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Scope and Limitations of the Double [4+3]-Cycloadditions of 2-Oxyallyl Cations to 2,2′-Methylenedifuran and Derivatives

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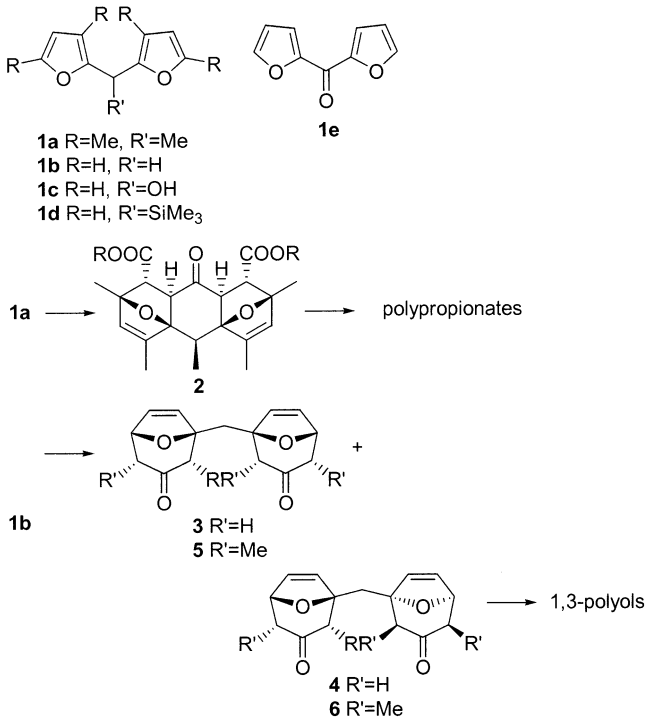
Abstract: The reactivity of various 2-oxyallyl cations toward 2,2′-methylenedifuran (**1b**), 2,2′-(hydroxymethyl)-difuran (**1c**), 2,2′-(trimethylsilylmethylene)difuran (**1d**), and di(2-furyl)methanone (**1e**) has been explored. Difuryl derivatives **1c**, **1d**, and **1e** refused to undergo formal double [4+3]-cycloadditions. Conditions have been found to convert **1b** into *meso*-1,1′-methylenedi[(1*R*,1′*S*,5*S*,5′*R*)- (**3**) and (±)-1,1′-methylenedi[(1*RS*,1′*SR*,5*SR*,5′*RS*)-8-oxabicyclo[3.2.1]oct-6-en-3-one] (**4**) that do not require $CF_3CH(OH)CF_3$ as solvent. High yields of *meso*-1,1′-methylenedi[(1*R*,1′*S*,2*S*,2′*R*,4*R*,4′*S*,-5*S*,5′*R*)- (**5**) and (±)-1,1′-methylenedi[(1*RS*,1′*RS*,2*SR*,2′*SR*,-4*RS*,4′*RS*,5*SR*,5′*SR*)-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one] (**6**) have been obtained when **1b** was reacted with 2,4-dibromopentan-3-one (**7h**) and NaI/Cu.

The simultaneous two-direction chain elongation followed by kinetic or chiral desymmetrization is a very attractive strategy for the construction of complicated compounds of biological interest.[1] We have used such strategy in our combinatorial approach to the synthesis of antitumor anthracyclines and analogues[2] based on the double Diels−Alder addition of 2,3,5,6-tetramethylidene-7-oxabicyclo[2.2.1]heptane derivatives.[3] More recently we have shown that double cycloaddition of diethyl (2*E*,5*E*)-4-oxohepta-2,5-dionate to 2,2′-ethylenebis[3,4-dimethylfurylfuran] (**1a**) gives a single adduct **2** that could be converted to complicated bicyclic and tricyclic polypropionates.[4]In parallel, we have investigated the formal [4+3]-cycloaddition of 2,2′-methylenedifuran (**1b**) and found conditions under which the 1,1,3-trichloro-2-oxyallyl cation (generated by base induced elimination of HCl from 1,1,3,3-tetrachloroacetone[5]) leads to a double cycloaddition to **1b** giving, after reductive workup, a 45:55 mixture of diketones **3** and **4** in 60% yield. The *meso* compound **3** could be converted into enantiomerically pure pentadeca-1,3,5,7,9,11,13,15-octols[6] via reaction sequences implying the asymmetric Sharpless dihydroxylation[7] as the desymmetrization step. Racemic *threo*-**4** can be converted into enantiomerically pure long-chain polyols via reaction sequences involving an enzymatic optical resolution.[8]

SCHEME 1



In this note we address the following questions: Can one realize formal double [4+3]-cycloadditions to 2,2′-methylenedifuran substituted at the methano linker such as derivatives **1c**−**e**? Can one exchange the expensive $CF_3CH(OH)CF_3$ (HFIP) solvent used in the generation of the 1,1,3-trichloro-2-oxyallyl cation for another solvent? Can one generate double adducts of **1b** with other 2-oxyallyl cation intermediates than the 1,1,3-trichloro-2-oxyallyl cation?

