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A Synthetic Approach to 11-Oxabicyclo[6.2.1]undecyl Bicyclics

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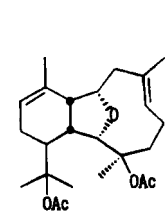
Through a sequence of reactions including Diels-Alder cycloaddition of a furan diene as the key step, 11-oxatricyclo[6.2.1.$0^{1,6}$]undecyl rings were synthesized from 5-methylfurfural with the goal of developing a synthetic protocol to 11-oxabicyclo[6.2.1]undecyl system. The strategy to incorporate an oxygen atom at C6 carbon of tricyclic **11** or **16** by Baeyer-Villiger oxidation was unsuccessful, implicating that there is too much steric congestion around the carbonyl ketone. As an alternative approach, bicyclic **23** and **24** were prepared from 2-methylfuran *via* known tricyclic **20**. Cyclization of bicyclic **23** and **24** under several reaction conditions also failed to produce hydroxylated product **25** and **26**.

Introduction

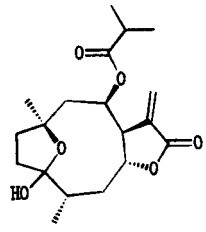
11-oxabicyclo[6.2.1]undecene skeleton constitutes a key structural feature in various natural products which are members of the furan-type germacranolide[1] or the eunicellanolide.[2] This bicyclic system contains a unique and interesting framework in which 5- and 9-membered rings were combined with an oxygen bridge. Recently, Boeckman and coworkers first synthesized (+)-eremantholide A by a strategy that forms this framework through cyclization of 9-membered ring at the final stage of their synthesis.[3] As a part of our study on the synthesis of zexbrevin[1a] and related compounds, we started an investigation to devise a general and efficient synthetic route to this type of bicyclics. Here we wish to report our results in the construction of the 11-oxabicyclo[6.2.1]undecene skeleton.

As depicted in retrosynthetic Scheme 1, we planned to build the bicyclic skeleton **1** from tricyclic 11-oxatricyclo[6.2.1.$0^{1,6}$]undecane ring system **2** by a ring expansion through a carbon-carbon bond cleavage.[4] The properly functionalized **2** might be formed from tricyclic **3** by concomitant epoxidation and Baeyer-Villiger oxidation. The tricyclic precursor **3** could be derived from the intramolecular Diels-Alder reaction of a furan diene such as **4**, which has numerous precedents.[5] Our synthetic approach, therefore, started with 5-methylfurfural as a starting material.

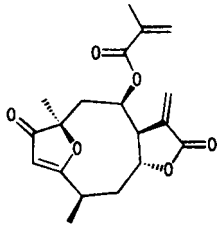
Synthesis of tricyclic ketone 11. Iodide **5**, which is a proper five-carbon side chain for the synthesis of enone **4**, was prepared from γ-hydroxymethyl-γ-butyrolactone[6] by successive reactions of LAH reduction, acetonide protection and iodide substitution as shown in Scheme 2. Even though Grignard formation from iodide **5** was not realized, lithi-



