Pergamon

Tetrahedron 55 (1999) 13205–13210

TETRAHEDRON

Preparation of Ketones from Esters *via* Substituted Cyclopropanols. Application to the Synthesis of (±)-Ipsenol, (±)-Ipsdienol and Amitinol, the Components of Aggregation Pheromones of the *Ips* Bark Beetles

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Received 23 June 1999; revised 16 August 1999; accepted 2 September 1999

Abstract: The regioselective two-step sequence of bromination-dehydrobromination of 2-(2,2-diethoxy)-1-methyl-1-cyclopropanol affords 3-(2,2-diethoxyethyl)-3-buten-2-one in high yield. The reduction of the latter, followed by chlorination and dehydrochlorination, provides 2-(2,2-diethoxyethyl)-1,3-butadiene that was used as a building block for the synthesis of (±)-ipsenol, (±)-ipsdienol and amitinol – the components of aggregation pheromones of the *Ips* bark beetles.

INTRODUCTION

Previously it was reported that titanium(IV) isopropoxide-catalysed reaction of carboxylic esters with an excess of ethylmagnesium bromide provides 1-substituted cyclopropanols in good to excellent yields.[1] This transformation is supposed to proceed *via* disproportionation of diethyltitanium intermediates into corresponding titanacyclopropane reagents which interact with esters as equivalents of ethylene 1,2-dicarbanion[2] $(CH_2\text{-}CH_2)^{2-}$. When the reaction is carried out in the presence of styrene[3] or functionalised alkenes[4] a displacement of ethylene from titanacyclopropane takes place and 1,2-disubstituted cyclopropanols are formed. Later it was revealed that olefin exchange proceeds much more efficiently in substituted titanacyclopropanes and for generation of such intermediates *i*-propyl-,[5] *n*-butyl-[6] and cyclohexylmagnesium halides[7] were recommended.

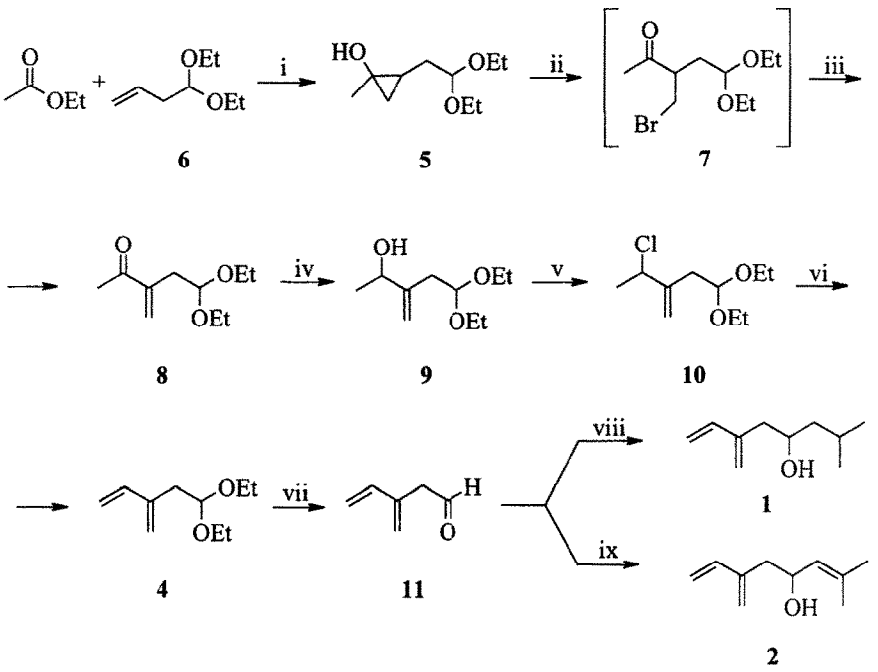
The transformation of esters into substituted cyclopropanols followed by regioselective opening of a three-carbon ring[8] provides a basis for a new and effective methodology of preparing ketones from esters.[9] Recently we successfully utilised this approach in a short synthesis of a component of female-produced sex pheromone of the German cockroach *Blatella germanica*.[10] In the current paper we describe the application of the same methodology for to the synthesis of (±)-ipsenol (**1**), (±)-ipsdienol (**2**)[11] and amitinol (**3**)[12] – the components of aggregation pheromones of the *Ips* bark beetles.[13]

RESULTS AND DISCUSSION

The dienic acetal **4** was chosen as a key intermediate for the synthesis of compounds **1**, **2** and **3** (Scheme 1). The construction of its branched carbon skeleton was based on the regioselective $C_1\text{-}C_3$ ring cleavage[14] of the 1.2-disubstituted cyclopropanol **5**. The latter was obtained in 80% yield by adding three equivalents of *n*-BuMgBr to a gently boiling etheral solution containing ethyl acetate, the functionalysed alkene **6** and $Ti(O\text{-}i\text{-}Pr)_4$.

