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Stereodivergent synthesis of new amino sugars, furanodictines A and B, starting from D-glucuronolactone

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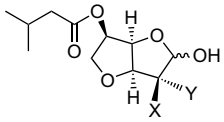
ABSTRACT

An efficient and divergent strategy for the total synthesis of the first 3,6-dihydroaminosugars, furanodictines A (2-acetamido-3,6-anhydro-2-deoxy-5-*O*-isovaleryl-D-glucofuranose) and B (2-acetamido-3,6-anhydro-2-deoxy-5-*O*-isovaleryl-D-mannofuranose), has been developed. The synthetic process is featured by readily accessible and stereodefined manipulation of highly functionalized bicyclic tetrahydrofuran derivatives incorporating the glucuronolactone (common starting material)-derived skeleton.

1. Introduction

Various physiologically active substances have been hitherto produced in nature and a great number of research groups have long been searching for natural products that may be helpful for drug development. Especially, pharmaceutical scientists are naturally interested in studying the secondary metabolites produced by cellular slime molds to explore their diversity as well as physiological and pharmacological activities. In 2001, Oshima et al. isolated furanodictines A (**1**) and B (**2**), which are secondary metabolites of the cellular slime mold *Dictyostelium discoideum*, from the multicellular fruit body by methanol extraction (Fig. 1)[1] with a view to clarify the potent biological diversity and apply to new drug development. Through detailed investigation by the same group, these compounds were unambiguously revealed to be the first examples of amino sugars isolated from natural sources with a 3,6-anhydrohexofuranose carbon skeleton and demonstrated to have physiological activity in promoting neuritogenesis in rat pheochromocytoma (PC-12) cells.[2] In addition, the absolute configurations of **1** and **2** were determined by achieving their asymmetric construction using *N*-acetyl-D-glucosamine and *N*-acetyl-D-mannosamine as starting materials, respectively, and comparing the spectral data with those of natural products.[1] Since then, their structural complexity coupled with highly novel characteristic as an antitumor agent for neuronal differentiation described above has made them inviting targets for synthesis. In 2004, the second and novel total synthesis of **1** has been accomplished in this laboratory featuring addition of an organometallic compound to the furanosylamine derivative prepared from D-arabinose as a starting material.[3] On the other hand, the formal total synthesis of **2** was reported by Mereyala et al. starting from D-glucose in the same year.[4] These synthetic procedures, however, generally require multi-step synthetic pathways or crucial techniques, and were not necessarily satisfactory to obtain target compounds. In these circumstances, we recently communicated a simple and effective asymmetric preparation of **2** using commercially available D-glucuronolactone (**3**) without separation of stereoisomers.[5] On the basis of our new findings in the preceding report, we have researched the stereodivergent strategy of both furanodictines, A (**1**) and B (**2**), employing **3** as a common starting material and herein wish to demonstrate the details of an efficient and convenient synthetic route for the stereoselective construction of these two amino sugars.

In formulating the synthetic plan for **1** and **2**, we recognized that the absolute configurations at C(3) and C(4) are the same as the configurations at the corresponding centers C(3) and C(4) of the protected common lactone (**4**) derived from D-glucuronolactone (**3**) (Fig. 2). Further, we envisioned that the stereogenic center C(2) of **1** with the α-NHAc group would originate from an azide-induced S_N2 substitution reaction of **II** obtained through debenzylation of **I**. Meanwhile, the remaining stereogenic center C(5) would have to be independently set in inversion of configuration of the hydroxylated



X=H, Y=NHAc: furanodictine A (1)
X=NHAc, Y=H: furanodictine B (2)

Figure 1. Furanodictines A and B.

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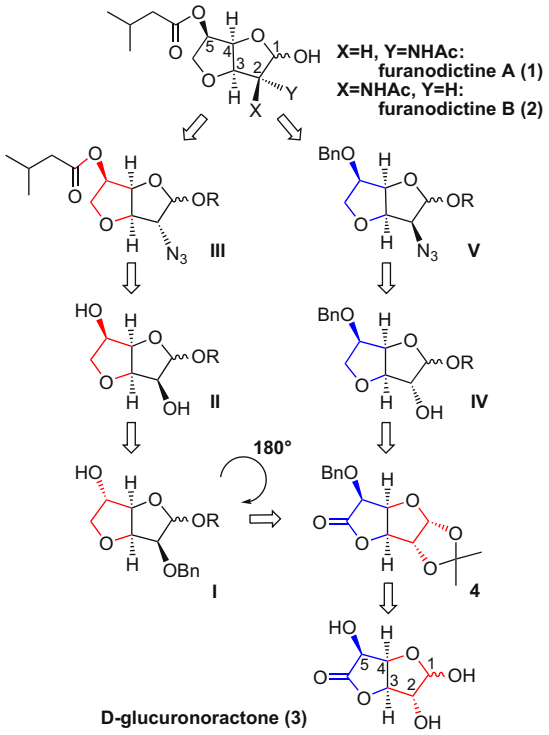


Figure 2. Retrosynthesis of furanodictines.

carbon of **I**, allowing the synthesis of the crucial intermediate **III**. On the other hand, the retrosynthesis of **2** could be simply performed by the introduction of an azide group through S_N2 reaction of **IV** obtained from **4**, followed by reduction of the azide group of **V**.

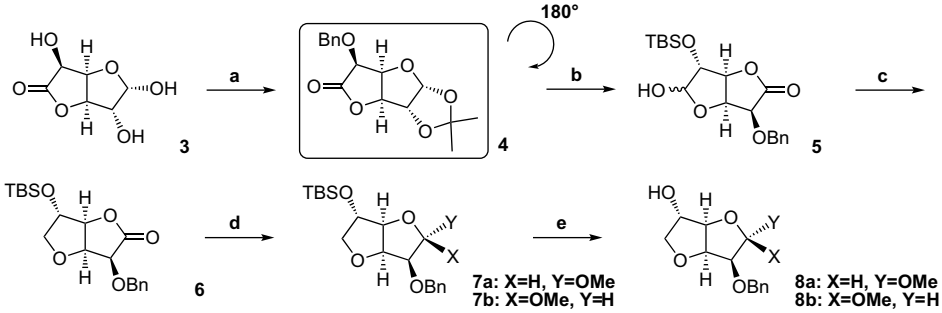
2. Results and discussion

2.1. Synthesis of furanodictine A (1)

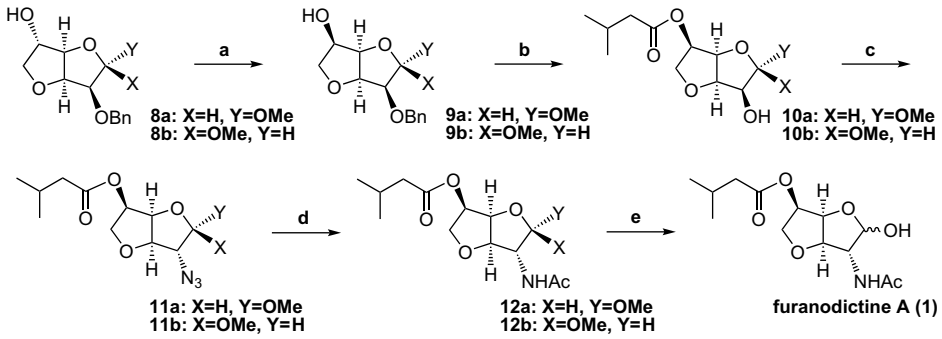
Our initial investigations were aimed at scrutinizing the feasibility of glycosylated bicyclic lactols such as **I** shown in Figure 2 for an azide-induced S_N2 substitution reaction followed by reduction of its azide group. As shown in Scheme 1, the common starting material **4** for the synthesis of furanodictines A (**1**) and B (**2**) was easily prepared from glucuronolactone (**3**) through successive protecting reactions with acetone and benzyl bromide in 95% yield.[6] Intrigued by the previous report regarding TBS-protection of an α-hydroxylactol with TBSOTf in the presence of Et_3N, where regioselective results were obtained at low temperature to achieve good yields,[7] we investigated the reactivity of **4** under the same reaction conditions after deacetalization with aq TFA. Remarkable enhancement in the regioselectivity together with the yield of these reactions was fortunately observed after detailed examination to yield **5** (180° rotated in Scheme 1) with complete regioselectivity in 91% isolated yield. Whereas direct deoxygenation of the remaining lactol-hydroxy group of **5** with an Et_3SiH/Lewis acid system resulted in the formation of a complex mixture and stepwise conversion via reduction followed by regioselective tosylation in the presence of Bu_2SnO[8] spontaneously caused cyclization to give the deoxygenated furanolactone derivative **6** in high yield. Then, **6** thus obtained was reduced with DIBAL-H and the Williamson type of etherification by treating with CH_3I under basic conditions afforded the desired glycosylated product **7** as a non-stereoselective anomeric mixture.[9] It was ascertained that these products of the α- and β-methyl glycosides, **7a** and **7b**, were easily separated from each other by column chromatography on silica gel (**7a**: R_f=0.71, **7b**: R_f=0.45 hexane/AcOEt=5/1, respectively).[10] Removal of the TBS protecting group in **7a** and **7b** was efficiently performed with TBAF to provide the desired intermediates **8** in quantitative yields, respectively.

With the desired compounds **8** in hand, which contain the reverse stereochemistry at C(5) required to synthesize natural (+)-furanodictine (**1**), we independently attempted the asymmetric preparation of the desired stereoisomers **9a** and **9b** derived from each anomer. The results from our survey are described in Scheme 2. To begin with, the inversion of configuration of the hydroxy-containing carbon of **8** was performed with AcOK in the presence of 18-crown-6 after derivation to the triflate with trifluoromethanesulfonic anhydride (Tf_2O), leading to the desired acetylated inversion product, but in low yield, together with the eliminated olefinic compound as a main component, whereas the reaction of **8** under Mitsunobu conditions[11] reversely failed to generate reaction products. These attempts led to a conclusion that reactions of **8** should be conducted under neutral conditions to allow the inversion of configuration. Thus, **8a** was oxidized effectively with tetrapropylammonium perruthenate (TPAP)/NMO reagent[12] to afford the corresponding ketone, which was readily treated with $NaBH_4$ in MeOH at 0 °C. We were delighted to find through detailed investigation of stereoselectivity that simple conditions described in Scheme 2 (see: Section 4) could effect these reactions beneficially, bringing about the desired reduction product **9a** as a single stereoisomer. Fortunately, the same results were also obtained upon reaction employing **8b**.[13]

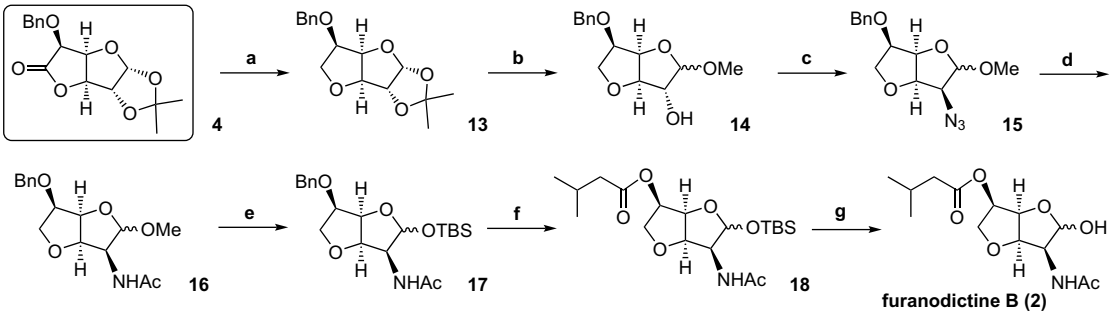
Then, we next focused our research on the total synthesis of **1**. Compounds **9a** and **9b** were subjected to esterification of the hydroxy group with the desired isovaleric acid counterpart in the presence of EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) and DMAP,[14] providing the esters in excellent yields, respectively, which were subsequently hydrogenated with H_2 on Pd/C to give the alcohols **10a** and **10b** also in high yields. For



Scheme 1. Reagents and conditions: (a) (i) acetone, concd H_2SO_4, 1 h, 97%; (ii) BnBr, Ag_2O, AcOEt, 10 h, 98%; (b) (i) aq TFA (TFA/H_2O=10/1), 10 °C, 12 h, 91%; (ii) TBSOTf, Et_3N, CH_2Cl_2, −78 °C, 30 min, 91%; (c) (i) $NaBH_4$, MeOH, −40 °C, 30 min, 97%; (ii) *p*-TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, 5 h, 82%; (d) (i) DIBAL-H, toluene, −78 °C, 15 min, 94%; (ii) MeI, *t*-BuOK, −78 °C to −15 °C, 2 h, 50% (**7a**), 46% (**7b**); (d) Bu_4NF, THF, 1 h, 99% (**8a**), 99% (**8b**).



Scheme 2. Reagents and conditions: (a) (i) TPAP, NMO, 4 Å MS, CH_2Cl_2, 12 h; (ii) $NaBH_4$, MeOH, 0 °C, 30 min, 84% (two steps) (**9a**), 79% (two steps) (**9b**); (b) (i) isovaleric acid, EDCI, DMAP, CH_2Cl_2, 30 min; (ii) H_2, 5% Pd/C, EtOH, 12 h, 88% (two steps) (**10a**), 90% (two steps) (**10b**); (c) (i) Tf_2O, pyridine, CH_2Cl_2, 1 h; (ii) NaN_3, DMF, 40 °C, 80 h, 97% (two steps) (**11a**), 96% (two steps) (**11b**); (d) (i) Ph_3P, H_2O, THF/CH_2Cl_2 (3/1), 2 h (for **11a**), H_2, 5% Pd/C, EtOH, 3 h (for **11b**); (ii) Ac_2O, pyridine, CH_2Cl_2, 3 h, 96% (two steps) (**12a**), 87% (two steps) (**12b**); (e) 70% aq AcOH, 110 °C, 20 h, 84% (from **12a** as well as **12b**).



