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Total Syntheses of the Non-Peptide Bradykinin B1 Receptor Antagonist Velutinol A and Its Analogs, *seco*-Pregnanes with a Cage-Like Moiety

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Abstract

We describe here the syntheses of velutinol A (**1**) and the structurally similar compounds **2**–**4** sharing a highly oxygenated *seco*-pregnane cage-like structure. The synthesis of velutinol A (**1**, 15,16-*seco*-pregnane) features the highly regioselective construction of Δ^{14} silyl enol ether from 15-keto-21,22-diol, followed by stereoselective introduction of a sterically hindered β-hydroxy group at the C14 position by Rubottom oxidation. Prolonged reaction time and the use of an excess amount of *m*CPBA at this step allowed double Rubottom oxidation, enabling us to introduce the requisite hydroxy groups at the C14 and C16 positions in one pot. Subsequent oxidative cleavage of the C15–16 bond, deprotection, and intramolecular acetalization allowed the concise total synthesis of velutinol A (**1**). Utilization of α,α-dihydroxyketone, the double Rubottom oxidation product, for formation of the ether F-ring by 5-*exo*-cyclization, and subsequent C14–21 oxidative cleavage, effectively achieved the synthesis of pentalinonside-aglycon (**2**). Construction of the 14,15-*seco*-structures of two other analogs, argeloside aglycon (**3**) and illustrol (**4**), was achieved by Baeyer–Villiger oxidation of 15(21)-keto derivatives. Introduction of the 20-oxo group potentially embedded in argeloside aglycon was accomplished by Wacker oxidation of Δ^{20}, which was constructed by Grieco–Nishizawa *syn*-β-elimination of the C21-primary alcohol obtained by reduction of the Baeyer–Villiger product. Intramolecular double acetalization of the 15,16-dihydroxy-14,20-oxo derivative to form the cage-like structure of the DEF-rings required a moderately weak acid. This step was the key to accessing argeloside aglycon (**3**), as otherwise the easily aromatized β,γ-dihydroxyketone moiety was transformed to furan. Sharpless asymmetric dihydroxylation of Δ^{20} to set the C20 stereocenter, followed by intramolecular double acetalization, achieved the stereoselective synthesis of illustrol With all synthesized compounds, structural requirements of steroidal bradykinine B1 receptor antagonist would be revealed.

Keywords: Bradykinin B1 receptor (B1R) | *seco*-Pregnane | Natural product syntheses

1. Introduction

G protein coupled receptors (GPCRs) are one of several superfamilies of proteins, consisting of an extracellular N-terminal domain, seven transmembrane helices domain, and

intracellular domains. GPCRs interact with G-proteins at the intracellular site and transduce a large number of signals across the cell membrane by binding signaling molecules such as ions, odorants, biogenic amines, lipids, peptides, and proteins at the extracellular side of the membrane. GPCRs have been proven to be promising drug targets, with more than 30% of drugs currently on the market being GPCR agonists or antagonists. The bradykinin receptor is a pharmacologically important receptor belonging to the GPCR family and plays important roles in the pathophysiological process of pain and inflammation.[1] The bradykinin receptor has two subtypes, referred to as bradykinin B1 receptor (B1R) and B2 receptor (B2R), and these subtypes differ in their level of expression and their binding to ligands. B2R is constitutively expressed in a number of tissues and evokes the acute pain response after activation by the nonapeptide bradykinin (H-Arg^1-Pro^2-Pro^3-Gly^4-Phe^5-Ser^6-Pro^7-Phe^8-Arg^9-OH), whereas a corresponding metabolite, des-Arg9-bradykinin (DABK), serves as the agonist for B1R,[2] which is inductively expressed at high levels in injured tissues.[3] Preclinical data accumulated to date suggest that B1R is involved in the propagation, potentiation, and maintenance of chronic pain.[4] Therefore, the up-regulation of B1R in response to inflammation would be an attractive target for drug development. In this context, the development of B1R antagonists has proceeded based on the structure-activity relationship (SAR) with its agonist ligand, DABK. Consequently, B1R antagonists identified to date have tended to be peptides,[5] which compromises their in vivo application.

Several non-peptide B1R selective antagonists have recently been identified.[6] Velutinol A (**1**, Figure 1), consisting of a 15,16-*seco*-14β,17α-pregn-5-ene core with a cage-like structure in the steroidal DEF-rings, is the first and only known non-peptide B1R antagonist natural product.[7]

Velutinol A (**1**) was isolated from the rhizomes of *Mandevilla velutina* (Apocynaceae), a plant native to the Brazilian savanna. Infusions or alcoholic extracts of these rhizomes are used as folk medicine for the treatment of venomous snake bites.[8]

We previously reported our preliminary construction of a complex structural model of velutinol A (**1**) and DABK bound to human B1R (hB1R) for comparison of binding site and mode of these antagonists. These models were generated with the homology module (Insight II) using a model of a meta-rhodopsin photointermediate in the bovine rhodopsin photocascade as the template (Figure 2A–C).[9]

Figure 2A and B show the complex model of velutinol A (**1**) bound to hB1R which suggested a characteristic receptor–ligand interaction in which three oxygen atoms in the cage-like structure of the DEF-rings of velutinol A (**1**) formed hydrogen bonds with Lys118 in the third transmembrane helix. Another hydrogen bond was observed between a hydrogen atom on the hemiacetal hydroxy group in the DEF-rings and Tyr266. It should be noted that electron density of the oxygen atom in the phenol moiety of Tyr266 was increased by hydrogen bond formation between the hydrogen atom of the phenolic hydroxy group and the carboxylate oxygen of Asp183, which strengthened hydrogen bonding between the hydroxy group of the hemiacetal moiety and Tyr266.

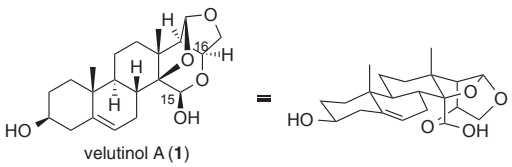


Figure 1. Structure of velutinol A.

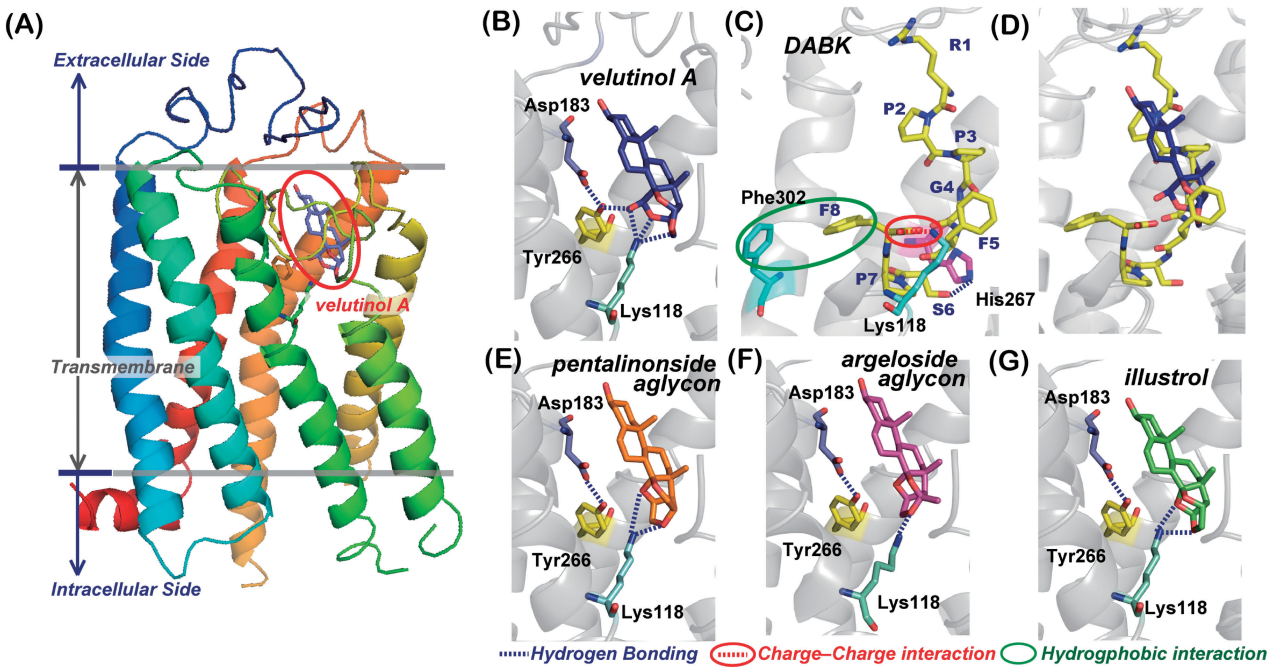


Figure 2. Complex structural models of (A and B) velutinol A (blue), (C) DABK (yellow), (E) pentalinonside aglycon (orange), (F) argeloside aglycon (magenta), and (G) illstrol (green) bound to hB1R. (D) Superposed structure of velutinol A and DABK bound to hB1R.

Table 1. Site-Directed Mutagenesis Data of DABK.[10b]

Entry	hB1R	*Ki* (nM)
1	WT	100 ± 25
2	Lys118Ala	2600 ± 1400
3	Lys118Ser	2800 ± 1100
4	Phe302Ala	3000 ± 610
5	His267Gln	4.3 ± 0.3

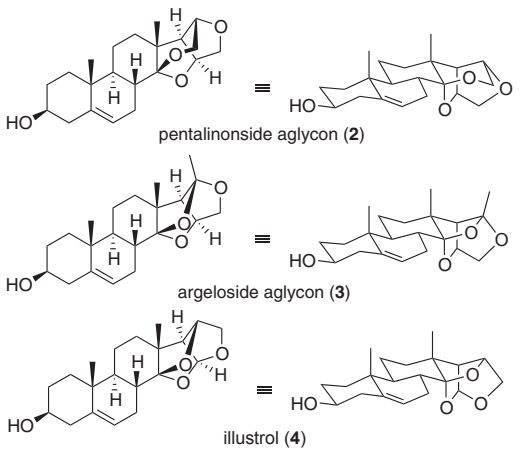


Figure 3. Highly oxygenated *seco*-pregnanes with cage-like structure.

Figure 2C shows a complex structural model of DABK bound to hB1R. Our docking model is consistent with the results of reported site-directed mutagenesis data (Table 1, reported by Ha *et al*).[10a] Thus, Lys118, His267 and Phe302, whose mutations considerably affected the affinity of hB1R for DABK,[10] interacted with DABK in our constructed hB1R–DABK complex model. The C-term (Phe8) of DABK bonded to Lys118 by charge–charge interaction in our model. A mutation of Lys118 to Ala or Ser led to approximately 27-fold decrease in affinity for DABK (Entries 2 and 3).[10b]

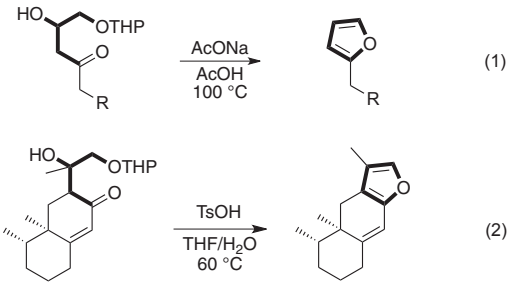
In addition, 30-fold loss of affinity for DABK in the case of a Phe302Ala mutant (Entry 5) supported plausibility of our model, since the mutation from Phe to Ala loses a hydrophobic interaction between Phe302 and the ligand (Phe8).[10b] Furthermore, our model was consistent with the increase in the affinity of DABK for a His267Gln mutant strengthening a hydrogen bond with ligand (Ser6).

To compare the binding mode in the pocket, a superposed structure of the complex models of DABK and velutinol A (**1**) was constructed as shown in Figure 2D. A superposed structure revealed that DABK and velutinol A (**1**) were positioned in the same pocket and the cage-like structure in velutinol A plays a role as a bioisostere of the carboxylate.

We therefore hypothesized that the *seco*-pregnane derivatives pentalinonside aglycon (**2**),[11] argeloside aglycon (**3**),[12] and illustrol (**4**),[13] which have similar cage-like structures, might have similar biological activities (Figure 3). To evaluate the binding mode of pentalinonside aglycon (**2**), argeloside aglycon (**3**), and illustrol (**4**), we constructed complex structural models of these three compounds bound to hB1R, respectively (Figure 2E–G). The cage-like moieties of these three compounds interacted with Lys118 as was observed in the case of velutinol A. However, Tyr266 interacted with none of these three molecules, whereas velutinol A formed a strong hydrogen bond. To investigate the mechanism of molecular recognition between the ligands and B1R, we developed a general synthetic route for the construction of cage-like *seco*-pregane derivatives **1**–**4**.[14–17] Among the natural *seco*-preganes, pentalinonside and argeloside form a glycosyl bond at C3-OH and the removal of the sugar moieties is difficult due to the presence of the acid-sensitive tricyclic acetals at the *seco*-D-ring. Thus, the synthesis of these derivatives may not only contribute to the structure-activity studies of the non-peptide steroid derivatives, but also impact the field of drug design as a new approach of bioisoteric replacement of carboxylate with drug likeness. In addition to our previous results,[14–17] this paper will detail our efforts and investigations towards the syntheses of *seco*-pregnane derivatives with the highly oxygenated cage-like structures. This synthetic strategy may be applicable to the syntheses of structural analogs of **1**–**4**.

2. Results and Discussion

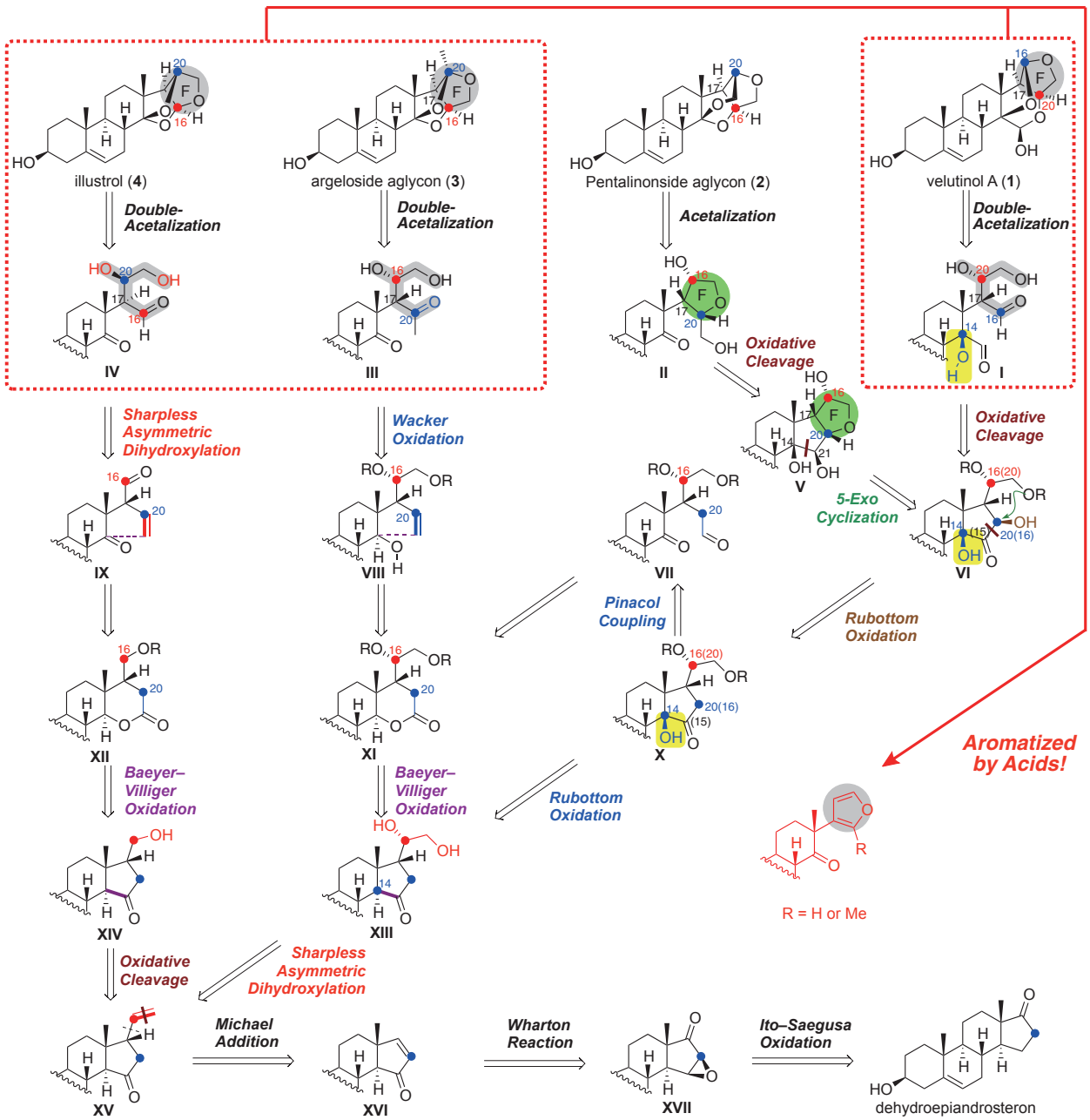
Synthetic Strategy. Scheme 2 outlines our retrosynthetic blueprint for compounds **1**–**4**. We expected that the DEF-rings embedded in compounds **1**, **3**, and **4**, and the DE-rings of compound **2**, could be constructed by intramolecular acetalization, and thus we chose compounds **I**–**IV** as the precursors. Dialdehyde **I** would also be derived from α,α-dihydroxyketone **VI** by oxidative cleavage of the C15–C16 bond. Ketone **I** can presumably be obtained from diol **V** via oxidative cleavage of the C14–21 bond; 5-*exo*-cyclization for annulation of the F-ring would be accomplished by intramolecular S_N2 addition of a C15 hydroxy group to the C20 position in α,α-dihydroketone **VI**. The hydroxy group at C20 in **VI** could be stereoselectively installed via Rubottom oxidation of α-hydroxyketone **XI**.[18] Stereoselective introduction of a *tert*-alcohol group at C14 in **X** could presumably be accomplished by two independent routes: 1) pinacol coupling[19] of keto–aldehyde **VII** derived from lactone **XI**, 2) Rubottom oxidation of α-hydroxyketone **XI**. The 20-oxo-group of **III** could be introduced by Wacker oxidation[20] of olefin **VIII**, whose *seco*-structure was constructed by regioselective Baeyer–Villiger oxidation of **XIV**. The stereochemistry at the C20 position of **IV** could be controlled by Sharpless asymmetric dihydroxylation,[21] and thus olefin **IX** was chosen as a precursor. As with compound **VIII**, Baeyer–Villiger oxidation would achieve construction of the *seco*-structure, and thus compound **XIV** was used as the precursor of **IX**. Both compounds **XIV** and **XIII** would be prepared via Sharpless asymmetric dihydroxylation or oxidative cleavage from olefin **XV**, which can be synthesized through stereospecific Michael addition of a soft vinyl anion derivative at the C17 position of enone **XVI**. Thus, olefin **XV** would be a common intermediate for compounds **1**–**4**. Ito–Saegusa oxidation[22] and Wharton reaction[23] would provide enone **XVI** from *epi*-andronsterone. Despite these rather simple strategies, the primary challenge for the synthesis of compounds **1**, **3**, and **4** was to escape the easy aromatization of the β,γ-dihydroxycarbonyl moiety in as well as the construction of the structurally equivalent F-ring moiety in **1**, **3**, and **4**. Specifically, since acids may promote the aromatization of **1**, **3**, **4, I**, **III**, and **IV** (Scheme 1, eq 1 and 2),[24]



