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A NEW METHOD FOR THE 1,4-OXYGENATION OF 1-ALKYLATED CYCLOPENTADIENES

E. J. Corey and Mukund M. Mehrotra
Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

Abstract: The diene 1 was efficiently transformed into the ketol 2 by a three-step process which includes a novel oxygenation by a chlorochromate reagent.

During the course of a recently completed total synthesis of the clavulone family of marine eicosanoids a three-step conversion of the readily available 1-alkylated cyclopentadiene 1 to the ketol 2 was effected by the sequence: (1) photosensitized ($^1\Delta_g$ O_2) oxygenation of 1; (2) endoperoxide reduction with sodium borohydride; and (3) oxidation of the resulting diol with pyridinium dichromate (58% overall yield).[1] Although this route served perfectly well for the laboratory synthesis, it was clear that a different process would be desirable for work on larger scale because of the well known difficulties associated with scaling up photooxygenation reactions. For this reason we decided to devise an alternative conversion of 1 to 2. The new methodology which is outlined herein is based on the known propensity of furans to react with pyridinium chlorochromate to give products which are derived in a formal sense from an initial 1,4-oxygenation (or 2,5- using furan numbering) process.[2]

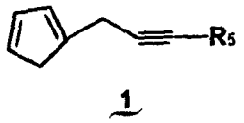
Treatment of 1 with 2-cyanopyridinium chlorochromate (3 equiv)[3,4] and powdered 4A molecular sieves in methylene chloride at 23 °C for 6 hr afforded after isolation the cyclopentenone 3 in 82% yield. Epoxidation of 3 with peroxyacetic acid in ethyl acetate at 23 °C for 15 hr gave the epoxy ketone 4 (91%) which was converted into the desired hydroxy enone 2 (91%) by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-catalyzed elimination (68% overall yield of 2 from 1). Although this new method has not been applied above the normal laboratory scale, our experience indicates that it can be used as a practical large-scale process.

The mechanism of the conversion of 1 to 3 by chlorochromate has not been demonstrated. One reasonable possibility based on the postulation of 1,4-addition[2b] of chlorochromate to the diene is outlined in Scheme 1. We do not exclude the possibility that the 1,4-chlorochromate adduct from 1 can decompose to monounsaturated epoxide 5 which then undergoes pyridinium catalyzed rearrangement to 3. The reaction of chlorochromate with 1,3-dienes is deserving of further study in terms of both synthetic applications and mechanism. Experimental details are as follows.[5,6]

Cyclopentenone 3. 2-Cyanopyridinium chlorochromate (580 mg, 2.41 mmol, 3.0 equiv) and powdered 4A sieves (300 mg) in anhydrous methylene chloride (6.0 ml) were stirred at 23° for ca. 1 hr. Cyclopentadiene 1 (140 mg, 0.80 mmol) in 2.0 ml of methylene chloride was then added. The color of the mixture changed from yellow-orange to dark brown. After ca. 6 hr, the mixture was diluted with 25 ml of anhydrous ether and filtered through Celite. The reaction vessel was washed with two 25-ml portions of ether and these were also passed through Celite. Concentration of the filtrate yielded 3 in almost pure condition. Pure 3 (126 mg, 82%) was obtained by flash chromatography on silica gel (15% ethyl acetate in hexane; R_f 0.44 on silica gel plates using 20% ethyl acetate in hexane). Vacuum distillation probably would be the preferred method of purification for large-scale preparation. For 3: IR (neat): 1752 $cm.^{-1}$; m/e 190 (M+). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.94 (m, 1H), 3.04 (d, J=1.0 Hz, 2H), 2.93 (d, J=2.3 Hz, 2H), 2.88 (br s, 2H), 2.12 - 2.24 (m, 2H), 1.44 - 1.58 (m, 2H), 1.20 - 1.40 (m, 4H), 0.90 (t, J=6.9 Hz, 3H).

Ketol 2. Cyclopentenone 3 (84 mg, 0.44 mmol) in 1.5 ml of ethyl acetate at 0° was treated dropwise with peracetic acid in ethyl acetate (1.10 ml, 1.77 mmol, 4 equiv). After 10 min the cooling bath was removed and the mixture was stirred at 23° for ca. 15 hr, then diluted with 20 ml of anhydrous toluene and concentrated in vacuo to ca. 5 ml volume. This process was repeated three more times. The crude epoxy ketone thus obtained was purified by a quick filtration through a 2" pad of silica gel, using 15% ethyl acetate in petroleum ether as eluent to afford pure 4 (83 mg, 91%). ^1H NMR ($CDCl_3$, 270 MHz): δ 3.72 (br s, 1H), 2.5 - 2.9 (m, 6H), 2.10 - 2.22 (m, 2H), 1.40 - 1.55 (m, 2H), 1.20 - 1.40 (m, 4H), 0.90 (t, J=6.7 Hz, 3H).

