Effect of C-9 Substituents on the Regioselectivity of A-Ring Reactions in Derivatives of the Wieland–Miescher Ketone

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The nature of C-9 substituents was found to have a significant influence on the regio- and stereochemistry of A-ring reactions in a variety of Wieland–Miescher ketone derivatives. For example, Pd-catalyzed hydrogenation of the C-9 dioxolanes resulted in much better selectivity for the *cis*-fused products vis-a-vis the corresponding C-9 ketone, with the parent Wieland–Miescher ketone itself and both C-4 methyl and C-4 carboalkoxy substituted analogues. In addition, methylation and acylation of A-ring enolates favored the C-2 isomer when a C-9 dioxolane group was present, but the C-4 substituted isomer was predominant with the corresponding C-9 ketone. These differences in regiochemistry may allow selective elaboration of *cis*-fused decalins during preparation of complex natural products.

The Wieland–Miescher ketone (**1**) and its derivatives have been used for many years as precursors to a wide variety of natural products, most of which contain *trans*-fused decalin systems. As a result, there is a substantial body of literature on the synthesis and reactivity of enone **1** itself,[1] some of its simple derivatives, and its *trans*-fused reduction products. In contrast, information on the reactivity of the corresponding *cis*-fused decalones is relatively sparse,[2ab] perhaps because *trans*-fused decalins are more common features in terpenoids[2c,d] and steroids than the corresponding *cis*-fused systems. A second factor may be that while conformational analysis of *trans*-fused systems can be based on assumption of a single predominant chair–chair conformation,[3] in the *cis*-fused series two conformations of similar energy may be found, thus rendering conformational analysis a more difficult task.[2] Our own interest in the eventual preparation of some marine natural products that incorporate a *cis*-fused decalin ring prompted this investigation of *cis*-fused decalin synthesis and reactivity.[4]

It has been known for some time that metal-catalyzed hydrogenation of enone **1** favors formation of the *cis*-fused product[5] and also that catalytic hydrogenation of the corresponding C-9 dioxolane (steroid numbering) over Pd/C gives strong cis selectivity (95:5).[6] As shown in Table 1, an 85:15 ratio in favor of the *cis* isomer **2** was obtained upon hydrogenation of enone **1** over $Pd/CaCO_3$ in pyridine.[4] One indication of the importance of the C-9 substituents to this process was observed upon hydrogenation of the corresponding dioxolane (**4**) under analogous conditions (entry 2). In this case, hydrogenation was both slower and more stereocontrolled, leading to exclusive formation of the *cis*-fused product (**5**).

Similar trends were observed with C-4 methyl-substituted analogues **6** and **10**. Kucherov and Gurvich reported that hydrogenation of dione **6** over $Pd/SrCO_3$ gave a single *cis*-fused diastereomer.[7] Surprisingly, this product was reported as the 4-β epimer (**7**), which would correspond to a sequence of exclusive hydrogenation from the β-face followed by complete inversion of the C-4 stereochemistry to place the methyl group in an equatorial orientation. Under our standard conditions for hydrogenation over $Pd/CaCO_3$, dione **6** gave primarily a mixture of the *cis*-fused products **7** (β-methyl) and **8** (α-methyl)[8] in a 2:3 ratio (GC), accompanied by a small amount of the *trans*-fused product **9**.

Upon hydrogenation of the corresponding dioxolane (**10**), only *cis*-fused products **11** and **12** were observed (90:10 ratio). A single crystal diffraction analysis[9] of the major hydrogenation product indicated an α-methyl orientation at C-4, consistent with *syn*-hydrogenation followed by ring flipping to place the C-4 methyl group in an equatorial orientation. Upon treatment of this mixture of compounds **11** and **12** with aqueous acid, hydrolysis of the dioxolane was accompanied by partial epimerization of the C-4 methyl group, yielding ap-

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(1) (a) Jung, M. E. *Tetrahedron* **1976**, *32*, 3–31. (b) Gawley, R. E. *Synthesis* **1976**, 777–794. For early reviews on the synthesis of steroids, see: (c) Akhrem, A. A.; Titov, Y. A. *Total Steroid Synthesis*; Plenum Press: New York, 1970. (d) Blickenstaff, R. T.; Ghosh, A.-C.; Wolf, G. C. *Total Synthesis of Steroids*; Academic Press: New York, 1974. (e) ApSimon, J. W.; Hooper, J. W. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley-Interscience: New York, 1973; Vol. 2, pp 610-615.

(2) (a) Heathcock, C. H.; Ratcliffe, R.; Van, J. *J. Org. Chem.* **1972**, *37*, 1796–1807. (b) Huffman, J. W.; Balke, W. H. *J. Org. Chem.* **1988**, *53*, 3828–3831. (c) Heathcock, C. H. In *Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley-Interscience: New York, 1973; Vol. 2, pp 197–558. (d) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley-Interscience: New York, 1983; Vol. 5.

