Total Synthesis of Furanether B. An Application of a [3 + 4] Annulation Strategy

Gary A. Molander* and John S. Carey

Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309-0215

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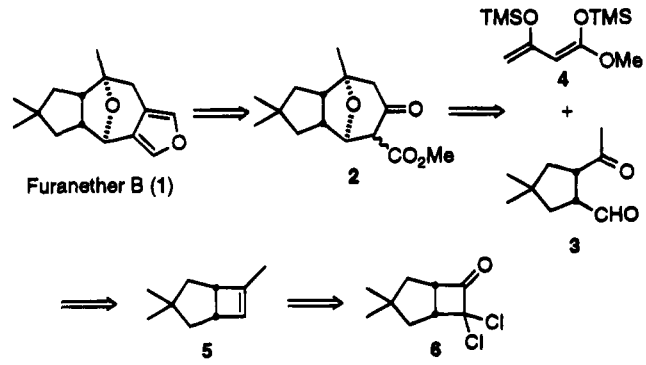
Furanether B has been synthesized by a route starting from the known dichloro ketone **6**. Crucial to the success of the synthesis was the preparation of cyclobutene **5** and oxidative cleavage of this substrate to provide the *cis*-1,4-keto aldehyde **3**. This dicarbonyl dielectrophile subsequently underwent a TMSOTf catalyzed [3 + 4] annulation with the bis(trimethylsilyl) enol ether **4** to afford the tricyclic ether **2**. Conversion of **2** into butenolide **19**, followed by DIBALH reduction, completed the synthesis.

In this contribution we report a total synthesis of the furanosesquiterpene furanether B (**1**), a lactarane metabolite isolated in 1980 from the yellow mushroom *Lactarius scrobiculatus*.[1] Although synthetic studies directed toward the lactarane carbon skeleton have been limited,[2] two complementary syntheses of furanether B have been reported.[3]

Previous reports from our laboratory have demonstrated that the Lewis acid-promoted [3 + 4] and [3 + 5] annulations of 1,4- and 1,5-dicarbonyl compounds with bis(trimethylsilyl) enol ether **4** afford oxabicyclo[3.2.1]-heptanones and oxabicyclo[3.3.1]octanones, respectively.[4] Subsequently, an oxabicyclo[3.2.1]heptanone was used as the platform for the stereoselective synthesis of *cis*-2,5-disubstituted tetrahydrofurans.[5] The critical eight-membered ring of (+)-dactylol was also established using a [3 + 5] annulation reaction in the course of the total synthesis of that molecule.[6]

Our approach to furanether B (Scheme 1) has relied upon a [3 + 4] annulation reaction to establish the bridged ether core of **1**. Studies of the synthesis of tricyclic ethers *via* the [3 + 4] annulation of *cis*-2-acetylcyclohexanecarboxaldehyde with the bisnucleophile **4** suggested that the reaction of the keto aldehyde **3** would give rise to **2**.[7] Tricyclic ether **2** possesses the correct stereochemistry observed in the natural product, as well as having the β-keto ester functionality suitably placed for the construction of the furan ring. The key to the synthesis was anticipated to be the preparation of the 1,4-keto aldehyde **3**, with the requisite *cis* configuration of the formyl and acetyl substituents on the cyclopentane ring.[8] Alkene **5** was considered to be a suitable precursor to **3** because the bicyclo[3.2.0]heptene skeleton would set the *cis* stereochemistry of the methine protons at the ring juncture. Additionally, oxidative cleavage of the double bond in **5** would unveil the two carbonyl functional groups present in **3**. In turn, alkene **5** was envisioned as arising from the previously reported dichloro ketone **6**.[9]

Scheme 1



Results and Discussion

At the outset, several different routes to **5** were envisioned. These included the alkylation of enol triflate **8**, a Shapiro reaction and subsequent alkylation of **9**, or dehydration of the tertiary alcohol **10** (Scheme 2). The dichloro ketone **6** required to assess the viability of all of these approaches was readily prepared on a multigram scale from 3,3-dimethylglutaric acid (five steps, 50% overall yield) following the procedures of Cane.[9] Heating **6** with excess zinc in acetic acid[9] effected a complete dechlorination to provide ketone **7** in 84% yield.

The first route examined, requiring formation of the enol triflate **8**, proved to be problematic. Treatment of **7** with LDA followed by addition of *N*-phenyltriflimide[10] afforded **8** in only 17% yield. A modest increase to 24% could be obtained using Comins's reagent,[11] whereas none of the desired product was obtained using triflic anhydride and 2,6-di-*tert*-butylpyridine.[12] Displacement of the triflate with lithium dimethylcuprate,[10] however, cleanly gave alkene **5**.

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(7) Molander, G. A.; Cameron, K. O. *J. Org. Chem.* **1993**, *58*, 5931.

(8) The dimethyl acetal of **3** has been synthesized as a mixture of *cis* and *trans* isomers. Deprotection then provided the *trans* keto aldehyde. Tinao-Wooldridge, L. V.; Moeller, K. D.; Hudson, C. M. *J. Org. Chem.* **1994**, *59*, 2381.

