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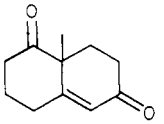
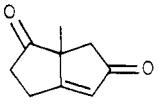
An Enantiodirected Cyclopentenone Annulation. Synthesis of a Useful Building Block for Condensed Cyclopentanoid Natural Products

Sir:

The Wieland–Miescher ketone (**1**) is well-known as a convenient building block for fused six-membered ring terpenes.[1a] Its importance is enhanced by its availability in optically active form.[1b]

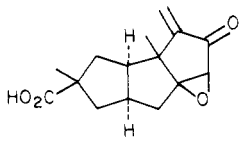


1

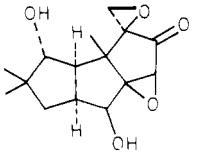


2

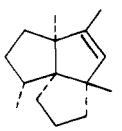
The bicyclo[3.3.0] analogue of the Wieland–Miescher ketone (**1**), enedione **2**, is a potentially versatile intermediate for the synthesis of a growing number of structurally interesting and biologically active fused five-membered ring natural products,[2] some of which are depicted below.



hirsutic acid



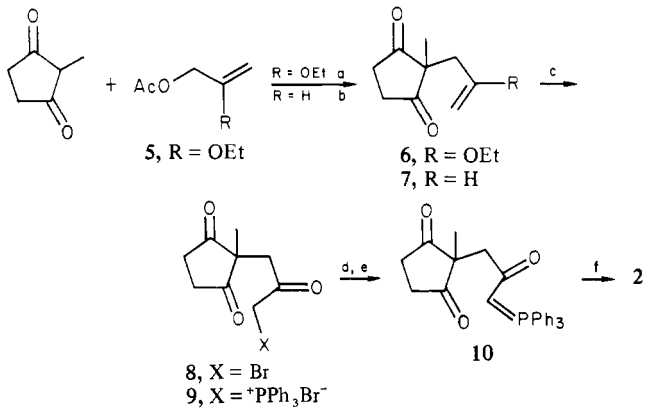
coriolin



isocomene

We now report an expedient synthesis of enedione **2** via a new cyclopentenone annulation sequence whose key features are (1) Pd(0)-directed C-alkylation of 2-methyl-1,3-cyclopentanedione, (2) intramolecular Wittig cyclization,[3b,4] and (3) the adaptability of this route for asymmetric synthesis, an important feature for the synthesis of natural products.

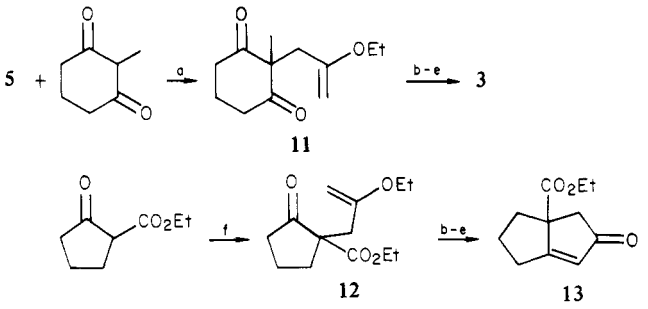
Scheme I



5, R = OEt
6, R = OEt
7, R = H
8, X = Br
9, X = $^{+}PPh_3Br^{-}$
10

[a] $Pd(Ph_3P)_4$ 1–10%, DBU, toluene, 80 °C. [b] $Pd(Ph_3P)_4$ 1%, THF, 25 °C. [c] NBS (2 equiv), H_2O (2 equiv), Me_2SO, 15–25 °C. [d] Ph_3P, benzene, 80 °C. [e] Aqueous K_2CO_3. [f] 40 °C.

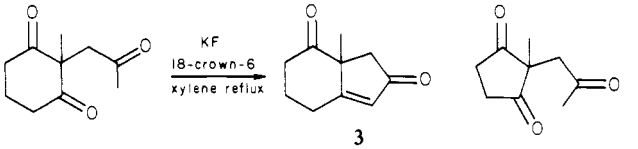
Scheme II



11
12
13

[a] $(Ph_3P)_4Pd$ (7.5%), DBU, THF, 3 days 25 °C. [b] NBS (2 equiv), H_2O (2 equiv), Me_2SO, 15–25 °C. [c] Ph_3P, benzene, 80 °C. [d] aqueous K_2CO_3. [e] 40 °C. [f] $(Ph_3P)_4Pd$ (5%), DBU, THF, 66 °C, 12 h.

