



# Two homoallyl/cyclopropylalkyl rearrangements accompanying a Wolff–Kishner type reduction

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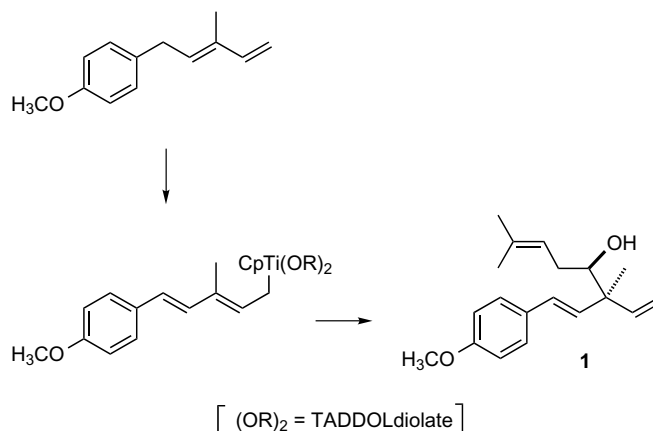
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**Abstract**—Conceived as a model study for the enantioselective synthesis of the natural product (*S*)-bakuchiol, the deoxygenation of a recently described trishomoallyl alcohol was attempted using the Kabalka modification of the Wolff–Kishner method after prior oxidation of the alcohol to the ketone. However, an unprecedented succession of homoallyl/cyclopropyl ring closure and ring opening altered the carbon skeleton profoundly. The crucial intermediates are assumed to be radicals although carbanions cannot yet be definitely ruled out. © 2001 Elsevier Science Ltd. All rights reserved.

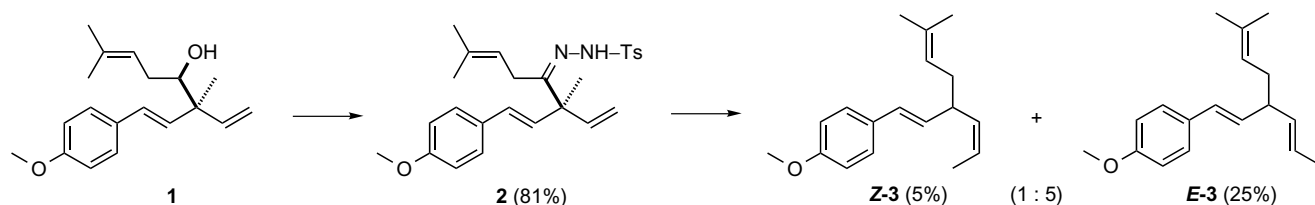
(*E*)-1-(4-Anisyl)-3,7-dimethyl-3-vinyl-1,7-octadien-4-ol (**1**)<sup>1</sup> can be enantio- and diastereoselectively prepared in a very simple way. It suffices to treat 5-(4-anisyl)-3-methyl-1,3-pentadiene consecutively with the butyllithium/potassium *tert*-butoxide superbases<sup>2</sup>, the Duthaler–Hafner complex<sup>3</sup> and 4-methyl-3-pentenal (Scheme 1)<sup>4,5</sup>.

In an attempt to convert it into the natural phenol (*S*)-bakuchiol,<sup>6–11</sup> a biocondensation product<sup>12</sup> of tyrosine and geranyl pyrophosphate, we oxidized the alcohol to the corresponding ketone<sup>13</sup> which was then submitted to the Kabalka modification<sup>15,16</sup> of Caglioti's variation<sup>17–19</sup> of the Wolff–Kishner method<sup>20,21</sup>. Upon treatment of the tosylhydrazone **2**<sup>22</sup> (Ts = *p*-toluenesulfonyl) with catechylborane, 1-(4-anisyl)-6-methyl-3-(1-methyl-1-propenyl)-1,5-heptadiene (**3**)<sup>23</sup> was isolated as the sole volatile product in 30% yield (Scheme 2). According to <sup>1</sup>H NMR and gas chromatography it was a 1:5 (*Z*/*E*)-1' mixture, the side chain (*E*)-configuration of the major component being clearly established by <sup>1</sup>H,<sup>1</sup>H HOESY.