(9) Cane, D. E.; Thomas, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 5295.

(10) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47 and references therein.

(11) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

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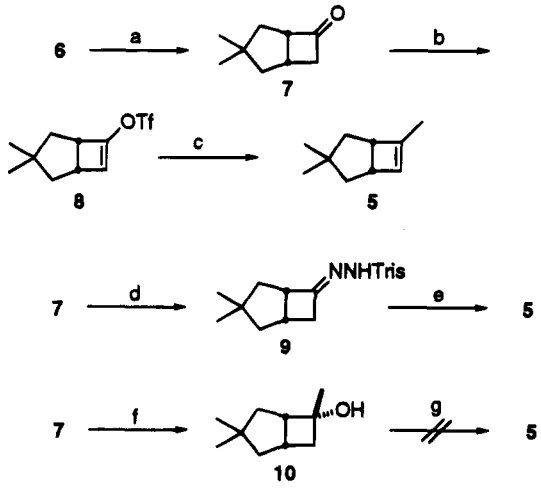
Scheme 2



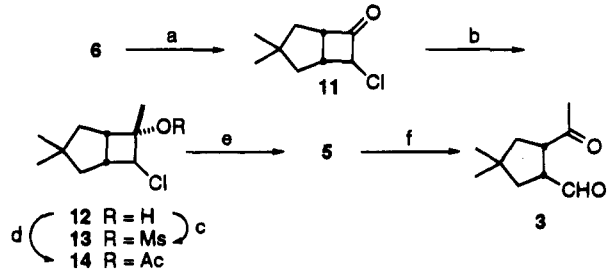
Key: (a) Zn, AcOH, rt to 70 °C; (b) LDA, 2-N(SO_2CF_3)-5-ClC_5H_5N, THF, -78 °C to rt; (c) Me_2CuLi, THF, -10 °C to rt; (d) HCl, $[(CH_3)_2CH]_3C_6H_2SO_2NHNH_2$, MeOH, -15 °C; (e) *t*-BuLi, Me_2SO_4, THF, -78 °C to 0 °C; (f) MeLi, THF, -78 °C; (g) see text.

In an alternate approach, the trisylhydrazone **9** was prepared as a mixture of geometrical isomers from ketone **7** and trisylhydrazide in the presence of acid (87%).[13] Shapiro reaction[14] of **9** using *t*-BuLi and quenching the vinyl anion with dimethyl sulfate afforded alkene **5** in *ca.* 50% yield. Unfortunately, **5** was contaminated with 10–20% of an unknown impurity, and purification was not possible because of the nonpolar and volatile nature of the products.

The dehydration route also proved problematic. Thus, addition of methyllithium to ketone **7** provided the tertiary alcohol **10** in 65% yield as a single diastereoisomer. Treatment of **10** under a variety of conditions used to dehydrate alcohols to alkenes[15] (BF_3·OEt_2; $SOCl_2$, pyridine; $POCl_3$, pyridine; P_2O_5; Burgess' reagent in either C_6H_6 or DMF; H_3PO_4, DMSO; DMSO, cat. I_2; DMSO, cat. TsOH; MsCl, DBU; TsCl, DBU) failed to deliver any **5**.

In view of the disappointing yields and/or contaminated products obtained through these initial efforts, a slightly different approach was undertaken. Thus, reductive elimination of a chlorohydrin or chlorohydrin derivative was investigated as a means to gain access to the desired substrate. Controlled reduction[16] of the dichloro ketone **6** using zinc in acetic acid allowed the isolation of the monochloro ketone **11** in 94% yield and as a single diastereoisomer (relative configuration of the chloride unknown, Scheme 3). Addition of methylmagnesium bromide to **11** afforded chlorohydrin **12** (87%), again as a single diastereoisomer. Treatment of **12** with sodium in liquid ammonia[17] resulted in simple dechlorination to provide **10** (87%) rather than the desired alkene **5**. Activation of the hydroxyl group was therefore required for alkene formation.

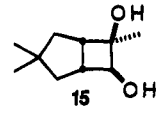
Scheme 3



Key: (a) Zn, AcOH, rt; (b) MeMgBr, Et_2O, -78 °C; (c) MsCl, NEt_3, CH_2Cl_2, -20 °C; (d) Ac_2O, NEt_3, DMAP, CH_2Cl_2, rt; (e) Na, NH_3, Me_2O -78 °C; (f) O_3, cat. $NaHCO_3$, PPh_3, EtOAc, -78 °C to rt.

Initially, mesylate **13** was prepared[18] and shown to undergo a very efficient reduction with sodium in liquid ammonia[19] to afford **5**. However, the formation of the mesylate could only be achieved on a small scale in an optimized yield of 61% using a large excess of reagents. Fortunately, acetate **14** could be synthesized from **12** in 85% yield and on a large scale. Reductive elimination of acetate **14** using sodium in liquid ammonia very cleanly afforded the alkene **5**. Because of the highly volatile nature of **5**, the alkene was not isolated, but rather used in subsequent reactions as a solution in pentane.