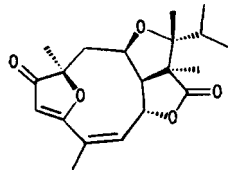
Calicophirin B



Tirotundin

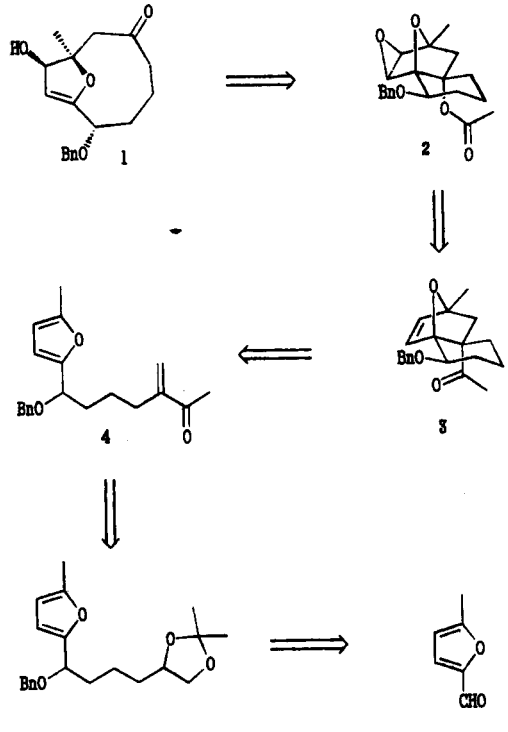


Zexbrevin

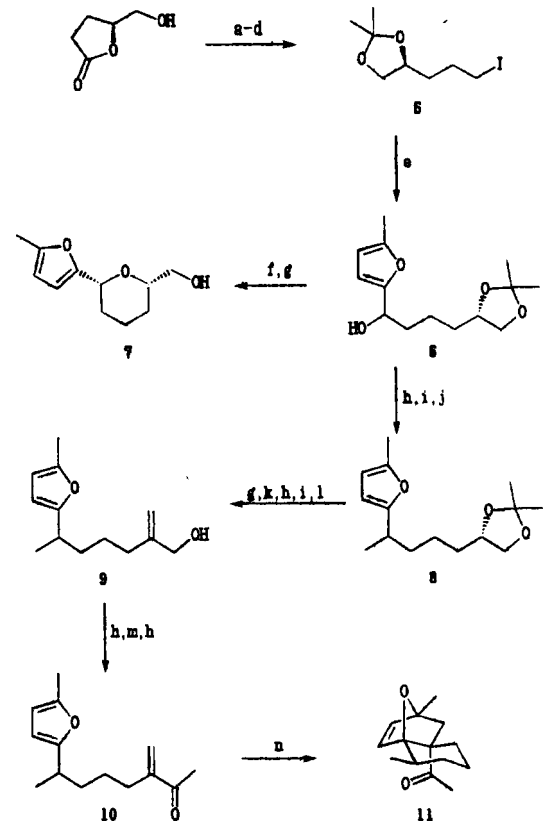


Eremantholide-A

ation with *t*-BuLi led us to the formation of carbanion which was successfully added to 5-methylfurfural to give acetonide **6**. Subsequently compound **6** was benzylated and subjected to hydrolytic conditions to remove the acetonide protecting group but this hydrolysis caused simultaneous solvolysis of a benzyloxy group to generate tetrahydropyran **7**. To circumvent this problem, the hydroxyl group in acetonide **6** was replaced by a methyl substituent to produce methyl analogue **8** through a series of reactions involving hydrogenolysis, TPAP oxidation,[7] Wittig olefination[8] and catalytic hydrogenation. The minor change in the original scheme, which put a methyl group at the benzyloxy position in the side arm, would not hurt our intention in the synthesis. The acetonide **8** was deprotected to a diol which

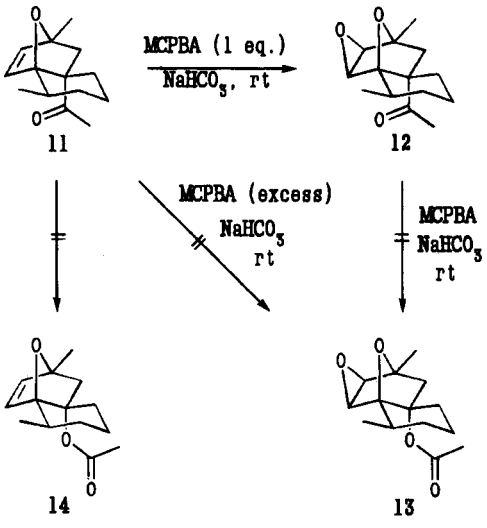


Scheme 1.



Scheme 2. Reagents and conditions: (a) $LiAlH_4$, THF, rt; (b) $(CH_3)_2C(OMe)_2$, cat. TsOH, acetone, rt; (c) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C→rt; (d) NaI, acetone, rt; (e) *t*-BuLi (2.05 eq.), pentane, −60 °C then 5-methylfurfural; (f) NaH, BnBr, Bu_4NI, THF, rt; (g) 5% HCl, THF, rt; (h) NMO, cat. TPAP, 4 Å mol. sieves, CH_2Cl_2, rt, 3 days; (i) $Ph_3P{=}CH_2$, THF, 0 °C→rt; (j) H_2, 10% Pd/C, EtOH; (k) TBDMSCl, Et_3N, cat. DMAP, CH_2Cl_2, rt; (l) TBAF, THF, rt; (m) MeMgI, THF, rt; (n) $BF_3{\cdot}OEt_2$ (0.1 eq.), CH_2Cl_2, −10 °C, 5 min.