(3) For some examples in which trans-fused decalins do not adopt chair–chair conformations, see: (a) Corey, E. J.; Das, J. *J. Am. Chem. Soc.* **1982**, *104*, 5551–5553. (b) McMurry, J. E.; Erion, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 2712–2720. (c) Tsuda, Y.; Yamaguchi, K.; Sakai, S.-i. *Chem. Pharm. Bull.* **1984**, *32*, 313–317.

(4) Taken in part from the PhD thesis of Kwangyong Park, University of Iowa, December, 1993.

(5) See, for example: Nazarov, I. N.; Zavyalov, S. I.; Burmistrova, M. S.; Gurvich, I. A.; Shmonina, L. I. *J. Gen. Chem. U.S.S.R.* **1956**, *26*, 465–468.

(6) (a) McMurry, J. E. *J. Am. Chem. Soc.* **1968**, *90*, 6821–6825. (b) Bauduin, G.; Pietrasanta, Y. *Tetrahedron* **1973**, *29*, 4225–4231. (c) A related C-9 tosyloxy compound also undergoes *cis*-selective hydrogenation; cf. Heathcock, C. A.; Badger, R. A.; Petterson, J. W., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 4133.

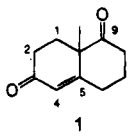
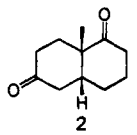
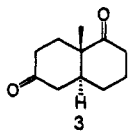
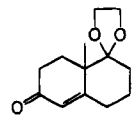
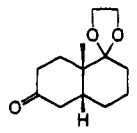
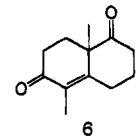
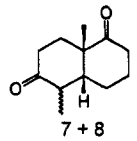
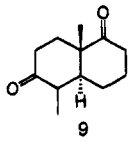
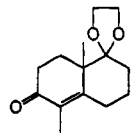
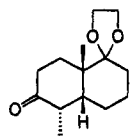
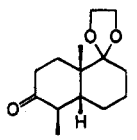
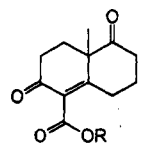
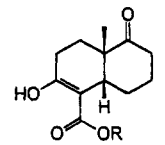
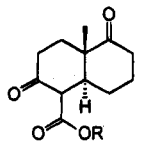
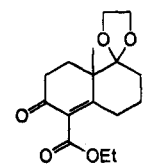
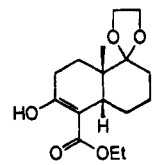
(7) Kucherov, V. F.; Gurvich, I. A. *J. Gen. Chem. USSR* **1961**, *31*, 731–737.

(8) Yordy, J. D; Reusch, W. *J. Am. Chem. Soc.* **1977**, *99*, 1965–1968. In this study, compound **8** was prepared by rearrangement of a cyclopropanol and assigned the α-methyl stereochemistry at C-4.

(9) Details of the diffraction analysis will be presented elsewhere. Swenson, D.; Park, K.; Scott, W. J.; Wiemer, D. F. *Acta Crystallogr.*, in press.

0022-3263/94/1959-6313$04.50/0

Table 1. Hydrogenation of Wieland–Miescher Ketone and Analogues with Pd/CaCO$_3$

Entry	Enone	Conditions pressure (psi) / day(s)	Products *cis*	Products *trans*	Isolated Yield (%)[a]
1	 1	50 / 1	 2	 3	86 (85:15)
2	 4	50 / 2	 5	–	90
3	 6	50 / 2	 7 + 8	 9	84 (36:53:11)[b]
4	 10	60 / 2	 11	 12	91 (90:10)
5	 R = Me 13	60 / 2	 14	 15	93 (53:47)[b]
6	R = Et 16		17	18	92 (60:40)[b]
7	 19	60 / 4	 20	–	94

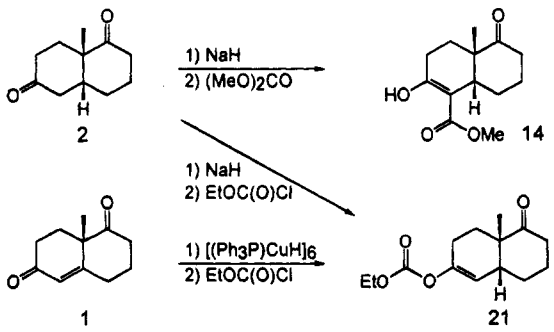
[a] Yield refers to the total yield for the mixture of diastereomers, with the diastereomer ratio given in parentheses. [b] Diastereomers were separated by column chromatography.

proximately a 1:1 mixture of the C-4 epimers (**7** and **8**) by ^{1}H NMR.