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00800-5

Bromination of crude cyclopropanol **5** with pyridinium perbromide[15] in ether at 0°C[16] and subsequent dehydrobromination of the intermediate β-bromøketone **7** with Al_2O_3 in pentane[14] at room temperature afforded 3-(2,2-diethoxyethyl)-3-buten-2-one (**8**) in 91% yield from ethyl acetate. Selective reduction of α-methyleneketone **8** with $LiAlH_4$ in ether at -15°C gave allylic alcohol **9**. The transformation of **9** into the corresponding chloride was achieved by treatment with an equimolar amount of MsCl in pyridine.[17] It is interesting to note that the only product obtained in doing so in 68% yield from **8** was 2-(1-chloroethyl)-4,4-diethoxy-1-butene (**10**); the formation of an allylic rearrangement product[17] was not observed (Scheme 1).

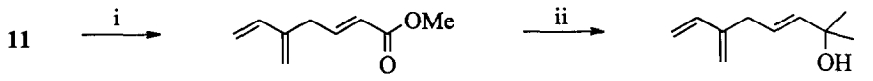


i) a) *n*-BuMgBr (3 equiv.), Ti(O-*i*-Pr)$_4$ (0.5 equiv.), Et_2O, reflux, b) H_2O/HO^-, 80% ii) Py·Br_2, Et_2O, 0°C, iii) Al_2O_3, pentane, r.t., 91% iv) $LiAlH_4$, Et_2O, -15°C, 90% v) MsCl, pyridine, r.t., 68% vi) t-BuOK, DMSO, 45°C, 90% vii) SiO_2, H_2O, tartaric acid, CH_2Cl_2, reflux viii) *i*-BuMgBr, Et_2O, 0°C, 52% ix) 2-methyl-1-propenylmagnesuim bromide, THF, -15°C, 44%.

Scheme 1

When treated with t-BuOK in DMSO,[18] the chloride **10** readily underwent dehydrochlorination to give the dienic acetal **4** in 90% yield. The latter was isolated in pure form after simple filtration of the pentane solution of crude **4** through a layer of alumina. For the deprotection of the aldehyde group in compound **4** a number of acidic reagents were tested. Treatment of **4** with aqueous AcOH or CF_3CO_2H at elevated or ambient temperature[19] led to the formation of a nearly 1 : 1 mixture of anticipated β,γ-unsaturated aldehyde **11** and its fully conjugated isomer. The acetal cleavage in two-phase systems HCO_2H–pentane[20] or CF_3CO_2H–pentane was also unsatisfactory due to partial or total decomposition of the reaction products. When a solution of **4** in CH_2Cl_2 was stirred for a long time at room temperature in the presence of SiO_2 activated with 10%

aqueous H_2SO_4 or AcOH[21] no reaction took place. Use of the oxalic acid–SiO_2 system[21] in the same conditions resulted in formation of a mixture of isomeric aldehydes containing 35-45% of the fully conjugated isomer. Finally, we found that refluxing in the presence of SiO_2 activated with 10% aqueous tartaric acid in CH_2Cl_2 is excellent for converting the acetal **4** into **11**. No α,β-unsaturated isomer was formed in this case. Spectroscopic characteristics of **11** were identical to those previously reported.[22] The treatment of crude aldehyde **11** with *i*-BuMgBr in Et_2O or with 2-methyl-1-propenylmagnesium bromide in THF led in accordance with published data[22,23] to title compounds **1** and **2**. The yields of (±)-ipsenol (**1**) and (±)-ipsdienol (**2**) from **4** after usual work-up and chromatography on silica gel were 52% and 44% correspondingly. ^{1}H NMR, IR and mass–spectra of compounds **1** and **2** thus obtained agreed with literature data.[22]



12 **3**

i) $Ph_3P{=}CHCO_2CH_3$, THF, reflux, 71%, ii) MeLi, Et_2O, r.t., 88%.

