Synthesis of 2-Substituted (±)-(2*R*,3*R*,5*R*)-Tetrahydrofuran-3,5-dicarboxylic Acid Derivatives†

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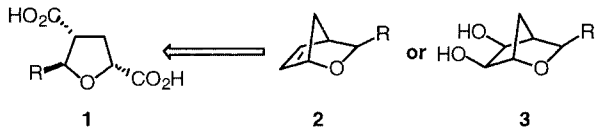
An efficient synthesis of 2-substituted (±)-(2*R*,3*R*,5*R*)-tetrahydrofuran-3,5-dicarboxylic acid derivatives has been developed. Starting from 5-norborne-2-ol, the key intermediate (±)-methyl 5,6-*exo*,*exo*-(isopropylidenedioxy)-2-oxabicyclo[2.2.1]heptane-3-*exo*-carboxylate (**15**) was synthesized in an efficient six-step sequence. The key transformation is the base-catalyzed methanolysis−rearrangement of (±)-6,7-*exo*,*exo*-(isopropylidenedioxy)-4-*exo*-iodo-2-oxabicyclo[3.2.1]octan-3-one (**14**). Further manipulation of the 3-substituent of (±)-methyl 5,6-*exo*,*exo*-(isopropylidenedioxy)-2-oxabicyclo[2.2.1]-heptane-3-*exo*-carboxylate (**15**) followed by deprotection of the diol moiety and ring opening catalyzed by $RuCl_3/NaIO_4$ gave the title compounds in good yield.

Introduction

Recently, our research effort in a drug discovery project required an efficient synthesis of 2-substituted (±)-(2*R*,3*R*,5*R*)-tetrahydrofuran-3,5-dicarboxylic acid derivatives (**1,** Scheme 1), where the C2 substituent R includes simple aliphatic or aryl groups as well as subtituents containing other functionalities.

An extensive literature search indicated that tetrahydrofurans of structure **1** are hitherto unknown. Even though saturated five-membered ring heterocyclics such as substituted tetrahydrofuran (THF) appear in a number of natural products,[1,2] synthesis of this class of compounds with desired substituents in a stereoselective manner remains to be a significant challenge. Reduction (catalytic hydrogenation) of furans represents one approach, which has the advantage that a variety of substituents can be introduced into the precursor furans, often regioseletively, via electrophilic substitution. However, this approach generally lacks stereoselectivity. Starting from ribose or deoxy-ribose is another common approach,[3] which offers the advantage of inexpensive chiral starting materials but suffers from limited option of stereochemistry and functional groups that can be introduced. A variety of methodologies have also been developed for forming the THF ring from acyclic precursors. These include cyclodehydration of 1,4-diols under acid catalysis or Mitsunobu conditions,[4,5] cycloetherification of 5-hydroxy-olefins (5-*exo* cyclization) or 4-hydroxy-olefins (5-*endo* cyclization) induced by halogens,[6] mercury,[7] selenium,[8] or transition metals,[9] and atom-transfer radical cyclization of acyclic ethers.[10] None of these methods appears to be suitable for the synthesis of **1**.

Scheme 1



1 **2** **3**

We report here a novel synthesis of hitherto unknown (±)-methyl 5,6-*exo*,*exo*-(isopropylidenedioxy)-2-oxabicyclo-[2.2.1]heptane-3-*exo*-carboxylate (**3**, R = CO_2Me) and its

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† Dedicated to Prof. Joseph B. Lambert of Northwestern University (Evanston, IL) on the occasion of his 60th birthday.

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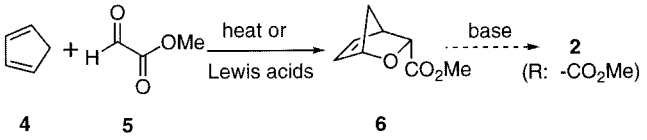
Scheme 2



subsequent conversion to **1** via oxidative ring opening. Together, this sequence provides a practical synthesis of 2-substituted (±)-(2*R*,3*R*,5*R*)-tetrahydrofuran-3,5-dicarboxylic acid derivatives (**1**) with complete control of the relative stereochemistry.