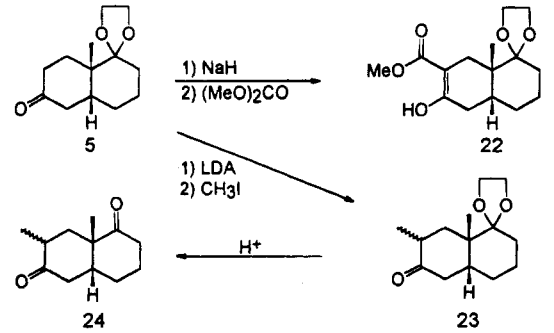
In the third set of decalins studied, hydrogenation of methyl ester **13** gave only a slight preference for the *cis*-fused isomer **14** (53:47). Similar results were observed with the ethyl ester **16**.[10] In contrast, hydrogenation of dioxolane **19** gave a single product identified as the *cis*-fused isomer **20**. The NMR spectra of the product β-keto esters indicate that the *trans*-fused products (**15** and **18**) exist as a diastereomer of the keto forms, while only the enol forms could be detected in the *cis*-fused series (**14**, **17**, and **20**).

(10) This compound has been prepared by a Pt-catalyzed reduction: Nazarov, N.; Zavyalov, S. I. *J. Gen. Chem. USSR* **1953**, *23*, 1793–1801.

It is reasonable to assume that the difference in the outcome of these reactions is rooted in the nature of the C-9 substituent and is expressed through the influence of this substituent on the decalin conformation. If this assumption is valid, it would not be surprising to see other differences in A-ring reactivity dependent upon the functionality at C-9. In fact, such differences have been observed in both enolate and enamine reactions. The enolate formed upon treatment of dione **2** with NaH can be trapped with a variety of electrophiles. For example, reaction of this sodium enolate with TMSCl affords a single silyl enol ether in virtually quantitative yield (GC). Reaction of the same enolate with dimethyl carbonate gave only the C-4 carbomethyoxy product (**14**), albeit in modest yield (46%), along with a substantial amount of a self-condensation product. Reaction of this enolate with ethyl chloroformate gave the carbonate **21** in high yield. Because carbonate **21** also was obtained by reaction of enone **1** with Stryker's reagent,[11] followed by treatment with ethyl chloroformate, formation of the C-4 enolate via both routes is verified.



In contrast to the dominant formation of the C-4 enolate from dione **2**, the C-2 enolate is preferentially formed from ketal **5**. Treatment of ketal **5** with NaH followed by reaction with TMSCl gave approximately a 3:1 mixture of silyl enol ethers in favor of the Δ^2 isomer as shown by ^{1}H NMR. When this enolate was allowed to react with dimethyl carbonate, the C-2 carbomethoxy product (**22**) was obtained in modest yield (40%) along with recovered ketone (43%). This set of experiments suggests that the thermodynamic enolate of the B-ring ketone **2** involves predominant loss of a C-4 proton, while the thermodynamic enolate of ketal **5** involves preferential loss of a C-2 proton.

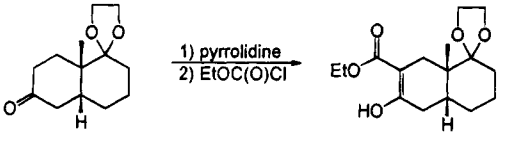


To test the regiochemistry of kinetic enolate formation, ketal **5** was treated with LDA under standard conditions

(11) (a) Mahoney, W. S.; Brestensky, D. M.; Stryker, K. M. *J. Am. Chem. Soc.* **1988**, *110*, 291–293. (b) Brestensky, D. M.; Huseland, D. E.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1988**, *29*, 3749–3752.

of kinetic control. Reaction of this enolate with methyl iodide gave only C-2 alkylated products (**23**) in 58% isolated yield. This regiochemistry was unequivocally established by hydrolysis of the ketal mixture (**23**), followed by comparison of the resulting methyl ketones (**24**) with literature data[8] for both the C-2 methyl compounds and authentic C-4 methyl products (**7** and **8**).

A similar trend was observed in reactions involving an A-ring enamine. For example, when diketone **2** was treated with pyrrolidine, the major product (ca. 95:5 GC ratio) appeared to be the Δ^3 enamine based on its ^{1}H NMR spectrum (δ 1.10 (s, 3H), 3.78 (s, 1H)). In contrast, when ketal **5** was treated with pyrrolidine, followed by reaction with ethyl chloroformate and hydrolysis, the C-2 substituted keto ester **25** was obtained in about 50% overall yield. Thus, it is reasonable to conclude that with a C-9 ketal, C-2 is the site of proton abstraction under both kinetic and thermodynamic conditions.