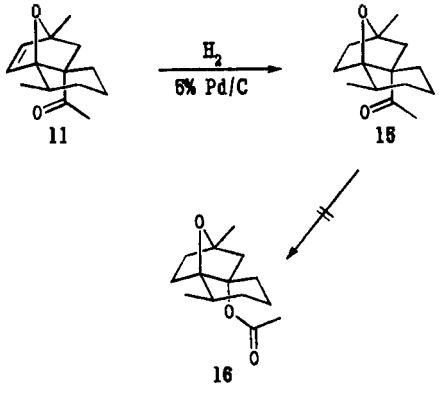
was selectively silylated by a TBDMS group. The resulting monosilylated compound was oxidized, methylenated by a Wittig procedure and desilylated with TBAF to give allylic alcohol **9**. A sequence of reactions including TPAP oxidation, Grignard addition and repeated oxidation converted allylic alcohol **9** to Diels-Alder precursor **10**. Once the enone **10** was in hand, attention was directed to the intramolecular Diels-Alder reaction. Generally, the Diels-Alder reaction of a furan with conventional dienophiles is known to be sluggish because of the aromatic character of the furan ring.[9] Several resolutions to this problem have been proposed[10] and also applied to the intramolecular version of the reaction.[11] With a high pressure reactor unavailable to us, we tried other reaction conditions including thermal reactions, use of $LiClO_4$[12] or Wilkinson's catalyst,[13] and Lewis acid catalysis.[14] Among these conditions, only Lewis acid catalysis made it possible to obtain some cyclized adduct **11**. The reaction with $BF_3{\cdot}Et_2O$, being the most reliable among various Lewis acid catalysis, yielded cycloadduct **11** in 33% with the starting enone **10** recovered in 63%. This Diels-Alder reaction exhibited fast reversibility and product **11** should be trapped within 5 minutes of reaction time to obtain the best result. Possibly several isom-



Scheme 3.

ers can be formed in the cycloaddition reaction but only one isomer was detected in our case. The stereochemistry of the adduct **11**, where its branched chain was oriented exo with respect to the oxygen bridge, was assigned in comparison with similar examples reported.[14a,b]

Attempted Baeyer-Villiger oxidation. Successful acquisition of tricyclic adduct **11** set the stage for epoxidation and Baeyer-Villiger oxidation[15] as shown in Scheme 3. Treatment of cycloadduct **11** with MCPBA generated epoxide **12** in good yield (84%). This epoxide, however, was unstable and easily decomposed in acidic or basic solutions (even in $CDCl_3$) to an unknown compound, which seemed to form from skeletal rearrangement and was not fully characterized. Unfortunately, Baeyer-Villiger oxidation with MCPBA could not transform cycloadduct **11** or epoxide **12** to key intermediate **13**, resulting in decomposition of starting material. Direct conversion of adduct **11** to acetate **14** also proved to be unsuccessful under conditions using 30% H_2O_2,[16] *t*-BuOOH[17] or bis(trimethylsilyl)peroxide.[18] To avoid uncertainty regarding the unstability of epoxide **12** during the reaction, cycloadduct **11** was hydrogenated to tricyclic **15** which is quite stable. Unexpectedly, attempted Baeyer-Villiger rearrangement of tricyclic **15** to ester **16** through the use of MCPBA under Kishi-Goto condition[19] or peroxytrifluoroacetic acid[20] showed no sign of reaction and the starting material was recovered (eq. 1). From these results,

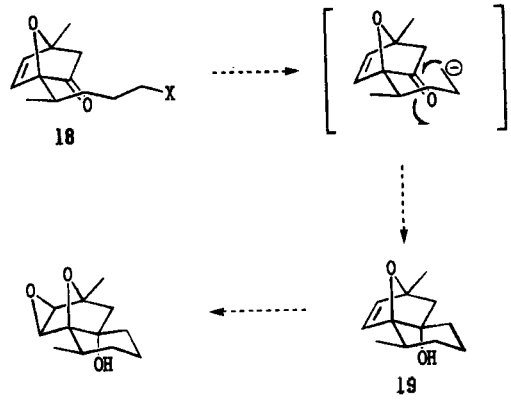


(1)

We concluded that the unreactivity of our tricyclic system under Baeyer-Villiger oxidation was probably caused by the steric congestion around the ketone carbonyl function. It was observed from the molecular model that both π-faces of the acetyl carbonyl group in our system were considerably shielded by the tricyclic template itself, thereby prohibiting nucleophiles from approaching to the carbonyl carbon. To bypass this obstacle, we also tried to perform reductive cleavage such as in Eq. 2. But various attempts to synthesize halide **17** proved unsuccessful.[21]

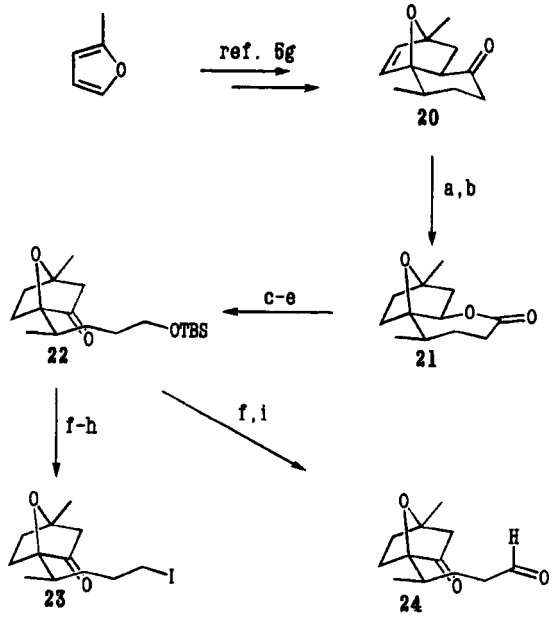
(2)