Scheme 3. Reagents and conditions: (a) (i) $LiAlH_4$, THF, 2 h; 92%; (ii) *p*-TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, 7 h; (iii) NaH, THF, 30 min, 72% (two steps); (b) DOWEX 50 W X-8 (H^+ form), MeOH, 12 h, 99%; (c) (i) Tf_2O, pyridine, CH_2Cl_2, 1 h; (ii) NaN_3, DMF, 60 °C, 80 h, 61% (two steps); (d) (i) Ph_3P, H_2O, THF/CH_2Cl_2 (3/1), 2 h; (ii) Ac_2O, CH_2Cl_2, 3 h, 65% (two steps); (e) (i) 70% aq AcOH, 110 °C, 20 h, 98%; (ii) TBSCl, imidazole, DMF, 3 h, 99%; (f) (i) H_2, 5% Pd/C, AcOEt, 12 h; 99%; (ii) isovaleric acid, EDCI, DMAP, CH_2Cl_2, 2 h; 88%; (g) Bu_4NF, THF, 1 h, 96%.

the purpose of introducing an acetamide group presented in furanodictines, treatment of **10a** and **10b** with Tf_2O in the presence of pyridine afforded the triflates, which were in turn successively subjected to nucleophilic S_N2 displacement reaction with NaN_3, smoothly affording the azide products **11** in quite high yields (97% (**11a**) and 96% (**11b**)) as a single isomer, respectively (determined by ^{13}C and ^1H NMR analyses). Reduction of the azide moiety of **11a** under Staudinger conditions with PPh_3/H_2O or hydrogenation of **11b** with 10% Pd on carbon[15] gave the corresponding labile primary amines, which were quickly effected by acetylation to furnish the desired acetamides **12a** and **12b** in satisfactory two-step yields, respectively. Finally, these compounds were readily deglycosylated at 110 °C in 70% aqueous acetic acid solution to complete the total synthesis of furanodicitne A (**1**), $[\alpha]_D^{22}$ +113.0 (*c* 0.8, $CHCl_3$) {natural **1**, $[\alpha]_D^{25}$ +100.4 (*c* 0.233, $CHCl_3$)[1] and synthetic **1**, $[\alpha]_D^{25}$ +118.5 (*c* 0.437, $CHCl_3$)[1]},[16] in 84% yields, respectively. Thus, one of the target compounds, **1**, was synthesized in 17 steps and 22% overall yield from commercially available D-glucuronolactone (**3**).

2.2. Synthesis of furanodictine B (2)

Having obtained and characterized synthetic furanodictine A (**1**), we turned our attention to the synthesis of furanodicitine B (**2**) also employing **3** as the same starting material via the conveniently functionalized lactone **4**. The results are summarized in Scheme 3. While direct hydrogenation of the lactol derived from DIBAL-H reduction of **4** with Et_3SiH in the presence of $BF_3\cdot OEt_2$ disappointingly yielded the inseparable mixture even at low temperature,[17] reduction of **4** with $LiAlH_4$ provided the diol in 92% yield, which was readily effected by regioselective tosylation in the presence of Bu_2SnO[8] as described in Scheme 1, followed by cyclization under basic conditions to lead to the tetrahydrofuran derivative **13** in high yield. Compound **13** thus obtained was subjected to methanolysis catalyzed by DOWEX 50 W X-8 (H^+ form), giving the methyl glycoside **14** quantitatively as an epimeric mixture (α/β=1/1.9).[18] Upon reaction with Tf_2O in the presence of pyridine followed by nucleophilic displacement with NaN_3 in the same manner described in Scheme 2, the hydroxy group of **14** was smoothly converted to the azide **15** in satisfactory yield with also complete inversion of configuration. Reduction of the azide intermediate **15** with Staudinger's (PPh_3/H_2O) system again[15] followed by acetylation gave the corresponding amide **16** in good yield. Next, we envisioned a more concise and convenient manner to achieve the total synthesis of furanodictine B (**2**) apart from methods hitherto reported.[1,3] After hydrolysis of the methyl glycoside part of **16** in refluxing 70% acetic acid solution, the resulting lactol part was protected with TBSCl to give the silyl ether **17** in 97% two-step yield. Obtained **17** was subjected to deprotection of the benzyl group and esterification of the remaining hydroxy function with the desired isovaleric acid in the presence of EDCI and DMAP[8] provided *O*-TBS ether **18** in 88% yield through a two-step sequence. Finally, **18** was readily deprotected with Bu_4NF to complete the total synthesis of furanodictine B (**2**), $[\alpha]_D^{26}$ +104.8 (*c* 0.86, $CHCl_3$) {natural **2**, $[\alpha]_D^{25}$ +85.6 (*c* 0.250, $CHCl_3$)[1] and synthetic **2**, $[\alpha]_D^{25}$ +98.4 (*c* 0.808, $CHCl_3$)[1]},[19] in 96% yield (15 steps and 18% overall yield from D-glucuronolactone). The spectral data of synthetic **1** and **2** were completely identical to those of the natural products in all respects.[1]

3. Conclusions

In summary, an efficient and stereodivergent strategy for the total synthesis of the first 3,6-dihydroaminosugars, furanodictines A and B, has been developed from the common starting material,

D-glucuronolactone. The synthetic process is featured by readily accessible and stereodefined manipulation of highly functionalized bicyclic tetrahydrofuran derivatives incorporating the glucuronolactone-derived skeleton and substantially performed under mild and ambient conditions through entire sequence. In addition, it is easily applicable to the preparation in relatively large amount since the starting material as well as the reagents employed is commercially available and the synthetic pathway is short and operationally simple.

4. Experimental section

4.1. General

All solvents and reagents were of reagent grade quality from Aldrich Chemical Company, Fluka, Acros, or Wako Pure Chemicals and used without any further purification. Melting points were measured on an automated melting point system (MPA 100, Stanford Research Systems). Fourier transform infrared (FTIR) spectra were recorded on a Shimadzu FTIR-8200A spectrometer. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra operating at the frequencies of 300 and 75 MHz, respectively, were measured with a JEOL JNM-AL300 spectrometer in chloroform-*d* ($CDCl_3$) unless otherwise stated. Chemical shifts are reported in parts per million (ppm) relative to TMS as internal standard (δ=0 ppm) for ^{1}H NMR, and $CDCl_3$ was used as internal standard (δ=77.0) for ^{13}C NMR. The coupling constants are reported in hertz (Hz). Optical rotations were measured in 1 dm path length cell of 2 mL capacity using a JASCO Model DIP-1000 polarimeter at a wavelength of 589 nm. Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm Merck silica gel 60-F_{254} precoated silica gel plates by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid in methanol followed by heating. Column chromatography was performed on Kanto Chemical silica gel 60N eluting with the indicated solvent system. The non-crystalline compounds were shown to be homogeneous by chromatographic methods and characterized by NMR, IR, high resolution mass spectra (HRMS), and microanalysis. High-performance liquid chromatography (HPLC) was carried out using a Shimadzu Model LC-10AD or 10AT intelligent pump and SPD-10A UV detector. HRMS were recorded on a JEOL JMS-T100CS spectrometer. Microanalyses were performed with a JSL Model JM 10.

4.2. Experimental procedures

*4.2.1. (1S,3R,4R,5S,8S)-8-Benzyloxy-7-keto-3,4-isopropylidenedioxy-2,6-dioxabicyclo[3.3.0]octane (**4**)*

4.2.1.1. Acetonide protection. To a solution of D-glucuronolactone **3** (3.00 g, 17.04 mmol) in acetone (45 mL) was added concd H_2SO_4 (2.5 mL) at 0 °C. After stirring for 1 h, the reaction mixture was quenched by addition of powdered $NaHCO_3$ (500 g), filtered, and evaporated to dryness to obtain a colorless oily residue. The residue was diluted with AcOEt (200 mL), washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude was recrystallized from toluene to give the corresponding acetonide (3.57 g, 16.5 mmol, 97%) as colorless crystals. R_f=0.37 (silica gel, hexane/AcOEt=1/2); $[\alpha]_D^{25}$ +55.2 (*c* 1.1, $CHCl_3$); IR (KBr) 3250 (O–H), 1792 (C=O), 1036 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (d, *J*=3.5 Hz, 1H, C*H*), 4.94 (dd, *J*=4.2, 3.5 Hz, 1H, C*H*), 4.83–4.82 (m, 2H, C*H*), 4.49 (dd, *J*=9.3, 4.2 Hz, 1H, C*H*), 2.75 (d, *J*=9.3 Hz, 1H, O*H*), 1.53 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6 (*C*), 113.7 (*C*), 106.6 (*C*H), 82.9 (*C*H), 81.2 (*C*H), 78.0 (*C*H), 70.6 (*C*H), 26.9 (CH_3), 26.5 (CH_3); HRMS (ESI^+) *m*/*z* calcd for $C_9H_{12}O_6$+Na: 239.0532, found: 239.0508.

4.2.1.2. Protection with BnBr. To a solution of acetonide (1.00 g, 4.61 mmol) and benzyl bromide (0.990 g, 5.77 mmol) in AcOEt (4.6 mL) was added silver oxide(I) (0.650 g, 2.77 mmol). After stirring for 10 h, the reaction mixture was filtered through a pad of Celite and washed with AcOEt (80 mL). The filtrate was concentrated in vacuo and the resulting residue was purified by column chromatography (silica gel, hexane/AcOEt=5/1) to give **4** (1.39 g, 0.566 mmol, 98%) as a colorless oil. R_f=0.35 (silica gel, hexane/AcOEt=2/1); $[\alpha]_D^{26}$ +46.2 (*c* 0.9, $CHCl_3$); IR (NaCl) 1800 (C=O), 1501 (C=C), 1142 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.23 (m, 5H, Ar*H*), 6.04 (d, *J*=3.7 Hz, 1H, C*H*), 4.92 (s, 2H, PhCH_2), 4.86 (dd, *J*=4.3, 2.9 Hz, 1H, C*H*), 4.79 (d, *J*=3.7 Hz, 1H, C*H*), 4.71 (d, *J*=2.9 Hz, 1H, C*H*), 4.25 (d, *J*=4.3 Hz, 1H, C*H*), 1.46 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7 (*C*), 136.1 (*C*), 128.1 (*C*H), 127.8 (*C*H), 128.6 (*C*), 112.7 (*C*), 106.6 (*C*H), 82.2 (*C*H), 81.4 (*C*H), 77.1 (*C*H), 74.6 (*C*H), 72.2 (CH_2), 26.5 (CH_3), 26.1 (CH_3); HRMS (ESI^+) *m*/*z* calcd for $C_{16}H_{18}O_6$+Na: 329.1001, found: 329.0979.

*4.2.2. (1S,4R,5S,8S)-8-Benzyloxy-4-(tert-butyldimethylsilyloxy)-3-hydroxy-7-keto-2,6-dioxabicyclo[3.3.0]octane (**5**)*

4.2.2.1. Deprotection of acetonide. A solution of **4** (1.50 g, 4.90 mmol) in 91% aqueous TFA (8 mL) was stirred at 10 °C for 12 h and then concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/AcOEt=1/2) to give the corresponding 1,2-diol (1.19 g, 4.46 mmol, 91%) as a colorless oil. R_f=0.35 (silica gel, hexane/AcOEt=1/2); IR (NaCl) 3550 (O–H), 2950 (C–H), 1789 (C=O), 1142 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.18 (m, 5H, Ar*H*), 5.35 (m, 1H, C*H*), 4.49–4.56 (m, 2H, C*H*, CH_2), 4.18–4.07 (m, 6H, C*H*, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) α-anomer: δ 174.1 (*C*), 136.1 (*C*), 128.5 (*C*H), 128.4 (*C*H), 128.3(*C*), 103.4 (*C*H), 84.2 (*C*H), 77.1 (*C*H), 74.7 (*C*H), 74.1 (C*H*), 72.4 (CH_2); β-anomer: δ 173.3 (*C*), 136.1 (*C*), 128.4 (*C*H), 128.3 (*C*H), 128.2 (*C*), 98.1 (C*H*), 83.7 (*C*H), 76.2 (*C*H), 74.6 (*C*H), 73.9 (C*H*), 72.4 (CH_2). Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.44; H, 5.60.

