3.88 (m, 1H), 3.84 (t, *J* = 8.5 Hz, 1H), 3.53 – 3.58 (m, 1H), 3.50 (t, *J* = 9.0 Hz, 1H), 1.95 (br s, 1H, OH), 1.17 – 1.29 (m, 3H), 1.10 – 1.13 (m, 18H), 1.08 (s, 9H), 1.02 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 138.6, 128.5, 128.5, 127.4, 82.2, 79.8, 78.2, 76.6, 75.4, 66.7, 27.5, 27.0, 22.8, 20.0, 18.5, 18.4, 13.0. MS (APCI, *m/z*) 554 $[M + NH_4]^+$. IR (KBr, $cm^{-1}$) 3472, 2942, 2863, 1471, 1164, 1109. Anal. calcd for $C_{29}H_{52}O_5Si_2$ C: 64.88, H: 9.76; Found C: 64.64, H: 9.99. $[\alpha]_D^{25} = -10.0°$ (c, 0.2, $CHCl_3$).

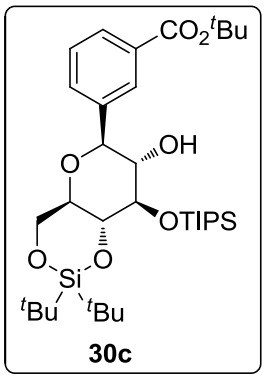
**(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-di-*tert*-butyl-6-(4-methoxyphenyl)-8-[(triisopropylsilyl)oxy]hexahydropyrano[3,2-d][1,3,2]dioxasilin-7-ol (30b**).



**30b**

Following the general method described above, the title compound **30b** was isolated in 60% yield as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.18 (d, *J* = 9.7 Hz, 1H), 4.17 (m, 1H), 3.89 (t, *J* = 10.0 Hz, 1H), 3.85 (m, 1H), 3.83 (t, *J* = 8.5 Hz, 1H), 3.79 (s, 3H), 3.53 – 3.57 (m, 1H), 3.46 – 3.51 (m, 1H), 1.94 (d, *J* = 2.7 Hz, 1H, OH), 1.17 – 1.29 (m, 3H), 1.10 – 1.13 (m, 18H), 1.08 (s, 9H), 1.02 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.8, 130.6, 128.6, 114.0, 81.9, 79.8, 78.2, 76.6, 75.3, 66.7, 55.3, 27.5, 27.0, 22.8, 20.0, 18.5, 18.4, 13.0. IR (nujol, $cm^{-1}$) 3601, 1613, 1514, 1463. MS (APCI, *m/z*) 584 $[M + NH_4]^+$. Anal. calcd for $C_{30}H_{54}O_6Si_2$ C: 63.56, H: 9.60; found C: 63.73, H: 9.75. $[\alpha]_D^{25} = -5.0°$ (c, 0.2, $CHCl_3$).

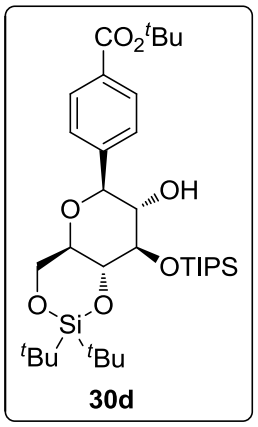
***tert*-Butyl 3-{(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-di-*tert*-butyl-7-hydroxy-8-[(triisopropylsilyl)oxy]hexahydropyrano[3,2-d][1,3,2]dioxasilin-6-yl}benzoate** (**30c**).




**30c**

Following the general method described above, the title compound **30c** was isolated in 52% yield as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.01 (t, *J* = 1.7 Hz, 1H), 7.94 (td, *J* = 1.5 Hz, 7.7 Hz, 1H), 7.54 (td, *J* = 1.5 Hz, 7.7 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 1H), 4.30 (d, *J* = 9.5 Hz, 1H), 4.18 (dd, *J* = 4.9 Hz, 10.3 Hz, 1H), 3.92 (t, *J* = 10.2 Hz, 1H), 3.87 – 3.89 (m, 1H), 3.85 (t, *J* = 8.3 Hz, 1H), 3.48 – 3.61 (m, 2H), 2.03 (d, *J* = 2.9 Hz, 1H, OH), 1.59 (s, 9H), 1.17 – 1.31 (m, 3H), 1.13 (d, *J* = 4.8 Hz, 12H), 1.11 (d, *J* = 4.8 Hz, 6H), 1.08 (s, 9H), 1.02 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.5, 138.9, 132.4, 131.5, 129.5, 128.3, 128.3, 81.7, 81.1, 79.9, 78.1, 76.6, 75.4, 66.6, 28.2, 27.5, 27.0, 22.8, 20.0, 18.5, 18.4, 13.0. IR (KBr, $cm^{-1}$) 3499, 1718, 1589, 1463. MS (APCI, *m/z*) 654 $[M + H]^+$. Anal. calcd for $C_{34}H_{60}O_7Si_2$ C: 64.11, H: 9.49; found C: 64.03, H: 9.65. $[\alpha]_D^{25} = -50.0°$ (c, 0.2, $CHCl_3$).

***tert*-Butyl 4-{(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-di-*tert*-butyl-7-hydroxy-8-[(triisopropylsilyl)oxy]hexahydropyrano[3,2-d][1,3,2]dioxasilin-6-yl}benzoate** (**30d**).

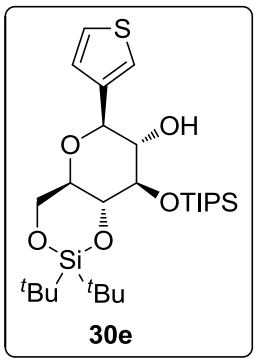



**30d**

Following the general method described above, the title compound **30d** was isolated in 41% yield as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.97 (td, *J* = 8.4 Hz, 1.8 Hz, 2H), 7.43 (td, *J* = 1.6 Hz, 8.3 Hz, 2H), 4.30 (d, *J* = 9.3 Hz, 1H), 4.19 (dd, *J* = 4.9 Hz, 10.3 Hz, 1H), 3.81 – 3.96 (m, 3H), 3.56 (ddd, *J* = 4.9 Hz, 9.0 Hz, 10.1 Hz, 1H), 3.43

(ddd, *J* = 2.8 Hz, 8.2 Hz, 9.6 Hz, 1H), 2.02 (d, *J* = 3.1 Hz, 1H, OH), 1.58 (s, 9H), 1.16 – 1.28 (m, 3H), 1.12 (d, *J* = 4.9 Hz, 12H), 1.10 (d, *J* = 5.1 Hz, 6H), 1.08 (s, 9H), 1.02 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.5, 143.2, 132.1, 129.5, 127.1, 81.6, 81.0, 79.9, 78.1, 76.7, 75.3, 66.6, 28.2, 27.5, 27.0, 22.8, 20.0, 18.5, 18.4, 13.0. IR (KBr, $cm^{-1}$) 3500, 1716, 1613, 1472. MS (APCI, *m/z*) 654 $[M + H]^+$. Anal. calcd for $C_{34}H_{60}O_7Si_2$ C: 64.11, H: 9.49; found C: 63.89, H: 9.76. $[\alpha]_D^{25}$ = –70.0° (c, 0.2, $CHCl_3$).

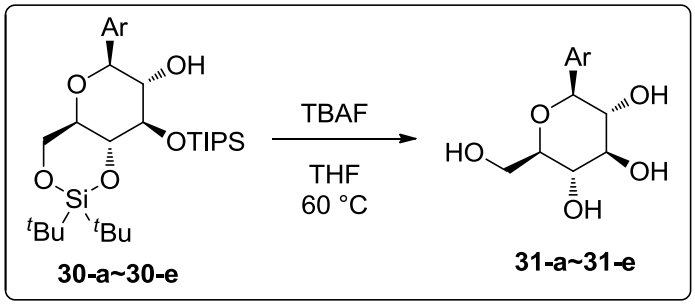
**(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-di-*tert*-butyl-6-(3-thienyl)-8-[(triisopropylsilyl)oxy]hexahydropyrano[3,2-d][1,3,2]dioxasilin-7-ol** (**30e**).



**30e**

Following the general method described above, the title compound **30e** was isolated in 49% yield as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.32-7.35 (m, 2H), 7.13 (dd, *J* = 2.5 Hz, 3.7 Hz, 1H), 4.37 (d, *J* = 9.8 Hz, 1H), 4.19 (dd, *J* = 5.0 Hz, 10.0 Hz, 1H), 3.80 – 3.91 (m, 3H), 3.48 – 3.56 (m, 2H), 2.04 (d, *J* = 2.9 Hz, 1H, OH), 1.11 – 1.14 (m, 21H), 1.07 (s, 9H), 1.01 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 139.8, 126.2, 123.2, 79.8, 78.2, 78.1, 76.3, 75.3, 66.6, 27.5, 27.0, 22.8, 20.0, 18.5, 18.4, 13.0. MS (APCI, *m/z*) 560 $[M + NH_4]^+$. IR (neat + $CHCl_3$, $cm^{-1}$) 3606, 2943, 2864, 1471, 1163, 1109. HRMS (ESI, *m/z*) calcd for $C_{27}H_{51}O_5SSi_2$ $[M + H]^+$ 543.2996, found 543.2989.

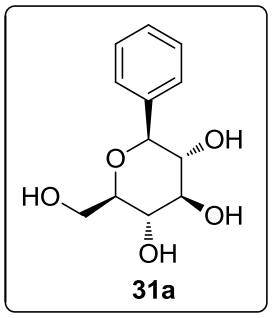
**Typical Experimental procedure for the synthesis of 1-aryl-β-D-glucopyranose (31a~31e)**



**30-a~30-e** **31-a~31-e**

To a solution of compound **31a~31e** (1 mmol) in THF (7.5 mL) was added tetra-*n*-butylammonium fluoride (TBAF) (1.0 M in THF, 5 mmol) dropwise, then the mixture was stirred at 60 °C for 4 hours. The mixture was concentrated and dried, then the crude material was purified by silica gel column chromatography to give compounds **31a~31e**.

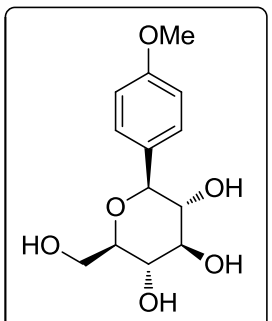
**(1*S*)-1,5-anhydro-1-phenyl-D-glucitol** (**31a**).



**31a**

Following the general method described above, the title compound **31a** was isolated in 43% yield as a colorless amorphous powder. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.23 – 7.38 (m, 5H), 4.95 (d, $J$ = 3.2 Hz, 1H), 4.94 (d, $J$ = 3.5 Hz, 1H), 4.78 (d, $J$ = 5.8 Hz, 1H), 4.45 (t, $J$ = 5.9 Hz, 1H), 4.01 (d, $J$ = 9.5 Hz, 1H), 3.67 – 3.73 (m, 1H), 3.42 – 3.47 (m, 1H), 3.21 – 3.30 (m, 3H), 3.14-3.19 (m, 2H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 140.3, 127.7, 127.5, 127.2, 81.3, 81.1, 78.4, 74.6, 70.3, 61.4. MS (APCI, *m/z*) 258 $[M + NH_4]^+$. IR (neat + $CHCl_3$, $cm^{-1}$) 3361, 2918, 1637, 1455, 1082, 1026. HRMS (ESI, *m/z*) calcd for $C_{12}H_{16}NaO_5$ $[M + Na]^+$ 263.0895, found 263.0896. $[\alpha]_D^{25}$ = +30.0° (c, 0.2, MeOH) (lit.[34] $[\alpha]_D$ = +30.3° (c, 1.9, MeOH)).

**(1*S*)-1,5-anhydro-1-(4-methoxyphenyl)-D-glucitol** (**31b**).

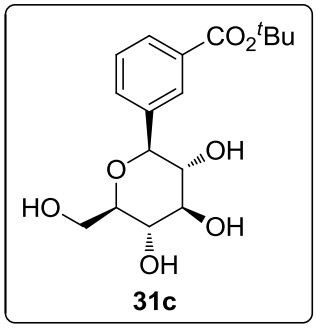


**31b**

Following the general method described above, the title compound **31b** was isolated in 52% yield as a colorless amorphous powder. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.25 (d, $J$ = 8.7 Hz, 2H), 6.86 (d, $J$ = 8.7 Hz, 2H), 4.92 (d, $J$ = 4.5 Hz, 1H), 4.91 (d, $J$ =

5.0 Hz, 1H), 4.71 (d, $J$ = 5.6 Hz, 1H), 4.43 (t, $J$ = 5.8 Hz, 1H), 3.95 (d, $J$ = 9.5 Hz, 1H), 3.73 (s, 3H), 3.67 – 3.72 (m, 1H), 3.40 – 3.46 (m, 1H), 3.10 – 3.30 (m, 4H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 158.5, 132.4, 128.8, 112.9, 81.0, 80.9, 78.4, 74.6, 70.4, 61.4, 54.9. MS (APCI, *m/z*) 288 $[M + NH_4]^+$. IR (KBr, $cm^{-1}$) 3403, 3238, 2924, 2854, 1509, 1459, 1105. HRMS (ESI, *m/z*) calcd for $C_{13}H_{18}NaO_6$ $[M + Na]^+$ 293.1001, found 293.1006. $[\alpha]_D^{25}$ = +27.0° (c, 0.2, MeOH).

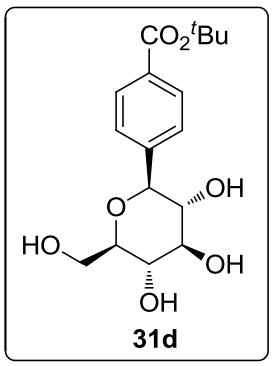
**(1*S*)-1,5-anhydro-1-(3-*tert*-butoxycarbonylphenyl)-D-glucitol** (**31c**).



**31c**

Following the general method described above, the title compound **31c** was isolated in 83% yield as a colorless amorphous powder. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.87 (t, $J$ = 1.6 Hz, 1H), 7.81 (td, $J$ = 1.5 Hz, 7.8 Hz, 1H), 7.59 (td, $J$ = 1.3 Hz, 7.6 Hz, 1H), 7.44 (t, $J$ = 7.7 Hz, 1H), 4.93 (d, $J$ = 5.1 Hz, 2H), 4.83 (d, $J$ = 5.6 Hz, 1H), 4.44 (t, $J$ = 5.7 Hz, 1H), 4.10 (d, $J$ = 9.5 Hz, 1H), 3.72 (ddd, $J$ = 1.8 Hz, 5.5 Hz, 13.7 Hz, 1H), 3.47 (quint, $J$ = 5.9 Hz, 1H), 3.12 – 3.33 (m, 4H), 1.55 (s, 9H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 165.0, 140.8, 132.2, 130.7, 128.3, 128.0, 127.8, 81.2, 80.9, 80.5, 78.2, 74.7, 70.3, 61.3, 27.7. MS (APCI, *m/z*) 358 $[M + NH_4]^+$. IR (nujol, $cm^{-1}$) 3352, 2920, 2852, 1711, 1458. HRMS (ESI, *m/z*) calcd for $C_{17}H_{24}NaO_7$ $[M + Na]^+$ 363.1420, found 363.1413. $[\alpha]_D^{25}$ = +227.72° (c, 0.2, $CHCl_3$).

**(1*S*)-1,5-anhydro-1-(4-*tert*-butoxycarbonylphenyl)-D-glucitol** (**31d**).

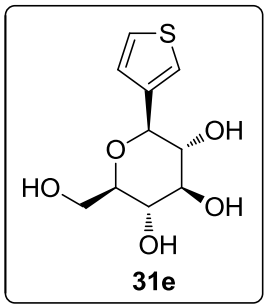


**31d**

Following the general method described above, the title compound **31d** was isolated

in 90% yield as a colorless amorphous powder. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.84 (d, $J$ = 8.3 Hz, 2H), 7.46 (d, $J$ = 8.3 Hz, 2H), 4.93 – 4.95 (m, 2H), 4.83 (d, $J$ = 5.9 Hz, 1H), 4.44 (t, $J$ = 5.7 Hz, 1H), 4.10 (d, $J$ = 9.3 Hz, 1H), 3.72 (ddd, $J$ = 1.8 Hz, 5.4 Hz, 11.8 Hz, 1H), 3.48 (quint, $J$ = 5.9 Hz, 1H), 3.14 – 3.33 (m, 3H), 3.10 (td, $J$ = 5.9 Hz, 9.0 Hz, 1H), 1.54 (s, 9H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 164.9, 145.3, 130.3, 128.3, 127.6, 81.1, 80.8, 80.4, 78.2, 75.0, 70.2, 61.3, 27.7. MS (APCI, *m/z*) 358 $[M + NH_4]^+$. IR (nujol, $cm^{-1}$) 3453, 2977, 2920, 2874, 1701, 1612. Anal. calcd for $C_{17}H_{24}O_7$ C: 59.99, H: 7.11; found C: 59.74, H: 7.33. $[\alpha]_D^{25}$ = +21.78° (c, 0.2, MeOH).

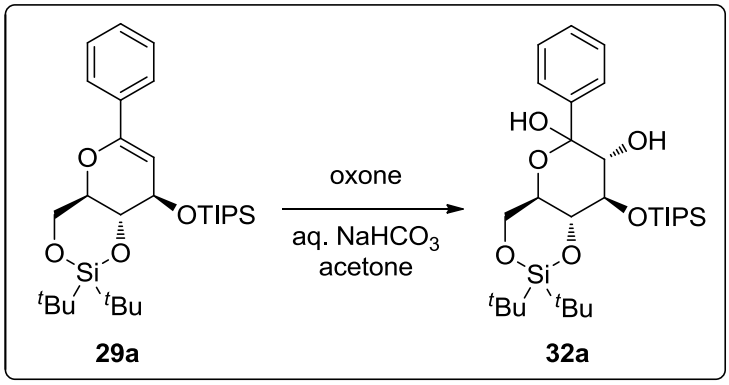
**(1*S*)-1,5-anhydro-1-(3-thienyl)-D-glucitol** (**31e**).



**31e**

Following the general method described above, the title compound **31e** was isolated in 37% yield as a colorless amorphous powder. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.40 – 7.43 (m, 2H), 7.12 (dd, $J$ = 1.5 Hz, 4.9 Hz, 1H), 4.91 (d, $J$ = 3.9 Hz, 1H), 4.88 (d, $J$ = 5.2 Hz, 1H), 4.83 (d, $J$ = 5.7 Hz,1 H), 4.41 (t, $J$ = 6.0 Hz, 1H), 4.12 (d, $J$ = 9.0 Hz, 1H), 3.69 (ddd, $J$ = 2.0 Hz, 5.6 Hz, 11.7 Hz, 1H), 3.43 (quint, $J$ = 6.0 Hz, 1H), 3.13-3.26 (m, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 141.5, 127.3, 124.8, 122.6, 81.0, 78.4, 77.3, 74.3, 70.3, 61.3. MS (APCI, *m/z*) 264 $[M + NH_4]^+$. IR (neat + $CHCl_3$, $cm^{-1}$) 3374, 2925, 1731, 1635, 1425, 1241, 1083. HRMS (ESI, *m/z*) calcd for $C_{10}H_{14}NaO_5S$ $[M + Na]^+$ 269.0460, found 269.0461.

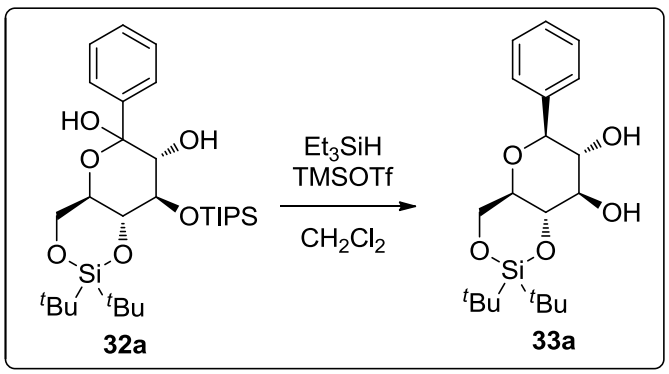
**(4a*R*,7*R*,8*R*,8a*R*)-2,2-di-*tert*-butyl-6-phenyl-8-[(triisopropylsilyl)oxy]hexahydropyrano[3,2-*d*][1,3,2]dioxasiline-6,7-diol (32a)**




**29a** **32a**

To a solution of compound **29a** (129 mg, 0.25 mmol) in acetone (10 mL) was added $NaHCO_3$ (210 mg, 2.50 mmol) at 0 °C, then oxone (461 mg, 1.50 mmol) in water (5 mL) was added and stirred at room temperature for 4 hours. The mixture was filtered and the filtrate was concentrated, then extracted with AcOEt, washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated and dried, then the crude material was purified by silica gel column chromatography (2% – 10% AcOEt in hexane) to give **32a** (75 mg, 60%) as a colorless amorphous gum and anomeric diastereomixture (approximately 10 : 1). $^1$H NMR (400 MHz, $CDCl_3$, major diastereomer) δ 7.56 – 7.58 (m, 2H), 7.34 – 7.40 (m, 3H), 4.14 (m, 2H), 4.05 (m, 1H), 3.99 (m, 1H), 3.88 (m, 1H), 3.50 (ddd, *J* = 1.2 Hz, 5.6 Hz, 8.6 Hz, 1H), 3.01 (d, *J* = 1.1 Hz, 1H), 2.13 (d, *J* = 5.5 Hz, 1H), 1.18 – 1.26 (m, 3H), 1.09 – 1.13 (m, 18H), 1.09 (s, 9H), 1.03 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$, major diastereomer) δ 141.8, 129.1, 128.8, 128.3, 125.8, 98.3, 78.3, 77.9, 76.8, 67.9, 66.9, 27.6, 27.0, 22.8, 20.0, 18.5, 18.4, 13.0. MS (ESI, *m/z*) 575 (M + Na). IR (nujol, cm$^{-1}$) 3435, 1463, 1377. HRMS (ESI) calcd for $C_{29}H_{53}O_6Si_2$ $[M + H]^+$ 553.3381, found 553.3367.

