Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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To cite this article: Ajoy K. Banerjee , Jose A. Azócar & William Vera (1999) Synthesis of an Intermediate for(±)-Platphyllide Through Thionyl Chloride-Pyridine Mediated Rearrangement, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:17, 2995-3001, DOI: 10.1080/00397919908086474

To link to this article: http://dx.doi.org/10.1080/00397919908086474

SYNTHETIC COMMUNICATIONS, 29(17), 2995-3001 (1999)

SYNTHESIS OF AN INTERMEDIATE FOR (±)-PLATPHYLLIDE THROUGH THIONYL CHLORIDE-PYRIDINE MEDIATED REARRANGEMENT

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Abstract - The cyclohexadienyl alcohol (3) on treatment with thionyl chloride and pyridine provided the tetrahydronaphthalene (4) whose transformation to the carbomethoxy tetralone (7), a key intermediate for platphyllide (8), has been accomplished in four steps.

Our previous work has demonstrated[1] that the several cyclohexadienyl alcohols undergo interesting rearrangements with thionyl chloride and pyridine originating potential intermediates for the synthesis of eudesmane sesquiterpenes. This observation encouraged us to examine the rearrangement of the cyclohexadienyl alcohol (3) with thionyl chloride and pyridine hoping to obtain the tetrahydronaphthalene (4) and aiming to its further transformation to the carbomethoxy tetralone (7). The synthesis of (7) would constitute an alternative, novel and convenient route for the synthesis of the desmethyl aromatic eudesmane platphyllide (8) whose synthesis has already been reported.[2] The present paper describes the structure of the product obtained during the rearrangement of the cyclohexadienyl alcohol (3) and the transformation of the resulting product to the tetralone (7)[2] which proved a valuable intermediate for platphyllide (8).

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The α,β-unsaturated ketone (1)[3] on dehydrogenation with 2,3-dichloro-5,6-dicyano benzoquinone (DDQ) afforded the dienone (2) in excellent yield which was converted to the cyclohexadienyl alcohol (3) by reduction with sodium borohydride in ethanol. This on treatment with thionyl chloride and pyridine underwent rearrangement yielding the tetrahydronaphthalene (4) in 40% yield. This transformation can be explained by assuming the formation of the intermediate (A) whose methyl group migrated followed by the elimination of the chlorosulfide group (-OSOCl) leading the formation of the intermediate (B) which rearranged to the naphthalene (4) (Fig I). Reduction of (4) with lithium aluminium hydride afforded the alcohol which without purification was subjected to oxidation[4] with barium manganate in methylene chloride to obtain the tetralone (5). The oxidation experiment repeated with Jones reagent[5] produced the tetralone (5) along with other undesired products as was evidenced in tlc.

To complete the synthesis, all that was required was the conversion of the aromatic methyl of (5) to carboxylic acid to obtain the compound (6) followed by its transformation to the compound (7) by esterification. There is a great variety of ways by which the oxidation of aromatic methyl to carboxylic acid can be accomplished. The method which proved successful for our work consisted in the treatment of the tetralone (5) with potassium permanganate and cyclohexyl-18-crown-6 at room temperature.[6] The compound (6), obtained in good yield, without purification was esterified with dimethyl sulfate to obtain the desired tetralone (7) in 70% yield whose spectroscopic data nicely matched with the data reported.[2] As this compound proved a very valuable intermediate for platphyllide (8)[2], the present alternative method constitutes an alternative approach for the synthesis of (±)-platphyllide.