Alternative attempts to introduce a hydroxyl group at C6 carbon of the tricyclic ring. From the viewpoint of our synthetic strategy, it is essential that the tricyclic system should have a hydroxyl group or its equivalent at C6 carbon of the ring to assist the C-C bond fragmentation which is the primal step in the synthesis. The failure of Baeyer-Villiger rearrangement, however, led us to drop the direct insertion of an oxygen atom as in Scheme 3 or Eq. 1. Instead we envisioned the desired hydroxylation in an indirect manner such as the cyclization of ketohalide

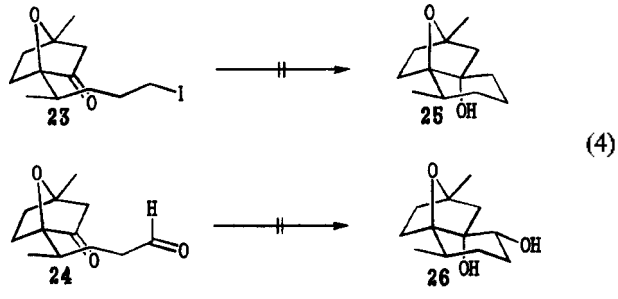


(3)

18 to tricyclic alcohol **19** (Eq. 3). Therefore we thought compound **23** was appropriate to test our modification of the original synthetic plan. As described in Scheme 4, synthesis of iodide **23** started from a known tricyclic **20**, which could be easily prepared from 2-methylfuran by a literature procedure.[5g] Catalytic hydrogenation followed by Baeyer-Villiger oxidation of tricyclic **20** furnished lactone **21**. Subsequently lactone **21** was reduced by $LiAlH_4$ to a diol, which was selectively protected with TBDMSCl and oxidized to ketone **22**. Deprotection of TBDMS group with TBAF, mesylation and Finkelstein reaction successfully afforded the desired iodide **23** in overall 43% yield from tricyclic **20**. Compound **21** was also converted by TBDMS protection and TPAP oxidation to ketoaldehyde **24**, which showed slow decomposition. With iodide **23** in hand, cyclization leading to the tricyclic skeleton **25** was performed in vain under various reaction conditions employing Mg,[22] *t*-BuLi[23] and SmI_2.[24] Similar coupling of ketoaldehyde **24** with SmI_2[24b] also turned out to be disappointing and proce-



Scheme 4. Reagents and conditions: (a) H_2, 10% Pd/C, EtOH; (b) MCPBA, $NaHCO_3$, CH_2Cl_2, rt; (c) $LiAlH_4$, Et_2O, 0 °C; (d) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, rt, 3 days; (e) PDC, 3 Å mol. sieves, CH_2Cl_2, rt; (f) TBAF, THF, rt; (g) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C→rt; (h) NaI, acetone, rt; (i) NMO, cat. TPAP, 4 Å mol. sieves, CH_2Cl_2, rt.



(4)

eded to decomposition of the starting material as in Eq. 4.

Here we have described the attempted construction of 6-hydroxy-11-oxatricyclo[6.2.1.$0^{1,6}$]undecyl rings with the goal of developing a synthetic approach to the 11-oxabicyclo[6.2.1]undecyl systems. Although it was unsuccessful to implant a hydroxy equivalent, which is an essential moiety for the execution of C-C bond cleavage according to our plan, at C6 carbon of the 11-oxatricyclo[6.2.1.$0^{1,6}$]undecyl system by several attempts, the knowledge related to the chemistry depicted in this paper would provide useful suggestions for the future modification of the synthesis. New approach to the targeting 11-oxabicyclo[6.2.1]undecyl ring has already been devised and is currently under way.

Experimentals

All reagents were purchased from Aldrich Chemical Co., Inc., and used without further purification. Merck Kieselgel 60 (230-400 mesh) was used for silica gel column chromatography. ^{1}H NMR spectra were obtained on a Bruker 100 MHz or Jeol 500 MHz NMR instrument. IR spectra were recorded on a Jasco IR R-100.