4.2.2.2. TBS-protection. To a solution of the 1,2-diol (0.200 g, 0.752 mmol) and triethylamine (0.230 g, 2.27 mmol) in CH_2Cl_2 (20 mL) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.300 g, 1.13 mmol) at −78 °C. After stirring for 30 min, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (10 mL) at −78 °C and extracted with ethyl acetate (10 mL×3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/AcOEt=5/1) to give **5** (0.260 g, 0.684 mmol, 91%) as a colorless oil. R_f=0.43 (silica gel, hexane/AcOEt=3/1); IR (NaCl) 3651 (O–H), 2954 (C–H), 1786 (C=O), 1471 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) α-anomer: δ 7.44–7.32 (m, 5H, Ar*H*), 5.52 (d, *J*=4.0 Hz, 1H, C*H*), 4.94 (d, *J*=12.1 Hz, 1H, PhC*H*), 4.83 (d, *J*=12.1 Hz, 1H, PhCH_2), 4.77 (dd, *J*=4.6, 3.3 Hz, 1H, C*H*), 4.56 (d, *J*=3.3 Hz, 1H, C*H*), 4.29 (m, 1H, C*H*), 4.17 (d, 1H, *J*=4.6 Hz, C*H*), 3.26–3.22 (br s, 1H, O*H*), 0.91 (s, 9H, CH_3), 0.18 (s, 6H, CH_3); β-anomer: δ 7.44–7.32 (m, 5H, Ar*H*), 5.64 (d, *J*=4.4 Hz, 1H, C*H*), 4.96 (d, *J*=12.3 Hz, 1H, PhCH_2), 4.86 (d, *J*=12.3 Hz, 1H, PhCH_2), 4.84 (m, 1H, C*H*), 4.66 (d, *J*=4.8 Hz, 1H, C*H*), 4.29 (m, 1H, C*H*), 4.22 (d, *J*=4.6 Hz, 1H, C*H*), 3.26–3.22 (br s, 1H, O*H*), 0.91 (s, 9H, CH_3), 0.13 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) α-anomer: δ 172.2 (*C*), 136.3 (*C*), 128.5 (*C*H), 128.3 (*C*H), 128.2 (*C*), 98.6 (*C*H), 84.6 (*C*H), 76.6 (*C*H), 75.1 (*C*H), 74.4 (*C*H), 72.4 (CH_2), 25.6 (*C*), 17.9 (CH_3), −5.0 (CH_3); β-anomer: δ 172.2 (*C*), 136.3 (*C*), 128.5 (*C*H), 128.3 (*C*H), 128.2 (*C*), 98.3 (*C*H), 84.0 (*C*H), 76.6 (*C*H), 75.1 (*C*H), 74.4 (*C*H), 72.1 (CH_2), 25.5 (*C*), 17.9 (CH_3), −5.0 (CH_3); HRMS (ESI^+) *m*/*z* calcd for $C_{19}H_{28}O_6Si$+Na: 403.1553, found: 403.1582.

*4.2.3. (1S,3S,4S,5S,8S)-4-Benzyloxy-8-(tert-butyldimethylsilyloxy)-3-keto-2,6-dioxabicyclo[3.3.0]octane (**6**)*

4.2.3.1. Reduction with $NaBH_4$. To a solution of **5** (0.900 g, 2.37 mmol) in MeOH (4.7 mL) was added $NaBH_4$ (0.178 g, 4.73 mmol) at −40 °C. After stirring for 30 min, the reaction mixture was quenched by addition of H_2O (10 mL) and extracted with AcOEt (20 mL×3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/AcOEt=2/1) to give the corresponding 1,4-diol (0.875 g, 2.29 mmol, 97%) as colorless crystals. R_f=0.21 (silica gel, hexane/AcOEt=2/1); $[\alpha]_D^{23}$ −16.7 (*c* 1.0, $CHCl_3$); IR (KBr) 3550 (O–H), 3035 (C–H), 1763 (C=O), 1498 (C=C), 1094 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.36 (m, 5H, Ar*H*), 5.02 (d, *J*=11.9 Hz, PhCH_2), 4.83 (d, *J*=11.9 Hz, PhCH_2), 4.37 (dd, *J*=4.4, 2.9 Hz, 1H, C*H*), 4.28 (dd, *J*=2.9, 2.6 Hz, 1H, C*H*), 4.20 (d, *J*=4.4 Hz, 1H, C*H*), 4.12 (ddd, *J*=8.3, 3.5, 2.6 Hz, 1H, C*H*), 3.76–3.69 (m, 2H, CH_2), 2.65 (s, 1H, O*H*), 2.12 (m, 1H, O*H*), 0.90 (s, 9H, CH_3), 0.17 (s, 3H, CH_3), 0.15 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0 (*C*),136.1 (*C*), 128.7 (*C*H), 128.6 (*C*H), 128.3 (*C*), 81.5 (*C*H), 75.6 (*C*H), 72.8 (CH_2), 71.4 (*C*H), 68.1 (*C*H), 63.4 (CH_2), 25.7 (*C*), 17.9 (CH_3), −4.6 (CH_3); HRMS (ESI^+) *m*/*z* calcd for $C_{19}H_{30}O_6Si$+Na: 405.1709, found: 405.1737.

4.2.3.2. Cyclization with TsCl. To a mixture of 1,4-diol (0.220 g, 0.575 mmol), triethylamine (0.176 g, 1.74 mmol), and di-*n*-butyltin oxide (0.0428 g, 0.172 mmol) in CH_2Cl_2 (1.2 mL) was added *p*-toluenesulfonyl chloride (0.124 g, 0.650 mmol). After stirring for 5 h, the reaction mixture was quenched by addition of H_2O (10 mL) and extracted with AcOEt (20 mL×3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/AcOEt=10/1) to give **6** (0.172 g, 0.472 mmol, 82%) as a colorless oil. R_f=0.71 (silica gel, hexane/AcOEt=2/1); $[\alpha]_D^{22}$ +43.5 (*c* 1.0, $CHCl_3$); IR (NaCl) 2952 (C–H), 1801 (C=O), 1560 (C=C), 1134 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44–7.26 (m, 5H, Ar*H*), 4.94 (d, *J*=12.3 Hz, 1H, PhCH_2), 4.87 (d, *J*=12.3 Hz, 1H, PhCH_2), 4.72 (dd, *J*=4.2, 3.7 Hz, 1H, C*H*), 4.62 (d, *J*=3.7 Hz, 1H, C*H*), 4.46 (d, *J*=4.2 Hz, 1H, C*H*), 4.15 (d, *J*=4.8 Hz, 1H, C*H*), 4.14 (dd, *J*=9.0, 4.8 Hz, 1H, CH_2), 3.86 (d, *J*=9.0 Hz, 1H, CH_2), 0.88 (s, 9H, CH_3), 0.10 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7 (*C*), 136.4 (*C*), 129.5 (*C*H), 128.3 (*C*H), 127.0 (*C*), 85.0 (*C*H), 76.8 (CH_2), 75.9 (*C*H), 75.4 (*C*H), 73.9 (*C*H), 72.3 (CH_2), 25.6 (CH_3), 17.9 (*C*), −4.9 (CH_3); HRMS (ESI^+) *m*/*z* calcd for $C_{19}H_{28}O_5Si$+Na: 387.1604, found: 387.1610.

*4.2.4. (1S,3S,4S,5S,8R)-4-Benzyloxy-8-(tert-butyldimethylsilyloxy)-3-methoxy-2,6-dioxabicyclo[3.3.0]octane (**7a**) and (1S,3R,4S,5S,8R)-4-benzyloxy-8-(tert-butyldimethylsilyloxy)-3-methoxy-2,6-dioxabicyclo[3.3.0]octane (**7b**)*

4.2.4.1. Reduction with DIBAL-H. To a solution of **6** (0.150 g, 0.412 mmol) in toluene (0.8 mL) was added diisobutylaluminium hydride (1.0 M solution in THF, 1.2 mL, 1.24 mmol) at −78 °C. After stirring for 30 min, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (10 mL), filtered through a pad of Celite, and extracted with AcOEt (20 mL×3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/AcOEt=4/1) to give the corresponding lactols (0.142 g, 0.388 mmol, 94%) as a colorless oil. R_f=0.18 (silica gel, hexane/AcOEt=5/1); IR (NaCl) 3323 (O–H), 2949 (C–H), 1497 (C=C), 1134 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) α-anomer: δ 7.35–7.25 (m, 5H, Ar*H*), 5.32 (dd, *J*=3.9, 3.8 Hz, 1H, C*H*), 4.78 (d, *J*=11.7 Hz, 1H, PhCH_2), 4.74 (dd, *J*=4.8, 4.4 Hz, 1H, C*H*), 4.58 (d, *J*=11.7 Hz, 1H, PhCH_2), 4.54 (d, *J*=4.4 Hz, 1H, C*H*), 4.27 (d, *J*=3.3 Hz, 1H, C*H*), 4.00 (dd, *J*=9.3, 3.3 Hz, 1H, CH_2), 3.83 (d, *J*=4.8, 3.8 Hz, 1H, C*H*), 3.80 (d, *J*=9.3 Hz, 1H, CH_2), 3.20 (d, *J*=3.9 Hz, 1H, O*H*), 0.88 (s, 9H, CH_3), 0.08 (s, 6H, CH_3); β-anomer: δ 7.35–7.25 (m, 5H, Ar*H*), 5.20 (dd, *J*=9.0, 4.8 Hz, 1H, C*H*), 4.75 (m, 1H, C*H*), 4.71 (s, 2H, PhCH_2), 4.63 (d, *J*=4.0 Hz, 1H, C*H*), 4.42 (dd, *J*=4.6, 2.3 Hz, 1H, C*H*), 4.35 (dd, *J*=9.3, 4.6 Hz, 1H, CH_2), 4.14 (d, *J*=9.0 Hz, 1H, O*H*), 3.88 (dd, *J*=4.8, 4.4 Hz, 1H, C*H*), 3.72 (dd, *J*=9.3, 2.3 Hz, 1H, CH_2), 0.88 (s, 9H, CH_3), 0.08 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) α-anomer: δ 137.6 (*C*), 128.3 (*C*H), 128.0 (*C*H), 127.9 (*C*), 101.9 (*C*H), 87.7 (*C*H), 84.1 (*C*H), 80.2 (*C*H), 77.7 (CH_2), 76.1 (*C*H), 72.3 (CH_2), 25.7 (*C*), 17.9 (*C*), −5.0 (CH_3); β-anomer: δ 136.9 (*C*), 128.5 (*C*H), 128.1 (*C*H), 127.7 (*C*), 96.2 (*C*H), 87.8 (*C*H), 84.1 (*C*H), 80.3 (*C*H), 78.2 (*C*H), 76.1 (CH_2), 72.1 (CH_2), 25.7 (CH_3), 17.9 (*C*), −4.9 (CH_3); HRMS (ESI^+) *m*/*z* calcd for $C_{19}H_{30}O_5Si$+Na: 389.1760, found: 389.1735.

4.2.4.2. Etherification with CH_3I. To a solution of the lactols (0.521 g, 1.42 mmol) in THF (7.1 mL) were added potassium *tert*-butoxide (0.479 g, 4.27 mmol), methyl iodide (4.04 g, 28.5 mmol), and tetra-*n*-butylammonium iodide (0.158 g, 0.427 mmol) at −78 °C and the resulting mixture was slowly warmed to −15 °C. After stirring for 2 h, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (20 mL) and extracted with AcOEt (20 mL×3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/AcOEt=11/1, 5/1) to give **7a** (0.270 g, 0.710 mmol, 50%) and **7b** (0.251 g, 0.660 mmol, 46%) as colorless oils. Compound **7a**: R_f=0.71 (silica gel, hexane/AcOEt=5/1); $[\alpha]_D^{22}$ +113.8 (*c* 1.0, $CHCl_3$); IR (NaCl) 3035 (C–H), 2930 (C–H), 1497 (C=C), 1124 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H, Ar*H*), 4.89 (d, *J*=2.8 Hz, 1H, C*H*), 4.79 (d, *J*=11.9 Hz, 1H, PhCH_2), 4.75 (d, *J*=4.9, 4.0 Hz, 1H, C*H*), 4.57 (d, *J*=11.9 Hz, 1H, PhCH_2), 4.43 (d, *J*=4.0 Hz, 1H, C*H*), 4.32 (d, *J*=3.3 Hz, 1H, C*H*), 4.04 (dd, *J*=9.4, 3.3 Hz, 1H, CH_2), 3.89 (dd, *J*=4.9, 2.8 Hz, 1H, C*H*), 3.84 (d, *J*=9.4 Hz, 1H, CH_2), 3.36 (s, 3H, CH_3), 0.88 (s, 9H, CH_3), 0.09 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7 (*C*), 129.3 (*C*H), 127.6 (*C*H), 127.4 (*C*), 108.6 (*C*H), 87.9 (*C*H), 83.0 (*C*H), 80.5 (*C*H), 76.4 (*C*H), 76.1 (CH_2), 72.6 (CH_2), 55.5 (CH_3), 25.7 (CH_3), 17.3 (CH_3), −4.9 (CH_3); HRMS (ESI^+) *m*/*z* calcd for $C_{20}H_{32}O_5Si$+Na: 403.1917, found: 403.1880. Compound **7b**: R_f=0.45 (silica gel, hexane/AcOEt=5/1); $[\alpha]_D^{22}$ +32.6 (*c* 1.0, $CHCl_3$); IR (NaCl) 3030 (C–H), 2952 (C–H), 1498 (C=C), 1097 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.27 (m, 5H, Ar*H*), 4.77 (d, *J*=12.5 Hz, 1H, PhCH_2), 4.75 (d, *J*=5.0 Hz, 1H, C*H*), 4.68 (d, *J*=12.5 Hz, 1H, PhCH_2), 4.65 (dd, *J*=4.8, 3.8 Hz, 1H, C*H*), 4.34 (d, *J*=4.0 Hz, 1H, C*H*), 4.30 (t, *J*=3.8 Hz, 1H, C*H*), 4.27 (m, 1H, CH_2), 3.75 (dd, *J*=11.2, 4.0 Hz, 1H, CH_2), 3.72 (dd, *J*=5.0, 4.8 Hz, 1H, C*H*), 3.40 (s, 3H, CH_3), 0.88 (s, 9H, CH_3), 0.08 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2 (*C*), 128.3 (*C*H), 128.2 (*C*H), 127.9 (*C*), 102.3 (*C*H), 88.5 (*C*H), 78.5 (*C*H), 78.1 (*C*H), 77.8 (*C*H), 75.1 (CH_2), 72.1 (CH_2), 55.8 (CH_3), 25.7 (CH_3), 18.0 (CH_3), −4.9 (CH_3); HRMS (ESI^+) *m*/*z* calcd for $C_{20}H_{32}O_5Si$+Na: 403.1917, found: 403.1926.

