Pergamon

Tetrahedron, Vol. 53, No. 6, pp. 2185-2188, 1997
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0040-4020/97 $17.00 + 0.00

PII: S0040-4020(96)01120-9

Synthesis of Decalin Synthons of Bioactive Terpenoids : Lewis Acid Catalyzed Diels-Alder Reactions

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Abstract : Diels-Alder reaction of 1,3,3-trimethyl-2-vinylcyclohexene **1** with conjugated ketones **2** - **7** in the presence of Lewis acid leads to *regio-* and *stereo*-selective formation of bicyclic adducts **8** - **13** versatile intermediates to labdanes, abietane and spongian diterpenoids. © 1997, Elsevier Science Ltd. All rights reserved.

Terpenoids having decalin system possess important biological activities[1], which include labdane diterpene forskolin[2], abietane diterpene taxodione[3], royleanone[4], sesquiterpenes polygodial[5] and isozonarol[6]. Mainly because of the important biological activities associated with these, as well as, related drimanes several synthetic studies have been reported[7,8].

Continuing our study on the synthesis of decalin systems of biologically active terpenoids[9], we report herein facile Lewis acid catalyzed regioselective cycloaddition reactions of 1,3,3-trimethyl-2-vinyl cyclohexene **1** with conjugated ketones **2** - **7**.

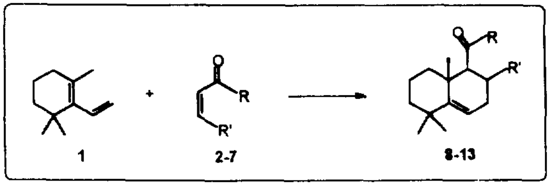
The addition of **1** (1 mmol) to the complex formed between dienophile **2** - **7** (2 mmol) and Lewis acid (0.25 mmol) in dry toluene (10 mL) at 0° C, followed by stirring at the temperature and for the time indicated in Table - **1**, yielded adducts **8** - **13** respectively.

Of paramount importance was the obtention of endo - adducts **8** - **13**, with excellent regioselectivity. The structure and stereochemistry of the adducts were confirmed by pmr Cosy studies. The H-9 proton in compound **9** appears at δ 2.36 as doublet (J = 12 Hz), H-8 proton appears as multiplet, whereas in compound **8**, H-9 proton appears at δ 2.52 as doublet of doublets (J= 2, 13 Hz). The regioselectivity in the formation of compound **13** was indicated by its cosy spectrum which showed crosspeak between C_8-H and isopropyl methyl protons .

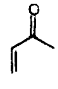
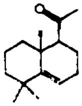
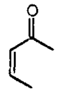
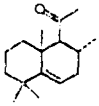
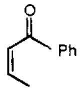
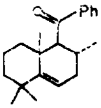
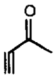
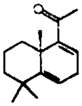
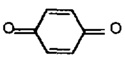
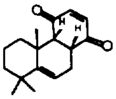
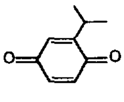
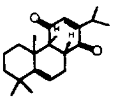
The chemistry described herein is notable by the fact that the adducts **8**, **9**, **11** are potential intermediates for the synthesis of C_{11} oxygenated labdane diterpene analogues. The adducts **10** and **11** also serve as intermediates for the synthesis of mero - sesquiterpene and sponginin diterpenes respectively. The adducts **12** and **13** are of abietane skeleton. Studies on further synthetic utility and biological activities of these adducts will be the subject of our subsequent communications.

TABLE - 1

The Diels - Alder reaction of 1 with dienophiles 2 - 7



1 2-7 8-13

Dienophile	Catalyst	Temperature	Time in hrs	Adduct	Yield %
 2	$AlCl_3$	0°C	3.5	 8	60
 3	$AlCl_3$	0°C	12	 9	40
 4	$AlCl_3$	0°C	24	 10	35
 5	$ZnBr_2$	130°C	4	 11	45
 6	$AlCl_3$	0°C	24	 12	80
 7	$AlCl_3$	0°C	24	 13	50

Acknowledgments : We thank RSIC and TIFR Bombay for high field NMR facility. Authors (SBH and TM) thank Godrej Soaps limited, Bombay and CSIR - Delhi respectively for financial assistance.