5 25

In conclusion, this series of experiments has identified some significant differences in the A-ring reactivity of decalones bearing C-9 carbonyl groups versus those bearing C-9 dioxolanes. These differences presumably result from conformational changes attendant upon changing from the sp^2 hybridization of the C-9 ketones to the sp^3 hybridization at C-9 of the dioxolanes, or the steric impact of the dioxolane ring. While these findings may make it more feasible to predict the regio- and stereochemical outcome of A-ring reactions, they also indicate that syntheses of *cis*-fused decalins which are highly substituted in the A-ring might profit from approaches based on strategies such as neighboring group participation or selective activation[12] that offer more predictable regio- and stereocontrol.

Experimental Section

THF, DME, and benzene were distilled from potassium or sodium benzophenone ketyl immediately prior to use. TMSCl, Et_3N, and pyridine were distilled over CaH_2. All reactions in these solvents were conducted under a positive pressure of an inert gas. NaH was washed with pentane, which had been distilled over CaH_2, and dried with a vacuum/nitrogen purge protocol just prior to use. Hydrogenation reactions were performed in a Fischer & Porter tube, with magnetic stirring, if conducted on less than a 1 g scale, or in a Parr 3911 hydrogenation apparatus on larger scales. Capillary GC analyses were run on a 12.5 m × 0.2 mm crosslinked methyl silicone column. Flash column chromatography was performed with silica gel of 40 μm average particle diameter. Bulb-to-bulb distillations were performed with a Kugelrohr apparatus (ot refers to oven temperature). NMR spectra (^{1}H at 300 or 600 MHz and ^{13}C at 75 MHz) were recorded with $CDCl_3$ as solvent and either residual $CHCl_3$ or $(CH_3)_4Si$ as internal standard. Low-resolution GC–mass spectra were obtained at an ionization potential of 70 eV. Elemental analyses were performed by Atlantic Microlab or in the University of Iowa Chemistry Department.

Pd/$CaCO_3$-Catalyzed Hydrogenation of Compound 1. General Procedure for Catalytic Hydrogenations in Pyridine.[1c,13] To a solution of ketone **1** (1.00 g, 5.62 mmol) in pyridine (50 mL) was added 5% Pd/$CaCO_3$ (0.970 g, 0.456 mmol Pd, 8.1 mol %) at rt. This mixture was stirred overnight under 50 psi of H_2. The reaction mixture was diluted with 150 mL of CH_2Cl_2 and filtered through a small pad of Celite. The filtrate was washed with aqueous NH_4Cl (2 × 150 mL), water (2 × 150 mL), and saturated NaCl (150 mL). After the resulting solution was dried ($MgSO_4$), concentration under reduced pressure gave a light yellow oil. Final purification by bulb-to-bulb distillation (ot 115–125 °C, 0.8 mmHg) gave a white solid (0.87 g, 86%). This solid was shown to consist of an 85:15 mixture of diastereomers **2** and **3** by integration of the methyl singlets at δ 1.35 (**2**) and 1.21 (**3**) in the ^{1}H NMR spectrum. Compound **2** was identical with samples obtained previously.[12]

(1β,6β)-2,2-(1,2-Ethylenedioxy)-1-methylbicyclo[4.4.0]-decan-8-one (5). According to the general procedure, a solution of enone **4** (1.25 g, 5.63 mmol) in pyridine (50 mL) was hydrogenated with 5% Pd/$CaCO_3$ (0.970 g, 0.456 mmol Pd, 8.1 mol%). After the standard workup, purification by flash column chromatography (0–15% EtOAc in hexane) gave compound **5** as a colorless solid (1.14 g, 90%): mp 52–54 °C [lit.[6a] mp 54–54.5 °C]; ^{1}H NMR δ 1.21 (s, 3H), 1.18–1.32 (m, 1H), 1.45–1.81 (m, 6H), 2.03–2.21 (m, 3H), 2.27–2.50 (m, 2H), 2.64 (dd, J = 5.8, 4.8 Hz, 1H), 3.97 (s, 4H); ^{13}C NMR δ 17.6, 22.1, 28.1, 28.9, 29.6, 37.7, 41.1, 42.5, 44.0, 64.8, 65.0, 112.3, 212.2; EIMS m/z (rel abundance) 224 (2), 209 (3), 181 (6), 112 (62), 99 (100), 86 (68).

(1β,6β,7β)- and (1β,6β,7α)-1,7-Dimethylbicyclo[4.4.0]-decane-2,8-dione (7 and 8). According to the general procedure, a solution of compound **6** (1.08 g, 5.63 mmol) in pyridine (50 mL) was treated with H_2 and 5% Pd/$CaCO_3$ (0.970 g, 0.456 mmol Pd, 8.1 mol %) at rt. After standard workup and concentration in vacuo, the resulting product was purified via bulb-to-bulb distillation to give a clear solid (0.92 g, 84%) containing compounds **7**, **8** and **9** in a 36:53:11 ratio (GC). After the individual compounds were separated by column chromatography (0–15% EtOAc in hexane), the spectra of compounds **7** and **8** compared well with published values.[8] The structure of compound **9** was inferred from MS data.

