



**Oxidative fragmentation of 1, 5-cyclooctadiene derivative:
A new entry into 14-membered macrocycle related to cembranoid group of
diterpenoids.**

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ABSTRACT

14-Membered cyclictetraketone was synthesized by subjecting 1,2,3,4,5,6,7,8,9,10-decahydrocycloocta[1,2-a:5,6-a']dipentene, a 1,5- cyclooctadiene derivative to oxidative fragmentation by Ruthenium oxide catalyzed periodate oxidation. The 1,5- cyclooctadiene derivative was synthesized by domino intermolecular alkylation and cycloalkylation of 2-(1-cyclopentenyl) ethanol, which was obtained from cyclopentanone by Reformatsky reaction followed by LAH reduction. This 14-membered macrocycle has the carbocyclic frame work of cembrane, a 14-membered cyclic naturally occurring diterpene.

Keywords: 1, 5-cyclooctadiene, Oxidative fragmentation, 14- membered macrocycle, cembrane .

INTRODUCTION

A number of diterpenoid natural products containing a 14-membered ring have been isolated from terrestrial and marine sources [1]. Cembrane (**Chart**) the first naturally occurring 14-membered cyclic diterpene, is found in pine oleoresins and is an example of a simple hydrocarbon member. The intriguing range of activities [1], the often dense array of functional groups and stereocenters, and a lack of a general method for the preparation of 14 member ring have made the cembrane an interesting problem for total synthesis. The reported methods [1] are tedious, require costly chemicals and time consuming.

EXPERIMENTAL SECTION

2-(1-cyclopentenyl)ethanol was synthesized from cyclopentanone and ethyl bromoacetate by following the literature procedure [2,3].

Domino intermolecular alkylation and cycloalkylation [4] of 2-(1-cyclopentenyl) ethanol in polyphosphoric acid (PPA);

A mixture of 2-(1-cyclopentenyl)ethanol (5 mmol) and PPA (10 g) was heated on steam bath for 4 hours. The reaction mixture was poured onto the ice and extracted with ethyl acetate (3 x 25 ml). The combined ethyl acetate extract was washed with 10% sodium carbonate, water (2 x 25 ml) and then dried (anhydrous sodium sulphate). Recovery of solvent afforded dark oil, which was purified by column chromatography using silica gel adsorbent. Elution with petroleum ether (600 ml) followed by recovery of solvent afforded a colourless oil (60.2 %) of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12-dodecahydrocycloocta [1, 2-a: 5, 6-a'] dipentene.

IR (KBr, cm^{-1}): 2924, 2860, 1604. ^1H NMR (300 MHz, CDCl_3): δ = 1.90 (m, 4H; H-2, H-9), 2.00 (s, 8H; H-4, H-5, H-6, H-7). 2.30 (t, 8H; H-1, H-3, H-8, H-10); ^{13}C NMR (75 MHz, CDCl_3): δ = 21.80 (C-2, C-9), 27.30 (C-4, C-5, C-6, C-7), 34.90 (C-1, C-3, C-8, C-10), 133.70 (C-1', C-3', C-5', C-6'); Mass: m/z 188 (M^+ , 60), 174 (14), 146 (10), 132 (12), 118 (98), 104 (100), 94 (14). UV: 231.2 (2.8412); Anal. Calcd for $\text{C}_{14}\text{H}_{20}$: % C 89.33, % H 10.64. Found: % C 89.30 % H 10.70