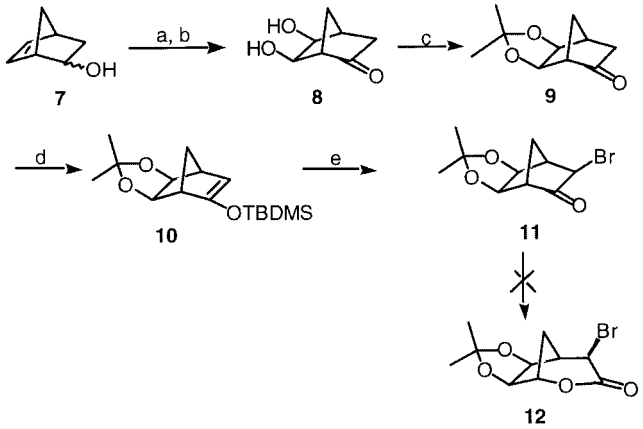
Results and Discussion

Our retrosynthetic analysis indicated that 2-oxabicyclo-[2.2.1]hept-5-ene **2** or 5,6-dihydroxy-2-oxabicyclo[2.2.2]-heptane **3** would serve as ideal precursors for the synthesis of **1** (Scheme 1). The bicyclic olefin **2** or diol **3** could be easily converted into the desired THF system **1** via oxidative ring opening with complete control of the relative stereochemistry. The C2 substituent R can either be set in the precursors **2** or **3**, or subjected to further manipulation after the ring opening.

Our initial effort was focused on the intermediacy of methyl 2-oxabicyclo[2.2.1]hept-5-ene-3-*exo*-carboxylate (**2**, R= CO_2Me), which seemingly can be prepared via the Diels−Alder reaction of cyclopentadiene **4** and methyl glyoxylate **5**. Such Diels−Alder reaction, if feasible, would normal give the *endo*-adduct **6** which assumingly can be epimierized to the desired *exo*-adduct (Scheme 2). Diels−Alder addition of electron-deficient aldehydes such as glyoxylate esters with electron-rich 1,3-dienes such as Danishesky's diene has been amply documented,[11,12] and the addition of **5** to cyclohexadiene has also been reported.[13] Surprisingly, the addition of aldehyde dienophiles to cyclopentadiene has not been described.

In our hands, no cycloaddition was observed after refluxing freshly distilled cyclopentadiene and methyl glyoxylate in toluene (120 °C) over extended time (5 days). We then examined this reaction under Lewis acid catalysis. With $BF_3{\cdot}Et_2O$ at −78 °C or $ZnCl_2$ at 0 °C, a complex mixture was obtained which contained only trace amount of the adduct as indicated by mass spectrometry. With $MgBr_2$ (0 °C to ambient temperature), a relatively clean reaction was observed with the formation of one major high R_f product whose ^{1}H NMR and mass spectra were consistent with the expected adduct. However, this material was very unstable (presumably decomposition by retro-Diels−Alder reaction) and could not be isolated on preparative scale.

Scheme 3[a]



[a] (a) DMSO, $(COCl)_2$, DCM, −78 °C to r.t, 85%; (b) OsO_4, NMMO, r.t. 3 h, 90%; (c) 2,2-dimethoxypropane, TsOH, r,t. 1 h, 90%; (d) LDA, *t*-$BuMe_2SiCl$, −78 °C; (e) Br_2, DCM, 0 °C, 76%.

We then turned our attention to developing an synthetic route utilizing diols of type **3** as the intermediates. Vogel and co-workers described the Baeyer−Villiger reaction of α-bromo ketone 3-*exo*-bromo-5,6-*exo,exo*-(isopropylidenedioxy)-7-oxabicyclo[2.2.1]heptan-2-one, giving the α-bromo bicyclic lactone, (±)-3-*exo*-bromo-6,7-*exo,exo*-(isopropylidenedioxy)-2,8-dioxabicyclo[3.2.1]octan-3-one. This α-bromo bicyclic lactone was, in turn, transformed into methyl 5,6-*exo,exo*-(isopropylidenedioxy)-2,7-dioxabicyclo[2.2.1]heptane-3-*exo*-carboxylate upon methanolysis in basic MeOH.[14] We anticipated that this sequence of reactions can be adopted for the synthesis of our key intermediate, 2-oxabicyclo[2.2.1]heptane system **3**.