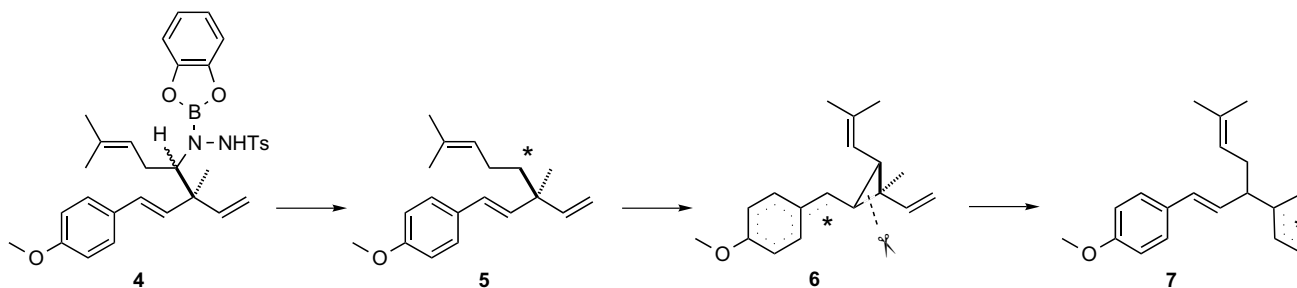
**Scheme 1.** The regioselective and enantioselective  $\alpha$ -hydroxy-alkylation of a chiral 2,4-pentadienyltitanium intermediate.

The reorganization of the backbone structure doubtlessly involves a homoallyl/cyclopropylalkyl rearrangement. The transient intermediate **5** generated by



**Scheme 2.** The reductive rearrangement of the *N*-(*p*-toluenesulfonyl)hydrazone **2**.

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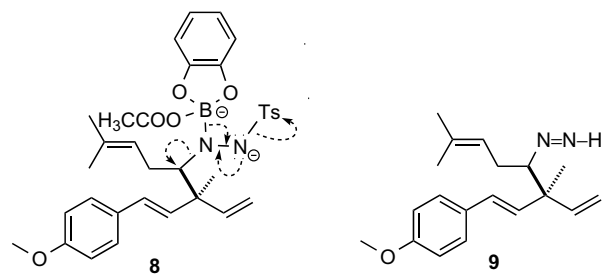


**Scheme 3.** Dediazotation triggering a ring closure/ring opening process.

the dediazotation of the catechylborane-tosylhydrazone adduct **4** immediately undergoes a sequence of rapid ring-closure and ring-opening to give rise to the benzylic and allylic species **5** and **7**, respectively (Scheme 3). The latter one eventually forms the final product, a 1:5 (*Z/E*) mixture of the hydrocarbon **3**.

The asterisk in formulas **5–7** stands either for an unpaired electron or a doublet which confers a negative charge to the atom where it is located. The symbol calls attention to a mechanistic dilemma: it is presently not possible to devise a clear-cut test for the radical or anionic nature of the observed rearrangement. The energetic differences between these mechanistic options should be too small to be conclusive, since the resonance stabilization of both a *p*-methoxybenzyl radical or anion and of both a prenyl-type radical or anion should approximate 20 kcal/mol. Thus, in either case, the cyclization of the first intermediate (**5**) and the ring-opening of the second (**6**) are exothermic, the anionic cyclization strongly ( $\Delta H_f^\circ \approx -20$  kcal/mol) and the three other potential steps moderately ( $\Delta H_f^\circ \approx -5$  kcal/mol). The carbanion route of the ordinary Wolff–Kishner reduction is well established.<sup>24–26</sup> To set free the same anion under Kabalka conditions, would require an unprecedented, though Hofmann–Curtius–Lossen related migration mechanism (characterized by the transition state **8**, Scheme 4). However, if the alkyldiazene **9** exists as a transient species as supposed in similar cases<sup>27</sup>, it would be a plausible precursor to the radical **5**. Even aryldiazenes tend to generate aryl radicals rather than arenide ions.<sup>28–30</sup>

The fact, that the hydrocarbon **3** is obtained only in poor yield and is accompanied by a considerable



**Scheme 4.** The two key intermediates, **8** and **9**, preceding carbanion or radical formation, respectively.

amount of unvolatile material, may be taken as evidence for the radical hypothesis.