As we shall see, conditions have now been found for the synthesis of **3** and **4** that use toluene as solvent instead of HFIP. We report also that 2,2′-methylenedifuran (**1b**) can be reacted with 2,4-dibromopentan-3-one (**7h**) to provide diketones **5** and **6**. The three 2,2′-methylenedifuran derivatives **1c**−**e** substituted at the methano linker by a hydroxyl, a silyl, and an oxo group, respectively, refused to yield products of double cycloadditions with 2-oxyallyl cation derivatives.

The 2,2′-methylenedifuran derivative **1c** was obtained by condensation of (2-furyl)lithium[9] onto furfuraldehyde

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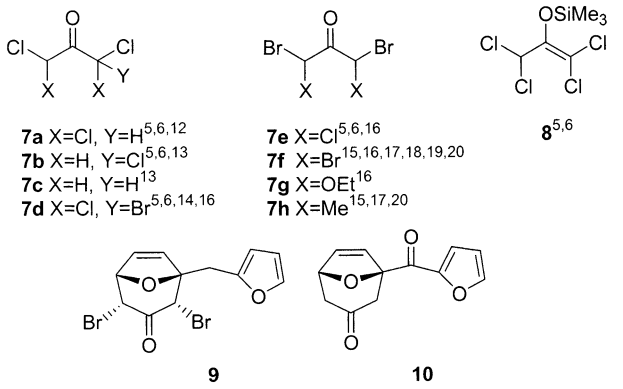
SCHEME 2



(56% yield). The preparation of the silylated derivative **1d** has already been described.[10] Di(2-furyl)methanone (**1e**) was obtained by reaction of (2-furyl)lithium[9] with *N*,*N*-dimethylcarbamate (53%).

One of the main difficulties with the search of optimal conditions for the double cycloadditions of **1** with 2-oxyallyl cation derivatives is the necessity to use an excess of the latter reagent rather than an excess of the furan derivative, as is the case under well-established conditions for the [4+3]-cycloadditions of simple furans.[11] Furthermore, furans are acid sensitive and polymerize readily in the presence of electrophilic reagents.

Because of the high synthetic potential of the 2,2′-methylenedifuran (**1b**) we have searched for conditions that do not require the expensive HFIP solvent as in our initial procedure.[6] This led us to explore the possibility of using other oxyallyl cation precursors than 1,1,3,3-tetrachloroacetone. Exploratory experiments were done with **7b**−**h**,[12−15] using basic conditions promoted by different bases (Et_3N, TMEDA) in various solvents (HFIP, CF_3CH_2OH, CH_3NO_2, CCl_3CN, CH_3CN, DMSO, toluene, CH_2Cl_2), as well as reductive conditions promoted by different reducing agents (Et_2Zn, $Fe(CO)_9$, Zn, $SnCl_2$, Cu) in aprotic solvents (toluene, dioxane, benzene, MeCN, THF), and applying established procedures.[5,6,16−20]

First, these studies did not bring any improvements. A mediocre yield in **3** + **4** (16%) was obtained for the reaction of **7b** with **1b** after reductive workup with Zn/Cu/NH_4Cl/MeOH.[21] In most cases polymeric material was found together with low yields of monocycloadducts. One of them, **9**, was isolated in 16% yield, when **1b** was reacted with 1,1,3,3-tetrabromoacetone (**7f**) in the presence of Et_2Zn in toluene at 0 °C. An acceptable yield of a 46:54 mixture of **3** + **4** (40%, 63% per cycloaddition) was obtained on reacting 1,3-dibromo-1,3-dichloroacetone (**7e**) with **1b** in toluene in the presence of Et_2Zn. With 1,3-dibromo-1,3-diethoxyacetone (**7g**), the same mixture was obtained in 30% yield under the same conditions. Thus, procedures are now available that do not use the expensive HFIP as solvent.

