

### SYNTHESIS OF *cis*-CIVETONE FROM A BUTADIENE TELOMER

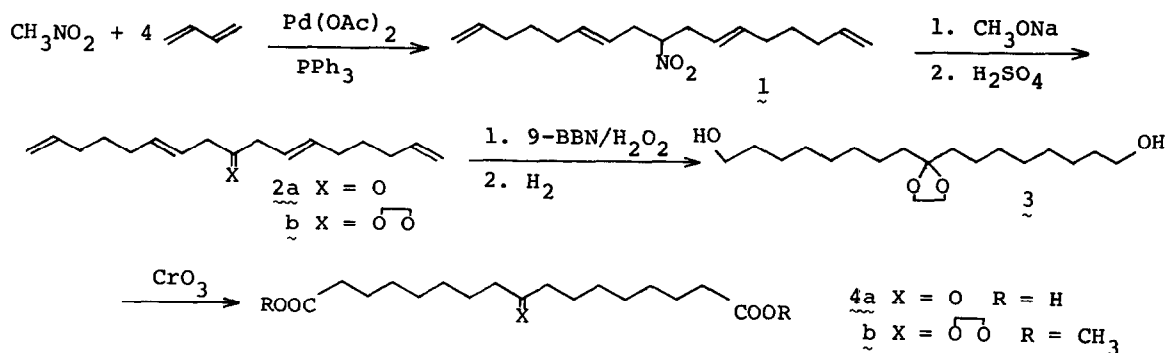
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Civetone is a naturally occurring unique symmetric 17 membered cyclic ketone with the *cis* double bond. Few synthetic studies for civetone have been attempted. 1-5 Stoll prepared *cis*-civetone by separating the *cis* and *trans*-mixture. 1 One promising starting material for the civetone synthesis seems to be 9-keto-1,17-heptadecanedioic acid 4a, so called civetonedicarboxylic acid. The acid was synthesized from azelaic acid 6 and aleuritic acid 5, but these methods are not practical. Conversion of civetonedicarboxylate to a mixture of *cis* and *trans*-civetone has been reported by Stoll 1 and Bhattacharyya 5. We now wish to report a novel synthetic method for civetonedicarboxylic acid 4a from an easily available butadiene telomer and the selective synthesis of *cis*-civetone from 4a.

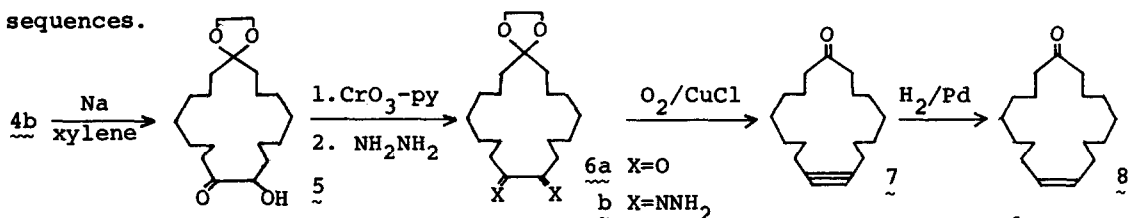
We have reported the palladium catalyzed telomerization of butadiene with nitroalkane 7. 9-Nitro-1,6,11,16-heptadecatetraene 1 (bp 135°C/2 mm) was prepared by the reaction of nitromethane with four moles of butadiene at room temperature using palladium acetate and triphenylphosphine (1 : 2.5) as the catalyst. This compound is an ideal starting material for the synthesis of 4a with a chain of 17 carbons and suitable functionality. The facile synthesis of 4a was achieved by the following sequences.



The nitro group of 1 was converted into ketone 2a in 87% yield by treatment with sodium methoxide and then with sulfuric acid at -50°C: bp 124°C/2 mm; IR (neat) 1720, 1640, 994, 970, 912 cm<sup>-1</sup>. The ketone 3 was protected by ketal formation: bp 125-130°C/2 mm. Selective hydroboration of the terminal double bonds of 2b was carried out with 9-borabicyclo[3.3.1]nonane to give 1,17-dihydroxy-6,11-heptadecadien-9-one (ketal) in 86% yield. The internal double bonds were reduced by palladium on carbon to give the diol 3. The oxidation of

the alcohols was carried out with the Jones reagent in acetone at 25°C to give 4a in 70% yield: mp 113-114°C, reported 114°C<sup>5</sup>; IR 1710, 1701 cm<sup>-1</sup>.

The conversion of 4a to *cis*-civetone was carried out by the following sequences.



The ketal of dimethyl civetonedicarboxylate (1550 mg; IR 1740 cm<sup>-1</sup>) in xylene (40 ml) was added dropwise in 2 hr to the refluxing xylene (50 ml) containing sodium dispersion (736 mg) with vigorous stirring. The crude oil was chromatographed (silica gel) to give the acyloin 5 in 65% yield (850 mg) as an oil: NMR δ 1.1-2.0 (m, 26H), 2.2-2.6 (m, 2H, CH<sub>2</sub>CO), 3.4 (broad s, 1H, OH), 3.8 (s, 4H, OCH<sub>2</sub>), 4.1 (t, 1H, CHO). The acyloin was oxidized to α-dione 6a with chromic anhydride pyridine complex (Collins reagent) in dichloromethane in 70% yield; IR (neat) 1710 cm<sup>-1</sup>; NMR δ 1.0-1.9 (m, 24H), 2.4-2.8 (m, 4H), 3.7 (s, 4H, OCH<sub>2</sub>). Then the diketone 6a was converted to dihydrazone 6b by refluxing with 80% hydrazine in *n*-propyl alcohol for 12 hr in 92% yield; IR 3370, 3200, 1620, 1580; NMR δ 1.0-2.0 (m, 24H), 2.5 (t, 4H), 3.8 (s, 4H, OCH<sub>2</sub>), 5.1 (broad s, 4H, NH<sub>2</sub>). The semi-solid dihydrazone was converted to the acetylene 7 by the copper catalyzed oxidation in pyridine.<sup>8,9</sup> CuCl (400 mg) in pyridine (25 ml) was treated with oxygen at room temperature for 30 min. Then a solution of 6b (300 mg) in pyridine (25 ml) was added dropwise over 1 hr under oxygen atmosphere. The crude product was treated with dilute hydrochloric acid to remove the ketal protection. Crude oily product was subjected to column chromatography to give dehydrocivetone 7 in 82% yield (172 mg): IR 1710 cm<sup>-1</sup>; NMR δ 1.1-2.0 (m, 20H), 2.0-2.5 (m, 8H); semicarbazone, mp 192-193°C, reported, 189-191°C.<sup>6</sup> Finally the triple bond was reduced by Lindler catalyst in hexane at room temperature in 10 min under atmospheric pressure of hydrogen selectively to give *cis*-civetone in 92% yield as a semi-solid; IR (neat) 1710 cm<sup>-1</sup>; NMR δ 1.0-1.8 (m, 20H), 1.8-2.1 (m, 4H, allylic), 2.1-2.5 (m, 4H, -CH<sub>2</sub>CO-), 5.4 (t, 2H, *cis*-olefin); semicarbazone, mp 184.5-186°C, reported, 186-187°C.

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