SYNTHESIS OF HYDROGENATED ISOZONAROL VIA DIELS ALDER REACTION: A CONVERGENT APPROACH TO ABC TRICYCLIC CORE OF MARINE SESQUITERPENOIDS

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Abstract - The synthesis of natural products plays an important role in organic and biological chemistry. These compounds show a great variety of chemical structures and a wide range of biological activities[1]. The synthetic utility and potential power of the Diels–Alder reaction[2] in organic chemistry is evident. The present paper relates to the synthesis of dihydroisozonarol by [4+2] cycloaddition reaction between 1,3,3-trimethyl-2-vinyl-1-cyclohexene and (E)-1-(2,5-dimethoxyphenyl) but-2-en-1-one followed by hydrogenation and demethylation.

Keywords - Sesquiterpenoids, Cylcoaddition, Diels Alder reaction

INTRODUCTION

Marine organisms are a rich source of biological diversity with production of structurally diverse, novel and biologically active marine metabolites[3] The compound like zonarol and isozonarol sesquiterpenes isolated from the brown algae, Dictyopteris zonarioides have been shown to exhibit strong inhibitory effect against plant pathogenic fungi[4]. Unsaturated ketones are among the most commonly used dienophiles in Diels-Alder reactions. In this paper we have discus synthesis of bicyclic sesquiterpenoid related to Isozornol[5], Isozarone[6], Wiedendiol-A[7], Wiedendioal-B[7], Siphonodytyal C[8]. These aromatic sesquiterpenoids share the common features of bicyclic skeleton and substituent at C-ring as well as an angular methyl group at the A/B ring junction. It may be noted that various bicyclic sesquiterpenoids reported in the literature possess a wide range of biological activity including Inhibition of HIV I reverse transcriptase[9], antitumor activity[10], antibiotic activity[11], fungi toxic[11], anti proliferative, cytotoxic, antirheumatic and anti inflammatory[12]. The majority of reported methods involved cyclization of a suitable alkene having carbonyl group to generate ethelyne part of the bicyclic core of the marine terpenoids. All these methods are tedious, multistep and over all yields are also low. In comparison the present method involving the generation of the carbocyclic core of the marine terpenoids in a single steps by Diels-Alder reaction. Retrosynthetic analysis of these sesquiterpenoid structures revealed that most of these compounds could be accessed by Diels Alder reaction between 1,3,3-trimethyl-2 –vinyl-1-cyclohexene (I) and a suitable crotonophenone derivative.

II. MATERIALS AND METHODS

The b.p. of petroleum ether (PE) used was in the range of 60 – 80^{0}C. Column chromatography (CC): silica gel (SiO_2 , 60 – 120 mesh; S.D. Fine Chemicals Ltd.). M.p.: EXPO HI-TECH Melting-point apparatus; uncorrected.UV Spectra: Shimadzu UV/VIS Spectrophotometer UV-2401PC using MeOH as solvent, λ_{max} in nm (e). IR Spectra: Perkin-Elmer Spectrum One FT-IR Spectrophotometer in KBr. ^{1}H- and ^{13}C-NMR spectra: Bruker AVANCE (^{1}H: 300; ^{13}C: 75 MHz) spectrometer in $CDCl_3$ and with TMS as an internal standard, δ in ppm and coupling constants J in Hz. EI-MS: 3200 Q TRAP LC-MS-MS System MDS SCI EX SHIMADZU PROMINANCE LC and Varian 500-MS (Model 210) LC-MS IT Mass spectrometer (at 70 eV, m/z (rel-%)). Elemental analyses: Euro-Vector EA 3000 elemental analyzer.

Retrosynthetic analysis of these sesquiterpenoid structures revealed that most of these compounds could be accessed by Diels Alder reaction between 1,3,3-trimethyl-2 –vinyl-1-cyclohexene (I) and a suitable crotonophenone derivative. The required diene, that is 1,3,3-trimethyl-2–vinyl-1-cyclohexene was prepared from citral an acyclic monoterepene as presented in Scheme-1.

Cycloaddition reaction between diene (I) and crotonophenone derivative (II) was then carried out and this resulted in the formation of the desired bicyclic compound (III) (Scheme-3). This reaction was found to be regioselective as well as stereoselective[13]. This reaction provided compound which can serve as key intermediates in the synthesis of bicyclic sesquiterpenoids zonarol and isozonarol analogues.