EXPERIMENTAL :

Lewis acid catalysed Diels - Alder reactions of diene 1 with dienophiles 2 - 7 :

1) **General Procedure**[10] :

To a solution of appropriate dienophile **2 - 7** (2 mmol) in dry toluene (10 mL) at 0°C under an atmosphere of nitrogen was added aluminium chloride (0.25 mmol) and the mixture was stirred for half an hour. To a dark brownish solution thus formed, a solution of diene **1** (1 mmol) in toluene (5 mL) was added dropwise over 15 min, and stirring was continued at the temperature and for the period mentioned in Table 1. The reaction mixture was quenched with water and extracted with ethyl acetate. The extracts were subjected to the usual work up to give the residue, which was subjected to purification on silica gel chromatography to give adducts **8 - 13** as colourless liquids, except when mentioned otherwise.

Compound 8 : **IR** (neat) : ν_{max} 2940, 1705, 1640, 1460, 1360, 1350, 1220 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) : δ 5.06 (1H, dd, J = 3, 4 Hz, C_6 - C$\underline{H}$), 2.52 (1H, dd, J=2, 13Hz, C_9 -C$\underline{H}$), 2.17 (3H, s, C_9 - COC$\underline{H}_3$), 2.14 (2H, m, C_7 - C$\underline{H}_2$) 1.25-2.00 (m, 8H), 1.22 (3H, s, C_{10} - C$\underline{H}_3$), 1.11, 1.06 (3H, each s, C4 - 2 x C$\underline{H}_3$). **Mass** : m/z 220 (M$^+$). **Anal.** calc. for $C_{15}H_{24}O$: C, 81.76 ; H, 10.98 ; found : C, 81.83 ; H, 11.02 %.

Compound 9 : **IR** (neat) : ν_{max} 2930, 1705, 1630, 1460, 1370, 1210 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) : δ 5.43 (1H, dd, J = 3, 4 Hz, C_6 -C$\underline{H}$), 2.36 (1H, d, J = 12Hz, C_9 - C$\underline{H}$), 2.25 (1H, m, C_7 -C$\underline{H}$), 2.17 (3H, s, C_9 -COC$\underline{H}_3$), 2.14 (1H, m, C_8 -C$\underline{H}$), 1.75 (1H, m, C_7 -C$\underline{H}$), 1.24 - 1.5 (6H, m), 1.22 (3H, s, C_{10} -C$\underline{H}_3$), 1.11, 1.07 (3H, each, s, C_4 -2 x C$\underline{H}_3$), 0.83 (3H, d, J = 7Hz, C_8 -C$\underline{H}_3$). **Mass** : m/z 234 (M$^+$). **Anal.** calc for $C_{16}H_{26}O$: C, 81.99 ; H,11.18 ; found : C, 81.93 ; H, 11.25%.

Compound 10 : **IR** (neat) : ν_{max} 2925, 1700, 1620, 1605, 1360, 1200 cm^{-1} ; **^{1}H NMR** (300 MHz, $CDCl_3$) : δ 7.6 - 7.45 (5H, -Ph), 6.33 (1H, dd, J = 3, 4 Hz, C_6 -C$\underline{H}$), 2.45 (1H, d, J = 12.1Hz, C_9 - C$\underline{H}$), 2.28 (1H, m, C_7 -C$\underline{H}$), 2.17 (3H, s, C_9 -COC$\underline{H}_3$), 2.05 (1H, m, C_8 -C$\underline{H}$), 1.82 (1H,m, C_7 -C$\underline{H}$), 1.2 - 1.4 (6H, m), 1.15 (3H, s, C_{10} -C$\underline{H}_3$), 1.09, 1.06 (3H, each, s, C_4 -2 x C$\underline{H}_3$), 0.9 (3H, d, J = 7Hz, C_8 - C$\underline{H}_3$). **Mass** : m/z 296 (M$^+$). **Anal.** calc for $C_{21}H_{28}O$: C, 85.08 ; H,9.52 ; found : C, 85.02 ; H, 9.59%.