Scheme 1. Furan formation reaction from β,γ-dihydroxy ketone.

appropriate acidic conditions are required for the conversion of **I**, **III**, and **IV** into **1**, **3**, and **4**.

Synthesis of Velutinol A.[14] The major challenge in the synthesis of velutinol A (**1**) was the selective introduction of the hydroxy group at the C14β position. For installing the hydroxy group stereoselectively, two methods were investigated: 1) pinacol coupling, and 2) Rubottom oxidation. There are pros and cons of both methods in terms of stereoselectivity and reaction steps. Figure 4 shows two plausible transition states of metal mediated pinacol coupling. As shown in Figure 4, **TS2**, leading to undesired *cis*-diol, would be energetically unfavorable compared to **TS1** because of steric hinderance between the C18-Me group and aldehyde in the case of metal mediated pinacol coupling. Thus, stereochemistry at C14 seems to be easy to control by the pinacol coupling route. However,



Scheme 2. Retrosynthetic Analysis.

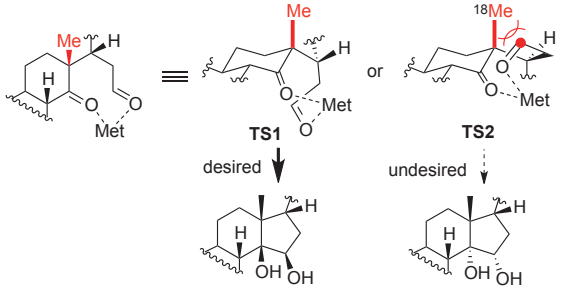
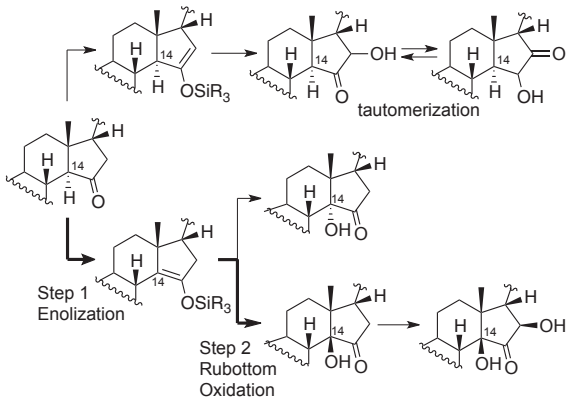


Figure 4. Plausible transition states of pinacol coupling.

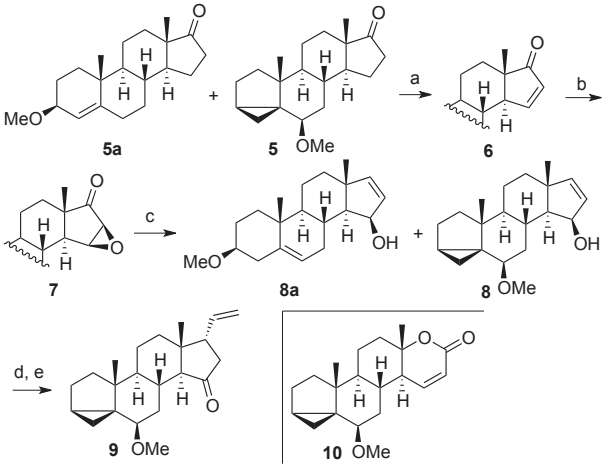


Scheme 3. Synthetic issue for the introduction of 14β-OH.

synthesis of keto–aldehyde needs more reaction steps compared to Rubottom methods as shown in Scheme 2 (**XIII**→**XI**→**VII**→**X**).

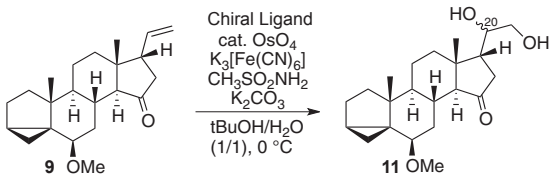
On the other hand, the Rubottom oxidation route has potential stereo- and regio-selectivity problems, even though it has an advantage in terms of reaction steps. To highlight the essence of the problems of the Rubottom oxidation route, Scheme 3 shows a hypothetical route based on silylenolization (step 1) followed by Rubottom oxidation (step 2).[18] In particular, step 1 would not be straightforward since enolization of the 15-keto derivative under basic conditions might occur at the undesired side to generate Δ^{15} due to steric hindrance, and the 16-α-hydroxy ketone derivative generated in the following Rubottom oxidation step would easily tautomerize. Even if Step 1 occurred with high regioselectivity, Step 2 must occur with high diastereofacial selectivity. With these issues in mind, we embarked on the synthesis of **1**.

Scheme 4 shows the synthesis of the key intermediate ketone **9** in five steps, starting from known compound **5**.[25,26] Ito–Saegusa oxidation of a mixture of **5** and **5a** was accomplished by using a catalytic amount of palladium acetate with 2 equiv. of *p*-benzoquinone as a re-oxidant of palladium (0) to afford enone **6** in 86% yield.[22b] When oxygen was used instead of *p*-benzoquinone,[22a,27] α,β-unsaturated lactone **10** was generated in 6% yield as a side product via Baeyer–Villiger-type rearrangement triggered by the palladium peroxide generated in the reaction.[28] This side reaction led to a low yield of enone **6** (73%). After treatment of enone **6** with NaClO (93%), the resulting epoxide **7** was converted to allyl alcohol **8** by hydrazine monohydrate in the presence of Et_3N and AcOH in 74% yield (**8**: 63%, **8a**: 11%). It should be noted that 3-MeO



Scheme 4. Synthesis of **9**. *Reagents and conditions*: a) LDA, TMSCl, THF, −78 °C; then $Pd(OAc)_2$, *p*-benzoquinone, DMSO, 60 °C, 2 h, 86% from **5**; b) NaClO, pyridine, EtOH, −10 °C, 20 min, 93%; c) $NH_2NH_2 \cdot H_2O$, Et_3N, AcOH, CH_3CN, 30 min, rt, 74% (**8**: 63%, **8a**: 10%); d) TPAP, NMO, CH_2Cl_2, rt, 92%; e) vinylmagnesium bromide, CuI, THF, −30 °C, 30 min, quant. LDA = lithium diisopropylamide, TMS = trimethylsilyl, THF = tetrahydrofuran, DMSO = dimethyl sulfoxide, rt = room temperature, TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine-*N*-oxide.

Table 2. Dihydroxylation of olefin **9**.



Entry	Chiral Ligand	Time [h]	Yield [%] (20*S*:20*R*)
1	$(DHQD)_2PHAL$	4	82 (1:1.7)
2	$(DHQ)_2PHAL$	3	97 (5.5:1)
3	$(DHQ)_2AQN$	2.5	76 (2.5:1)
4	$(DHQ)_2PYR$	2.0	87 (7.7:1)

DHQ = dihydroquinoline, DHQD = dihydroquinidine. PHAL = phthalazine derivative. AQN = anthraquinone derivative. PYR = diphenylpyrimidine derivative.

derivative contaminated from compound **5** was separable at this stage to give pure **8**. Oxidation of the alcohol group in **8** by tetrapropylammonium perruthenate (TPAP, 92%)[29] followed by substrate-controlled Michael addition of a vinyl copper reagent to the resulting enone, provided olefin **9**.

Sharpless asymmetric dihydroxylation was applied to olefin **9** for stereoselective introduction of the C20-hydroxy group (Table 2).[21] First, the use of $(DHQD)_2PHAL$ as a chiral ligand gave the desired 20*S*-**11** and its diastereomer 20*R*-**11** in 30% and 52% yield, respectively (Entry 1). It is worth noting that 20*R*-**11** and 20*S*-**11** were easily separable by silica-gel column chromatography. As we expected, 20*S*-**11** was obtained as the major diastereomer (82%) concomitant with 20*R*-**11** (15%) when a catalytic amount of $(DHQ)_2PHAL$ was used instead of its diastereomer $(DHQD)_2PHAL$ (Entries 1 and 2). To gain

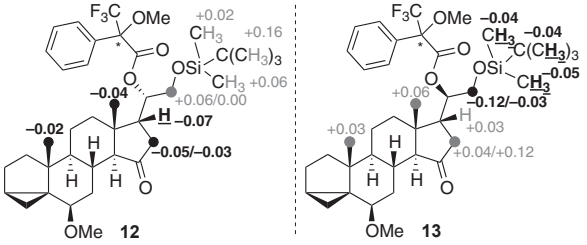


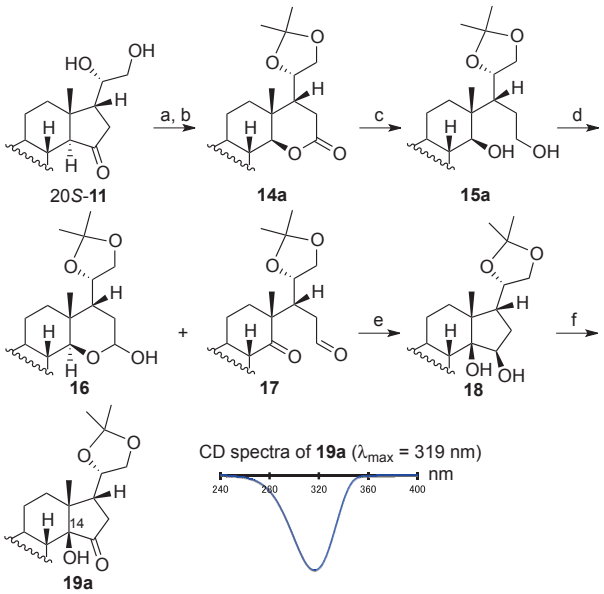
Figure 5. $\Delta\delta^{SR}$ values for the MTPA esters of compound **12** and **13**.

higher diastereoselectivity, another chiral ligand, $(DHQ)_2AQN$, was also examined, but unfortunately it gave lower selectivity compared to $(DHQ)_2PHAL$ (Entry 3). Although higher selectivity was obtained when $(DHQ)_2PYR$ was employed (Entry 4), the yield of 20*R*-**11** (77%) was lower than that of Entry 2. We also tested the diastereomers of the catalysts (Entries 3, 4) and similarly observed lower selectivity.

The absolute stereochemistry at C20 was determined by the Mosher method (Figure 5).[30] Thus, after protection of each primary alcohol at the C21 position in diol 20*S*-**11** and 20*R*-**11** as TBS, each secondary alcohol at C21 was derivatized with the two enantiomers of (*R*)- and (*S*)-α-methoxy-α-trifluoromethyl-α-phenylacetic acid (MTPA), respectively, to afford (*R*)- and (*S*)-MTPA-**12** and (*R*)- and (*S*)-MTPA-**13**. The ^{1}H NMR spectra of the four derivatives were recorded and each $\Delta\delta^{SR}$ value [= δ(*S*)-MTPA-**12** − δ(*R*)-MTPA-**12** or δ(*S*)-MTPA-**13** − δ(*R*)-MTPA-**13**] was calculated. As a result, the absolute stereochemistry of C20 in **12** and **13** was determined as shown in Figure 5, which indicates the stereochemistry of C20 in 20*S*-**11** and 20*R*-**11**.

With the requisite ketones 20*S*-**11** in hand, we investigated the pinacol route (Scheme 5). After protection of diol moiety of 20*S*-**11** as an acetonide (91%), the resulting ketone was converted to lactone **14a** by Beayer–Villiger reaction using *m*CPBA (69%), whose lactone moiety was reduced by $LiAlH_4$ to afford diol **15a** in a quantitative yield. Contrary to our expectation, subsequent Swern oxidation gave lactol **16** as a major product in addition to keto–aldehyde **17** as a minor product. The requisite keto–aldehyde **17** was then converted into diol **18** by intramolecular pinacol coupling. Thus, SmI_2 in THF (1.0 M) was added to a solution of keto–aldehyde **17** in degassed THF/MeOH at 0 °C until the reaction mixture turned dark blue (~2.5 equiv. of SmI_2). Stirring at 0 °C for 10 min afforded diol **18** in 65% yield. Stereochemistry at C14 was determined after conversion of diol **18** to α-ketal **19a** by TPAP oxidation. Thus, a negative Cotton effect at 319 nm observed in the circular dichroism (CD) spectrum of **19a** suggested that **19a** would possess *cis*-fused CD rings according to the octant rule.[31]

For the other synthetic route, the Rubottom oxidation route was conducted. First of all, we transformed ketones 20*S*-**11** to ketones **20**, **22**, and **25a** and investigated the regio-selective construction of Δ^{14} enol, one of the key reactions of this synthesis (Table 3). We first applied the enolization reaction to ketone **20** by treatment with 2,6-lutidine and TBSOTf in CH_2Cl_2 at 0 °C and obtained Δ^{14}-silyl enol ether **21**, the desired regio-isomer, as a major product (Entry 1). The same result

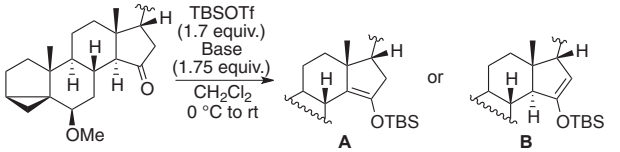


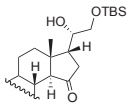
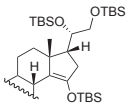
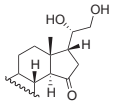
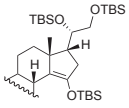
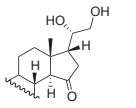
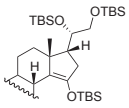
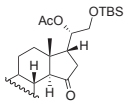
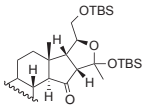
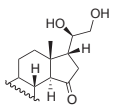
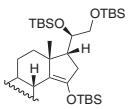
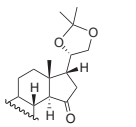
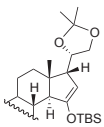
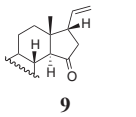
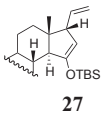
Scheme 5. Investigation of pinacol route. *Reagents and conditions*: a) 2-methoxypropene, cat. $TsOH\cdot H_2O$, DMF, rt, 30 min, 91%; b) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 1 d, 69%; c) $LiAlH_4$, THF, 0 °C, 5 min, quant.; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C (1 h) to rt, 46% for **16**, 25% for **17**; e) SmI_2, THF/MeOH (10/1), 0 °C, 10 min, 65%; f) TPAP, NMO, CH_2Cl_2, rt, 2 h, 85%.

was obtained when 20*S*-**11** was used as the starting material (Entry 2). Furthermore, the reaction proceeded in a fully regioselective manner when Et_3N was used instead of 2,6-lutidine to produce **21** (92% yield, Entry 3). According to the results shown in Entries 1 and 2, the sterically more hindered H14 reacted rather than H16. On the other hand, when compound **22** was treated under the same conditions, ketal **23** was obtained in 30% yield concomitant with 15-keto-20,21-di-TBS ether in 54% yield (Entry 4). In other words, the first step was enolization to form Δ^{15} enol, which reacted with the carbonyl of the C20 acetate group to afford cyclized compound **23**. When the epimer at C20,20*R*-**11** was employed, lower regioselectivity and a lower yield were obtained (Entry 5). These results indicated the participation of the hydroxy group at C20, as shown in Figure 6, to form the Δ^{14} enol in the case of **20** and 20*S*-**11**, as otherwise nucleophilic attack on the less hindered H16 took place to afford Δ^{15} enol. To conform this prediction, ketones **25a** and **9** were treated under the same conditions as 20*S*-**11**, resulting in the formation of Δ^{15} isomers as the sole products (Entries 6 and 7).

