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STEREOSPECIFIC ANNULATION AND SEQUENTIAL RING-OPENING OF (*R*)-CARVONE: FORMATION OF A NOVEL TRICYCLIC DIONE

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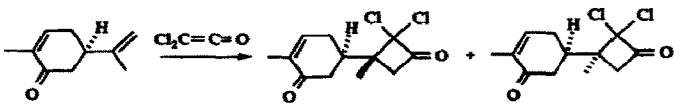
Abstract: *Free radical annulation followed by trimethylsilyl iodide-promoted ring-opening of (R)-carvone-dichloroketene adducts leads to an unusual carbon skeleton rearrangement. The carbonyl group of carvone enhances the reactivity of the radical cyclization, changes the ring-opening pathway and leads to the formation of a new tricyclic dione product.*

We recently discovered a reaction sequence that interpolates the elements of ketene into a 1,5-diene and forms a new seven-membered ring ketone (eq 1).[1,2] This method consists of

(1)

three steps: 2 + 2 cycloaddition of dichloroketene,[3] free radical 1,5-cyclization,[4] and TMSI-ZnI_2 ring-opening.[5]

We report here a new variation of this reaction sequence starting with (*R*)-carvone. The diastereomeric adducts ***(R,R)*-1** and ***(R,S)*-1** are obtained in good yield by treatment of readily available (*R*)-carvone with dichloroketone (eq 2). The ***(R,R)*-1** isomer is isolated from the

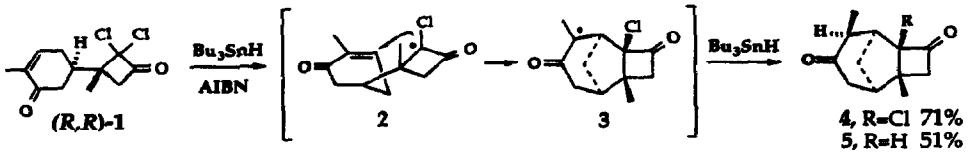


(R)-carvone **(R,R)-1 69%** **(R,S)-1 12%**

(2)

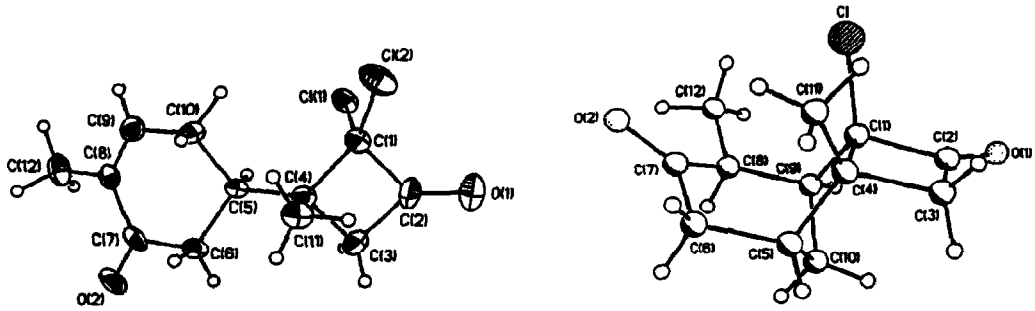
mixture by crystallization (mp 129-130 °C). The diastereomeric dichlorocyclobutanones ***(R,R)*-1** and ***(R,S)*-1** undergo annulation in stereospecific fashion. Thus, treatment of ***R,R*-1** with tri-*n*-butyltin hydride leads to an α-acyl radical **2** (Scheme 1). Cycloaddition of the radical center to the

Scheme 1



enone double bond then yields a second, stable, α-acyl radical 3. Selective hydrogen transfer from the less hindered face of radical 3 gives the *anti*-annulation product 4 as a single diastereomer (Scheme 1). If excess Bu_3SnH is employed, the second chlorine can be reduced generating 5. The structures of *(R,R)*-1 and 4 have been established by X -ray crystal structure analysis (Figure 1).

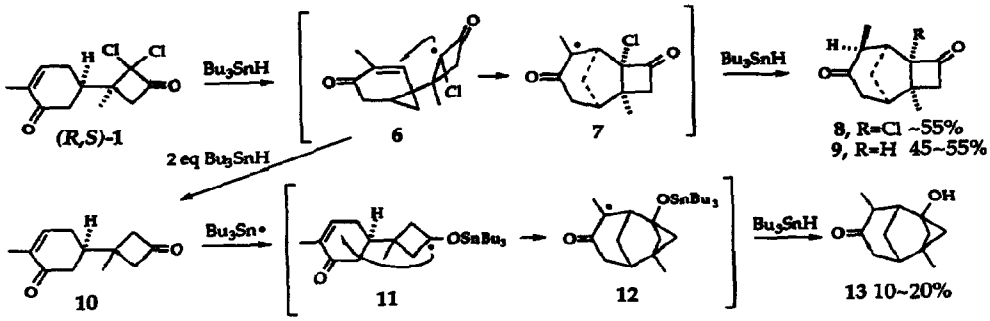
Figure 1. X-Ray Structures of *(R,R)*-1 and 4