Scheme 2

Compound **11** was successfully utilised by us for the synthesis of amitinol (**3**)[12] (Scheme 2). The reaction of crude aldehyde **11** with carbomethoxymethylenetriphenylphosphorane in THF under reflux afforded methyl (2*E*)-5-methylene-2,6-heptadienoate (**12**) in 71% yield from acetal **4**. Upon the treatment of the ester **12** with two equivalents of MeLi in ether amitinol (**3**) was obtained in 88% yield after usual work-up and chromatography on SiO_2.

To summarise, dienic acetal **4**, a direct precursor of the aldehyde **11** obtained earlier in low yield from 2-butyne-1,4-diol,[22,23] was prepared from ethyl acetate and alkene **6** in six steps in 40% overall yield and was successfully used as the key intermediate in the syntheses of (±)-ipsenol (**1**), (±)-ipsdienol (**2**) and amitinol (**3**), the components of aggregation pheromones of the *Ips* bark beetles.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker AC-200 (200 MHz) or Tesla BS-467A (60 MHz) spectrometer. IR spectra were measured on a Specord 75 IR spectrophotometer. Mass spectra were obtained with a Hewlett Packard GC MS 5890/5972 spectrometer at an ionisation voltage of 70 eV. Chromatographic separations were performed on Al_2O_3 (neutral, activity III) and on Silica gel 60 Merck (70-230 mesh). All solvents obtained from commercial suppliers were distilled before use. Tetrahydrofuran and diethyl ether were freshly distilled from sodium prior to use. Dimethylsulfoxide, pyridine and dichloromethane were distilled from calcium hydride.

2-(2,2-Diethoxyethyl)-1-methyl-1-cyclopropanol (5): To a gently boiling solution of vinylacetic aldehyde diethyl acetal (**6**) (7.73 mL, 44.4 mmol), ethyl acetate (4.42 mL, 44.4 mmol) and Ti(O-*i*-Pr)$_4$ (6.53 mL, 22.2 mmol) in dry Et_2O (30 mL) a solution of *n*-BuMgBr (133.2 mmol) in Et_2O (110 mL) was added dropwise over a period of 3 h. After the addition of *n*-BuMgBr was complete the reaction mixture was stirred for 1 h and poured into 10% aqueous NaOH (150 mL). The aqueous layer was separated and extracted with Et_2O (4×50 mL). The combined organic solutions were dried over $MgSO_4$. After evaporation of the solvent

the crude product **5** was purified by column chromatography on Al_2O_3 (cyclohexane–1,4-dioxane, 9:1 v/v) or used without purification. The yield of pure substituted cyclopropanol **5** obtained as thick colourless oil was 6.69 g (80%). IR (CCl_4): 3593, 3473, 3067, 1440, 1367, 533 cm^{-1}; ^1H NMR (60 MHz, CCl_4), δ (ppm): 0.52-1.13 (m, 3H), 1.00 (t, J=7 Hz, 6H), 1.18 (s, 3H), 1.18-1.7 (m, 2H), 3.10-3.65 (m, 4H), 3.80 (bs, 1H), 4.30 (t, J=7 Hz, 1H). MS m/z, (rel.int., %): 187.10 ($(M-1)^+$, 0.04), 143.20 (53.40), 116.15 (16.75), 103.20 (100), 97.10 (42.33), 75.05 (76.06), 47.10 (92.93), 43.10 (84.54), 41.15 (22.91), 29.15 (37.29). Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.94; H, 10.79.