Rubottom oxidation was applied to the silyl enol ether **21** to introduce a hydroxy group at the 14-position (Scheme 6).[18] Thus, **21** was treated with *m*CPBA (1.05 equiv.) in CH_2Cl_2 at 0 °C for 20 min to afford α-ketol **19b** in 54% yield along with hydroxy enol **29** in 26% yield. An extended reaction (10 h) resulted in only enol **29** in 87% yield without α-ketol **19b**. The stereochemistry at the C14 position of α-ketol **19b** was determined by CD spectroscopic analysis. Observation of a negative Cotton effect at 318 nm in the CD spectrum suggested that **19b** possessed *cis*-fused CD rings, in accordance with the octant rule.[31] Enol **29** was then treated with *m*CPBA, followed by

Table 3. Enolization of 15-keto derivatives



Entry	Ketone	Major product	Base	Time /h	Yield/% (**A**:**B**[a])
1[b]	 **20**	 **21**	2,6-lutidine	6	73 (1:0)
2[c]	 20*S*-**11**	 **21**	2,6-lutidine	0.3	87 (9:1)
3[c]	 20*S*-**11**	 **21**	Et_3N	1.0	92 (1:0)
4	 **22**	 **23**	2,6-lutidine	48	17[d] (0:1)
5[c]	 20*R*-**11**	 **24**	2,6-lutidine	0.3	30[e] (3:1)
6	 **25a**	 **26**	2,6-lutidine	36	81 (0:1)
7	 **9**	 **27**	2,6-lutidine	0.3	95 (0:1)

[a] The diastereomeric ratio was determined by ^{1}H NMR. [b] 3.4 equiv. of TBSOTf and 3.5 equiv. of 2,6-lutidine were used. [c] 4.9 equiv. of TBSOTf and 5.2 equiv. of base were used. [d] Recovery of starting material in 74% yield. [e] The 15-keto-20,21-di-TBS ether was obtained in 54% yield. TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

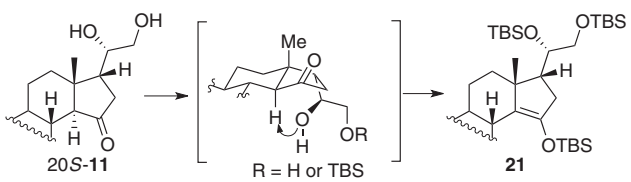
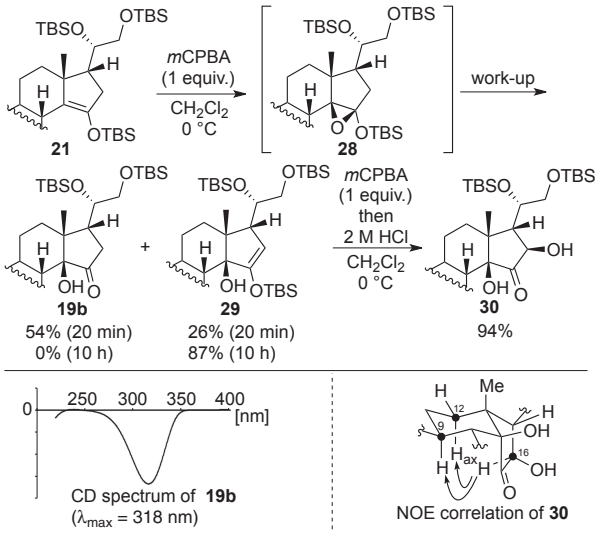
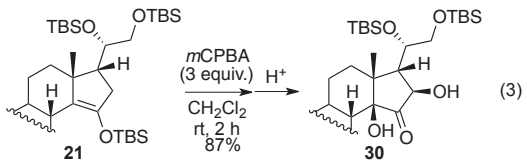


Figure 6. Plausible mechanism of regio-selective enolization of 20*S*-**11**.



Scheme 6. Synthesis of **30**. *m*CPBA = *m*-chloroperbenzoic acid.



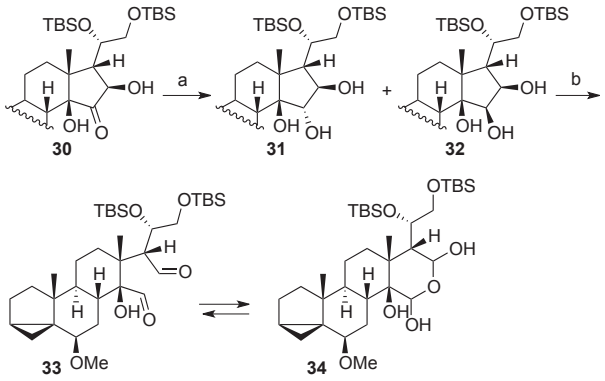
Scheme 7. Double Rubottom oxidation of enol **21**.

exposure to 2 M HCl to give α,α-dihydroketone **30** in 94% yield. The stereochemical assignment of ketone **30** was established by nuclear Overhauser effect (NOE) experiments. The NOE correlation between H-16 and H_{ax}-12 revealed the stereochemistry at C16 and C14 shown in Scheme 6.

According to these results, "double Rubottom oxidation" was achieved by treatment of enol **21** with 3 equiv. of *m*CPBA in CH_2Cl_2 at room temperature for 2 hours to provide keto-diol **30** with a yield of 87% (Scheme 7, eq 3).[32] Thus, the Rubottom oxidation route was highly stereoselective and has fewer steps than the pinacol route.

The reduction of keto-diol **25** by $NaBH_4$ in MeOH at 0 °C completed within 10 min, giving the desired 15,16-*cis*-triol **32** and undesired 15,16-*trans*-triol **31** in yields of 74% and 23%, respectively (Scheme 8). On the other hand, $LiAlH_4$ took longer reaction time (20 min) to reduce **30** in a less selective manner compared to $NaBH_4$ to give **32** in 40% and **31** in 45% yields.

To determine each stereochemistry at the C15 positions of **31** and **32**, the hydroxy groups at the C16 position of **31** and the C15/C16 positions of **32** were protected as MTPA and acetonide, respectively. The NOE correlation between H-16 and H_{ax}-12, H-15 and H-7/H-17 in **35** indicated the stereochemistry of C15 as shown in Figure 7. The stereochemistry of C15 in **36** was also determined by the NOE correlation between H-16 and H_{ax}-12, H-15 and H_{ax}-7/H-9. Therefore, the stereochemistry of C15 in triols **31** and **32** was confirmed as shown in Scheme 8. Oxidative cleavage of the C15–16 bond of **32** for construction of the 15,16-*seco*-structure was achieved by using $NaIO_4$ to afford a mixture of the dialdehyde **33** and the cyclic compound **34** (81%).



Scheme 8. Total synthesis of velutinol A. *Reagents and conditions*: a) $NaBH_4$, MeOH, 0 °C, 10 min, **32**: 74%, **31**: 23%; b) $NaIO_4$, THF/H_2O (1:1), 5 h, 81%.

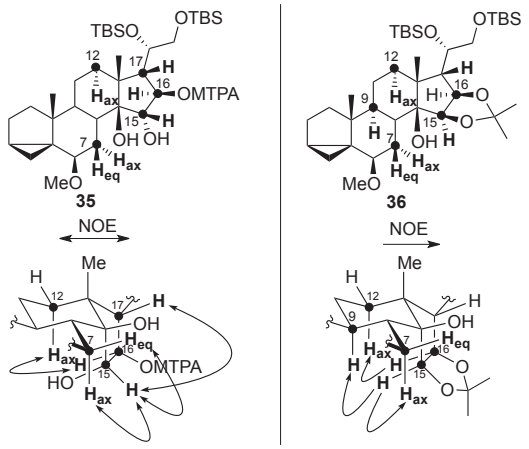
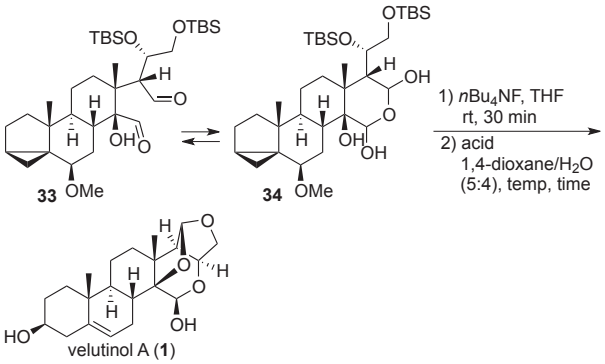


Figure 7. Stereochemical assignment of triol **35** and **36**.

The final stage of synthesis required the deprotection of the AB ring moiety and detachment of the TBS groups, followed by an intramolecular double acetalization. To achieve total synthesis of velutinol A, we carefully investigated appropriate acids for the construction of the cage like moiety and conversion of the AB ring moiety (Table 4), since the β,γ-dihydroxycarbonyl moiety and its structural equivalents would be easily aromatized.[24] Thus, after removal of the TBS groups by nBu$_4$NF, the resulting crude diol was treated with AcOH (Entry 1) or 1 M HCl (Entry 2) at room temperature. However, these treatments resulted in no reaction. The final desired product was then obtained in 7% when TsOH was used at reflux condition (Entry 3). These results suggested that conversion to the AB ring moiety would need stronger acid, and the β,γ-dihydroxycarbonyl moiety and its structural equivalents resist aromatization in these strong acidic condition. After some optimization of reaction conditions, the conversion of the AB ring moiety, detachment of the TBS groups, and the intramolecular double acetalization were achieved using a strong acid. Thus, exposure of the mixture of **33** and **34** to $HClO_4$ in 1,4-dioxane/H_2O provided velutinol A (**1**) in 88% yield (Entry 4).

The final product was identical to an authentic sample.[8] It should be noted that addition of conc. HCl aq. was essential for obtaining the acetalized (cage-like) structure before purification

Table 4. Investigation of final stage.



Entry	acid	Temp.	Time	Yield/%
1	AcOH	rt	1 d	No reaction
2	1 M HCl	rt	1 d	No reaction
3	TsOH	Reflux	2 h	7
4[a]	$HClO_4$	rt	2 h	88[b]

[a] $HClO_4$ was directly added to the mixture of **33** and **34** without using nBu$_4$NF. [b] conc. HCl aq. was needed to observe velutinol A in NMR measurement, also see below.

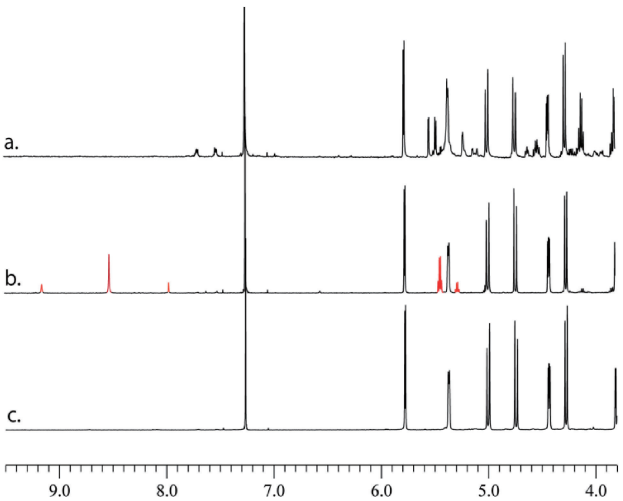


Figure 8. $CDCl_3$, 500 MHz for ^{1}H NMR spectra (9.5–3.8 ppm) of; a) reaction crude, b) products after the purification of reaction crude by silica gel, and c) product after addition of conc. HCl aq. to the purified products.

by silica gel, as shown in Figure 8. In the absence of this acid treatment, peaks assignable to *hemi*-acetal protons (the red peaks at ~5.25 ppm and ~5.45 ppm) and hydroxy proton of *hemi*-acetal shifted to low magnetic field by hydrogen bonding (~9.18 ppm, ~8.55 ppm, and ~7.98 ppm) were detected as shown in Figure 8b.

Synthesis of the Pentalinonside Aglycon.[15] *Pentalinon andrieuxii* Mueller-Itrgoviensis, a native Mexican plant growing in the Yucatan Peninsula, has been used as a Mayan folk medicine for the treatment of cutaneous leishmaniasis lesions. As part of the discovery of naturally occurring anti-leishmania agents, pentalinonside (**37**, Figure 9), a novel polyoxygenated 14,15-*seco*-pregnane with a β-diginosyl group at C3 and cage-like DEF-rings, was isolated from the hexane-soluble extract of the roots of *P. andrieuxii* in 2012.[11] Although isolated from

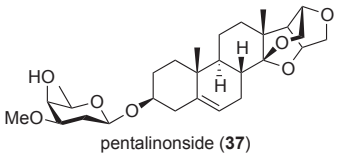
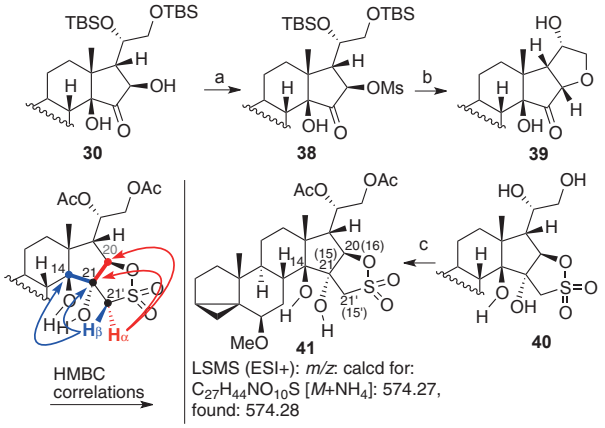


Figure 9. Structure of pentalinoside (**37**).

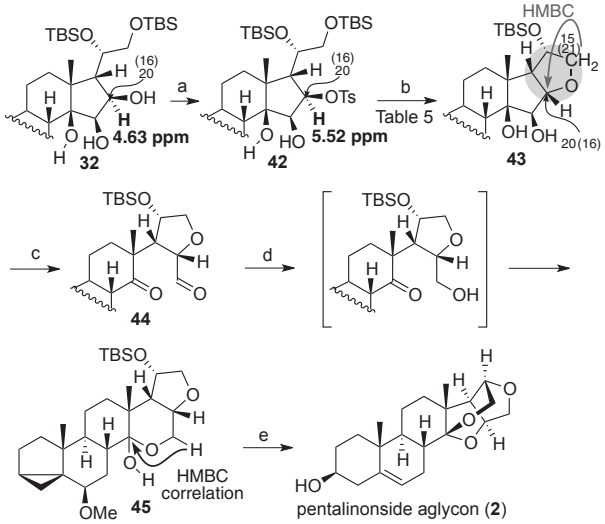


Scheme 9. Unsuccessful route for F-ring formation. *Reagents and conditions*: a) MsCl, pyridine, rt, 2.5 h, 88%; b) nBu$_4$NF, THF, rt, 12 h, **39**: 0%, **40**: 45%; c) pyridine, Ac$_2$O, rt, 10 min, 86%. Ms = methanesulfonyl.

bioactive extracts, pentalinonside (**37**) does not exhibit anti-leishmania activity. However, due to its structural similarity to velutinol A (**1**), our main goal was the synthesis of the pentalinonside aglycon (**2**), even though the biological activities of pentalinonside (**37**) have not yet been specified.

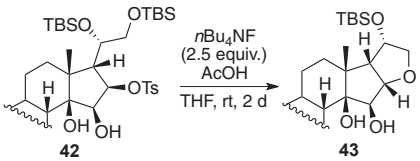
As shown in our retrosynthetic analysis (vide ante, Scheme 2), the synthesis begins from α,α-dihydoxyketone **30** (Scheme 9). To construct the E-ring moiety via 5-*exo*-cyclization, the C20(16)-hydroxy group was mesylated. Unfortunately, removal of the TBS groups of ketone **38** by nBu$_4$NF resulted in the formation of an oxatholanedioxide ring to afford **40** instead of **39** in 45% yield.[33] The structure of **40** was confirmed by heteronuclear multiple bond correlation (HMBC) experiments of diacetate **41**, easily accessible from compound **40**. After protection of the 15(21), 16(20)-dihydroxy groups as acetyl groups (86%), the HMBCs of **41** were measured. HMBC from H21′α to C20(16)/C21(15) and from H21′(15′)β to C14/C21(15) indicated the formation of an oxatholanedioxide ring, and this was further supported by mass spectrometry.