Compound **7**: ^{1}H NMR δ 1.03 (d, J = 6.7 Hz, 3H), 1.20–1.35 (m, 1H), 1.49 (s, 3H), 1.43–1.68 (m, 2H), 1.77–1.87 (m, 1H), 1.99–2.13 (m, 2H), 2.28–2.65 (m, 5H), 2.91 (overlapping dq, J = 6.2 Hz, 1H); ^{13}C NMR δ 12.0, 19.2, 22.3, 25.1, 32.2, 37.2, 37.8, 44.1, 49.8, 52.8, 211.4, 213.7; EIMS m/z (rel abundance) 194 (32), 137 (29), 127 (91), 111 (53), 68 (100).

Compound **8**: mp 96–97 °C (lit.[8] mp 98–100 °C); ^{1}H NMR δ 1.00 (d, J = 6.5 Hz, 3H), 1.30 (s, 3H), 1.28–1.39 (m, 1H), 1.77–2.04 (m, 4H), 2.12–2.39 (m, 4H), 2.53–2.74 (m, 3H); ^{13}C NMR δ 11.2, 20.9, 22.6, 26.4, 35.0, 37.5, 38.7, 43.8, 49.3, 52.7, 213.0, 214.0; EIMS m/z (rel abundance) 194 (39), 138 (20), 127 (100), 111 (50), 68 (94).

Compound **9**: EIMS m/z (rel abundance) 194 (32), 179 (5), 166 (4), 137 (29), 127 (90), 111 (52), 68 (100).

(1β,6β,7α)- and (1β,6β,7β)-2,2-(1,2-Ethylenedioxy)-1,7-dimethylbicyclo[4.4.0]decan-8-one (11 and 12). According to the general procedure, a solution of enone **10** (1.33 g, 5.64 mmol) in pyridine (50 mL) was treated with H_2 and 5% Pd/$CaCO_3$ (0.970 g, 0.456 mmol of Pd, 8.1 mol %) at rt. After standard workup and final purification by column chromatography (0–15% EtOAc in hexane), a clear solid (1.22 g, 91%) consisting of compounds **11** and **12** was obtained in a 90:10 ratio based on integration of the methyl singlets at δ 1.27 (**11**) and 1.12 (**12**) in the ^{1}H NMR spectrum.

Compound **11**: mp 78–81 °C; ^{1}H NMR δ 0.77–0.92 (m, 1H), 0.96 (d, J = 6.5 Hz, 3H), 1.27 (s, 3H), 1.37–1.70 (m, 5H), 1.76–1.84 (m, 1H), 1.94–2.05 (m, 1H), 2.10–2.31 (m, 2H), 2.40–2.52 (m, 1H), 2.86 (overlapping dq, J = 6.1 Hz, 1H), 3.98 (s, 4H); ^{13}C NMR δ 11.9, 16.9, 22.1, 22.3, 29.3, 29.4, 37.7, 42.6, 43.6, 49.3, 64.9, 65.0, 112.3, 213.3; EIMS m/z (rel abundance) 238 (4), 209 (15), 112 (63), 99 (100), 86 (71). Anal. Calcd for $C_{14}H_{22}O_3$; C, 70.56; H, 9.30. Found: C, 70.41; H, 9.26.

Hydrolysis of Compounds 11 and 12. A mixture of compounds **11** and **12** (ca. 10 mg, 90:10 ratio) was dissolved in ether (~3 mL) and treated with 10% aqueous HCl (~2 mL)

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at rt. After the mixture was stirred overnight, it was diluted with ether and washed with water twice and saturated NaCl. After concentration under reduced pressure, a mixture of compounds **7** and **8** (ca. 56:44 ratio by ^{1}H NMR based on integration of the resonances at δ 1.03 (d) and 1.00 (d)) was obtained as a colorless oil.

(1β,6β)- and (1β,6α)-1-Methyl-7-carbomethoxybicyclo-[4.4.0]decane-2,8-dione (14 and 15). According to the general procedure, a solution of enone **13** (1.33 g, 5.64 mmol) in pyridine (50 mL) was treated with H_2 and 5% Pd/$CaCO_3$ (0.970 g, 0.456 mmol Pd, 8.1 mol %) at rt. After standard workup and purification by column chromatography (0–25% EtOAc in hexane), compound **14** was obtained as a clear oil that crystallized upon standing at rt (0.66 g, 49%), followed by compound **15** as a white solid (0.59 g, 44%).