4-(3-Iodopropyl)-2,2-dimethyl-[1,3]dioxolane (5). To a THF solution (75 mL) of γ-hydroxymethyl-γ-butyrolactone (4.00 g, 34.4 mmol) at 0 °C was added $LiAlH_4$ (1.44 g, 37.9 mmol) portionwise. The reaction mixture was warmed slowly to room temperature and stirring was maintained for 1 hr. The mixture was quenched with 20% NaOH (5 mL) and water (5 mL), dried over $MgSO_4$, filtered through a Celite pad, and washed with additional THF (500 mL). The resulting organic layer was concentrated to give a crude diol (3.07 g) which was used in the next step without further purification. To a stirred solution of the crude diol in acetone (15 mL) was added $TsOH \cdot H_2O$ (63 mg, 1.2 mol%) and 2,2-dimethoxypropane (3.4 mL, 27.7 mmol) at room temperature. The resulting mixture was stirred for 1 hr before being quenched with saturated $NaHCO_3$ solution (10 mL). Acetone was removed under reduced pressure and the residual solution was extracted with EtOAc (3 20 mL). The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated to leave a crude acetonide that was purified by column chromatography on silica gel (elution with 50% EtOAc in hexane; 2.96 g, 54% two step overall). A solution of the above acetonide (1.00 g, 6.20 mmol) and Et_3N (3.16 g, 31.0 mmol) in CH_2Cl_2 (12 mL) was cooled to 0 °C and treated with CH_3SO_2Cl (0.73 mL, 7.4 mmol). The reaction mixture was slowly warm to room temperature and stirred for 1 hr. CH_2Cl_2 was removed under reduced pressure and the residual mixture was diluted with EtOAc (20 mL). Normal work-up yielded a crude methanesulfonate (1.60 g) which was used directly in the next step. An acetone solution (20 mL) of the material obtained above and NaI (14.2 g, 94.4 mmol) was stirred for 3 hr at room temperature. The resulting mixture was treated with 10% $Na_2S_2O_3$ solution (10 mL) to remove iodine. Acetone was evaporated and the residual solution was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated to provide a residue. Purification by silica gel chromatography (elution with 10% EtOAc in hexane) afforded iodide **5** (1.41 g, 80% two step overall); IR (neat, cm^{-1}) 2960, 2910, 2850, 1450, 1370, 1360, 1230, 1210, 1050; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.41 (s, 3H), 1.54-1.79 (m, 2H), 1.79-2.17 (m, 2H), 3.23 (t, *J*=6.6 Hz, 2H), 3.42-3.68 (m, 1H), 3.97-4.27 (m, 2H).

4-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-1-(5-methylfuran-2-yl)-1-butanol (6). A solution of iodide **5** (1.67 g, 6.18 mmol) in anhydrous pentane (15 mL) was cooled to − 55 °C and *t*-BuLi (7.3 mL, 12.4 mmol, 1.7 M in pentane) was slowly added to it. The resulting solution was stirred for 20 min and treated with a THF solution (5 mL) of 5-methylfurfural (720 mg, 6.49 mmol) by a cannula. The mixture was slowly warmed up to room temperature over 40 min before being quenched with saturated NH_4Cl solution. Normal work-up and purification by silica gel chromatography (elution with 25% EtOAc in hexane) provided acetonide **6** (1.17 g, 75%); IR (neat, cm $^{-1}$) 3420, 2960, 2920, 2850, 1730, 1560, 1450, 1360, 1250, 1220; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.40 (s, 3H), 1.22-2.10 (m, 6H), 2.27 (s, 3H), 3.37-3.63 (m, 1H), 3.91-4.25 (m, 2H), 4.47-4.72 (m, 1H), 5.80-5.94 (m, 1H), 6.09 (d, *J*=3.0 Hz, 1H).

2,2-Dimethyl-4-[4-(5-methylfuran-2-yl)pentyl]-[1,

3]dioxolane (8). To a stirred solution of acetonide **6** (1.44 g, 5.67 mmol) in CH_2Cl_2 (5 mL) was added NMO (1.31 g, 11.2 mmol), 4 Å molecular sieves (2.84 g, 0.5 g/mmol) and TPAP (96 mg, 5 mol%). The resulting mixture was stirred at room temperature for 40 min, diluted with 25% EtOAc in hexane (25 mL), filtered through a silica gel column (elution with 25% EtOAc in hexane), and evaporated to give the ketone (1.31 g) which was used in the next step. To a stirred THF solution (20 mL) of methyltriphenylphosphonium iodide (3.15 g, 7.79 mmol) was added *n*-BuLi (4.7 mL, 7.50 mmol, 1.6 M in hexane) at − 15 °C. The resulting mixture was stirred for 20 min, warmed to 0 °C, and treated with a solution of the above ketone (1.31 g, 5.19 mmol) in THF (8 mL). The mixture was stirred at 0 °C for 30 min and warmed to room temperature before being quenched with saturated NH_4Cl (10 mL). The resulting solution was extracted with EtOAc (3×20 mL) and the usual work-up followed by silica gel chromatography (elution with 25% EtOAc in hexane) produced the methylenated product (1.00 g) and starting ketone (0.19 g). Recovered ketone was resubjected to the olefination procedure with the combined yield of 1.19 g (82% two step overall). A solution of the above olefin (1.17 g, 4.65 mmol) in ethanol (10 mL) containing 10 mg of 10% Pd/C was hydrogenated under an atmosphere of hydrogen (balloon) for 3 hr. The reaction mixture was filtered through a Celite and the filtrate was evaporated. Purification by silica gel chromatography gave compound **8** (1.11 g, 94%); IR (neat, cm^{-1}) 2970, 2920, 2850, 1560, 1450, 1370, 1360, 1240, 1220, 1050; ^1H NMR (100 MHz, $CDCl_3$) δ 1.20 (d, *J*=7.0 Hz, 3H), 1.34 (s, 3H), 1.40 (s, 3H), 1.10-1.80 (m, 6H), 2.24 (s, 3H), 2.55-2.90 (m, 1H), 3.38-3.60 (m, 1H), 3.38-4.20 (m, 2H), 5.82 (s, 2H).