To prevent annulation, triol **32** was used as the starting material and the *p*-toluenesulfonyl (Ts) group was attached to the C20(16) hydroxy group (Scheme 10). The first step was regioselective installation of the tosyl group at C20(16). We anticipated that the nucleophilicity of the hydroxy group at C21(15) is weaker than that of C20(16) because of neighboring group participation from the C14 hydroxy group. Therefore, triol **32** was treated with TsCl in the presence of 4-dimethylaminopyridine (DMAP) in CH_2Cl_2, which gave tosylate **42** as a sole product in a 93% yield. The ^{1}H NMR value assigned to H20(16) was shifted from 4.63 ppm to 5.52 ppm after tosylation, confirming installation of the Ts group at the C20(16) hydroxy group.



Scheme 10. Synthesis of pentalinonside aglycon (**2**). *Reagents and conditions*: a) TsCl, DMAP, CH_2Cl_2, rt, 2 h, 93%; b) nBu$_4$NF/AcOH (1:2), THF, reflux, 2 h, 71%, yields and conditions see Table 5; c) $NaIO_4$, THF/H_2O (1:1), rt, 5 h, 81%; d) $NaBH_4$, MeOH, 0 °C, 10 min, 71%; e) $HClO_4$, 1,4-dioxane/H_2O (5:4), rt, 2 h, 95%. Ts = toluenesulfonyl, DMAP = 4-dimethylaminopyridine.

Table 5. Optimization of the *exo*-cyclization for the construction of F-ring.



Entry	AcOH/equiv.	Yield/%	
		43	**42** (recovery of s. m.)
1[a]	—	—	—
2	2.5	32	35
3	5.0	46	35
4[b]	5.0	71	—

[a] Triol **46** and tetrol **47** were obtained in 89% and 9%, respectively. [b] The reaction was performed under reflux conditions for 2 h.

Table 5 summarizes the optimization process of the key 5-*exo*-cyclization reaction for construction of the F-ring. First, nBu$_4$NF was used not only for removal of the TBS groups but also as a weak base for the intramolecular S_N2-type reaction (Entry 1). Despite quantitative conversion of **42**, E2-elimination was the major reaction instead of F-ring annulation, affording triol **46** (89%) and tetrol **47** (9%, Figure 10). For triol **46**, the hydroxide at C16(20) generated by fluoride attack on the silyl-group assisted E2-elimination (path a.), and for tetrol **47**, protonation of the hydroxide at C16(20) prevented E2-elimination (path b.). These results suggested that selective desilylation at C15(21), and not at C16(20), would prevent E2-elimination and activation of the tosylate to induce S_N1 and provide desired product **43**. For this purpose, diol **11** was treated with nBu$_4$NF in the presence of AcOH (Entries 2–5).

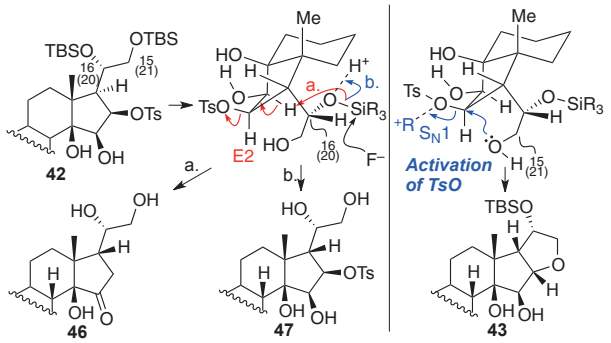


Figure 10. Reaction pathway to byproducts **46** and **47**.

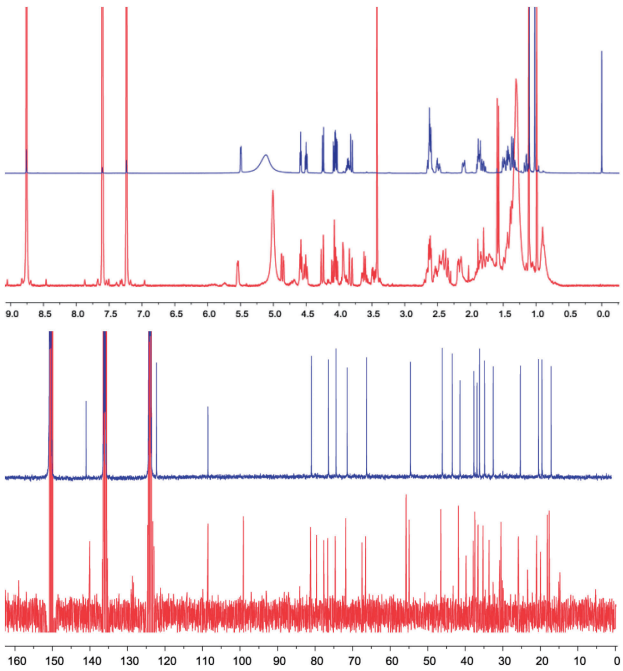


Figure 11. ^{1}H NMR and ^{13}C NMR spectra of synthetic aglycon (blue, 500 MHz for ^{1}H- and 125 MHz for ^{13}C NMR, pyridine-d_5) and natural pentalinonside (red, 400 MHz for ^{1}H- and 100 MHz for ^{13}C NMR, pyridine-d_5).

The desired product **43** was obtained in 32% yield, concomitant with the recovery of **42** in 35% yield when 2.5 equiv. of AcOH were used (Entry 2). Addition of 5.0 equiv. of AcOH raised the yield of **43** to 46% (Entry 3). Finally, refluxing for 2 h in the presence of 5.0 equiv. of AcOH gave **43** in 71% yield (Entry 4). The structural elucidation of compound **43** was established based on the HMBC between H15(21) and C20(16).

Oxidative cleavage of the C14–21(15) bond of compound **43** was achieved using $NaIO_4$ to afford keto–aldehyde **44** (81%, Scheme 10). The C20(16)-oxo group in **44** was selectively reduced using $NaBH_4$ at 0 °C to give hemi-ketal **45** [71%, confirmed by HMBC correlation between H21(15) and C14]. The final conversion was achieved with $HClO_4$ to give pentalinonside aglycon (**2**) in 95% yield. The structure of **2** was confirmed by comparing the ^{1}H NMR and ^{13}C NMR spectra of the synthetic aglycon and authentic pentalinonside (Figure 11 and Table 6).[11] The NMR peaks of **2** were analogous to those of pentalinonside (**37**), except for those assigned as H2–H4 and C2–C4, which are the positions adjacent to the glycoside bond.

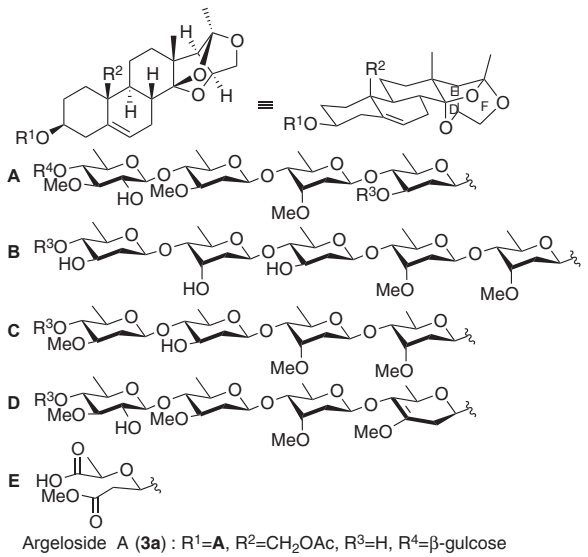
Table 6. ^{13}C- and ^{1}H NMR spectroscopic data of the natural pentalinonside and synthetic aglycon (**2**).

Position	natural pentalinonside[a] δ_C [ppm]	natural pentalinonside[a] δ_H [ppm] (J [Hz])	synthetic aglycon[b] δ_C [ppm]	synthetic aglycon[b] δ_H [ppm] (J [Hz])
1	37.5	α 1.05 m β 1.75 m	37.7	α 1.18–1.10 m β 1.90–1.83 m
2	30.4	α 2.13 m β 1.68 m	**32.5**	α 2.13–2.06 m β **1.83–1.73** m
3	77.3	3.90 m	**71.2**	**3.89–3.81** m
4	39.4	α 2.59 m β 2.40 m	**43.4**	α and β **2.63–2.58** m
5	139.7	—	140.4	—
6	122.6	5.52 t (2.5)	121.8	5.49–5.45 m
7	25.5	2.40 m 2.50 m	25.4	2.52–2.44 m 2.66–2.60 m
8	36.2	1.85 m	36.2	1.89–1.84 m
9	46.1	1.42 m	46.0	1.45–1.40 m
10	41.4	—	41.3	—
11	20.6	α and β 1.43 m	20.5	1.34–1.28 m 1.52–1.46 m
12	34.9	α 1.38 m β 1.67 m	34.8	α 1.38–1.32 m β 1.49–1.43 m
13	37.1	—	36.8	—
14	108.2	—	108.1	—
15	74.3	α 4.02 dd (10.0, 4.4) β 4.23 d (10.0)	74.2	α 4.03 dd (10.1, 4.6) β 4.23 d (10.1)
16	80.9	4.56 t (4.5)	80.7	4.57 t (4.6)
17	54.6	2.60 dd (7.6, 4.4)	54.5	2.61 dd (8.0, 4.6)
18	17.3	1.08 s	17.2	1.10 s
19	19.6	0.97 s	19.6	1.02 s
20	76.3	4.49 ddd (7.6, 6.0, 1.5)	76.2	4.49 ddd (8.0, 5.8, 1.2)
21	66.2	α 4.05 dd (12.4, 6.0) β 3.79 dd (12.4, 1.3)	66.1	α 4.06 dd (12.6, 5.8) β 3.80 dd (12.6, 1.2)

[a] pyridine-d_5, 400 MHz for ^{1}H- and 100 MHz for ^{13}C NMR, see ref 10. [b] pyridine-d_5, 500 MHz for ^{1}H- and 125 MHz for ^{13}C NMR.

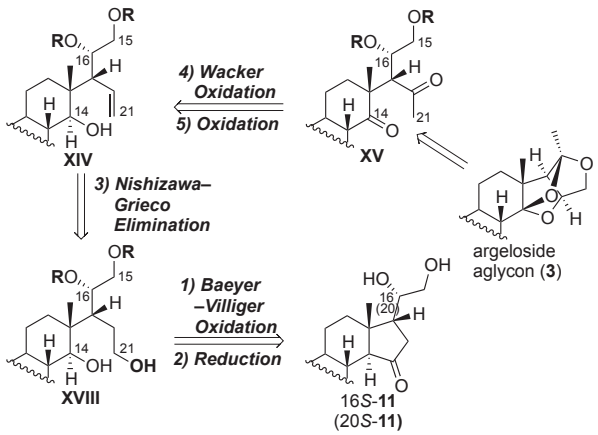
Synthesis of the Argeloside Aglycon.[16] More than ten 14,15-*seco*-pregnane glycosides with a cage-like structure in the DEF-rings, generally referred to as "argelosides", were recently isolated from the alcoholic extracts of the leaves and hairy seeds of the Egyptian medicinal plant *Solenostemma argel* Hayne (Asclepiadaceae, Figure 12).[12,34]

This plant grows in the eastern desert and along the Nile in southern Egypt.[35] Some argeloside congeners have potent anti-inflammatory activities, as evaluated by their inhibition in LPS-stimulated RAW 264.7 mouse cells of the release of TNF-α, a potent pro-inflammatory cytokine capable of inducing an inflammatory response.[12b] On the other hand, the aglycon of the argeloside, which is structurally similar to velutinol A, has not been isolated from natural sources.[12,36] Thus, we focused our attention on the aglycon of argeloside.



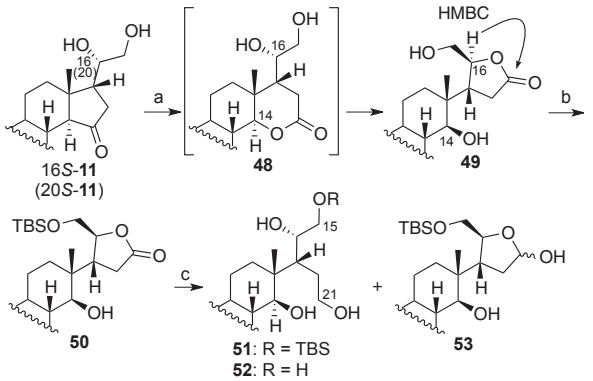
Argeloside A (**3a**) : R^1=**A**, R^2=CH_2OAc, R^3=H, R^4=β-gulcose
B (**3b**) : R^1=**B**, R^2=CH_2OAc, R^3=β-gulcose
C (**3c**) : R^1=**A**, R^2=Me, R^3=Me, R^4=H
D (**3d**) : R^1=**A**, R^2=CH_2OH, R^3=Me, R^4=H
E (**3e**) : R^1=**A**, R^2=CH_2OAc, R^3=Me, R^4=H
F (**3f**) : R^1=**A**, R^2=Me, R^3=H, R^4=β-gulcose
G (**3g**) : R^1=**A**, R^2=Me, R^3=Me, R^4=β-gulcose
H (**3h**) : R^1=**A**, R^2=CH_2OAc, R^3=Me, R^4=β-gulcose
I (**3i**) : R^1=**A**, R^2=Me, R^3=H, R^4=H
J (**3j**) : R^1=**A**, R^2=CH_2OAc, R^3=H, R^4=H
K (**3k**) : R^1=**C**, R^2=Me, R^3=β-gulcose
L (**3l**) : R^1=**C**, R^2=CH_2OAc, R^3=β-gulcose
M (**3m**): R^1=**A**, R^2=CH_2OH, R^3=Me, R^4=β-gulcose
N (**3n**) : R^1=**D**, R^2=CH_2OH, R^3=β-gulcose
O (**3o**) : R^1=**E**, R^2=Me

Figure 12. Structure of argelosides.

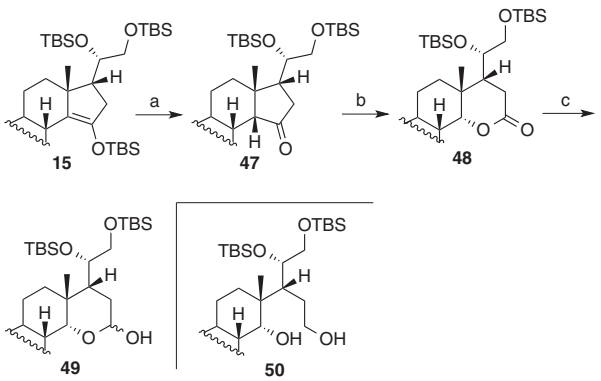


Scheme 11. Details of the synthetic strategy.

Scheme 11 details a synthetic strategy to the final structure **3** from diol 16*S*-**11** (20*S*-**11**). The oxo groups in compound **XV** at the C14 and 20 positions could respectively be constructed by the oxidation of C14-OH and Wacker oxidation[20] of Δ^{20} in olefin **XIV**, easily accessible from diprotected-tetrol **XVIII** through Nishizawa–Grieco elimination.[37] From this retrosynthetic analysis, it is obvious that the crucial point in accessing compound **XVIII** is the discrimination of *prim*-alcohols C15-OH, C21-OH/*sec*-alcohols C14-OH, and C16-OH before or after Baeyer–Villiger oxidation of diol 16*S*-**11**. In particular, the discrimination of C15-OH and C21-OH is more important because steric hindrance around the secondary alcohol at C14



Scheme 12. Investigation of the synthetic route to argeloside aglycon (**3**). *Reagents and conditions*: a) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 1 d, 77%; b) TBSCl, imidazole, DMF, 0 °C, 20 min, 97%; c) $LiAlH_4$, THF, 0 °C, 1 min, 60% for **52**, 28% for **53**.

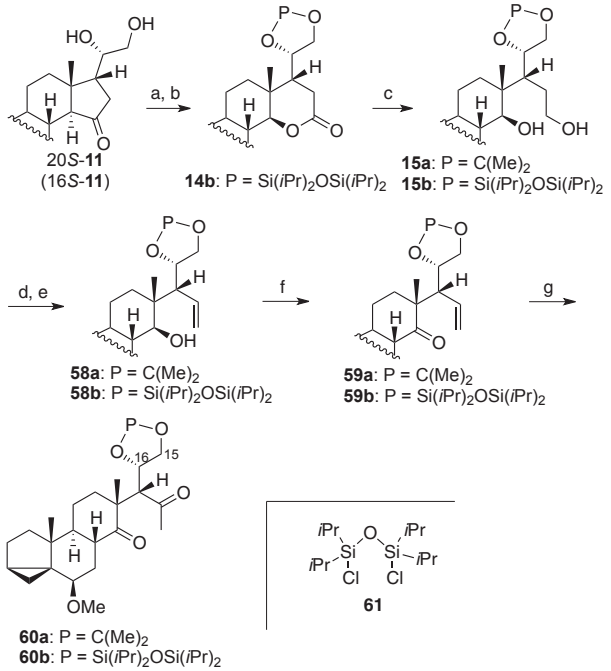


Scheme 13. Unsuccessful synthetic route to the argeloside aglycon (**3**). *Reagents and conditions*: a) 1 M HCl, THF, 0 °C, 2 h, 80%; b) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 2 d, 55%; c) $LiAlH_4$, THF, 0 °C to rt, 1 d, 96%.

is considerably different from that of C16, allowing these alcohols to be distinguished.