Compound **14**: mp 73–74 °C; ^{1}H NMR δ 1.10 (s, 3H), 1.34–1.73 (m, 3H), 1.92–2.20 (m, 3H), 2.32–2.39 (m, 3H), 2.45–2.56 (m, 2H), 3.78 (s, 3H), 12.33 (s, 1H); ^{13}C NMR δ 19.1, 24.5, 25.5, 26.3, 30.2, 38.0, 41.9, 47.4, 51.5, 101.0, 171.1, 172.7, 214.9. Anal. Calcd for $C_{13}H_{18}O_4$; C, 65.53; H, 7.61. Found: C, 65.69; H, 7.66.

Compound **15**: ^{1}H NMR δ 1.35 (s, 3H), 1.55–1.78 (m, 3H), 1.88–2.13 (m, 3H), 2.26–2.75 (m, 5H), 3.41 (d, J = 12.9 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR δ 15.9, 25.3, 25.7, 31.9, 37.1 (2C), 46.6, 46.9, 52.2, 58.9, 169.5, 204.1, 212.6.

(1β,6β)- and (1β,6α)-1-Methyl-7-carbethoxybicyclo[4.4.0]-decane-2,8-dione (17 and 18). According to the general procedure, a solution of compound **16** (1.40 g, 5.60 mmol) in pyridine (50 mL) was treated with H_2 and 5% Pd/$CaCO_3$ (0.970 g, 0.456 mmol Pd, 8.1 mol %) at rt. After standard workup and purification by column chromatography (0–25% EtOAc in hexane), compound **17** was obtained as a clear oil (0.78 g. 55%) followed by compound **18** as a white solid (0.52 g, 37%).

Compound **17**: ^{1}H NMR δ 1.10 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.30–1.76 (m, 3H), 1.92–2.20 (m, 3H), 2.34–2.40 (m, 3H), 2.45–2.57 (m, 2H), 4.15–4.34 (m, 2H), 12.42 (s, 1H); ^{13}C NMR δ 14.2, 19.1, 24.5, 25.5, 26.3, 30.2, 38.1, 42.0, 47.5, 60.4, 101.1, 170.9, 172.3, 215.0. Anal. Calcd for $C_{14}H_{20}O_4$; C, 66.65; H, 7.99. Found: C, 66.52; H, 8.06.

Compound **18**: mp 80–81 °C; ^{1}H NMR 1.29 (t, J = 7.1 Hz, 3H), 1.35 (s, 3H), 1.55–1.79 (m, 3H), 1.89–2.12 (m, 3H), 2.26–2.57 (m, 4H), 2.64–2.75 (m, 1H), 3.38 (d, J = 12.8 Hz, 1H), 4.17–4.32 (m, 2H); ^{13}C NMR 14.2, 15.9, 25.3, 25.6, 31.9, 37.2 (2C), 46.6, 46.9, 58.9, 61.2, 169.0, 204.1, 212.7; ^{1}H NMR (C_6D_6) δ 0.56 (s, 3H), 1.03 (t, J = 7.1 Hz, 3H), 1.08–1.23 (m, 2H), 1.35–1.42 (m, 2H), 1.56–1.75 (m, 3H), 1.94–2.17 (m, 4H), 3.06 (d, J = 12.8 Hz, 1H), 4.01–4.17 (m, 2H); ^{13}C NMR (C_6D_6) 14.2, 15.3, 25.3, 25.6, 32.2, 36.9, 37.1, 46.5, 46.7, 59.0, 60.9, 168.9, 203.0, 210.5. Anal. Calcd for $C_{14}H_{20}O_4$; C, 66.65; H, 7.99. Found: C, 66.75; H, 8.21.

(1β,6β)-2,2-(1,2-Ethylenedioxy)-1-methyl-7-carbethoxybicyclo[4.4.0]decan-8-one (20). According to the standard procedure, a solution of compound **19** (1.65 g, 5.62 mmol) in pyridine (50 mL) was treated with H_2 and 5% Pd/$CaCO_3$ (0.970 g, 0.456 mmol Pd, 8.1 mol %) at rt. After standard workup, the resulting light yellow oil was purified by column chromatography (0–25% EtOAc in hexane) to give compound **20** as a clear oil (1.56 g, 94%): ^{1}H NMR δ 0.89 (s, 3H), 1.07–1.19 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.55–1.64 (m, 5H), 1.81–2.01 (m, 2H), 2.29–2.34 (m, 2H), 2.47 (br dd, J = 12.1, 3.2 Hz, 1H), 3.92–4.04 (m, 4H), 4.10–4.31 (m, 2H), 12.36 (s, 1H); ^{13}C NMR δ 14.2, 16.1, 22.3, 23.2, 26.1, 30.0, 30.6, 38.8, 40.9, 60.0, 64.8, 65.0, 102.0, 112.4, 171.3, 172.7. Anal. Calcd for $C_{16}H_{24}O_5$; C, 64.84; H, 8.16. Found: C, 65.01; H, 8.15.