An additional route was also sought to prepare the naphthalene (4) (Fig II) in better yield. In this alternative route the dienone (2) in toluene was subjected to dienone-phenol rearrangement by heating with p-TsOH at reflux temperature hoping to obtain the compound (9) whose transformation to the tetrahydronaphthalene (4) could easily be achieved. This process yielded a crystalline derivative whose

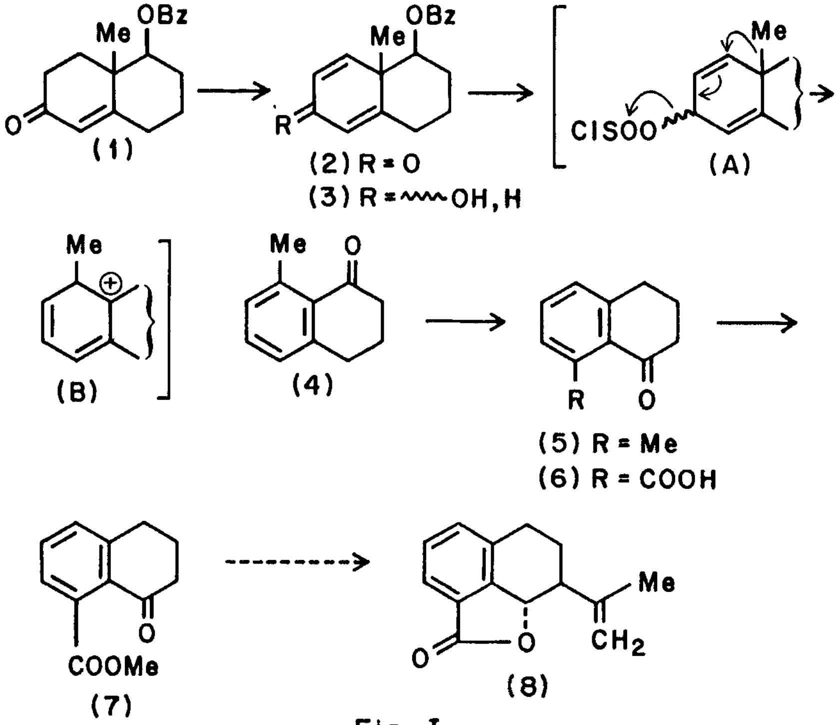
Me
OBz
O
(1)
R
(2) R = O
(3) R = ~~OH, H
ClSOO
(A)
Me
(B)
(4)
(5) R = Me
(6) R = COOH
COOMe
(7)
CH2
(8)

Fig. I

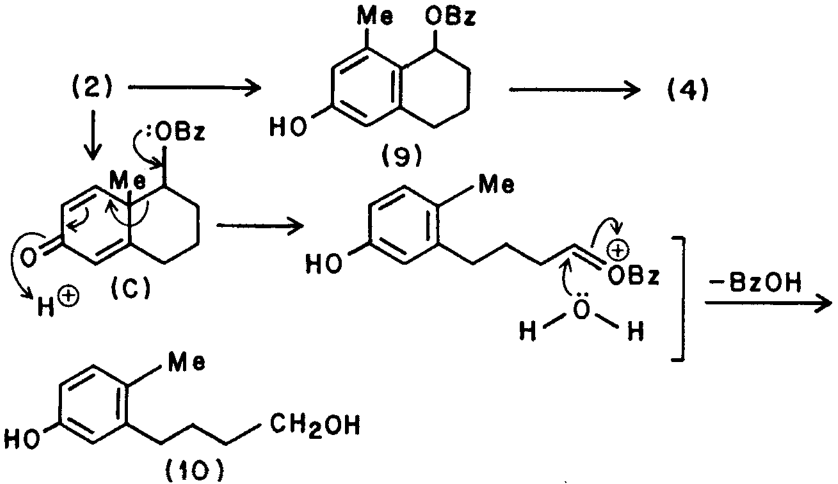
(2)
(4)
Me
OBz
HO
(9)
:OBz
O
H⊕
(C)
⊕OBz
H
Ö
−BzOH
CH2OH
(10)