With these points in mind, we started the synthesis with the diol 16*S*-**11** (Scheme 12). Treatment of diol 16*S*-**11** with *m*CPBA gave lactone **49** equipped with the distinguished secondary alcohols at C14 and C16 in 77% yield via intermolecular lactone exchange of the Baeyer–Villiger oxidation product **48**. The structure of lactone **49** was established from the 2D-NMR spectrum, with the HMBC between H15 and C21 indicating the formation of γ-lactone, as illustrated in Scheme 12. After selective protection of the primary alcohol moiety at C15 as TBS, the resulting lactone **50** was reduced by $LiAlH_4$ to afford tetrol **52** in 60% yield and lactol **53** in 28% yield, instead of the desired triol **51** (with the primary alcohols at C15 and C21 distinguished). To obtain the triol **51**, other reducing agents were examined but resulted in the formation of lactol **53** as the sole product (e.g., Dibal-H, 63%; Red-Al, 87%; $LiBH_4$, 99%). Thus, we decided to abandon this synthetic route.

As an alternative synthetic route, we utilized the enol **21**, the intermediate in velutinol A (**1**) synthesis (Scheme 13). The silyl enol ether moiety of **21** was selectively hydrolyzed with

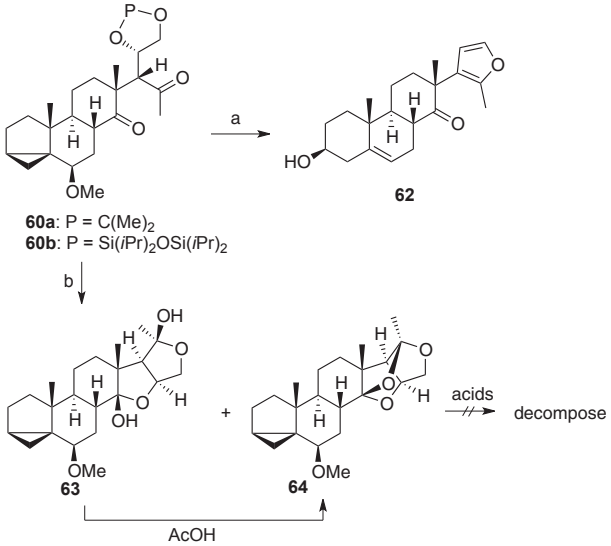


Scheme 14. Investigation of the protecting group for 20,21-diol moiety of 20*S*-**11**. *Reagents and conditions*: a) disilyl-ether **61**, imidazole, DMF, rt, 30 min, 82%; b) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 3 d, 56% (19% recovery); c) $LiAlH_4$, THF, 0 °C, 2 h, 99%; d) 2-nitrophenylselenyl cyanide, nBu_3P, THF, rt, **a**: 20 min, 96%; **b**: 3 h, quant.; e) 30% H_2O_2 aq. THF, rt, **a**: 3.5 h, 98%; **b**: 3 h, quant.; f) TPAP, NMO, CH_2Cl_2, rt, **a**: 1 d, 96%; **b**: 5 h, 90%; g) cat. $PdCl_2$, CuCl, O_2, DMF/THF/H_2O, rt, **a**: 20 min, 95%; **b**: 6 h, 55%.

1 M aq. HCl in THF to afford the 15-ketone **54** with *cis*-fused CD-rings in 80% yield. Baeyer–Villiger oxidation of ketone **54** was examined by treatment with *m*CPBA in the presence of $NaHCO_3$ to give lactone **55** in 55% yield. Unfortunately, the reduction of lactone **55** provided only lactol **56**, the *semi*-reduced product, which was resistant to further reduction to the desired 14,21-diol **57**.[38] These results suggest that *cis*-fused lactol moiety in compound **56** is extremely stable which might prevent equilibration with hydroxy-aldehyde derivatives. We therefore examined strategies for the preparation and reduction of the *trans*-fused lactone. For preparing the *trans*-fused lactone, appropriate conditions and a protecting group for 15,16-diol moiety to prevent enolization of the 15-ketone were required.

Actually, the acetonide was an option for protecting the diol moiety as shown in Scheme 5 (vide ante), which led to difficulty of deprotection in acidic conditions because of aromatization. Thus, towards the accomplishment of the synthesis, bis-silyl ether was also chosen for the protection of diol moiety (Scheme 14).

After the diol moiety of compound 20*S*-**11** was protected as bis-silyl ether (82%) by using **61**, treatment with *m*CPBA of the resulting ketones possessing *trans*-fused CD-rings afforded the lactones **14b** (56%). With the requisite lactones **14b** with *trans*-fused CD-rings in hand, reduction of **14b** with $LiAlH_4$ cleanly gave diol **15b** (99%).

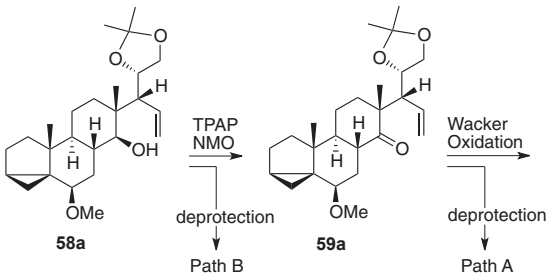


Scheme 15. Conversion of **60** towards the argeloside aglycon (**3**). *Reagents and conditions*: a) $HClO_4$, 1,4-dioxane/H_2O, rt, 2 h, 68%; b) nBu_4NF, AcOH, THF, rt, 6 h, then AcOH, 66%.

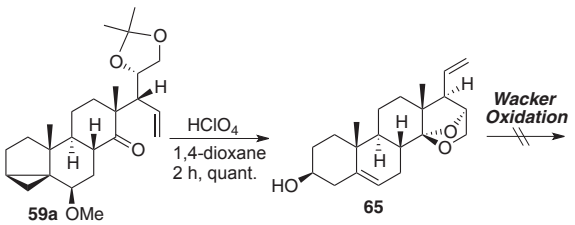
The next stage was the selective dehydration of the primary alcohol at C15 using the Nishizawa–Grieco method.[34] Thus, after treatment of the alcohols **15a** and **b** with 2-nitrophenyl-selenyl cyanide in the presence of nBu_3P, the resulting selenides were exposed to 30% hydrogen peroxide, providing olefins **58a** and **58b** in 84% and 100% yield, respectively (two steps). Ketones **59a** and **b**, resulting from TPAP oxidation of the C14-OH in olefins **58a** and **b**, were treated with catalytic amounts of $PdCl_2$ and CuCl in an O_2 atmosphere (Wacker oxidation[20] conditions) to introduce an oxo group at C20 to yield diketones **60a** (91%, two steps) and **60b** (50%, two steps). It should be noted that the reactivity of the reactants in the Baeyer–Villiger reaction, reduction, and Wacker oxidation were strongly influenced by the steric hindrance of the 15,16-diol protecting groups.

To remove the acetonide and restore the hydroxy group at C3 and Δ^5 from the 3,5-cyclo-6-methoxy protection, the diketone **60a** was treated with $HClO_4$ (Scheme 15). Unfortunately, this treatment only resulted in the undesirable formation of furan **62** instead of argeloside aglycon (**3**). Other acids, such as TsOH, HCl, pyridinium *para*-toluenesulfonate, and trifluoroacetic acid (TFA) were also examined in an effort to obtain the desired product **3**; however, all the acidic conditions only induced the decomposition of **60a**. Therefore, although a strong acid was needed for removal of the acetonide moiety, the β,γ-diol ketone moiety appeared to be unstable under the strongly acidic conditions.

In an alternative route, the bis-silyl ether moiety of compound **60b** was removed by using nBu_4NF in the presence of AcOH to afford two separable products, **63** and **64**. Because bishemiketal **63** was easily converted to **64** by exposure to AcOH, **60b** was directly converted to **64** in 66% yield by the addition of excess AcOH after treatment of **60b** with nBu_4NF/AcOH. However, against our expectations, final conversion of the AB-ring moiety using acids such as TsOH, TFA, and $HClO_4$ led to a complex mixture, and furan **62** was the only



Scheme 16. Remaining choices for the final approach to argeloside aglycon.



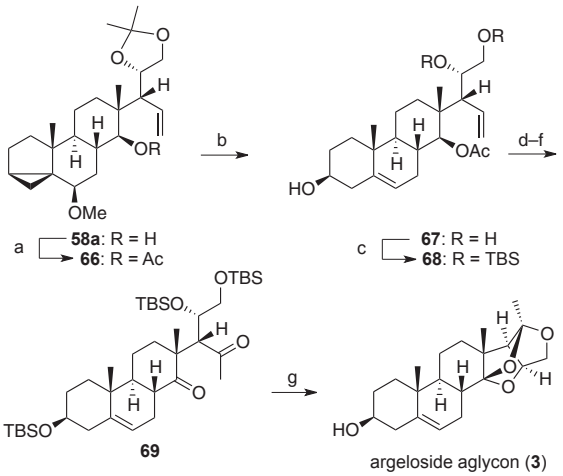
Scheme 17. Deprotection of **59a** in advance of Wacker oxidation (Path A).

identifiable product. Further investigations revealed that the DEF-ring moiety in **64** was as unstable as the β,γ-diol ketone moiety in **60** under the acidic conditions required for recovery of the hydroxy group at C3 and Δ^5 from the 3,5-cyclo-6-methoxy moiety. Our results suggest that the oxo group at C20 causes decomposition or aromatization. Therefore, we concluded that reconsidering the synthetic route or another alternative deprotection process would be necessary to obtain the argeloside aglycon.

As described above, the γ-dihydroxyketone moiety in the seco-E ring did not tolerate the acidic conditions necessary for the recovery of the 3β-hydroxy-5-ene moiety in the AB ring from the 6β-methoxy-3,5-cyclopropane moiety, being converted to the furan moiety or a complex mixture. Thus, the AB ring moiety was deprotected in a step prior to Wacker oxidation (Path a) or TPAP oxidation (Path B) before the generation of the acid-sensitive tricyclic cage-like moiety (Scheme 16).

We first investigated removal of the acetonide and conversion of the AB-rings before constructing the oxo group at C20 (Scheme 17). Treatment of ketone **59a** with $HClO_4$ resulted in the formation of internally ketalized product **65** in quantitative yield. This result suggested that deprotection should be performed in advance of Wacker oxidation. However, subsequent Wacker oxidation led to decomposition of the product.

After several fruitful and thorough investigations, we were pleased to identify a successful synthetic route to access argeloside aglycon (**3**, Scheme 18). Following protection of the C14-hydroxy group of **58a** as acetyl (89%), removal of the diol protecting groups and restoration of the 3-hydroxy group and Δ^5 in the AB-ring moiety were achieved by using $HClO_4$ (90%). The resulting triol **67** was then reprotected with the TBS groups (80%), followed by removal of the acyl group using $LiAlH_4$ to give the corresponding alcohol (80%). The C14-hydroxy group of this alcohol was oxidized via TPAP oxidation[29] to give the corresponding ketone in 81% yield. The subsequent Wacker oxidation of $\Delta^{20,38}$ afforded diketone **69**.



Scheme 18. Successful route to aglycone (**3**, Path B). *Reagents and conditions*: a) Ac_2O, DMAP, pyridine, rt, 1 h, 89%; b) $HClO_4$, 1,4-dioxane/H_2O, rt, 2 h, 90%; c) TBSOTf, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h, 80%; d) $LiAlH_4$, THF, 0 °C to rt, 8.5 h, 80%; e) TPAP, NMO, CH_2Cl_2, rt, 2 h, 81%; f) cat. $PdCl_2$, CuCl, O_2, DMA/H_2O, rt, 5 h, 69%; g) nBu$_4$NF, THF, rt, 1 d then AcOH, 74%. DMA = *N*,*N*-dimethylacetoamide.

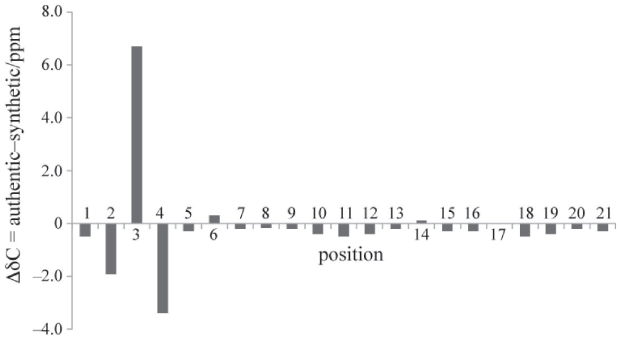


Figure 13. ΔδC value of authentic argeloside C aglycon and synthetic aglycon.

The final stage of the synthesis required removal of the three TBS groups and an intramolecular double ketalization. The reaction conditions used for the conversion of **63** to **64** (vide ante, Scheme 15) provided useful information for these present conversions. Thus, after confirming removal of all the TBS groups by nBu$_4$NF treatment by NMR, intramolecular double ketalization was achieved by treating the resulting polar products with AcOH to afford compound **3** in 86% yield in one pot.

The structure of **3** was elucidated through comparison of the ^{1}H and ^{13}C NMR spectroscopic data with those of the aglycon portion of argeloside C (**3c**, vide ante, Figure 13).[12c] As shown in Figure 13, the ΔδC (= ^{13}C NMR δ of authentic argeloside C aglycon – ^{13}C NMR δ of synthetic aglycon) value of each carbon indicated that the ^{13}C NMR peaks of **3** were analogous to those of argeloside C (**3a**), except for those assigned as C2–C4, which are the positions adjacent to the glycoside bond.

Synthesis of Illustrol and Its Glycoside.[17] In 1993, illustrol (**4**) was isolated from hydroalcoholic extracts of the rhizomes of *Mandevilla illustris* Vel. Woodson (Apocynaceae), a native Brazilian plant used in folk medicine to treat inflam-

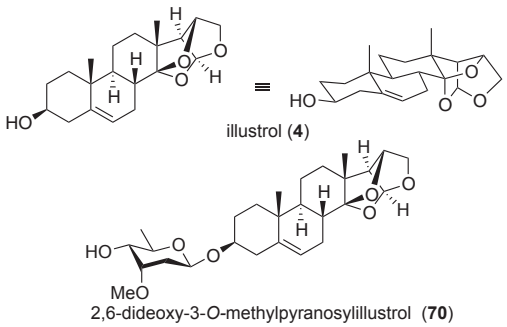
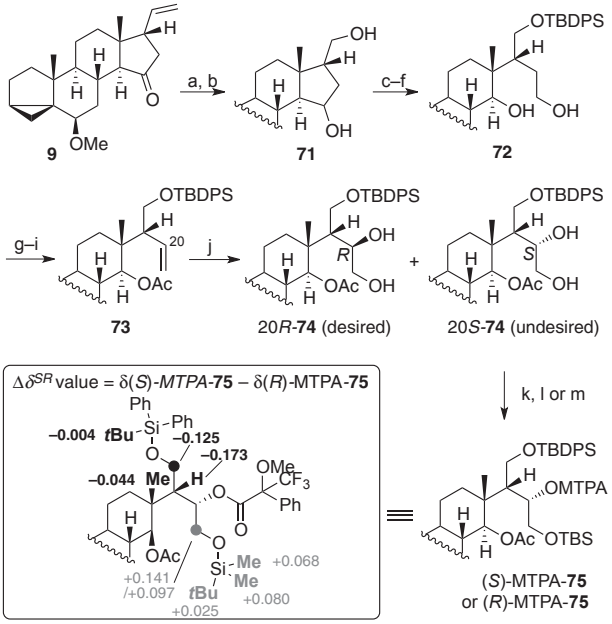


Figure 14. Structures of illustrol (**4**) and its glycoside **70**.

mation and snake bites.[39] Illustrol (**4**, Figure 14), consisting of a 14,15-*seco*-15-*nor*-pregnane core with a cage-like framing of DEF-rings, is structurally related to the selective B1R antagonist velutinol A. However, although illustrol was isolated from extracts of the rhizomes of *M. illustris* and shows an antagonistic effect to bradykinin-induced responses,[40] and despite its structural similarity to the B1R antagonist velutinol A (**1**),[13] illustrol does not exhibit significant biological activity. On the other hand, 2,6-dideoxy-3-*O*-methylpyranosylillustrol (**70**), isolated from ethyl acetate extracts of the rhizomes of *M. illustris*, was found to inhibit rat paw edema induced by carrageenan, dextran, and the B1R agonist des-Arg-9-bradykinin,[7] without affecting edema caused by bradykinin B2R agonists.[41] From these results, we believe that compound **70** is a B1R-selective non-peptide antagonist.