Thus, commercially available 5-norbornen-2-ol (**7**) was converted to the protected dihydroxy ketone **9** via standard procedure of Swern oxidation, dihydroxylation and protection (Scheme 3). We initially sought to follow the exact reaction sequence of Auberson and Vogel.[14] Accordingly, ketone **9** was converted to the enol silyl ether **10** according to literature procedure.[15] Treatment of **10** with Br_2 in CH_2Cl_2 gave the desired α-bromo ketone **11**. The ratio of *exo:endo* bromide was found to be substantially temperature dependent. At −55 °C, the *exo*-bromide (δ 3.72 for C2 H) dominated in a 2:1 ratio over the *endo*-bromide. This ratio was reduced to 1:1 at −78 °C but increased to 10:1 when the reaction was carried out at 0 °C. The α-bromo ketone **11** was then subjected to Baeyer−Villiger conditions, with disappointing results. With MCPBA as the reagent, no reaction was observed. Urea hydrogen peroxide complex has been used to react with trifluoroacetic anhydride to generate per-trifluoroacetic acid which is known to be a stronger oxidant,[16] and the reagent of choice for Auberson and Vogel.[14] Several variations of this procedure were tried; all failed to effect the conversion of **11** to the corresponding lactone **12**.

Unable to convert the α-bromo ketone **11** to the corresponding lactone **12**, we then sought to alternate

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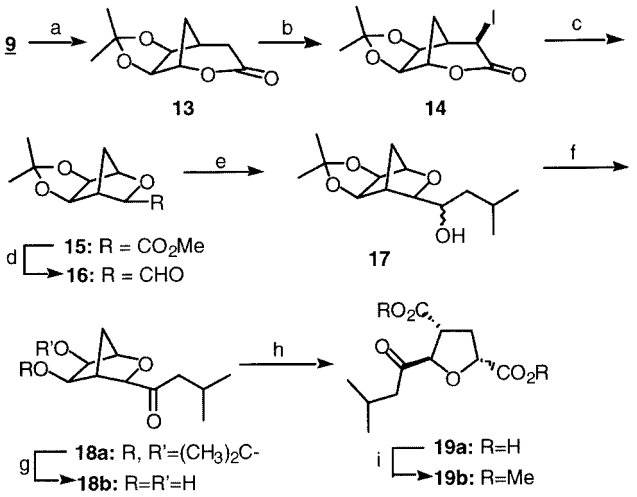
Scheme 4[a]



[a] (a) MCPBA, $CHCl_3$, then aluminum oxide, 50%; (b) LHMDS, I_2, −78 °C, 0.5 h, 81%; (c) K_2CO_3, MeOH, r.t., 0.5 h, 80−90%; (d) DIBALH, DCM, −78 °C, 1 h, 80%; (e) isobutylmagnesium bromide, 0 °C, 1 h; (f) DMSO, $(COCl)_2$, DCM, −78 °C to r.t, 51% for three steps; (g) 2 N HCl, MeOH, 40 °C, 2 h, 98%; (h) $RuCl_3 \cdot H_2O$, $NaIO_4$, r.t., 4 h; (i) MeI, CH_2Cl_2, DIEA, 68% for two steps.

the reaction sequence by carrying out the Baeyer−Villiger rearrangement first (Scheme 4). Thus, when ketone **9** was treated with MCPBA, a mixture of two lactones (regioisomers) was obtained in quantitative yield. The regioselectivity of the Baeyer−Villiger reation of 2-norbornanones has been shown to be dependent on the substitution pattern.[17] With ketone **9**, the ratio of the two regioisomers was found to be 1:1 (NMR result) and varied little with different reagents (MCPBA or peracetic acid) and temperature (ambient temperature, 0 °C, −20 °C). These two regioisomeric lactones were found inseparatable chromatographically. By serendipity, we discovered that the undesired (methylene-migrated) lactone decomposed completely when the mixture was treated with aluminum oxide for 30 min, giving the desired (methine migrated) lactone **13**. This result is consistent with reported poor stability of the methylene-migrated lactones of 2-norbornanone.[18]