**(4a*R*,6*S*,7*R*,8*R*,8a*S*)-2,2-di-*tert*-butyl-6-phenylhexahydropyrano[3,2-*d*][1,3,2]dioxasiline-7,8-diol (33a)**

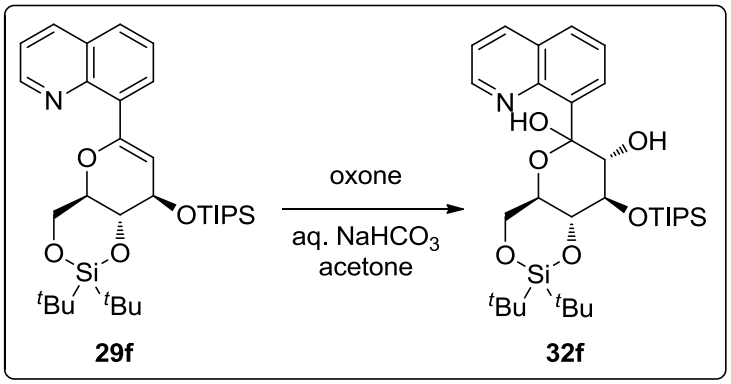



**32a** **33a**

To a solution of compound **32a** (50 mg, 0.0904 mmol) in methylene chloride (5 mL)

was added triethylsilane (0.06 mL, 0.376 mmol) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.06 mL, 0.332 mmol) at –78 °C. After being stirred at –78 °C for 1 hour and room temperature for 1.5 hours, the mixture was quenched by saturated aq. $NaHCO_3$ and extracted with $CHCl_3$, washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated and dried, then the crude material was purified by silica gel column chromatography (10% – 20% AcOEt in hexane) to give compound **33a** (18 mg, 52%) as a colorless amorphous powder. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.39 (m, 5H), 4.26 (d, *J* = 9.4 Hz, 1H), 4.21 (dd, *J* = 5.2 Hz, 10.2 Hz, 1H), 3.91 (t, *J* = 10.2 Hz, 1H), 3.82 (t, *J* = 9.1 Hz, 1H), 3.70 (t, *J* = 8.7 Hz, 1H), 3.62 (t, *J* = 9.1 Hz, 1H), 3.57 – 3.61 (m, 1H), 2.81 (d, *J* = 1.5 Hz, 1H), 2.10 (d, *J* = 2.7 Hz, 1H), 1.09 (s, 9H), 1.03 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 138.0, 128.7, 128.6, 127.5, 82.2, 78.2, 77.2, 74.8, 74.8, 66.5, 27.5, 27.0, 22.7, 20.0. MS (APCI, *m/z*) 398 (M + $NH_4$). IR (KBr, $cm^{-1}$) 3460, 1474, 1388. HRMS (ESI) calcd for $C_{20}H_{33}O_5Si$ $[M + H]^+$ 381.2097, found 381.2092.

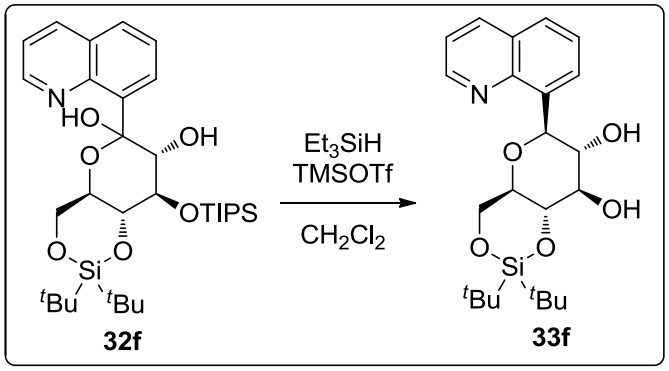
**(4a*R*,7*R*,8*R*,8a*R*)-2,2-di-*tert*-butyl-6-quinolin-8-yl-8-[(triisopropylsilyl)oxy]hexahydropyrano[3,2-*d*][1,3,2]dioxasiline-6,7-diol (32f)**




To a solution of compound **29f** (300 mg, 0.526 mmol) in acetone (20 mL) was added $NaHCO_3$ (442 mg, 5.26 mmol) at 0 °C, then oxone (970 mg, 3.16 mmol) in water (10 mL) was added and stirred at room temperature for 4 hours. The mixture was filtered and the filtrate was concentrated, then extracted with AcOEt, washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated and dried, then the crude material was purified by silica gel column chromatography (5% – 20% AcOEt in hexane) to give compound **32f** (215 mg, 68%) as a colorless amorphous powder and anomeric diastereomixture (approximately 10 : 1). $^1$H NMR (400 MHz, $CDCl_3$, major diastereomer) δ 11.60 (s, 1H), 8.79 (dd, *J* = 1.8 Hz, 4.3 Hz, 1H), 8.24 (dd, *J* = 1.8 Hz, 8.4 Hz, 1H), 7.92 (dd, *J* = 1.4 Hz, 7.4 Hz, 1H), 7.82 (dd, *J* = 1.1 Hz, 8.8 Hz, 1H), 7.61 (t,

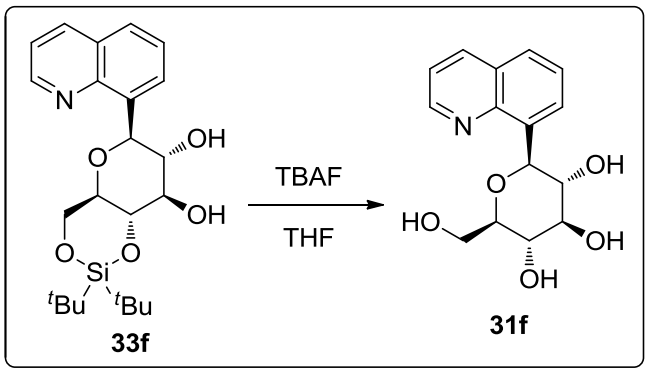
*J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 4.3 Hz, 8.4 Hz, 1H), 4.30 (td, *J* = 5.0 Hz, 10.0 Hz, 1H), 4.19 (t, *J* = 8.5 Hz, 1H), 4.13 (dd, *J* = 5.0 Hz, 9.9 Hz, 1H), 3.86 – 3.93 (m, 3H), 2.31 (s, 1H), 1.18 – 1.31 (m, 3H), 1.04 – 1.16 (m ,18H), 1.09 (s, 9H), 1.05 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$, major diastereomer) δ 147.3, 146.7, 137.9, 134.7, 129.1, 128.7, 128.7, 127.0, 120.7, 101.6, 78.7, 78.2, 77.1, 67.4, 67.3, 27.6, 27.1, 22.8, 20.0, 18.5, 18.5, 13.0. MS (ESI, *m/z*) 604 $[M + H]^+$. IR (KBr, $cm^{-1}$) 3450, 1471, 1166, 1072. HRMS (ESI) calcd for $C_{32}H_{54}NO_6Si_2$ $[M + H]^+$ 604.3490, found 604.3473.

**(4a*R*,6*S*,7*R*,8*R*,8a*S*)-2,2-di-*tert*-butyl-6-quinolin-8-yl-hexahydropyrano[3,2-*d*][1,3,2]dioxasiline-7,8-diol (33f)**




To a solution of compound **32f** (214 mg, 0.354 mmol) in methylene chloride (10 mL) was added triethylsilane (0.28 mL, 1.75 mmol) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.32 mL, 1.77 mmol) at –78 °C. After being stirred at –78 °C for 1 hour and room temperature for 1.5 hours, the mixture was quenched by saturated aq. $NaHCO_3$ and extracted with $CHCl_3$, washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated and dried, then the crude material was purified by silica gel column chromatography (5% – 10% AcOEt in hexane) to give compound **33f** (14 mg, 7%) as a colorless amorphous powder. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.82 (dd, *J* = 1.9 Hz, 4.4 Hz, 1H), 8.26 (dd, *J* = 1.8 Hz, 8.4 Hz, 1H), 7.93 (dt, *J* = 1.2 Hz, 7.3 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 7.7 Hz, 1H), 5.55 (d, *J* = 8.5 Hz, 1H), 4.94 (t, *J* = 7.4 Hz, 1H), 4.31 (m, 1H), 4.15 (dd, *J* = 6.7 Hz, 8.4 Hz, 1H), 4.02 – 4.06 (m, 2H), 3.84 – 3.89 (m, 1H), 2.23 (s, 1H), 1.08 (s, 9H), 1.01 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 148.8, 145.2, 138.7, 137.7, 128.6, 127.1, 127.1, 125.8, 121.2, 82.5, 81.6, 80.3, 74.8, 73.9, 64.8, 27.2, 27.2, 21.4, 21.3. MS (APCI, *m/z*) 432 (M + H). IR (KBr, $cm^{-1}$) 3448, 1470, 1162, 1086. HRMS (ESI) calcd for $C_{23}H_{34}NO_5Si$ $[M + H]^+$ 432.2206, found 432.2215. $[\alpha]_D^{25}$ = +132.86° (c, 0.7, $CHCl_3$).

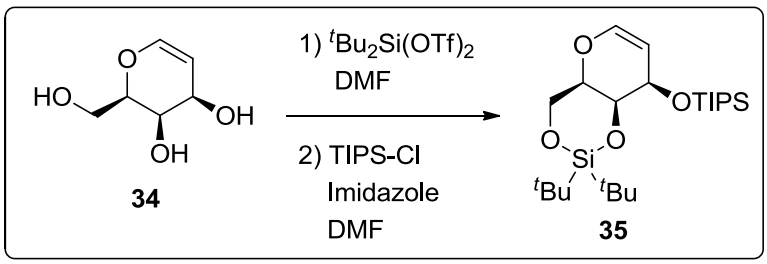
**(1*S*)-1,5-anhydro-1-(quinolin-8-yl)-D-glucitol (31f)**




To a solution of compound **33f** (14 mg, 0.0324 mmol) in THF (1 mL) was added TBAF (1.0 M in THF, 0.5 mL, 0.5 mmol) dropwise, then the mixture was stirred at 60 °C for 4 hours. The mixture was concentrated and dried, then the crude material was purified by silica gel column chromatography (10% MeOH in AcOEt) to give **31f** (3 mg, 33%) as a colorless amorphous powder. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 8.85 (dd, $J$ = 1.8 Hz, 4.3 Hz, 1H), 8.38 (dd, $J$ = 1.7 Hz, 8.3 Hz, 1H), 7.89 (dd, $J$ = 1.2 Hz, 8.1 Hz, 1H), 7.59 (dd, $J$ = 6.6 Hz, 7.4 Hz, 1H), 7.55 (t, $J$ = 3.7 Hz, 7.8 Hz, 1H), 5.31 (d, $J$ = 3.8 Hz, 1H), 4.29 (t, $J$ = 2.8 Hz, 1H), 4.14 (ddd, $J$ = 3.3 Hz, 6.0 Hz, 9.1 Hz, 1H), 4.07 (dd, $J$ = 3.3 Hz, 8.3 Hz, 1H), 3.87 (dd, 3.3 Hz, 11.6 Hz, 1H), 3.71 (dd, $J$ = 5.8 Hz, 11.6 Hz, 1H). $^{13}$C NMR (100 MHz, $CD_3OD$) δ 150.1, 146.2, 138.9, 138.3, 130.0, 129.3, 127.7, 122.4, 97.3, 88.7, 85.0, 82.8, 79.7, 71.2, 65.6. MS (APCI, *m/z*) 292 (M + H). IR (nujol, cm$^{-1}$) 3380, 2924, 1455, 1082, 1026. HRMS (ESI) calcd for $C_{15}H_{17}NNaO_5$ $[M + Na]^+$ 314.1004, found 314.1030.

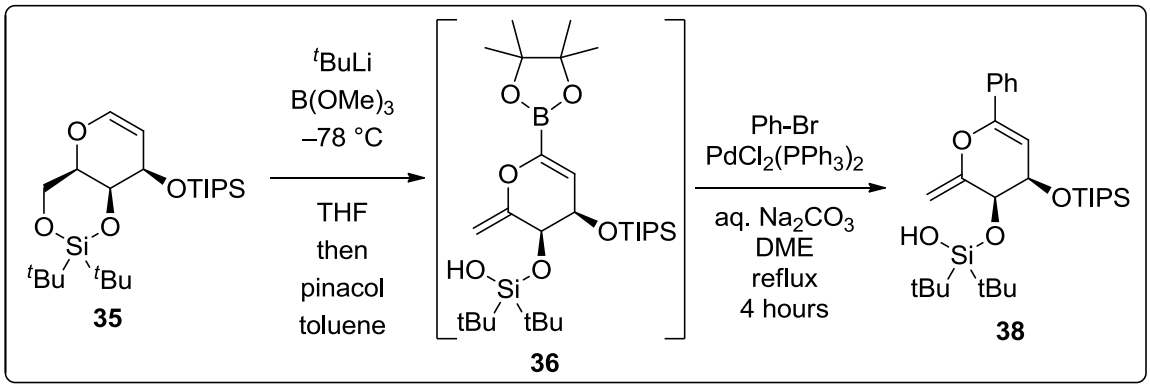
## 第３章に関する実験の部

**(4a*R*,8*R*,8a*S*)-2,2-di-*tert*-butyl-8-[(triisopropylsilyl)oxy]-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasiline (35)**




To a solution of D-galactal **34** (2.76 g, 18.9 mmol) in DMF (90 mL) was added di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (10 g, 29.4 mmol) in methylene chloride (25 mL) at –40 °C dropwise, then stirred at –40 °C for 1 hour. To a mixture was added pyridine (3.82 mL, 47.2 mmol) at –40 °C, then stirred at 0 °C for 1 hour. The reaction mixture was diluted with $Et_2O$, then washed with water and brine, dried over sodium sulfate, filtered and concentrated to give bridged-silyl alcohol[22] (6.82 g) as an oil which was used without further purification. To a solution of bridged-silyl alcohol (6.82 g) in DMF was added imidazole (3.22 g, 47.3 mmol) and triisopropylsilyl chloride (5.26 mL, 24.6 mmol), then stirred at 50 °C for 18 hours. The mixture was cooled to ambient temperature, water was added and extracted with $Et_2O$, washed with water and brine, dried over sodium sulfate, and filtered. After the filtrate was concentrated, the residue was purified by silica gel column chromatography (5% AcOEt in hexane) to give **35** (7.11 g, 85%) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 6.25 (d, *J* = 6.2 Hz, 1H), 4.62 – 4.68 (dd, *J* = 1.6 Hz, 6.3 Hz, 1H), 4.60 (m, 1H), 4.38 (m, 1H), 4.19 – 4.31 (m, 2H), 3.85 (m, 1H), 0.82 – 1.14 (m, 39H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 143.23, 103.99, 73.53, 69.42, 67.56, 65.80, 27.39, 26.83, 23.18, 20.60, 17.78, 17.74, 12.09. MS (APCI, *m/z*) 443 $[M + H]^+$. IR (neat, $cm^{-1}$) 2940, 2863, 1652, 1473, 1178, 1110, 1082. HRMS (ESI, *m/z*) calcd for $C_{23}H_{46}NaO_4Si_2$ $[M + Na]^+$ 465.2832, found 465.2837. $[\alpha]_D^{25}$ = +14.2° (c, 0.5, $CHCl_3$)

**2,6-anhydro-1,5-dideoxy-3-*O*-[di-*tert*-butyl(hydroxy)silyl]-6-phenyl-4-*O*-(triisopropylsilyl)-D-erythro-hexa-1,5-dienitol (38)**

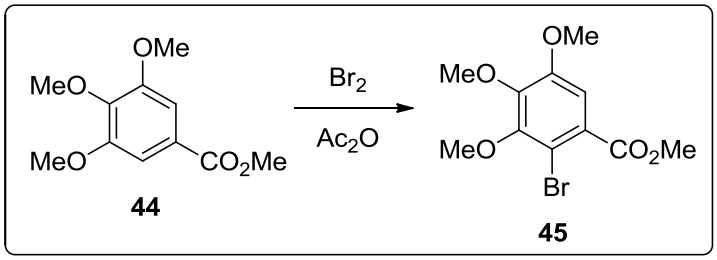



To a solution of **35** (21.28 g, 48.06 mmol) in THF (160 mL) was added *tert*-butyllithium (1.50 M, 103 mL, 154.5 mmol) at –78 °C dropwise, then stirred at 0 °C for 1 hour. To a mixture was added trimethyl borate (19.4 mL, 174 mmol) at –78 °C, then stirred at 0 °C for 15 minutes and gradually warmed to room temperature and stirred for 1 hour. The mixture was quenched by $H_2O$, then the mixture was extracted with ether, washed with brine, dried over sodium sulfate, filtered, the filtrate was evaporated under reduced pressure to give crude boronic acid as a colorless viscous oil. To a solution of boronic acid in toluene (250 mL) was added pinacol (4.91 g, 41.6 mmol), then the mixture was stirred at room temperature for overnight. The reaction mixture was washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure to afford quantitative yield of glucal-boronic acid ester **36** (27.4 g, 99%) as a colorless viscous oil.

To a mixture of boronic acid ester **36** (1.60 g, 2.81 mmol) and bromobenzene (157 mg, 1.00 mmol) in DME (10 mL) was added dichlorobis(triphenylphosphine)palladium (35 mg, 0.05 mmol) and 2 M aq $Na_2CO_3$ (2.5 mL, 5.00 mmol), then the mixture was refluxed for 4 hours. The mixture was cooled to ambient temperature and diluted with AcOEt, then washed with water, brine, dried over sodium sulfate, and filtered. After the filtrate was concentrated, the crude material was purified by silica gel column chromatography (5% – 10% AcOEt in hexane) to give compound **38** (520 mg, 99%) as a colorless oil. $^1$H NMR (400 MHz, DMSO-$d_6$, 75 °C) δ 7.59 – 7.61 (m, 2H), 7.36 – 7.39 (m, 3H), 5.98 (m, 1H, Si-OH), 5.64 (d, $J$ = 5.8 Hz, 1H), 4.75 – 4.77 (m, 2H), 4.67 – 4.68 (m, 1H), 4.55 – 4.57 (m, 1H), 0.98 – 1.17 (m, 39H). $^{13}$C NMR (100 MHz, DMSO-$d_6$, 75 °C) δ 156.02, 150.11, 133.24, 128.88, 128.37, 124.67, 99.28, 91.38, 70.00, 66.25, 20.59, 20.11, 18.03, 17.99, 17.92, 17.88, 12.57, 12.51. MS (APCI, *m/z*) 536 [M + $NH_4$]$^+$. IR (neat, cm$^{-1}$) 3478, 1722, 1669, 1471. HRMS (ESI, *m/z*) calcd for $C_{29}H_{50}NaO_4Si_2$ [M + Na]$^+$ 541.3145, found 541.3162. $[\alpha]_D^{25}$ = –70.0° (c, 0.6, $CHCl_3$)

# 第４章に関する実験の部

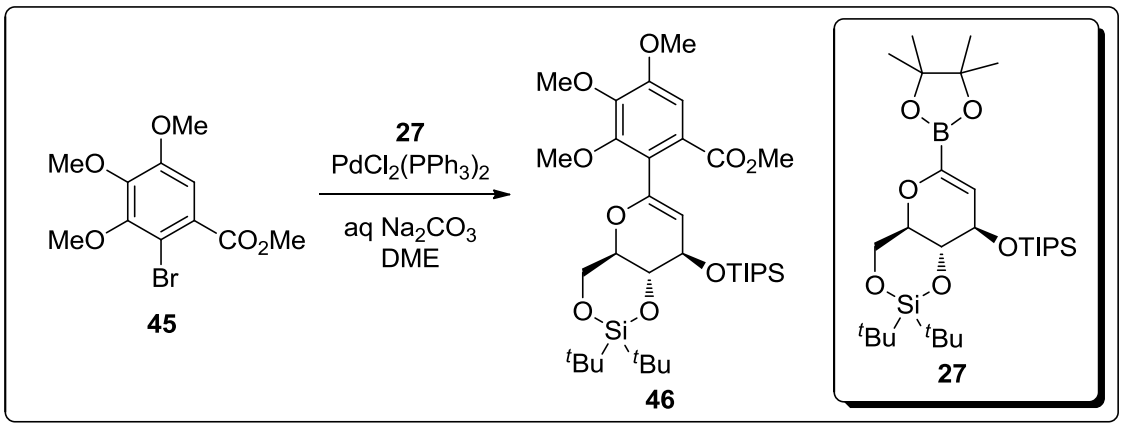
**Methyl 2-bromo-3,4,5-trimethoxybenzoate (45)**[35]




**44** **45**

To a solution of methyl 3,4,5-trimethoxybenzoate **44** (4.5 g, 20.0 mmol) in acetic anhydride (25 mL) was added bromine (3.2 g, 20.0 mmol) in acetic anhydride (15 mL) dropwise at 0 °C, and the mixture was stirred at 0 °C for 4 hours and r.t. for 1 hour. After acetic anhydride was concentrated, the crude material was purified by silica gel column chromatography (10% – 20% AcOEt in hexane) to give compound **45** (4.95 g, 82%) as a colorless oil. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H), 3.89 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 166.5, 152.4, 151.6, 146.1, 127.6, 110.2, 109.6, 61.2, 61.0, 56.3, 52.5. MS (APCI, *m/z*) 305 / 307 $[M + H]^+$. IR (neat, $cm^{-1}$) 1734, 1484, 1386, 1339. Anal. calcd for $C_{11}H_{13}BrO_5$ C: 43.30, H: 4.29; found C: 43.32, H: 4.40.

