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Diels-Alder Reaction of *R*-(–)-Carvone with Isoprene

Tony K. M. Shing,* Ho Y. Lo, and Thomas C. W. Mak†

Department of Chemistry, The Chinese University of Hong Kong, Shatin, Hong Kong, China

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Abstract

Diels-Alder reactions of *R*-(–)-carvone with isoprene using different Lewis acids as catalysts have been studied. The best results were obtained with $EtAlCl_2$ at 25 °C for 48 hours. The yields are quantitative and the d.e. is 86.8%. Regioselective dihydroxylation at the endocyclic double bond of the cycloadduct followed by acetonation gave a crystalline acetonide, the structure and stereochemistry of which were confirmed by an X-ray crystallographic analysis. Hence the stereochemical outcome of the Diels-Alder reaction is now established and the reaction occurred preponderantly in an *anti* orientation with respect to the isopropylene group in *R*-(–)-carvone.

Keywords: cycloadditions; Diels-Alder reactions; terpenes and terpenoids

Carvone, commercially available in both enantiomers, has been a popular chiral starting material in natural product synthesis.[1] In continuation with our endeavor in using carvone as a starting material in making terpenoid natural products,[2] we need to obtain the Diels-Alder cycloadduct **1** of *R*-(–)-carvone and isoprene for elaboration. Such a decalin system containing a stereo-defined angular methyl group would be a valuable synthetic precursor for miscellaneous terpenoid natural products.

Lewis acid catalyzed Diels-Alder reaction of *R*-(–)-carvone with various dienes has been widely studied.[3] However, to the best of our knowledge, no direct proof on the stereochemistry of cycloadduct **1** has been established and perhaps this has limited its application in synthesis. Here, we report an extensive study on the Lewis acid catalyzed Diels-Alder reactions of *R*-(–)-carvone with isoprene. Using different Lewis acids at 25 °C or at 0 °C, Diels-Alder cycloadduct **1** and the minor diastereomer **2** could be obtained with d.e. ranging from 76% to 94.5%. Compounds **1** and **2** were isolated as a mixture of *anti* and *syn* adducts which could not be separated by flash column chromatography on silica gel. The mixture was then diluted to form a 10^{-3} M standard solution with CH_2Cl_2 and the resulting solution was injected into the GC-FID and GC-MS to determine the ratio of the two diastereomers. The results are shown in Table 1.

The use of $AlCl_3$ as catalyst for the Diels-Alder reaction of *R*-(–)-carvone with isoprene at 25 °C was first reported by Fringuelli *et al.*[3b] In our hands, the major problem using $AlCl_3$ as the catalyst at 25 °C was that the polymerization of isoprene and carvone

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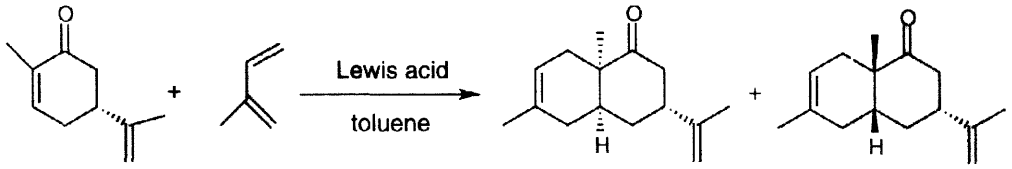
occurred at a similar rate to that of the Diels-Alder reaction. As a result, the yield of the cycloadducts (52%) was not as good as that (80%) reported by Fringuelli *et al.*[3b] and about 33% of the starting carvone could be recovered. Performing the experiments at 0 °C diminished the polymerization problem, however, the percentage of conversion after 2 weeks is still low (52%) and the long reaction time is impractical. Furthermore, $AlCl_3$ is a fuming solid which is rather difficult to handle. $AlCl_3$ forms aggregates that impede stirring during the reaction and decrease the surface area for catalysis. $EtAlCl_2$ and Et_2AlCl were selected to replace $AlCl_3$ because they are both commercially available in n-hexane solutions that obviate the use of a dry box for handling, and they do not form aggregates during the reaction.