*4.2.5. (1R,3S,4S,5S,8S)-4-Benzyloxy-8-hydroxy-3-methoxy-2,6-dioxabicyclo[3.3.0]octane (**8a**)*

To a solution of **7a** (0.453 g, 1.19 mmol) in THF (2.4 mL) was added tetrabutylammonium fluoride (1.0 M solution in THF, 2.38 mL, 2.38 mmol). After stirring for 1 h, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (10 mL) and extracted with AcOEt (20 mL×3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/AcOEt=5/1) to give **8a** (0.313 g, 1.18 mmol, 99%) as a colorless oil. R_f=0.10 (silica gel, hexane/AcOEt=2/1); $[\alpha]_D^{23}$ +146.4 (*c* 1.0, $CHCl_3$); IR (NaCl) 3435 (O–H), 2939 (C–H), 1499 (C=C), 1148 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5H, Ar*H*), 4.88 (d, *J*=2.0 Hz, 1H, C*H*), 4.79 (dd, *J*=5.7,

4.5 Hz, 1H, C*H*), 4.77 (d, *J*=11.7 Hz, 1H, PhC*H*$_2$), 4.55 (d, *J*=11.7 Hz, 1H, PhC*H*$_2$), 4.48 (d, *J*=4.5 Hz, 1H, C*H*), 4.30 (d, *J*=3.2 Hz, 1H, C*H*), 4.03 (dd, *J*=10.0, 3.2 Hz, 1H, C*H*$_2$), 3.89 (d, *J*=10.0 Hz, 1H, C*H*$_2$), 3.88 (dd, *J*=5.7, 2.0 Hz, 1H, C*H*), 3.32 (s, 3H, C*H*$_3$), 2.84 (br s, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6 (*C*), 128.3 (*C*H), 127.7 (*C*H), 127.6 (*C*), 108.5 (*C*H), 87.3 (*C*H), 82.7 (*C*H), 80.5 (*C*H), 75.4 (*C*H), 75.3 (*C*H$_2$), 72.7 (*C*H$_2$), 55.0 (*C*H$_3$); HRMS (ESI$^+$) *m*/*z* calcd for $C_{14}H_{18}O_5$+Na: 289.1052, found: 289.1028.

*4.2.6. (1R,3R,4S,5S,8S)-4-Benzyloxy-8-hydroxy-3-methoxy-2,6-dioxabicyclo[3.3.0]octane (**8b**)*

To a solution of **7b** (0.0639 g, 0.168 mmol) in THF (0.35 mL) was added tetrabutylammonium fluoride (1.0 M solution in THF, 0.34 mL, 0.34 mmol). After stirring for 1 h, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (3 mL) and extracted with AcOEt (10 mL×3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/AcOEt=1/3) to give **8b** (0.0443 g, 0.166 mmol, 99%) as a colorless oil. R_f=0.10 (silica gel, hexane/AcOEt=1/2); $[\alpha]_D^{19}$ +22.9 (*c* 1.0, $CHCl_3$); IR (NaCl) 3491 (O–H), 2991 (C–H), 1498 (C=C), 1107 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59–7.13 (m, 5H, Ar*H*), 4.75 (d, *J*=12.3 Hz, 1H, PhC*H*$_2$), 4.70 (d, *J*=5.0 Hz, 1H, C*H*), 4.64 (d, *J*=12.3 Hz, 1H, PhC*H*$_2$), 4.63 (dd, *J*=5.0, 4.6 Hz, 1H, C*H*), 4.41 (d, *J*=4.6 Hz, 1H, C*H*), 4.29 (dd, *J*=9.5, 3.7 Hz, 1H, C*H*$_2$), 4.24 (d, *J*=3.7 Hz, 1H, C*H*), 3.80 (d, *J*=9.5 Hz, 1H, C*H*$_2$), 3.70 (t, *J*=5.0 Hz, 1H, C*H*), 3.48–3.38 (m, 4H, O*H*, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.0 (*C*), 128.3 (*C*H), 128.1 (*C*H), 127.9 (*C*), 101.9 (*C*H), 87.5 (*C*H), 78.5 (*C*H), 78.0 (*C*H), 76.7 (*C*H), 74.6 (*C*H$_2$), 72.1 (*C*H$_2$), 55.5 (*C*H$_3$). Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.19; H, 6.48.

*4.2.7. (1R,3S,4S,5S,8R)-4-Benzyloxy-8-hydroxy-3-methoxy-2,6-dioxabicyclo[3.3.0]octane (**9a**)*

4.2.7.1. TPAP oxidation. To a mixture of **8a** (0.173 g, 0.650 mmol), molecular sieves (4 Å, 0.173 g), and NMO (97 wt %, 0.152 g, 1.30 mmol) in CH_2Cl_2 (6.5 mL) was added tetrapropylammonium perruthenate (0.0228 g, 0.0650 mmol). After stirring for 12 h, the reaction mixture was filtered through a pad of Celite and washed with ethyl acetate. The filtrate was concentrated in vacuo and the resulting residue was purified by column chromatography (silica gel, hexane/AcOEt=1/1) to give the corresponding ketone (0.149 g, 0.566 mmol, 87%) as a colorless oil. R_f=0.50 (silica gel, hexane/AcOEt=1/2); $[\alpha]_D^{25}$ +153.7 (*c* 1.0, $CHCl_3$); IR (NaCl) 2935 (C–H), 1771 (C=O), 1498 (C=C), 1109 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H, Ar*H*), 5.13 (dd, *J*=7.3, 5.1 Hz, 1H, C*H*), 4.99 (s, 1H, C*H*), 4.73 (d, *J*=11.9 Hz, 1H, PhC*H*$_2$), 4.65 (d, *J*=11.9 Hz, 1H, PhC*H*$_2$), 4.42 (d, *J*=7.3 Hz, 1H, C*H*), 4.33 (dd, *J*=17.4 Hz, 1H, C*H*$_2$), 4.09 (d, *J*=17.4 Hz, 1H, C*H*$_2$), 3.96 (d, *J*=5.1 Hz, 1H, C*H*), 3.35 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.8 (*C*), 137.4 (*C*), 128.4 (*C*H), 127.8 (*C*H), 128.3 (*C*), 108.3 (*C*H), 81.9 (*C*H), 81.0 (*C*H), 76.6 (*C*H), 72.7 (*C*H$_2$), 71.7 (*C*H$_2$), 55.4 (*C*H$_3$). Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.74; H, 6.19.

4.2.7.2. Stereoselective reduction with $NaBH_4$. To a solution of the ketone (0.0211 g, 0.0799 mmol) in EtOH (0.8 mL) was added $NaBH_4$ (0.00360 g, 0.0953 mmol) at 0 °C. After stirring for 30 min, the reaction mixture was quenched by addition of H_2O (3 mL) and extracted with ethyl acetate (20 mL×3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/AcOEt=2/1) to give **9a** (0.0206 g, 0.0775 mmol, 97%) as a colorless oil. R_f=0.20 (silica gel, hexane/AcOEt=1/2); $[\alpha]_D^{25}$ +151.0 (*c* 1.0, $CHCl_3$); IR (NaCl) 3450 (O–H) 2935 (C–H), 1499 (C=C), 1141 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H, Ar*H*), 5.03 (d, *J*=5.3 Hz, 1H, C*H*), 4.82 (d, *J*=11.7 Hz, 1H, PhC*H*$_2$), 4.73 (dd, *J*=5.7, 5.5 Hz, 1H, C*H*), 4.64 (d, *J*=5.5 Hz, 1H, C*H*), 4.59 (d, *J*=11.7 Hz, 1H, PhC*H*$_2$), 4.20 (ddd, *J*=10.6, 5.7, 5.3 Hz, 1H, C*H*), 4.02 (dd, *J*=9.3, 5.3 Hz, 1H, C*H*$_2$), 3.88 (dd, *J*=5.7, 5.3 Hz, 1H, C*H*), 3.81 (dd, *J*=9.3, 5.7 Hz, 1H, C*H*$_2$), 3.37 (s, 3H, CH_3), 3.05 (d, *J*=10.6 Hz, 1H, O*H*); ^{13}C NMR ($CDCl_3$) δ 137.4 (*C*), 128.5 (*C*H), 127.9 (*C*H), 127.9 (*C*), 109.0 (*C*H), 81.5 (*C*H), 81.2 (*C*H), 75.2 (*C*H), 73.7 (*C*H), 73.3 (*C*H$_2$), 71.2 (*C*H$_2$), 55.3 (*C*H$_3$); HRMS (ESI$^+$) *m*/*z* calcd for $C_{14}H_{18}O_5$+Na: 373.1627, found: 373.1640.

*4.2.8. (1R,3R,4S,5S,8R)-4-Benzyloxy-8-hydroxy-3-methoxy-2,6-dioxabicyclo[3.3.0]octane (**9b**)*

4.2.8.1. TPAP oxidation. To a mixture of **8b** (0.410 g, 1.54 mmol), molecular sieves (4 Å, 0.410 g), and NMO (97 wt %, 0.372 g, 3.08 mmol) in CH_2Cl_2 (15.5 mL) was added tetrapropylammonium perruthenate (0.0541 g, 0.154 mmol). After stirring for 12 h, the reaction mixture was filtered through a pad of Celite and washed with ethyl acetate. The filtrate was concentrated in vacuo and the resulting residue was purified by column chromatography (silica gel, hexane/AcOEt=1/1) to give the corresponding ketone (0.353 g, 1.34 mmol, 87%) as a colorless oil. R_f=0.50 (silica gel, toluene/acetone=10/1); $[\alpha]_D^{22}$ +46.3 (*c* 0.8, $CHCl_3$); IR (NaCl) 2935 (C–H), 1771 (C=O), 1498 (C=C), 1109 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.26 (m, 5H, Ar*H*), 4.83 (d, *J*=7.0, 6.2 Hz, 1H, C*H*), 4.83 (d, *J*=12.3 Hz, 1H, PhC*H*$_2$), 4.75 (d, *J*=4.2 Hz, 1H, PhC*H*$_2$), 4.67 (d, *J*=12.3 Hz, 1H, PhC*H*$_2$), 4.38 (d, *J*=17.4 Hz, 1H, C*H*$_2$), 4.33 (d, *J*=7.0 Hz, 1H, C*H*), 4.00 (d, *J*=17.4 Hz, 1H, C*H*$_2$), 3.74 (dd, *J*=6.2, 4.2 Hz, 1H, C*H*), 3.29 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.5 (*C*=O), 137.0 (*C*), 128.5 (*C*H), 128.3 (*C*H), 128.2 (*C*), 101.6 (*C*H), 78.7 (*C*H), 76.6 (*C*H), 75.2 (*C*H), 72.7 (*C*H$_2$), 69.4 (*C*H$_2$), 55.1 (*C*H$_3$). Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.60; H, 5.99.

4.2.8.2. Stereoselective reduction with $NaBH_4$. To a solution of the ketone (0.223 g, 0.844 mmol) in EtOH (8.5 mL) was added $NaBH_4$ (0.0383 g, 1.01 mmol) at 0 °C. After stirring for 30 min, the reaction mixture was quenched by addition of H_2O (10 mL) and extracted with ethyl acetate (20 mL×3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/AcOEt=2/1) to give **9b** (0.205 g, 0.770 mmol, 91%) as a colorless oil. R_f=0.20 (hexane/AcOEt=1/2); $[\alpha]_D^{23}$ −16.7 (*c* 1.0, $CHCl_3$); IR (NaCl) 3583 (O–H), 2956 (C–H), 1498 (C=C), 1103 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.29 (m, 5H, Ar*H*), 4.82 (d, *J*=5.1 Hz, 1H, C*H*), 4.78 (d, *J*=12.5 Hz, 1H, PhC*H*$_2$), 4.66 (d, *J*=12.5 Hz, 1H, PhC*H*$_2$), 4.55 (d, *J*=5.5 Hz, 1H, C*H*), 4.44 (dd, *J*=5.5, 5.3 Hz, 1H, C*H*), 4.23 (ddd, *J*=10.6, 6.1, 4.2 Hz, 1H, C*H*$_2$), 3.90 (dd, *J*=9.3, 6.1 Hz, 1H, C*H*$_2$), 3.89 (dd, *J*=9.3, 4.2 Hz, 1H, C*H*), 3.80 (dd, *J*=5.3, 5.1 Hz, 1H, C*H*), 3.50 (s, 3H, C*H*$_3$), 2.74 (d, *J*=10.6 Hz, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.1 (*C*), 128.5 (*C*H), 128.3 (*C*H), 128.1 (*C*), 103.0 (*C*H), 81.9 (*C*H), 78.6 (*C*H), 78.5 (*C*H), 73.7 (*C*H), 72.6 (*C*H$_2$), 71.8 (*C*H$_2$), 57.0 (*C*H$_3$). Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.54; H, 7.17.