**Methyl 2-{(4a*R*,8*R*,8a*R*)-2,2-di-*tert*-butyl-8-[(triisopropylsilyl)oxy]-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasilin-6-yl}-3,4,5-trimethoxybenzoate (46)**

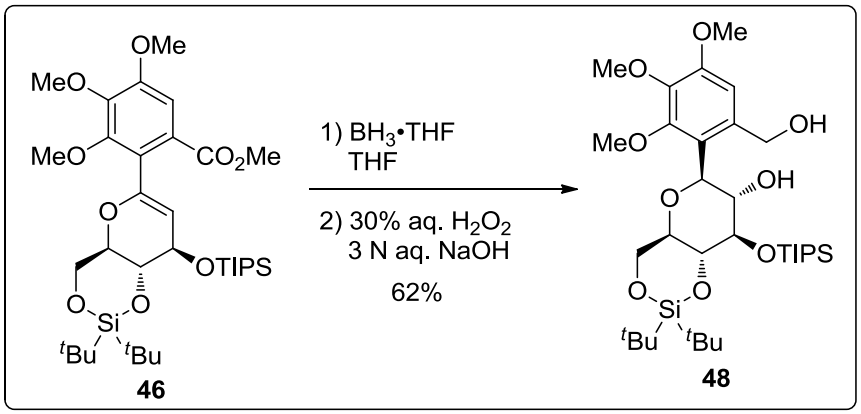



**45** **46** **27**

To a mixture of boronic acid ester **27** (1.42 g, 2.50 mmol) and bromide **45** (305 mg, 1.00 mmol) in DME (10 mL) was added dichlorobis(triphenylphosphine)palladium (35 mg) and 2 M aq $Na_2CO_3$ (2.5 mL, 5.00 mmol), then the mixture was refluxed for 3

hours. The mixture was cooled to ambient temperature and diluted with AcOEt, then washed with water, brine, dried over sodium sulfate, and filtered. After the filtrate was concentrated, the crude material was purified by silica gel column chromatography (5% – 10% AcOEt in hexane) to give compound **46** (722 mg, 99%) as a colorless amorphous powder. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 1H), 4.80 (d, *J* = 2.2 Hz, 1H), 4.56 (dd, *J* = 2.3 Hz, 6.7 Hz, 1H), 4.17 (m, 1H), 4.09 (m, 1H), 3.99 – 4.04 (m, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 1.08 (s, 9H), 1.02 (s, 9H), 1.07 – 1.12 (m, 21H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.9, 153.6, 152.4, 147.3, 145.2, 127.4, 123.2, 108.8, 106.0, 77.9, 73.4, 71.9, 66.1, 61.7, 60.9, 56.2, 52.2, 27.5, 27.0, 22.8, 19.9, 18.2, 12.5. MS (ESI, *m/z*) 667 $[M + H]^+$. IR (neat, $cm^{-1}$) 1721, 1463, 1342, 1109, 1059. HRMS (ESI, *m/z*) calcd for $C_{34}H_{58}NaO_9Si_2$ $[M + Na]^+$ 689.3517, found 689.3541. $[\alpha]_D^{25}$ = – 54.0° (c, 0.2, $CHCl_3$).

**2-{(4a*R*,8*R*,8a*R*)-2,2-di-*tert*-butyl-8-[(triisopropylsilyl)oxy]-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasilin-6-yl}-3,4,5-trimethoxybenzyl alcohol (48)**

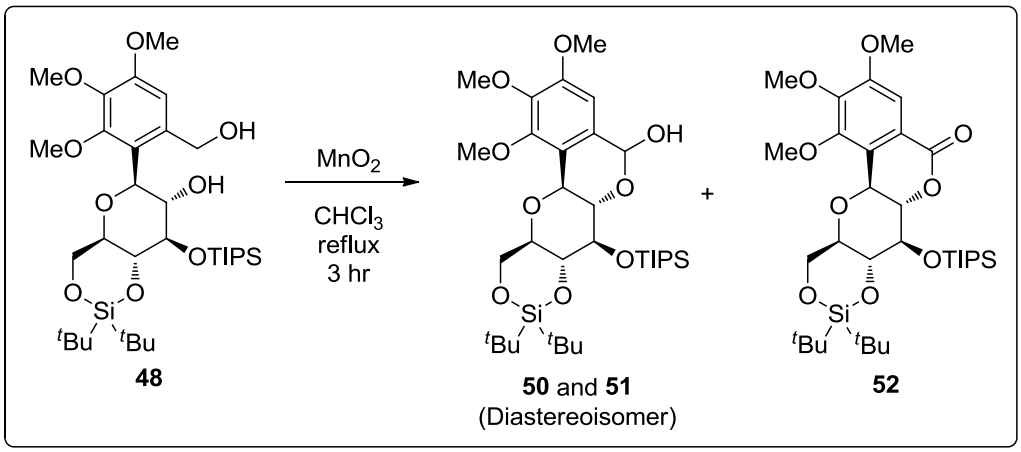



To a solution of compound **46** (870 mg, 1.30 mmol) in THF (15 mL) was added borane-tetrahydrofuran complex (1.0 M in THF, 6.5 mL, 6.50 mmol) dropwise at 0 °C. After being stirred at 0 °C for overnight, the mixture was added 30% aqueous hydrogen peroxide (10 mL) and 3 N aqueous sodium hydroxide (10 mL), and stirred at 0 °C for 4 hours. The reaction mixture was neutralized with 10% aqueous citric acid and extracted with $Et_2O$, washed with brine, dried over sodium sulfate, and filtered. After the filtrate was concentrated, the crude material was purified by silica gel column chromatography (5% – 20% AcOEt in hexane) to give compound **48** (516 mg, 62%) as a colorless amorphous powder. $^1$H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 1H), 4.85 (d, *J* = 12.1 Hz, 1H), 4.37 (dd, *J* = 8.7 Hz, 11.1 Hz, 1H), 4.19 (dd, *J* = 5.0 Hz, 10.2 Hz, 1H), 3.84 – 3.94 (m, 13H), 3.76 – 3.82 (m, 1H), 3.54 (td, *J* = 4.8 Hz, 9.6 Hz, 1H), 1.54 – 1.55 (m, 2H), 1.18 – 1.32 (m, 3H), 0.99 – 1.13 (m, 18H), 1.08 (s, 9H), 1.03 (s, 9H). $^{13}$C

NMR (100 MHz, $CDCl_3$)[36] δ 154.4, 151.9, 151.7, 135.6, 108.1, 97.4, 79.9, 78.1, 77.2, 75.9, 73.9, 66.4, 61.5, 60.9, 55.9, 27.5, 27.0, 22.8, 20.0, 18.5, 18.4, 13.0. MS (APCI, *m/z*) 674 $[M + NH_4]^+$. IR (nujol, $cm^{-1}$) 3421, 1599, 1467, 1329, 1166. HRMS (ESI) calcd for $C_{33}H_{60}NaO_9Si_2$ $[M + Na]^+$ 679.3674, found 679.3692. $[\alpha]_D^{25}$ = +6.0° (c, 0.2, $CHCl_3$).

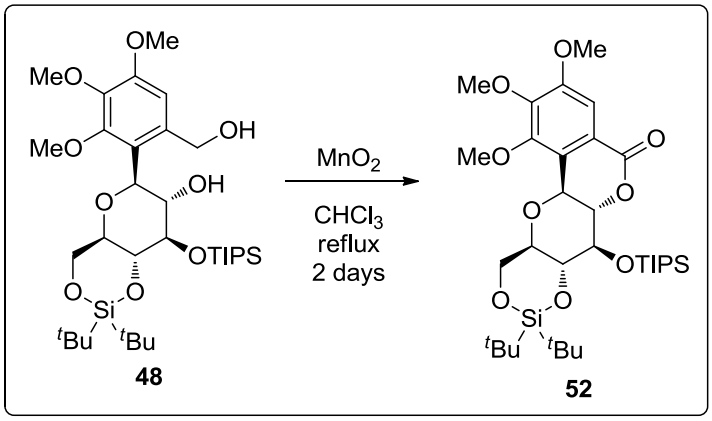
**(5*RS*, 6a*S*,7*R*,7a*R*,11a*R*,12a*S*)-9,9-di-*tert*-butyl-1,2,3-trimethoxy-7-[(triisopropylsilyl)oxy]-6a,7,7a,11,11a,12a-hexahydro-5*H*-[1,3,2]dioxasilino[4',5':5,6]pyrano[3,2-*c*]isochromen-5-ol (50 and 51)**

**(6a*S*,7*R*,7a*R*,11a*R*,12a*S*)-9,9-di-*tert*-butyl-1,2,3-trimethoxy-7-[(triisopropylsilyl)oxy]-6a,7,7a,11,11a,12a-hexahydro-5*H*-[1,3,2]dioxasilino[4',5':5,6]pyrano[3,2-*c*]isochromen-5-one (52)**



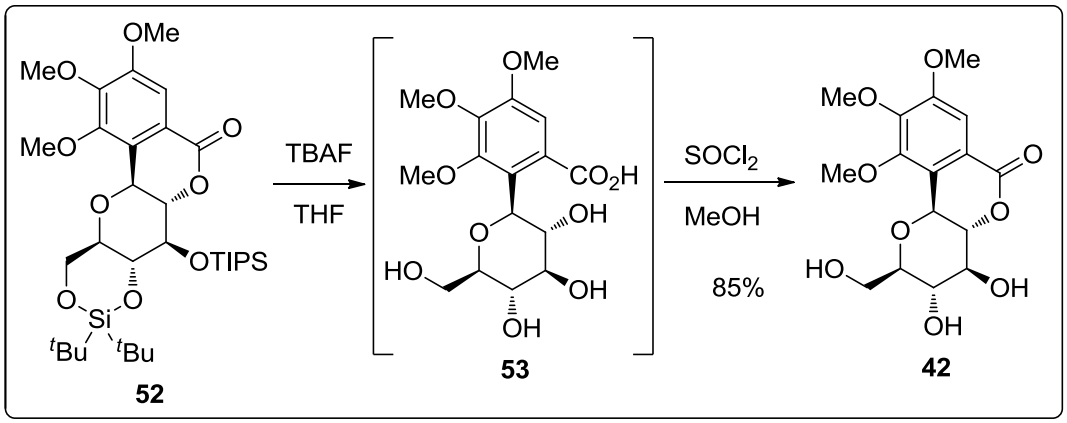

To a solution of compound **48** (180 mg, 0.274 mmol) in chloroform (5 mL) was added manganese dioxide (480 mg, 5.48 mmol), then the mixture was refluxed for 3 hr. After being cooled to ambient temperature, the insoluble material was filtered off and the filtrate was concentrated. The crude material was purified by silica gel column chromatography (10% – 20% AcOEt in hexane) to give lactol **50** (47 mg, 26%), **51** (68 mg, 38%), and lactone **52** (29 mg, 16%). $^1$H NMR of **50** (400 MHz, $CDCl_3$) δ 6.75 (s, 1H), 5.84 (d, *J* = 9.1 Hz, 1H), 4.51 (d, *J* = 9.4 Hz, 1H), 4.28 (dd, *J* = 4.8 Hz, 10.0 Hz, 1H), 3.79 – 3.99 (m, 3H), 3.85 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.67 (m, 1H), 3.36 (t, *J* = 9.2 Hz, 1H), 2.80 (d, *J* = 9.1 Hz, 1H), 1.20 – 1.28 (m, 3H), 1.10 – 1.16 (m, 18H), 1.06 (s, 9H), 1.02 (s, 9H). $^1$H NMR of **51** (400 MHz, $CDCl_3$) δ 6.60 (s, 1H), 5.90 (d, *J* = 9.4 Hz, 1H), 4.41 (d, *J* = 9.4 Hz, 1H), 4.29 (dd, *J* = 4.8 Hz, 10.0 Hz, 1H), 3.83 – 3.97 (m, 4H), 3.85 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.65 (m, 1H), 2.73 (d, *J* = 4.4 Hz, 1H), 1.18 – 1.27 (m, 3H), 1.10 – 1.16 (m, 18H), 1.06 (s, 9H), 1.02 (s, 9H). Spectra data of **52** exists in alternative experience shown below.

**(6a*S*,7*R*,7a*R*,11a*R*,12a*S*)-9,9-di-*tert*-butyl-1,2,3-trimethoxy-7-[(triisopropylsilyl)oxy]-6a,7,7a,11,11a,12a-hexahydro-5*H*-[1,3,2]dioxasilino[4',5':5,6]pyrano[3,2-*c*]isochromen-5-one (52)**




To a solution of compound **48** (300 mg, 0.46 mmol) in chloroform (5 mL) was added manganese dioxide (794 mg, 11.2 mmol), then the mixture was refluxed for 2 days. After being cooled to ambient temperature, the insoluble material was filtered off and the filtrate was concentrated. The crude material was purified by silica gel column chromatography (10% – 20% AcOEt in hexane) to give lactone **52** (255 mg, 86%) as a colorless amorphous powder. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 4.75 (d, $J$ = 10.2 Hz, 1H), 4.33 (dd, $J$ = 5.0 Hz, 9.9 Hz, 1H), 4.10 (m, 1H), 4.03 (m, 1H), 3.96 (m, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.87 (dd, $J$ = 8.0 Hz, 9.6 Hz, 1H), 3.78 (s, 3H), 3.64 (td, $J$ = 5.0 Hz, 9.9 Hz, 1H), 1.22 – 1.34 (m, 3H), 1.12 – 1.16 (m, 18H), 1.06 (s, 9H), 1.02 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.6, 153.6, 151.2, 148.7, 125.9, 119.5, 109.9, 81.1, 78.5, 75.7, 73.0, 66.4, 61.6, 61.1, 56.2, 27.5, 27.0, 22.8, 20.0, 18.4, 12.8. MS (APCI, *m/z*) 653 $[M + H]^+$. IR (nujol, $cm^{-1}$) 1737, 1597, 1469, 1332. HRMS (ESI, *m/z*) calcd for $C_{33}H_{57}O_9Si_2$ $[M + H]^+$ 653.3541, found 653.3535. $[\alpha]_D^{25}$ = –47.0° (c, 0.2, $CHCl_3$).

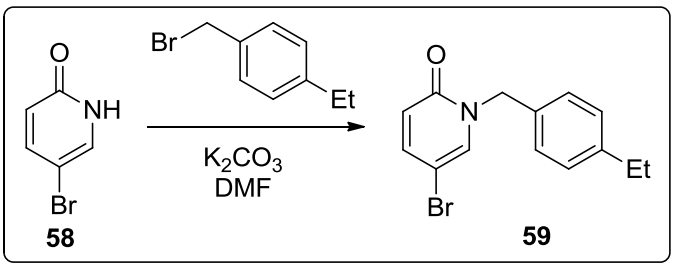
**Tri-*O*-methylnorbergenin (42)**




To a solution of lactone **52** (125 mg, 0.191 mmol) in THF (4 mL) was added TBAF (1.0 M in THF, 1.5 mL, 1.5 mmol), then the mixture was stirred at 70 °C for 4 hours. After the mixture was concentrated, the crude material was dissolved in MeOH (10 mL). To a mixture was added thionyl chloride (1.2 mL, 16.5 mmol) at 0 °C, then the mixture was stirred at room temperature for overnight. After the solvent was concentrated, the crude material was purified by silica gel column chromatography (0% – 10% MeOH in AcOEt) to give tri-*O*-methylnorbergenin **42** (59 mg, 85%) as a colorless amorphous powder. The analytical data was correspondent with reported data.[25] $^{1}$H NMR (400 MHz, MeOH) δ 7.43 (s, 1H), 4.80 (d, $J$ = 10.3 Hz, 1H), 3.69 – 4.03 (m, 13H), 3.43 – 3.55 (m, 2H). $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.33 (s, 1H), 5.58 (d, $J$ = 5.4 Hz, 1H, $D_2O$ exchangeable), 5.30 (d, $J$ = 5.4 Hz, 1H, $D_2O$ exchangeable), 4.80 (d, $J$ = 10.3 Hz, 1H), 4.52 (dd, $J$ = 4.8 Hz, 6.0 Hz, 1H, $D_2O$ exchangeable), 3.91 (t, $J$ = 10.0 Hz, 1H, $D_2O$ exchangeable), 3.85 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.64 – 3.70 (m, 1H), 3.50 – 3.57 (m, 2H), 3.24 – 3.46 (m, 3H). $^{13}$C NMR (100 MHz, $CD_3OD$) δ 166.0, 155.1, 152.6, 150.0, 127.9, 120.4, 110.9, 82.7, 81.8, 76.0, 73.2, 71.7, 62.7, 62.3, 61.6, 56.8. MS (APCI, *m/z*) 374 $[M + NH_4]^+$. IR (KBr, cm$^{-1}$) 3516, 3425, 1708 (C=O), 1620, 1591, 1463. HRMS (ESI, *m/z*) calcd for $C_{16}H_{21}O_9$ $[M + H]^+$ 357.1186, found 357.1193. $[\alpha]_D^{25}$ = –27.3° (c, 0.22, MeOH) (lit.[25] $[\alpha]_D^{23}$ = –27.1° (c, 1, MeOH)).

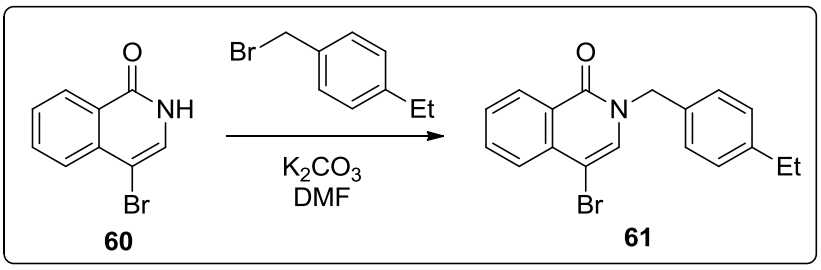
# 第５章に関する実験の部

**5-bromo-1-(4-ethylbenzyl)pyridin-2(1*H*)-one (59)**



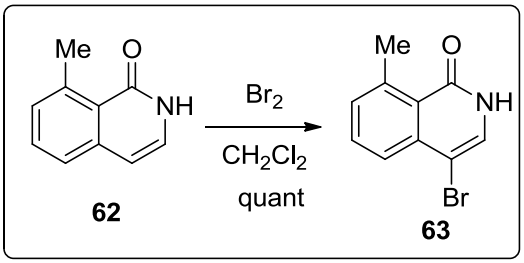

To a suspension of **58** (1.04 g, 5.98 mmol) in DMF (15 mL) was added 4-ethylbenzyl bromide (1.43 g, 7.18 mmol) and potassium carbonate (1.66 g, 12.0 mmol), and the mixture was stirred at room temperature for overnight. The reaction mixture was diluted with AcOEt, and washed successively with water and brine. The extract was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 10 : 1 – 3 : 1) to give titled compound **59** (1.58 g, 90%) as colorless crystals. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 2.2 Hz, 1H), 7.31 (dd, *J* = 2.7 Hz, 9.5 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 6.52 (d, *J* = 9.6 Hz, 1H), 5.06 (s, 2H), 2.64 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.8 Hz, 3H). MS (APCI, *m/z*) 292/294 (M + H). IR (nujol, $cm^{-1}$) 1662 (C=O), 1585.

**4-bromo-2-(4-ethylbenzyl)isoquinolin-1(2*H*)-one (61)**



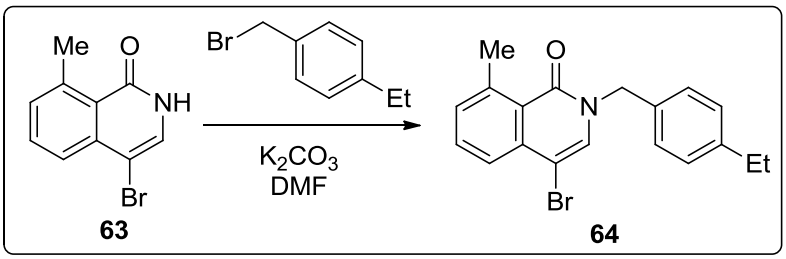

The title compound was prepared in the same manner as described for **59** using **60**[37] instead of **58** in 96% yield as slightly yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 0.7 Hz, 1.5 Hz, 1H), 7.79 – 7.82 (m, 1H), 7.74 (td, *J* = 1.5 Hz, 7.0 Hz, 1H), 7.53 – 7.59 (m, 1H), 7.36 (s, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 5.16 (s, 2H), 2.63 (q, *J* = 7.7 Hz, 2H), 1.22 (t, *J* = 7.6 Hz, 3H). MS (APCI, *m/z*) 342/344 (M + H). IR (neat, $cm^{-1}$) 1654 (C=O).