Ozonolysis of **5** to the desired keto aldehyde **3** proved to be solvent dependent. The use of methanol as solvent or cosolvent led to the formation of mixtures of dimethyl acetals and dimethyl ketals, and thus ethyl acetate was used for this oxidative cleavage.[20] Because reduction of the intermediate ozonide to the dicarbonyl compound proceeded much more rapidly with triphenylphosphine than with dimethyl sulfide the former was utilized to generate the desired keto aldehyde. The *cis*-keto aldehyde **3** readily epimerized to the *trans* isomer when subjected to standard flash chromatography, but column chromatography using pH 7 silica gel provided a >20:1 mixture of *cis* to *trans* isomers in 47% overall yield from the acetate **14**. Interestingly, treatment of alkene **5** with catalytic OsO_4 and 2 equiv of *N*-methylmorpholine *N*-oxide[21] gave directly the *cis*-keto aldehyde **3** rather than the anticipated diol **15**, albeit in only 23% yield.



The [3 + 4] annulation of keto aldehyde **3** with the bis(trimethylsilyl) enol ether **4**[4b] in the presence of a catalytic quantity of TMSOTf provided a 70% yield of the tricyclic ether **2** (Scheme 4). The regio- and stereochemical outcome of this annulation was consistent with the mechanism proposed for previous annulations of keto aldehydes.[4a,4b,7] The *trans* relationship between the ether bridge and the methine hydrogens at the ring juncture arises from attack of the nucleophilic reagent on the exo face of the bicyclic oxocarbenium ion intermediate.[7]

Structural assignment of **2** by NMR analysis was difficult because the β-keto ester functionality exists as

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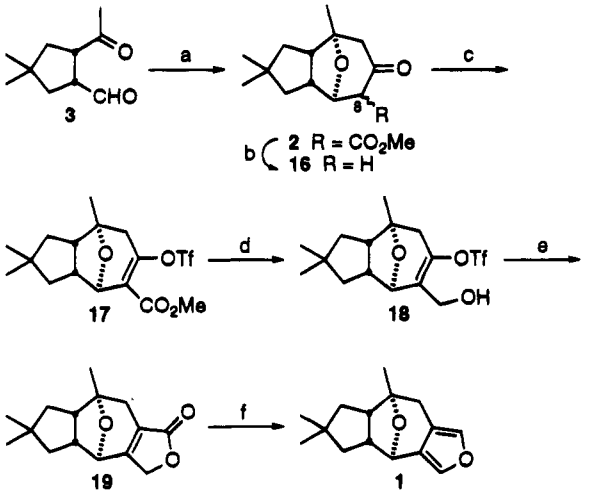
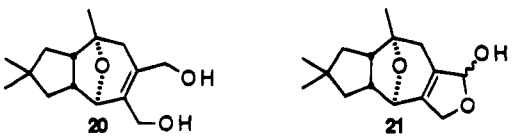
Scheme 4



Key: (a) cat. TMSOTf, 4, CH_2Cl_2, -78 °C; (b) NaCl, H_2O, DMSO, 140 °C; (c) NaH, 2-N(SO_2CF_3)$_2$-5-ClC_5H_5N, THF, 0 °C to rt; (d) DIBALH, THF, -55 °C to rt; (e) cat. $Pd(PPh_3)_4$, CO, NBu_3, LiCl, CH_3CN, 60 °C; (f) DIBALH, CH_2Cl_2, -78 °C, then 1N H_2SO_4, -78 °C to rt.

an equilibrium mixture of tautomers (the two keto ester diastereoisomers epimeric at C-8 plus the enol). The structure was therefore established by completing a formal total synthesis of furanether B.[3b] Decarboxylation[22] of **2** provided the tricyclic ketone **16** (65%), the ^{1}H NMR spectrum of which was identical to that of an authentic spectrum.

An alternative synthesis of the natural product was undertaken to exploit the suitably placed functionality present in the annulation product **2**. Following the precedent of Crisp,[23] the β-keto ester **2** was readily converted to the butenolide **19**. Deprotonation of **2** with sodium hydride followed by the addition of Comins's reagent[11] afforded the enol triflate **17** in 78% yield. Reduction of the ester functionality in **17** with DIBALH[23] provided the hydroxy enol triflate **18** in 85% yield. In turn, **18** underwent a palladium catalyzed carbonylation[23] to afford the α,β-butenolide **19** in 90% yield. Reduction of butenolide **19** to a furan initially proved troublesome. The use of 1 equiv of DIBALH in either THF or toluene[24] led to significant amounts of diol **20**[25] being formed, as well as recovery of the butenolide **19**. The use of 1 equiv of other reducing agents such as Red-Al[27] or disiamylborane[28] gave equally disappointing results. Optimum results were obtained by using 1.1 equiv of DIBALH in CH_2Cl_2 as the solvent. These conditions cleanly provided the intermediate lactol **21** which then underwent dehydration/aromatization upon quenching with 1 N H_2SO_4 to yield furanether B (**1**) (90%). The ^{1}H NMR spectrum of **1** was identical to that of an authentic spectrum.



