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AN APPROACH TO THE PHENANTHRENE NUCLEUS VIA THIONIUM IONS AND EPOXYKETONE CYCLIZATIONS

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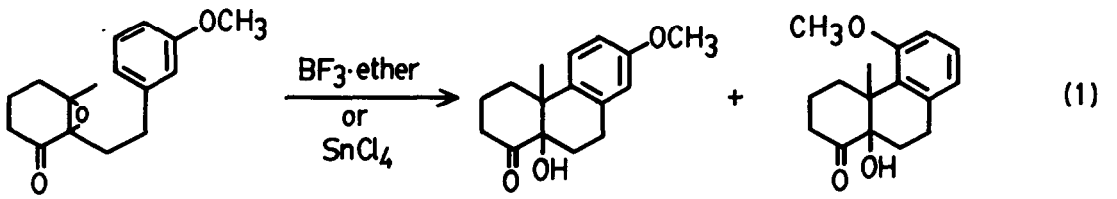
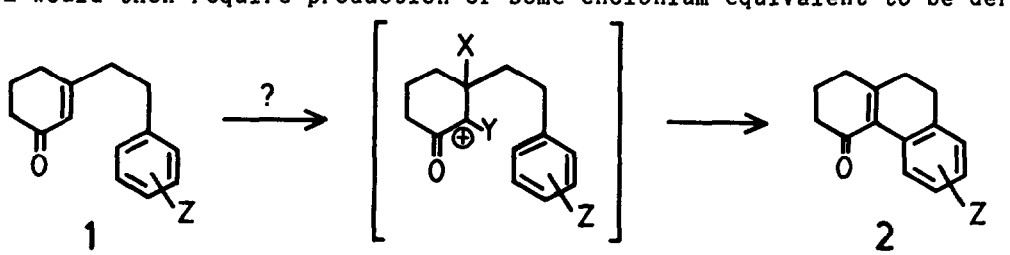
ABSTRACT: A sulfur version of a directed aldol-type condensation followed by a cyclization of an α,β-epoxyketone produces the phenanthrene nucleus, common in many natural products.

The widespread presence of the phenanthrene nucleus in terpenes has led to many innovative approaches.[1] A cyclization strategy involving creation of a carbocationic center β to a carbonyl group either in an enone[2] or epoxyketone[3] (see eq 1) is well documented. The alternative mode invoking a carbocationic



(1)

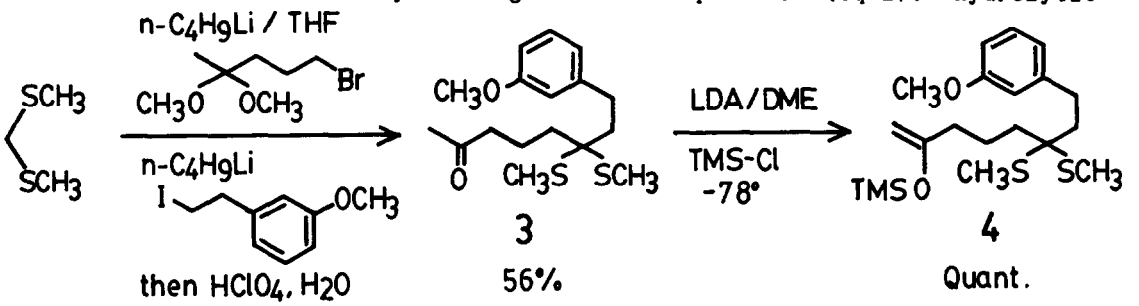
center α to a carbonyl group would seem less probable. Our recent work utilizing thionium ion initiated cyclizations provided a facile entry into 3-substituted-cycloalkenones.[4] Application of this methodology to a synthesis of 2 would then require production of some enolonium equivalent to be derived

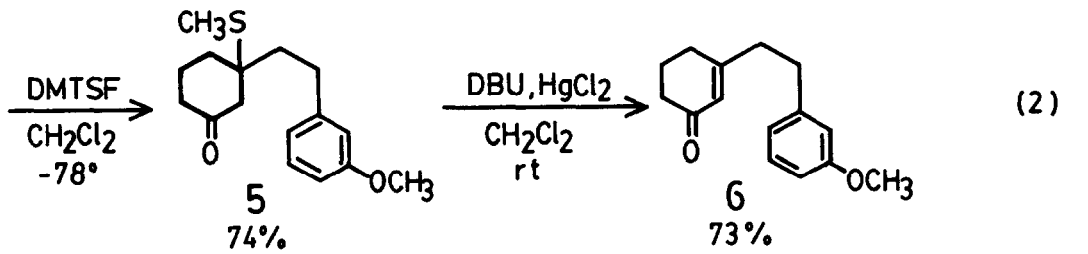


from 1 for initiation of such a cyclization. In this letter, we wish to report the easy availability of 1 and a novel cyclization to 2.