3-(2,2-Diethoxyethyl)-3-buten-2-one (8): To a stirred solution of substituted cyclopropanol **5** (6.65 g, 35.4 mmol) in dry Et_2O (150 mL) pyridinium perbromide (8.46 g, 35.4 mmol) was added gradually at 0°C. When addition was complete the reaction mixture was allowed to warm to room temperature and stirring was continued for 2 h. Then the reaction mixture was filtered through Al_2O_3, the solvent was evaporated and the residue diluted with pentane (170 mL). Al_2O_3 (neutral, activity III, 55 g) was added to the solution and the mixture was stirred at room temperature for 12 h. The solid was filtered off and washed with Et_2O (3×35 mL). The evaporation of the solvent afforded 5.98 g (91%) of practically pure **8.** Colourless oil; IR (CCl_4): 3093, 1667, 1627, 933 cm^{-1}; ^1H NMR (60 MHz, CCl_4), δ (ppm): 1.00 (t, J=7 Hz, 6H), 2.16 (s, 3H), 2.36 (d, J=6.8 Hz, 2H), 3.06-3.70 (m, 4H), 4.33 (t, J=6.8 Hz, 1H), 5.67 (bs, 1H), 5.82 (bs, 1H). MS m/z, (rel.int., %): 186.05 (M^+, 0.20), 113.00 (19.34), 103.05 (80.27), 85.08 (16.83), 74.95 (59.33), 68.95 (22.17), 47.00 (100), 43.00 (69.56), 28.29 (39.11). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.43; H, 9.78.

3-(2,2-Diethoxyethyl)-3-buten-2-ol (9): To a stirred suspension of $LiAlH_4$ (0.61 g, 15.9 mmol) in Et_2O (90 mL) a solution of ketone **8** (5.90 g, 31.8 mmol) in Et_2O (90 mL) was added dropwise at -15°C. When addition was over the mixture was stirred for 15 min and carefully worked-up with wet Na_2SO_4. The solid phase was removed by filtration and the filtrate was dried with $MgSO_4$. After removal of solvent, the residue was purified by chromatography on Al_2O_3; elution with cyclohexane–1,4-dioxane (9:1 v/v) gave 5.37 g (90%) of **9** as a colourless oil. IR (CCl_4): 3616, 3467, 3060, 2979, 2860, 900 cm-1; ^1H NMR (60 MHz, CCl_4), δ (ppm): 1.17 (t, J=7 Hz, 6H), 1.23 (d, J=7 Hz, 3H), 2.33 (dd, J_1=7 Hz, J_2=4 Hz, 2H), 3.03 (bs, 1H), 3.23-3.80 (m, 4H), 4.17 (q, J=7 Hz, 1H), 4.53 (t, J=7 Hz, 1H), 4.87 (bs, 1H), 5.03 (bs, 1H); MS m/z, (rel.int., %): 187.05 (M^+, 0.15), 103.05 (100), 97.00 (39.41), 74.95 (75.15), 68.95 (25.86), 46.95 (98.36), 43.05 (34.83), 41.05 (32.95), 28.95 (40.31). Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.94; H, 10.79.

2-(1-Chloroethyl)-4,4-diethoxy-1-butene (10): To a solution of alcohol **9** (5.30 g, 28.14 mmol) in dry pyridine (20 mL) methanesulfonyl chloride (3.38 mL, 29.1 mmol) was added and the mixture was left for 2 h at room temperature. Then the mixture was poured on ice and extracted with hexane (4×35 mL). The combined organic layers were passed through a 15 cm column containing Al_2O_3 (20 g). The solvent was evaporated under reduced pressure to leave practically pure chloride **10** (3.96 g, 68%). Colourless liquid; IR (CCl_4): 2960, 2860, 1440, 1360, 907,707 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ (ppm): 1.28 (t, J=6.8 Hz, 6H), 1.60 (d, J=6.9 Hz, 3H), 2.23-2.38 (m, 2H), 3.42-3.61 (m, 2H), 3.61-3.80 (m, 2H), 4.64 (q, J=6.9 Hz, 1H), 4.80 (t, J=6.8 Hz, 1H), 5.2 (bs, 1H), 5.31 (bs, 1H); Anal. Calcd for $C_{10}H_{19}ClO_2$: C, 58.11; H, 9.26. Found: C, 58.10; H, 9.22.

2-(2,2-Diethoxyethyl)-1,3-butadiene (4): To a stirred solution of t-BuOK (3.33 g, 29.7 mmol) in DMSO (35 mL) a solution of chloride **10** (3.90 g, 18.9 mmol) in DMSO (15 mL) was added dropwise over a period of 10 min. After stirring at 60-65°C for 4 h the mixture was poured into cold water and extracted with pentane (4×35 mL). The combined pentane layers were dried with $MgSO_4$ and passed through a 15 cm column with Al_2O_3 (20 g) to give after solvent evaporation pure acetal **4** as a slightly yellowish liquid (2.89 g, 90%).