III. RESULTS AND DISCUSSION

We have undertaken the synthesis of carbocylic frame work of marine sesquiterpenoid listed in Table- 1. The retrosynthetic analysis revealed that the carbocyclic framework of these compounds could be

accessed by Diels-Alder reaction between a suitable diene and a crotonophenone derivative as a dienophile. The required diene visualized for this purpose would be 1, 3, 3-trimethyl-2-vinyl-1-cyclohexene (I) (Chart-1). This diene would form ring 'A' with trimethyl groups of the bicyclic framework. The benzyl group could be added by selection of a suitable dienophile such as crotonophenone derivative(II)(Chart-1). Further, the Diels-Alder cycloaddition reaction between the diene and the dienophile would generate the ring B having a double bond between C-8 and C-8a and also create the two stereocenteres with trans configuration in ring B as present in these marine terpenoids. Additionally, the double bond between C-8 and C-8a can be subsequently reduced to create another two stereocenteres at AB ring junction with trans configuration and finally the C-9 carbonyl can also be converted to methylene / exocyclic double bond /-OH as present in these natural products (Chart-2). Thus by Diels-Alder cycloaddition reaction between above diene and a suitable crotonophenone derivative as a dienophile it should be possible to synthesize the marine terpenoids listed in Table-1.

Chart-1

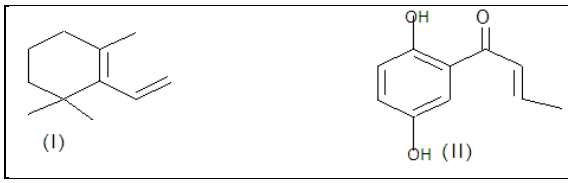
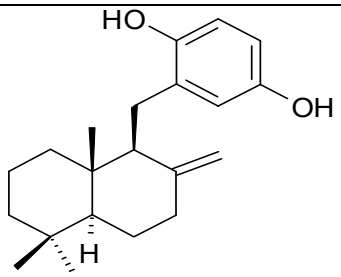
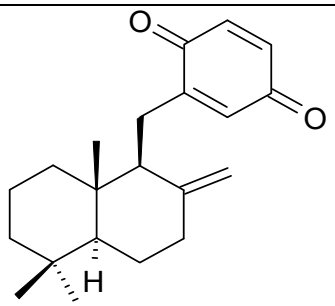
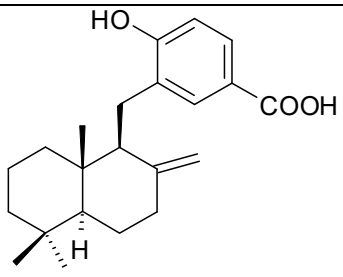
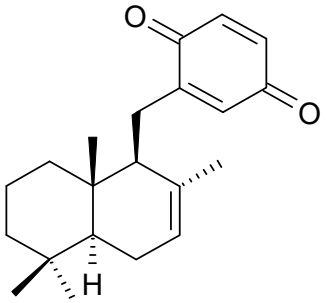
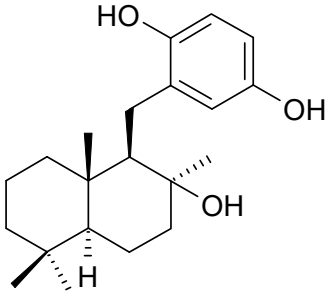
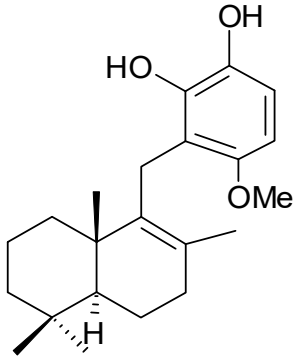
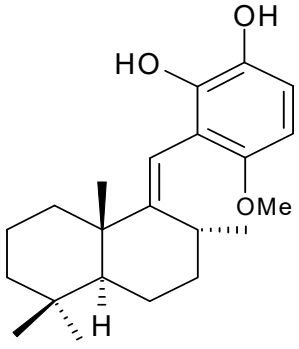
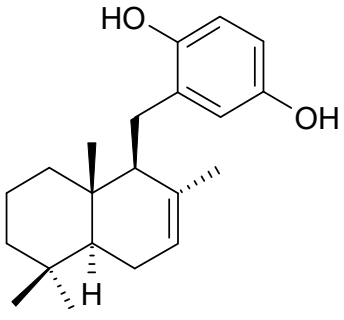
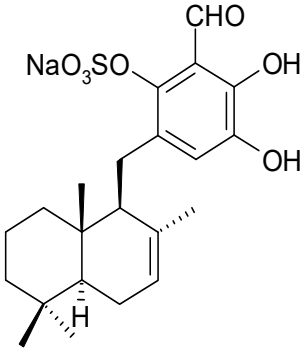
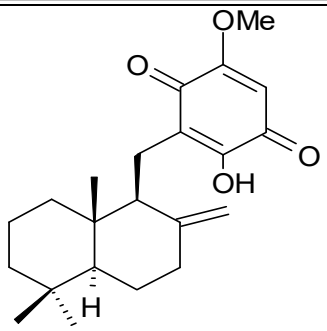
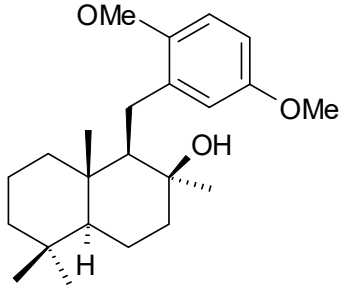