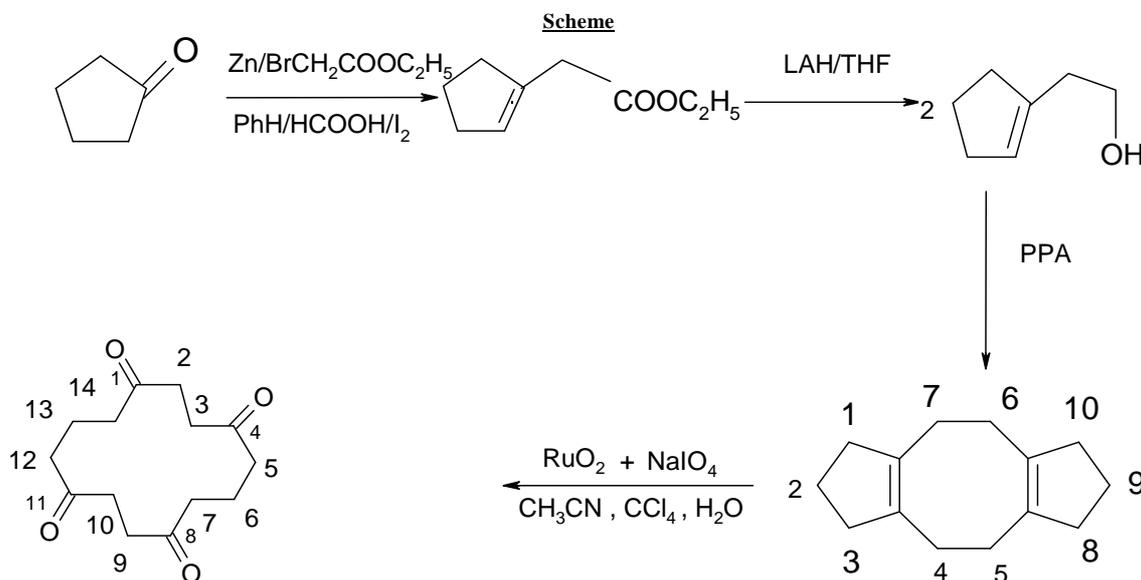
Ruthenium tetroxide catalysed periodate oxidation of 1,2,3,4,5,6,7,8,9,10-decahydrocycloocta[1,2-a:5,6-a']dipentene:

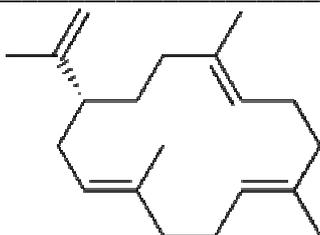
To a well stirred solution of 1,2,3,4,5,6,7,8,9,10,11,12-dodecahydrocycloocta[1,2-a:5,6-a'] dipentene (0.05 mol) in acetonitrile (2 ml), carbon tetrachloride (2 ml) and distilled water (3 ml) were added. To this solution ruthenium dioxide (0.015 mol) and sodium metaperiodate (0.83 mol) were added. The reaction mixture was then stirred for 4 hours at room temperature. The reaction on work up followed by purification by column chromatography (pet ether, 400 ml) gave a brown colored oil (79.4 %) of 1,4,8,11-cyclotetradecatetrone

IR (KBr, cm^{-1}): 2922, 2852, and 1707. ^1H NMR (300 MHz, CDCl_3): δ = 1.75 (m, 4H; H-6, H-13), 2.50 (t, 8H; H-5, H-7, H-12, H-14), 2.75 (s, 8H; H-2, H-3, H-9, H-10); ^{13}C NMR (75 MHz, CDCl_3): δ = 18.40 (C-6, C-13), 41.00 (C-2, C-3, C-9, C-10), 43.20 (C-5, C-7, C-12, C-14), 211.70 (C-1, C-4, C-8, C-11); Mass: m/z 252 (M^+ , 64), 226 (34), 224 (34), 196 (36), 182 (100), 168 (8), 126 (20), 140 (48), 98 (10), 84 (10). UV: 210 (2.4044), 248.7 (2.0862). Anal. calcd for $\text{C}_{14}\text{H}_{20}\text{O}_4$: % C 66.65, % H 7.99. found % C 66.70 % H 7.89.

RESULTS AND DISCUSSION

Fragmentation of cyclic olefins to generate a larger ring is well documented in the literature [5]; however to the best of our knowledge fragmentation of 1, 5-cyclooctadienes has not been reported. This led us to explore the feasibility of fragmentation of 1,2,3,4,5,6,7,8,9,10-decahydrocycloocta[1,2-a:5,6-a']dipentene to generate a 14-membered macrocycle. Several reagents have been reported for carrying out the fragmentation [6] of cyclic olefins. For the present work we have selected RuO_4 catalysed periodate oxidation due to its simplicity and efficiency [7].





Oxidative fragmentation of 1,2,3,4,5,6,7,8,9,10-decahydrocycloocta[1,2-a:5,6-a']dipentene with RuO₄ catalyzed periodate oxidation resulted in the formation of a 14-membered macrocycle namely, 1,4,8,11-cyclotetradecatetrone in a good yield. The required 1, 5-cyclooctadiene derivative was synthesized by domino intermolecular alkylation and cycloalkylation of 2-(1-cyclopentenyl) ethanol in PPA. 2-(1-Cyclopentenyl) ethanol was prepared from cyclopentanone and ethyl bromoacetate by Reformatsky reaction followed by LAH reduction (Scheme).

CONCLUSION

In conclusion we have developed a short synthesis of 14-membered macrocyclic tetraketone, having the carbocyclic framework of cembranoid group of diterpenoids by utilizing easily available and inexpensive chemicals.

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