Fig. II

spectroscopic properties indicated the formation of a product far removed from the desired product (9). In the IR spectrum the product exhibited the absence of the ester group and the presence of a strong hydroxyl group. The ^1H NMR spectrum showed signals for one methyl group attached directly to the aromatic nucleus (δ 2.26), eight protons (4 CH_2) (δ 1.09-1.81) (4H), (δ 2.41-2.72) (4H), hydroxyl group attached to aromatic nucleus (δ 5.24) and three aromatic protons (δ 6.66-6.98). These spectroscopic data along with our previous observations[7] led us to assign the structure (10) to the rearrangement product. In the mass spectrum the compound (10) the parent ion was not observed but the m/z values displayed at 162 (M^+-H_2O), 147 (M^+-H_2O-Me) and 134 (M^+-H_2O-C_2H_4) indicated the fragments produced after splitting of the parent molecule. The mechanism of the formation of the compound (10) is depicted in Fig II. No further corroboration was sought to confirm the structure of the product (10). We believe that it is important to mention here that some bicyclic δ-hydroxy enones on treatment with acid also undergo aromatization along with skeletal rearrangement.[8,9]

Experimental

Unless otherwise stated, IR spectra were taken on a Nicolet FT instrument. NMR spectra were recorded on a Varian A-90 spectrometer in $CDCl_3$ using TMS as internal standard and Bruker AM 300 using leuterated solvents. Mass spectra were run on Kratos MS25RFA and in a gas chromatograph Hewlett Packard 5890 quadropolar 5972 series S. The expression "workup" indicated that the solution is diluted with water, extracted with ether, washed with brine, dried ($MgSO_4$) and evaporated under pressure. Column chromatography was performed in silica gel 60 (Merck). Microanalyses were carried out in the Chemistry Department, IVIC, Caracas.

4a-Methyl-5-benzoyl-5,6,7,8-tetrahydro-2(4a-H)naphthalenone (2) - To a solution of the benzoate (1) (2.01 g) in freshly distilled dioxane (200 ml) was added DDQ (2.98 g) and the resulting solution was refluxed for 72 h. The reaction mixture was cooled, filtered and concentrated to yield a dark material which on chromatographic purification (diethyl ether: hexane, 85:15) afforded the dienone (2) (1.49 g, 75%), m.p. 90-92° (from diethyl ether-hexane), m/z 160 (M^+-C_6H_5COOH); ν_{max} 1645 (CO) and 1710 cm^{-1} (ester CO), δ 1.13 (3H, s, 4a-Me), 6.01-6.84 (3H, m, vinyl protons), 7.42-8.22 (5H, m, aromatic protons) (Found: C, 76.52; H, 6.39. $C_{18}H_{18}O_3$ requires C, 76.57; H, 6.43%).

1-Methyl-5-benzoyl-5,6,7,8-tetrahydronaphthalene (4) - To a solution of the dienone (2) (1.54 g) and $CeCl_3$, 6 H_2O (2.12 g) in ethanol (90 ml), cooled to 0°C was added sodium borohydride (1.12 g) in portion-wise within 15 min. The reaction mixture was stirred for 30 min and diluted with water. Workup afforded alcohol (3) (1.32 g); m/z 144 (M^+-C_6H_5COOH-H_2O); ν_{max} 1715 (CO) and 3405 cm^{-1} (OH). The alcohol (3) without further purification was immediately utilized for the next step.

To a solution of the alcohol (3) 1.31 g) in pyridine (25 ml) was added freshly distilled thionyl chloride (2 ml) and stirred at room temperature for 18 hr. Workup followed by chromatographic purification (hexane: diethyl ether, 9:1) afforded the tetrahydronaphthalene (4) (580 mg; 40%); m/z 144 (M^+-C_6H_5COOH) and 129 (M^+-C_6H_5COOH-Me); ν_{max} 1715 (ester CO); δ 2.26 (3H, S, Me), 2.66 (2H, t, J=9 Hz, benzyl protons), 7.45-8.12 (8H, m, aromatic protons) (Found: C, 81.21; H, 6.84. $C_{18}H_{18}O_2$ requires C, 81.17; H, 6.81%).

