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## Enantioselective Synthesis of Highly Functionalised Cyclohexanones Starting from R-(-)-Carvone

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Abstract: Copper (1) catalysed conjugate addition of methylmagnesium iodide to R-(-)-carvone and trapping the enolate as its trimethylsilyl enol ether, followed by a trityl perchlorate (TrClO4) catalysed Mukaiyama-aldol reaction, is an efficient method for the preparation of highly functionalised cyclohexanones which can be used as starting compounds in the total syntheses of enantiomerically pure clerodanes. © 1998 Elsevier Science Ltd. All rights reserved.

Copper (I) catalysed conjugate addition of methylmagnesium iodide to enones leads to enolates that can be captured as their silyl enol ethers and a catalysed Mukaiyama-aldol reaction then allows the clean introduction of a second substituent. When these two reactions are applied to one of the enantiomers of carvone, highly functionalised chiral cyclohexanones are obtained that are excellent starting compounds for the total synthesis of enantiomerically pure natural products<sup>1,2</sup>. Carvone is especially useful in such total syntheses because the isopropenyl group determines the stereochemistry of the 1,4-conjugate addition and the stereochemical outcome of the Mukaiyama-aldol reaction. In this way the configurations at C2 and C3 in the carvone intermediates are fixed, and the isopropenyl group can then be removed without further consequences for the stereochemical integrity of the compound. This isopropenyl group can be transformed by ozonolysis into a hydroxyl group<sup>3</sup>, an acetate<sup>3</sup>, a double bond<sup>4</sup> or a carbonyl group<sup>5</sup> for further functionalisation of the cyclohexane ring.

It seemed to us that also the problem of the total synthesis of clerodanes could be attacked using this strategy. Not only the highly functionalised ring B of clerodanes can be constructed in a few reaction steps (see scheme 1) but starting from R-(-)- or S-(+)-carvone both types of natural occurring clerodanes can be obtained without the necessity of separation of enantiomers. For this reason several examples of copper (I) catalysed conjugate addition of methylmagnesium iodide, followed by trapping of the enolate as its trimethylsilyl enol ether and the subsequent introduction of a functionalised sidechain via a Lewis acid catalysed Mukaiyama-aldol reaction, were investigated.

The efficiency of trityl perchlorate (TrClO<sub>4</sub>) or trityl hexachloroantimonate as catalyst for the Mukaiyama aldol reaction has been published in the literature,<sup>6-8</sup> but to our knowledge this Mukaiyama addition never has been used for the preparation of highly substituted cyclohexanones. In Table 1 several functional groups are mentioned that were introduced using the same standard procedure with TrClO<sub>4</sub> as a Lewis acid catalyst.





(a) i, MeMgI, CuBr·Me<sub>2</sub>S, ether, THF, HMPA, TMSiCl, ii, Et<sub>3</sub>N; (b) i, CH<sub>2</sub>Cl<sub>2</sub>, TrClO<sub>4</sub>, -78 $^{\circ}$ C, ii, aqueous NaHCO<sub>3</sub>.

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Entry	Reagent	Products/R	Reaction Time	Isolated Yield (threo/erythro)
1	CH <sub>2</sub> O	TMSiOCH <sub>2</sub> 3	20 min	71% a
2			20 min	80%
3	MeO MeO	MeO MeO 5	72 hr	40%
4		CSS 6	20 min	90% 96% <sup>b</sup>
5		7	20 min	80% (2:1)
6	PhS	PhS <b>8</b>	4 hr	40% (2:1) <sup>c</sup> 86% <sup>d</sup>
7	O O OMe	$ \begin{array}{c}                                     $	20 hr	73% (two diastereoisomers)

(a) quenched with  $Et_3N$ ; (b)  $ZnCl_2$ ,  $CH_2Cl_2$ ,  $0^{\circ}C$ ; (c) RT; (d) i,  $CH_2Cl_2$ ,  $SnCl_4$ ,  $-78^{\circ}C$ , ii, silica,  $Et_3N$ .

In a standard procedure 4.2 mmol of silyl enol ether 2 and 1.1 eq. of the acetal were dissolved in 20 ml of  $CH_2Cl_2$  and cooled to -78°C. Then 0.13-0.42 mmol TrClO<sub>4</sub> dissolved in  $CH_2Cl_2$  was added dropwise. After the reaction was finished, which was checked by TLC and GC, the reaction mixture was quenched with aqueous NaHCO<sub>3</sub> solution or in case of formaldehyde, with Et<sub>3</sub>N. Extraction with diethyl ether and flash column chromatography using silica gel with petroleum ether and ethyl acetate as eluent, gave the pure reaction products. Results and yields are mentioned in Table 1. NMR, IR and mass spectral data are in accordance with the proposed structures.

In general the products were obtained in good yield but adaptations of the general procedure proved to be necessary to get high yields. In entry 1 the product was captured as its silyl ether by adding triethylamine to the cold solution. The reaction in entry 5 was surprisingly fast probably due to the relatively high stability of the intermediate carbocation. For entry 5 and 6 mixtures of threo and erythro isomers were found. For entry 3 and 7 the reactions were rather slow probably due to steric hindrance. After two days at -78°C only 10% of compound 8 was formed in entry 6; by raising the temperature to room temperature the conversion was complete after 4 hours. In entry 7 racemic 2-methoxy-hexahydro-furo[2,3-b]furan was used, so four diastereoisomers are possible. To our surprise only two are formed in a one to one mixture. Compound  $9b^9$  can be completely separated from its diastereoisomer by crystallization from diisopropyl ether. Compound  $9a^{10}$  is obtained as an oil after evaporation of the diisopropyl ether. The structure of 9b was determined by X-ray crystallography<sup>11</sup>.