(1β,6β)-1-Methyl-7-carbomethoxybicyclo[4.4.0]decane-2,8-dione (14). To NaH (0.045 g of a 60% oil dispersion, 1.13 mmol, 2.0 equiv) was added ketone **2** (0.100 g, 0.556 mmol) in DME (4.0 mL) at rt. The mixture was heated at reflux for 3 h and then allowed to cool to rt. To the resulting enolate was added dimethyl carbonate (0.19 mL, 2.25 mmol, 4.0 equiv), and this mixture was stirred at rt overnight. After addition of ether (20 mL), the reaction was quenched by addition of aqueous NH_4Cl (20 mL). The resulting organic layer then was washed with aqueous NH_4Cl (20 mL), water (3 × 20 mL), and a saturated NaCl solution (20 mL). After the organic layer was dried ($MgSO_4$), concentration in vacuo gave compound **14** contaminated with a self-condensation product that was not characterized further. The initial product was purified via radial chromatography (0–25% EtOAc in hexane) to give pure compound **14** (60.2 mg, 46%) as a clear oil, identical with material prepared previously.

Carbethoxy Enol Ether 21 via ((Ph$_3$P)CuH)$_6$ Reduction of Compound 1. To a solution of Wieland–Miescher ketone (**1**, 0.148 g, 0.83 mmol) in 2 mL of anhydrous benzene was added ethyl chloroformate (0.40 mL, 4.2 mmol, 5.1 equiv), and the mixture was stirred for 20 min under Ar. To this solution was added a solution of ((Ph$_3$P)CuH)$_6$[11] (0.82 g, 0.42 mmol, 0.51 equiv) in 5 mL of anhydrous benzene via cannula. The vessel was sealed, and the reaction mixture was stirred for 6 h at rt. The reaction vessel was opened, and the solution was diluted with ether. The resulting mixture was filtered through a sintered glass funnel, and volatiles were removed under reduced pressure to give a light yellow oil (0.17 g) composed of compounds **21**, **2**, and unreacted starting material in a 63:26:11 ratio (by GC). For compound **21**: ^{1}H NMR δ 1.13 (s, 3H, angular CH_3), 1.25 (t, J = 7.1 Hz, 3H, CH_3CH_2O–), 4.13 (q, J = 7.1 Hz, 2H, –OCH_2CH_3), 5.21 (s, 1H, vinyl H); EIMS m/z (rel abundance) 252 (100), 193 (16), 180 (28), 165 (38), 137 (48), 110 (100).

Carbethoxy Enol Ether 21 via the Sodium Enolate of Compound 2. According to the procedure described for compound **14**, ketone **2** was treated with NaH (0.045 g of a 60% oil dispersion, 1.13 mmol, 2.0 equiv) in DME and then with ethyl chloroformate (0.060 mL, 0.628 mmol, 1.13 equiv). After standard workup and concentration under reduced pressure, compound **21** (0.13 g, 93%) was obtained as an oil. This material was identical to that prepared previously.

(1β,6β)-2,2-(1,2-Ethylenedioxy)-1-methyl-9-carbomethoxybicyclo[4.4.0]decan-8-one (22). To a suspension of NaH (0.11g of a 60% oil dispersion, 2.7 mmol, 2.1 equiv) in DME was added a solution of ketone **5** (0.30 g, 1.3 mmol) in DME (9 mL). The mixture was heated at reflux for 3 h and then allowed to cool to rt. To the resulting solution was added dimethyl carbonate (0.40 mL, 4.7 mmol, 3.6 equiv), and this mixture was stirred at rt overnight. Workup as described for compound **14** and concentration under reduced pressure gave compound **22** as an oil contaminated with unreacted starting material. The oil was purified by radial chromatography to give ketone **22** (0.15 g, 40%), preceded by unreacted starting material (0.13 g, 43%): mp 94–96 °C; ^{1}H NMR δ 0.91 (s, 3H), 1.20–1.87 (m, 7H), 1.94 (d, J = 18.8 Hz, 1H), 2.14 (d, J = 16.6 Hz, 1H), 2.42 (d, J = 16.8 Hz, 1H), 2.53–2.62 (dddd, J = 18.7, 6.5, 2.6, 1.6 Hz, 1H), 3.74 (s, 3H), 3.95–3.98 (m, 4H), 12.12 (s, 1H); ^{13}C NMR δ 18.0, 22.5, 27.0, 28.6, 30.1, 32.6, 37.5, 40.7, 51.2, 64.9, 65.2, 94.5, 112.3, 169.9, 173.1. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.65; H, 8.05.