With the 2,2′-methylenedifuran substituted at the methano linker we failed to detect any trace of the corresponding products of double [4+3]-cycloaddition. In the case of di(2-furyl)methanone (**1e**), the "classical" basic conditions with 1,1,3,3-tetrachloroacetone (**7a**), Et_3N, and HFIP, only polymeric material was obtained. The method using 1,1,3,3-tetrabromoacetone (**7f**) and Et_2Zn gave 40% yield of monoadduct **10**. The *endo* relative configuration of the 2- and 4-bromo substituent was established by its ^{1}H NMR spectrum (vicinal coupling $^3J_{H,H}$ coupling constants and 2D-NOESY).

With 2,4-dibromopentan-3-one (**7h**) and in the presence of NaI/Cu in CH_3CN,[20] 2,2′-methylenedifuran (**1b**) gave an excellent yield (90%) of a 1:1 mixture of diketones **5** and **6** that were readily separated in 44% and 41% yield, respectively, by flash chromatography. These two compounds are potential precursors in the synthesis of long-chain polypropionates, assuming the methods developed for the asymmetric synthesis of 1,3-polyols based on **3** and **4** can be applied to **5** and **6**. The relative *endo* configuration of the four methyl substituents in **5** and **6** has been determined by their ^{1}H NMR data and confirmed by 2D-NOESY.

This study suggests that only the most stable ("softest") electrophilic intermediate **12** or **14** generated by heterolysis of polyhaloketones **7** or under reductive conditions (Scheme 3) is able to generate products of formal [4+3]-cycloaddition competitively with the polymerization of 2,2′-methylenedifuran (**1b**).

Among the different methods reported for the [4+3]-cycloaddition of furan, only those involving the 1,1,3-trichloro-2-oxyallyl, 1,3-dichloro-2-oxyallyl, and 1,3-dimethyl-2-oxyallyl species generate products of double cycloaddition with **1b**. The substituted derivatives **1c**−**d** refuse to undergo the double cycloaddition for steric or/and electronic reasons. Alcohol **1c** polymerizes very readily due to its ability to be ionized into a cationic species. In the case of ketone **1e**, conjugation of a furan and carbonyl moiety retards the cycloadditions.

Conditions have now been found that allow for the conversion of 2,2′-methylenedifuran (**1b**) into the valuable *meso*-1,1′-methylenedi[(1*R*,1′*S*,5*S*,5′*R*)-8-oxabicyclo-[3.2.1]oct-6-en-3-one] (**3**) and (±)-1,1′-methylenedi[(1*RS*,-1′*SR*,5*SR*,5′*RS*)-8-oxabicyclo[3.2.1]oct-6-en-3-one] (**4**) that do not require HFIP as solvent, but toluene. We have shown that formal double [4+3]-cycloadditions of 2-oxy-

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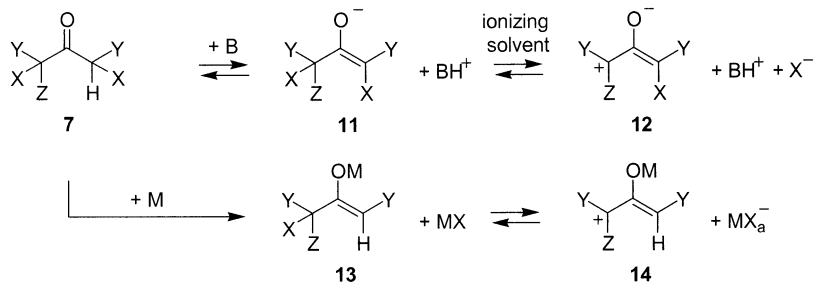
SCHEME 3



allyl cation intermediates to 2,2′-methylenedifuran are not possible yet with derivatives substituted at the methano linker between the two furyl groups. By using 2,4-dibromopentan-3-one and 2,2′methylenedifuran (**1b**), *meso*-1,1′-methylenedi[(1*R*,1′*S*,2*S*,2′*R*,4*R*,4′*S*,5*S*,5′*R*)- (**5**) and (±)-1,1′-methylenedi[(1*RS*,1′*RS*,2*SR*,2′*SR*,4*RS*,4′*RS*,-5*SR*,5′*SR*)-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one] (**6**) are obtained in good yields.

Experimental Section

General Remarks. See ref 22. Flash column chromatography (FC) was performed on Merck silica gel (230−400 mesh, no. 9385). Thin-layer chromatography (TLC) was carried out on silica gel (Merck aluminum foils). ^{1}H NMR and ^{13}C NMR signal assignments were confirmed by coupled ^{13}C NMR, 2D-COSY, HMQC, or HSQC, and when required by 2D-NOESY spectra. *J* values are given in hertz.