*4.2.9. (1R,3S,4S,5R,8R)-4-Hydroxy-3-methoxy-2,6-dioxabicyclo[3.3.0]oct-8-yl isovalerate (**10a**)*

4.2.9.1. Esterification with isovaleric acid. To a solution of **9a** (0.0694 g, 0.261 mmol), 4-dimethylaminopyridine (63.7 mg, 0.521 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.100 g, 0.522 mmol) in CH_2Cl_2 (0.5 mL) was added isovaleric acid (53.3 mg, 0.522 mmol). After stirring for 30 min, the reaction mixture was quenched by addition of H_2O (5 mL) and extracted with ethyl acetate (20 mL×3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by

column chromatography (silica gel, hexane/AcOEt=10/1) to give the corresponding ester (0.0904 g, 0.258 mmol, 99%) as a colorless oil. R_f=0.82 (silica gel, hexane/AcOEt=2/1); $[\alpha]_D^{25}$ +151.1 (*c* 1.0, $CHCl_3$); IR (NaCl) 2959 (C–H), 1740 (C=O), 1497 (C=C), 1122 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5H, Ar*H*), 5.02 (ddd, *J*=7.0, 6.6, 5.3 Hz, 1H, C*H*), 4.99 (d, *J*=2.6 Hz, 1H, C*H*), 4.78 (d, *J*=11.7 Hz, 1H, PhCH_2), 4.73 (t, *J*=5.1 Hz, 1H, C*H*), 4.66 (dd, *J*=5.3, 5.1 Hz, 1H, C*H*), 4.59 (d, *J*=11.7 Hz, 1H, PhCH_2), 4.10 (dd, *J*=8.6, 7.0 Hz, 1H, CH_2), 3.90 (dd, *J*=5.1, 2.6 Hz, 1H, C*H*), 3.88 (dd, *J*=8.6, 6.6 Hz, 1H, CH_2), 3.37 (s, 3H, CH_3), 2.28–2.26 (m, 2H, CH_2), 2.15 (m, 1H, C*H*), 0.97 (d, *J*=6.6 Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ 137.4 (*C*), 128.5 (CH_2), 127.9 (CH_2), 127.9 (*C*), 109.0 (*C*H), 81.5 (*C*H), 81.2 (*C*H), 75.2 (*C*H), 73.7 (*C*H), 73.3 (CH_2), 71.2 (CH_2), 55.3 (CH_3);^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5 (*C*), 137.7 (*C*), 128.3 (*C*H), 127.8 (*C*H), 127.7 (*C*), 108.9 (*C*H), 82.7 (*C*H), 80.8 (*C*H), 78.7 (*C*H), 72.8 (*C*H), 72.7 (CH_2), 69.4 (CH_2), 55.5 (CH_3), 42.9 (CH_2), 25.6 (*C*H), 22.3 (CH_3), 22.2 (CH_3); HRMS (ESI^+) *m*/*z* calcd for $C_{19}H_{26}O_6$+Na: 373.1627, found: 373.1640.

4.2.9.2. Deprotection of benzyl group by hydrogenolysis. A solution of the ester (0.0452 g, 0.129 mmol) in EtOH (1.0 mL) was hydrogenated in the presence of 5% Pd on activated carbon (0.025 g) at room temperature for 12 h. Pd catalyst was removed by filtration through a pad of Celite and washed with ethyl acetate (50 mL). The filtrate was concentrated in vacuo and the resulting residue was purified by column chromatography (silica gel, hexane/AcOEt=5/1) to give **10a** (0.0299 g, 0.115 mmol, 89%) as a colorless oil. R_f=0.30 (silica gel, hexane/AcOEt=2/1); $[\alpha]_D^{25}$ +170.0 (*c* 1.0, $CHCl_3$); IR (NaCl) 3415 (O–H), 2960 (C–H), 1747 (C=O), 1182 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.13 (ddd, *J*=7.2, 6.2, 6.1 Hz, 1H, C*H*), 4.93 (d, *J*=1.0 Hz, 1H, C*H*), 4.80 (dd, *J*=6.1, 5.1 Hz, 1H, C*H*), 4.68 (dd, *J*=5.9, 5.1 Hz, 1H, C*H*), 4.55 (dd, *J*=9.0, 6.2 Hz, 1H, CH_2), 4.05 (ddd, *J*=5.9, 5.1, 1.0 Hz, 1H, C*H*), 3.88 (dd, *J*=9.0, 7.2 Hz, 1H, CH_2), 3.38 (s, 3H, CH_3), 3.05 (d, *J*=5.1 Hz, 1H, O*H*), 2.34–2.26 (m, 2H, CH_2), 2.14 (m, 1H, C*H*), 0.98 (d, *J*=6.6 Hz, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3 (*C*), 111.4 (*C*H), 81.1 (*C*H), 79.4 (*C*H), 75.1 (*C*H), 72.1 (*C*H), 68.3 (CH_2), 55.4 (CH_3), 43.0 (CH_2), 25.6 (*C*H), 22.2 (CH_3), 22.2 (CH_3); HRMS (ESI^+) *m*/*z* calcd for $C_{12}H_{20}O_6$+Na: 283.1158, found: 283.1132.

*4.2.10. (1R,3R,4S,5R,8R)-4-Hydroxy-3-methoxy-2,6-dioxabicyclo[3.3.0]oct-8-yl isovalerate (**10b**)*

4.2.10.1. Esterification with isovaleric acid. To a solution of **9b** (0.164 g, 0.616 mmol), 4-dimethylaminopyridine (0.149 g, 1.22 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.234 g, 1.22 mmol) in CH_2Cl_2 (1.2 mL) was added isovaleric acid (0.125 g, 1.22 mmol). After stirring for 30 min, the reaction mixture was quenched by addition of H_2O (5 mL) and extracted with ethyl acetate (20 mL×3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/AcOEt=5/1) to give the corresponding ester (0.201 g, 0.574 mmol, 93%) as a colorless oil. R_f=0.82 (silica gel, hexane/AcOEt=1/2); $[\alpha]_D^{29}$ +77.0 (*c* 1.0, $CHCl_3$); IR (NaCl) 2929 (C–H), 1736 (C=O), 1122 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.26 (m, 5H, Ar*H*), 5.02 (ddd, *J*=7.9, 5.5, 3.7 Hz, 1H, C*H*), 4.77 (d, *J*=5.1 Hz, 1H, C*H*), 4.76 (d, *J*=12.4 Hz, 1H, PhCH_2), 4.73 (dd, *J*=4.9, 3.7 Hz, 1H, C*H*), 4.67 (d, *J*=12.4 Hz, 1H, PhCH_2), 4.56 (dd, *J*=5.1, 4.9 Hz, 1H, C*H*), 4.12 (dd, *J*=9.3, 7.9 Hz, 1H, CH_2), 3.88 (dd, *J*=9.3, 5.5 Hz, 1H, CH_2), 3.90 (t, *J*=5.1 Hz, 1H, C*H*), 3.44 (s, 3H, CH_3), 2.27–2.24 (m, 2H, CH_2), 2.14 (m, 1H, C*H*), 0.97 (d, *J*=6.6 Hz, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3 (*C*), 137.1 (*C*), 128.4 (*C*H), 128.2 (*C*H), 128.0 (*C*), 101.7 (*C*H), 78.9 (*C*H), 78.8 (*C*H), 77.2 (*C*H), 73.1 (CH_2), 72.4 (CH_2), 68.5 (CH_2), 55.4 (CH_3), 42.9 (CH_2), 25.6 (*C*H), 22.2 (CH_3), 22.2 (CH_3). Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 65.19; H, 7.21.

4.2.10.2. Deprotection of benzyl group by hydrogenolysis. A solution of the ester (0.190 g, 0.543 mmol) in EtOH (2.5 mL) was hydrogenated in the presence of 5% Pd on activated carbon (0.050 g) at room temperature for 12 h. Pd catalyst was removed by filtration through a pad of Celite and washed with ethyl acetate (50 mL). The filtrate was concentrated in vacuo and the resulting residue was purified by column chromatography (silica gel, hexane/AcOEt=2/1) to give **10b** (0.137 g, 0.527 mmol, 97%) as a colorless oil. R_f=0.30 (silica gel, hexane/AcOEt=2/1); $[\alpha]_D^{29}$ +66.8 (*c* 1.0, $CHCl_3$); IR (NaCl) 3583 (O–H), 2960 (C–H), 1737 (C=O), 1122 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.00 (ddd, *J*=8.0, 5.5, 5.3 Hz, 1H, C*H*), 4.83 (d, *J*=5.0 Hz, 1H, C*H*), 4.82 (dd, *J*=5.5, 5.1 Hz, 1H, C*H*), 4.51 (dd, *J*=5.3, 5.1 Hz, 1H, C*H*), 4.12 (ddd, *J*=11.5, 5.3, 5.0 Hz, 1H, C*H*), 4.09 (dd, *J*=9.3, 5.3 Hz, 1H, CH_2), 3.91 (dd, *J*=9.3, 8.0 Hz, 1H, CH_2), 3.45 (s, 3H, CH_3), 3.05 (d, *J*=11.5 Hz, 1H, O*H*), 2.28–2.26 (m, 2H, CH_2), 2.14 (m, 1H, C*H*), 0.98 (d, *J*=6.6 Hz, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3 (*C*), 102.0 (*C*H), 80.2 (*C*H), 78.8 (*C*H), 77.2 (*C*H), 73.4 (*C*H), 68.3 (CH_2), 55.4 (CH_3), 43.0 (CH_2), 25.6 (*C*H), 22.2 (CH_3), 22.2 (CH_3). Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.33; H, 7.35.

*4.2.11. (1S,3S,4R,5R,8R)-4-Azido-3-methoxy-2,6-dioxabicyclo[3.3.0]oct-8-yl isovalerate (**11a**)*

To a solution of **10a** (0.0900 g, 0.346 mmol) and pyridine (0.0821 g, 1.04 mmol) in CH_2Cl_2 (0.7 mL) was added trifluoromethanesulfonic anhydride (0.195 g, 0.691 mmol) at 0 °C. After stirring for 1 h, the reaction mixture was quenched by addition of H_2O (2 mL) and extracted with ethyl acetate (20 mL×3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the corresponding trifluoromethanesulfonate, which was used without further purification. To a solution of this crude in DMF (0.7 mL) was added sodium azide (0.0676 g, 1.04 mmol). After stirring for 80 h at 40 °C, the reaction mixture was quenched by addition of H_2O (5 mL) and extracted with ethyl acetate (20 mL×3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/AcOEt=11/1) to give **11a** (0.0957 g, 0.336 mmol, 97%) as a colorless oil. R_f=0.43 (silica gel, hexane/AcOEt=10/1); $[\alpha]_D^{25}$ +267.1 (*c* 1.0, $CHCl_3$); IR (NaCl) 2961 (C–H), 2110 (N=N^+=N^-), 1744 (C=O), 1188 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.08 (d, *J*=4.4 Hz, 1H, C*H*), 5.03 (ddd, *J*=7.2, 6.1, 5.5 Hz, 1H, C*H*), 4.82 (dd, *J*=5.9, 5.5 Hz, 1H, C*H*), 4.72 (dd, *J*=5.9, 4.2 Hz, 1H, C*H*), 4.08 (dd, *J*=9.3, 6.1 Hz, 1H, CH_2), 3.78 (dd, *J*=9.3, 7.2 Hz, 1H, CH_2), 3.72 (dd, *J*=4.4, 4.2 Hz, 1H, C*H*), 3.43 (s, 3H, CH_3), 2.32–2.21 (m, 2H, CH_2), 2.14 (m, 1H, C*H*), 0.98 (d, *J*=6.6 Hz, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (*C*), 105.4 (*C*H), 84.9 (*C*H), 77.7 (*C*H), 71.7 (*C*H), 69.0 (CH_2), 66.8 (*C*H), 55.5 (CH_3), 42.9 (CH_2), 25.6 (*C*H), 22.2 (CH_3), 22.1 (CH_3); HRMS (ESI^+) *m*/*z* calcd for $C_{12}H_{19}N_3O_5$+Na: 308.1222, found: 308.1207.

*4.2.12. (1S,3R,4R,5R,8R)-4-Azido-3-methoxy-2,6-dioxabicyclo[3.3.0]oct-8-yl isovalerate (**11b**)*

To a solution of **10b** (0.128 g, 0.492 mmol) and pyridine (0.116 g, 1.47 mmol) in CH_2Cl_2 (1.0 mL) was added trifluoromethanesulfonic anhydride (0.278 g, 0.985 mmol) at 0 °C. After stirring for 1 h, the reaction mixture was quenched by addition of H_2O (2 mL) and extracted with ethyl acetate (20 mL×3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the corresponding trifluoromethanesulfonate, which was used without further purification. To a solution of this crude in DMF (1.0 mL) was added sodium azide (0.0961 g, 1.48 mmol). After stirring for 80 h at 40 °C, the reaction mixture was quenched by addition of H_2O (5 mL) and extracted with ethyl acetate (20 mL×3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by

column chromatography (silica gel, hexane/AcOEt=7/1) to give **11b** (0.135 g, 0.473 mmol, 96%) as a colorless oil. R_f=0.40 (silica gel, hexane/AcOEt=5/1); $[\alpha]_D^{29}$ +77.0 (*c* 1.0, $CHCl_3$); IR (NaCl) 2963 (C–H), 2108 (N=N$^+$=N$^-$), 1742 (C=O), 1117 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99 (ddd, *J*=7.3, 5.3, 3.3 Hz, 1H, C*H*), 4.99–4.96 (m, 2H, C*H*), 4.57 (d, *J*=3.8 Hz, 1H, C*H*), 4.08 (dd, *J*=8.4, 7.3 Hz, 1H, CH_2), 3.91 (dd, *J*=5.7, 3.8 Hz, 1H, C*H*), 3.89 (dd, *J*=8.4, 5.3 Hz, 1H, CH_2), 3.42 (s, 3H, CH_3), 2.28–2.26 (m, 2H, CH_2), 2.14 (m, 1H, C*H*), 0.98 (d, *J*=6.6 Hz, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3 (*C*), 108.6 (*C*H), 85.5 (*C*H), 81.5 (*C*H), 72.6 (*C*H), 70.8 (*C*H), 68.5 (*C*H_2), 55.4 (*C*H_3), 43.0 (*C*H_2), 25.7 (*C*H), 22.3 (*C*H_3), 22.3 (*C*H_3). Anal. Calcd for $C_{12}H_{19}N_3O_5$: C, 50.52; H, 6.71; N, 14.73. Found: C, 50.81; H, 6.64; N, 14.70.