Table 1. Lewis acid catalyzed Diels-Alder reactions of *R*-(–)-carvone with isoprene



R-(–)-carvone isoprene **1** **2**

Entry	Lewis acid	Temp (°C)	Reaction time (h)	Yield % (conversion %)	Product ratio (**1** : **2**)[a]	d.e.(%)
1	$AlCl_3$	25	48	52 (67)[b]	9.1 : 1	80.2
2	$AlCl_3$	0	336	91 (52)[c]	9.8 : 1	81.5
3	$EtAlCl_2$	25	48	100 (100)	11.6 : 1	84
4	$EtAlCl_2$	0	408	100 (8.7)	14.1 : 1	86.8
5	Et_2AlCl	25	96	38.7 (30.4)[b]	7.6 : 1	76.7
6	Et_2AlCl	0	408	no reaction	nil	nil
7	$TiCl_4$	25	168	15.5 (15)[b]	9.1 : 1	80.2
8	$TiCl_4$	0	336	98 (3.7)	35.9 : 1	94.5
9	BF_3•OEt_2	25	24	polymerization[b]	nil	nil
10	BF_3•OEt_2	0	24	polymerization[b]	nil	nil
11	$SnCl_4$	25	264	0 (0)[c]	nil	nil
12	$SnCl_4$	0	336	0 (0)[c]	nil	nil

a : determined by GC-FID and GC-MS
b : polymerization of isoprene and carvone
c : polymerization of isoprene

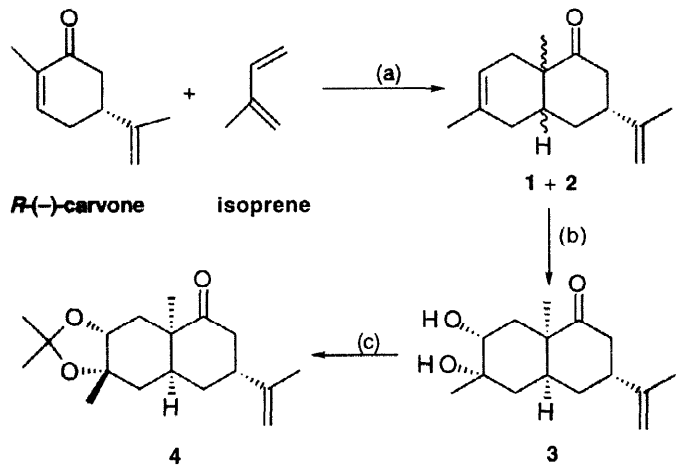
The results of using $EtAlCl_2$ at 25 °C were encouraging. Polymerization did not occur before the completion of the Diels-Alder reaction within 48 hours. The yields were quantitative, and the d.e. of 86.8% was higher than that using $AlCl_3$. Conducting the experiment at 0 °C was unsatisfactory because the rate of the Diels-Alder reaction was very slow, only achieving 8.7% conversion after 17 days.

Et_2AlCl was not an effective catalyst for the Diels-Alder reaction because at 25 °C the rate of the cycloaddition reaction was slow and the problem of polymerization of isoprene

and carvone was serious. No Diels-Alder reaction or polymerization was observed when the experiment was conducted at 0 °C.

Lewis acids other than aluminum species were also studied. $TiCl_4$ was shown to be a poor catalyst for the Diels-Alder reaction at 25 °C but it caused rapid polymerization of isoprene. Performing the reaction at 0 °C alleviated the problem of polymerization, but 3.7% conversion in 2 weeks was too low to be practical. Interestingly, these conditions at 0 °C afforded the cycloadducts with the highest diastereoselectivity (94.5%).

No Diels-Alder reaction was observable using $SnCl_4$ as catalyst at both temperatures and carvone could be recovered quantitatively, apart from the polymerization of isoprene. $BF_3{\cdot}OEt_2$ appeared to promote only polymerization of isoprene and carvone at both temperatures, and no Diels-Alder adducts or starting material could be isolated from the reaction mixture.



Scheme. *Reaction conditions:* (a) $EtAlCl_2$, rt., 48h, 100%; (b) OsO_4(cat.), NMO, rt., 24h, 80% (45% conversion); (c) acetone, TsOH, reflux, 5h, 70% (66% conversion).

The stereochemistry of the major cycloadduct was deduced by Fringuelli *et al.*[3b] to be **1** on the basis of ^{13}C NMR chemical shifts. In order to verify unequivocally the constitution and the stereochemistry of **1**, an X-ray analysis of a crystalline derivative was warranted. To this end, the inseparable cycloadducts from the reaction at 25 °C using $EtAlCl_2$ as catalyst were chosen for further synthetic manipulation. Hence, the mixture of cycloadducts was subjected to a regio- and stereo-selective dihydroxylation for 24 hours, using a catalytic amount of OsO_4[4] (Scheme). The reagent attacked selectively the endocyclic double bond at the less hindered convex face of the *cis*-decalin system to give diol **3** (85% yield) that was confirmed to be enantiopure by ^{13}C NMR spectroscopy. Isopropylidenation of the diol **3** with acidic acetone gave colorless crystalline acetonide **4** in 70% yield. The structure and the absolute configuration of compound **4** was unambiguously confirmed as illustrated by an X-ray crystallographic analysis (Figure 1). Consequently, it is now established that the Diels-Alder reaction occurred preponderantly in an *anti* orientation with respect to the isopropylene group in *R*-(–)-carvone.