α-Halogenation of lactone **13** was the next hurdle. When the lithium enolate of **13** generated with LHMDS was treated with Br_2, the expected α-bromolactone was obtained but in a consistently low yield (∼20%). Fortunately, the iodination procedure described by Rathke and Lindert worked satisfactorily.[19] Thus, when a solution of the lithium enolate of **13** in THF was cannulated to a solution of I_2 in THF at − 78 °C, a clean reaction was observed, giving the iodolactone **14** in 81% yield. An X-ray crystal structure of **14** was obtained (Supporting Information), confirming the *exo*-configuration of the iodo-substituent. When **14** was treated with K_2CO_3 in methanol according to the procedure of Auberson and Vogel,[14] it was converted smoothly to the key intermediate **15** in 80% yield. The *exo* configuration of the methyl ester functionality of **15** was readily established based on the NMR studies. The C3 proton appeared at 3.8 ppm and did not couple with the C4 proton, indicating the *endo*-disposition of this proton.

The intermediate **15** can be deprotected directly and subjected to oxidative ring opening to give the desired THF derivative (**1**, R = CO_2Me). Alternatively, the carboxymethyl functionality of **15** can be elaborated into other desirable groups at this stage before the deprotection and ring opening. As an illustration, we chose to reduce the ester **15** to the aldehyde **16** with DIBALH. The aldehyde **16** was then reacted with isobutyl magnusium bromide to give alcohol **17**, which was oxidized to ketone **18a**. The diol moiety of **18a** was then deprotected and oxidative ring opening with $NaIO_4$ in the presence of catalytic amount of $RuCl_3$ gave (±)-(2*R*,3*R*,5*R*)-2-(3′-methyl-1′-oxobutyl)tetrahydrofuran-3,5-dicarboxylic acid, **19a**, in good yield.

To confirm the structure of the THF derivatives thus obtained, **19a** was converted to the corresponding dimethyl ester **19b**, and NMR studies were carried out on **19b**. Proton signals were assigned based on COSY experiments in both $CDCl_3$ and DMSO-d_6, and NOEs were measured in ROESY spectrum. A modest NOE was observed between H3 and H5, indicating the cis-relationship of the two carboxyl groups. A weak NOE was also observed between H3 and side-chain proton H6 while no NOE was observed between protons H2 and H3, indicating that the C2 substituent and C3 carboxyl group were trans to each other.[20] Additionally, a single-crystal X-ray structure of a compound derived from **19** was obtained, providing direct prove of the configuration of **19**.[21]

In summary, we have developed a practical synthesis of the unprecedented 2-substituted (±)-(2*R*,3*R*,5*R*)-tetrahydrofuran-3,5-dicarboxylic acids such as compound **19**. The synthesis utilizes inexpensive starting material and offers complete control of the relative stereochemistry. It is conceivable that both the bicyclic intermediate **15** or THF derivative **19** can be valuable intermediates for the synthesis of structurally more complex compounds.

Experimental Section

General Methods. Commercially available solvents were used as received, and reagents were purchased from Aldrich Chem. Co. (Milwaukee, WI), unless noted otherwise. THF solvent was distilled from Na−benzophenone. Column chromatography was performed with the solvent systems indicated using E. Merck silica gel 60 (70−230 mesh). Unless noted otherwise, all the reactions were conducted under an atmosphere of nitrogen and organic solutions were dried with $MgSO_4$. ^1H NMR spectra were recorded on a GE AE-300 (300 MHz) using tetramethylsilane as an internal standard. Elementary analysis were performed by Robertson Micolit Laboratories, Madison, NJ. X-ray crystallography of compound **14** was performed by Dr. Roger Henry of The Analytical Chemistry Department, Pharmaceutical Discovery, Abbott Laboratories.