The compounds **3**, **4**, **5**, **6** and **8** possess suitable sidechains for further elaboration to those occuring in several natural products. Compound **9a** is especially suitable for further conversion into dihydroclerodin **4**, after removal of the isopropenyl group and a series of transformations as depicted in scheme 2.

Ozonolysis of **9a** followed by addition of  $Cu(OAc)_2$  and  $FeSO_4$ <sup>4</sup> provided enone **10**<sup>12</sup>. Addition of thiophenol to **10** followed by chlorination with chloreal<sup>13</sup> and concomitant dehydrochlorination<sup>14,15</sup> gave compound **11** in very good yield. Reduction and hydrolysis of **11** gave rise to enone **12**<sup>16</sup>(Scheme 2). For the annulation of ring A of clerodanes several opportunities are now available, such as 1,2-addition to the carbonyl in **9a**, **10** or **11** or 1,4-conjugate addition in **12**.

## Scheme 2



(a) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, MeOH, Cu(OAc)<sub>2</sub>, FeSO<sub>4</sub>, 60%; (b) PhSH, Et<sub>3</sub>N, pentane, 0°C, 87%; (c) Chloreal, benzene, ether, 0°C, 92%; (d) LiAlH<sub>4</sub>, ether, 1 h; (e) PTSA, CH<sub>3</sub>Cl, 60%

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- (9) **9b** <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200MHz)  $\delta$  0.89 (s, 3H), 0.89 (d, J=7.0Hz, 3H), 1.52 (m, 1H), 1.69 (bs, 3H), 1.69 (m, 2H), 2.16-1.92 (m, 4H), 2.33 (m, 1H), 2.55 (m, 1H), 2.71 (d, J= 12.6Hz, 1H), 2.82 (m, 1H), 3.87 (m, 2H), 4.63 (dd, J= 9.6Hz, 6.2Hz, 1H), 4.75 (m, 2H), 5.66 (d, J=5.0Hz, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 50MHz)  $\delta$  13.4 (q), 16.7 (q), 20.4 (q), 32.6 (t), 33.0 (t), 33.1 (t), 36.8 (d), 40.4 (d), 41.9 (d), 43.3 (t), 54.3 (s), 68.0 (t), 82.6 (t), 109.0 (d), 109.4 (t), 147.4 (s), 213.4 (s)
- (10) 9a <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200MHz) δ 0.82 (s, 3H), 0.84 (d, J=5.0Hz, 3H), 1.45 (ddd, J=13.4Hz, 6.8Hz, 5.2Hz, 1H), 1.50-2.31 (m, 7H), 1.67 (bs, 3H), 2.48 (m, 2H), 2.80 (m, 1H), 3.87 (dd, J=8.6Hz, 4.6Hz, 2H), 4.70 (m, 3H), 5.69 (d, J=5.0Hz, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 50MHz) δ 12.8 (q), 16.7 (q), 20.5 (q), 32.6 (t), 32.9 (t), 33.0 (t), 36.2, (d), 40.5 (d), 42.6 (d), 44.8 (t), 56.0 (s), 67.8 (t), 80.3 (d), 109.5 (d), 109.7(t), 147.4 (s), 213.2 (s)
- (11) We thank the late Nora Veldman of the Bijvoet Center for Biomolecular Research, University of Utrecht, for the X-ray analysis of compound **9b**.
- (12) **10** <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200MHz)  $\delta$  0.91 (s, 3H), 0.94 (d, 3H), 1.38 (ddd, J=13.4Hz, 6.8Hz, 5.2Hz, 1H), 1.65 (m, 1H), 1.89-2.17 (m, 3H), 2.48 (m, 1H), 2.88 (m, 2H), 3.82 (m, 2H), 4.45 (dd, J=8.8Hz, 6.6Hz, 1H), 5.67 (d, J=5.0Hz, 1H), 5.88 (ddd, J=10.0Hz, 2.8Hz, 1.2Hz, 1H), 6.77 (m, 6.76, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 50MHz)  $\delta$  12.6 (q), 16.3 (q), 31.7 (t), 32.8 (t), 33.0 (t), 34.8 (t), 42.6 (d), 53.0 (s), 67.7 (t), 80.0 (d), 109.6 (d), 128.8 (d), 147.7 (d), 202.2 (s)
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- (16) 12 <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200MHz) δ 0.94 (d, J=6.6Hz, 3H), 1.13 (s, 3H), 1.61-1.75 (m, 3H), 1.98-2.30 (m, 4H), 2.84 (m, 1H), 3.88 (dd, J=7.8Hz, 4.8Hz, 2H), 4.17 (dd, J=10Hz, 6.5Hz, 1H), 5.73 (d, 5Hz, 1H) 5.97 (d, J=10Hz, 1H), 6.89 (d, J=10Hz, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 50MHz) δ 15.5 (q), 16.4 (q), 32.8 (t), 34.3 (d) 34.7 (t), 42.0 (t), 42.4 (d), 42.5 (s), 68.4 (t), 83.1 (d), 109.0 (d), 129.1 (d), 155.1 (d), 199.5 (s)