In summary, $EtAlCl_2$ was demonstrated to be an excellent catalyst for the Diels-Alder reaction of *R*-(−)-carvone with isoprene at 25 °C. The major cycloadduct of the reaction is the *anti*-addition product with respect to the isopropylene group in *R*-(−)-carvone and the newly created stereocenters in **1** were confirmed to be (5*S*,10*R*) by an X-ray crystallographic analysis. In general, the undesirable polymerization reaction was alleviated at 0 °C and the yields and the d.e.s of the Diels-Alder reaction were improved. The only shortcoming encountered at 0 °C was the slow rate of Diels-Alder reaction.

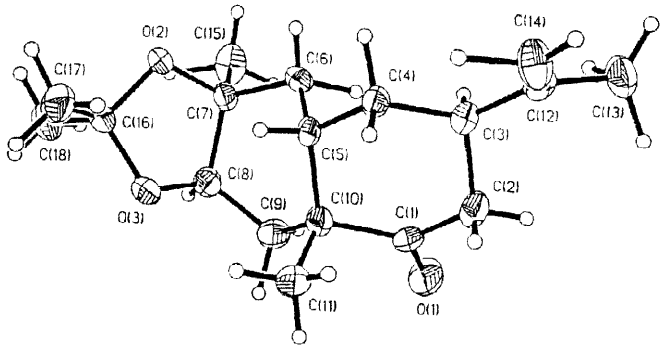


Figure 1 Perspective view of the molecular structure of of compound **4**. The thermal ellipsoids are drawn at the 50% probability level.

Experimental Section

General. IR spectra were recorded on a FT-IR spectrophotometer as thin films on potassium bromide discs. Optical rotations were obtained at 589 nm. GC-FID studies were performed on a gas chromatograph with fused silica capillaries column, injector temperature (220 °C), detector temperature (250 °C) and oven temperature raised from 80 °C to 180 °C in a rate of 5°C per min, GC-MS studies were performed on a GC with fused silica capillaries column and a GC/MS system with ion trap detector (ITD), injector temperature (250 °C), transfer line temperature (250 °C), oven temperature raised from 80 °C to 180 °C in a rate of 5 °C per min, EIMS by 70 eV electron beam. NMR spectra were measured at 300.13 MHz (^1H) or at 75.47 MHz (^{13}C), in $CDCl_3$ solutions, unless stated otherwise. All chemical shifts were recorded in ppm relative to tetramethylsilane ($\delta = 0.0$). Spin-spin coupling constants in Hz (*J*) were measured directly from the spectra. Carbon and hydrogen elemental analyses were carried out by MEDAC Ltd, Department of Chemistry, Brunel University, Uxbridge, U.K. All reactions were monitored by analytical thin-layer chromatography (TLC) using E. Merck precoated with silica gel $60F_{254}$ (E. Merck) and compounds were visualized with a spray of 5% w/v dodecamolybdo-phosphoric acid in ethanol and subsequent heating. E. Merck silica gel 60 (230–400 mesh) was used for flash chromatography. All solvents were reagent grade unless otherwise stated. Toluene was dried by sodium and distilled from sodium under nitrogen. Other reagents were purchased from commercial suppliers and were used without purification.

Typical Procedure for Diels-Alder Reaction. $EtAlCl_2$ in 1M n-hexane solution (1 mL, 1.0 mmol) was added to a solution of *R*-(−)-carvone (751 mg, 5.0 mmol) in 10 mL of