2,2′-(Hydroxymethyl)difuran (1c). To a solution of furan (500 mg, 7.34 mmol) in anhydrous ether (5 mL) was added dropwise a 1.6 M solution of BuLi in THF (4.58 mL, 7.34 mmol). The solution was heated under reflux for 15 min, while a white suspension appears. After the mixture was cooled to −50 °C, furfural (775 mg, 8.07 mmol) was added dropwise and the solution was left under stirring overnight. The reaction was quenched by addition of brine (5 mL). The aqueous layer was extracted by EtOAc (10 mL, twice). The organic phase was dried ($MgSO_4$) and distilled under reduced pressure (bp 160 °C, 1 mBar) and gave 683 mg (56%) of **1f**, which decomposes at room temperature, but can be stored at −80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (m, 2H), 6.36 (dd, 2H, ^3J = 1.8, ^3J = 3.3), 6.30 (dd, 2H, ^3J = 3.3, ^4J = 0.6), 5.80 (d, 1H, ^3J = 5.1), 2.48 (d, 1H, ^3J = 5.1).

Di(2-furyl)methanone (1e). To a solution of furan (500 mg, 7.34 mmol) in anhydrous ether (5 mL) was added dropwise a 1.6 M solution of BuLi in THF (4.58 mL, 7.34 mmol). The solution was heated under reflux for 15 min, while a white suspension appears. After the mixture was cooled to −25 °C, *N*,*N*-dimethylethylcarbamate (268 mg, 3.67 mmol) was added dropwise and the solution was allowed to warm to 20 °C and left under stirring for 1 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (8 mL) and the aqueous layer was extracted with CH_2Cl_2 (10 mL, twice). The organic phase was dried ($MgSO_4$) and purified by flash chromatography (silica gel, Et_2O/PE 1:1) and gave 320 mg (53%) of **1e** as a colorless oil. The product was precipitated in PE as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (dd, 2H, ^3J = 1.8, ^3J = 1.6), 7.56 (dd, 2H, ^3J = 3.7, ^3J = 1.8), 6.61 (dd, 2H, ^3J = 3.7, ^4J = 1.6). Anal. Calcd for $C_9H_6O_3$: C, 66.67, H, 3.73. Found: C, 66.69, H, 3.78.

***meso*-1,1′-Methylenedi[(1*R*,1′S,5*S*,5′*R*)-3-oxo-8-oxabicyclo-[3.2.1]oct-6-ene-1-yl] (3) and 1,1′-Methylenedi[(1*RS*,1′*SR*,-5*SR*,5′*RS*)-3-oxo-8-oxabicyclo[3.2.1]oct-6-ene-1-yl] (4).** To a 1.1 M solution of Et_2Zn (5.87 mL, 6.46 mmol) in toluene containing **1b** (200 mg, 1.35 mmol) was added dropwise **7e** (999 mg, 3.50 mmol) at − 40 °C. After 24 h under stirring, the solution was allowed to warm to room temperature. After one night under stirring, **7e** (384 mg, 1.35 mmol) was added dropwise and allowed to react for 3 h. This latter addition was repeated. The solution was diluted with EtOAc (10 mL) and quenched by sat. NH_4Cl in methanol (10 mL). The solvents were removed and the brown residue was dissolved in sat. NH_4Cl in methanol (30 mL). Zn/Cu couple (1 g) was added portionwise to the vigorously stirred mixture. After stirring at room temperature for 4 d, the precipitate was filtered off on Celite and the solvent evaporated. The residue was taken up in Et_2O (20 mL) and silica gel (5 g) was added. After 20 min under stirring, filtration, rinsing with Et_2O, and evaporation, the brown residue was deposited over silica gel. Flash chromatography (silica gel, Et_2O/PE 3:1) afforded 141 mg (40%) of **3** and **4** as a 45:55 mixture. Spectral data of this mixture were identical with those reported for these compounds.[6]