In a one pot alkylation, the anion of bis(methylthio)methane in THF (n-C_4H_9Li) was alkylated with 4,4-dimethoxy-1-bromo pentane (-78° to rt), and

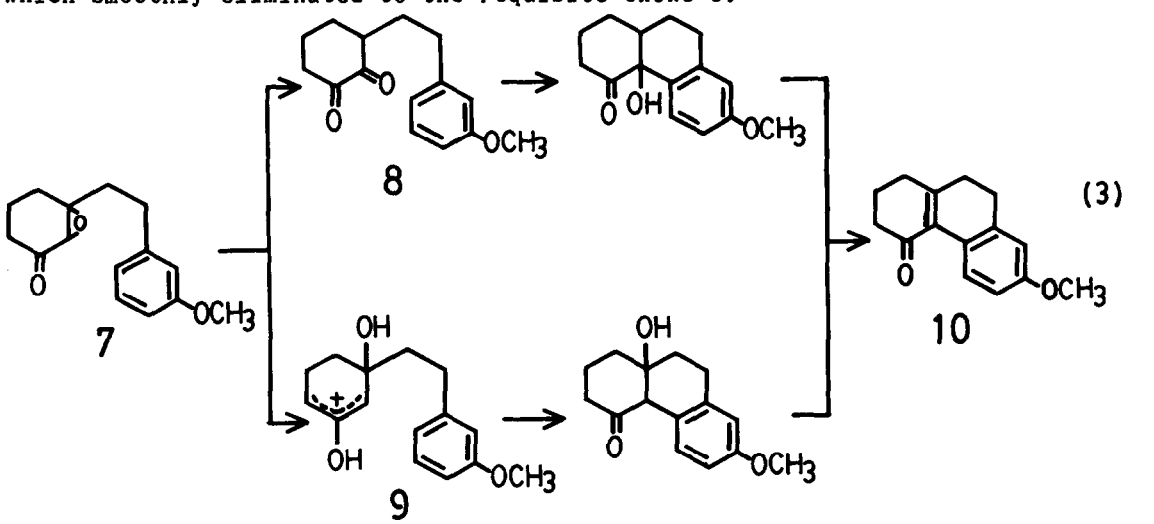
the anion of the product, generated by addition of n-C_4H_9Li at -78° with subsequent warming to 0°, was alkylated with m-methoxyphenethyl iodide initially at -78° followed by warming to room temperature (eq 2). Hydrolytic





(2)

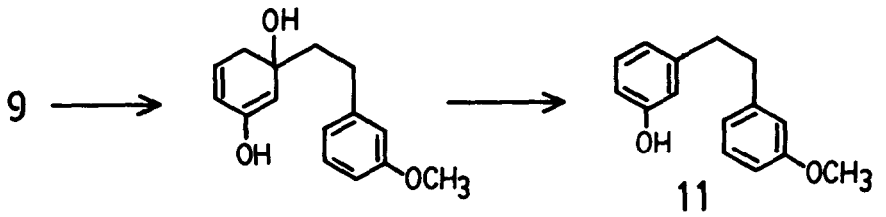
work-up (CH_2Cl_2, H_2O, $HClO_4$, 0° → rt) gave a 56% yield, after distillation, of 3.[5] Standard formation of the enol silyl ether[4,6] followed by cyclization with dimethylmethylthiosulfonium fluoroborate[4] (DMTSF) produced 5[5] in 74% yield which smoothly eliminated to the requisite enone 6.[5]



(3)

The α,β-epoxyketone 7,[5] readily available by standard nucleophilic epoxidation conditions (30% H_2O_2, NaOH, CH_3OH, rt, 80% yield),[7] was envisioned to generate an enolonium equivalent in one of two ways - either as an α

-dicarbonyl such as 8[8] or via the hydroxyallyl cation 9 (eq 3).[9] Gratifyingly, treatment of 7 with camphorsulfonic acid in refluxing xylene gave a 70% isolated yield of the desired cyclization product 10,[5] mp 108-108.5° Contrastingly. boron trifluoride-etherate gave unsatisfactory results. The only by-product of the reaction was the non-cyclized phenol 11.