On the basis of our retrosynthetic analysis (vide ante, Scheme 2), we first synthesized olefin **73** and investigated the diastereoselectivity of its dihydroxylation (Scheme 19). Following oxidative cleavage and construction of the 15-*nor*-structure of olefin **9** by using OsO_4–$NaIO_4$ (71%), the resulting keto–aldehyde was reduced to diol **71** with $NaBH_4$ in 94% yield. The primary alcohol of **71** at C16 was protected as TBDPS (88%), and subsequent oxidation of the remaining secondary alcohol at C21 via TPAP[24] (92%) gave the corresponding 21-keto-derivative (92%). Baeyer–Villiger oxidation of the 21-keto-derivative using *m*CPBA achieved construction of the *seco*-structure to afford the corresponding lactone in 87% yield, followed by reduction to diol **72** using $LiAlH_4$ (86%). Diol **72** was easily converted to the olefin **73** via Nishizawa–Grieco elimination[37] (80% for 2 steps), followed by protection of C14-OH as Ac (91%).

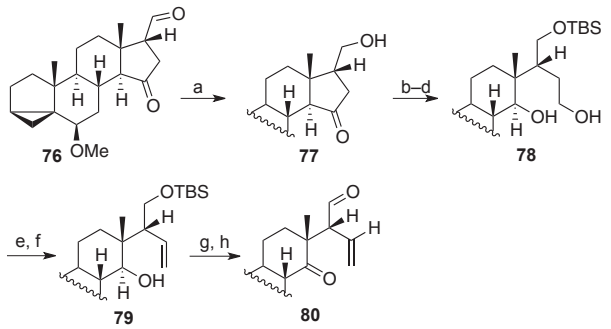
With the requisite olefin **73** in hand, we investigated its dihydroxylation. Thus, olefin **73** was treated with a catalytic amount of OsO_4 in the presence of a stoichiometric amount of NMO at room temperature for 10 h to give a mixture of undesired diol 20*S*-**74** and desired diol 20*R*-**74** in 60% yield with a diastereoselectivity of 5.9:1, along with 28% recovery of the starting material. Structural determination of the major diastereomer 20*S*-**74** was established as follows. After protection of the C20-OH in compound 20*S*-**74** as TBS, the resulting alcohol was treated with (*S*)-MTPACl or (*R*)-MTPACl in the presence of DMAP to give (*S*)- and (*R*)-MTPA-**75** in 80% and 72% yield, respectively, and the $\Delta\delta^{SR}$ value [= δ(*S*)-MTPA-**75** − δ(*R*)-MTPA-**75**] was calculated.[30] The $\Delta\delta^{SR}$ value shown in Scheme 19 determined the absolute configuration of C20 in the major diastereomer **74** to be *S*.



Scheme 19. Unsuccessful route toward illutsrol (**4**). *Reagents and conditions*: a) OsO_4, $NaIO_4$, 1,4-dioxane, H_2O, rt, 6 h, 71%; b) $NaBH_4$, MeOH, rt, 70 min, 94%; c) TBDPSCl, imidazole, DMF, 0 °C, 3.3 h, 88%; d) cat. TPAP, NMO, CH_2Cl_2, rt, 1 h, 92%; e) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 12 h, 87%; f) $LiAlH_4$, THF, 0 °C, 2.5 h, 62%; g) 2-nitrophenylselenyl cyanide, nBu_3P, THF, rt, 70 min, 86%; h) H_2O_2, THF, rt, 1.7 h, 93%; i) Ac_2O, DMAP, CH_2Cl_2, rt, 4.3 h, 91%; j) cat. OsO_4, NMO, acetone, rt, 10 h, 61% (20*S*-**74**:20*R*-**74** = 5.9:1, recovery 28%); k) TBSCl, imidazole, DMF, rt, 1 h, 69%; l) (*S*)-MTPACl, DMAP, CH_2Cl_2, rt, 12 h, 80%; m) (*R*)-MTPACl, DMAP, CH_2Cl_2, rt, 12 h, 72%.

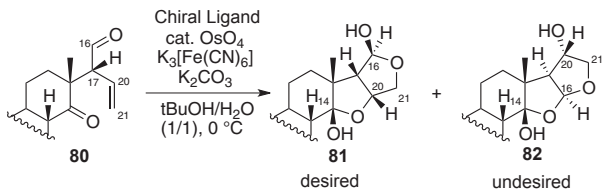
After the investigation of alternative promising routes, illustrol (**4**) was finally synthesized starting from keto–aldehyde **76** (Scheme 20). The formyl group of the ketoaldehyde was selectively reduced to alcohol with $NaBH_4$ at low temperature (−40 °C) to afford alcohol **77** in 68% yield and recovery of **76** (28%). After protection of the primary alcohol of **77** as TBS (98%), Baeyer–Villiger oxidation using *m*CPBA gave the corresponding lactone (88%), which was reduced with $LiAlH_4$ to afford diol **78** in 87% yield. Diol **78** was converted to olefin **79** via the Nishizawa–Grieco protocol.[37] Thus, diol **79** was treated with 2-nitrophenylselenyl cyanide and nBu_3P to give the corresponding selenide (95%); the selenium moiety was then oxidized by using 30% H_2O_2 to afford olefin **79** with concomitant *syn*-elimination of the resulting selenoxide (94%). After detachment of the TBS protecting group with nBu_4NF, Swern oxidation of the resulting diol afforded the desired ketoaldehyde **80** without epimerization of the C17 position. Notably, careful and rapid silica-gel column chromatography was critical for obtaining a good isolation yield of ketoaldehyde **80**, since otherwise the isolation yield of ketoaldehyde **80** was decreased due to decomposition.

With the requisite olefin **80** in hand, we performed asymmetric dihydroxylation (Table 7). First, olefin **80** was treated with a catalytic amount of OsO_4 in the presence of a stoichiometric amount of NMO at 0 °C to afford the desired diol **83** and



Scheme 20. Synthesis of olefin **80**. *Reagents and conditions*: a) $NaBH_4$, MeOH, −40 °C, 30 min, 68% (recovery 28%); b) TBSCl, imidazole, DMF, 30 min, 95%; c) *m*CPBA, $NaHCO_3$, CH_2Cl_2, rt, 1 d, 88%; d) $LiAlH_4$, THF, 0 °C, 30 min, 87%; e) 2-nitrophenylselenyl cyanide, nBu_3P, THF, 0 °C, 20 min, 95%; f) H_2O_2, THF, rt, 5 h, 94%; g) nBu_4NF, THF, rt, 10 min, quant.; h) DMSO, $(COCl)_2$, −78 °C, 8 h, 97%.

Table 7. Dihydroxylation of Δ^{20}.



Entry	Chiral Ligands	Time [h]	Yield [%] (**81**:**82**[b])
1[a]	—	14	quant. (59:41)
2	$(DHQ)_2PHAL$	22	77 (62:38)
3	$(DHQD)_2PHAL$	22	63 (65:35)
4	$(DHQ)_2PYR$	22	55 (73:27)
5	$(DHQD)_2PYR$	18	85 (**81** only)

[a] Solvent: acetone, reagents: cat. OsO_4, NMO. [b] 5:1 mixture of **82** and **84** by ^1H NMR analysis.

the undesired diol **84** (vide infra, Figure 15), which were spontaneously converted into compound **81** (59%) and **82** (41%), respectively, concomitant with double acetalization (Entry 1). Sharpless asymmetric dihydroxylation was also applied to olefin **80**.[21] Thus, treatment of olefin **80** with a stoichiometric amount of $K_3[Fe(CN)_6]$ and K_2CO_3 and a catalytic amount of OsO_4 in the presence of a catalytic amount of $(DHQ)_2PHAL$ at 0 °C afforded compound **81** and **82** in 48% and 29% yield, respectively (Entry 2). Surprisingly, the same selectivity was obtained even though $(DHQD)_2PHAL$, the diastereomer of $(DHQD)_2PHAL$, was used as the chiral ligand (Entry 3). The diastereomer ratio was raised to 73:27 when $(DHQ)_2PYR$ was used (Entry 4). Finally, perfect selectivity and high yield were achieved by using $(DHQD)_2PYR$ (Entry 5). Thus, treatment of olefin **80** with typical Sharpless asymmetric dihydroxylation conditions by using $(DHQD)_2PYR$ as the chiral ligand gave compound **81** in 88% yield and no detectable **82**.

The structures of **81** and **82** were confirmed by NOE and HMBC experiments For compound **81**, formation of a hexahydrofuro[3,4-*b*]furan skeleton was confirmed by HMBC correlation between H16 and C21 ($^3J_{CH}$) and between H21 and C14 ($^4J_{CH}$), and the stereochemistry at C14, C16, C17, and C20 was

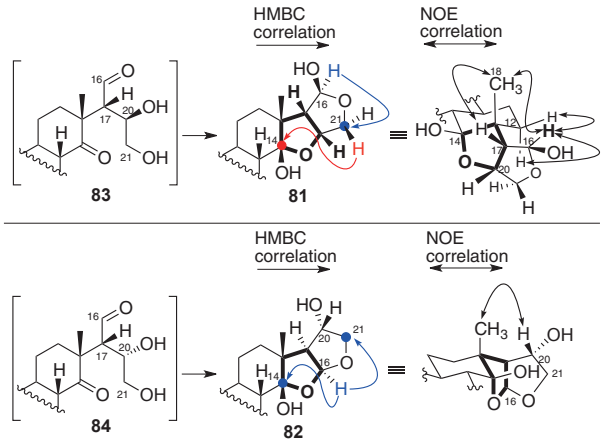
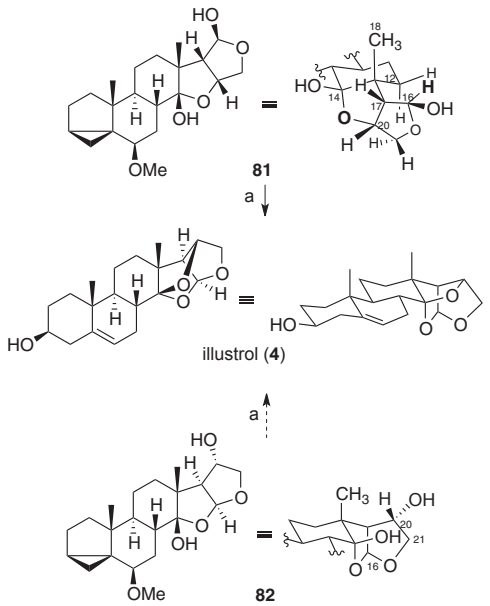


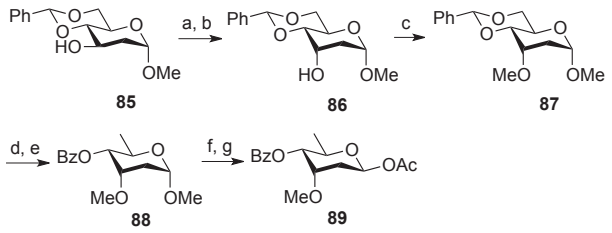
Figure 15. Structural determination of **81** and **82**.



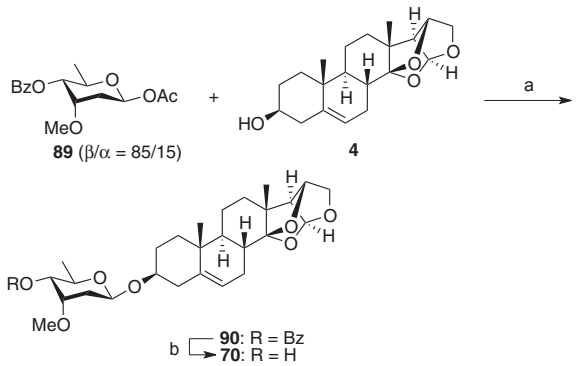
Scheme 21. Total Synthesis of illustrol. *Reagents and conditions*: a) $HClO_4$, 1,4-dioxane, H_2O, rt, 2 h, quant.

determined by NOE correlation between H16 and H12α/H12β. The structure of **81** was also supported with other evidence (i.e., NOE correlations between H16 and H18). For compound **82**, HMBC correlation between H16 and C14 and between H16 and C21 indicated the formation of a hexahydrofuro-[2,3-*b*]furan skeleton, and the NOE correlation between H18 and H20 established the stereochemistry at C20, as shown Figure 15.

The final step for the synthesis of illustrol (**4**), the construction of the DEF cage-like rings and concomitant conversion of the AB-rings, were achieved by the exposure of **81** to $HClO_4$, providing illustrol (**4**) in quantitative yield (Scheme 21). This synthetic product was identical to an authentic specimen.[13] It should be noted that compound **82** is structurally more similar to illustrol (**4**) than is **81** (see also Figure 15). Compound **82** was thus subjected to the same conditions as used for the conversion of **81** to illustrol (**4**). However, contrary to our expectation, the reaction resulted in the production of a complex mixture instead of illustrol (**4**).



Scheme 22. Synthesis of Sugar Moiety **89**. *Reagents and conditions*: a) TPAP, NMO, rt, 16 h, 70%; b) $NaBH_4$, MeOH, 0 °C, 20 min, 87%; c) MeI, NaH, DMF, 0 °C, 1 h, 99%; d) $BaCO_3$, NBS, CCl_4, 60 °C, 2 h, 83%; e) nBu$_3$SnH, AIBN, benzene, reflux, 40 min, 93%; f) AcOH, H_2O, reflux, 2 h; g) Ac_2O, pyridine, 30 min, 77% (β:α = 85:15, 2 steps). NBS = *N*-bromosuccinimide, AIBN = azobisisobutyronitrile.



Scheme 23. Total synthesis of glycoside of illustrol **70**. *Reagents and conditions*: a) $BF_3 \cdot OEt_2$, CH_2Cl_2, 0 °C to rt, 20 min, 71%; b) MeONa, MeOH, rt, 12 h, quant.

Scheme 22 shows the synthesis of the sugar moiety of **70**. Inversion of the 3-OH moiety of the known compound **85** derived from 2-deoxy-D-glucose[42] was established by a simple oxidation and reduction method using TPAP and $NaBH_4$ to afford compound **86** (61% yield for 2 steps). After protection of the 3-OH moiety as the methyl ether using MeI in the presence of NaH (99%), the 1,3-dioxane ring was cleaved by treatment with NBS (83%). The resulting bromobenzoate derivative was reductively debrominated with nBu$_3$SnH in the presence of AIBN to afford **88** in 93% yield. Hydrolysis and acetylation of the anomeric position gave compound **89** in a moderate yield (77% for 2 steps).

With the requisite illustrol (**4**) and compound **89** in hand, we synthesized 2,6-dideoxy-3-*O*-methylpyranosylillustrol (Scheme 23). The β-selective glycosidation of illustrol (**4**) was achieved by using 2,6-dideoxypyranoside **89** as the glycosyl donor. Thus, compounds **4** and **89** were treated with a catalytic amount of $BF_3 \cdot OEt_2$ at 0 °C for 20 min to give β-glycoside **90** as a sole product in 71% yield. The high stereoselectivity obtained may have resulted from hindrance of α-side attack at the C1′ position by electronic repulsion between the axially oriented α-OMe group at the C3′ position and the alcoholic oxygen. Removal of the benzoyl group of β-anomer **90** was accomplished with MeONa to afford 2,6-dideoxy-3-*O*-methylpyranosylillustrol (**70**) in a quantitative yield, and **70** was shown to be identical to an authentic specimen.[41,43]

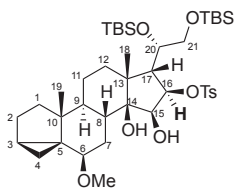
3. Conclusion

Syntheses of the non-peptide bradykinin B1 receptor antagonist velutinol A and its derivatives, the *seco*-pregnanes with cage-like moiety, have been accomplished. Construction of highly oxygenated structures were established by the combination of three of five oxidative processes: 1) Sharpless asymmetric dihydroxylation, 2) Rubottom oxidation, 3) Baeyer–Villiger oxidation, 4) Wacker oxidation, 5) Oxidative cleavage via $NaIO_5$. The syntheses of these aglycon derivatives may be useful for the structure-activity studies of non-peptide ligands for the bradykinin B1 receptor (B1R). Now, construction of an appropriate in vitro assay system for **1**–**4** is under investigation.

4. Experimental

General Method. All the experiments involving air- and moisture-sensitive compounds were conducted under an atmosphere of dry argon. Dichloromethane and *N*,*N*-dimethylformamide were distilled from CaH_2 and stored over 4 Å molecular sieves. Anhydrous tetrahydrofuran from Kanto Chemicals (water: 0.002%max) was directly used as solvent. For TLC analysis, Marck precoated plates (silica gel 60 F_{254}, art 5715, 0.25 mm) were used. For flash column chromatography, silica gel 60N (Spherical, neutral, 23–210 μm) from Kanto Chemicals was used. Melting point (M.p.) determinations were performed using a Yanako P-J3 instrument. ^{1}H and ^{13}C NMR spectra were recorded using a JEOL ECA-500 (500 MHz), or a Bruker Avance-400 (400 MHz) spectrometer in the solvent indicated; chemical shifts (δ) are given in ppm relative to tetramethylsilane and coupling constants (J) are reported in Hz. Multiplicities are described by the following abbreviations; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Attenuated total reflectance Fourier-transform infrared (ATR-FTIR) spectra were recorded using a Shimadzu IRAffinity-1 equipped with a Shimadzu MIRacle single reflection ATR accessory, wavenumbers ($\tilde{\nu}$) in cm^{-1}. Optical rotations ($[\alpha]_D$) were measured using a JASCO P-2300 polarimeter. High-resolution mass spectra (HRMS) were obtained with a Bruker micrOTOF II spectrometer (ESI+).