4.2.13. *(1S,3S,4R,5R,8R)-4-Acetamido-3-methoxy-2,6-dioxabicyclo[3.3.0]oct-8-yl isovalerate (**12a**)*

To a solution of **11a** (0.0900 g, 0.316 mmol) and H_2O (0.2 mL) in CH_2Cl_2/THF (3/1, 1.3 mL) was added triphenylphosphine (0.207 g, 0.789 mmol) at 0 °C. After stirring for 2 h, the reaction mixture was quenched by addition of 3% aqueous HCl (5 mL) and extracted with CH_2Cl_2 (20 mL×3). The combined organic extracts were washed with 3% aqueous NaOH (10 mL) and concentrated in vacuo to give the corresponding amine, which was used without further purification. To a solution of the crude amine and pyridine (0.0749 g, 0.947 mmol) in CH_2Cl_2 (0.3 mL) was added acetic anhydride (0.0645 g, 0.632 mmol). After stirring for 3 h, the reaction mixture was quenched by addition of H_2O (3 mL) and extracted with ethyl acetate (10 mL×3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/AcOEt=1/2) to give **12a** (0.0913 g, 0.303 mmol, 96%) as a colorless oil. R_f=0.18 (silica gel, hexane/AcOEt=1/2); $[\alpha]_D^{23}$ +183.8 (*c* 1.0, $CHCl_3$); IR (NaCl) 3311 (N–H), 2963 (C–H), 1736 (C=O), 1636 (C=O), 1191 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (d, *J*=6.8 Hz, 1H, C*H*), 5.02 (d, *J*=4.2 Hz, 1H, C*H*), 4.99 (ddd, *J*=7.9, 6.2, 5.5 Hz, 1H, C*H*), 4.73 (t, *J*=5.1 Hz, 1H, C*H*), 4.48 (dd, *J*=5.5, 5.1 Hz, 1H, C*H*), 4.46 (ddd, *J*=6.8, 5.1, 4.2 Hz, 1H, C*H*), 4.06 (dd, *J*=9.3, 6.2 Hz, 1H, CH_2), 3.78 (dd, *J*=9.3, 7.9 Hz, 1H, CH_2), 3.37 (s, 3H, CH_3), 2.28–2.25 (m, 2H, CH_2), 2.14 (m, 1H, C*H*), 2.02 (s, 3H, CH_3), 0.98 (d, *J*=6.4 Hz, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5 (*C*), 169.8 (*C*), 104.1 (*C*H), 87.5 (*C*H), 77.7 (*C*H), 72.0 (*C*H), 68.3 (*C*H_2), 58.9 (*C*H), 55.1 (*C*H_3), 43.0 (*C*H_2), 25.7 (*C*H), 23.2 (*C*H_3), 22.3 (*C*H_3), 22.2 (*C*H_3); HRMS (ESI$^+$) *m*/*z* calcd for $C_{14}H_{23}NO_6$+Na: 324.1423, found: 324.1403.

4.2.14. *(1S,3R,4R,5R,8R)-4-Acetamido-3-methoxy-2,6-dioxabicyclo[3.3.0]oct-8-yl isovalerate (**12b**)*

A solution of **11b** (0.0638 g, 0.224 mmol) in EtOH (2.0 mL) was hydrogenated in the presence of 5% Pd on activated carbon (0.050 g) at room temperature for 3 h. The Pd catalyst was removed by filtration through a pad of Celite and washed with ethyl acetate (30 mL). The filtrate was concentrated in vacuo to give the corresponding amine, which was used without further purification. To a solution of the crude amine and pyridine (0.0538 g, 0.671 mmol) in CH_2Cl_2 (0.2 mL) was added acetic anhydride (0.0457 g, 0.448 mmol). After stirring for 3 h, the reaction mixture was quenched by addition of H_2O (3 mL) and extracted with ethyl acetate (10 mL×3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/AcOEt=1/2) to give **12b** (0.0586 g, 0.195 mmol, 87%) as a colorless oil. R_f=0.15 (silica gel, hexane/AcOEt=1/2); $[\alpha]_D^{23}$ +65.6 (*c* 1.0, $CHCl_3$); IR (NaCl) 3281 (N–H), 2961 (C–H), 1740 (C=O), 1659 (C=O), 1192 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (d, *J*=7.1 Hz, 1H, C*H*), 4.97 (ddd, *J*=7.3, 5.3, 3.1 Hz, 1H, C*H*), 4.93 (dd, *J*=4.4, 3.1 Hz, 1H, C*H*), 4.90 (s, 1H, C*H*), 4.51 (d, *J*=4.4 Hz, 1H, C*H*), 4.33 (d, *J*=7.1 Hz, 1H, C*H*), 4.06 (dd, *J*=8.4, 7.3 Hz, 1H, CH_2), 3.78 (dd, *J*=8.4, 5.3 Hz, 1H, CH_2), 3.40 (s, 3H, CH_3), 2.28–2.26 (m, 2H, CH_2), 2.13 (m, 1H, C*H*), 1.99 (s, 3H, CH_3), 0.98 (d, *J*=6.4 Hz, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5 (*C*), 169.9 (*C*), 109.5 (*C*H), 86.3 (*C*H), 81.1 (*C*H), 73.0 (*C*H), 68.4 (*C*H_2), 62.1 (*C*H), 55.3 (*C*H_3), 43.0 (*C*H_2), 25.6 (*C*H), 23.0 (*C*H_3), 22.3 (*C*H_3), 22.2 (*C*H_3). Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65. Found: C, 55.66; H, 7.46; N, 5.05.

4.2.15. *Furanodictine A (**1**)*

A solution of **12a** (0.0190 g, 0.0621 mmol) in 70% aqueous AcOH (1.0 mL) was heated under reflux. After 20 h, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (3 mL) and extracted with ethyl acetate (10 mL×3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, AcOEt) to give **1** (0.0150 g, 0.0522 mmol, 84%) as a colorless oil. Under identical conditions, reaction of **12b** gave virtually the same yield of **1**. R_f=0.20 (silica gel, AcOEt); $[\alpha]_D^{22}$ +113.0 (*c* 0.8, $CHCl_3$); IR (NaCl) 3350 (O–H), 3281 (N–H), 2961 (C–H), 1738 (C=O), 1659 (C=O), 1190 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) α-anomer: δ 6.17 (d, *J*=7.5 Hz, 1H, N*H*), 5.55 (dd, *J*=4.4, 3.8 Hz, 1H, C*H*), 4.99 (ddd, *J*=7.3, 6.2, 5.5 Hz, 1H, C*H*), 4.89 (dd, *J*=5.5, 5.4 Hz, 1H, C*H*), 4.56 (dd, *J*=5.4, 3.8 Hz, 1H, C*H*), 4.39 (ddd, *J*=7.5, 4.4, 3.8 Hz, 1H, C*H*), 4.06 (dd, *J*=9.3, 6.2 Hz, 1H, CH_2), 3.95 (d, *J*=3.8 Hz, 1H, O*H*), 3.81 (dd, *J*=9.3, 7.3 Hz, 1H, CH_2), 2.28–2.24 (m, 2H, CH_2), 2.11 (m, 1H, C*H*), 2.03 (s, 3H, CH_3), 0.97 (d, *J*=6.6 Hz, 3H, CH_3), 0.96 (d, *J*=6.6 Hz, 3H, CH_3); β-anomer: δ 5.79 (d, *J*=6.8 Hz, 1H, N*H*), 5.23 (d, *J*=9.2 Hz, 1H, C*H*), 5.10 (ddd, *J*=6.1, 5.9, 4.2 Hz, 1H, C*H*), 4.90 (m, 1H, C*H*), 4.42–4.36 (m, 2H, C*H*), 4.13 (dd, *J*=10.1, 4.2 Hz, 1H, CH_2), 3.81 (dd, *J*=10.1, 6.1 Hz, 1H, CH_2), 3.68 (d, *J*=9.2 Hz, 1H, O*H*), 2.28–2.24 (m, 2H, CH_2), 2.11 (m, 1H, C*H*), 1.99 (s, 3H, CH_3), 0.98 (d, *J*=6.6 Hz, 3H, CH_3), 0.97 (d, *J*=6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) α-anomer: δ 172.6 (*C*), 170.5 (*C*), 98.1 (*C*H), 87.0 (*C*H), 78.0 (*C*H), 72.3 (*C*H), 68.6 (*C*H_2), 58.7 (*C*H), 43.0 (*C*H_2), 25.6 (*C*H), 23.1 (*C*H_3), 22.4 (*C*H_3), 22.3 (*C*H_3); β-anomer: δ 172.7 (*C*), 170.0 (*C*), 103.5 (*C*H), 86.7 (*C*H), 81.9 (*C*H), 73.1 (*C*H), 71.2 (*C*H_2), 60.9 (*C*H), 42.9 (*C*H_2), 25.5 (*C*H), 23.0 (*C*H_3), 22.4 (*C*H_3), 22.3 (*C*H_3); HRMS (ESI$^+$) *m*/*z* calcd for $C_{13}H_{21}NO_6$+Na: 310.1267, found: 310.1241. Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.66; H, 7.03; N, 4.93.

4.2.16. *(1R,3R,4R,5S,8R)-8-Benzyloxy-3,4-isopropylidenedioxy-2,6-dioxabicyclo[3.3.0]octane (**13**)*

4.2.16.1. Reduction with $LiAlH_4$. To a solution of **4** (1.26 g, 4.12 mmol) in THF (32 mL) was added lithium aluminum hydride (0.469 g, 12.3 mmol) at 0 °C. After stirring for 2 h, the reaction mixture was quenched by addition of 50% aqueous THF (30 mL), filtered through a pad of Celite, and extracted with ethyl acetate (20 mL×3). The combined organic extracts were washed with brine (40 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/AcOEt=1/1) to give the corresponding 1,4-diol (1.17 g, 3.77 mmol, 92%) as colorless needles. R_f=0.30 (silica gel, hexane/AcOEt=1/2); $[\alpha]_D^{26}$ −7.1 (*c* 1.0, $CHCl_3$); IR (NaCl) 3323 (O–H), 2949 (C–H), 1497 (C=C), 1134 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5H, Ar*H*), 5.95 (d, *J*=3.7 Hz, 1H, C*H*), 4.79 (d, *J*=11.5 Hz, 1H, PhCH_2), 4.70 (d, *J*=11.5 Hz, 1H, PhCH_2), 4.49 (d, *J*=3.7 Hz, 1H, C*H*), 4.29 (d, *J*=2.6 Hz, 1H, C*H*), 4.17 (dd, *J*=5.1, 2.6 Hz, 1H, C*H*), 4.01 (ddd, *J*=5.1, 5.0, 4.4 Hz, 1H, C*H*), 3.90–3.71 (m, 2H, CH_2), 3.31 (br s, 1H, O*H*), 2.01 (br s, 1H, O*H*), 1.48 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5 (*C*), 128.5 (*C*H), 128.3 (*C*H), 127.2 (*C*), 111.7 (*C*), 104.4 (*C*H), 85.2 (*C*H), 79.4 (*C*H), 77.9 (*C*H), 75.6 (*C*H), 73.8 (*C*H_2), 62.3 (*C*H_2), 26.7 (*C*H_3), 26.1 (*C*H_3); HRMS (ESI$^+$) *m*/*z* calcd for $C_{16}H_{22}O_6Si$+Na: 333.1314, found: 333.1320.

4.2.16.2. Tosylation and cyclization. To a mixture of 1,4-diol (0.781 g, 2.52 mmol), triethylamine (0.510 g, 5.04 mmol), and di-*n*-butyltin oxide (0.188 g, 0.755 mmol) in CH_2Cl_2 (3.9 mL) was added *p*-toluenesulfonyl chloride (0.576 g, 3.02 mmol) at 0 °C. After stirring for 7 h, the reaction mixture was quenched by addition of H_2O (10 mL) and extracted with ethyl acetate (30 mL×3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the corresponding tosylate, which was used without further purification. To a solution of the crude tosylate in THF (6.2 mL) was added sodium hydride (0.181 g, 7.54 mmol) at 0 °C. After stirring for 30 min, the reaction mixture was quenched by addition of satd NH_4Cl (10 mL) and extracted with ethyl acetate (30 mL×3). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/AcOEt=6/1) to give **13** (0.531 g, 1.82 mmol, 72%) as a colorless oil. R_f=0.71 (silica gel, hexane/AcOEt=1/2); $[\alpha]_D^{22}$ +83.2 (*c* 0.9, $CHCl_3$); IR (NaCl) 2952 (C–H), 1496 (C=C), 1134 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5H, Ar*H*), 6.01 (d, *J*=3.7 Hz, 1H, C*H*), 4.83 (dd, *J*=3.8, 3.7 Hz, 1H, C*H*), 4.74 (d, *J*=11.7 Hz, 1H, PhCH_2), 4.58 (d, *J*=3.7 Hz, 1H, C*H*), 4.56 (d, *J*=11.7 Hz, 1H, PhCH_2), 4.47 (d, *J*=3.7 Hz, 1H, C*H*), 4.07 (ddd, *J*=7.0, 4.8, 3.8 Hz, 1H, C*H*), 3.90 (dd, *J*=8.3, 7.0 Hz, 1H, C*H*), 3.69 (dd, *J*=8.3, 4.8 Hz, 1H, C*H*), 1.50 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5 (*C*), 128.5 (*C*H), 128.0 (*C*H), 127.9 (*C*), 112.3 (*C*), 107.2 (*C*H), 85.6 (*C*H), 85.1 (*C*H), 80.7 (*C*H), 78.6 (*C*H), 72.4 (*C*H_2), 69.6 (*C*H_2), 27.3 (*C*H_3), 26.7 (*C*H_3); HRMS (ESI^+) *m*/*z* calcd for $C_{16}H_{20}O_5Si$+Na: 315.1208, found: 315.1194.