8-Methyl-1-tetralone (5) - To lithium aluminium hydride (500 mg) in tetrahydrofuran (80 ml) was added in tetrahydronaphthalene (4) (400 mg). After heating the mixture for 4 hr, water was added. The usual workup yielded an alcohol (238 mg), m/z 162 (M^+) and 144 (M^+-H_2O); ν_{max} 3470 cm^{-1} (OH).

To a solution of the alcohol (235 mg) in methylene chloride (30 ml) was added dry powder of barium manganate (1.52 g) at room temperature. The mixture was stirred for 6 hr, diluted with methylene chloride (20 ml) and then filtered. The workup afforded oily material which on chromatographic purification (hexane:dietyl ether, 4:6) yielded the tetralone (5) (216 mg, 90%); m/z 160 (M^+) and 145 (M^+-

Me); ν_{max} 1682 cm^{-1} (CO); δ 2.28 (3H, s, Me), 2.64 (2H, t, J=9 Hz, benzyl protons), 7.24-7.52 (3H, m, aromatic protons) (Found: C, 82.49; H, 7.57. $C_{11}H_{12}O$ requires C, 82.46; H, 7.55%).

8-Carbomethoxy-α-tetralone (7) - To a solution of potassium parmanganate (3 g) in dry benzene (10 ml) was added the tetralone (5) (210 mg) followed by the addition of dicylohexyl-18-crown-6 (30 mg). The deep brown solution was stirred at room temperature for 5 days. The reaction mixture was filtered and the residue was dissolved in an aqueous sodium hydroxide solution (20 ml, 5%). After filtration of the manganese oxide, the alcaline solution was extracted with ether to remove the traces of the crown ether. The alkaline extract was acidified with dilute hydrochloric acid and extracted with ether. The workup yielded the acid (6) (175 mg), very low melting solid, ν_{max} 1705-1710 cm^{-1} (unresolved acid CO and ketonic CO) and without purification was utilized for the next step.

To a solution of the acid (6) (170 mg) in acetone (5 ml) was added anhydrous potassium carbonate (80 mg) and dimethyl sulfate (850 mg) and then refluxed for 12 hr. Workup followed by chromatographic purification (hexane:diethyl ether, 4:6) afforded the carbomethoxy tetralone (7) (187 mg, 70%) m/z 204 (M^+), ν_{max} 1680 (CO) and 1720 cm^{-1} (ester); δ 2.68 (2H, t, benzyl protons), 3.65 (3H, m, OMe), 7.24-7.48 (3H, m, aromatic protons) (Found: C, 70.61; H, 5.95. $C_{12}H_{12}O_3$ requires C, 70.57; H, 5.92%).

4-Methyl-3-(butyl-4-ol-phenol) (10) - To the dienone (2) (200 mg) dissolved in toluene (15 ml), aqueous hydrochloric acid (3 ml, 10%) was added and heated under reflux for 1 hr. The workup followed by purification (hexane:diethyl ether, 80:10) yielded the phenol (10) (95 mg; 75%), m.p. 169-172°C (from diethyl ether). m/z 162 (M^+-H_2O), 147 (M^+-H_2O-Me) and 134 (M^+-H_2O-C_2H_4); ν_{max} 3409 cm^{-1} (OH); δ 2.26 (3H, s, Me), 2.41-2.72 (4H, m), 1-09-1-81 (4H, m), 5.24 (OH), 6.66-6.98 (3H, m, aromatic protons) (Found: C, 73.33; H, 8.97. $C_{11}H_{16}O_2$ requires C, 73.30; H, 8.95).

Acknowledgement

The authors are grateful to the Head of the Chemistry Department, IVIC, for giving special grant for the completion of the work which constitutes a part of the work of Project SI-98000387 of CONICIT.

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(Received in the USA 05 February 1999)