In conclusion, an efficient synthesis of furanether B has been achieved using a regio- and stereoselective [3 + 4] annulation reaction to establish the bridged ether core of the natural product. The synthesis demonstrates that this annulative approach to bicyclic ethers can be utilized effectively for the rapid construction of the core unit of such targets.

Experimental Section

Reagents. THF was distilled immediately prior to use from sodium benzophenone ketyl under argon. Acetonitrile and CH_2Cl_2 were distilled from CaH_2 under argon. Neutral (pH 7) silica gel was purchased from Mallinckrodt (Silica Gel 150, 60–200 mesh). Standard benchtop techniques were employed for the handling air sensitive reagents.[29]

***cis*-3,3-Dimethylbicyclo[3.2.0]heptan-6-one (7).** Zinc (23.22 g, 355.0 mmol) was added portionwise to a stirred solution of **6** (7.36 g, 35.6 mmol) in acetic acid (75 mL) at rt, and then the resulting reaction mixture was heated to 70 °C for 2 h. Upon cooling to rt pentane was added, and the mixture was filtered through Celite. The organic phase was washed with saturated $NaHCO_3$ and then brine and dried over $MgSO_4$. Concentration *in vacuo* followed by Kugelrohr distillation (ot 60 °C/0.5 mmHg) provided **7** as a colorless oil (4.10 g, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66–3.60 (m, 1H), 3.14 (ddd, J = 17.9, 9.0, 3.8 Hz, 1H), 2.89–2.83 (m, 1H), 2.63 (dt, J = 17.9, 3.6 Hz, 1H), 1.90–1.84 (m, 1H), 1.71 (dd, J = 13.2, 5.3 Hz, 1H), 1.58–1.52 (m, 1H), 1.36 (dd, J = 13.3, 5.5 Hz, 1H), 1.03 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.2, 65.6, 52.1, 47.8, 44.9, 42.7, 29.7, 28.6, 28.6; IR (neat) 1778 cm^{-1}; HRMS calcd for $C_9H_{14}O$: 138.1045, found 138.1040; LRMS (EI) m/z 138. Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.80; H, 10.24.

***cis*-3,3-Dimethyl-6-[[(trifluoromethyl)sulfonyl]oxy]-bicyclo[3.2.0]hept-6-ene (8).** To a stirred solution of diisopropylamine (646 mg, 6.40 mmol) in THF (7 mL) at −25 °C was slowly added *n*-BuLi (1.6 M in hexanes, 4.00 mL, 6.40 mmol). After 30 min, the solution was cooled to −78 °C, **7** (700 mg, 5.07 mmol) in THF (7 mL) was added dropwise, and the resulting solution was stirred at 0 °C for 2 h. Upon cooling to −78 °C 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (3.01 g, 7.67 mmol) in THF (7 mL) was added dropwise and the solution was left at −78 °C for 2 h before warming to rt. The solution was diluted with ether, and the organic phase was washed with water, then brine, and dried over $MgSO_4$. Concentration *in vacuo* followed by flash chromatography (hexanes) afforded **8** as a colorless oil (333 mg, 24%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44 (s, 1H), 3.63–3.59 (m, 1H), 3.08 (dt, J = 7.4, 3.2 Hz, 1H), 1.62 (dd, J = 13.5, 3.2 Hz, 1H), 1.49–1.36 (m, 3H), 1.10 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 120.0, 118.5 (q, $^1J_{CF}$ = 321 Hz), 53.4, 45.2, 41.4, 40.4, 38.8, 30.9, 30.3; IR (neat) 1427, 1142 cm^{-1}; LRMS (EI) m/z 270.

***cis*-3,3-Dimethyl-6-[[(2,4,6-triisopropylphenyl)sulfonyl]-hydrazono]bicyclo[3.2.0]heptane (9).** To a stirred solution of **7** (1.00 g, 7.25 mmol) in MeOH (7 mL) at rt was added 2,4,6-triisopropylbenzenesulfonyl hydrazide (2.16 g, 7.25 mmol) and then concentrated HCl (75 μL). The reaction mixture was chilled at −15 °C overnight and filtered. The product was washed with cold MeOH (10 mL) and dried *in vacuo* to afford the white solid **9** as a mixture of geometrical isomers (2.64 g, 87%): mp 122–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16–6.98 (m, 3H), 4.22–4.11 (m, 2H), 3.56–3.37 (m, 1H), 3.07–2.72 (m, 3H), 2.51–2.30 (m, 1H), 1.82–1.52 (m, 3H), 1.42–