**4-bromo-8-methylisoquinolin-1(2*H*)-one (63)**



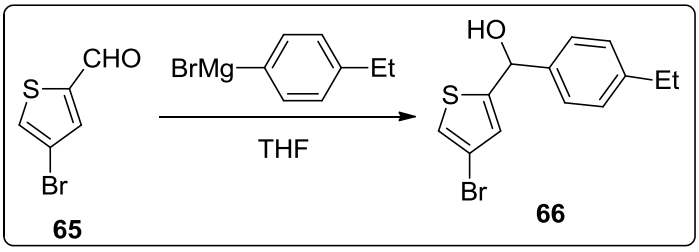

To a solution of **62**[38] (1.15 g, 7.22 mmol) in $CH_2Cl_2$ (20 mL) was added a solution of bromine (1.26 g, 7.88 mmol) in $CH_2Cl_2$ (4 mL), and the mixture was stirred at room temperature for 1 h. The precipitate was filtered and washed with $Et_2O$ to give titled compound **63** (1.86 g, quant) as colorless crystals. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 11.34 (s, 1H), 7.63 – 7.69 (m, 2H), 7.49 (d, $J$ = 5.6 Hz, 1H), 7.35 (d, $J$ = 7.1 Hz, 1H), 2.82 (s, 3H). MS (APCI, *m/z*) 238/240 (M + H).

**4-bromo-2-(4-ethylbenzyl)-8-methylisoquinolin-1(2*H*)-one (64)**




The title compound was prepared in the same manner as described for **59** using **63** instead of **58** in 75% yield as colorless crystals. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.67 – 7.73 (m, 1H), 7.55 (t, $J$ = 7.5 Hz, 1H), 7.34 (s, 1H), 7.31 (d, $J$ = 7.5 Hz, 1H), 7.24 (d, $J$ = 7.1 Hz, 2H), 7.18 (d, $J$ = 8.2 Hz, 2H), 5.11 (s, 2H), 2.96 (s, 3H), 2.63 (q, $J$ = 7.5 Hz, 2H), 1.22 (t, $J$ = 7.7 Hz, 3H). MS (APCI, *m/z*) not ionized.

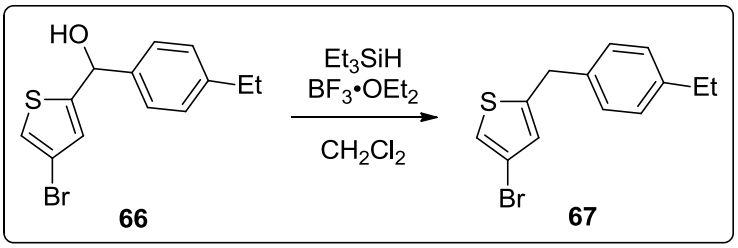
**(4-bromo-2-thienyl)(4-ethylphenyl)methanol (66)**




To a suspension of **65** (4.78 g, 25 mmol) in THF (40 mL) was added 4-ethylphenylmangesium bromide solution (0.5 N THF solution, 50 mL, 100 mmol) at 0

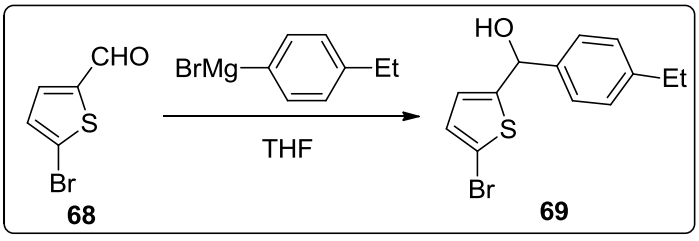
ºC over 10 min. After being stirred at 0 ºC for 30 min, the reaction mixture was quenched with saturated aqueous $NH_4Cl$ and extracted with AcOEt. The extract was washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 97 : 3 – 84 : 16) to give titled compound **66** (5.37 g, 72%) as colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, $J$ = 7.9 Hz, 2H), 7.21 (d, $J$ = 7.9 Hz, 2H), 7.15 (d, $J$ = 1.5 Hz, 1H), 6.76 (dd, $J$ = 1.1 Hz, 1.5 Hz, 1H), 5.95 (d, $J$ = 4.1 Hz, 1H), 2.66 (q, $J$ = 7.7 Hz, 2H), 2.37 (d, $J$ = 4.0 Hz, 1H), 1.24 (t, $J$ = 7.7 Hz, 3H). MS (APCI, *m/z*) 279/281 (M + H – $H_2O$).

**4-bromo-2-(4-ethylbenzyl)thiophene (67)**



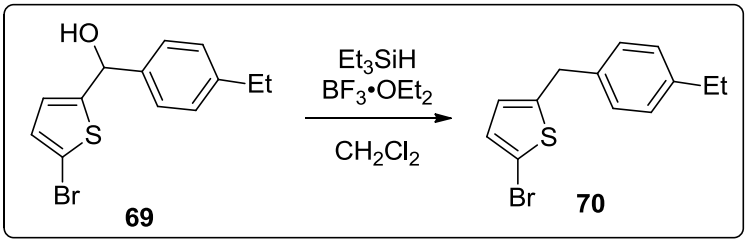

To a cold (–78 ºC) solution of **66** (297 mg, 1 mmol) in $CH_2Cl_2$ (3 mL) was added $Et_3SiH$ (319 μL, 2 mmol) and $BF_3 \cdot OEt_2$ (190 μL, 1.5 mmol), and the mixture was gradually warmed to room temperature over a period of 1 h. The reaction mixture was basified with saturated aqueous $NaHCO_3$ and extracted with $CH_2Cl_2$. The extract was washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 100 : 0 – 95 : 5) to give titled compound **67** (280 mg, 50%) as colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.13 – 7.14 (m, 4H), 7.02 (d, $J$ = 1.5 Hz, 1H), 6.68 – 6.71 (m, 1H), 4.06 (s, 2H), 2.63 (q, $J$ = 7.5 Hz, 2H), 1.23 (t, $J$ = 7.5 Hz, 3H). MS (APCI, *m/z*) not ionized.

**(5-bromo-2-thienyl)(4-ethylphenyl)methanol (69)**



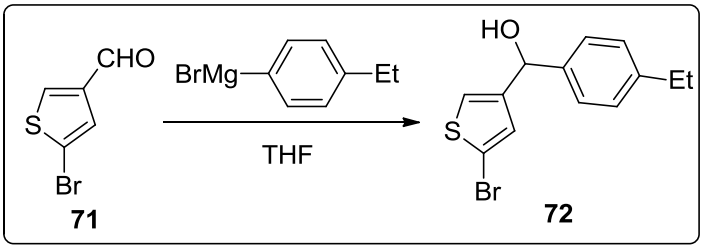
The title compound was prepared in the same manner as described for **66** using **68** instead of **65** in quantitative yield as slightly yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 1.4 Hz, 1H), 6.77 (dd, *J* = 1.1 Hz, 1.5 Hz, 1H), 5.95 (d, *J* = 3.8 Hz, 1H), 2.66 (q, *J* = 7.7 Hz, 2H), 2.39 (d, *J* = 4.1 Hz, 1H), 1.24 (t, *J* = 7.5 Hz, 3H). MS (APCI, *m/z*) 279/281 (M + H – $H_2O$).

**2-bromo-5-(4-ethylbenzyl)thiophene (70)**



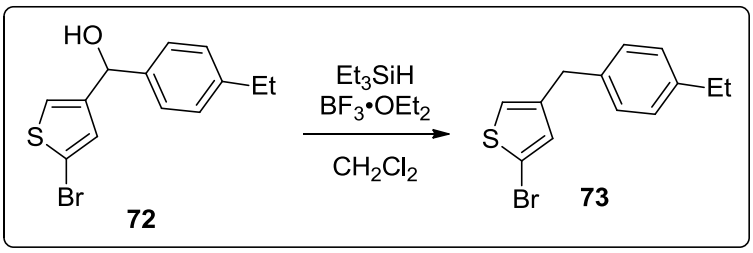

The title compound was prepared in the same manner as described for **67** using **69** instead of **66** in 70% yield as colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.14 (m, 4H), 7.02 (d, *J* = 1.5 Hz, 1H), 6.70 (d, *J* = 1.5 Hz, 1H), 4.06 (s, 2H), 2.63 (q, *J* = 7.5 Hz, 2H), 1.23 (t, *J* = 7.5 Hz, 3H). MS (GC-EI, *m/z*) 280/282 ($M^+$).

**(5-bromo-3-thienyl)(4-ethylphenyl)methanol (72)**



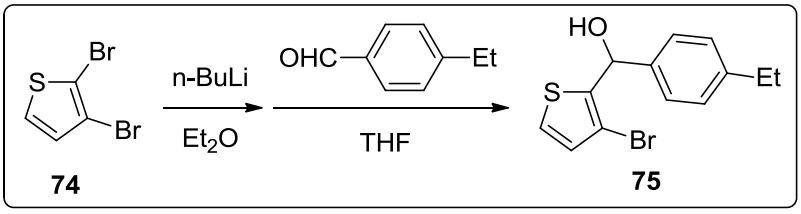

The title compound was prepared in the same manner as described for **66** using **71** instead of **65** in 75% yield as slightly yellow oil. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.29 (s, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.01 (s, 1H), 5.86 (d, *J* = 4.5 Hz, 1H), 5.63 (d, *J* = 4.3 Hz, 1H), 2.57 (q, *J* = 7.7 Hz, 2H), 1.16 (t, *J* = 7.5 Hz, 3H). MS (APCI, *m/z*) 279/281 (M + H – $H_2O$).

**2-bromo-4-(4-ethylbenzyl)thiophene (73)**



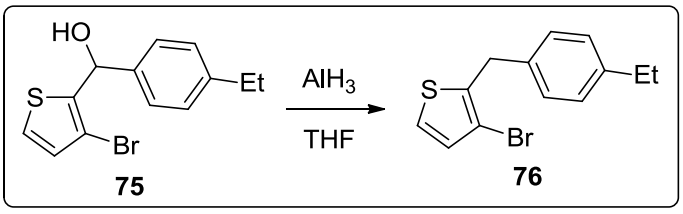

The title compound was prepared in the same manner as described for **67** using **72** instead of **66** in 63% yield as colorless oil. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.18 (br s, 1H), 7.13 (s, 4H), 7.02 (br s, 1H), 3.83 (s, 2H), 2.56 (q, $J$ = 7.6 Hz, 2H), 1.15 (t, $J$ = 7.6 Hz, 3H). MS (GC-EI, *m/z*) 280/282 ($M^+$).

**(3-bromo-2-thienyl)(4-ethylphenyl)methanol (75)**



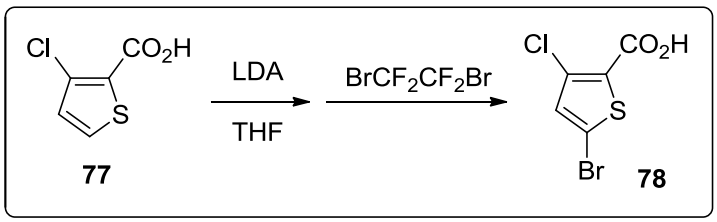

To a cold (–78 ºC) solution of *n*-BuLi (2.44 M in *n*-hexane, 18.5 mL, 45 mmol) in $Et_2O$ (30 mL) was added 2,3-dibromothiophene (**74**, 10.9 g, 45 mmol) in $Et_2O$ (10 mL). After being stirred at –78 ºC for 1 h, a solution of 4-ethylbenzaldehyde (6.03 g, 45 mmol) in $Et_2O$ (5 mL) was added dropwise over 1 h. After 10 min, the reaction mixture was quenched with saturated aqueous $NH_4Cl$ and extracted with $Et_2O$. The extract was washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 96 : 4 – 75 : 25) to give titled compound **75** (12.46 g, 93%) as colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, $J$ = 8.1 Hz, 2H), 7.23 (dd, $J$ = 0.5 Hz, 5.2 Hz, 1H), 7.19 (d, $J$ = 8.2 Hz, 2H), 6.92 (d, $J$ = 5.3 Hz, 1H), 6.13 (d, $J$ = 3.3 Hz, 1H), 2.64 (q, $J$ = 7.5 Hz, 2H), 2.45 (d, $J$ = 3.5 Hz, 1H), 1.23 (t, $J$ = 7.5 Hz, 3H). MS (APCI, *m/z*) 279/281 (M + H – $H_2O$).

**3-bromo-2-(4-ethylbenzyl)thiophene (76)**



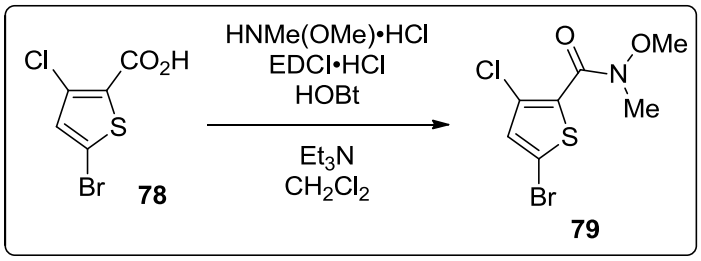
To an ice-cold (0 ºC) suspension of $LiAlH_4$ (2.6 g, 68.5 mmol) and $AlCl_3$ (9.0 g, 67.4 mmol) in $Et_2O$ (35 mL) was added **75** (12.4 g, 42 mmol) in $Et_2O$ (10 mL). After being stirred at room temperature for 18 hours, the reaction mixture was poured into ice water and extracted with $Et_2O$. The extract was washed with saturated aqueous $NaHCO_3$, brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane) to give titled compound **76** (8.77 g, 75%) as colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.11 – 7.19 (m, 5H), 6.92 (d, *J* = 5.3 Hz, 1H), 4.08 (s, 2H), 2.62 (q, *J* = 7.5 Hz, 2H), 1.22 (t, *J* = 7.5 Hz, 3H). MS (GC-EI, *m/z*) 280/282 ($M^+$).

**5-bromo-3-chlorothiophene-2-carboxylic acid (78)**

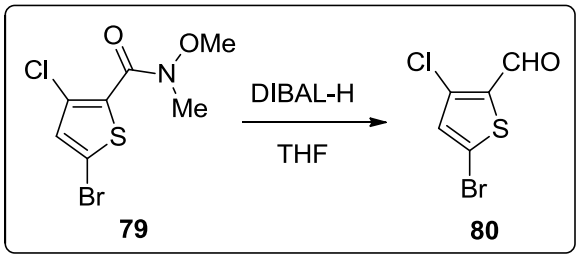



To a cold (–78 ºC) solution of *i*-$Pr_2NH$ (6.80 mL, 48.5 mmol) in THF (75 mL) was added *n*-BuLi (1.59 M in *n*-hexane, 30.5 mL, 48.5 mmol) dropwise over 10 min. After being stirred at –78 ºC for 30 min, a solution of 3-chlorothiophene-2-carboxylic acid (**77**, 3.92 g, 24 mmol) in THF (40 mL) was added dropwise over 5 min. After being stirred for 30 min, 1,2-dibromo-1,1,2,2-tetrafluoroethane (6.00 mL, 50.1 mmol) was added to a reaction mixture, and stirred for 30 min. The reaction mixture was poured into $H_2O$ (100 mL) and 10% aqueous HCl was added to adjust pH 2. After being extracted with AcOEt, the extract was washed with brine and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was triturated with *i*-$Pr_2O$ – *n*-hexane to give titled compound **78** (3.79 g, 65%) as colorless oil. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.62 (s, 1H), 7.48 (s, 1H). MS (ESI, *m/z*) 239/241/243 (M - H).

**5-bromo-3-chlorothiophene-2-carbaldehyde (80)**



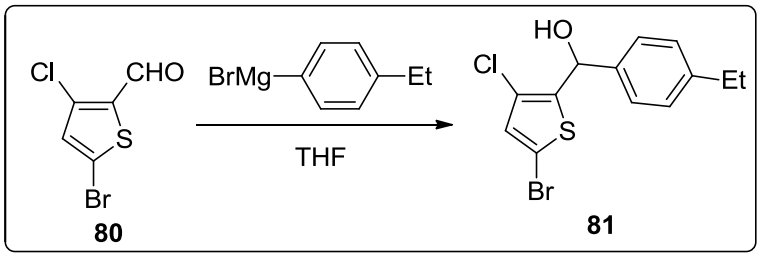
To a mixture of **78** (3.79 g, 15.7 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.84 g, 18.9 mmol) in $CH_2Cl_2$ (110 mL) was added HOBt (3.18 g, 23.5 mmol) and EDCI·HCl (4.51 g, 23.5 mmol) at 0 ºC, then $Et_3N$ (11.0 mL, 78.9 mmol) was added and the mixture was stirred at room temperature for 18 hours. After the mixture was poured into $H_2O$, extracted with $CHCl_3$, and organic layer was combined and washed with brine, dried over $Na_2SO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (5% – 15% AcOEt in hexane) to give Weinreb amide **79** (2.46 g, 55%) as a yellow oil.



**79** **80**

To a solution of above Weinreb amide **79** (2.73 g, 9.59 mmol) in THF (50 mL) was added DIBAL-H (1.0 M solution in toluene, 11.0 mL, 11.0 mmol) dropwise over 15 minutes at –78 ºC. After being stirred for 30 minutes, AcOEt (7.2 mL) was added and the mixture was gradually warmed to 0 ºC, then 10% aq. HCl (10 mL) was added and poured into $H_2O$ (50 mL). The resulting mixture was extracted with AcOEt, and combined organic layer was washed with saturated aq. $NaHCO_3$ and brine, dried over $Na_2SO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (0% – 3% AcOEt in hexane) to give titled compound **80** (2.03 g, 94%) as a pale yellow oil. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.86 (s, 1H), 7.66 (s, 1H). MS (ESI, *m/z*) 239/241/243 (M + H + MeOH – $H_2O$).

**(5-bromo-3-chloro-2-thienyl)(4-ethylphenyl)methanol (81)**

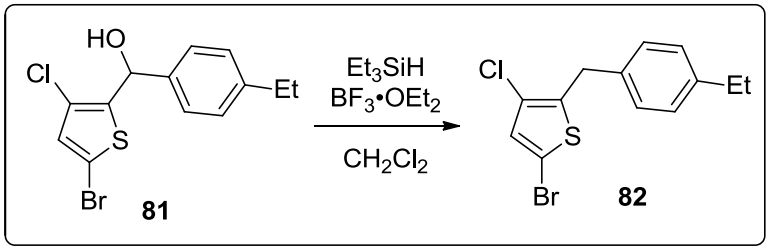


**80** **81**

The title compound was prepared in the same manner as described for **66** using **80** instead of **65** in quantitative yield as slightly yellow oil. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.28 (d, $J$ = 8.0 Hz, 2H), 7.18 (d, $J$ = 7.2 Hz, 2H), 7.17 (s, 1H), 6.50 (d, $J$ =

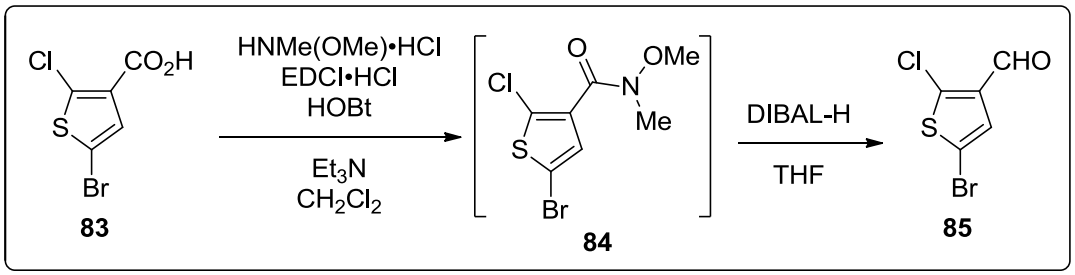
3.7 Hz, 1H), 5.87 (d, *J* = 3.6 Hz, 1H), 2.57 (q, *J* = 7.5 Hz, 2H), 1.15 (t, *J* = 7.6 Hz, 3H). MS (APCI, *m/z*) 313/315/317 (M + H – $H_2O$).

**5-bromo-3-chloro-2-(4-ethylbenzyl)thiophene (82)**



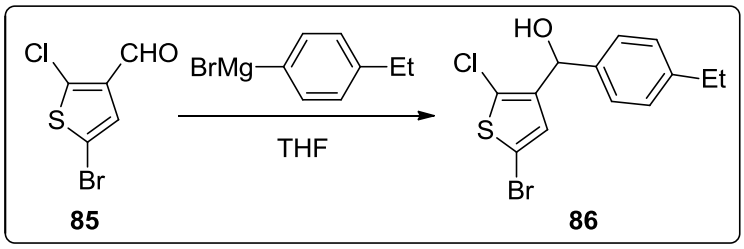

The title compound was prepared in the same manner as described for **67** using **81** instead of **66** in 83% yield as colorless oil. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.24 (s, 1H), 7.16 (m, 4H), 4.09 (s, 2H), 2.57 (q, *J* = 7.5 Hz, 2H), 1.16 (t, *J* = 7.5 Hz, 3H). MS (APCI, *m/z*) not ionized.