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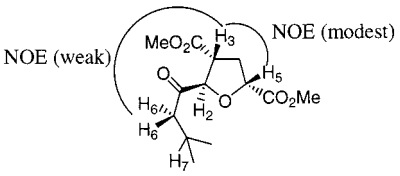
(20) Summary of NOEs observed from the ROESY spectrum of **19b**:



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(±)-5,6-*exo,exo*-Dihydroxylbicyclo[2.2.1]heptan-2-one (8). In a three-necked flask equipped with a mechanical stirrer, a N_2 inlet, and an additional funnel, a solution of oxalyl chloride (2.0 M in DCM, 136 mL, 0.272 mol) in DCM (250 mL) was cooled to −78 °C, and a solution of DMSO (40 mL) in 40 mL of DCM was added dropwise over 30 min. After stirring for an additional 5 min, a solution of 5-norboren-2-ol (24 mg, 0.218 mol) in 40 mL of DCM was added dropwise. The solution was then stirred for another 10 min, and triethylamine (150 mL) was added over 40 min. The mixture was stirred for 10 min at −78 °C and then allowed to warm to 0 °C over 1 h. Water (250 mL) was added. Following the separation of two layers, the organic layer was washed with 0.2 N HCl (4 × 200 mL) and brine (2 × 200 mL). After drying ($MgSO_4$), the solution was concentrated to about 80 mL. The residue was distilled with a 12 in. Vigerex column at reduced pressure to give (±)-bicyclo[2.2.1]hept-5-en-2-one, bp 100−105 °C /15 mmHg, 20.1 g, 86.0%. ^{1}H NMR ($CDCl_3$): 1.85 (dd, 1H), 1.90−2.00 (m, 2H), 3.00 (bs, 1H), 3.20 (bs, 1H), 6.01 (t, 1H), 6.58 (t, 1H).

A solution of (±)-bicyclo[2.2.1]hept-5-en-2-one (10.8 g, 0.1 mol) and *N*-methyl morpholine oxide (12.7 g, 0.12 mol) in 300 mL of 90% THF−water was cooled with a water bath. A solution of osmium tetraoxide (2.5 wt % in t-BuOH, 8.0 mL) was added. After stirring for 5 h at ambient temperature, the solvents were evaporated, and the resulting residue was dried in vacuo. The residue was then taken up in 100 mL of EtOAc, dried ($MgSO_4$), and filtered. The filtrate was passed through a short silica gel plug, eluting further with EtOAc. Concentration of the EtOAc solution gave **8** as a thick oil (14.5 g) which was used directly for the next step.

(±)-5,6-*exo,exo*-(Isopropylidenedioxy)bicyclo[2.2.1]-heptan-2-one (9). A solution of **8** (14.5 g, crude) in 250 mL of 2,2-dimethoxypropane was cooled to 0 °C, and *p*-TsOH (125 mg) was added. The solution was stirred for 30 min when TLC indicated complete reaction. The solution was directly loaded on to a aluminum oxide (neutral) column and eluted with 15−30% EtOAc in hexane, giving 11.9 g of a white solid (65% for two steps). MS (DCI-NH_3): *m*/*z* 200 for (M + NH_4), base peak. ^{1}H NMR ($CDCl_3$): 1.34 (s, 3H), 1.50 (s, 3H), 1.63−1.74 (m, 2H), 2.12−2.20 (m, 2H), 2.70−2.76 (m, 2H), 4.28 (d, 1H), 4.34 (d, 1H). ^{13}C NMR ($CDCl_3$): 21.1, 25.3, 31.2, 39.4, 39.5, 55.3, 76.8, 81.2, 111.2, 214.0. Anal. Calcd for $C_{10}H_{14}O_3$: 65.92% C, 7.75% H. Found: 66.01% C, 7.79% H.