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(25) The use of excess DIBALH led to the almost exclusive formation of the diol **20**. Oxidation[26] of the diol to the furan **1** could be achieved using PCC (40–50% yield over two steps); however, the furan contained variable amounts of an unknown, inseparable impurity.
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1.22 (m, 19H), 1.03–0.84 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 161.8, 153.1, 153.0, 151.3, 151.2, 131.7, 131.5, 123.8, 123.7, 52.5, 49.5, 47.9, 47.7, 45.2, 45.2, 44.0, 42.7, 39.1, 37.3, 34.2, 33.2, 33.0, 29.9, 29.9, 29.1, 28.7, 28.3, 24.9, 24.8, 23.6, 23.6; IR (neat) 3211, 1683, 1326, 1165 cm^{-1}; HRMS calcd for $C_{24}H_{38}N_2O_2S$: 418.2654, found 418.2652; LRMS (CI) *m/z* 419 ($M^+ + H$). Anal. Calcd for $C_{24}H_{38}N_2O_2S$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.84; H, 9.25; N, 6.71.

(1*R,5*R**,6*S**)-3,3,6-Trimethylbicyclo[3.2.0]heptan-6-ol (10).** Methyllithium (1.4 M in ether, 1.68 mL, 2.35 mmol) was added to a stirred solution of **7** (260 mg, 1.88 mmol) in THF (4 mL) at −78 °C. After 2 h saturated aqueous NH_4Cl was added and the solution was allowed to warm to rt. Ether was added and the organic phase was washed with water and then brine and dried over $MgSO_4$. Concentration *in vacuo* followed by Kugelrohr distillation (ot 60 °C/1 mmHg) provided **10** as a white solid (189 mg, 65%): mp 55–56 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67–2.60 (m, 1H), 2.32–2.16 (m, 2H), 1.70–1.63 (m, 3H), 1.60 (br s, 1H), 1.44 (ddd, *J* = 12.6, 8.3, 2.0 Hz, 1H), 1.36 (s, 3H), 1.23–1.18 (m, 1H), 1.11 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.7, 52.4, 48.9, 45.4, 44.3, 40.4, 29.6, 29.5, 28.8, 28.5; IR (neat) 3361 cm^{-1}; HRMS calcd for $C_{10}H_{18}O$: 154.1358, found 154.1354; LRMS (EI) *m/z* 154. Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.86; H, 12.03.

***cis*-7-Chloro-3,3-dimethylbicyclo[3.2.0]heptan-6-one (11).** Zinc (3.87 g, 59.2 mmol) was added portionwise over 45 min to a stirred solution of **6** (11.13 g, 53.77 mmol) in acetic acid (110 mL) at rt. After 3 h more zinc (200 mg, 3.06 mmol) was added and the resulting reaction mixture was stirred for 16 h. Hexanes were added, and the organic phase was washed with water, saturated $NaHCO_3$, and then brine and dried over $MgSO_4$. Concentration *in vacuo* followed by Kugelrohr distillation (ot 60 °C/0.3 mmHg) provided a single diastereoisomer of **11** as a colorless oil (8.69 g, 94%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (dd, *J* = 9.2, 3.0 Hz, 1H), 3.70–3.64 (m, 1H), 3.34–3.25 (m, 1H), 1.78–1.56 (m, 4H), 1.06 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 62.4, 61.6, 44.3, 42.6, 41.5, 38.6, 28.7, 28.2; IR (neat) 1790 cm^{-1}; HRMS calcd for $C_9H_{13}{}^{35}ClO + H^+$: 173.0733, found 173.0741; LRMS (CI) *m/z* 190 ($M^+ + NH_4$). Anal. Calcd for $C_9H_{13}ClO$: C, 62.61; H, 7.59. Found: C, 62.57; H, 7.54.

(1*R,5*S**,6*S**)-7-Chloro-3,3,6-trimethylbicyclo[3.2.0]-heptan-6-ol (12).** Methylmagnesium bromide (3.0 M in ether, 18.08 mL, 54.24 mmol) was added dropwise to a stirred solution of **11** (8.51 g, 49.3 mmol) in ether (200 mL) at −78 °C. After 1 h saturated aqueous NH_4Cl was added and the solution was warmed to rt. Ether was added and the organic phase was washed with water and then brine and dried over $MgSO_4$. Concentration *in vacuo* followed by Kugelrohr distillation (ot 50 °C/1 mmHg) provided a single diastereoisomer of **12** as a colorless oil (8.07 g, 87%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (dd, *J* = 7.7, 1.6 Hz, 1H), 2.96–2.88 (m, 1H), 2.64–2.58 (m, 1H), 2.31 (s, 1H), 1.80–1.74 (m, 2H), 1.47–1.36 (m, 2H), 1.34 (s, 3H), 1.11 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.9, 65.2, 49.3, 43.3, 41.5, 40.1, 39.5, 28.9, 28.3, 27.8; IR (neat) 3472 cm^{-1}; HRMS calcd for $C_{10}H_{17}{}^{35}ClO$: 188.0968, found 188.0964; LRMS (CI) *m/z* 206 ($M^+ + NH_4$). Anal. Calcd for $C_{10}H_{17}ClO$: C, 63.65; H, 9.08. Found: C, 64.00; H, 9.27.