Table -1

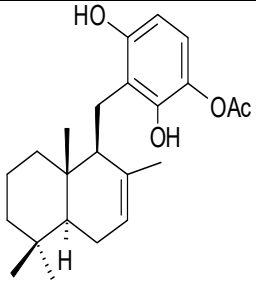
 Zonarol	 Zonarone	 Zonaroic acid
 Isozonarone	 Yahazunol	 Wiedendiol A
 Wiedendiol B	 Isozonarol(1)	 Siphonodictyal C



Hyatellaquinone



Yahazunol dimethyl ether



20-*O*-Acetyl-21-hydroxy-*ent*-isozonarol

Experimental:

Step: 1

Diels-Alder reaction of 1,3,3-trimethyl-2-vinyl-1-cyclohexene(I)with (E)-1-(2,5-dimethoxyphenyl) but-2-en-1-one(II) at 120 ^{0}C: Formation of (±) (1,2,3,4,4a,5,6,7-octahydro-1,1,4a,6-tetramethylnaphthalen-5-yl)(2,5-dimethoxyphenyl)methanone(III):

A mixture of 1,3,3-trimethyl-2-vinyl-1-cyclohexene (I) (0.01 mol) and (E)-1-(2,5-dimethoxyphenyl) but-2-en-1-one(II) (0.01 mol) in a sealed glass tube was heated at 120^{0}C in an oil bath. The thus obtained colourless oil was purified by Column chromatography to yield(±)(1,2,3,4,4a,5,6,7-octahydro-1,1,4a,6-tetramethylnaphthalen-5-yl)(2,5-dimethoxyphenyl)methanone (III) (Scheme-1)

UV/ VIS: 212.3 (4.21),241.0 (4.04),285.3 (4.03); 1H-NMR ($CDCl_3$):2937(ν C-H),1667 (ν C=O),1621 (ν C=C),1599(ν Ar C=C) 1H-NMR ($CDCl_3$):7.276-7.286 (d, 1H; Ar-H-15),(J = 3 Hz), 7.002-7.043 (dd, 1H; Ar-H-13),(J = 3.3 Hz,9Hz),6.916-6.886 (d, 1H; Ar-H-12),(J = 9 Hz),5.340 -5.364(t, 1H; H-8), (J = 3.6 Hz),3.861(s, 3H;C-11 -OCH3),3.780(s, 3H;C-14 -OCH3),2.453 -2.466 (d, 1H; H-5), (J = 3.6Hz),2.214-2.308 (m, 2H; H-7), 1.575-1.639 (m, 1H; H-6), 1.349-1.433(m, 6H; H-2, 3, 4),1.190(s, 3H; CH_3-4a),1.157 (s, 3H; CH_3-1equi).1.151(s, 3H; CH_3-1axi),0.852-0.876(d, 3H; CH_3-6),(J = 7.2Hz). 13C-NMR ($CDCl_3$):188.5 (C-9), 160.1 (C-11),158.3(C-14), 145.9 (C-10),139.9(C-8a),132.4(C-12),131.0(C-13), 130.7(C-15),114.7(C-8), 55.9(C-11-OCH_3),55.3(C-14-OCH_3), 37.8(C-5),32.8(C-4a), 31.7(C-7),31.2(C-6), 30.3(C-1),29.1 (C-4), 28.1(C-3),25.8(C-2), 23.3(CH_3-C-4a),22.6 (CH_3-$C1_{equi}$),19.0 (CH_3-$C1_{axi}$),18.6(CH_3-C6). MS: m/z 356(M^+,15), 329(25), 284(25), 228(12), 205(72), 190(100), 164(45), 150(72), 135(18), 91(18), 77(25).