Compound 11 : **IR** (neat) : ν_{max} 2980, 2930, 1680, 1630, 1600, 1430, 1370, 1350 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) : δ 6.1 (1H, t, J = 4 Hz, C_8 - C$\underline{H}$), 5.75 (1H, dd, J = 6, 9 Hz, C_6 - C$\underline{H}$), 2.3 (3H, s, C_9 -COC$\underline{H}_3$), 2.21 - 2.27 (1H, m, C_7 -C$\underline{H}$), 2.12 - 2.17 (1H, m, C_7 - C$\underline{H}$), 1.12 - 1.55 (6H, m), 0.96 (3H, s, C_{10} -C$\underline{H}_3$), 0.89, 0.85 (3H, each, s, C_4 -2 x C$\underline{H}_3$). **Mass** : m/z : 218 (M$^+$). **Anal.** calc for $C_{15}H_{22}O$: C, 82.52 ; H, 10.16 ; found : C, 82.64 ; H, 10.22% .

Compound 12 : **IR** (neat) : ν_{max} 2930, 2870, 1680, 1650, 1600, 1360, 1330, 1260 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) : δ 6.61, 6.47 (1H each, d, J = 10 Hz, C_{11} and C_{12} -C$\underline{H}$), 5.32 (1H, dd, J = 3, 4 Hz, C_6 - C$\underline{H}$) , 3.48 (1H, ddd, J= 5, 6, and 11 Hz, C_8 - C$\underline{H}$), 2.94 (1H, d, J= 5 Hz, C_9 - C$\underline{H}$), 2.4 (1H, m, C_1 - $\underline{H}$ axial), 2.36 (1H, m, C_7 - C$\underline{H}$), 2.15 (1H, m, C_7 - C$\underline{H}$), 1.72 - 1.91 (1H, m), 1.48 - 1.68 (3H, m), 1.10 - 1.16 (1H, m), 1.24 (3H, s, C_{10} - C$\underline{H}_3$), 1.08, 1.09 (3H each, s, C_4-2 x C$\underline{H}_3$). **Mass** : m/z : 258 (M$^+$). **Anal.** calc. for $C_{17}H_{22}O_2$: C, 79.03 ; H, 8.58 ; found ; C, 79.12 ; H, 8.52%.

Compound 13 : **IR** ($CHCl_3$) : ν_{max} 2970, 1670, 1630, 1460, 1390, 1370 cm^{-1} ; **^1H NMR** spectrum (300 MHz, $CDCl_3$) : δ 6.39 (1H, d, J=1.3 Hz, C_{12} - $C\underline{H}$), 5.81 (1H, dd, J=1.2, 6.5 Hz, C_6 - $C\underline{H}$), 3.32 (1H, d, J=8.2 Hz, C_9- $C\underline{H}$), 3.02 (1H, dd, J=2.2, 8.2 Hz, C_8 - $C\underline{H}$), 2.93 (1H, dsep, J=1.3, 6.8 Hz, C_{13} - $C\underline{H}$), 2.71 (1H, m, C_7 - $C\underline{H}$), 1.84 (2H, m), 1.66 (3H, d, J=1.7 Hz, C_{10} - $C\underline{H}_3$), 1.05, 1.01 (3H, each, d, J=6.8 Hz, - CH-(CH_3 $)_2$, 1.16, 0.86 (3H each, s, C_4 - 2 x $C\underline{H}_3$). **Mass** : m/e : 300 (M^+). **Anal.** calc. for $C_{20}H_{28}O_2$: C, 79.96 ; H, 9.39 ; found : C, 79.92 ; H, 9.32 %.

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10. A mixture of diene **1** (1 mmol), dienophile **5** (2 mmol), zinc bromide (0.25 mmol) and toluene (2 mL) were sealed in glass tube and heated at 130°C for 4 hrs to obtain the adduct 11.

(*Received in UK* 3 *October* 1996; *revised* 4 *December* 1996; *accepted* 5 *December* 1996)