dry toluene. The solution was stirred at rt under nitrogen for 20 min for complexation. Isoprene (1.36 mL, 15.0 mmol) was added and the solution was stirred at rt under nitrogen for 48 h. Ice water (10 mL) was added to the solution and the mixture was extracted with Et_2O. The combined organic layer was dried over $MgSO_4$ and filtered. The solvent was removed from the filtrate under reduced pressure. Flash chromatography (hexane:EtOAc = 10:1) of the residue led to a mixture of octalone **1** and **2** (1.09 g) as a colorless oil in quantitative yield; *Rf* 0.43 (hexane:Et_2O = 8:1); $[\alpha]_D^{20}$ +17.5 (*c* 0.6, $CHCl_3$); GC-FID (retention time for **1**, 24.3 min; **2**, 23.9 min); GC-MS (retention time for **1**, 1419 s; **2**, 1407 s). MS m/z 218 (M^+) for **1** and **2**; ^1H NMR δ 1.15 (s, 3H), 1.62 (s, 3H), 1.73 (s, 3H), 4.69 (br s, 1H), 4.80 (br s, 1H), 5.28 (br s, 1H); ^{13}C NMR δ 21.9, 23.5, 24.2, 30.8, 32.8, 33.4, 38.1, 41.6, 41.9, 47.5, 111.7, 118.5, 131.8, 147.9, 215.6; IR (KBr) 2926, 1703, 1637, 896 cm^{-1}; EIMS *m/z* 218 (M^+, 16.9), 175 (39), 157 (49), 91 (1), 67 (94); Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.38; H, 9.93.

Diol 3. A solution of a mixture of dienes **1** and **2** (200 mg, 0.92 mmol), NMO·H_2O (435 mg, 3.2 mmol), and a catalytic amount of OsO_4 (10 mg) in 10 mL aqueous acetone (5:1, acetone:H_2O) was stirred at rt for 24 h. The reaction was quenched with saturated $Na_2S_2O_3$ (5 mL) and then extracted with EtOAc (20 mL × 3). The combined organic layer was filtered through a short pad of silica gel and eluted with EtOAc. Concentration of the filtrate followed by flash chromatography (hexane:EtOAc = 1:1) afforded firstly the starting dienes (110 mg, 45% conversion) and then the diol **3** as a colorless oil (88.4 mg, 85%); *Rf* 0.3 (hexane:EtOAc = 1:1); $[\alpha]_D^{20}$ +61.2 (*c* 0.5, $CHCl_3$); ^1H NMR δ 1.22 (s, 3H), 1.27 (s, 3H), 1.74 (s, 3H), 1.87 (br s, 1H), 2.00 (br s, 1H), 3.57 (d, *J* = 11.4, 1H), 4.75 (s, 1H), 4.77 (s, 1H); ^{13}C NMR δ 20.4, 26.7, 27.2, 30.3, 37.8, 38.6, 40.1, 41.1, 42.6, 49.4, 71.1, 71.4, 109.8, 147.3, 215.0; IR (KBr) 3417, 2907, 1694, 1637, 1067 cm^{-1}; EIMS *m/z* 252 (M^+, 1.03), 253 (M^++ 1, 1.67), 235 (11), 191 (7.9), 165 (1); Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.23; H, 9.87.

Acetonide 4. A solution of the diol **3** (500 mg, 1.98 mmol) and *p*-toluenesulfonic acid monohydrate (5 mg) in acetone (10 mL) was heated under reflux for 5 h. Saturated $NaHCO_3$ solution (5 mL) was added and the mixture was extracted with Et_2O (20 mL × 3). The combined organic layer was filtered through a short pad of silica gel and eluted with Et_2O. Concentration of the filtrate followed by flash chromatography (hexane:EtOAc = 10:1) afforded firstly the acetonide **4** as a white solid (272 mg, 70%) and then the starting diol **3** (165 mg, 66% conversion); mp 67.1–67.3 °C; *Rf* 0.25 (hexane:EtOAc = 10:1); $[\alpha]_D^{20}$ –41.8 (*c* 3.0, $CHCl_3$); ^1H NMR δ 1.27 (s, 3H), 1.34 (s, 3H), 1.36 (s, 3H), 1.45 (s, 3H), 1.71 (s, 3H), 4.11 (t, *J* = 3 Hz, 1H), 4.70 (s, 1H), 4.75 (s, 1H); ^{13}C NMR δ 20.4, 25.4, 27.0, 27.1, 27.9, 30.7, 32.9, 36.3, 40.6, 41.1, 43.1, 46.7, 79.2, 80.1, 106.9, 109.6, 147.5, 216.5; IR (KBr) 2971, 1698, 1647,1073, 1192 cm^{-1}; EIMS *m/z* 293 (M^++ 1, 3.47) 277 (80), 235 (1), 217 (40); Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.92 H, 9.78.

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References and notes

* To whom correspondence should be addressed. Fax: (852)-2603 5057. E-mail: tonyshing@cuhk.edu.hk

† Enquiries concerning the X-ray analysis should be directed to TCWM.

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