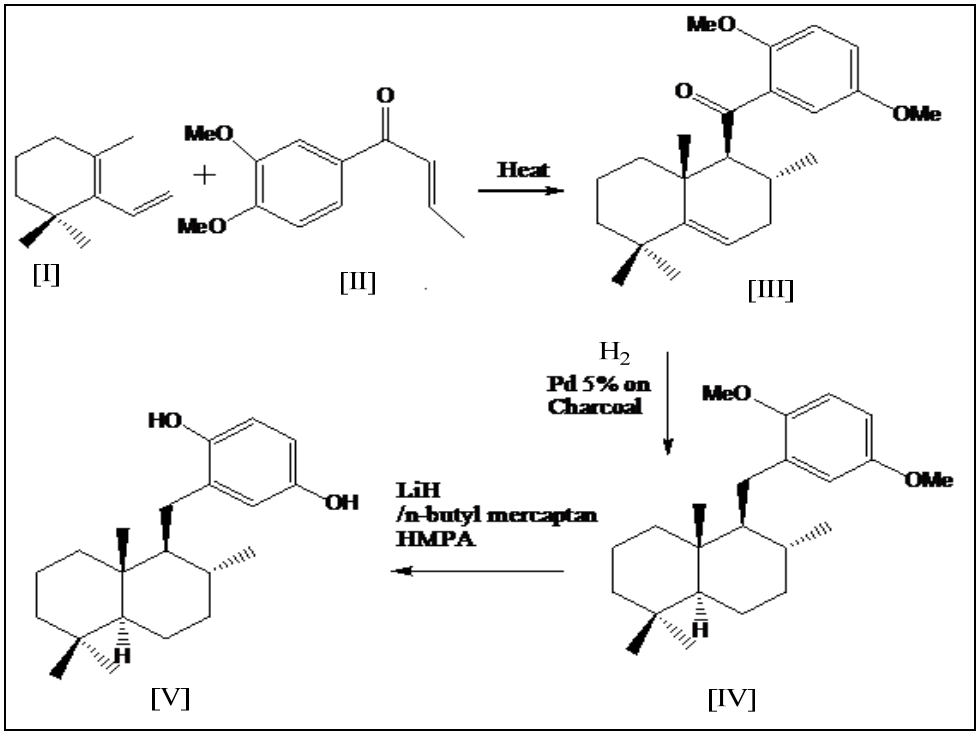
The ^{1}H-NMR data shows a doublet, double doublet and doublet at δ 7.276-7.286, δ 7.002-7.043 and δ 6.916-6.886 respectively for three aromatic protons. A triplet at δ 5.340 -5.364 is assigned to H-8 olefinic proton. A doublet at δ 2.453 -2.466 is assigned to H-5 of structure III and a multiplet at δ 1.575-1.639 is assigned to H-6 of structure III. A doublet appearing at δ 0.852-0.876 ppm for three protons is assigned to CH_3 at C-6. Thus the above pmr data suggests the formation of the cycloadduct having the structure as III.

Step: 2

Reduction of (±) (1,2,3,4,4a,5,6,7-octahydro-1,1,4a,6-tetramethylnaphthalen-5-yl)(2,5-dimethoxyphenyl)methanone (III)by catalytic hydrogenation with Palladium (5%) on charcoal : Formation of (±)-5-(2,5-dimethoxybenzyl)-decahydro-1,1,4a,6-tetramethylnaphthalene(IV):