(±)-2-[Dimethyl(*tert*-butyl)siloxy]-5,6-*exo,exo*-(isopropylidenedioxy)bicyclo[2.2.1]heptan-2-ene (10). Compound **10** was prepared according to the literature procedure.[15]

(±)-3-Bromo-5,6-*exo,exo*-(isopropylidenedioxy)bicyclo-[2.2.1]heptan-2-one (11), A solution of bromine (0.196 mL, 3.80 mmol) in 30 mL of CH_2Cl_2 was added dropwise to a flask containing **10** (1.02 g, 3.45 mmol) and 10 mL of CH_2Cl_2 cooled to 0 °C over 30 min. The reaction was then quenched with 60 mL of saturated $NaHCO_3$ solution. After separating two phases, the aqueous phase was washed with brine (2 × 30 mL) and dried. After filtration and concentration, flash chromatography on silica gel column (20% EtOAc−hexane) gave 0.61 g of a solid (60%). MS (ESI−): *m*/*z* 259, 261 for (M − H), base peak. ^{1}H NMR ($CDCl_3$): 1.35 (s, 3H), 1.50 (s, 3H), 2.20 (bs, 2H), 2.86 (bs, 2H), 3.70 (s, 1H), 4.24−4.40 (m, 2H).

(±)-6,7-*exo,exo*-(Isopropylidenedioxy)-2-oxabicyclo[3.2.1]-octan-3-one (13). To a solution of **9** (14.76 g, 0.081 mol) in 500 mL of DCM was added $NaHCO_3$ (13.6 g, 0.16 mol). The mixture was cooled with a water bath, and MCPBA (30.3 g, ∼60%) was added portionwise over 30 min. The solution was then stirred for 2 h at ambient temperature and washed with 10% aqueous $Na_2S_2O_5$ (500 mL), saturated $NaHCO_3$ solution (3 × 200 mL), and brine (3 × 200 mL). The organic solution was then dried ($MgSO_4$), filtered, and concentrated. The residue was loaded onto an aluminum oxide (neutral) column and allowed to stand for 30 min and then eluted with 10−25% EtOAc in hexane, giving 7.7 g of a white solid (50% yield). MS (DCI−NH_3): *m*/*z* 216 for (M + NH_4), base peak. ^{1}H NMR ($CDCl_3$): 1.30 (s, 3H), 1.45 (s, 3H), 1.84 (d, 1H), 2.10−2.20 (m, 1H), 2.48−2.56 (m, 2H), 2.80 (dd, 1H), 4.56 (d, 1H), 4.60 (s, 1H), 4.70 (d, 1H). ^{13}C NMR ($CDCl_3$): 23.79, 25.58, 29.17, 35.97, 36.51, 80.70, 82.49, 82.55, 83.24, 110.83, 167.95. Anal. Calcd for $C_{10}H_{14}O_4$: 60.59% C, 7.12% H. Found: 60.52% C, 6.97% H.

(±)-6,7-*exo,exo*-(Isopropylidenedioxy)-4-*exo*-iodo-2-oxabicyclo[3.2.1]octan-3-one (14). To a mixture of lithium bis(trimethylsilyl)amide (1.0 M in THF, 32.6 mL) and distilled THF (60 mL), cooled to −78 °C, was added a solution of **13** (5.87 g, 29.6 mmol) in 60 mL of THF over 30 min. After stirring for another 30 min, this solution was then cannulated into a flask containing a solution of iodine (8.3 g, 32.6 mmol) in 60 mL of THF cooled to −78 °C over 30 min. The resulting solution was stirred for another 10 min and quenched with 300 mL of 5% aqueous citric acid. The mixture was then extracted with EtOAc (3 × 100 mL). The combined EtOAc solution was washed with 10% aqueous $Na_2S_2O_3$ solution (2 × 100 mL) and brine (2 × 200 mL) and dried ($MgSO_4$). After filtration, the solution was evaporated and the residue chromatograhed on a silica gel column eluting with 15−25% EtOAc in hexane, giving 7.55 g of white crystalline solid. Yield: 79.0%. MS (DCI-NH_3): *m*/*z* 342 for (M + NH_4), base peak. ^{1}H NMR ($CDCl_3$): 1.30 (s, 3H), 1.45 (s, 3H), 1.55 (s, 1H), 2.12−2.20 (m, 1H), 2.42 (d, 1H), 2.80 (m, 1H), 4.56 (d, 1H), 4.54 (d, 1H), 4.70 (m, 2H). Anal. Calcd for $C_{10}H_{13}IO_4$: 37.06% C, 4.04% H, 39.15% I. Found: 37.08% C, 3.98% H, 39.55% I.