Epoxy ketone 4 (30 mg, 0.145 mmol) in 1.0 ml of anhydrous methylene chloride at -50° was treated with DBU (10 μl, 0.07 mmol, 0.46 equiv). The reaction was followed by tlc after workup of aliquots with a biphasic mixture of ether/10% HCl. After 6.0 hr the methylene chloride was evaporated and the crude product was purified by filtration through a 1" pad of silica gel using 40% ethyl acetate/hexane as the eluent to give pure ketol 2^1 (27.4 mg, 91%). IR (neat): 3420, 1720 $cm.^{-1}$; m/e 206 (M+). ^1H NMR ($CDCl_3$, 270 MHz): δ 7.47 (d, J=5.6 Hz, 1H), 6.17 (d, J=5.6Hz, 1H), 2.45 - 2.7 (m, 4H), 2.10 - 2.22 (m, 2H), 1.42 - 1.55 (m, 2H), 1.22 - 1.40 (m, 4H), 0.90 (t, J=6.9 Hz, 3H).



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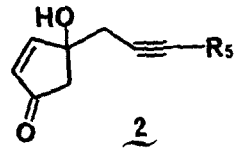

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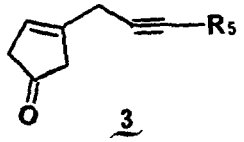

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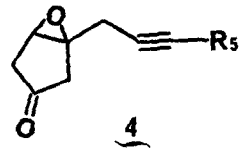

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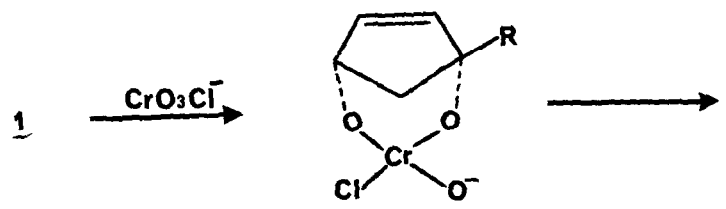
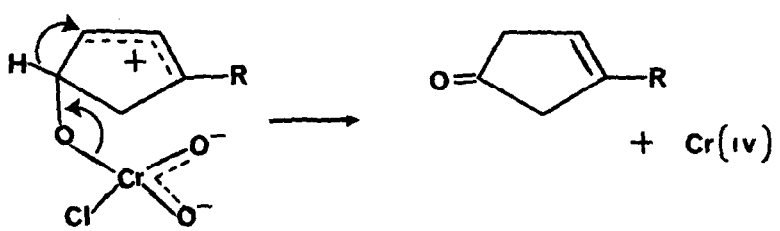
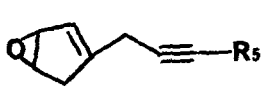
SCHEME 1:







5

R_5 = n-C_5H_{11}

R = CH_2—C≡C—C_5H_{11}-n

References and Notes

1. E. J. Corey and M. M. Mehrotra, J. Am. Chem. Soc., 106, 3384 (1984). For another synthesis of clavulones see H. Nagaoka, T. Miakoshi, and Y. Yamada, Tetrahedron Letters, 25, 3621 (1984).

2. See (a) D. G. Piancatelli, A. Scettri and M. D'Auria, Tetrahedron, 36, 661 (1980); (b) idem, Synthesis, 245 (1982); (c) see also, M. Suzaki, Y. Oda and R. Noyori, J. Am. Chem. Soc., 101, 1623 (1979).

3. This reagent was more effective than pyridinium chlorochromate. For a recent review of Cr(VI) mediated oxidations, see G. Cainelli and G. Cardillo, Eds., "Chromium Oxidations in Organic Chemistry," Springer Verlag, 1984.

4. 2-Cyanopyridinium chlorochromate was prepared by the following procedure (J. W. Suggs, Ph.D. dissertation, Harvard University, 1976, p. 127). 2-Cyanopyridine (7.5 g, 72 mmol) in 8.0 ml of 12N HCl is added with stirring to a solution of chromium trioxide (7.2 g, 72 mmol) in 15 ml of 6N HCl at 0°. The resulting solution is stirred at 0° for ca. 10 min by which time a yellow-orange solid precipitates. Precipitation can be induced by seeding with PCC. The crystals are collected on a sintered glass funnel and dried in vacuo over P_2O_5 to afford 13.84 g (80%) of yellow-orange needles which can be stored indefinitely at 4°.

5. Satisfactory spectroscopic data were obtained for new compounds 3 and 4.

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