*4.2.17. (1R,4R,5R,8R)-8-Benzyloxy-3-methoxy-4-hydroxy-2,6-dioxabicyclo[3.3.0]octane (**14**)*

To a solution of **13** (0.129 g, 0.442 mmol) in methanol (3 mL) was added DOWEX 50 W X-8 (H^+ form, 0.5 g) at room temperature. After stirring for 12 h, the reaction mixture was filtered through a pad of Celite and washed with methanol (50 mL). The filtrate was concentrated in vacuo and the resulting residue was purified by column chromatography (silica gel, hexane/AcOEt=3/2) to give **14** (0.116 g, 0.436 mmol, 99%) as a colorless oil. R_f=0.23 (silica gel, hexane/AcOEt=1/1); IR (NaCl) 3350 (O–H), 2937 (C–H), 1499 (C=C), 1107 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) α-anomer: δ 7.37–7.26 (m, 5H, Ar*H*), 5.10 (d, *J*=4.4 Hz, 1H, C*H*), 4.71 (d, *J*=12.1 Hz, 1H, PhCH_2), 4.59 (d, *J*=12.1 Hz, 1H, PhCH_2), 4.58 (m, 1H, C*H*), 4.43 (d, *J*=4.4 Hz, 1H, C*H*), 4.14 (br s, 1H, O*H*), 4.06–3.76 (m, 3H, C*H*, CH_2), 3.45 (m, 1H, C*H*), 3.50 (s, 3H, CH_3); β-anomer: δ 7.37–7.26 (m, 5H, Ar*H*), 4.98 (s, 1H, C*H*), 4.78 (d, *J*=11.5 Hz, 1H, PhCH_2), 4.54 (d, *J*=11.5 Hz, 1H, PhCH_2), 4.42 (s, 1H, C*H*), 4.19 (br s, 1H, O*H*), 4.06–3.76 (m, 4H, C*H*, CH_2), 3.59 (m, 1H, C*H*), 3.43 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) α-anomer: δ 137.5 (*C*), 128.5 (*C*H), 128.1 (*C*H), 127.9 (*C*), 104.5 (*C*H), 88.3 (*C*H), 80.7 (*C*H), 78.2 (*C*H), 77.8 (*C*H), 72.7 (*C*H_2), 68.4 (*C*H_2), 55.4 (*C*H_3); β-anomer: δ 137.5 (*C*), 128.4 (*C*H), 128.1 (*C*H), 127.9 (*C*), 110.7 (*C*H), 87.6 (*C*H), 81.5 (*C*H), 78.4 (*C*H), 78.1 (*C*H), 72.1 (*C*H_2), 69.4 (*C*H_2), 55.2 (*C*H_3); HRMS (ESI^+) *m*/*z* calcd for $C_{14}H_{18}O_5Si$+Na: 289.1052, found: 289.1024.

*4.2.18. (1S,4S,5R,8R)-4-Azido-8-benzyloxy-3-methoxy-2,6-dioxabicyclo[3.3.0]octane (**15**)*

To a solution of **14** (0.164 g, 0.616 mmol) and pyridine (0.146 g, 1.85 mmol) in CH_2Cl_2 (1.2 mL) was added trifluoromethanesulfonic anhydride (0.348 g, 1.23 mmol) at 0 °C. After stirring for 1 h, the reaction mixture was quenched by addition of H_2O (5 mL) and extracted with ethyl acetate (20 mL×3). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the corresponding trifluoromethanesulfonate, which was used without further purification. To a solution of the crude trifluoromethanesulfonate in DMF (1.2 mL) was added sodium azide (0.0802 g, 1.23 mmol). After stirring for 80 h at 60 °C, the reaction mixture was quenched by addition of H_2O (10 mL) and extracted with ethyl acetate (20 mL×3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/AcOEt=7/1) to give **15** (0.110 g, 0.378 mmol, 61%) as a colorless oil. R_f=0.39 (silica gel, hexane/AcOEt=3/1); $[\alpha]_D^{25}$ +261.0 (*c* 1.0, $CHCl_3$); IR (NaCl) 3031 (C–H), 2112 (N=N^+=N^-), 1497 (C=C), 1107 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.26 (m, 5H, Ar*H*), 5.08 (d, *J*=2.2 Hz, 1H, C*H*), 4.77 (dd, *J*=6.1, 4.8 Hz, 1H, C*H*), 4.72 (d, *J*=12.3 Hz, 1H, PhCH_2), 4.60 (d, *J*=12.3 Hz, 1H, PhCH_2), 4.58 (dd, *J*=4.8, 4.6 Hz, 1H, C*H*), 4.03 (ddd, *J*=6.8, 4.8, 4.6 Hz, 1H, C*H*), 3.96 (dd, *J*=8.6, 6.8 Hz, 1H, CH_2), 3.87 (dd, *J*=6.1, 2.2 Hz, 1H, C*H*), 3.75 (dd, *J*=8.6, 4.8 Hz, 1H, CH_2), 3.40 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5 (*C*), 128.5 (*C*H), 128.1 (*C*H), 128.0 (*C*), 108.6 (*C*H), 82.2 (*C*H), 79.3 (*C*H), 78.3 (*C*H), 72.8 (*C*H_2), 69.9 (*C*H_2), 67.5 (*C*H), 55.7 (*C*H_3); HRMS (ESI^+) *m*/*z* calcd for $C_{14}H_{17}N_3O_4$+Na: 314.1117, found: 314.1100.

*4.2.19. (1S,4S,5R,8R)-4-Acetamido-8-benzyloxy-3-methoxy-2,6-dioxabicyclo[3.3.0]octane (**16**)*

To a solution of **15** (0.0600 g, 0.206 mmol) and H_2O (0.1 mL) in CH_2Cl_2/THF (3/1, 0.8 mL) was added triphenylphosphine (0.118 g, 0.450 mmol) at 0 °C. After stirring for 2 h, the reaction mixture was quenched by addition of 3% aqueous HCl (5 mL) and extracted with CH_2Cl_2 (20 mL×3). The combined organic extracts were washed with 3% aqueous NaOH (10 mL) and concentrated in vacuo to give the corresponding amine, which was used without further purification. To a solution of the crude amine and pyridine (57.1 mg, 0.722 mmol) in CH_2Cl_2 (0.1 mL) was added acetic anhydride (0.0369 g, 0.361 mmol). After stirring for 3 h, the reaction mixture was quenched by addition of H_2O (3 mL) and extracted with AcOEt (10 mL×3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, AcOEt) to give **16** (0.0411 g, 0.134 mmol, 65%) as a colorless oil. R_f=0.18 (silica gel, hexane/AcOEt=1/2); $[\alpha]_D^{28}$ +108.1 (*c* 1.0, $CHCl_3$); IR (NaCl) 3314 (N–H), 2969 (C–H), 1647 (C=O), 1547 (C=C), 1105 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.26 (m, 5H, Ar*H*), 6.38 (d, *J*=6.2 Hz, 1H, N*H*), 4.96 (d, *J*=1.3 Hz, 1H, C*H*), 4.77 (d, *J*=11.3 Hz, 1H, PhCH_2), 4.71–4.68 (m, 2H, C*H*), 4.59 (d, *J*=11.3 Hz, 1H, PhCH_2), 4.29 (ddd, *J*=6.2, 4.7, 1.3 Hz, 1H, C*H*), 4.08 (m, 1H, C*H*), 4.06 (dd, *J*=9.3, 5.3 Hz, 1H, CH_2), 3.78 (dd, *J*=9.3, 5.9 Hz, 1H, CH_2), 3.39 (s, 3H, CH_3), 1.84 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1 (*C*), 137.4 (*C*), 128.6 (*C*H), 128.2 (*C*H), 128.1 (*C*), 111.2 (*C*H), 80.9 (*C*H), 80.5 (*C*H), 77.7 (*C*H), 72.9 (*C*H_2), 72.2 (*C*H_2), 56.4 (*C*H), 55.2 (*C*H_3), 23.0 (*C*H_3); HRMS (ESI^+) *m*/*z* calcd for $C_{16}H_{21}NO_5$+Na: 330.1317, found: 330.1302.

*4.2.20. (1S,4S,5R,8R)-4-Acetamido-8-benzyloxy-3-(tert-butyldimethylsilyloxy)-2,6-dioxabicyclo[3.3.0]octane (**17**)*

4.2.20.1. Hydrolysis. A solution of **16** (0.0340 g, 0.111 mmol) in 70% aqueous AcOH (4.0 mL) was heated under reflux. After 20 h, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (3 mL) and extracted with AcOEt (10 mL×3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, AcOEt/methanol=35/1) to give the corresponding lactols (0.0320 g, 0.109 mmol, 98%) as a colorless oil. R_f=0.25 (silica gel, AcOEt/methanol=35/1); $[\alpha]_D^{23}$ +113.6 (*c* 1.0, $CHCl_3$); IR (NaCl) 3350 (O–H), 3281 (N–H), 2965 (C–H), 1680 (C=O), 1508 (C=C), 1190 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) α-anomer: δ 7.36–7.27 (m, 5H, Ar*H*), 6.41 (d, *J*=7.0 Hz, 1H, N*H*), 5.35 (d, *J*=3.1 Hz, 1H, C*H*), 4.89 (dd, *J*=5.0, 4.8 Hz, 1H, C*H*), 4.81 (m, 1H, C*H*), 4.80 (d, *J*=11.3 Hz, 1H, PhCH_2), 4.53 (d, *J*=11.3 Hz, 1H, PhCH_2), 4.24 (ddd, *J*=7.0, 5.0, 3.1 Hz, 1H, C*H*), 4.07 (m, 1H, C*H*), 3.93

(dd, J=9.2, 5.5 Hz, 1H, CH_2), 3.81 (dd, J=9.2, 6.2 Hz, 1H, CH_2), 2.63 (br s, 1H, OH), 2.17 (s, 3H, CH_3); β-anomer: δ 7.36–7.27 (m, 5H, ArH), 6.22 (d, J=8.4 Hz, 1H, NH), 5.42 (d, J=4.4 Hz, 1H, CH), 4.81 (d, J=11.9 Hz, 1H, PhCH_2), 4.64 (dd, J=5.9, 5.5 Hz, 1H, CH), 4.54 (d, J=11.9 Hz, 1H, PhCH_2), 4.46 (dd, J=5.5, 5.3 Hz, 1H, CH), 4.41 (ddd, J=6.6, 5.3, 4.6 Hz, 1H, CH), 4.07 (ddd, J=8.4, 5.9, 4.7 Hz, 1H, CH), 3.74 (dd, J=7.4, 4.6 Hz, 1H, CH_2), 3.73 (dd, J=7.4, 6.6 Hz, 1H, CH_2), 2.04 (br s, 1H, OH), 2.01 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) α-anomer: δ 170.2 (*C*), 137.0 (*C*), 128.5 (*C*H), 128.2 (*C*H), 128.1 (*C*), 104.5 (*C*H), 80.6 (*C*H), 80.3 (*C*H), 78.1 (*C*H), 72.7 (*C*H_2), 71.6 (*C*H_2), 58.7 (*C*H), 23.0 (*C*H_3); β-anomer: δ 170.2 (*C*), 137.0 (*C*), 128.6 (*C*H), 128.2 (*C*H), 128.1 (*C*), 96.8 (*C*H), 82.6 (*C*H), 78.3 (*C*H), 72.9 (*C*H_2), 71.9 (*C*H_2), 71.7 (*C*H), 58.7 (*C*H), 23.1 (*C*H_3); HRMS (ESI$^+$) m/z calcd for $C_{15}H_{19}NO_5$+Na: 316.1161, found: 316.1146.