(4)

This new cyclization is best envisioned as proceeding through 9. The isolation of 11 and the failure of boron trifluoride as a catalyst support this view. As shown in eq 4, simple deprotonation of 9 followed by dehydration nicely accounts for the by-product. Isomerizations of epoxyketones under acid conditions provide good analogy for this suggestion.[9] The direct formation of the enolonium ion from epoxyketones in acid complements the recent reports of Marino[10] and Wender[11] on the use of the enol derivatives of such substrates as enolonium equivalents. It is interesting to note that this new initiator for cationic cyclizations[12] produces 10 in a completely regiocontrolled process; whereas, the alternative type of epoxyketone initiated cyclization (eq 1) gave a 1:1 regioisomeric mixture.[2]

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5. 3 IR (neat): 1720, 1600, 1586 cm.$^{-1}$ NMR ($CDCl_3$): δ1.6-2.0 (m, 6H), 1.98

(s, 6H), 2.09 (s,3H), 2.43 (t, J=6Hz, 2H), 2.6-2.9 (m, 2H), 3.72 (s, 3H), 6.6-6.8 (m, 3H), 7.0-7.2 (m, 1H). Calc'd for $C_{17}H_{26}O_2S_2$: 326.1375. Found: 326.1375. **5** IR (neat): 1712, 1602, 1586 cm.$^{-1}$ NMR (270 MHz, $CDCl_3$): δ1.5-2.1 (m, 6H), 1.95 (s, 3H), 2.1-2.4 (m, 2H), 2.42 (d, J=15 Hz, 1H), 2.52 (dt, J=15, 1 Hz, 1H), 2.6-3.0 (m, 2H), 3.78 (s, 3H), 6.7-7.0 (m, 3H), 7.2-7.4 (m, 1H). ^{13}C NMR (15 MHz, $CDCl_3$): δ9.77, 21.53, 30.14, 33.68, 40.25, 40.96, 50.85, 50.96, 54.93, 110.97, 114.11, 120.52, 129.24, 143.37, 159,55, 207.91. Calc'd for $C_{16}H_{22}O_2S$: 278.1340. Found: 278.1340. **6** IR (neat): 1672, 1630, 1618, 1608, 1590, 1495, 1465 cm.$^{-1}$ NMR (270 MHz, $CDCl_3$): δ1.98 (quint., J=6.3, 2H), 2.30 (t, J=5.7 Hz, 2H), 2.36 (t, J=6.7 Hz, 2H), 2.52 (t, J=7.9 Hz, 2H), 2.80 (t, J=7.9 Hz, 2H), 3.79 (s, 3H), 5.90 (quint., J=1.2 Hz, 1H), 6.7-6.8 (m, 3H), 7.21 (t, J=7.8 Hz, 1H). ^{13}C NMR (15 MHz, $CDCl_3$): δ22.75, 29.92, 33.51, 37.38, 39.47, 55.15, 111.46, 114.22, 120.57, 126.09, 129.46, 124.27, 159.77, 165.01, 199.46. Calc'd for $C_{15}H_{18}O$: 230.1307. Found: 230.1307. **7** IR (neat): 1710, 1600, 1582, 1488 cm.$^{-1}$ NMR (270 MHz, $CDCl_3$): δ1.5-1.7 (m, 1H), 1.8-2.2 (m, 6H), 2.4-2.5 (m, 1H), 2.69 (t, J=8 Hz, 2H), 3.04 (s, 1H), 3.77 (s, 3H), 6.6-6.8 (m, 3H), 7.19 (t, J=7.6 Hz, 1H). Calc'd for $C_{15}H_{18}O_3$: 246.1256. Found: 246.1255. **10** IR (CCl_4): 1675, 1610, 1498 cm.$^{-1}$ NMR (270 MHz, $CDCl_3$): δ2.03 (quint., J=6.3 Hz, 2H), 2.40 (t, J=7.5 Hz, 2H), 2.54 (t, J=6.3 Hz, 2H), 2.56 (t, J=6.3 Hz, 2H), 2.71 (t, J=7.5 Hz, 2H), 3.80 (s, 3H), 6.69 (d, J=2.8 Hz, 1H), 6.76 (dd, J=8.8, 2.8 Hz, 1H), 8.02 (d, J=8.8 Hz, 1H). ^{13}C NMR (15 MHz, $CDCl_3$): δ21.97(t), 27.82(t), 30.75(t), 32.13(t), 39.36(t), 55.15(q), 110.86(d), 113.23(d), 123.89(s), 128.30(d), 130.18(s), 137.47(s), 157.61(s), 158.27(s), 197.25(s). Anal. Calc'd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. MW, 228.1150. Found: C, 78.85; H, 7.09; MW, 228.1151.

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