(±)-Methyl 5,6-*exo,exo*-(Isopropylidenedioxy)-2-oxabicyclo[2.2.1]heptane-3-*exo*-carboxylate (15). To a solution of compound **14** (7.55 g, 23.3 mmol) in 300 mL of MeOH (predried with 4 Å sieves) was added K_2CO_3 (3.54 g, 25.6 mmol). The mixture was stirred vigorously for 30 min. The undissolved potassium carbonate was removed by filtration, and the filtrate was concentrated to dryness. The residue was triturated with EtOAc several times until complete extraction of the product (TLC). The EtOAc solution was then concentrated and directly chromatographed on a silica gel column eluting with 10−25% EtOAc in hexane, giving 4.86 g of a white solid. Yield: 92.0%. MS (DCI-NH_3): *m*/*z* 246 for (M + NH_4), base peak. ^{1}H NMR ($CDCl_3$): 1.30 (s, 3H), 1.45 (s, 3H), 1.62 (d, 1H), 1.85 (d, 1H), 2.82 (s, 1H), 3.78 (s, 3H), 3.80 (s, 1H), 4.20 (d, 1H), 4.30 (d, 1H), 4.40 (s, 1H). Anal. Calcd for $C_{11}H_{16}O_5$: 57.88% C, 7.07% H. Found: 57.98% C, 7.10% H.

(±)-3-*exo*-Formyl-5,6-*exo,exo*-(isopropylidenedioxy)-2-oxabicyclo[2.2.1]heptane (16). To a well-stirred solution of compound **15** (0.82 g, 3.62 mmol) in 30 mL of anhydrous DCM at −78 °C was added a solution of diisobutylaluminum hydride in toluene (1.0 M, 5.77 mL) dropwise. The mixture was then stirred at −78 °C for 1 h and quenched with 2 mL of MeOH and 15 mL of saturated aqueous sodium potassium tartrate solution. The mixture was then stirred vigorously and allowed to warm to ambient temperature over 1 h. The phases were separated, and the aqueous phase was extracted with Et_2O (5 × 50 mL). After drying, solvent removal gave 0.8 g of an oil as the crude product which was used directly for the next step.

(±)-3-*exo*-(1′-Hydroxy-3′-methylbutyl)-5,6-*exo,exo*-(isopropylidenedioxy)-2-oxabicyclo[2.2.1]heptane (17). To a solution of the aldehyde **16** (0.99 g, 5.0 mmol) in 50 mL of anhydrous THF at −78 °C was added a solution of isobutylmagnesium chloride (2.0 M in ether, 30 mL) dropwise over 30 min. The mixture was then allowed to warm to ambient temperature over 2 h and quenched with 100 mL of saturated aqueous NH_4Cl solution. The solution was then extracted with Et_2O (3 × 100 mL). The combined etheral solution was washed with brine (3 × 100 mL) and dried. After filtration, evaporation of solvent gave crude **17** as an oil (1.28 g) which was used directly for the next step.

(±)-3-*exo*-(1′-Oxo-3′-methylbutyl)-5,6-*exo,exo*-(isopropylidenedioxy)-2-oxabicyclo[2.2.1]heptane (18a). A solution of oxalyl chloride (2.0 M in DCM, 3.76 mL, 7.3 mmol) was mixed with 10 mL of anhydrous DCM, and the solution was cooled to −78 °C. A solution of DMSO (1.06 mL) in 10 mL of anhydrous DCM was then added dropwise. After stirring for 10 min, a solution of alcohol **17** (∼1.28 g, 5.0 mmol) in anhydrous DCM (10 mL) was added dropwise, and the solution was stirred for another 10 min. Triethylamine (4.3 mL) in 10 mL of DCM was then added. The mixture was then stirred at −78 °C for 2 h and allowed to warm to ambient temperature.