4.2.20.2. TBS-protection. To a solution of the lactols (0.0320 g, 0.109 mmol) and imidazole (0.0260 g, 0.382 mmol) in DMF (1.0 mL) was added *tert*-butyldimethylsilyl chloride (0.0444 g, 0.295 mmol). After stirring for 3 h, the reaction mixture was quenched by addition of H_2O (3 mL) and extracted with AcOEt (10 mL×3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/AcOEt=1/1) to give **17** (0.0440 g, 0.108 mmol, 99%) as a colorless oil. R_f=0.30 (silica gel, hexane/AcOEt=1/1); $[\alpha]_D^{25}$ +78.4 (*c* 0.9, $CHCl_3$); IR (NaCl) 3308 (N–H), 2955 (C–H), 1659 (C=O), 1107 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.42 (m, 5H, ArH), 6.40 (d, J=7.1 Hz, 1H, NH), 5.37 (d, J=1.3 Hz, 1H, CH), 4.97 (dd, J=6.2, 4.6 Hz, 1H, CH), 4.95 (dd, J=4.6, 4.4 Hz, 1H, CH), 4.78 (d, J=11.0 Hz, 1H, PhCH_2), 4.55 (d, J=11.0 Hz, 1H, PhCH_2), 4.22 (ddd, J=7.1, 6.2, 1.3 Hz, 1H, CH), 4.06 (dd, J=4.7, 4.4 Hz, 1H, CH), 3.94 (d, J=4.7 Hz, 2H, CH_2), 1.79 (s, 3H, CH_3), 0.91 (s, 9H, CH_3), 0.15 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1 (*C*), 137.5 (*C*), 128.5 (*C*H), 128.2 (*C*H), 128.1 (*C*), 103.4 (*C*H), 81.0 (*C*H), 80.6 (*C*H), 77.5 (*C*H), 73.1 (*C*H_2), 72.8 (*C*H_2), 58.0 (*C*H), 25.9 (*C*), 23.0 (*C*H_3), 17.9 (*C*H_3), −4.6 (*C*H_3), −5.2 (*C*H_3); HRMS (ESI$^+$) m/z calcd for $C_{21}H_{33}NO_5Si$+Na: 430.2026, found: 430.2051.

*4.2.21. (1S,4S,5R,8R)-4-Acetamido-3-(tert-butyldimethylsilyloxy)-2,6-dioxabicyclo[3.3.0]oct-8-yl isovalerate (**18**)*

4.2.21.1. Deprotection of benzyl group by hydrogenolysis. A solution of **17** (0.0190 g, 0.0467 mmol) in ethyl acetate (1.0 mL) was hydrogenated in the presence of 5% Pd on activated carbon (0.025 g) at room temperature for 12 h. The Pd catalyst was removed by filtration through a pad of Celite and washed with ethyl acetate (30 mL). The filtrate was concentrated in vacuo and the resulting residue was purified by column chromatography (silica gel, hexane/AcOEt=1/2) to give the corresponding alcohol (0.0147 g, 0.0463 mmol, 99%) as a colorless oil. R_f=0.40 (silica gel, hexane/AcOEt=1/2); $[\alpha]_D^{25}$ +78.4 (*c* 0.9, $CHCl_3$); IR (NaCl) 3415 (N–H), 3300 (O–H), 2930 (C–H), 1655 (C=O), 1109 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34 (d, J=6.0 Hz, 1H, NH), 5.43 (s, 1H, CH), 4.82–4.75 (m, 2H, CH), 4.23 (m, 2H, CH), 4.00 (dd, J=10.1, 2.6 Hz, 1H, CH_2), 3.90 (dd, J=10.1, 3.7 Hz, 1H, CH_2), 2.67 (br s, 1H, OH), 2.01 (s, 3H, CH_3), 0.90 (s, 9H, CH_3), 0.13 (d, J=6.6 Hz, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2 (*C*), 105.9 (*C*H), 81.9 (*C*H), 77.4 (*C*H), 76.1 (*C*H), 70.2 (*C*H_2), 57.6 (*C*H), 25.6 (*C*), 23.2 (*C*H_3), 17.9 (*C*H_3), −4.7 (*C*H_3), −5.3 (*C*H_3); HRMS (ESI$^+$) m/z calcd for $C_{14}H_{27}NO_5Si$+Na: 340.1556, found: 340.1583.

4.2.21.2. Esterification with isovaleric acid. To a solution of the alcohol (0.0160 g, 0.0504 mmol), 4-dimethylaminopyridine (0.0062 mg, 0.0507 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.0193 mg, 0.101 mmol) in CH_2Cl_2 (0.3 mL) was added isovaleric acid (0.0155 mg, 0.152 mmol) at room temperature. After stirring for 2 h, the reaction mixture was quenched by addition of H_2O (2 mL) and extracted with ethyl acetate (20 mL×3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/AcOEt=2/1) to give **18** (0.0178 g, 0.0444 mmol, 88%) as a colorless oil. R_f=0.25 (silica gel, hexane/AcOEt=2/1); $[\alpha]_D^{23}$ +90.2 (*c* 1.0, $CHCl_3$); IR (NaCl) 3271 (N–H), 2950 (C–H), 1736 (C=O), 1497 (C=C), 1109 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (d, J=5.9 Hz, 1H, NH), 5.29 (d, J=1.7 Hz, 1H, CH), 5.15 (dd, J=5.8, 5.7 Hz, 1H, CH), 4.86 (d, J=5.1 Hz, 1H, CH), 4.70 (dd, J=6.4, 5.1 Hz, 1H, CH), 4.17 (ddd, J=6.4, 5.9, 1.7 Hz, 1H, CH), 4.05 (dd, J=9.5, 5.7 Hz, 1H, CH_2), 3.85 (dd, J=9.5, 5.8 Hz, 1H, CH_2), 2.23–2.20 (m, 2H, CH_2), 2.09 (m, 1H, CH), 1.99 (s, 3H, CH_3), 0.95 (d, J=6.6 Hz, 6H, CH_3), 0.86 (s, 9H, CH_3), 0.97 (d, J=6.6 Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ 172.0 (*C*), 170.0 (*C*), 104.5 (*C*H), 80.7 (*C*H), 79.7 (*C*H), 72.2 (*C*H), 71.1 (*C*H_2), 59.0 (*C*H), 43.0 (*C*H_2), 25.6 (*C*H), 25.5 (*C*), 23.1 (*C*H_3), 22.3 (*C*H_3), 22.2 (*C*H_3), 17.8 (*C*H_3), −4.7 (*C*H_3), −5.3 (*C*H_3); HRMS (ESI$^+$) m/z calcd for $C_{19}H_{35}NO_6Si$+Na: 424.2131, found: 424.2149.

*4.2.22. Furanodictine B (**2**)*

To a solution of **18** (0.0160 g, 0.0399 mmol) in THF (0.4 mL) was added tetrabutylammonium fluoride (1.0 M solution in THF, 0.04 mL, 0.04 mmol). After stirring for 1 h, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (1 mL) and extracted with AcOEt (10 mL×3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, AcOEt) to give **2** (0.0110 g, 0.0383 mmol, 96%) as a colorless oil: R_f=0.20 (AcOEt); $[\alpha]_D^{26}$ +104.8 (*c* 0.9, $CHCl_3$); IR (NaCl) 3413 (O–H), 3281 (N–H), 2939 (C–H), 1744 (C=O), 1659 (C=O), 1190 (C–O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) α-anomer: δ 6.20 (d, J=6.2 Hz, 1H, NH), 5.24 (d, J=4.0 Hz, 1H, CH), 5.17 (dt, J=6.2, 5.0 Hz, 1H, CH), 4.98 (t, J=5.0 Hz, 1H, CH), 4.61 (dd, J=6.2, 5.0 Hz, 1H, CH), 4.22 (dt, J=6.2, 4.0 Hz, 1H, CH), 4.06 (dd, J=9.5, 6.2 Hz, 1H, CH_2), 3.83 (dd, J=9.5, 6.2 Hz, 1H, CH_2), 3.40 (br s, 1H, OH), 2.26 (dd, J=15.0, 7.3 Hz, 1H, CH_2), 2.22 (dd, J=15.0, 7.3 Hz, 1H, CH_2), 2.12 (m, 1H, CH), 2.04 (s, 3H, CH_3), 0.98 (d, J=6.6 Hz, 3H, CH_3), 0.96 (d, J=6.6 Hz, 3H, CH_3); β-anomer: δ 6.18 (d, J=7.9 Hz, 1H, NH), 5.55 (d, J=5.0 Hz, 1H, OH), 5.38 (dd, J=5.3, 5.0 Hz, 1H, CH), 5.17 (dt, J=6.2, 5.1 Hz, 1H, CH), 4.98 (dd, J=5.1, 4.8 Hz, 1H, CH), 4.53 (dd, J=5.3, 4.8 Hz, 1H, CH), 4.45 (dt, J=7.9, 5.3 Hz, 1H, CH), 4.08 (dd, J=9.2, 6.2 Hz, 1H, CH_2), 3.98 (dd, J=9.2, 6.2 Hz, 1H, CH_2), 2.28 (dd, J=15.0, 7.3 Hz, 1H, CH_2), 2.24 (dd, J=15.0, 7.3 Hz, 1H, CH_2), 2.12 (m, 1H, CH), 2.04 (s, 3H, CH_3), 0.99 (d, J=6.6 Hz, 3H, CH_3), 0.97 (d, J=6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) α-anomer: δ 172.3 (*C*), 170.2 (*C*), 103.7 (*C*H), 80.3 (*C*H), 79.8 (*C*H), 72.8 (*C*H), 70.7 (*C*H_2), 59.2 (*C*H), 43.0 (*C*H_2), 25.6 (*C*H), 23.1 (*C*H_3), 22.4 (*C*H_3), 22.3 (*C*H_3); β-anomer: δ 172.3 (*C*), 170.2 (*C*), 96.6 (*C*H), 80.7 (*C*H), 80.6 (*C*H), 73.4 (*C*H), 71.2 (*C*H_2), 54.6 (*C*H), 43.0 (*C*H_2), 25.6 (*C*H), 23.1 (*C*H_3), 22.4 (*C*H_3), 22.3 (*C*H_3); HRMS (ESI$^+$) m/z calcd for $C_{13}H_{21}NO_6$+Na: 310.1267, found: 310.1268.

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References and notes

1. Kikuchi, H.; Saito, Y.; Komiya, J.; Takaya, Y.; Honma, S.; Nakahata, N.; Ito, A.; Oshima, Y. *J. Org. Chem.* **2001**, *66*, 6982.
2. Maeda, Y.; Inouye, K.; Takeuchi, I. *Dictyostelium A Model System for Cell and Development Biology*. Frontiers Science Series No. 21; Universal Academy.: Tokyo, 1997.
3. Yoda, H.; Suzuki, Y.; Takabe, K. *Tetrahedron Lett.* **2004**, *45*, 1599.

4. Mereyala, H. B.; Baseeruddin, M.; Koduru, S. R. *Tetrahedron: Asymmetry* **2004**, *15*, 3457.
5. Matsuura, D.; Nojiri, T.; Suzuki, Y.; Takabe, K.; Yoda, H. *Synlett* **2005**, 287.
6. (a) Yoda, H.; Nakaseko, Y.; Takabe, K. *Tetrahedron Lett.* **2004**, *45*, 4217; (b) Matsuura, D.; Takabe, K.; Yoda, H. *Tetrahedron Lett.* **2006**, *47*, 1371.
7. Boger, D. L.; Ichikawa, S.; Zhong, W. *J. Am. Chem. Soc.* **2001**, *123*, 4167.
8. (a) Martinelli, M. J.; Vaidyanathan, R.; Khau, V. V. *Tetrahedron Lett.* **2000**, *41*, 3773; (b) Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett.* **1999**, *1*, 447.
9. Etherification with Ag_2O as a base interestingly gave the α-anomer predominantly in 95% isolated yield (α/β=93/7, determined by ^{1}H NMR analysis).
10. It is not necessary to separate the two anomeric mixture, since these compounds should be hydrolyzed to the corresponding lactol function at the final stage for the synthesis of **1**, resulting in an anomeric mixture again. This process, however, possesses desirable advantages of not only avoiding any confusion in identification on TLC at each stage of work, but being able to proceed without extra separation of reaction products.
11. Mitsunobu, O. *Synthesis* **1981**, 1.
12. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
13. Determined by ^{13}C and ^{1}H NMR analyses. We postulate at present that this high stereoselective performance could be attributed to the convexity of the cis-configurated bicyclic structure. It would proceed through the preferential attack of H^- to the carbonyl function from the bottom face of the ketones, respectively, due to the shielding effect of the bis-furan group independent of stereochemistry of the anomer center.
14. Yoda, H.; Egawa, T.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 1643.
15. For Staudinger reaction, see: (a) Staudinger, H.; Meyer, J. *Helv. Chem. Acta* **1919**, *2*, 635; (b) Homer, L.; Gross, A. *Ann.* **1955**, *591*, 117; (c) Hank-ovszky, H. O.; Hideg, K.; Lex, L. *Synthesis* **1981**, 147 and recent examples, see; (d) Eipert, M.; Maichle-Moessmer, C.; Maier, M. E. *Tetrahedron* **2003**, *59*, 7949; (e) Lucas, S.; Luther, L. M.; Burke, S. D. *Org. Lett.* **2004**, *6*, 2965 Both reactions under Staudinger conditions and hydrogenation ones with 10% Pd on carbon could be applicable for the preparation of **12a** or **12b**.
16. Synthesized furanodictine A (**1**) from **12a** as well as **12b** in this report was a mixture of two anomers {α/β=6.3/1 (natural, α/β=7/1)[1]}. In conclusion, serious differences were not observed between α- and β-anomer of **7** upon carrying out the total synthesis of **1** independently. Furanodictine A previously reported in this laboratory[3] was composed of two anomers {α/β=3.9/1; $[\alpha]_D^{27}$ +132.6 (*c* 0.72, $CHCl_3$)}. The slight difference of the specific rotations between synthetic and natural **1** should be attributed to the ratio of these two anomers (α- and β-form).
17. These results would be attributed to the torsional strain based on the cis-configurated bis-furan structure.
18. The ratio of the two anomers was easily determined by ^{1}H NMR, since the observed coupling constant corresponding to the α-anomer was 4.4 Hz, indicating the cis-relationship and the other β-one has no coupling constant.
19. Synthesized furanodictine B in this report was a mixture {α/β=1/2.4 (natural, α/β=2/3)[1]} of two anomers. The reason for the difference of the specific rotations, see Ref. 16.