***meso*-1,1′-Methylenedi[(1*R*,1′*S*,2*S*,2′*R*,4*R*,4′*S*,5*S*,5′*R*)-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one] (5) and (±)-1,1′-Methylenedi[(1*RS*,1′*RS*,2*SR*,2′*SR*,4*RS*,4′*RS*,5*SR*,5′*SR*)-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one] (6).** Anhydrous acetonitrile (30 mL), followed by flame dried NaI (18 g, 120 mmol) and **1c** (740 mg, 5 mmol) were added to freshly activated Cu powder (3.8 g, 60 mmol). The mixture was heated to reflux and 2,4-dibromopentan-3-one (4.84 g, 20 mmol) was added dropwise over 30 min. As the reaction proceeded the solution turned into a yellow suspension. After 1 h under reflux, the solvent was evaporated under reduced pressure and the remaining mixture diluted with water (25 mL) and CH_2Cl_2 (25 mL). The solution was stirred for 10 min and then filtrated on Celite. The aqueous layer was extracted with CH_2Cl_2 (30 mL, 3 times). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to yield a yellow oil. Flash chromatography (silica gel, CH_2Cl_2/Et_2O/PE 54:6:40) gave 703 mg of **5** (44%) and 625 mg of **6** (41%). Both fractions can be recrystallized from hexane to give white crystals.

Data for **5**: Mp 132−135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (d, 2H, ^3J = 6.0), 6.18 (dd, 2H, ^3J = 6.0, ^3J = 1.7), 4.82 (dd, 2H, ^3J = 4.7, ^3J = 1.7), 2.78 (q, 2H, ^3J = 7.0), 2.73 (qd, 2H, ^3J = 7.0, ^3J = 4.7), 2.39, 2.38 (2d, 2H, ^2J = 15.6), 1.06, 0.95 (2d, 12H, ^3J = 7.0). Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13, H, 7.65. Found: C, 72.07, H, 7.75.

Data for **6**: Mp 162−166 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (d, 2H, ^3J = 6.1), 6.05 (dd, 2H, ^3J = 6.1, ^3J = 1.7), 4.78 (dd, 2H, ^3J = 4.6, ^3J = 1.7), 2.74 (qd, 2H, ^3J = 7.0, ^3J = 4.6), 2.68 (q, 2H, ^3J = 7.0), 2.37 (s, 2H), 1.06, 0.96 (2d, 12H, ^3J = 7.0). Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13, H, 7.65. Found: C, 72.07, H, 7.60.

1,3-Dibromo-1,3-dichloroacetone (7e). In a two-necked flask surmounted by a cooler connected to two basic traps, HBr (48%, 4 mL, 1 mL per mmol of ketone) was added dropwise to a solution of 1,3-dichloroacetone (5 g, 0.04 mol) in 50 mL of CH_2Cl_2. At room temperature, Br_2 (4.04 mL, 0.08 mol) was added dropwise via dropping funnel. After 6 days under stirring, the solution was extracted with a saturated aqueous solution of $NaHCO_3$ (100 mL, twice) and until decoloration with a 10% aqueous solution of $NaHSO_3$. After evaporation to dryness, the crude product was distilled under reduced pressure (bp 65−67 °C, 4 mBar) and gave 9.45 g (58%) of an irritating yellowish liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.50, 6.46 (2s).

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1,3-Dibromo-1,3-diethoxyacetone (7g). To a solution of 1,3-diethoxypropan-2-ol (1.82 g, 19.04 mmol) and dry molecular sieves (3 Å, 10 g) in anhydrous CH_2Cl_2 (100 mL) was added PCC (10 g, 46.40 mmol). The mixture was stirred for 5 h and quenched by addition of Et_2O (100 mL) and silica gel (25 g). After filtration over a Celite path, the solvents were removed under reflux with cooling at −20 °C. Purification by flash chromatography (silica gel, PE/EtOAc 3:1) afforded 2.75 g (99%) of 1,3-diethoxypopan-2-one.

A two-necked round-bottom flask fitted with a dropping funnel and condenser was charged with 1,3-diethoxypropanone (500 mg, 3.42 mmol) and PBr_3 (500 μL). The solution was cooled to 0 °C and Br_2 (440 μL, 8.55 mmol) was added dropwise. The solution was stirred for 15 h and allowed to warm to 20 °C. The reaction was diluted with CH_2Cl_2 (30 mL) and quenched with sat. $Na_2S_2O_5$ (10 mL). The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (5 mL, twice). The combined organic layer was dried (Na_2SO_4) and the solvents removed under vacuum: 956 mg (93%) of **7g**, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.49, 6.47 (s, 2H), 4.07, 4.04, 3.73, 3.71 (q, 4H, ^3J = 7.0), 1.38 (t, 6H, ^3J = 7.0).