(±)-(1,2,3,4,4a,5,6,7-octahydro-1,1,4a,6-tetramethylnaphthalen-5-yl)(2,5-dimethoxyphenyl)methanone(III) (0.0712 gm,0.0002mol) in methanol(30 ml)was taken in a hydrogenation bottle and then palladium on charcoal(5%,0.110gm)was added and the reduction was carried out at room temperature for 2 hours at 30 psi pressure. The reaction mixture was filtered and evaporated to give colourless oil of (±)-5-(2,5-dimethoxy benzyl)-decahydro-1,1,4a,6-tetramethylnaphthalene(IV), (0.037gm, yield 54.0 %). Anal. Calcd. For $C_{23}H_{36}O_2$: C, 80.18; H,10.53; Found: C, 79.92; H, 10.88. The IR, ^{1}H-NMR and mass spectral data of this compound was also in agreement with the reported data Thus having successfully synthesized the carbocyclic core present in marine sesqui terpenoids listed in Table-1.All these compounds could be accessed from (±)-(1,2,3,4,4a,5,6,7-octahydro-1,1,4a,6-tetramethylnaphthalen-5- yl)(phenyl) methanone (III) which was synthesized earlier. This required the reduction of carbonyl and C8-C8a double bond, demethylation of 11, 14 dimethoxy groups CrO_3 oxidation and oxidative degradation.

Scheme-1



Step: 3

Demethylation of (±)-5-(2,5-dimethoxy benzyl)-decahydro-1,1,4a,6-tetramethylnaphthalene (IV)by lithium n-butyl marcaptan in hexamethylphosphoric triamide : Formation of (±)-2-((decahydro-1,1,4a,6-tetramethylnaphathalen-5yl)methyl)benzene-1,4-diol(V)(Hydrogenated isozonarol):

Lithium hydride (0.04 gm, 5mmol) was washed with pentane to remove mineral oil and was flushed with dry nitrogen. Hexamethylphosphoric triamide (HMPA, 2 ml) was added and stirred. To this slurry, n-butyl mercaptan (0.451gm, 5 mmol) was added drop wise and stirred until the evolution of hydrogen had stopped (10 rnin).(±)-5-(2,5-dimethoxybenzyl)-decahydro-1,1,4a,6-etramethylnaphthalene(IV) i.e. 6,7 dihydro Isozonarol dimethyl ether (0.069 gm, 0.2 mmol) in HMPA (2 ml) was added and heated at 145 ^{0}C for 26 h. The reaction mixture was cooled to room temperature, diluted with 10% hydrochloric acid solution and extracted with ether (3 X 25 ml). The combined ethereal extracts were washed with water (3 X 10 ml) and saturated sodium chloride solution (25 ml), dried ($MgSO_4$), filtered, and evaporated in vacuo to give 0.075gm of crude product. This material was purified by chromatography on silica gel, eluting with 65% petroleum ether-35% ether. Fractions 6 to 10 gave (±)-2-((decahydro-1,1,4a,6-tetramethylnaphathalen-5yl)methy)benzene-1,4-diol(V),(0.05 gm, yield 86%) as colourless solid ,m.p. 167^{0}C.Anal. Calcd. For $C_{21}H_{32}O_2$: C, 79.70; H,10.10; Found: C, 79.03; H, 9.92. The IR, ^{1}H-NMR and mass spectral data of this compound was also in agreement with the reported data.[14]

CONCLUSIONS

We have accomplished the first highly stereoselective [4 + 2] cycloaddition reaction using crotonophenone as dienophiles and thereby demon-started the potential of this reaction in constructing the bicyclic core of the marine sesquiterpenoids related to Zonarol and isozonarol analogues in a convergent manner. In the synthesis (E)-1-(2, 5-dimethoxyphenyl) but-2-en-1-one(II) has been utilized as dienophile for the first time in Diels-Alder reaction with electron rich diene to generate bicyclic compound of (±) (1,2,3,4,4a,5,6,7-octahydro-1,1,4a,6-tetramethylnaphthalen-5-yl)(2,5-dimethoxyphenyl)methanone (III)(Step-1) which can serve as a key intermediate for bicyclic sesquiterpenoids. The above cycloaddition reaction was found to be regioselective and stereoselective. The yield of cycloadduct was improved by carrying out the cycloaddition reactions in presence of Lewis acid catalyst, $SnCl_4$.The time required for cycloaddition reaction has also been reduced from several days to minutes by carrying out the cycloaddition reactions under microwave irradiation and yield was also enhanced. The cycloadduct (III) obtained from the diene(I)and (E)-1-(2, 5-dimethoxyphenyl) but-2-en-1-one (II)was subjected to catalytic hydrogenation which resulted in the formation of 6,7-dihydro dimethyl ether of isozonarol (IV)(Step-2), which was then converted into 6,7-dihydroisozonarol (V)(Step-3).

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