2-[4-(5-Methylfuran-2-yl)pentyl]-2-propen-1-ol (9). A stirred THF solution (6 mL) of acetonide **8** (1.12 g, 4.44 mmol) was treated with 1 N HCl (6 mL) and the resulting solution was stirred at room temperature for 2 hr before being quenched with saturated $NaHCO_3$ and extracted with EtOAc (3×15 mL). Normal work-up and concentration gave the diol which was used in the next step without further purification. To a CH_2Cl_2 solution (90 mL) of the diol was added Et_3N (2.25 g, 22.2 mmol), DMAP (54 mg, 0.44 mmol) and TBDMSCl (1.00 g, 6.67 mmol) at room temperature. The reaction mixture was stirred for 3 days and washed with saturated $NaHCO_3$. Usual work-up followed by silica gel chromatography (elution with 4.8% EtOAc in hexane) gave the monosilylated diol (1.30 g, 93% two step overall). To a CH_2Cl_2 solution (8 mL) of the above silylated product (1.30 g, 4.00 mmol) was added NMO (0.93 mg, 8.00 mmol), 4 Å molecular sieves (2.0 g) and TPAP (70 mg, 5 mol%) at room temperature and the resulting solution was stirred for 20 min before being diluted with 10% EtOAc in hexane (25 mL) and filtered through a silica gel column (elution with 10% EtOAc in hexane). Solvent evaporation afforded the desired ketone (1.26 g, 98%). To a stirred THF solution (15 mL) of methyltriphenylphosphonium iodide (2.36 g, 5.80 mmol) was added *n*-BuLi (3.6 mL, 5.8 mmol, 1.6 M in hexane) at − 15 °C. The resulting mixture was stirred for 20 min and treated with a THF solution (5 mL) of the above ketone (1.26 g, 3.90 mmol). The reaction mixture was warmed up to room temperature, stirred for 40 min, quenched with saturated NH_4Cl, and extracted with EtOAc (3×15 mL). Normal work-up and purification by silica gel chromatography (elution with 3.2% EtOAc in hexane) delivered the methylenated product (1.19 g, 95%). To a THF solution (10 mL) of the product obtained above (1.19 g, 3.70 mmol) was added TBAF (7.4 mL, 7.40 mmol, 1.0 M in THF) at room temperature. The reaction mixture was stirred for 30 min, quenched with saturated NH_4Cl, and extracted with EtOAc (3×15 mL). Usual work-up followed by chromatography on silica gel (elution with 25% EtOAc in hexane) finally produced allylic alcohol **9** (0.77 g, 100%); IR (neat, cm^{-1}) 3310, 2950, 2915, 2850, 1650, 1610, 1560, 1450, 1220, 1005, 880; ^1H NMR (100 MHz, $CDCl_3$) δ 1.19 (d, *J*=7.0 Hz, 3H), 1.31-1.78 (m, 4H), 1.92-2.18 (m, 2H), 2.23 (s, 3H), 2.56-2.91 (m, 1H), 4.03 (s, 2H), 4.84 (m, 1H), 4.99 (m, 1H), 5.81 (s, 2H).