**5-bromo-2-chlorothiophene-3-carbaldehyde (85)**




The title compound was prepared in the same manner as described for **80** using **83** instead of **78** in 31% yield as colorless oil. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.84 (s, 1H), 7.53 (s, 1H). MS (ESI, *m/z*) 239/241/243 (M - H).

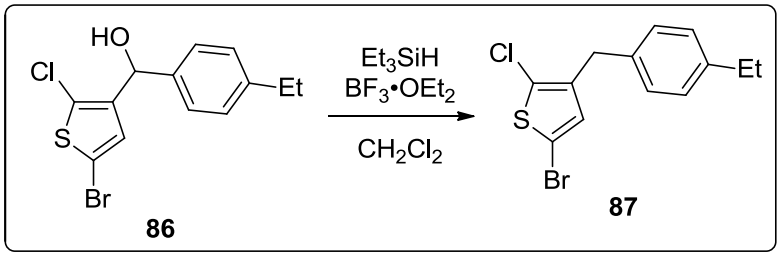
**(5-bromo-2-chloro-3-thienyl)(4-ethylphenyl)methanol (86)**




The title compound was prepared in the same manner as described for **66** using **85** instead of **65** in 70% yield as slightly yellow oil. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.27 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.14 (s, 1H), 6.08 (d, *J* = 4.5 Hz, 1H),

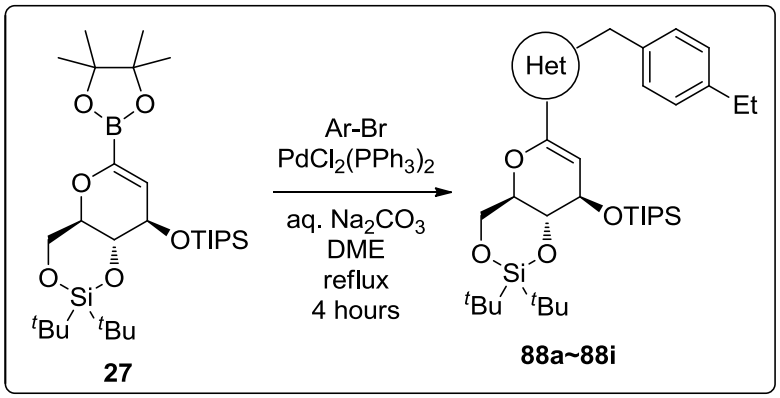
5.70 (d, *J* = 4.7 Hz, 1H), 2.56 (q, *J* = 7.7 Hz, 2H), 1.15 (t, *J* = 7.5 Hz, 3H). MS (APCI, *m/z*) 313/315/317 (M + H).

**5-bromo-2-chloro-3-(4-ethylbenzyl)thiophene (87)**

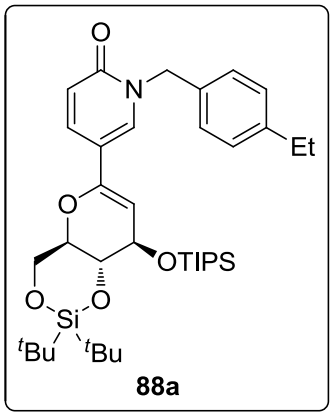



The title compound was prepared in the same manner as described for **67** using **86** instead of **66** in 89% yield as colorless oil. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.14 (m, 4H), 7.10 (s, 1H), 3.83 (s, 2H), 2.55 (q, *J* = 7.5 Hz, 2H), 1.15 (t, *J* = 7.7 Hz, 3H). MS (APCI, *m/z*) not ionized.

**Typical Experimental procedure for the synthesis of 1-arylglucal derivative (88a~88i)**



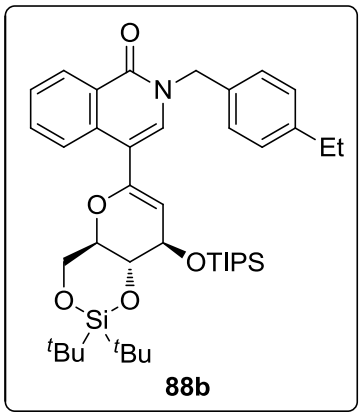

**(5-{(4a*R*,8*R*,8a*R*)-2,2-di-*tert*-butyl-8-[(triisopropylsilyl)oxy]-4,4a,8,8a-tetrahydro pyrano[3,2-d][1,3,2]dioxasilin-6-yl}-1-(4-ethylbenzyl)pyridin-2(1*H*)-one (88a))**



**88a**

To a mixture of boronic acid ester **27** (1.42 g, 2.5 mmol) and aryl bromide **59** (293 mg, 1.00 mmol) in DME (5 mL) was added dichlorobis(triphenylphosphine)palladium (35 mg, 0.05 mmol) and 2 M aq $Na_2CO_3$ (2.5 mL, 5.00 mmol), then the mixture was refluxed for 4 hours. The mixture was cooled to ambient temperature and diluted with AcOEt, then washed with water, brine, dried over sodium sulfate, and filtered. After the filtrate was concentrated, the crude material was purified by silica gel column chromatography (5% – 30% AcOEt in hexane) to give compound **88a** (276 mg, 42%) as colorless crystals. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 2.4 Hz, 1H), 7.40 (dd, *J* = 2.7 Hz, 9.5 Hz, 1H), 7.14 – 7.20 (m, 4H), 6.57 (d, *J* = 9.5 Hz, 1H), 5.16 (d, *J* = 14.5 Hz, 1H), 5.03 (d, *J* = 14.5 Hz, 1H), 4.93 (d, *J* = 2.4 Hz, 1H), 4.52 (dd, *J* = 2.4 Hz, 6.8 Hz, 1H), 4.20 (dd, *J* = 5.0 Hz, 10.2 Hz, 1H), 3.97 – 4.05 (m, 2H), 3.83 – 3.93 (m, 1H), 2.63 (q, *J* = 7.5 Hz, 2H), 1.22 (t, *J* = 7.7 Hz, 3H), 1.08 – 1.15 (m, 21H), 1.06 (s, 9H), 0.99 (s, 9H). MS (ESI, *m/z*) 654 (M + H).

**4-{(4a*R*,8*R*,8a*R*)-2,2-di-*tert*-butyl-8-[(triisopropylsilyl)oxy]-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasilin-6-yl}-2-(4-ethylbenzyl)isoquinolin-1(2*H*)-one (88b)**

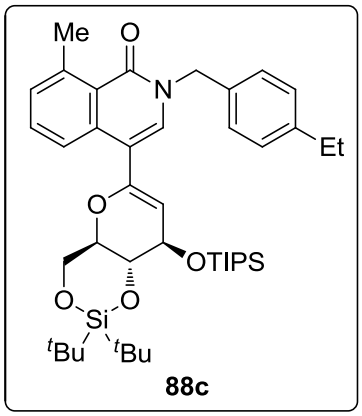


**88b**

The title compound was prepared in the same manner as described for **88a** using **61** instead of **59** in 25% yield as colorless amorphous solid. $^1$H NMR (300 MHz, $CDCl_3$)

δ 8.46 (dd, *J* = 0.8 Hz, 8.1 Hz, 1H), 7.60 – 7.73 (m, 2H), 7.46 – 7.52 (m, 1H), 7.23 – 7.29 (m, 3H), 7.15 (d, *J* = 8.3 Hz, 2H), 5.17 (d, *J* = 14.3 Hz, 1H), 5.12 (d, *J* = 14.5 Hz, 1H), 4.90 (d, *J* = 2.2 Hz, 1H), 4.54 (dd, *J* = 2.4 Hz, 6.8 Hz, 1H), 4.20 – 4.25 (m, 1H), 4.00 – 4.18 (m, 3H), 2.63 (q, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.5 Hz, 3H), 1.06 – 1.13 (m, 21H), 1.09 (s, 9H), 1.02 (s, 9H). MS (APCI, *m/z*) 704 (M + H).

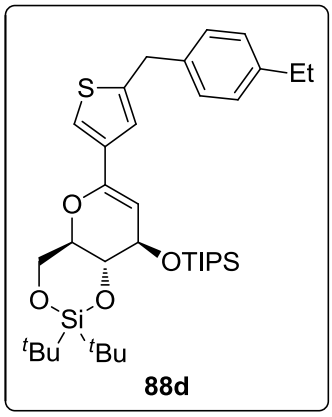
**4-{(4a*R*,8*R*,8a*R*)-2,2-di-*tert*-butyl-8-[(triisopropylsilyl)oxy]-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasilin-6-yl}-2-(4-ethylbenzyl)-8-methylisoquinolin-1(2*H*)-one (88c)**



**88c**

The title compound was prepared in the same manner as described for **88a** using **64** instead of **59** in 47% yield as colorless gum. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.50 (m, 2H), 7.35 (s, 1H), 7.13 – 7.17 (m, 5H), 5.17 (d, *J* = 14.7 Hz, 1H), 5.05 (d, *J* = 14.5 Hz, 1H), 4.87 (d, *J* = 2.2 Hz, 1H), 4.53 (dd, *J* = 2.2 Hz, 6.8 Hz, 1H), 4.18 – 4.23 (m, 1H), 4.07 – 4.17 (m, 1H), 4.00 – 4.05 (m, 2H), 2.93 (s, 3H), 2.63 (q, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.5 Hz, 3H), 1.07 – 1.12 (m, 21H), 1.08 (s, 9H), 1.02 (s, 9H). MS (APCI, *m/z*) 718 (M + H).

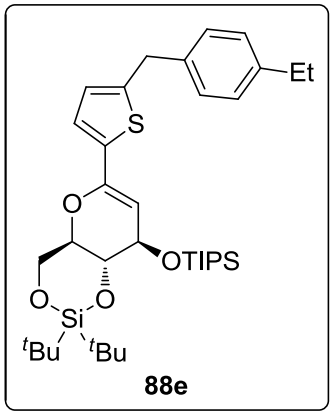
**(4a*R*,8*R*,8a*R*)-2,2-di-*tert*-butyl-6-[5-(4-ethylbenzyl)-3-thienyl]-8-[(triisopropylsilyl)oxy]-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasiline (88d)**




**88d**

The title compound was prepared in the same manner as described for **88a** using **67** instead of **59** in 16% yield as colorless syrup. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, *J* = 1.4 Hz, 1H), 7.12 – 7.14 (m, 4H), 6.82 (d, *J* = 1.4 Hz, 1H), 5.03 (d, *J* = 2.2 Hz, 1H), 4.52 (dd, *J* = 2.2 Hz, 6.8 Hz, 1H), 4.26 (dd, *J* = 5.1 Hz, 9.1 Hz, 1H), 3.90 – 4.10 (m, 5H), 2.63 (q, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.5 Hz, 3H), 1.08 – 1.14 (m, 21H), 1.08 (s, 9H), 1.00 (s, 9H). MS (APCI, *m/z*) 643 (M + H).

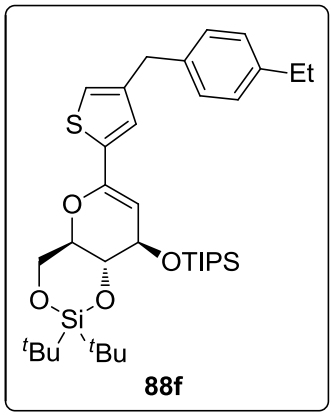
**(4a*R*,8*R*,8a*R*)-2,2-di-*tert*-butyl-6-[5-(4-ethylbenzyl)-2-thienyl]-8-[(triisopropylsilyl)oxy]-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasiline (88e)**




**88e**

The title compound was prepared in the same manner as described for **88a** using **70** instead of **59** in 40% yield as pale yellow semisolid. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.14 – 7.19 (m, 5H), 6.94 (s, 1H), 5.05 (d, *J* = 2.2 Hz, 1H), 4.52 – 4.55 (m, 1H), 4.20 – 4.24 (m, 1H), 3.80 – 4.14 (m, 6H), 2.57 (q, *J* = 7.6 Hz, 2H), 1.16 (t, *J* = 7.5 Hz, 3H), 1.05 – 1.11 (m, 21H), 1.04 (s, 9H), 0.97 (s, 9H). MS (APCI, *m/z*) 643 (M + H).

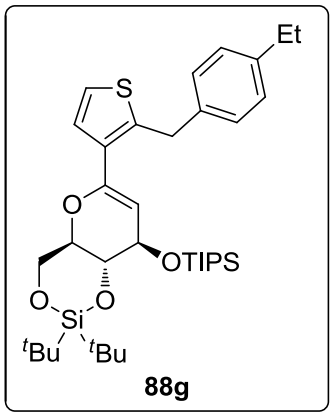
**(4a*R*,8*R*,8a*R*)-2,2-di-*tert*-butyl-6-[4-(4-ethylbenzyl)-2-thienyl]-8-[(triisopropylsilyl)oxy]-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasiline (88f)**



**88f**

The title compound was prepared in the same manner as described for **88a** using **73** instead of **59** in 40% yield as pale yellow oil. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 6.98 – 7.17 (m, 6H), 5.06 (d, $J$ = 2.2 Hz, 1H), 4.49 – 4.52 (m, 1H), 4.20 – 4.22 (m, 1H), 3.80 – 4.00 (m, 6H), 2.55 (q, $J$ = 7.6 Hz, 2H), 1.15 (t, $J$ = 7.6 Hz, 3H), 1.05 – 1.10 (m, 21H), 1.03 (s, 9H), 0.96 (s, 9H). MS (APCI, *m/z*) 643 (M + H).

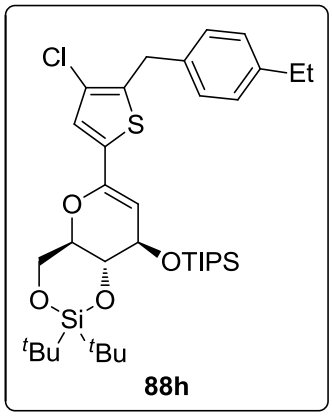
**(4a*R*,8*R*,8a*R*)-2,2-di-*tert*-butyl-6-[2-(4-ethylbenzyl)-3-thienyl]-8-[(triisopropylsilyl)oxy]-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasiline (88g)**



**88g**

The title compound was prepared in the same manner as described for **88a** using **76** instead of **59** in 53% yield as colorless amorphous solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.05 – 7.13 (m, 4H), 7.05 (d, $J$ = 5.3 Hz, 1H), 7.00 (d, $J$ = 5.3 Hz, 1H), 4.88 (d, $J$ = 2.2 Hz, 1H), 4.47 (dd, $J$ = 2.2 Hz, 6.9 Hz, 1H), 4.25 (ABq, $J$ = 16.3 Hz, 1H), 4.20 (ABq, $J$ = 16.3 Hz, 1H), 3.94 – 4.06 (m, 3H), 3.79 – 3.89 (m, 1H), 2.61 (q, $J$ = 7.7 Hz, 2H), 1.22 (t, $J$ = 7.5 Hz, 3H), 1.04 – 1.12 (m, 21H), 0.99 (s, 9H), 0.85 (s, 9H). MS (APCI, *m/z*) 643 (M + H).

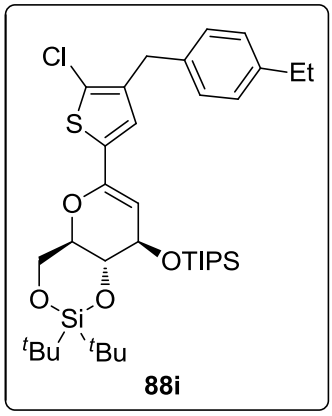
**(4a*R*,8*R*,8a*R*)-2,2-di-*tert*-butyl-6-[4-chloro-5-(4-ethylbenzyl)-2-thienyl]-8-[(triisopropylsilyl)oxy]-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasiline (88h)**



**88h**

The title compound was prepared in the same manner as described for **88a** using **82** instead of **59** in 68% yield as colorless viscous oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.13 (m, 4H), 6.93 (s, 1H), 5.05 (d, *J* = 2.5 Hz, 1H), 4.50 (dd, *J* = 2.4 Hz, 6.6 Hz, 1H), 4.23 (dd, *J* = 4.9 Hz, 10.2 Hz, 1H), 4.04 (s, 2H), 3.90 – 4.08 (m, 3H), 2.62 (q, *J* = 7.7 Hz, 2H), 1.22 (t, *J* = 7.7 Hz, 3H), 1.08 – 1.14 (m, 21H), 1.06 (s, 9H), 0.98 (s, 9H). MS (ESI, *m/z*) 677/679 (M + H).

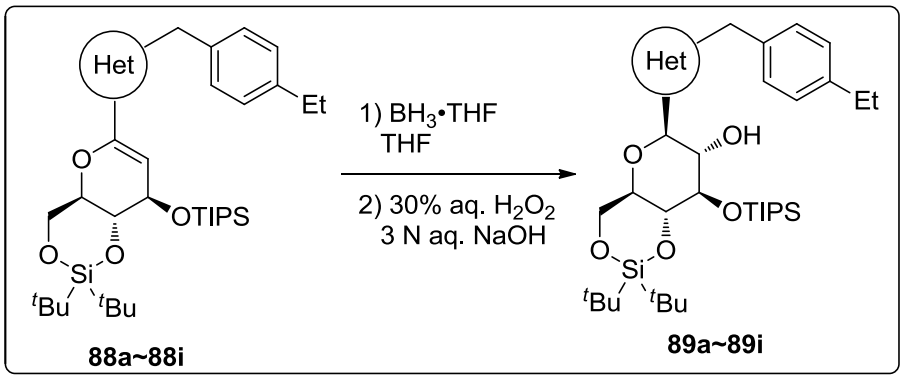
**(4a*R*,8*R*,8a*R*)-2,2-di-*tert*-butyl-6-[5-chloro-4-(4-ethylbenzyl)-2-thienyl]-8-[(triisopropylsilyl)oxy]-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasiline (88i)**



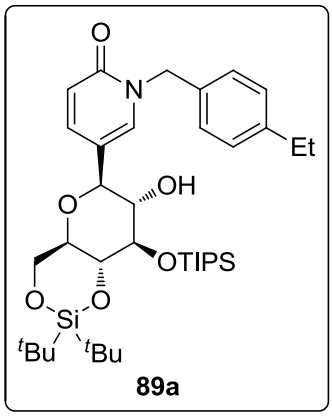
**88i**

The title compound was prepared in the same manner as described for **88a** using **87** instead of **59** in 59% yield as colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.3 Hz, 2H), 6.76 (s, 1H), 5.00 (d, *J* = 2.5 Hz, 1H), 4.49 (dd, *J* = 2.4 Hz, 6.6 Hz, 1H), 4.22 (dd, *J* = 4.8 Hz, 10.4 Hz, 1H), 3.98 – 4.06 (m, 2H), 3.92 (dd, *J* = 4.6 Hz, 9.9 Hz, 1H), 3.83 (s, 2H), 2.60 (q, *J* = 7.7 Hz, 2H), 1.22 (t, *J* = 7.7 Hz, 3H), 1.08 – 1.13 (m, 21H), 1.05 (s, 9H), 0.98 (s, 9H). MS (ESI, *m/z*) 677/679 (M + H).

**Typical Experimental procedure for the synthesis of β-D-glucopyranosyl derivative (89a~89i)**

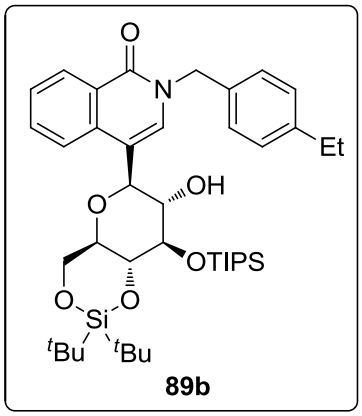



**(5-{(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-di-*tert*-butyl-7-hydroxy-8-[(triisopropylsilyl)oxy]hexahydropyrano[3,2-d][1,3,2]dioxasilin-6-yl}-1-(4-ethylbenzyl)pyridin-2(1*H*)-one (89a))**




To a solution of compound **88a** (260 mg, 0.398 mmol) in THF (5 mL) was added borane-tetrahydrofuran complex (1.0 M in THF, 1.06 mL, 1.06 mmol) dropwise at 0 °C. After being stirred at 0 °C for overnight, the mixture was added 30% aqueous hydrogen peroxide (5 mL) and 3 N aqueous sodium hydroxide (5 mL), and stirred at 0 °C for 4 hours. The reaction mixture was extracted with $Et_2O$, washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated and dried, then the crude material was purified by silica gel column chromatography (5% – 35% AcOEt in hexane) to give compound **89a** (59 mg, 22%) as colorless amorphous powder. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 2.5 Hz, 9.3 Hz, 1H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.54 (d, *J* = 9.7 Hz, 1H), 5.24 (d, *J* = 14.3 Hz, 1H), 4.88 (d, *J* = 14.4 Hz, 1H), 4.12 (dd, *J* = 4.9 Hz, 10.1 Hz, 1H), 3.96 (d, *J* = 9.5 Hz, 1H), 3.72 – 3.87 (m, 3H), 3.43 – 3.50 (m, 1H), 3.33 – 3.42 (m, 1H), 2.62 (q, *J* = 7.5 Hz, 2H), 2.43 (d, *J* = 2.9 Hz, 1H), 1.21 (t, *J* = 7.5 Hz, 3H), 1.09 – 1.14 (m, 21H), 1.06 (s, 9H), 0.99 (s, 9H). MS (APCI, *m/z*) 672 (M + H).