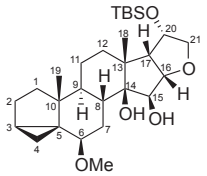
Compound 42.



TsCl (315.1 mg, 1.65 mmol) and DMAP (403.2 mg, 3.30 mmol) were added to a solution of compound **32** (103.3 mg, 0.165 mmol) in CH_2Cl_2 (3.0 mL) at room temperature. After stirring for 2 h, the reaction was stopped by adding water, and the mixture was extracted with EtOAc (×3). The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel hexane/EtOAc = 8:2) to afford compound **42** (120.0 mg, 93%) as a colorless oil whose ^{1}H NMR in $CDCl_3$ showed the contamination of ~6 mol% EtOAc. $[\alpha]_D^{20} = +27.7$ ($c = 0.200$, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$): $\delta = 7.86$ (d, $J = 8.1$ Hz, 2H, Ar***H***), 7.31 (d, $J = 8.1$ Hz, 2H, Ar***H***), 5.52 (t, $J = 7.9$ Hz, 1H, H-16), 3.68 (dd,

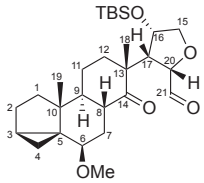
$J = 5.6$, 8,4 Hz, 1H, H-20), 3.30 (s, 3H, OC$\underline{\boldsymbol{H}_3}$-6), 4.39 (dd, $J = 5.2$, 7.9 Hz, 1H, H-15), 3.28 (dd, $J = 5.6$, 9.6 Hz, 1H, H-21), 3.24 (d, $J = 5.2$ Hz, O$\underline{\boldsymbol{H}}$-15), 3.10 (dd, $J = 8.4$, 9.6 Hz, 1H, H-21), 2.84 (t, $J = 2.9$ Hz, 1H, H-6), 2.81 (s, 1H, O$\underline{\boldsymbol{H}}$-14), 2.65 (d, $J = 7.9$ Hz, 1H, H-17), 2.43 (s, 3H, Ts), 2.17 (td, $J = 2.9$, 13.6 Hz, 1H, H-7), 1.98 (dt, $J = 2.9$, 12.3 Hz, 1H, H-8), 1.88–1.78 (m, 1H, H-2), 1.57 (dd, $J = 7.4$, 12.5 Hz, 1H, H-2), 1.52–1.44 (m, 2H, H-1 and H-7), 1.44–1.33 (m, 2H, H-11 and H-12), 1.32–0.99 (m, 3H, H-12, H-11 and H-9), 1.02 (s, 3H, H-18), 1.00 (s, 3H, H-19), 0.98–0.85 (m, 2H, H-3 and H-1), 0.89 (s, 9H, OSiC(C$\underline{\boldsymbol{H}_3}$)$_3$), 0.81 (s, 9H, OSiC(C$\underline{\boldsymbol{H}_3}$)$_3$), 0.62 (dd, $J = 3.7$, 5.0 Hz, 1H, H-4), 0.46 (dd, $J = 5.0$, 7.9 Hz, 1H, H-4), 0.05 (s, 3H, OSiC$\underline{\boldsymbol{H}_3}$), 0.03 (s, 3H, OSiC$\underline{\boldsymbol{H}_3}$), −0.07 (s, 3H, OSiC$\underline{\boldsymbol{H}_3}$), −0.09 ppm (s, 3H, OSiC$\underline{\boldsymbol{H}_3}$); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 144.7 (C$\underline{\boldsymbol{Ar}}$), 134.1 (C$\underline{\boldsymbol{Ar}}$), 129.7 (2C, C$\underline{\boldsymbol{Ar}}$), 127.9 (2C, C$\underline{\boldsymbol{Ar}}$), 82.0 (C-6), 81.5 (C-14), 78.6 (C-16), 69.6 (C-15), 69.5 (C-20), 65.8 (C-21), 56.5 (O$\underline{\boldsymbol{C}}H_3$-6), 52.5 (C-17), 43.9 (C-13), 43.7 (C-10), 43.4 (C-9), 35.8 (C-8), 35.3 (C-5), 33.7 (C-1), 32.7 (C-11), 29.6 (C-7), 26.2 (3C, OSiC($\underline{\boldsymbol{C}}H_3$)$_3$), 25.9 (3C, OSiC($\underline{\boldsymbol{C}}H_3$)$_3$), 25.0 (C-2), 21.9 (C-3), 21.6 (2C, OSO$_2$Ph-4-$\underline{\boldsymbol{C}}H_3$-16 and C-12), 19.4 (C-19), 18.3 (OSi$\underline{\boldsymbol{C}}$(CH$_3$)$_3$), 18.2 (OSi$\underline{\boldsymbol{C}}$(CH$_3$)$_3$), 18.1 (C-18), 13.2 (C-4), −3.2 (OSi$\underline{\boldsymbol{C}}H_3$), −4.6 (OSi$\underline{\boldsymbol{C}}H_3$), −5.4 ppm (2C, OSi$\underline{\boldsymbol{C}}H_3$); IR (ATR): $\tilde{\nu}$ = 3527, 3494, 3357, 2953, 2929, 2884, 2855, 1728, 1600, 1471, 1463, 1360, 1252, 1174, 1098, 1079, 1007, 899, 832, 813, 776, 757, 675 cm^{-1}; HRMS (ESI): m/z calcd for $C_{41}H_{74}NO_8SSi_2$ $[M + NH_4]^+$: 796.4668, found: 796.4672.

Compound 43.



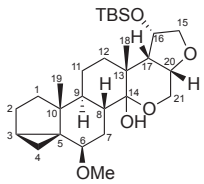
Tetrabuthylammonium fluoride (1.0 mol/L in THF, 1.2 mL, 1.2 mmol) and AcOH (0.14 mL, 2.35 mmol) were added to a solution of compound **42** (365.4 mg, 0.469 mmol) in THF (5.0 mL) at room temperature. After stirring for 2 h at 60 °C, the reaction was stopped by adding water, and the mixture was extracted with EtOAc (×3). The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 9:1) to afford compound **43** (163.5 mg, 71%) as a colorless oil. $[\alpha]_D^{20} = +26.1$ ($c = 0.340$, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$): δ = 4.74 (q, $J = 8.3$ Hz, 1H, H-20), 4.40 (brs, 1H, H-15), 4.21 (dd, $J = 1.9$, 7.2 Hz, 1H, H-16), 3.96 (t, $J = 8.3$ Hz, 1H, H-21), 3.62 (t, $J = 8.3$ Hz, 1H, H-21), 3.34 (s, 3H, OC$\underline{\boldsymbol{H}_3}$-6), 2.85 (t, $J = 2.9$ Hz, 1H, H-6), 2.81 (br s, 1H, O$\underline{\boldsymbol{H}}$-15), 2.77 (dd, $J = 7.2$, 8.3 Hz, 1H, H-17), 2.25–2.20 (m, 1H, O$\underline{\boldsymbol{H}}$-14), 2.20 (td, $J = 3.2$, 13.6 Hz, 1H, H-12), 2.11 (td, $J = 2.9$, 13.5 Hz, 1H, H-7), 1.96–1.87 (m, 1H, H-8), 1.85–1.73 (m, 1H, H-2), 1.65 (dt, $J = 4.0$, 13.6 Hz, 1H, H-12), 1.59–1.40 (m, 4H, H-1, H-2, H-7 and H-11), 1.39–1.27 (m, 1H, H-11), 1.27–1.16 (m, 1H, H-9), 1.19 (s, 3H, H-18), 1.02 (s, 3H, H-19), 0.96–0.84 (m, 2H, H-3 and H-1), 0.89 (s, 9H, OSiC(C$\underline{\boldsymbol{H}_3}$)$_3$-20), 0.65 (dd, $J = 3.7$, 5.0 Hz, 1H, H-4), 0.48 (dd, $J = 5.0$, 7.9 Hz, 1H, H-4), 0.07 (s, 3H, OSiC$\underline{\boldsymbol{H}_3}$-20), 0.03 ppm (s, 3H, OSiC$\underline{\boldsymbol{H}_3}$-20); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 92.6 (C-16), 86.4 (C-14), 82.0 (C-6), 79.3 (C-15), 74.6 (C-21), 74.2 (C-20), 56.6 (O$\underline{\boldsymbol{C}}H_3$-6), 54.3 (C-17), 47.6 (C-13), 43.7 (C-10), 43.6 (C-9), 36.2 (C-8), 34.6 (C-5), 33.7 (C-1), 30.8 (2C, C-7 and C-12), 25.9 (3C, OSiC($\underline{\boldsymbol{C}}H_3$)$_3$-20), 24.9 (C-2), 22.2 (C-11), 21.5 (C-3), 19.6 (C-18), 19.3 (C-19), 18.0 (OSi$\underline{\boldsymbol{C}}$(CH$_3$)$_3$-20), 13.4 (C-4), −5.0 (OSi$\underline{\boldsymbol{C}}H_3$-20), −5.1 ppm (OSi$\underline{\boldsymbol{C}}H_3$-20); IR (ATR): $\tilde{\nu}$ = 3510, 3392, 3004, 2953, 2927, 2876, 2815, 1472, 1461, 1375, 1253, 1139, 1100, 1037, 1017, 915, 859, 836, 776 cm^{-1}; HRMS (ESI): m/z calcd for $C_{28}H_{52}NO_5Si$ $[M + NH_4]^+$: 510.3609, found: 510.3608.

Compound 44.



Sodium periodate (558.6 mg, 2.61 mmol) was added to a solution of compound **43** (128.7 mg, 0.261 mmol) in THF/H_2O (1:1) (3.0 mL) at room temperature. After stirring for 2 h, the reaction was stopped by adding water, and the mixture was extracted with EtOAc (×3). The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 8:2) to give compound **44** (105.7 mg, 81%) as a colorless oil. $[\alpha]_D^{20} = +19.0$ ($c = 0.270$, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$): δ = 9.74 (d, $J = 4.2$ Hz, 1H, H-21), 4.82 (t, $J = 2.9$ Hz, 1H, H-16), 4.39 (dd, $J = 4.2$, 8.8 Hz, 1H, H-20), 4.03 (dd, $J = 2.9$, 9.2 Hz, 1H, H-15), 3.94 (d, $J = 9.2$ Hz, 1H, H-15), 3.33 (s, 3H, OC$\underline{\boldsymbol{H}_3}$-6), 2.94 (dt, $J = 3.0$, 12.3 Hz, 1H, H-8), 2.88 (t, $J = 2.3$ Hz, 1H, H-6), 2.64 (dd, $J = 2.9$, 8.8 Hz, 1H, H-17), 2.27–2.15 (m, 2H, H-12 and H-7), 1.83–1.64 (m, 2H, H-2 and H-11), 1.61–1.42 (m, 5H, H-2, H-11, H-12, H-1 and H-7), 1.33 (s, 3H, H-18), 1.31–1.18 (m, 1H, H-9), 1.10 (s, 3H, H-19), 0.98–0.82 (m, 2H, H-3 and H-1), 0.88 (s, 9H, OSiC(C$\underline{\boldsymbol{H}_3}$)$_3$-16) 0.67 (dd, $J = 3.9$, 5.2 Hz, 1H, H-4), 0.49 (dd, $J = 5.2$, 8.2 Hz, 1H, H-4), 0.09 (s, 3H, OSiC$\underline{\boldsymbol{H}_3}$-16), 0.05 ppm (s, 3H, OSiC$\underline{\boldsymbol{H}_3}$-16); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 216.4 (C-14), 204.8 (C-21), 82.6 (C-20), 81.7 (C-6), 77.8 (C-15), 72.6 (C-16), 56.7 (O$\underline{\boldsymbol{C}}H_3$-6), 56.2 (C-17), 48.3 (C-13), 48.0 (C-9), 44.2 (C-10), 40.9 (C-8), 37.2 (C-12), 34.3 (C-5), 33.5 (C-1), 30.1 (C-7), 25.8 (3C, OSiC($\underline{\boldsymbol{C}}H_3$)$_3$-16), 24.8 (C-2), 22.3 (C-18), 21.8 (C-11), 21.3 (C-3), 18.8 (C-19), 17.7 (OSi$\underline{\boldsymbol{C}}$(CH$_3$)$_3$-16), 13.2 (C-4), −4.3 (OSi$\underline{\boldsymbol{C}}H_3$-16), −4.6 ppm (OSi$\underline{\boldsymbol{C}}H_3$-16); IR (ATR): $\tilde{\nu}$ = 2953, 2928, 2859, 2821, 1723, 1698, 1460, 1378, 1255, 1092, 1019, 1002, 990, 938, 829, 811, 775, 754 cm^{-1}; HRMS (ESI): m/z calcd for $C_{28}H_{47}O_5Si$ $[M + H]^+$: 491.3187, found: 491.3216.

Compound 45.

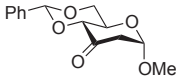


$NaBH_4$ (0.9 mg, 0.0240 mmol) was added to a solution of compound **44** (9.8 mg, 0.0199 mmol) in MeOH (0.5 mL) at 0 °C. After stirring for 10 min at 0 °C, the reaction was stopped by adding 0.1 N AcOH, and the mixture was extracted with EtOAc (×3). The combined organic extract was washed with brine,

dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 9:1) to afford compound **45** (7.0 mg, 71%) as a colorless oil whose ^{1}H NMR in $CDCl_3$ showed the contamination of ~5 mol% of minor isomer and ~10 mol% of EtOAc. $[\alpha]_D^{20} = -2.9$ ($c = 0.140$, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$): $\delta = 4.76$ (ddd, $J = 7.2$, 8.0, 8.9 Hz, 1H, H-16), 4.05 (dd, $J = 3.1$, 13.1 Hz, 1H, H-21), 3.93 (dd, $J = 8.0$, 8.9 Hz, 1H, H-15), 3.85 (d, $J = 13.1$ Hz, 1H, H-21), 3.71 (dd, $J = 3.1$, 4.3 Hz, 1H, H-20), 3.56 (t, $J = 8.0$ Hz, 1H, H-15), 3.35 (s, 3H, OC***H*****$_3$**-6), 2.90 (t, $J = 3.0$ Hz, 1H, H-6), 2.27 (dd, $J = 4.3$, 7.2 Hz, 1H, H-17), 2.19–2.16 (m, 1H, H-8), 2.16–2.01 (m, 2H, H-12), 1.88–1.75 (m, 2H, H-2 and H-7), 1.63 (ddd, $J = 3.0$, 12.1, 13.2 Hz, 1H, H-7), 1.54–1.45 (m, 2H, H-2 and H-1), 1.43–1.32 (m, 3H, H-9 and H-11), 1.23 (s, 3H, H-18), 1.01 (s, 3H, H-19), 0.95–0.79 (m, 2H, H-3 and H-1), 0.91 (s, 9H, OSiC(C***H*****$_3$)$_3$-16), 0.65 (dd, $J = 4.0$, 5.0 Hz, 1H, H-4), 0.46 (dd, $J = 5.0$, 8.1 Hz, 1H, H-4), 0.08 (s, 3H, OSiC***H*****$_3$-16), 0.05 ppm (s, 3H, OSiC***H*****$_3$-16); ^{13}C NMR (100 Hz, $CDCl_3$): $\delta = 99.0$ (C-14), 82.2 (C-6), 76.1 (C-16), 74.9 (C-20), 72.4 (C-15), 61.0 (C-21), 56.7 (O***C***H$_3$-6), 45.3 (C-17), 43.5 (C-10), 41.7 (C-9), 38.5 (C-13), 36.0 (C-8), 34.5 (C-5), 33.5 (C-1), 30.0 (C-12), 28.3 (C-7), 25.9 (3C, OSiC(***C***H$_3$)$_3$-16), 24.9 (C-2), 21.6 (C-11), 21.4 (C-3), 21.1 (C-18), 19.1 (C-19), 18.0 (OSi***C***(CH$_3$)$_3$-16), 13.3 (C-4), −4.9 (OSi***C***H$_3$-16), −5.0 ppm (OSi***C***H$_3$-16); IR (ATR): $\tilde{\nu} = 3526$, 3473, 3342, 2955, 2929, 2859, 1728, 1471, 1463, 1442, 1388, 1377, 1259, 1252, 1131, 1088, 1059, 1037, 1013, 911, 870, 836, 776 cm^{-1}; HRMS (ESI): m/z calcd for $C_{28}H_{48}NaO_5Si$ $[M + Na]^+$: 515.3163, found: 515.3186.