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- 1-(4-Methoxyphenyl)-3,7-dimethyl-3-vinyl-1,6-octadien-4-one: The alcohol **1** (8.6 g, 30 mmol) was added to a solution of 1,1,1-triacetyloxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one<sup>14</sup> (14 g, 33 mmol) in dichloromethane (0.10 L). After 45 min at 25°C, the mixture was absorbed on silica gel and the product eluted with a 1:4 (v/v) mixture of diethyl ether and hexanes; 7.8 g (91%); mp –35 to –31°C; bp 134–135°C/0.1 mmHg;  $n_D^{20}$  1.5993. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.33 (2H, dt, *J*=8.7, 2.5),

- 6.87 (2H, dt,  $J=8.7, 2.5$ ), 6.41 (1H, d,  $J=16.2$ ), 6.27 (1H, d,  $J=16.2$ ), 6.17 (1H, dd,  $J=17.5, 10.6$ ), 5.28 (1H, t,  $J=6.8$ ), 5.27 (1H, d,  $J=10.6$ ), 5.21 (1H, d,  $J=17.5$ ), 3.82 (3H, s), 3.26 (2H, d,  $J=6.8$ ), 1.73 (3H, s), 1.58 (3H, s), 1.43 (3H, s).  $C_{19}H_{24}O_2$  (284.40): calcd C 80.24, H 8.50; found C 79.98, H 8.13%.
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22. *1-(4-Methoxyphenyl)-3,7-dimethyl-3-vinyl-1,6-octadien-4-one p-toluenesulfonylhydrazide (2)*: 4-Methoxybenzenesulfonic acid hydrazide (*p*-toluenesulfohydrazide; 4.7 g, 25 mmol) was added to a solution of the ketone (7.1 g, 25 mmol) described in the preceding paragraph in ethanol (10 mL) and the suspension was stirred for 15 h at +25°C. The product was isolated by chromatography on silica gel using a 2:3 (v/v) mixture of diethyl ether and hexanes as the eluent; mp -16 to -14°C; 10.1 g (89%).  $^1H$  NMR ( $CDCl_3$ , 400 MHz):  $\delta$  7.80 (2H, dt,  $J=8.3, 1.9$ ), 7.67 (1H, s), 7.27 (2H, dt,  $J=8.3, 1.9$ ), 7.26 (2H, dt,  $J=8.7, 2.4$ ), 6.86 (2H, dt,  $J=8.7, 2.4$ ), 6.18 (1H, d,  $J=16.2$ ), 6.09 (1H, d,  $J=16.2$ ), 5.94 (1H, dd,  $J=17.6, 10.6$ ), 5.15 (1H, dd,  $J=10.6, 1.0$ ), 5.02 (1H, dd,  $J=17.6, 1.0$ ), 4.59 (1H, t,  $J=6.6$ ), 3.82 (3H, s), 2.86 (2H, d,  $J=6.6$ ), 2.42 (3H, s), 1.73 (3H, s), 1.70 (3H, s), 1.33 (3H, s).  $C_{24}H_{32}N_2O_3S$  (452.62): calcd C 69.00, H 7.12; found C 68.89, H 7.17%.
23. *(1E,5E)-1-(4-Methoxyphenyl)-6-methyl-3-(1-methyl-1-propenyl)-1,5-heptadiene (3)*: 1,3,2-Benzodioxaborole ('catecholborane'; 1.1 mL, 1.2 g, 10 mmol) was added dropwise to a solution of hydrazone **2** (4.5 g, 10 mmol) in dichloromethane (50 mL) cooled to 0°C. Monitoring the reaction by NMR revealed the instantaneous formation of the adduct in a 1:1 diastereomeric ratio. The mixture was treated with methanol (5.0 mL) and tetrabutylammonium acetate (9.0 g, 30 mmol). After 4 h at +25°C, chromatography on silica gel (eluent: diethyl ether and hexanes in a 1:4 ratio) followed by distillation afforded a colorless liquid; bp 128–130°C/0.2 mmHg;  $n_D^{20}$  1.5390; 0.81 g (30%).  $^1H$  NMR ( $CDCl_3$ , 400 MHz):  $\delta$  7.29 (2H, dt,  $J=8.8, 2.5$ ), 6.84 (2H, dt,  $J=8.8, 2.5$ ), 6.29 (1H, d,  $J=15.9$ ), 6.03 (1H, dd,  $J=15.9, 7.6$ ), 5.34 (1H, q,  $J=6.6$ ), 5.10 (1H, t,  $J=6.9$ ), 3.81 (3H, s), 2.77 (1H, q,  $J=7.5$ ), 2.2 (2H, m), 1.69 (3H, s), 1.63 (3H, s), 1.61 (3H, d,  $J=6.6$ ), 1.60 (3H, s).  $C_{19}H_{26}O$  (270.41): calcd C 84.39, H 9.69; found C 84.49, H 9.62%.
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