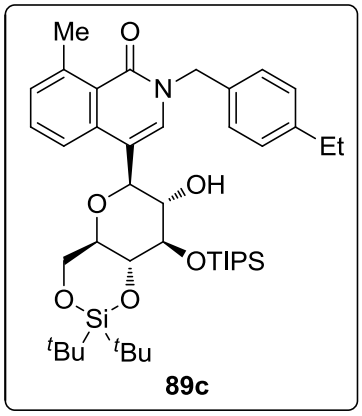
**4-{(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-di-*tert*-butyl-7-hydroxy-8-[(triisopropylsilyl)oxy]hexahydropyrano[3,2-d][1,3,2]dioxasilin-6-yl}-2-(4-ethylbenzyl)isoquinolin-1(2*H*)-one (89b)**



**89b**

The title compound was prepared in the same manner as described for **89a** using **88b** instead of **88a** in 61% yield as colorless foam. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 0.9 Hz, 8.0 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.64 – 7.70 (m, 1H), 7.46 – 7.53 (m, 1H), 7.19 – 7.27 (m, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 5.33 (d, *J* = 14.7 Hz, 1H), 4.95 (d, *J* = 14.5 Hz, 1H), 4.44 (d, *J* = 9.3 Hz, 1H), 4.16 (dd, *J* = 4.9 Hz, 10.2 Hz, 1H), 3.74 – 3.94 (m, 4H), 3.52 – 3.60 (m, 1H), 2.62 (q, *J* = 7.6 Hz, 2H), 2.18 (d, *J* = 2.5 Hz, 1H), 1.20 (t, *J* = 7.7 Hz, 3H), 1.09 – 1.15 (m, 21H), 1.08 (s, 9H), 1.02 (s, 9H). MS (APCI, *m/z*) 722 (M + H).

**4-{(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-di-*tert*-butyl-7-hydroxy-8-[(triisopropylsilyl)oxy]hexahydropyrano[3,2-d][1,3,2]dioxasilin-6-yl}-2-(4-ethylbenzyl)-8-methylisoquinolin-1(2*H*)-one (89c)**

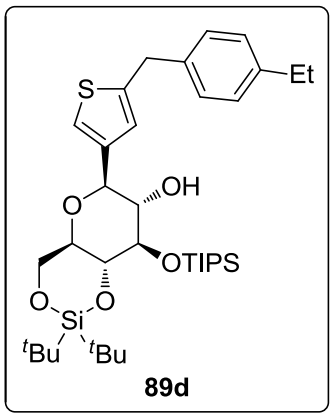


**89c**

The title compound was prepared in the same manner as described for **89a** using **88c** instead of **88a** in 37% yield as colorless amorphous powder. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 1H), 7.50 (t, *J* = 8.2 Hz, 1H), 7.12 – 7.26 (m, 6H), 5.30 (d,

*J* = 14.7 Hz, 1H), 4.93 (d, *J* = 14.8 Hz, 1H), 4.43 (d, *J* = 9.0 Hz, 1H), 4.16 (dd, *J* = 4.9 Hz, 10.2 Hz, 1H), 3.74 – 3.93 (m, 4H), 3.52 – 3.59 (m, 1H), 2.91 (s, 3H), 2.62 (q, *J* = 7.5 Hz, 2H), 2.14 (d, *J* = 2.5 Hz, 1H), 1.21 (t, *J* = 7.5 Hz, 3H), 1.10 – 1.14 (m, 21H), 1.08 (s, 9H), 1.02 (s, 9H). MS (APCI, *m/z*) 736 (M + H).

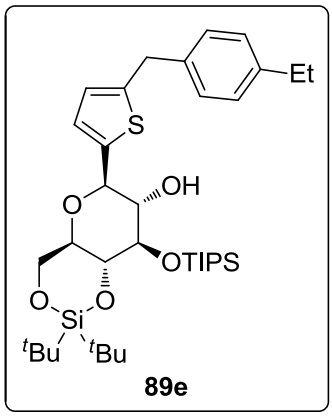
**(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-di-*tert*-butyl-6-[5-(4-ethylbenzyl)-3-thienyl]-8-[(triisopropyl silyl)oxy]hexahydropyrano[3,2-d][1,3,2]dioxasilin-7-ol (89d)**



**89d**

The title compound was prepared in the same manner as described for **89a** using **88d** instead of **88a** in 42% yield as colorless syrup. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.13 – 7.16 (m, 4H), 7.10 (d, *J* = 0.9 Hz, 1H), 6.82 (d, *J* = 1.3 Hz, 1H), 4.26 (d, *J* = 9.5 Hz, 1H), 4.17 (dd, *J* = 4.9 Hz, 10.1 Hz, 1H), 4.07 (s, 2H), 3.74 – 3.91 (m, 3H), 3.44 – 3.53 (m, 2H), 2.63 (q, *J* = 7.5 Hz, 2H), 2.03 (d, *J* = 2.8 Hz, 1H), 1.22 (t, *J* = 7.5 Hz, 3H), 1.09 – 1.14 (m, 21H), 1.06 (s, 9H), 1.00 (s, 9H). MS (APCI, *m/z*) 678 (M + $NH_4$).

**(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-di-*tert*-butyl-6-[5-(4-ethylbenzyl)-2-thienyl]-8-[(triisopropyl silyl)oxy]hexahydropyrano[3,2-d][1,3,2]dioxasilin-7-ol (89e)**

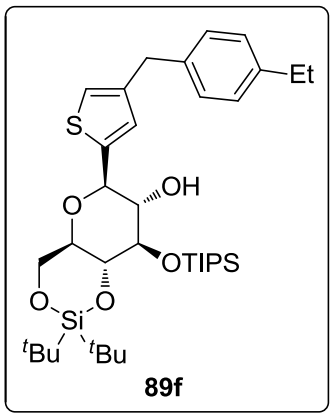


**89e**

The title compound was prepared in the same manner as described for **89a** using **88e** instead of **88a** in 66% yield as colorless oil. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.12 –

7.18 (m, 5H), 6.84 (s, 1H), 4.89 (d, *J* = 7.7 Hz, 1H), 4.21 (d, *J* = 9.7 Hz, 1H), 4.02 – 4.08 (m, 3H), 3.70 – 3.76 (m, 1H), 3.64 – 3.68 (m, 2H), 3.40 – 3.48 (m, 1H), 3.20 – 3.26 (m, 1H), 2.56 (q, *J* = 7.6 Hz, 2H), 1.15 (t, *J* = 7.7 Hz, 3H), 1.04 – 1.09 (m, 21H), 1.02 (s, 9H), 0.96 (s, 9H). MS (APCI, *m/z*) 678 (M + $NH_4$).

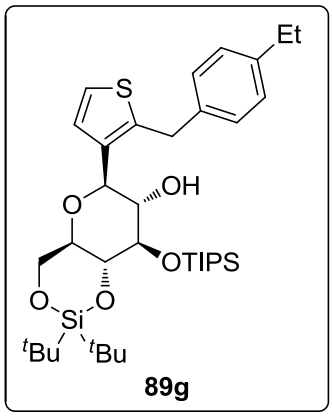
**(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-di-*tert*-butyl-6-[4-(4-ethylbenzyl)-2-thienyl]-8-[(triisopropyl silyl)oxy]hexahydropyrano[3,2-d][1,3,2]dioxasilin-7-ol (89f)**




**89f**

The title compound was prepared in the same manner as described for **89a** using **88f** instead of **88a** in 61% yield as colorless oil. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.03 – 7.17 (m, 5H), 6.86 (s, 1H), 5.04 (d, *J* = 6.9 Hz, 1H), 4.44 (d, *J* = 9.5 Hz, 1H), 4.00 – 4.05 (m, 1H), 3.80 – 3.85 (m, 3H), 3.62 – 3.75 (m, 2H), 3.47 – 3.54 (m, 1H), 3.16 – 3.22 (m, 1H), 2.55 (q, *J* = 7.6 Hz, 2H), 1.15 (t, *J* = 7.7 Hz, 3H), 1.05 – 1.08 (m, 21H), 1.01 (s, 9H), 0.96 (s, 9H). MS (APCI, *m/z*) 678 (M + $NH_4$).

**(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-di-*tert*-butyl-6-[2-(4-ethylbenzyl)-3-thienyl]-8-[(triisopropyl silyl)oxy]hexahydropyrano[3,2-d][1,3,2]dioxasilin-7-ol (89g)**

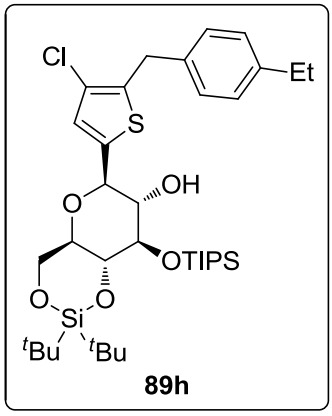



**89g**

The title compound was prepared in the same manner as described for **89a** using **88g** instead of **88a** in 60% yield as colorless gum. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.10 –

7.18 (m, 5H), 7.00 (d, $J$ = 5.3 Hz, 1H), 4.40 (d, $J$ = 9.7 Hz, 1H), 4.16 (ABq, $J$ = 16.1 Hz, 2H), 4.12 (dd, $J$ = 5.0 Hz, 10.3 Hz, 1H), 3.74 (m, 3H), 3.58 (ddd, $J$ = 2.9 Hz, 8.2 Hz, 10.6 Hz, 1H), 3.44 (ddd, $J$ = 4.9 Hz, 8.7 Hz, 10.0 Hz, 1H), 2.62 (q, $J$ = 7.5 Hz, 2H), 1.90 (d, $J$ = 2.9 Hz, 1H), 1.22 (t, $J$ = 7.5 Hz, 3H), 1.10 – 1.14 (m, 21H), 1.06 (s, 9H), 1.01 (s, 9H). MS (APCI, *m/z*) 678 (M + $NH_4$).

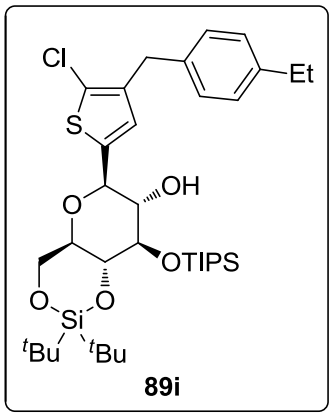
**(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-di-*tert*-butyl-6-[4-chloro-5-(4-ethylbenzyl)-2-thienyl]-8-[(triisopropylsilyl)oxy]hexahydropyrano[3,2-d][1,3,2]dioxasilin-7-ol (89h)**



**89h**

The title compound was prepared in the same manner as described for **89a** using **88h** instead of **88a** in 46% yield as colorless viscous oil. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.14 – 7.16 (m, 4H), 6.94 (s, 1H), 5.22 (d, $J$ = 7.6 Hz, 1H), 4.43 (d, $J$ = 9.6 Hz, 1H), 4.04 (dd, $J$ = 4.8 Hz, 10.1 Hz, 1H), 3.80 (Abq, $J$ = 16.0 Hz, 2H), 3.60 – 3.73 (m, 3H), 3.49 – 3.55 (m, 1H), 3.10 – 3.15 (m, 1H), 2.57 (q, $J$ = 7.6 Hz, 2H), 1.16 (t, $J$ = 7.7 Hz, 3H), 1.05 – 1.08 (m, 21H), 1.00 (s, 9H), 0.96 (s, 9H). MS (APCI, *m/z*) 712/714 (M + $NH_4$).

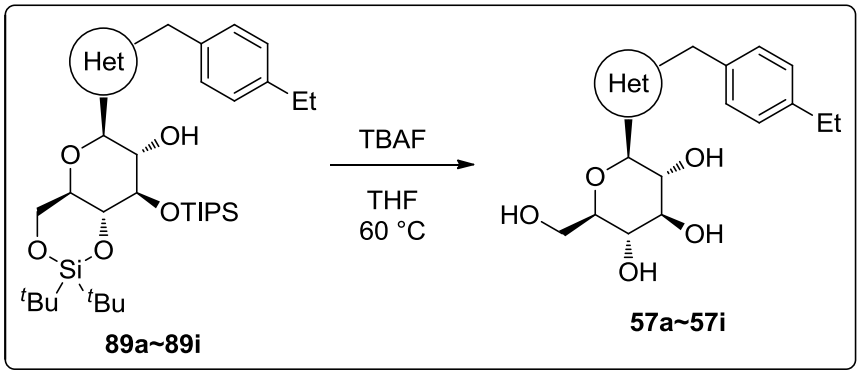
**(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-di-*tert*-butyl-6-[5-chloro-4-(4-ethylbenzyl)-2-thienyl]-8-[(triisopropylsilyl)oxy]hexahydropyrano[3,2-d][1,3,2]dioxasilin-7-ol (89i)**



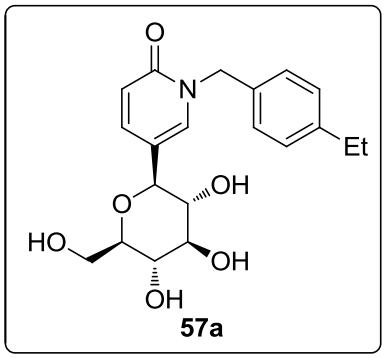
**89i**

The title compound was prepared in the same manner as described for **89a** using **88i** instead of **88a** in 37% yield as colorless viscous oil. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.09 – 7.15 (m, 4H), 6.81 (s, 1H), 5.20 (d, $J$ = 7.7 Hz, 1H), 4.41 (d, $J$ = 9.5 Hz, 1H), 4.04 (dd, $J$ = 4.9 Hz, 10.0 Hz, 1H), 3.80 (Abq, $J$ = 15.1 Hz, 2H), 3.68 – 3.74 (m, 1H), 3.60 – 3.68 (m, 1H), 3.49 – 3.54 (m, 1H), 3.36 – 3.42 (m, 1H), 3.09 – 3.16 (m, 1H), 2.55 (q, $J$ = 7.5 Hz, 2H), 1.15 (t, $J$ = 7.5 Hz, 3H), 1.04 – 1.10 (m, 21H), 1.00 (s, 9H), 0.95 (s, 9H). MS (APCI, *m/z*) 712/714 (M + $NH_4$).

**Typical Experimental procedure for the synthesis of 1-aryl-β-D-glucopyranose (57a~57i)**



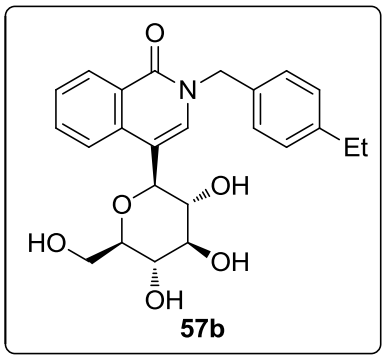

**(4-(β-D-glucopyranosyl)-2-(4-ethylbenzyl)isoquinolin-1(2*H*)-one (57a))**




To a solution of compound **89a** (55 mg, 0.0818 mmol) in THF (2 mL) was added tetra-*n*-butylammonium fluoride (TBAF) (1.0 M in THF, 0.41 mL, 0.41 mmol) dropwise, then the mixture was stirred at 60 °C for 3 hours. The mixture was concentrated and dried, then the crude material was purified by silica gel column chromatography (0% – 12% MeOH in $CHCl_3$) to give compound **57a** (10 mg, 33%) as a colorless powder. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7.73 (d, $J$ = 2.2 Hz, 1H), 7.42 (dd, $J$ = 2.6 Hz, 9.3 Hz, 1H), 7.23 (d, $J$ = 8.3 Hz, 2H), 7.15 (d, $J$ = 8.3 Hz, 2H), 6.39 (d, $J$ = 9.4 Hz, 1H), 5.10 (d, $J$ = 14.1 Hz, 1H), 5.00 (d, $J$ = 14.4 Hz, 1H), 4.90 – 4.97 (m, 3H), 4.43 (t, $J$ = 6.0 Hz, 1H), 3.82 (d, $J$ = 9.3 Hz, 1H), 3.62 – 3.70 (m, 1H), 3.36 – 3.44 (m,

1H), 3.08 – 3.24 (m, 4H), 2.56 (q, *J* = 7.8 Hz, 2H), 1.15 (t, *J* = 7.5 Hz, 3H). MS (APCI, *m/z*) 376 (M + H).

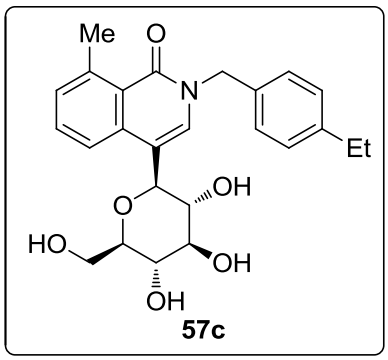
**4-(β-D-glucopyranosyl)-2-(4-ethylbenzyl)isoquinolin-1(2*H*)-one (57b)**



**57b**

The title compound was prepared in the same manner as described for **57a** using **89b** instead of **89a** in 81% yield as colorless powder. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.27 (dd, *J* = 1.0 Hz, 8.0 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.71 (dt, *J* = 1.5 Hz, 5.0 Hz, 1H), 7.57 (s, 1H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.16 (d, d, *J* = 8.2 Hz, 1H), 5.17 (d, *J* = 14.4 Hz, 1H), 5.12 (d, *J* = 14.4 Hz, 1H), 5.01 (d, *J* = 4.7 Hz, 1H), 4.98 (d, *J* = 5.0 Hz, 1H), 4.90 (d, *J* = 5.6 Hz, 1H), 4.42 (t, *J* = 5.8 Hz, 1H), 4.28 (d, *J* = 9.9 Hz, 1H), 3.69 (dd, *J* = 5.3 Hz, 10.1 Hz, 1H), 3.52 – 3.58 (m, 1H), 3.42 – 3.48 (m, 1H), 3.24 – 3.33 (m, 3H), 2.56 (q, *J* = 7.5 Hz, 2H), 1.14 (t, *J* = 7.6 Hz, 3H). MS (APCI, *m/z*) 426 (M + H).

**4-(β-D-glucopyranosyl)-2-(4-ethylbenzyl)-8-methylisoquinolin-1(2*H*)-one (57c)**

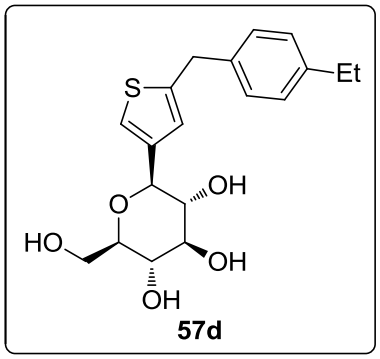


**57c**

The title compound was prepared in the same manner as described for **57a** using **89c** instead of **89a** in 72% yield as colorless powder. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.78 (d, *J* = 8.2 Hz, 1H), 7.54 (s, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 5.10 (s, 2H), 5.00 (d, *J* = 4.5 Hz, 1H), 4.96 (d, *J* = 5.0 Hz, 1H), 4.86 (d, *J* = 5.5 Hz, 1H), 4.40 (t, *J* = 5.8 Hz, 1H), 4.26 (d, *J* =

9.3 Hz, 1H), 3.68 (dd, *J* = 5.4 Hz, 10.4 Hz, 1H), 3.52 – 3.58 (m, 1H), 3.42 – 3.47 (m, 1H), 3.20 – 3.30 (m, 4H),2.82 (s, 3H), 2.56 (q, *J* = 7.5 Hz, 2H), 1.14 (t, *J* = 7.5 Hz, 3H). MS (APCI, *m/z*) 440 (M + H).

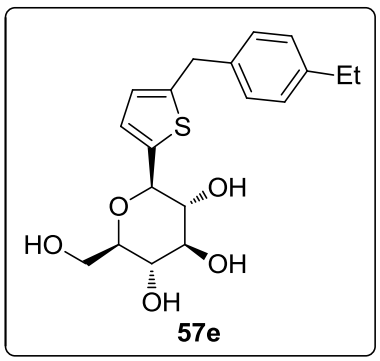
**(1*S*)-1,5-anhydro-1-[5-(4-ethylbenzyl)-3-thienyl]-D-glucitol (57d)**



**57d**

The title compound was prepared in the same manner as described for **57a** using **89d** instead of **89a** in 57% yield as colorless powder. $^1$H NMR (500 MHz, DMSO-$d_6$ + $D_2O$) δ 7.18 (d, *J* = 8.1 Hz, 2H), 7.17 (s, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.86 (s, 1H), 4.05 (s, 2H), 4.02 (d, *J* = 9.3 Hz, 1H), 3.66 (d, *J* = 11.7 Hz, 1H), 3.41 (dd, *J* = 5.9 Hz, 11.5 Hz, 1H), 3.08 – 3.24 (m, 4H), 2.57 (q, *J* = 7.7 Hz, 2H), 1.16 (t, *J* = 7.5 Hz, 3H). MS (APCI, *m/z*) 382 (M + $NH_4$).