(1β,6β)-2,2-(1,2-Ethylenedioxy)-1,9-dimethylbicyclo[4.4.0]-decan-8-one (23). A solution of ketone **5** (0.10 g, 0.446 mmol) in anhydrous THF (1 mL) was added dropwise via syringe to a stirred solution of lithium diisopropylamine [prepared in situ from diisopropylamine (0.080 mL) and n-BuLi (0.23 mL, 2.36 M)] in THF (3 mL) at −78 °C. After 45 min the resulting enolate was treated with methyl iodide (0.06 mL, 0.96 mmol, 2.2 equiv), and the mixture was allowed to warm to rt overnight. The reaction mixture was quenched by addition of 1 N acetic acid/ether and diluted with ether (20 mL). After the ethereal solution was washed with water (2 × 20 mL) and saturated NaCl, the organic layer was dried ($MgSO_4$), and concentrated in vacuo to give an oil containing unreacted starting material and compound **23** in a 40:60 ratio. Final purification via radial chromatography (0–15% EtOAc in hexane) gave compound **23** (0.62 g, 58%) as a mixture of two diastereomers: ^{1}H NMR δ 0.94 (d, J = 6.5 Hz, 1.2H), 1.01 (d, J = 6.4 Hz, 1.8H), 1.11 (s, 1.2H), 1.27 (s, 1.8H), 0.95–1.12 (m, 1H), 1.40–2.15 (m, 9H), 2.30–2.37 (m, 0.4H), 2.48–2.63 (m, 0.6H), 2.69–2.76 (m, 0.6H), 2.87–3.02 (m, 0.4H), 3.95–4.00 (m, 4H); ^{13}C NMR δ 14.5, 15.2, 17.8, 19.1, 22.5, 25.8, 26.9, 28.2, 29.5, 30.9, 38.3, 40.7, 42.3, 42.3, 43.3, 43.9, 44.2, 45.0, 64.0, 64.6, 64.9, 65.0, 112.2, 113.3, 213.2, 216.0; EIMS m/z (rel abundance) 238 (12), 223 (3), 195 (6), 112 (63), 99 (100).

(1β,6β)-1,9-Dimethylbicyclo[4.4.0]decane-2,8-dione (24). Compound **23** (~0.01 g) was dissolved in ether (~3 mL) and treated with excess of a 10% aqueous HCl solution (~2 mL) at rt. After the solution was stirred overnight, the reaction mixture was washed with water twice and saturated NaCl. Volatiles were removed under reduced pressure to give compounds **24**[8] as a colorless oil in nearly quantitative yield and a 60:40 ratio of C-2 diastereomers: ^{1}H NMR for the major diastereomer δ 0.99 (d, J = 6.4 Hz, 3H), 1.29 (s, 3H); for the minor diastereomer δ 1.04 (d, J = 6.5 Hz, 3H), 1.47 (s, 3H); ^{13}C NMR δ 14.1, 14.2, 20.3, 21.9, 25.1, 25.8, 25.9, 28.2, 37.2, 37.6, 40.6, 40.9, 41.5, 43.7, 44.0, 44.1, 46.4, 47.0, 49.3, 49.4, 211.3, 213.1, 213.7, 214.4.

(1β,6β)-2,2-(1,2-Ethylenedioxy)-1-methyl-9-carbethoxybicyclo[4.4.0]decan-8-one (25). To anhydrous benzene (60 mL) were added compound **5** (2.86 g, 12.8 mmol) and pyrrolidine (1.30 mL, 15.6 mmol, 1.22 equiv) at rt. The mixture was heated under reflux for 5 h while water was azeotropically removed and then allowed to cool to rt. To this solution was added ethyl chloroformate (3.0 mL, 31.4 mmol, 2.45 equiv), and the resulting mixture was heated under reflux overnight. The reaction mixture was quenched by addition of aqueous NH_4Cl (5%, 30 mL) and stirred overnight at rt to allow complete hydrolysis of the enamine. The organic layer was washed with water (3 × 60 mL) and saturated NaCl, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting oil was purified by column chromatography (0–15% EtOAc in hexane) to give compound **25** as a clear solid (1.92 g, 51%): mp 103–105 °C; ^{1}H NMR δ 0.91 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.25–1.37 (m, 2H), 1.45–1.67 (m, 3H), 1.71–1.86 (m, 2H), 1.94 (d, J = 18.7 Hz, 1H), 2.14 (d, J = 16.5 Hz, 1H), 2.41 (d, J = 17.0 Hz, 1H), 2.53–2.61 (dddd, J = 18.9, 6.2, 2.7 Hz, 1H), 3.95–4.00 (m, 4H), 4.20 (q, J = 7.1 Hz, 2H), 12.27 (s, 1H); ^{13}C NMR δ 14.3, 18.0, 22.6, 27.0, 28.6, 30.1, 32.7, 37.6, 40.7, 60.3, 64.9, 65.3, 94.7, 112.4, 169.9, 172.9. Anal. Calcd for $C_{16}H_{24}O_5$; C, 64.84; H, 8.16. Found: C, 64.69; H, 8.18.

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