3-methylene-7-(5-methylfuran-2-yl)-2-octanone (10). A CH_2Cl_2 solution (5 mL) of allylic alcohol **9** (400 mg, 1.92 mmol), NMO (450 mg, 3.74 mmol), 4 Å molecular sieves (960 mg, 0.5 g/mmol), and TPAP (34 mg, 5 mol%) was stirred at room temperature for 4 hr. The reaction mixture was diluted with 20% EtOAc in hexane (25 mL) and filtered through a silica gel column. Solvent evaporation afforded the aldehyde product which was directly used in the next step. To a diethyl ether (5 mL) of the above aldehyde was used MeMgI (1 mL, 3 mmol, 3 M in diethyl ether) at 0 °C and the resulting solution was stirred for 1 hr before being quenched with saturated NH_4Cl and extracted with EtOAc (3×15 mL). Solvent evaporation provided a crude alcohol which was used in the next step without further purification. To a CH_2Cl_2 solution (5 mL) of the crude alcohol from above was added NMO (370 mg, 3.4 mmol), 4 Å molecular sieves (800 mg), and TPAP (29 mg, 5 mol%) at room temperature and the resulting solution was stirred for 2 hr before being diluted with 20% EtOAc in hexane (30 mL) and filtered through a silica gel column. Purification by silica gel chromatography (elution with 20% EtOAc in hexane) gave enone **10** (270 mg, 64% three step overall); IR (neat, cm^{-1}) 2950, 2920, 2850, 1675, 1620, 1560, 1450, 1430, 1360, 1220, 1010; ^1H NMR (100 MHz, $CDCl_3$) δ 1.20 (d, *J*=6.9 Hz, 3H), 1.25-1.81 (m, 4H), 2.25 (s, 3H), 2.32 (s, 3H), 2.15-2.35 (m, 2H), 2.58-3.00 (m, 1H), 5.74 (m, 1H), 5.82 (s, 2H), 5.99 (s, 1H).

1-(2,8-Dimethyl-11-oxatricyclo[6.2.1.$0^{1,6}$]undec-9-en-6-yl)ethanone (11). A solution of enone **10** (255 mg, 1.16 mmol) in CH_2Cl_2 (10 mL) was cooled down to − 10 °C and treated with $BF_3 \cdot OEt_2$ (14.2 μL, 0.116 mmol). The reaction mixture was stirred at that temperature for 5 min and quenched with saturated $NaHCO_3$. Aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and combined organic layers were washed with water. Drying and solvent evaportion followed by silica gel chromatography furnished the desired tricyclic **11** (84 mg, 33%) with 162 mg of starting enone **10** recovered; IR (neat, cm^{-1}) 1950, 1920, 1850, 1690, 1450, 1380, 1350, 1160, 1110; ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (d, *J*=7.0 Hz, 3H), 1.18-1.27 (m, 1H), 1.30 (dq, *J*=3.1, 13.0 Hz, 1H), 1.57 (s, 3H), 1.53-1.63 (m, 2H), 1.66 (d, *J*=11.1 Hz, 1 H), 1.77 (dt, *J*=2.7, 14.0 Hz, 1H), 1.79 (d, *J*=11.1 Hz, 1H), 2.04 (s, 3H), 2.12 (d, *J*=14.0 Hz, 1H), 2.44 (m, 1H), 6.05 (d, *J*=5.5 Hz, 1H), 6.25 (d, *J*=5.5 Hz, 1H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 17.26, 19.29, 22.46,

27.65, 30.56, 31.61, 35.93, 47.48, 61.43, 85.09, 90.96, 139.81, 211.25.

2,9-Dimethyl-6,12-dioxatricyclo[7.2.1.0^{1,7}]dodecan-5-one (21). A solution of tricyclic **20** (150 mg, 0.780 mmol) in ethanol (5 mL) containing 10% Pd/C (10 mg, catalytic amount) was hydrogenated under an atmosphere of hydrogen (balloon) for 30 min. The reaction mixture was filtered through a Celite and the filtrate was evaporated to give a crude product (160 mg) which was used in the next step without further purification. To a CH_2Cl_2 solution (8 mL) of the above product (160 mg) was added m-chloroperbenzoic acid (631 mg, 2.08 mmol) and $NaHCO_3$ (350 mg, 4.17 mmol) and the resulting mixture was stirred at room temperature for 2 days. 10% Na_2SO_3 solution (5 mL) was introduced and the layers were separated after 1 hr of rapid stirring. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and the combined organic phases were washed with saturated $NaHCO_3$ (20 mL) and water (30 mL) prior to drying and solvent evaporation. The residue was purified by silica gel chromatography (elution with 40% EtOAc in hexane) to give 142 mg of lactone **21** (81% two step overall); IR (neat, cm^{-1}) 2960, 2920, 2850, 1730, 1465, 1440, 1380, 1320, 1270, 1190, 1095; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (d, *J*=7.3 Hz, 3H), 1.52 (s, 3H), 1.53-1.66 (series of m, 4H), 1.78 (dm, *J*=13.2 Hz, 1H), 1.84 (m, 1H), 1.91 (m, 1H), 2.15 (dd, *J*=7.1, 13.4 Hz, 1H), 2.21 (d of quintet, *J*=4.9, 7.3 Hz, 1H), 2.62 (ddd, *J*=6.5, 8.7, 15.0 Hz, 1H), 2.70 (dt, *J*=15.0, 5.9 Hz, 1H), 4.54 (dd, *J*=2.9, 7.3 Hz, 1H).