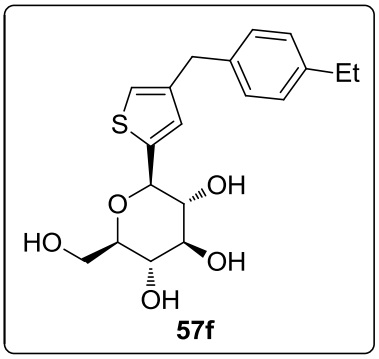
**(1*S*)-1,5-anhydro-1-[5-(4-ethylbenzyl)-2-thienyl]-D-glucitol (57e)**



**57e**

The title compound was prepared in the same manner as described for **57a** using **89e** instead of **89a** in 46% yield as colorless powder. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.17 (d, *J* = 8.2 Hz, 2H), 7.16 (s, 1H), 7.14 (d, *J* = 8.2 Hz, 1H), 6.85 (s, 1H), 4.86 (d, *J* = 4.7 Hz, 1H), 4.85 (d, *J* = 5.3 Hz, 1H), 4.81 (d, *J* = 5.6 Hz, 1H), 4.44 (t, *J* = 6.0 Hz, 1H), 4.04 (s, 2H), 4.00 (d, *J* = 9.2 Hz, 1H), 3.64 – 3.70 (m, 1H), 3.41 (dd, *J* = 6.1 Hz, 10.7 Hz, 1H), 3.10 – 3.24 (m, 4H), 2.56 (q, *J* = 7.8 Hz, 2H), 1.16 (t, *J* = 7.6 Hz, 3H). MS (APCI, *m/z*) 382 (M + $NH_4$).

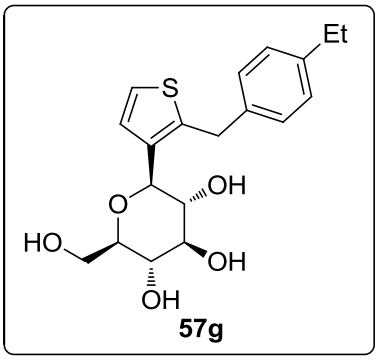
**(1*S*)-1,5-anhydro-1-[4-(4-ethylbenzyl)-2-thienyl]-D-glucitol (57f)**



**57f**

The title compound was prepared in the same manner as described for **57a** using **89f** instead of **89a** in 33% yield as colorless powder. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.14 (d, $J$ = 8.2 Hz, 2H), 7.11 (d, $J$ = 8.2 Hz, 2H), 7.04 (s, 1H), 6.87 (s, 1H), 4.98 (d, $J$ = 5.8 Hz, 1H), 4.94 (d, $J$ = 5.0 Hz, 1H), 4.91 (d, $J$ = 5.3 Hz, 1H), 4.44 (t, $J$ = 5.7 Hz, 1H), 4.20 (d, $J$ = 9.5 Hz, 1H), 3.82 (s, 2H), 3.67 (dd, $J$ = 5.6 Hz, 9.9 Hz, 1H), 3.36 – 3.42 (m, 1H), 3.17 – 3.24 (m, 2H), 3.06 – 3.16 (m, 2H), 2.55 (q, $J$ = 7.5 Hz, 2H), 1.15 (t, $J$ = 7.5 Hz, 3H). MS (APCI, *m/z*) 382 (M + $NH_4$).

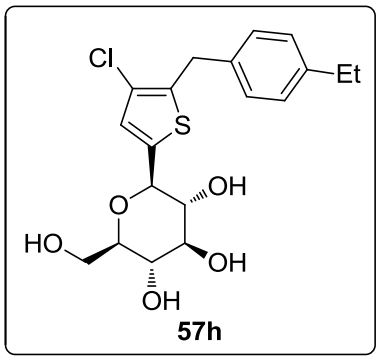
**(1*S*)-1,5-anhydro-1-[2-(4-ethylbenzyl)-3-thienyl]-D-glucitol (57g)**



**57g**

The title compound was prepared in the same manner as described for **57a** using **89g** instead of **89a** in 81% yield as colorless powder. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.20 (d, $J$ = 8.5 Hz, 2H), 7.19 (d, $J$ = 5.1 Hz, 1H), 7.11 (d, $J$ = 8.0 Hz, 2H), 6.98 (d, $J$ = 5.3 Hz, 1H), 4.96 (d, $J$ = 4.5 Hz, 1H), 4.90 (d, $J$ = 5.1 Hz, 1H), 4.85 (d, $J$ = 5.6 Hz, 1H), 4.42 (t, $J$ = 5.8 Hz, 1H), 4.25 (d, $J$ = 9.3 Hz, 1H), 4.10 (ABq, $J$ = 15.9 Hz, 2H), 3.67 (dd, $J$ = 5.6 Hz, 9.9 Hz, 1H), 3.40 – 3.48 (m, 1H), 3.24 – 3.37 (m, 2H), 3.20 – 3.24 (m, 1H), 3.14 – 3.20 (m, 1H), 2.56 (q, $J$ = 7.5 Hz, 2H), 1.16 (t, $J$ = 7.5 Hz, 3H). MS (APCI, *m/z*) 382 (M + $NH_4$).

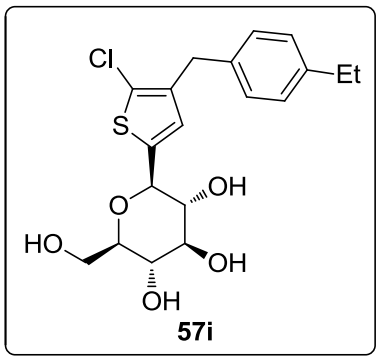
**(1*S*)-1,5-anhydro-1-[4-chloro-5-(4-ethylbenzyl)-2-thienyl]-D-glucitol (57h)**



**57h**

The title compound was prepared in the same manner as described for **57a** using **89h** instead of **89a** in 87% yield as colorless amorphous powder. $^1$H NMR (500 MHz, DMSO-$d_6$ + $D_2O$) δ 7.16 (s, 4H), 6.96 (s, 1H), 4.22 (d, *J* = 9.7 Hz, 1H), 4.02 (s, 2H), 3.66 (d, *J* = 11.7 Hz, 1H), 3.40 (dd, *J* = 5.6 Hz, 11.2 Hz, 1H), 3.20 – 3.26 (m, 2H), 3.02 – 3.12 (m, 2H), 2.57 (q, *J* = 7.4 Hz, 2H), 1.16 (t, *J* = 7.6 Hz, 3H). MS (APCI, *m/z*) 416/418 (M + $NH_4$).

**(1*S*)-1,5-anhydro-1-[5-chloro-4-(4-ethylbenzyl)-2-thienyl]-D-glucitol (57i)**



**57i**

The title compound was prepared in the same manner as described for **57a** using **89i** instead of **89a** in 92% yield as colorless powder. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.13 (s, 4H), 6.84 (s, 1H), 5.18 (d, *J* = 5.9 Hz, 1H), 4.99 (d, *J* = 5.0 Hz, 1H), 4.94 (d, *J* = 5.5 Hz, 1H), 4.46 (t, *J* = 5.8 Hz, 1H), 4.17 (d, *J* = 9.5 Hz, 1H), 3.80 (s, 2H), 3.66 (dd, *J* = 5.7 Hz, 10.2 Hz, 1H), 3.36 – 3.43 (m, 1H), 3.17 – 3.26 (m, 2H), 3.02 – 3.11 (m, 2H), 2.55 (q, *J* = 7.5 Hz, 2H), 1.14 (t, *J* = 7.7 Hz, 3H). MS (APCI, *m/z*) 416/418 (M + $NH_4$).

**Pharmacology**

**Sodium-Dependent Glucose Uptake in CHO cells Expressing hSGLT2 (in vitro test)**

Parental CHOK cells expressing hSGLT2[39] were used in these experiments. For the uptake assay, cells were seeded into 24-well plates, and were post-confluent on the day of assay.

Cells were rinsed one time with 400 μL Assay Buffer (137 mM NaCl, 5 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 50 mM HEPES, 20 mM Tris Base, pH 7.4), and were pre-incubated with the solutions of compounds (250 μL) for 10 min at 37 °C. The transport reaction was initiated by addition of 50 μL AMG / $^{14}$C-AMG solution (16.7 μCi; final concentration, 0.5 mM) and incubated for 120 min at 37 °C. After the incubation, the AMG uptake was halted by aspiration of the incubation mixture followed by immediate washing three times with PBS. The cells were solubilized in 0.3 N NaOH of 300 μL and the radioactivity associated with the cells was monitored by a liquid scintillation counter (Quantasmart™ (Packard, Boston, MA, USA)). Inhibitory concentration of 50% ($IC_{50}$) was calculated by nonlinear least squares analysis using a four-parameter logistic model (Prism version 4; GraphPad Software, San Diego, CA, USA).

**UGE Study (in vivo test)**

Male SD rats aged 4-5 weeks were obtained from Japan SLC (Shizuoka, Japan) and were used for experiments at 6 weeks of age after acclimation period. The animals were divided into experimental groups matched for body weight (n = 3). The compounds were prepared in vehicles as suspension or solution. UGE studies were performed after two-day acclimation period in metabolic cages. The compounds or vehicle were orally administered at a dose of 30 mg/kg in 0.2% CMC/0.2% Tween 80. Urine samples were collected for 24 hours using metabolic cages to measure urinary glucose excretion. Urine glucose contents were determined by an enzymatic assay kit (UGLU-L, Serotec, Hokkaido, Japan). All animals were allowed free access to a standard pellet diet (CRF1; Oriental Yeast Co., Ltd., Tokyo, Japan) and tap water. All animal experimental procedures were approved by Institutional Animal Care and Use Committee of Mitsubishi Tanabe Pharma Corporation.

X-Ray data of **27** (CCDC-860013)

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_diffrn_measurement_method ¥w
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_diffrn_reflns_number 16345
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_diffrn_reflns_theta_max 68.23
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_diffrn_reflns_limit_h_min              -13
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_diffrn_reflns_limit_k_max               15
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_diffrn_reflns_limit_l_max               16

#=============================================================
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# REFINEMENT DATA

_refine_special_details
;
      Refinement was performed using all reflections. The weighted
      R-factor (wR) and goodness of fit (S) are based on F^2^.
      R-factor (gt) are based on F. The threshold expression of
      F^2^ > 2.0 sigma(F^2^) is used only for calculating R-factor (gt).
;
_reflns_number_total                     9280
_reflns_number_gt                        8985
_reflns_threshold_expression             F^2^>2.0¥s(F^2^)
_refine_ls_structure_factor_coef         Fsqd
_refine_ls_R_factor_gt                   0.0631
_refine_ls_wR_factor_ref                 0.1854
_refine_ls_hydrogen_treatment            refall
_refine_ls_number_reflns                 9280
_refine_ls_number_parameters             688
_refine_ls_goodness_of_fit_ref           1.331
_refine_ls_weighting_scheme              calc
_refine_ls_weighting_details
    'w = 1/[¥s^2^(Fo^2^)+(0.1000P)^2^+0.0000P] where P=(Fo^2^+2Fc^2^)/3'
_refine_ls_shift/su_max                  0.0040
_refine_diff_density_max                 0.50
_refine_diff_density_min                 -0.33
_refine_ls_extinction_method             SHELXL
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_refine_ls_extinction_coef                0.0020(3)
_refine_ls_abs_structure_details
     'Flack, H. D. (1983), Acta Cryst. A39, 876-881.    3744 Friedel Pairs'
_refine_ls_abs_structure_Flack            0.04(2)

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(1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
;
   'H' 'H'    0.000 0.000
;
International Tables for Crystallography
(1992, Vol. C, Table 6.1.1.4)
;
   'B' 'B'    0.009 0.004
;
International Tables for Crystallography
(1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
;
   'O' 'O'    0.049 0.032
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International Tables for Crystallography
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;
   'Si' 'Si'    0.254 0.330
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International Tables for Crystallography
(1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
;
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# ATOMIC COORDINATES AND THERMAL PARAMETERS

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O(2) O 0.5487(2) 0.7356(2) 0.80748(19) 0.0373(6) Uani 1.00 1 d . . .
C(3) C 0.4739(3) 0.6862(3) 0.9329(2) 0.0312(8) Uani 1.00 1 d . . .
C(4) C 0.3549(3) 0.6250(3) 0.9623(2) 0.0327(8) Uani 1.00 1 d . . .
C(5) C 0.2926(3) 0.5550(3) 1.0953(3) 0.0357(8) Uani 1.00 1 d . . .
C(6) C 0.3493(3) 0.5286(3) 1.1668(3) 0.0337(8) Uani 1.00 1 d . . .
O(7) O 0.4739(2) 0.5589(2) 1.1273(2) 0.0390(6) Uani 1.00 1 d . . .
C(8) C 0.5430(3) 0.5992(3) 1.0022(2) 0.0324(7) Uani 1.00 1 d . . .
C(9) C 0.6667(4) 0.6490(4) 0.9765(3) 0.0453(10) Uani 1.00 1 d . . .
O(10) O 0.7482(2) 0.6933(2) 0.8527(2) 0.0439(7) Uani 1.00 1 d . . .
C(11) C 0.7360(4) 0.9304(3) 0.6938(3) 0.0534(12) Uani 1.00 1 d . . .
C(12) C 0.6706(7) 0.9547(4) 0.8022(5) 0.109(3) Uani 1.00 1 d . . .
C(13) C 0.8740(7) 0.9602(6) 0.6505(7) 0.113(2) Uani 1.00 1 d . . .
C(14) C 0.7026(8) 1.0091(5) 0.5929(6) 0.103(2) Uani 1.00 1 d . . .
C(15) C 0.7660(4) 0.7106(3) 0.6350(3) 0.0497(11) Uani 1.00 1 d . . .
C(16) C 0.9083(5) 0.7255(6) 0.5837(5) 0.085(2) Uani 1.00 1 d . . .

C(17) C 0.7285(7) 0.7765(7) 0.5315(4) 0.099(2) Uani 1.00 1 d . . .
C(18) C 0.7230(6) 0.5816(4) 0.6961(4) 0.0813(19) Uani 1.00 1 d . . .
O(19) O 0.2753(2) 0.7072(2) 0.9217(2) 0.0404(6) Uani 1.00 1 d . . .
Si(20) Si 0.23178(12) 0.73835(11) 0.81310(10) 0.0474(3) Uani 1.00 1 d . . .
C(21) C 0.2350(14) 0.6005(11) 0.7907(11) 0.184(6) Uani 1.00 1 d . . .
C(22) C 0.3613(14) 0.5887(16) 0.7118(16) 0.276(11) Uani 1.00 1 d . . .
C(23) C 0.1222(15) 0.6046(13) 0.7495(9) 0.250(10) Uani 1.00 1 d . . .
C(24) C 0.3305(7) 0.8706(8) 0.6782(6) 0.130(4) Uani 1.00 1 d . . .
C(25) C 0.3559(11) 0.9653(6) 0.7109(10) 0.174(6) Uani 1.00 1 d . . .
C(26) C 0.2824(11) 0.9225(12) 0.5808(8) 0.222(8) Uani 1.00 1 d . . .
C(27) C 0.0659(8) 0.7645(15) 0.8699(7) 0.184(7) Uani 1.00 1 d . . .
C(28) C -0.0027(9) 0.6353(16) 0.9846(6) 0.257(11) Uani 1.00 1 d . . .
C(29) C 0.0358(16) 0.8593(19) 0.9011(14) 0.274(13) Uani 1.00 1 d . . .
B(30) B 0.2839(4) 0.4649(3) 1.3077(3) 0.0344(9) Uani 1.00 1 d . . .
O(31) O 0.3432(2) 0.4571(2) 1.3762(2) 0.0428(6) Uani 1.00 1 d . . .
C(32) C 0.2641(3) 0.3765(3) 1.4983(3) 0.0431(10) Uani 1.00 1 d . . .
C(33) C 0.1349(4) 0.3799(3) 1.4946(3) 0.0396(9) Uani 1.00 1 d . . .
O(34) O 0.1659(2) 0.4140(2) 1.3688(2) 0.0416(6) Uani 1.00 1 d . . .
C(35) C 0.3143(5) 0.2595(4) 1.5254(4) 0.0722(16) Uani 1.00 1 d . . .
C(36) C 0.2750(5) 0.4207(6) 1.5789(4) 0.0669(15) Uani 1.00 1 d . . .
C(37) C 0.0556(4) 0.2641(4) 1.5676(3) 0.0535(12) Uani 1.00 1 d . . .
C(38) C 0.0628(4) 0.4738(4) 1.5194(3) 0.0503(11) Uani 1.00 1 d . . .
Si(39) Si 0.23927(9) 0.06105(8) 1.12588(8) 0.0350(2) Uani 1.00 1 d . . .
O(40) O 0.3868(2) 0.1103(2) 1.0684(2) 0.0353(6) Uani 1.00 1 d . . .
C(41) C 0.4518(3) 0.1968(2) 0.9482(2) 0.0314(8) Uani 1.00 1 d . . .
C(42) C 0.5888(3) 0.1865(2) 0.9109(2) 0.0285(7) Uani 1.00 1 d . . .
C(43) C 0.6520(3) 0.2589(3) 0.7773(2) 0.0323(7) Uani 1.00 1 d . . .
C(44) C 0.5938(3) 0.2959(3) 0.7047(3) 0.0325(8) Uani 1.00 1 d . . .
O(45) O 0.4683(2) 0.2679(2) 0.7454(2) 0.0440(7) Uani 1.00 1 d . . .
C(46) C 0.4072(3) 0.1786(3) 0.8676(2) 0.0368(8) Uani 1.00 1 d . . .
C(47) C 0.2713(3) 0.1874(4) 0.8962(3) 0.0427(9) Uani 1.00 1 d . . .
O(48) O 0.1999(2) 0.1015(2) 1.0129(2) 0.0448(7) Uani 1.00 1 d . . .
C(49) C 0.2285(4) -0.1049(3) 1.1985(3) 0.0454(10) Uani 1.00 1 d . . .
C(50) C 0.0944(5) -0.1560(4) 1.2327(4) 0.0673(14) Uani 1.00 1 d . . .
C(51) C 0.2597(6) -0.1564(4) 1.3092(4) 0.0725(15) Uani 1.00 1 d . . .
C(52) C 0.3208(5) -0.1402(4) 1.1088(4) 0.0623(13) Uani 1.00 1 d . . .

C(53) C 0.1453(4) 0.1344(4) 1.2203(3) 0.0509(11) Uani 1.00 1 d . . .
C(54) C 0.1841(6) 0.1109(7) 1.3201(5) 0.096(2) Uani 1.00 1 d . . .
C(55) C 0.0051(4) 0.0987(5) 1.2724(4) 0.0646(13) Uani 1.00 1 d . . .
C(56) C 0.1706(6) 0.2669(4) 1.1361(5) 0.094(2) Uani 1.00 1 d . . .
O(57) O 0.6381(2) 0.2289(2) 0.9668(2) 0.0360(6) Uani 1.00 1 d . . .
Si(58) Si 0.69773(10) 0.15693(9) 1.06661(8) 0.0366(2) Uani 1.00 1 d . . .
C(59) C 0.5819(4) 0.1463(4) 1.2103(3) 0.0543(11) Uani 1.00 1 d . . .
C(60) C 0.5206(5) 0.2608(5) 1.1976(4) 0.0673(14) Uani 1.00 1 d . . .
C(61) C 0.6334(6) 0.1070(6) 1.3062(4) 0.091(2) Uani 1.00 1 d . . .
C(62) C 0.7342(5) 0.0061(4) 1.0786(4) 0.0615(13) Uani 1.00 1 d . . .
C(63) C 0.6229(6) -0.0817(4) 1.1453(5) 0.0841(18) Uani 1.00 1 d . . .
C(64) C 0.8348(6) -0.0428(5) 1.1271(6) 0.0854(19) Uani 1.00 1 d . . .
C(65) C 0.8443(5) 0.2465(4) 1.0100(4) 0.0591(12) Uani 1.00 1 d . . .
C(66) C 0.8282(7) 0.3684(5) 1.0043(6) 0.095(2) Uani 1.00 1 d . . .
C(67) C 0.9357(6) 0.2595(7) 0.8867(5) 0.089(2) Uani 1.00 1 d . . .
B(68) B 0.6577(4) 0.3708(3) 0.5683(3) 0.0321(9) Uani 1.00 1 d . . .
O(69) O 0.5961(2) 0.3915(2) 0.4969(2) 0.0434(7) Uani 1.00 1 d . . .
C(70) C 0.6758(3) 0.4784(3) 0.3771(3) 0.0437(10) Uani 1.00 1 d . . .
C(71) C 0.8066(3) 0.4663(3) 0.3820(3) 0.0368(8) Uani 1.00 1 d . . .
O(72) O 0.7750(2) 0.4204(2) 0.5092(2) 0.0359(6) Uani 1.00 1 d . . .
C(73) C 0.6655(5) 0.4456(7) 0.2904(4) 0.081(2) Uani 1.00 1 d . . .
C(74) C 0.6269(5) 0.5944(4) 0.3670(5) 0.0786(18) Uani 1.00 1 d . . .
C(75) C 0.8725(4) 0.3755(4) 0.3480(4) 0.0534(11) Uani 1.00 1 d . . .
C(76) C 0.8907(5) 0.5807(4) 0.3151(3) 0.0596(13) Uani 1.00 1 d . . .
H(1) H 0.4550 0.7510 0.9563 0.037 Uiso 1.00 1 c R . .
H(2) H 0.3723 0.5709 0.9252 0.039 Uiso 1.00 1 c R . .
H(3) H 0.2073 0.5284 1.1295 0.043 Uiso 1.00 1 c R . .
H(4) H 0.5543 0.5303 0.9852 0.039 Uiso 1.00 1 c R . .
H(5) H 0.6553 0.7134 0.9989 0.054 Uiso 1.00 1 c R . .
H(6) H 0.7049 0.5870 1.0253 0.054 Uiso 1.00 1 c R . .
H(7) H 0.5875 0.9764 0.8080 0.131 Uiso 1.00 1 c R . .
H(8) H 0.7183 1.0193 0.7926 0.131 Uiso 1.00 1 c R . .
H(9) H 0.6645 0.8838 0.8747 0.131 Uiso 1.00 1 c R . .
H(10) H 0.8925 0.9507 0.7169 0.136 Uiso 1.00 1 c R . .
H(11) H 0.8983 1.0417 0.5880 0.136 Uiso 1.00 1 c R . .
H(12) H 0.9199 0.9073 0.6187 0.136 Uiso 1.00 1 c R . .