IR (CCl_4): 3073, 2973, 1440, 1360, 906 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ (ppm): 1.18 (t, J=6.8 Hz, 6H), 2.50 (d, J=7 Hz, 2H), 3.39-3.52 (m, 2H), 3.53-3.70 (m, 2H), 4.63 (t, J=7 Hz, 1H), 4.99-5.30 (m, 4H), 6.36 (dd, J_1=18 Hz, J_2=11 Hz, 1H); MS m/z, (rel.int., %):170.05 (M^+, 0.12), 124.05 (7.22), 103.10 (58.56), 81.05 (38.97), 74.95 (55.13), 69.05 (21.47) 46.95 (100), 41.05 (42.07), 28.95 (38.18). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.56; H, 10.70.

3-Methylene-4-pentenal (11): To a vigorously stirred suspension of SiO_2 (16.44 g) in CH_2Cl_2 (50 mL) 10% aqueous solution of tartaric acid (1.65 g) was added. When the aqueous phase disappeared acetal **4** (2.80 g, 16.4 mmol) was added and the mixture was gently refluxed for 12 h. After filtration and washing the solid with CH_2Cl_2 solvent was removed to leave crude aldehyde **11** (1.42 g). It was pure enough and used for further transformations without purification. The sample of analytically pure **11** as a clear colourless liquid was obtained after column chromatography on silica gel (hexane–ether, 5:1 v/v). IR, ^1H NMR and MS data were identical to those previously reported for **11**.[22]

(±)-2-Methyl-6-methylene-7-octen-4-ol ((±)-ipsenol) (1) and (±)-2-methyl-6-methylene-2,7-octadien-4-ol ((±)-ipsdienol) (2) were obtained in 52% and 44% yield from **4** correspondingly by treatment of the crude aldehyde **11** with appropriate Grignard reagents following the published procedures.[22]

Methyl (2*E*)-5-methylene-2,6-heptadienoate (12): To a solution of crude aldehyde **11** (0.43 g, 4.48 mmol) in THF (10 mL) carbomethoxymethylenetriphenylphosphorane (1.64 g, 4.92 mmol) was added and the mixture was gently refluxed for 5 h. Then the mixture was diluted with hexane (30 mL) and the precipitate was filtered off. The filtrate was concentrated and separated by chromatography on silica gel. Elution with hexane–ether (4:1 v/v) gave the ester **12** (0.53 g, 71% from **4**). Colourless liquid; IR (CCl_4): 3086, 1730, 1653 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ (ppm): 3.12 (bd, J=6.5 Hz, 2H), 3.72 (s, 3H), 5.00-5.28 (m, 4H), 5.88 (bd, J=15.5 Hz, 1H), 6.42 (dd, J_1=18 Hz, J_2=11 Hz, 1H), 7.02 (dt, $^3J_1$=15.5 Hz, $^3J_2$=6.5 Hz, 1H); MS m/z, (rel.int., %): 152.10 (M^+,1.42), 137.05 (4.62), 121.05 (14.15), 93.05 (100), 92.05 (40.96), 91.05 (69.80), 77.05 (50.09), 65.00 (13.42), 59.00 (11.01), 53.00 (24.34), 39.05 (27.06), 27.05 (18.75). Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.01; H, 7.90.

(3*E*)-2-Methyl-6-methylene-3,7-octadien-2-ol (amitinol) (3): To a stirred mixture of small pieces of Li (0.09 g, 12.6 mmol) and Et_2O (4 mL) MeI (1 drop) was added. When the reaction had begun a solution of MeI (0.52 mL, 6.12 mmol) and the ester **12** (0.40 g, 2.63 mmol) in Et_2O (20 mL) was added dropwise maintaining gentle boiling of the reaction mixture. When addition was over the mixture was stirred for 30 min, cooled to 0°C and quenched with cold water (10 mL). Layers were separated and the aqueous one was extracted with Et_2O (3×5 mL). The combined etheral solutions were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (hexane-ether (4:1 v/v)) to yield amitinol **3** as a colourless oil (0.35 g, 88%). IR, ^1H NMR and MS data were identical to those previously reported for **3**.[12]

ACKNOWLEDGEMENT

We are grateful to INTAS (project 96-1325) for financial support of this work.

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