(1*R,5*S**,6*S**)-7-Chloro-6-[(methylsulfonyl)oxy]-3,3,6-trimethylbicyclo[3.2.0]heptane (13).** A stirred solution of **12** (50 mg, 0.27 mmol) in CH_2Cl_2 (1 mL) at −20 °C was treated with NEt_3 (320 mg, 3.16 mmol) followed by MsCl (303 mg, 2.65 mmol). After 12 h, further portions of NEt_3 (161 mg, 1.59 mmol) and MsCl (152 mg, 1.33 mmol) were added. After a further 6 h the solution was warmed to rt and CH_2Cl_2 was added. The organic phase was washed with water and then brine and dried over $MgSO_4$. Concentration *in vacuo* followed by flash chromatography (10:1 hexanes/EtOAc) provided a single diastereoisomer of **13** as a white solid (42 mg, 61%): mp 48–50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (dd, *J* = 7.1, 3.6 Hz, 1H), 3.07 (s, 3H), 2.94–2.83 (m, 2H), 1.98–1.94 (m, 1H), 1.90–1.85 (m, 1H), 1.88 (s, 3H), 1.63–1.58 (m, 1H), 1.54–1.48 (m, 1H), 1.13 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.7, 65.2, 53.3, 43.4, 42.3, 40.6, 40.3, 37.9, 28.9, 27.6, 26.6; IR (neat) 1345 cm^{-1}; HRMS calcd for $C_{11}H_{19}{}^{35}ClO_3S$: 266.0743, found 266.0734; LRMS (CI) *m/z* 284 ($M^+ + NH_4$). Anal. Calcd for $C_{11}H_{19}ClO_3S$: C, 49.52; H, 7.18. Found: C, 49.48; H, 7.15.

(1*R,5*S**,6*S**)-6-Acetoxy-7-chloro-3,3,6-trimethylbicyclo-[3.2.0]heptane (14).** To a stirred solution of **12** (7.85 g, 41.6 mmol) in CH_2Cl_2 (100 mL) were added NEt_3 (21.0 g, 208 mmol), Ac_2O (17.0 g, 167 mmol), and then DMAP (760 mg, 6.25 mmol). After 60 h CH_2Cl_2 was added and the organic phase was washed with 10% HCl, saturated $NaHCO_3$ and then brine and dried over $MgSO_4$. Concentration *in vacuo* followed by flash chromatography (20:1 hexanes/EtOAc) provided a single diastereoisomer of **14** as a colorless oil (8.11 g, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38–4.35 (m, 1H), 2.91–2.85 (m, 2H), 2.04 (s, 3H), 1.92 (dd, *J* = 13.5, 3.8 Hz, 1H), 1.68–1.62 (m, 1H), 1.66 (s, 3H), 1.49–1.43 (m, 2H), 1.10 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 77.1, 65.2, 52.1, 43.2, 41.9, 40.5, 37.9, 28.9, 27.6, 25.4, 21.4; IR (neat) 1741 cm^{-1}; HRMS calcd for $C_{12}H_{19}{}^{35}ClO_2 + NH_4^+$: 248.1417, found 248.1426; LRMS (CI) *m/z* 248 ($M^+ + NH_4$).

***cis*-2-Acetyl-4,4-dimethylcyclopentane-1-carboxaldehyde (3).** A solution of **14** (1.04 g, 4.53 mmol) in dimethyl ether (20 mL) at −78 °C was added to a stirred solution of freshly cut sodium (600 mg, 26 mmol) in ammonia (100 mL) at −78 °C. After 1.5 h saturated aqueous NH_4Cl was added dropwise to destroy the excess metal. The solution was allowed to warm slowly to rt, and the solvents were allowed to evaporate. Pentane was added and the solid was removed by filtration and washed with pentane. Most of the pentane was removed by distillation to leave approximately 1.2 g of a solution of **5** in pentane. Ozone was bubbled through a stirred solution of the alkene **5** (4.5 mmol) in pentane and $NaHCO_3$ (22 mg, 0.26 mmol) in EtOAc (20 mL) at −78 °C. After 10 min the solution turned blue and was purged with N_2 for 10 min. Triphenylphosphine (1.19 g, 4.54 mmol) was added, and the solution was warmed to rt. After 2 h, half of the EtOAc was removed *in vacuo*, and the stirred solution was diluted with pentane (100 mL). After standing at −15 °C for 16 h the precipitate was removed by filtration through Celite and washed with pentane. Concentration of the organic phase *in vacuo* followed by column chromatography (silica gel 60–200 mesh, pH 7, eluent 6:1 hexanes/EtOAc) provided **3** as a colorless oil (358 mg, 47%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, *J* = 2.1 Hz, 1H), 3.46–3.40 (m, 1H), 2.99 (qd, *J* = 8.6, 2.1 Hz, 1H), 2.14 (s, 3H), 1.88–1.80 (m, 2H), 1.73–1.64 (m, 2H), 1.10 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.9, 202.2, 55.1, 52.5, 44.1, 40.7, 38.9, 29.3, 29.2, 28.7; IR (neat) 1714 cm^{-1}; HRMS calcd for $C_{10}H_{16}O_2 + H^+$: 169.1228, found 169.1237; LRMS (CI) *m/z* 169 ($M^+ + H$).