Previous methods of cyclopentenone annulation[3a,b] have generally not been used for the synthesis of bicyclo[3.3.0] compounds, and most are not applicable to the synthesis of **2** because of the known tendencies of 2,2-disubstituted-1,3-cyclopentanediones to undergo deacylation reactions.[5] For example, in the more favorable cyclohexanedione series, formation of the cyclopentenone ring was not possible by using a number of standard aldol conditions; however, low yields of enone **3** were available by using



3
4

fluoride ion catalyzed cyclization.[6] Triketone **4** did not give enone **2** under a variety of aldol conditions and was recovered unchanged from the above fluoride conditions.

Palladium(0)-catalyzed[7] reaction of 2-methyl-1,3-cyclopentanedione with 2-ethoxy-3-acetoxy-1-propene[8] (**5**) produced

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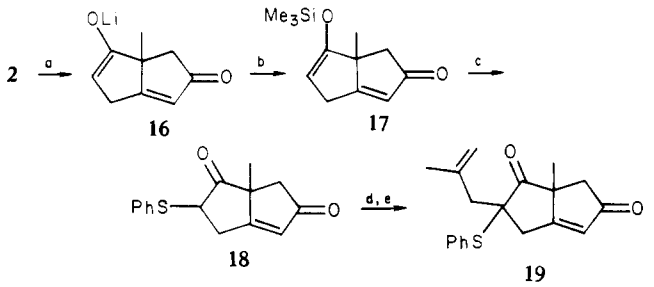
the crystalline enol ether **6** in 76% yield (see Scheme I).[9] The high yield of C-alkylated product was in direct contrast to the generally observed reaction of cyclopentanedione anions. For example, 2-methyl-1,3-cyclopentanedione reacts with allyl bromide to produce the C-alkylated product **7** in a maximum yield of 30%.[10] Under our conditions, however, 2-methyl-1,3-cyclopentanedione reacts with allyl acetate to give 2-allyl-2-methyl-1,3-cyclopentanedione (**7**) in 94% yield.

Treatment of enol ether **6** with NBS and water[11] produced bromo ketone **8** in 89% crude yield. Compound **8** was then directly converted into crystalline enedione **2** in 75–82% yield by formation of phosphonium salt **9**, generation of ylide **10** with aqueous K_2CO_3, and cyclization at 40 °C. No evidence of any product resulting from deacylation was observed, attesting to the mildness of the cyclization conditions. In a typical experimental procedure, a solution of bromo ketone **8** (1 equiv) and triphenylphosphine[12] (1 equiv) in benzene was refluxed under nitrogen for 7 h. The reaction mixture was cooled, diluted with methylene chloride to dissolve the white precipitate, and washed with saturated aqueous potassium carbonate. The organic phase was dried over Na_2SO_4, concentrated under reduced pressure, dissolved in dichloromethane, and heated under reflux for 12 h. Concentration under reduced pressure followed by preparative thin-layer chromatography (silica gel, Et_2O) or column chromatography (silica gel, 1:1 ether/hexane) gave enedione **7** (80%) which solidifies upon evaporative distillation; bp ~70 °C (0.4 mm Hg), mp 41–43 °C.[13]

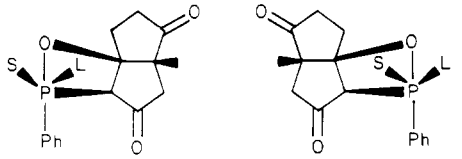
In an analogous fashion, 2-methyl-1,3-cyclohexanedione has been alkylated in 81% yield to give enol ether **11** (see Scheme II). Bromination and cyclization as before gave a 64% yield of the known[6] bicyclic enedione **3**. To demonstrate the general utility of this cyclopentenone annulation sequence for the formation of bicyclo[3.3.0] systems, we have alkylated 2-carbethoxycyclopentanone in 86% yield to produce **12**, which was cyclized to give cyclopentenone **13** in 62% yield.[13]

For use in natural product synthesis, it was desirable to produce enedione **2** in optically active form. Toward this end, we reacted bromo ketone **8** with (*R*)-(−)-methylpropylphenylphosphine[14] followed by aqueous K_2CO_3 treatment. Since very little is known about the transfer of chiralty from phosphorus in the Wittig reaction,[15] we were pleased to find that this reaction gave optically active enedione **2** as a 65:35 mixture of (+) and (−) enantiomers as determined by chiral shift reagents.[16a] A rationale for this high induction may be found in the highly ordered nature of the Wittig cyclization and the known geometrical preferences of five-coordinate phosphorus[17a] as summarized in the two diastereometric intermediates **14** and **15**. The fact that optically active methyl-1-naphthylphenylphosphine gives virtually no enantiomeric excess agrees with this picture.[17b]

Scheme III



[a] LDA, THF, −78 °C, 45 min. [b] Me_3SiCl, HMPA, −78 to 25 °C. [c] PhSCl, CH_2Cl_2, −78 °C. [d] LDA, THF, −78 °C. [e] Methallyl iodide, HMPA, room temperature.