The solution was washed with water (100 mL), 5% aqueous citric acid (100 mL), saturated $NaHCO_3$ (100 mL), and brine. After drying and concentration, the crude material was purified by flash chromatography on a silica gel column using 5−20% EtOAc−hexane to give a white solid, 0.65 g, 51% for three steps. MS (DCI-NH_3): *m*/*z* 272 for (M + NH_4) base peak. ^{1}H NMR ($CDCl_3$): 0.84 (dd, 6H), 1.30 (s, 3H), 1.34, 1.38 (bd, 1H), 1.43 (s, 3H), 1.77, 1.82 (dd, 1H), 2.10−2.10 (m, 1H), 2.30−2.50 (dq, 2H), 2.86 (s, 1H), 3.62 (s, 1H), 4.16−4.20 (m, 1H), 4.28−4.32 (bd, 1H), 4.37 (s, 1H). Anal. Calcd for $C_{14}H_{22}O_4$: 66.12% C, 8.72% H. Found, 65.99% C, 8.58% H.

(±)-3-*exo*-(1′-Oxo-3′-methylbutyl)-5, 6-*exo*,*exo*-dihydroxy-2-oxabicyclo[2.2.1]heptane (18b). Compound **18a** (0.64 g, 0.25 mmol) was dissolved in 12.5 mL of MeOH and 12.5 mL of 2 M HCl. The solution was stirred at 60 °C for 2.5 h. After cooling to ambient temperature, the solution was partially concentrated and then extracted with EtOAc (4 × 50 mL). The combined EtOAc solution was washed with saturated aqueous $NaHCO_3$ solution (2 × 50 mL) and brine (2 × 50 mL) and dried. After filtration, removal of solvent gave a off-white crystalline solid, 0.53 g, 98.0%. MS (DCI-NH_3): *m*/*z* 232 for (M + NH_4), base peak. ^{1}H NMR ($CDCl_3$): 0.92 (dd, 6H), 1.34, 1.44 (bd, 1H), 1.77, 1.82 (dd, 1H), 2.10−2.20 (m, 1H), 2.30−2.45 (dq, 2H), 2.65 (d, 1H), 2.74−2.80 (m, 2H), 3.72 (s, 1H), 3.94−4.00 (m, 1H), 4.00−4.05 (bd, 1H), 4.24 (s, 1H).

Dimethyl (±)-(2*R*,3*R*,5*R*)-2-(1′-Oxo-3′-methylbutyl)tetrahydrofuran-3,5-dicarboxylate (19b). Compound **18b** (0.50 g, 2.3 mmol) was dissolved in a mixture CH_3CN (6.5 mL), CCl_4 (6.5 mL), and H_2O (10 mL). To this solution were added sodium periodate (2.1 g, 10 mmol) and $RuCl_3 \cdot H_2O$ (10 mg). The solution was stirred at ambient temperature for 3 h and filtered to remove the solid. The filtrate was directly loaded on a short silica gel column and eluted with 5% MeOH in EtOAc containing 5% HOAc. The resulting crude **19a** (yellow oil, 0.53 g) was dissolved in EtOAc (25 mL). *N*,*N*-Diisopropylethylamine (1.73 mL, 12 mmol) and methyl iodide (2.98 mL, 46 mmol) were added, and the mixture was stirred at 50 °C for 2 h. The mixture was filtered to remove the solid, and the filtrate was concentrated. The residue was purified by flash chromatography on a silica gel column eluting with 10−40% EtOAc in hexane, giving a colorless liquid (0.40 g, 68.0% for two steps). MS (DCI-NH_3): *m*/*z* 290 for (M + NH_4), base peak. ^{1}H NMR ($CDCl_3$): 0.92 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 2.19 (m, 1H, H_7), 2.40−2.60 (m, 4H, H_{6a}, H_{6b}, H_{3a}, H_{3b}), 3.30 (m, 1H, H_3), 3.75 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.65 (dd, 1H, H_5), 4.85 (d, 1H, H_2). HRMS: $C_{13}H_{21}O_6$, calcd: 273.1338, found: 273.1339.

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Supporting Information Available: ORTEP figure of the X-ray structure of **14** and ^{1}H NMR spectrum of **18a**, **18b**, and **19b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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