(1*R,2*R**,6*S**,7*R**)-8-(Methoxycarbonyl)-1,4,4-trimethyl-11-oxatricyclo[5.3.1.0^{2,6}]undecan-9-one (2).** To a stirred solution of **3** (523 mg, 3.11 mmol) in CH_2Cl_2 (31 mL) at −78 °C was added a solution of TMSOTf (173 mg, 0.778 mmol) in CH_2Cl_2 (8 mL) at −78 °C. After 5 min a solution of 1,3-bis-(trimethylsiloxy)-1-methoxybuta-1,3-diene (**4**) (970 mg, 3.73 mmol) in CH_2Cl_2 (37 mL) at −78 °C was added. After 5.5 h at −78 °C, pH 7 phosphate buffer was added, and the solution was allowed to warm to rt. CH_2Cl_2 was added, and the organic phase was washed with water and then brine and dried over $MgSO_4$. Concentration *in vacuo* followed by flash chromatography (8:1 hexanes/EtOAc) provided the tautomeric mixture **2** as a colorless oil (580 mg, 70%): IR (neat) 1742, 1721 cm^{-1}; HRMS calcd for $C_{15}H_{22}O_4$: 266.1518, found 266.1523; LRMS (EI) *m/z* 266. Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.29; H, 8.51.

(1*R,2*R**,6*S**,7*S**)-1,4,4-Trimethyl-11-oxatricyclo-[5.3.1.0^{2,6}]undecan-9-one (16).** NaCl (32 mg, 0.55 mmol) was added to a stirred solution of **2** (97 mg, 0.37 mmol) in DMSO (750 μL) and water (20 μL) and heated at 140 °C for 16 h. Upon cooling to rt, ether was added and the organic phase was washed with water and then brine and dried over $MgSO_4$. Concentration *in vacuo* followed by flash chromatography (6:1 hexanes/EtOAc) provided **16** as a white solid (49 mg, 65%): mp 42–43 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (d, *J* = 3.7 Hz, 1H), 2.58 (dd, *J* = 14.9, 4.8 Hz, 1H), 2.52–2.46 (m, 2H), 2.42 (d, *J* = 15.2 Hz, 1H), 2.31 (dd, *J* = 15.2, 1.6 Hz, 1H), 2.26 (dt, *J* = 15.0, 1.6 Hz, 1H), 1.78–1.68 (m, 1H), 1.40–1.28 (m,

2H), 1.29 (s, 3H), 1.20–1.15 (m, 1H), 1.02 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.0, 82.7, 80.1, 55.7, 51.6, 49.1, 48.5, 47.2, 42.7, 41.1, 28.0, 25.8, 22.0; IR (neat) 1722 cm^{-1}; HRMS calcd for $C_{13}H_{20}O_2$: 208.1463, found 208.1465; LRMS (EI) m/z 208. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.10; H, 9.85.

(1*R,2*R**,6*S**,7*R**)-8-Methoxycarbonyl-9-[[(trifluoromethyl)sulfonyl]oxy]-1,4,4-trimethyl-11-oxatricyclo[5.3.1.0^{2,6}]undec-8-ene (17).** **2** (135 mg, 0.508 mmol) in THF (2 mL) was added to a stirred suspension of NaH (60% dispersion in mineral oil, 22 mg, 0.55 mmol) in THF (2 mL) at −5 °C. After 1 h 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (209 mg, 0.532 mmol) in THF (2 mL) was added at 0 °C. The solution was allowed to slowly warm to rt and was left for 16 h before being diluted with ether. The organic phase was washed with water, 10% citric acid, 10% NaOH, and then brine and dried over $MgSO_4$. Concentration *in vacuo* followed by flash chromatography (15:1 hexanes/EtOAc) provided **17** as a colorless oil (156 mg, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.64 (s, 1H), 3.81 (s, 3H), 2.93–2.86 (m, 1H), 2.65 (d, J = 18.5 Hz, 1H), 2.54–2.47 (m, 1H), 2.23 (d, J = 18.5 Hz, 1H), 1.73–1.67 (m, 1H), 1.41–1.44 (m, 1H), 1.35 (s, 3H), 1.35–1.30 (m, 1H), 1.24–1.18 (m, 1H), 1.04 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 149.6, 127.1, 118.0 (q, $^1J_{CF}$ = 320 Hz), 81.1, 76.5, 55.8, 52.0, 51.9, 45.8, 43.0, 42.8, 40.8, 28.0, 25.6, 22.2; IR (neat) 1722, 1427, 1211 cm^{-1}; HRMS calcd for $C_{16}H_{21}F_3O_6S$: 398.1011, found 398.100; LRMS (EI) m/z 398. Anal. Calcd for $C_{16}H_{21}F_3O_6S$: C, 48.24; H, 5.31. Found: C, 48.15; H, 5.38.