The commercially available bisphosphine (*R*)-DIOP produces enone **2** in a 70:30 mixture of (+) and (−) enantiomers.[16b] These preliminary results demonstrate the potential for high optical induction by manipulation of substitution on phosphorus. It should also be pointed out that the phosphine oxides are produced with complete retention of configuration at phosphorus in the Wittig reaction and can be recycled to optically active phosphines by reduction with either inversion[14] or retention.[18]

Finally, we have demonstrated that selective transformations can be carried out on enedione **2**. For example, treatment of **2** with lithium diisopropylamide generates the kinetic enolate **16**,[19] as evidenced by chlorotrimethylsilane quench to produce enol silyl ether **17** as the only detectable isomer (Scheme III). Treatment of **17** with phenylsulfenyl chloride produces the α-phenyl thioketone **18**.[20] Generation of the anion of **18**, followed by methallyl iodide quench, produces the alkylated product[20] in 68% yield.

In developing a route to enedione **2**, we have uncovered a mild, general cyclopentenone annulation adaptable to asymmetric synthesis which we hope will find broad applicability. Furthermore, preliminary results indicate the possibility of a good asymmetric synthesis of **2** as well as the ability to perform regio- and stereoselective transformations toward natural products.

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(8) Compound **5** is available in 40–50% yield by reaction of α-lithioethylvinyl ether with paraformaldehyde followed by acetylation (Ac_2O, pyridine), see ref 6. Compound **5**, a convenient enolonium equivalent, is easily obtained in an analytically pure form by distillation and showed no decomposition after several months of storage at room temperature. In comparison, 3-bromo-2-ethoxy-1-propene is unstable at room temperature and cannot be readily obtained in a pure form. See: Jacobson, R. M.; Raths, R. A.; McDonald, J. H., III *J. Org. Chem.* **1977**, *42*, 2545.

(9) All new compounds exhibited spectra consistent with the assigned structures and gave satisfactory elemental analysis and/or high-resolution mass spectra.

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(12) Tri-*n*-butylphosphine could also be used.

(13) Compound **2**: IR ($CHCl_3$) 1740, 1700, 1625 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.41 (3 H, s), 2.31 (1 H, d, J = 18 Hz), ~2.4 (1 H, m), 2.64 (1 H, d, J = 18 Hz), 2.8–3.3 (3 H, m), 6.02 (1 H, d); ^{13}C NMR (C_6D_6), ppm downfield from TMS, 22.91, 24.23, 38.15, 44.83, 56.42, 125.82, 184.28, 206.83, 211.49; MS calcd for $C_9H_{10}O_2$, 150.0678; found, 150.0671. Anal. $C_9H_{10}O_2$: C, H. Compound **13**: bp 80 °C (Kugel-Rohr, 0.5 mmHg); IR ($CHCl_3$) 1725 (s, br) cm^{-1}; NMR ($CDCl_3$) δ 1.21 (3 H, t), 1.45 (1 H, m), 1.8–3.2 (7 H, m), 4.02 (2 H, q), 5.91 (1 H, narrow t); MS calcd for $C_{11}H_{14}O_3$, 194.0939; found, 194.0939.

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(16) (a) $[\alpha]^{25}_D$ +40.1° (MeOH) after correction for the fact that the starting phosphine was 69% optically pure. The shift studies were performed with 10% tris[(perfluoropropyl)camphorato]europium(III) in $CDCl_3$. The integration was performed on a pair of doublets (δ 3.91 and δ 3.94, 270 MHz) whose ratio was 1:1 in the racemic compound: Goering, H. L.; Eikenberry, J. N.; Koermer, G. S. *J. Am. Chem. Soc.* **1971**, *93*, 5913. (b) $[\alpha]^{25}_D$ +55.2° (MeOH).

(17) (a) Gorenstein, D. G. *J. Am. Chem. Soc.* **1970**, *92*, 634. Muetterties, E. L.; Schunn, R. A. *Q. Rev., Chem. Soc.* **1966**, *20*, 245. (b) Electron-withdrawing substituents are known to prefer the apical position in pentacoordinate phosphorus.[17a] Naphthyl and phenyl substituents are more electronegative than alkyl substituents—a fact leading to the preference depicted in **14** and **15**. The similarity of phenyl and naphthyl to each other creates the expectation that they both will populate the apical position nearly equally and thus the lack of asymmetric induction with methyl-1-naphthylphenylphosphine.

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(19) This behavior is similar to that observed for the Wieland–Miescher ketone, see: Grieco, P. A.; Ferrino, S.; Oguri, T. *J. Org. Chem.* **1979**, *44*, 2953.

(20) Only one stereoisomer is produced. Due to steric considerations, we believe that the entering group is syn to the methyl group.

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