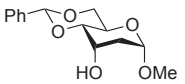
Pentalinonside Aglycon (2). $HClO_4$ (0.1 mL) was added to a solution of **45** (2.4 mg, 4.87 µmol) in 1,4-dioxane/H_2O (5:4) (0.5 mL) at room temperature. After stirring for 2 h at room temperature, the reaction was stopped by adding water, and the mixture was extracted with EtOAc (×3). The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/Et_2O/CH_3CN = 4:5:1) to afford pentalinonside aglycon (**2**, 1.6 mg, 95%) as a white solid. M.p. 206.2–206.4 °C; $[\alpha]_D^{20} = -37.19$ ($c = 0.32$, MeOH); ^{1}H NMR (500 MHz, pyridine-d_5): $\delta = 5.49$–5.45 (m, 1H, H-6), 4.57 (t, 1H, $J = 4.6$ Hz, H-16), 4.49 (ddd, 1H, $J = 8.0$, 5.8, 1.2 Hz, H-20), 4.23 (d, 1H, $J = 10.1$ Hz, H-15b), 4.06 (dd, 1H, $J = 12.6$, 5.8 Hz, H-21a), 4.03 (dd, 1H, $J = 10.1$, 4.6 Hz, H-15a), 3.89–3.81 (m, 1H, H-3), 3.80 (dd, 1H, $J = 12.6$, 1.2 Hz, H-21b), 2.66–2.60 (m, 1H, H-7), 2.63–2.58 (m, 2H, H-4), 2.61 (dd, 1H, $J = 8.0$, 4.6 Hz, H-17), 2.52–2.44 (m, 1H, H-7), 2.13–2.06 (m, 1H, H-2a), 1.90–1.83 (m, 1H, H-1b), 1.89–1.84 (m, 1H, H-8), 1.83–1.73 (m, 1H, H-2b), 1.52–1.46 (m, 1H, H-11), 1.49–1.43 (m, 1H, H-12b), 1.45–1.40 (m, 1H, H-9), 1.38–1.32 (m, 1H, H-12a), 1.34–1.28 (m, 1H, H-11), 1.18–1.10 (m, 1H, H-1a), 1.1 (s, 3H, H-18), 1.02 (s, 3H, H-19) ppm; ^{13}C NMR (125 MHz, pyridine-d_5): $\delta = 140.4$ (C-5), 121.8 (C-6), 108.1 (C-14), 80.7 (C-16), 76.2 (C-20), 74.2 (C-15), 71.2 (C-3), 66.1 (C-21), 54.5 (C-17), 46.0 (C-9), 43.4 (C-4), 41.3 (C-10), 37.7 (C-1), 36.8 (C-13), 36.2 (C-8), 34.8 (C-12), 32.5 (C-2), 25.4 (C-7), 20.5 (C-11), 19.6 (C-19), 17.2 (C-18) ppm; IR (ATR): $\tilde{\nu} = 3309$, 2927, 1439, 1381, 1364, 1269, 1202, 1169, 1133, 1101, 1052, 1019, 986, 972, 954 cm^{-1}; HRMS (EI): m/z calcd for $C_{21}H_{31}O_4$ $[M + H]^+$: 347.2217, found: 347.2223.

(2*R*,4a*R*,6*S*,8a*R*)-6-Methoxy-2-phenyltetrahydropyrano-[3,2-*d*][1,3]dioxin-8(4*H*)-one.



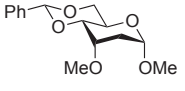
Tetrapropylammonium perruthenate (420.3 mg, 1.20 mmol) and 4-methylmorpholine (18.2 g, 155.4 mmol) were added to a solution of compound **85** (6.37 g, 23.9 mmol) in CH_2Cl_2 (150 mL) at room temperature. After 1 h at room temperature, the reaction was stopped by adding water, and the mixture was extracted with EtOAc (×3). The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 7:3) to afford (2*R*,4a*R*,6*S*,8a*R*)-6-methoxy-2-phenyltetrahydropyrano [3,2-*d*][1,3]dioxin-8(4*H*)-one (4.60 g, 73%) as a white solid. M.p. = 175.0–176.1 °C; $[\alpha]_D^{20} = +122.3$ ($c = 0.575$, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$): $\delta = 7.53$–7.47 (m, 2H), 7.39–7.33 (m, 3H), 5.58 (s, 1H), 5.14 (d, $J = 4.7$ Hz, 1H), 4.37 (dd, $J = 4.7$, 10.2 Hz, 1H), 4.30 (dd, $J = 1.1$, 10.2 Hz, 1H), 4.15 (dt, $J = 4.7$, 10.2 Hz, 1H), 3.91 (t, $J = 10.2$ Hz, 1H), 3.38 (s, 3H), 2.83 (ddd, $J = 1.1$, 4.7, 14.6 Hz, 1H), 2.66 ppm (d, $J = 14.6$ Hz, 1H); ^{13}C NMR (100 Hz, $CDCl_3$): $\delta = 197.4$, 136.5, 129.3, 128.3, 126.4, 102.2, 100.6, 83.1, 69.5, 65.1, 55.0, 46.4 ppm; IR (ATR): $\tilde{\nu} = 2940$, 1730 (C=O), 1451, 1403, 1379, 1273, 1131, 1090, 1017, 978, 908, 748, 696, 655 cm^{-1}; HRMS (ESI): m/z calcd for $C_{14}H_{17}O_5$ $[M + H]^+$: 265.1071, found: 265.1097.

Compound 86.



$NaBH_4$ (790.2 mg, 20.9 mmol) was added to a solution of (2*R*,4a*R*,6*S*,8a*R*)-6-methoxy-2-phenyltetrahydropyrano[3,2-*d*]-[1,3]dioxin-8(4*H*)-one (4.60 g, 17.4 mmol) in MeOH (100 mL) at 0 °C. After stirring for 10 min at 0 °C, the reaction was stopped by adding 0.1 M AcOH, and the mixture was extracted with EtOAc (×3). The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 7:3) to afford compound **86** (4.60 g, quant.) as a colorless oil. $[\alpha]_D^{20} = +108.29$ ($c = 0.525$, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$): $\delta = 7.54$–7.48 (m, 2H), 7.40–7.31 (m, 3H), 5.63 (s, 1H), 4.80 (dd, $J = 0.8$, 4.0 Hz, 1H), 4.33 (dd, $J = 5.1$, 9.9 Hz, 1H), 4.24 (dt, $J = 5.1$, 9.9 Hz, 1H), 4.19 (qd, $J = 3.0$, 6.2 Hz, 1H), 3.78 (t, $J = 9.9$ Hz, 1H), 3.61 (dd, $J = 3.0$, 9.9 Hz, 1H), 3.41 (s, 3H), 3.01 (d, $J = 6.2$ Hz, 1H, OH), 2.20 (ddd, $J = 0.8$, 3.0, 14.9 Hz, 1H), 2.01 ppm (ddd, $J = 3.0$, 4.0, 14.9 Hz, 1H); ^{13}C NMR (100 Hz, $CDCl_3$): $\delta = 137.3$, 129.1, 128.3, 126.3, 102.1, 98.7, 79.7, 69.4, 65.0, 58.2, 55.5, 35.5 ppm; IR (ATR): $\tilde{\nu} = 3503$ (OH), 2933, 1459, 1410, 1389, 1184, 1134, 1112, 1095, 1042, 993, 964, 927, 862, 772, 710 cm^{-1}; HRMS (ESI): m/z calcd for $C_{14}H_{19}O_5$ $[M + H]^+$: 267.1227, found: 267.1234.

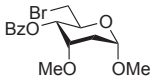
Compound 87.



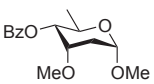
Sodium hydride (319.2 mg, 7.98 mmol) was added to a solution of compound **86** (1.76 g, 6.65 mmol) in DMF (30 mL) at 0 °C. After 1 h at room temperature, the reaction mixture was cooled to 0 °C. Iodomethane was added to the reaction mixture at 0 °C.

After stirring for 20 min at 0 °C, the reaction was stopped by adding water, and the mixture was extracted with EtOAc (×3). The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 7:3) to afford compound **87** (1.85 g, 99%) as a white solid. M.p. = 81.5–82.6 °C; $[\alpha]_D^{20} = +83.53$ ($c = 0.230$, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.53–7.46 (m, 2H), 7.40–7.30 (m, 3H), 5.53 (s, 1H), 4.69 (dd, $J = 0.7$, 4.6 Hz, 1H), 4.38–4.27 (m, 2H), 3.81–3.77 (m, 1H), 3.74–3.66 (m, 2H), 3.55 (s, 3H), 3.39 (s, 3H), 2.22 (ddd, $J = 0.7$, 2.8, 14.9 Hz, 1H), 1.93 ppm (ddd, $J = 3.6$, 4.6, 14.9 Hz, 1H); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 137.7, 129.0, 128.3, 126.2, 102.3, 97.9, 80.7, 73.7, 69.6, 59.6, 58.1, 55.6, 34.3 ppm; IR (ATR): $\tilde{\nu} = 2932$, 1716 (C=O), 1385, 1123, 1098, 1042, 1001, 984, 962, 907, 771, 704 cm^{-1}; HRMS (ESI): m/z calcd for $C_{15}H_{21}O_5$ $[M + H]^+$: 281.1384, found: 281.1393.

(2*S*,3*S*,4*S*,6*S*)-2-(Bromomethyl)-4,6-dimethoxytetrahydro-2*H*-pyran-3-yl Benzoate.

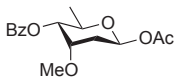


Barium carbonate (541.1 mg, 2.74 mmol) and *N*-bromosuccinimide (1.00 g, 5.94 mmol) were added to a solution of compound **87** (1.28 g, 4.57 mmol) in CCl_4 (50 mL) at room temperature. After stirring for 2 h at 60 °C, the reaction was stopped by adding water, and the mixture was extracted with EtOAc (×3). The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 8:2) to afford (2*S*,3*S*,4*S*,6*S*)-2-(iodomethyl)-4,6-dimethoxytetrahydro-2*H*-pyran-3-yl benzoate (1.46 g, 89%) as a colorless oil. $[\alpha]_D^{20} = +119.49$ ($c = 1.13$, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$): δ = 8.09–8.05 (m, 2H), 7.62–7.57 (m, 1H), 7.50–7.44 (m, 2H), 5.06 (dd, $J = 3.2$, 9.6 Hz, 1H), 4.83 (dd, $J = 1.1$, 4.7 Hz, 1H), 4.54 (ddd, $J = 2.6$, 6.6, 9.6 Hz, 1H), 3.95 (dt, $J = 3.2$, 3.5 Hz, 1H), 3.65 (dd, $J = 2.6$, 11.1 Hz, 1H), 3.55 (dd, $J = 6.6$, 11.1 Hz, 1H), 3.46 (s, 3H), 3.40 (s, 3H), 2.26 (ddd, $J = 1.1$, 3.5, 14.9 Hz, 1H), 2.00 ppm (ddd, $J = 3.5$, 4.7, 14.9 Hz, 1H); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 165.5, 133.4, 129.8, 129.5, 128.5, 98.1, 73.9, 72.6, 65.1, 58.6, 55.8, 33.4, 32.6 ppm; IR (ATR): $\tilde{\nu} = 2932$, 2897, 2825, 1717 (C=O), 1280, 1260, 1096, 1052, 1025, 983, 712 cm^{-1}; HRMS (ESI): m/z calcd for $C_{15}H_{20}BrO_5$ $[M + H]^+$: 359.0489, found: 359.0491.



Tributyltin hydride (1.7 mL, 6.22 mmol) and azobisisobutyronitrile (510.4 mg, 3.11 mmol) were added to a solution of (2*S*,3*S*,4*S*,6*S*)-2-(iodomethyl)-4,6-dimethoxy-tetrahydro-2*H*-pyran-3-yl benzoate (1.86 g, 5.18 mmol) in benzene (50 mL) at room temperature. After stirring for 40 min at 80 °C, the reaction was stopped by adding water, and the mixture was extracted with EtOAc (×3). The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 8:2) to afford compound **88** (1.35 g, 93%) as a colorless oil. $[\alpha]_D^{20} = +120.39$ ($c = 0.905$, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$): δ = 8.12–8.05 (m, 2H), 7.61–7.55 (m, 1H), 7.49–7.42 (m, 2H), 4.88 (dd, $J = 3.2$, 9.3 Hz, 1H), 4.72 (dd, $J = 1.6$, 4.5 Hz, 1H), 4.40 (qd, $J = 6.3$, 9.3 Hz, 1H), 3.86 (dt, $J = 3.2$, 3.8 Hz, 1H), 3.41 (s, 3H), 3.40 (s, 3H), 2.23 (ddd, $J = 1.6$, 3.8, 14.7 Hz, 1H), 1.96 (ddd, $J = 3.8$, 4.5, 14.7 Hz, 1H), 1.25 ppm (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 165.9, 133.2, 129.9, 129.8, 128.4, 97.7, 75.0, 74.2, 62.2, 58.6, 55.6, 33.0, 17.6 ppm; IR (ATR): $\tilde{\nu} = 2978$, 2932, 2830, 1716 (C=O), 1451, 1344, 1263, 1200, 1106, 1053, 1018, 1026, 990, 711 cm^{-1}; HRMS (ESI): m/z calcd for $C_{15}H_{24}NO_5$ $[M + NH_4]^+$: 298.1649, found: 298.1645.

Compound 89.



H_2O (1.5 mL) were added to a solution of compound **88** (271.6 mg, 0.969 mmol) in acetic acid (5.0 mL) at room temperature. After stirring for 2 h at 80 °C, the reaction was stopped by adding water, and the mixture was extracted with EtOAc (×3). The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/Et_2O/CH_3CN = 6:3:1) to afford crude containing with (2*R*,3*R*,4*S*)-6-hydroxy-4-methoxy-2-methyltetrahydro-2*H*-pyran-3-ylbenzoate (251.8 mg) as a colorless oil which was used for the next reaction without further purification. Ac_2O (0.25 mL) were added to a solution of crude material containing with (2*R*,3*R*,4*S*)-6-hydroxy-4-methoxy-2-methyl tetrahydro-2*H*-pyran-3-yl benzoate (13.1 mg) in pyridine (0.5 mL) at room temperature. After stirring for 30 min at room temperature, the reaction was stopped by adding water, and the mixture was extracted with EtOAc (×3). The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 7:3) to afford compound **89** (14.0 mg, 77% for 2 steps, β:α = 85:15) as a colorless oil. **89**β: $[\alpha]_D^{20} = +29.59$ ($c = 0.785$, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$): δ = 8.09–8.05 (m, 2H), 7.62–7.56 (m, 1H), 7.49–7.43 (m, 2H), 6.10 (dd, $J = 2.4$, 9.0 Hz, 1H), 4.85 (dd, $J = 2.8$, 8.9 Hz, 1H), 4.32 (qd, $J = 6.4$, 8.9 Hz, 1H), 3.98 (td, $J = 2.8$, 4.8 Hz, 1H), 3.40 (s, 3H), 2.27 (ddd, $J = 2.4$, 4.8, 13.6 Hz, 1H), 2.12 (s, 3H), 1.86 (ddd, $J = 2.8$, 9.0, 13.6 Hz, 1H), 1.30 ppm (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 169.2, 165.9, 133.3, 129.8 (2C), 128.5, 91.1, 74.6, 74.1, 69.5, 58.1, 33.5, 21.2, 18.2 ppm; IR (ATR): $\tilde{\nu} = 2978$, 2943, 2897, 2841, 1753 (C=O), 1713 (C=O), 1451, 1354, 1270, 1218, 1121, 1094, 1056, 1010, 726 cm^{-1}; HRMS (ESI): m/z calcd for $C_{16}H_{20}NaO_6$ $[M + Na]^+$: 331.1152, found: 331.1179; **89**α: ^{1}H NMR (400 Hz, $CDCl_3$): δ = 8.11–8.07 (m, 2H), 7.61–7.56 (m, 1H), 7.49–7.43 (m, 2H), 6.10 (dd, $J = 1.6$, 4.2 Hz, 1H), 4.88 (dd, $J = 3.0$, 9.5 Hz, 1H), 4.52 (qd, $J = 6.3$, 9.5 Hz, 1H), 3.93 (td, $J = 3.0$, 3.9 Hz, 1H), 3.38 (s, 3H), 2.36 (ddd, $J = 1.6$, 3.9, 15.2 Hz, 1H), 2.12 (s, 3H), 2.00 (ddd, $J = 3.0$, 4.2, 15.2 Hz, 1H), 1.27 ppm (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (100 Hz, $CDCl_3$): δ = 170.0, 165.8, 133.3, 129.8 (2C), 128.5, 90.9, 74.5, 73.2, 64.7, 57.4, 30.8, 21.3, 17.6 ppm.

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Supporting Information

Experimental and copies of ^{1}H and ^{13}C NMR spectra of all the compounds on successful route, copy of CD spectra of compound **30**. This material is available on https://doi.org/10.1246/bcsj.20190048.

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