(1*R,2*R**,6*S**,7*R**)-8-(Hydroxymethyl)-9-[[(trifluoromethyl)sulfonyl]oxy]-1,4,4-trimethyl-11-oxatricyclo[5.3.1.0^{2,6}]undec-8-ene (18).** DIBALH (1.0 M in hexanes, 700 μL, 0.70 mmol) was added to a stirred solution of **17** (127 mg, 0.319 mmol) in THF (3 mL) at −55 °C, and the solution was allowed to warm to rt. After 1.5 h saturated aqueous NH_4Cl was added, the solution was diluted with EtOAc, and then Celite was added. The suspension was filtered through Celite and washed with EtOAc. Concentration *in vacuo* followed by flash chromatography (6:1 hexanes/EtOAc) provided **18** as a colorless oil (98 mg, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39–4.33 (m, 2H), 4.20–4.15 (m, 1H), 2.90–2.84 (m, 1H), 2.61 (d, J = 17.3 Hz, 1H), 2.56–2.48 (m, 1H), 2.20 (d, J = 17.2 Hz, 1H), 1.68–1.62 (m, 1H), 1.53–1.43 (m, 2H), 1.36–1.30 (m, 4H), 1.22–1.16 (m, 1H), 1.04 (s, 3H), 0.87 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 134.6, 118.3 (q, $^1J_{CF}$ = 320 Hz), 81.5, 77.8, 56.9, 55.4, 52.2, 46.0, 42.9, 42.5, 41.1, 28.2, 25.9, 22.5; IR (neat) 3424, 1211 cm^{-1}; HRMS calcd for $C_{15}H_{21}F_3O_5S$: 370.1062, found 370.1069; LRMS (EI) m/z 370. Anal. Calcd for $C_{15}H_{21}F_3O_5S$: C, 48.64; H, 5.71. Found: C, 48.67; H, 5.73.

(1*R,8*R**,9*S**,13*R**)-5,14-Dioxa-1,11,11-trimethyltetracyclo[6.5.1.0^{3,7}.0^{9,13}]tetradec-3(7)-en-4-one (19).** CO was continuously bubbled through a stirred solution of **18** (410 mg, 1.11 mmol), NBu_3 (411 mg, 2.22 mmol), LiCl (47 mg, 1.1 mmol), and $Pd(PPh_3)_4$ (115 mg, 0.100 mmol) in acetonitrile (35 mL) at 60 °C. After 2 h the solution was cooled to rt, diluted with ether, and filtered through Celite. Preabsorption onto silica gel followed by flash chromatography (5:1 to 3:1 hexanes/EtOAc) provided **19** as a white solid (247 mg, 90%): mp 182–183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88–4.76 (m, 2H), 4.37 (s, 1H), 2.85–2.79 (m, 1H), 2.51–2.45 (m, 2H), 2.20–2.14 (m, 1H), 1.68–1.61 (m, 1H), 1.54–1.47 (m, 1H), 1.44–1.39 (m, 1H), 1.39 (s, 3H), 1.29–1.24 (m, 1H), 1.07 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 165.3, 122.6, 80.4, 75.6, 69.3, 55.4, 51.9, 45.7, 42.7, 41.3, 35.8, 28.2, 25.9, 22.8; IR (neat) 1754 cm^{-1}; HRMS calcd for $C_{15}H_{20}O_3$: 248.1412, found 248.1403; LRMS (EI) m/z 248. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.36; H, 8.41.

Furanether B (1). DIBALH (1.0 M in hexanes, 100 μL, 0.10 mmol) was added to a stirred solution of **19** (22.5 mg, 0.091 mmol) in CH_2Cl_2 (1 mL) at −78 °C. After 30 min, 1 N H_2SO_4 was added and the solution was stirred at −78 °C for 15 min prior to being warmed to rt. The solution was diluted with CH_2Cl_2 and dried over $MgSO_4$. Concentration *in vacuo* followed by flash chromatography (10:1 hexanes/EtOAc) provided **1** as a white solid (19 mg, 90%): mp 62–63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 1H), 7.09 (s, 1H), 4.76 (s, 1H), 2.78–2.67 (m, 2H), 2.57–2.50 (m, 2H), 1.69–1.64 (m, 1H), 1.45–1.42 (m, 2H), 1.37 (s, 3H), 1.31–1.25 (m, 1H), 1.05 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 133.1, 126.5, 117.0, 80.0, 75.3, 55.9, 50.9, 46.0, 42.9, 41.5, 35.1, 28.4, 26.0, 23.7; IR (neat) 2951 cm^{-1}; HRMS calcd for $C_{15}H_{20}O_2$: 232.1463, found 232.1454; LRMS (EI) m/z 232. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.62. Found: C, 77.22; H, 8.75.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds for which no elemental analysis was obtained and for **1**, **2**, and **16** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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