H(13) H 0.7733 1.0258 0.5180 0.124 Uiso 1.00 1 c R . .
H(14) H 0.6801 1.0829 0.5970 0.124 Uiso 1.00 1 c R . .
H(15) H 0.6324 0.9706 0.5971 0.124 Uiso 1.00 1 c R . .
H(16) H 0.9393 0.8020 0.5132 0.102 Uiso 1.00 1 c R . .
H(17) H 0.9407 0.6627 0.5617 0.102 Uiso 1.00 1 c R . .
H(18) H 0.9355 0.7213 0.6434 0.102 Uiso 1.00 1 c R . .
H(19) H 0.6514 0.7372 0.5485 0.119 Uiso 1.00 1 c R . .
H(20) H 0.7936 0.7776 0.4596 0.119 Uiso 1.00 1 c R . .
H(21) H 0.7163 0.8573 0.5195 0.119 Uiso 1.00 1 c R . .
H(22) H 0.7830 0.5358 0.7264 0.098 Uiso 1.00 1 c R . .
H(23) H 0.7158 0.5597 0.6394 0.098 Uiso 1.00 1 c R . .
H(24) H 0.6424 0.5652 0.7623 0.098 Uiso 1.00 1 c R . .
H(25) H 0.2130 0.5308 0.8705 0.220 Uiso 1.00 1 c R . .
H(26) H 0.3694 0.6269 0.6294 0.331 Uiso 1.00 1 c R . .
H(27) H 0.3727 0.5052 0.7364 0.331 Uiso 1.00 1 c R . .
H(28) H 0.4241 0.6262 0.7182 0.331 Uiso 1.00 1 c R . .
H(29) H 0.0468 0.5616 0.8197 0.300 Uiso 1.00 1 c R . .
H(30) H 0.1447 0.5681 0.6966 0.300 Uiso 1.00 1 c R . .
H(31) H 0.1078 0.6865 0.7077 0.300 Uiso 1.00 1 c R . .
H(32) H 0.4123 0.8435 0.6448 0.156 Uiso 1.00 1 c R . .
H(33) H 0.2914 1.0191 0.7090 0.209 Uiso 1.00 1 c R . .
H(34) H 0.4366 1.0098 0.6535 0.209 Uiso 1.00 1 c R . .
H(35) H 0.3555 0.9262 0.7907 0.209 Uiso 1.00 1 c R . .
H(36) H 0.3146 0.8834 0.5300 0.266 Uiso 1.00 1 c R . .
H(37) H 0.3098 1.0068 0.5330 0.266 Uiso 1.00 1 c R . .
H(38) H 0.1920 0.9107 0.6165 0.266 Uiso 1.00 1 c R . .
H(39) H 0.0350 0.7796 0.8076 0.221 Uiso 1.00 1 c R . .
H(40) H -0.0330 0.5891 0.9581 0.309 Uiso 1.00 1 c R . .
H(41) H -0.0723 0.6478 1.0457 0.309 Uiso 1.00 1 c R . .
H(42) H 0.0567 0.5927 1.0176 0.309 Uiso 1.00 1 c R . .
H(43) H 0.0234 0.8307 0.9840 0.329 Uiso 1.00 1 c R . .
H(44) H -0.0401 0.8890 0.8913 0.329 Uiso 1.00 1 c R . .
H(45) H 0.1036 0.9227 0.8494 0.329 Uiso 1.00 1 c R . .
H(46) H 0.2756 0.2140 1.5040 0.087 Uiso 1.00 1 c R . .
H(47) H 0.2964 0.2166 1.6103 0.087 Uiso 1.00 1 c R . .
H(48) H 0.4039 0.2713 1.4795 0.087 Uiso 1.00 1 c R . .

H(49) H 0.3428 0.3863 1.6025 0.080 Uiso 1.00 1 c R . .
H(50) H 0.1975 0.3979 1.6497 0.080 Uiso 1.00 1 c R . .
H(51) H 0.2917 0.5066 1.5366 0.080 Uiso 1.00 1 c R . .
H(52) H -0.0316 0.2782 1.5879 0.064 Uiso 1.00 1 c R . .
H(53) H 0.0693 0.2189 1.6406 0.064 Uiso 1.00 1 c R . .
H(54) H 0.0774 0.2197 1.5219 0.064 Uiso 1.00 1 c R . .
H(55) H 0.1196 0.5357 1.5033 0.060 Uiso 1.00 1 c R . .
H(56) H 0.0045 0.4396 1.6029 0.060 Uiso 1.00 1 c R . .
H(57) H 0.0171 0.5074 1.4684 0.060 Uiso 1.00 1 c R . .
H(58) H 0.4352 0.2769 0.9421 0.038 Uiso 1.00 1 c R . .
H(59) H 0.6040 0.1023 0.9333 0.034 Uiso 1.00 1 c R . .
H(60) H 0.7387 0.2791 0.7433 0.039 Uiso 1.00 1 c R . .
H(61) H 0.4269 0.0996 0.8717 0.044 Uiso 1.00 1 c R . .
H(62) H 0.2515 0.2667 0.8887 0.051 Uiso 1.00 1 c R . .
H(63) H 0.2504 0.1763 0.8389 0.051 Uiso 1.00 1 c R . .
H(64) H 0.0404 -0.1681 1.3131 0.081 Uiso 1.00 1 c R . .
H(65) H 0.0989 -0.2312 1.2299 0.081 Uiso 1.00 1 c R . .
H(66) H 0.0610 -0.1004 1.1763 0.081 Uiso 1.00 1 c R . .
H(67) H 0.3483 -0.1646 1.2853 0.087 Uiso 1.00 1 c R . .
H(68) H 0.2128 -0.2336 1.3664 0.087 Uiso 1.00 1 c R . .
H(69) H 0.2377 -0.1035 1.3458 0.087 Uiso 1.00 1 c R . .
H(70) H 0.2818 -0.1485 1.0619 0.075 Uiso 1.00 1 c R . .
H(71) H 0.3492 -0.2153 1.1502 0.075 Uiso 1.00 1 c R . .
H(72) H 0.3915 -0.0798 1.0560 0.075 Uiso 1.00 1 c R . .
H(73) H 0.1355 0.0401 1.3913 0.116 Uiso 1.00 1 c R . .
H(74) H 0.1697 0.1782 1.3374 0.116 Uiso 1.00 1 c R . .
H(75) H 0.2721 0.0994 1.2960 0.116 Uiso 1.00 1 c R . .
H(76) H -0.0299 0.1535 1.2170 0.078 Uiso 1.00 1 c R . .
H(77) H -0.0352 0.1010 1.3485 0.078 Uiso 1.00 1 c R . .
H(78) H -0.0084 0.0188 1.2845 0.078 Uiso 1.00 1 c R . .
H(79) H 0.2429 0.2990 1.1348 0.113 Uiso 1.00 1 c R . .
H(80) H 0.0986 0.3061 1.1639 0.113 Uiso 1.00 1 c R . .
H(81) H 0.1863 0.2803 1.0559 0.113 Uiso 1.00 1 c R . .
H(82) H 0.5149 0.0844 1.2402 0.065 Uiso 1.00 1 c R . .
H(83) H 0.5688 0.3111 1.2063 0.081 Uiso 1.00 1 c R . .
H(84) H 0.4365 0.2417 1.2593 0.081 Uiso 1.00 1 c R . .

H(85) H 0.5176 0.3022 1.1192 0.081 Uiso 1.00 1 c R . .
H(86) H 0.6224 0.0210 1.3506 0.109 Uiso 1.00 1 c R . .
H(87) H 0.5891 0.1404 1.3606 0.109 Uiso 1.00 1 c R . .
H(88) H 0.7216 0.1345 1.2685 0.109 Uiso 1.00 1 c R . .
H(89) H 0.7696 0.0160 0.9956 0.074 Uiso 1.00 1 c R . .
H(90) H 0.6085 -0.1235 1.2295 0.101 Uiso 1.00 1 c R . .
H(91) H 0.6367 -0.1383 1.1134 0.101 Uiso 1.00 1 c R . .
H(92) H 0.5507 -0.0411 1.1368 0.101 Uiso 1.00 1 c R . .
H(93) H 0.9164 -0.0167 1.0612 0.102 Uiso 1.00 1 c R . .
H(94) H 0.8223 -0.1289 1.1679 0.102 Uiso 1.00 1 c R . .
H(95) H 0.8295 -0.0138 1.1830 0.102 Uiso 1.00 1 c R . .
H(96) H 0.8844 0.2028 1.0666 0.071 Uiso 1.00 1 c R . .
H(97) H 0.8314 0.4254 0.9259 0.114 Uiso 1.00 1 c R . .
H(98) H 0.8946 0.3915 1.0178 0.114 Uiso 1.00 1 c R . .
H(99) H 0.7482 0.3664 1.0655 0.114 Uiso 1.00 1 c R . .
H(100) H 0.9881 0.1948 0.8973 0.106 Uiso 1.00 1 c R . .
H(101) H 0.9876 0.3346 0.8422 0.106 Uiso 1.00 1 c R . .
H(102) H 0.8893 0.2573 0.8428 0.106 Uiso 1.00 1 c R . .
H(103) H 0.7279 0.3927 0.2754 0.097 Uiso 1.00 1 c R . .
H(104) H 0.6789 0.5167 0.2158 0.097 Uiso 1.00 1 c R . .
H(105) H 0.5830 0.4059 0.3228 0.097 Uiso 1.00 1 c R . .
H(106) H 0.5634 0.6091 0.3352 0.094 Uiso 1.00 1 c R . .
H(107) H 0.6946 0.6577 0.3136 0.094 Uiso 1.00 1 c R . .
H(108) H 0.5908 0.5916 0.4456 0.094 Uiso 1.00 1 c R . .
H(109) H 0.9614 0.3906 0.3235 0.064 Uiso 1.00 1 c R . .
H(110) H 0.8574 0.3789 0.2821 0.064 Uiso 1.00 1 c R . .
H(111) H 0.8420 0.2975 0.4162 0.064 Uiso 1.00 1 c R . .
H(112) H 0.8404 0.6469 0.3073 0.071 Uiso 1.00 1 c R . .
H(113) H 0.9466 0.5906 0.2360 0.071 Uiso 1.00 1 c R . .
H(114) H 0.9393 0.5782 0.3590 0.071 Uiso 1.00 1 c R . .

loop_
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_atom_site_aniso_U_23
Si(1) 0.0368(6) 0.0340(4) 0.0223(4) -0.0025(4) -0.0014(4) -0.0106(3)
O(2) 0.0372(17) 0.0425(13) 0.0158(11) 0.0029(11) -0.0031(11) -0.0066(10)
C(3) 0.034(2) 0.0321(16) 0.0144(14) -0.0039(14) 0.0007(14) -0.0078(13)
C(4) 0.033(2) 0.0332(17) 0.0253(16) -0.0013(15) -0.0103(15) -0.0087(14)
C(5) 0.034(2) 0.0330(17) 0.0266(17) -0.0089(15) -0.0042(15) -0.0070(14)
C(6) 0.036(2) 0.0333(17) 0.0196(16) -0.0031(15) -0.0073(15) -0.0043(13)
O(7) 0.0269(16) 0.0548(15) 0.0186(11) -0.0027(12) -0.0021(10) -0.0082(10)
C(8) 0.032(2) 0.0354(17) 0.0172(14) -0.0015(14) -0.0026(13) -0.0071(13)
C(9) 0.041(2) 0.054(2) 0.0245(18) -0.008(2) -0.0078(17) -0.0072(16)
O(10) 0.0317(17) 0.0564(16) 0.0273(13) 0.0006(13) -0.0026(11) -0.0134(12)
C(11) 0.066(3) 0.037(2) 0.038(2) -0.012(2) -0.004(2) -0.0132(17)
C(12) 0.155(7) 0.051(2) 0.072(3) -0.024(3) 0.025(3) -0.042(2)
C(13) 0.087(5) 0.087(4) 0.149(6) -0.037(3) 0.004(4) -0.076(4)
C(14) 0.147(7) 0.044(2) 0.106(5) 0.000(3) -0.067(5) -0.008(3)
C(15) 0.051(2) 0.047(2) 0.036(2) 0.0034(19) 0.0005(19) -0.0223(18)
C(16) 0.059(4) 0.095(4) 0.080(3) -0.000(3) 0.014(3) -0.058(3)
C(17) 0.131(6) 0.132(5) 0.054(3) 0.039(4) -0.037(3) -0.062(3)
C(18) 0.106(5) 0.063(3) 0.063(3) -0.011(3) 0.001(3) -0.045(2)
O(19) 0.0387(16) 0.0509(15) 0.0292(12) 0.0067(12) -0.0153(11) -0.0155(11)
Si(20) 0.0558(8) 0.0513(6) 0.0334(5) 0.0020(5) -0.0251(5) -0.0113(4)
C(21) 0.314(18) 0.192(10) 0.209(11) 0.107(11) -0.211(13) -0.146(9)
C(22) 0.269(17) 0.50(2) 0.45(2) 0.288(19) -0.299(18) -0.45(2)
C(23) 0.35(2) 0.264(16) 0.122(8) -0.178(16) -0.119(11) -0.019(9)
C(24) 0.087(5) 0.147(7) 0.071(4) -0.017(5) -0.047(4) 0.036(4)
C(25) 0.223(12) 0.064(4) 0.249(12) -0.012(6) -0.192(11) 0.006(6)
C(26) 0.171(11) 0.251(15) 0.102(6) -0.049(10) -0.088(7) 0.074(8)
C(27) 0.068(5) 0.38(2) 0.082(5) 0.048(8) -0.045(4) -0.076(9)
C(28) 0.094(7) 0.50(2) 0.055(4) -0.139(12) -0.018(4) -0.004(9)
C(29) 0.254(19) 0.46(3) 0.241(16) 0.27(2) -0.153(15) -0.26(2)
B(30) 0.034(2) 0.0331(19) 0.0220(19) -0.0053(17) -0.0080(17) -0.0027(15)
O(31) 0.0265(16) 0.0619(17) 0.0204(11) -0.0053(12) -0.0032(10) -0.0068(11)
C(32) 0.027(2) 0.059(2) 0.0214(17) 0.0012(18) -0.0056(16) -0.0042(16)

C(33) 0.040(2) 0.043(2) 0.0195(16) -0.0094(17) -0.0088(16) -0.0025(15)
O(34) 0.0372(17) 0.0532(15) 0.0218(12) -0.0106(13) -0.0078(11) -0.0076(11)
C(35) 0.059(3) 0.068(3) 0.051(2) 0.016(2) -0.014(2) -0.005(2)
C(36) 0.041(3) 0.116(4) 0.035(2) -0.005(2) -0.017(2) -0.024(2)
C(37) 0.041(2) 0.061(2) 0.031(2) -0.020(2) -0.0033(18) -0.0029(18)
C(38) 0.050(3) 0.056(2) 0.033(2) 0.007(2) -0.0117(19) -0.0156(19)
Si(39) 0.0338(6) 0.0361(4) 0.0242(4) -0.0032(4) -0.0039(4) -0.0104(4)
O(40) 0.0337(16) 0.0393(13) 0.0205(11) -0.0058(11) -0.0050(10) -0.0070(10)
C(41) 0.039(2) 0.0272(15) 0.0170(15) 0.0004(14) -0.0070(14) -0.0043(12)
C(42) 0.031(2) 0.0283(15) 0.0232(15) 0.0001(14) -0.0103(14) -0.0091(13)
C(43) 0.030(2) 0.0364(18) 0.0244(16) 0.0050(15) -0.0091(14) -0.0114(14)
C(44) 0.024(2) 0.0408(18) 0.0283(18) 0.0035(15) -0.0063(15) -0.0156(15)
O(45) 0.0307(17) 0.0611(17) 0.0194(11) -0.0050(13) -0.0070(11) -0.0027(11)
C(46) 0.035(2) 0.0408(19) 0.0223(16) -0.0026(16) -0.0090(15) -0.0052(14)
C(47) 0.028(2) 0.059(2) 0.0308(18) -0.0030(18) -0.0117(16) -0.0117(17)
O(48) 0.0296(17) 0.0604(17) 0.0280(12) -0.0071(13) -0.0052(11) -0.0105(12)
C(49) 0.047(2) 0.041(2) 0.0333(19) -0.0100(18) -0.0071(18) -0.0107(16)
C(50) 0.062(3) 0.058(2) 0.060(2) -0.016(2) -0.006(2) -0.022(2)
C(51) 0.086(4) 0.052(2) 0.050(2) -0.008(2) -0.027(2) 0.002(2)
C(52) 0.061(3) 0.045(2) 0.068(2) -0.001(2) -0.009(2) -0.029(2)
C(53) 0.040(2) 0.054(2) 0.047(2) 0.0012(19) -0.0005(19) -0.028(2)
C(54) 0.078(4) 0.162(7) 0.091(4) 0.025(4) -0.029(3) -0.097(5)
C(55) 0.044(3) 0.079(3) 0.068(3) 0.009(2) -0.008(2) -0.043(2)
C(56) 0.094(4) 0.052(2) 0.087(4) -0.003(2) 0.025(3) -0.042(2)
O(57) 0.0433(17) 0.0378(13) 0.0310(12) 0.0032(11) -0.0208(11) -0.0137(10)
Si(58) 0.0382(6) 0.0425(5) 0.0277(4) 0.0048(4) -0.0162(4) -0.0125(4)
C(59) 0.053(3) 0.068(2) 0.034(2) 0.004(2) -0.016(2) -0.018(2)
C(60) 0.078(4) 0.087(3) 0.052(2) 0.024(3) -0.029(2) -0.044(2)
C(61) 0.108(5) 0.120(5) 0.033(2) 0.029(4) -0.028(2) -0.028(2)
C(62) 0.079(3) 0.058(2) 0.071(3) 0.030(2) -0.053(2) -0.033(2)
C(63) 0.106(5) 0.037(2) 0.101(4) 0.009(2) -0.059(4) -0.011(2)
C(64) 0.094(5) 0.069(3) 0.109(4) 0.040(3) -0.067(4) -0.037(3)
C(65) 0.059(3) 0.071(3) 0.041(2) -0.004(2) -0.025(2) -0.016(2)
C(66) 0.105(5) 0.069(3) 0.091(4) -0.031(3) -0.007(3) -0.040(3)
C(67) 0.051(4) 0.112(5) 0.068(3) -0.012(3) -0.001(3) -0.029(3)
B(68) 0.031(2) 0.037(2) 0.028(2) 0.0026(17) -0.0138(18) -0.0121(16)

O(69) 0.0365(18) 0.0561(16) 0.0228(12) -0.0083(13) -0.0129(11) -0.0030(11)
C(70) 0.027(2) 0.057(2) 0.0255(19) -0.0054(18) -0.0063(16) -0.0037(17)
C(71) 0.036(2) 0.0430(19) 0.0229(17) -0.0024(17) -0.0110(16) -0.0078(15)
O(72) 0.0288(15) 0.0490(14) 0.0186(11) -0.0045(11) -0.0081(10) -0.0062(10)
C(73) 0.039(3) 0.158(6) 0.034(2) -0.016(3) -0.006(2) -0.038(3)
C(74) 0.055(3) 0.053(2) 0.077(3) 0.014(2) -0.024(2) 0.006(2)
C(75) 0.044(3) 0.072(3) 0.040(2) 0.010(2) -0.013(2) -0.026(2)
C(76) 0.072(3) 0.053(2) 0.039(2) -0.020(2) -0.017(2) -0.0093(19)

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# End of CIF

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# 主論文目録

本学位論文内容は下記の発表論文による。

1. Sakamaki, S.; Kawanishi, E.; Nomura, S.; Ishikawa, T. Aryl-β-*C*-glucosidation using glucal boronate: application to the synthesis of tri-*O*-methylnorbergenin. *Tetrahedron* **2012**, *68*, 5744.

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主査　千葉大学大学院教授（薬学研究院）　薬学博士　高山　廣光
副査　千葉大学大学院教授（薬学研究院）　薬学博士　西田　篤司
副査　千葉大学大学院教授（薬学研究院）　薬学博士　濱田　康正
副査　千葉大学大学院教授（薬学研究院）　理学博士　石橋　正己