R,R-1 4

Radical cyclization of *(R,S)*-1 proceeds through a less sterically favorable transition state (Scheme 2), with the four-membered ring folding on top of the six-membered ring, leading to formation of *syn*-annulation product 8, a diastereomer of 4. There is competition with the

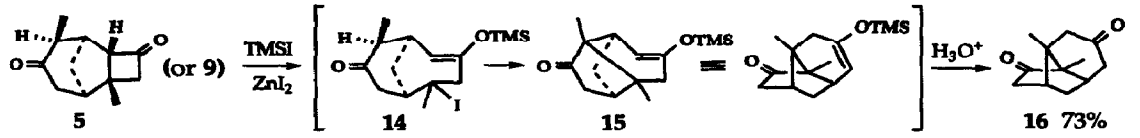
Scheme 2



radical cycloaddition (6 → 7). Thus, reduction of the carbon-chlorine bonds and addition of tributyltin radical to the cyclobutanone carbonyl (6 → 10 → 11) yields the O-stannyl ketyl 11[6] (Scheme 2). 1,6-Cyclization of 11 gives alcohol 13[7] as a minor product.

Treatment of 5 or 9 with TMSI leads, by internal alkylation, to the unusual tricyclic dione 16 (Scheme 3). Thus, when the cyclobutanone adduct 5 (or 9) is treated with TMSI-ZnI_2, the

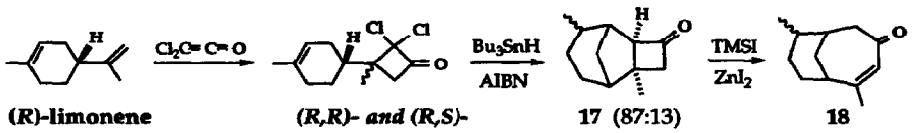
Scheme 3



expected ring opening will produce the reactive iodide 14. Enolization and internal alkylation of 14, yielding 15, may be assisted by trans-silylation. Hydrolytic workup then leads to the tricyclic dione 16.[8] The tricyclic sesquiterpenes sativene, copacamphene, and sinularene possess this kind of ring skeleton.[9]

We have also studied the analogous reaction of (*R*)-limonene (Scheme 4).[1] Dichloroketene

Scheme 4



addition gives a diastereomeric mixture, which cannot be separated by chromatography. Tri-*n*-butyltin hydride treatment of the mixture gives cyclization product 17 as a mixture of two diastereomers, together with a minor amount of direct reduction product. As expected, treatment of 17 with TMSI-ZnI_2 yielded ring-opening product 18.

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(7) Data for **13**: ^{1}H NMR ($CDCl_3$) δ 0.80 (d, *J*=7.0 Hz, 3 H), 1.16 (s, 3 H), 1.36-1.76, (m, 4 H), 1.92 (m, 3 H), 2.08 (m, 2 H), 2.27 (d, *J*=18.7 Hz, 1 H), 2.43 (d, *J*=17.8 Hz, 1 H), 3.80 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.3 (q, *J*=126 Hz), 29.2 (q, *J*=127 Hz), 36.7 (s), 39.2 (t, *J*=130 Hz), 40.5 (t, *J*=130 Hz), 42.3 (d, *J*=138 Hz), 42.7 (d, *J*=134 Hz), 43.6 (t, *J*=126 Hz), 45.4 (d, *J*=130 Hz), 48.4 (t, *J*=133 Hz), 79.3 (s), 215.9 (s); IR (neat) 3505 (br, OH), 1716 (s, C=O) cm^{-1}; MS *m/e* (rel. intensity) 194 (20, M$^+$), 176 (8), 166 (3), 151 (7), 123 (29), 109 (100) 96 (63); HRMS calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1286.

(8) Data for **16**: mp 128-131 °C; ^{1}H NMR ($CDCl_3$) δ 0.91 (s, 3 H), 1.07 (s, 3 H), 1.48-1.82 (m, 2 H), 1.93 (d, *J*=18.1, 1 H), 2.01 (m, 1 H), 2.23 (d, *J*=19.4, 1 H), 2.30-2.56 (5 H); ^{13}C NMR ($CDCl_3$) δ 8.1 (q, *J*=126 Hz), 19.0 (q, *J*=129 Hz), 34.9 (t, *J*=134 Hz), 35.7 (d, *J*=142 Hz), 43.3 (d, *J*=129 Hz), 43.7 (t, *J*=132 Hz), 44.4 (t, *J*=130 Hz), 48.2 (t, *J*=129 Hz), 49.0 (s), 57.5 (s), 210.0 (s), 218.4 (s); IR (neat) 1740 (s, C=O), 1717 (m, C=O) cm^{-1}; MS *m/e* (rel. intensity) 192 (57, M$^+$), 177 (2), 164 (3), 150 (32), 135 (16), 123 (32), 107 (100), 93 (64), 77 (43), 67 (39); HRMS calcd for $C_{12}H_{16}O_2$ 192.1105, found 192.1134.

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