1-(4-t-butyldimethylsilyloxy-1-methylbutyl)-4-methyl-7-oxabicyclo[2.2.1]heptan-2-one (22). To a diethyl ether solution (4 mL) of lactone **21** (100 mg, 0.476 mmol) at 0 °C was added $LiAlH_4$ (25 mg, 0.666 mmol). The reaction mixture was stirred for 10 min and quenched with water. A 5% solution of sodium potassium tartrate (10 mL) was added and the resulting solution was stirred until the phase was cleanly separated. The aqueous phase was extracted with diethyl ether (3×10 mL) and the combined organic layers were washed with water, dried over $MgSO_4$, and concentrated. To a stirred solution of the residue in CH_2Cl_2 (7 mL) was added TBDMSCl (82 mg, 0.539 mmol), DMAP (4.6 mg, 0.036 mmol) and Et_3N (250 μL, 1.80 mmol) at room temperature. The reaction mixture was stirred for 3 days, diluted with CH_2Cl_2 (15 mL), washed with 10% HCl (10 mL) and water, and dried over $MgSO_4$. Solvent evaporation followed by silica gel chromatography produced 97 mg of the silyl alcohol (66% two step overall). To a stirred solution of the above alcohol (97 mg, 0.295 mmol) in CH_2Cl_2 (3 mL) was treated with pyridinium dichromate (223 mg, 0.590 mmol) and powdered 3 Å molecular sieves (163 mg). After 5 hr, the reaction mixture was diluted with diethyl ether (40 mL), filtered through a pad of Celite and anhydrous $MgSO_4$, and evaporated to afford ketone **22** (101 mg, 100%); IR (neat, cm^{-1}) 2950, 2920, 2855, 2850, 1760, 1460, 1380, 1085, 820; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.05 (d, *J*=6.8 Hz, 3H), 1.36-1.53 (series of m, 3H), 1.55 (s, 3H), 1.57-1.72 (series of m, 3H), 1.77 (m, 1H), 1.87 (dt, *J*=4.4, 12.2 Hz, 1H), 1.97 (m, 1H), 2.22 (s, 2H), 3.59 (dt, *J*=2.4, 6.3 Hz, 2H).

1-(4-Iodo-1-methylbutyl)-4-methyl-7-oxabicyclo [2.2.1]heptan-2-one (23). To a THF solution (3 mL) of ketone **22** (100 mg, 0.304 mmol) was added TBAF (0.61 mL, 0.608 mmol, 1.0 M in THF) at room temperature. The reaction mixture was stirred for 4 hr, quenched with saturated NH_4Cl, and extracted with EtOAc (3×15 mL). Usual work-up followed by silica gel chromatography (elution with 50% EtOAc in hexane) produced an alcohol product (64 mg, 100%). A solution of the alcohol obtained above (64 mg, 0.304 mmol), CH_3SO_2Cl (28 μL, 0.366 mmol), and Et_3N (0.25 mL, 1.82 mmol) in CH_2Cl_2 (3 mL) was stirred at 0 °C for 10 min. The reaction mixture was warmed up to room temperature, diluted with diethyl ether (20 mL), and washed with 10% HCl (10 mL) and water. Drying and solvent evaporation provided a residue which was used in the next step without further purification. An acetone solution (5 mL) of the crude methanesulfonate and NaI (907 mg, 6.06 mmol) was stirred overnight at room temperature. The reaction mixture was treated with 10% $Na_2S_2O_3$ solution (10 mL). Acetone was evaporated and the residual solution was extracted with EtOAc (3 10 mL). Usual work-up and purification by silica gel chromatography (elution with 25% EtOAc in hexane) afforded iodide **23** (84 mg, 86%); IR (neat, cm^{-1}) 2960, 2930, 2860, 1750, 1460, 1400, 1380, 1320, 1250, 1220, 1160, 1020, 840; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (d, *J*=7.3 Hz, 3H), 1.55 (s, 3H), 1.49-1.66 (series of m, 3H), 1.71 (ddm, *J*=4.9, 11.7 Hz, 1H), 1.74-1.83 (series of m, 2H), 1.89 (dt, *J*=4.4, 12.2 Hz, 1H), 1.93-2.05 (series of m, 2H). 2.23 (s, 2H), 3.14 (dt, *J*=9.6, 7.3 Hz, 1H), 3.20 (ddd, *J*=6.3, 7.6, 9.6 Hz, 1H).

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