{**[2,2-Dichloro-1-(dichloromethyl)vinyl]oxy**}**trimethylsilane (8).** To a solution of **7a** (5 g, 25 mmol) and trimethylchlorosilane (2.98 g, 27.5 mmol) in anhydrous ether (40 mL) was added dropwise anhydrous Et_3N (4.18 mL, 30 mmol). After the solution was stirred overnight, the white suspension was filtrated and the solvent evaporated. Distillation under reduced pressure (bp 110−115 °C, 5 mBar) in a Kugelrohr afforded 5.1 g (87%) of **8** as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81 (s, 1H), 0.38 (s, 9H).

(1*R*,2*S*,4*R*,5*S*)-2,4-Dibromo-1-(2-furylmethyl)-8-oxabicyclo[3.2.1]oct-6-en-3-one (9). A 1 M solution of Et_2Zn (1.83 mL, 2.02 mmol) in toluene was added dropwise to a solution of **1c** (200 mg, 1.34 mmol), TMSCl (211 mg, 1.94 mmol), and **2e** (701 mg, 1.87 mmol) in 10 mL of anhydrous toluene at 0 °C. The solution was allowed to warm to 20 °C and was stirred overnight (TLC, Et_2O/PE 1:1). After dilution with EtOAc, the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL). The aqueous phase was extracted with EtOAc (5 mL, twice). The combined organic extracts were filtrated over a Celite path and dried ($MgSO_4$). The brown residue was purified by flash chromatography (silica gel, Et_2O/PE 1:4) to afford 75 mg (16%) of a white solid that decomposes slowly at 20 °C, but can be stored at −80 °C for weeks. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (dd, 1H, ^3J = 1.8, ^4J = 0.4), 6.49 (dd, 1H, ^3J = 1.7, ^3J = 6.0), 6.43 (d, 1H, ^3J = 6.0), 6.36 (dd, 1H, ^3J = 1.8, ^4J = 3.1), 6.30 (dd, 1H, ^3J = 3.1, ^4J = 0.4), 6.17 (dd, 1H, ^3J = 1.7, ^3J = 4.8), 4.81 (d, 1H, ^3J = 4.8), 4.70 (s, 1H), 3.51 (d, 1H, ^2J = 15.5), 3.36 (d, 1H, ^2J = 15.5). Anal. Calcd for $C_{12}H_{10}Br_2O_3$: C, 39.81, H, 2.78. Found: C, 39.75, H, 2.80.

(1*S*,5*R*)-1-(2-Furoyl)-8-oxabicyclo[3.2.1]oct-6-en-3-one (10). To an ice-cooled solution of **1h** (240 mg, 1.48 mmol) and **2e** (720 mg, 1.92 mmol) in anhydrous benzene (25 mL) was added dropwise a 1 M solution of Et_2Zn (2.2 mL, 2.2 mmol) in hexane. After being stirred overnight at 20 °C (TLC, Et_2O/PE 1:1), the reaction was quenched with EtOAc (15 mL) and a saturated aqueous solution of NH_4Cl (15 mL). The organic layer was filtrated over a Celite path and dried (Na_2SO_4). After solvent evaporation, the brown residue was redissolved in a sat. NH_4Cl solution in MeOH (6 mL) and freshly prepared Zn/Cu couple (1 g) was added portionwise. After 5 days (TLC, Et_2O/PE 9:1), the solution was filtrated over a Celite path. After solvent evaporation and redissolution in EtOAc (30 mL), the organic layer was extracted with Na_2EDTA (10 mL, twice) and washed with brine (10 mL, twice). The solution was dried over Na_2SO_4 and the solvents evaporated. Purification by flash chromatography (silica gel, Et_2O/PE 8:2) afforded 129 mg (40%) of **10** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (dd, 1H, ^4J = 0.8, ^3J = 1.6), 7.60 (dd, 1H, ^4J = 0.8, ^3J = 3.5), 6.57 (dd, 1H, ^3J = 1.6, ^3J = 3.5), 6.44 (d, 1H, ^3J = 5.9), 6.37 (dd, 1H, ^3J = 5.9, ^3J = 1.9), 5.31 (dt, 1H, ^3J = 1.8, ^3J = 5.4), 2.89 (d, 1H, ^3J = 16.7), 2.83 (dd, 1H, ^3J = 16.7, ^3J = 5.4), 2.79 (d, 1H, ^3J = 16.7), 2.42 (d, 1H, ^3J = 16.7).

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Supporting Information Available: Detailed ^{1}H and ^{13}C NMR spectra and signal assignments, IR and MS spectra of all described compounds, as well as complementary data to the initial publications for **7a**, **7d**, and **7f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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