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Regiospecific Baeyer-Villiger Oxidation of α,α-Dichlorocyclobutanones: A Norbisabolide γ-lactone Analogue[1]

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REGIOSPECIFIC BAEYER-VILLIGER OXIDATION OF α,α-DICHLOROCYCLOBUTANONES: A NORBISABOLIDE γ-LACTONE ANALOGUE[1]

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ABSTRACT: Details and methodological comparisons are presented on the preparation of a norbisabolide γ-lactone analogue (4) via dichloroketene cycloaddition to limonene followed by regioselective Baeyer-Villiger oxidation (CH_3CO_3H) of the α,α-dichlorocyclobutanones **3** and C-Cl reduction (Zn/HOAc). The sequence of reduction followed by oxidation (HOCl) applied to **3** produced **4** in much better yield.

Bisaboloid sesquiterpenes (**1**) are found in nature as olefins, alcohols, keto-esters, lactones, etc[2] and some have biological activity.[3] A

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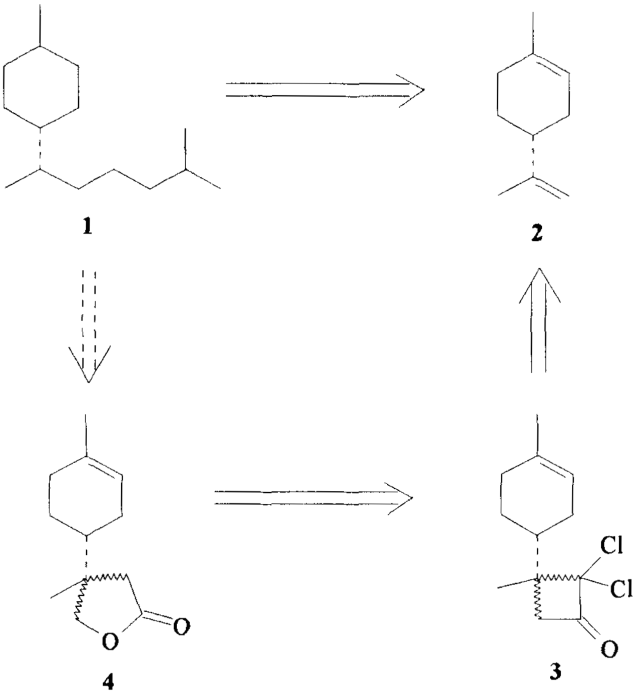
possible route to the bisaboloid family involves reactions at the disubstituted double bond of limonene[4] (**2**) and among these, the cycloaddition of dichloroketene. This reaction with limonene, originally published by Mehta,[5] produced the diastereomeric α,α-dichlorocyclobutanones **3** (whose structures were assigned based on IR and NMR data only), formed apparently, chemo- and regiospecifically. In this communication, we describe an easy synthesis of the γ-lactone **4** (a potencial bisaboloid precursor) using Baeyer-Villiger oxidation of the α,α-dichloro-cyclobutanones[6] **3** (Scheme 1).

SCHEME 1



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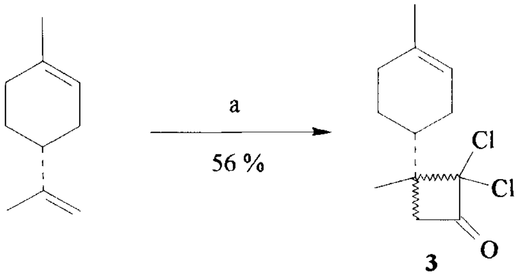
To continue our work on selective reactions at the disubstituted double bond of limonene,[7] we needed a multigram quantity of **3**. We attempted to reproduce Mehta's[5] ultrasonic irradiation of CCl_3COCl/Zn to generate dichloroketene, which in his hands gave 80% yield of **3**, but failed, probably because our only available ultrasonic generator was 50 kHz while his was 35 kHz.[8] Attempts to use $CCl_3COCl/Zn(Cu)$ in the presence of complexing agents like $POCl_3$[9] or glyme[10] gave low yields of **3** (20-30%), along with oligomers of limonene (probably due to the formation of the Lewis acid $ZnCl_2$[11]). A diastereomeric mixture (*ca.* 1:1 by High Resolution Gas Chromatography - HRGC) of **3** was easily prepared in 56% isolated yield on a multigram scale. Crucial to this process was the generation of dichloroketene via simultaneous equimolar addition (to avoid local high concentrations and reduce homopolymerization of the ketene[12]) of $CHCl_2COCl$ and NEt_3 to a large excess of limonene (Scheme 2).

SCHEME 2



a: $CHCl_2COCl$ / NEt_3 / 60° C / 4 h

Highly regioselective ring expansion of α,α-dichlorocyclobutanones with diazomethane to α,α-dichlorocyclopentanones has been described by the Greene group.[13] We decided to investigate the regioselectivity in an

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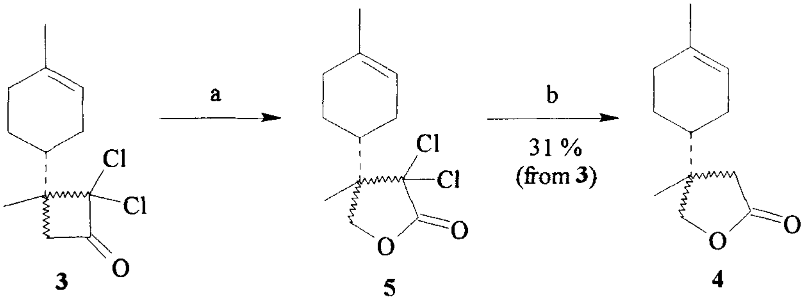
analogous reaction, the Baeyer-Villiger oxidation of **3**. Using Petterson's condition in aqueous HOCl,[14] we obtained a complex mixture of products (HRGC). Oxidation of **3** using CH_3CO_3H at 0°C led to regioselective formation of a diastereomeric mixture (*ca.* 1:1 by HRGC) of the unstable α, α-dichloro-γ-butyrolactones **5**, which were immediately dechlorinated with Zn/HOAc at room temperature to give the diastereomeric γ-butyrolactones (*ca.* 1:1 by HRGC) in 31% total yield from **3** (Scheme 3).

SCHEME 3



a: H_2O_2 / HOAc / H_2O / 0°C / 48 h
b: Zn / HOAc / r.t. / 3 h

The formation of **5** appears to be 100% regioselective, with insertion of the oxygen between the carbonyl and the dichloromethylene carbon atoms. The explanation could be, in analogy to the diazomethane reaction with α,α-dichlorocyclobutanones,[13a] that the electronegative chlorine atoms destabilize one transition state relative to the other (compare paths **a** and **b** in Scheme 4), which gives exclusively **5**, without any trace of the regiomeric γ,γ-dichloro-γ-butyrolactones **5'**.

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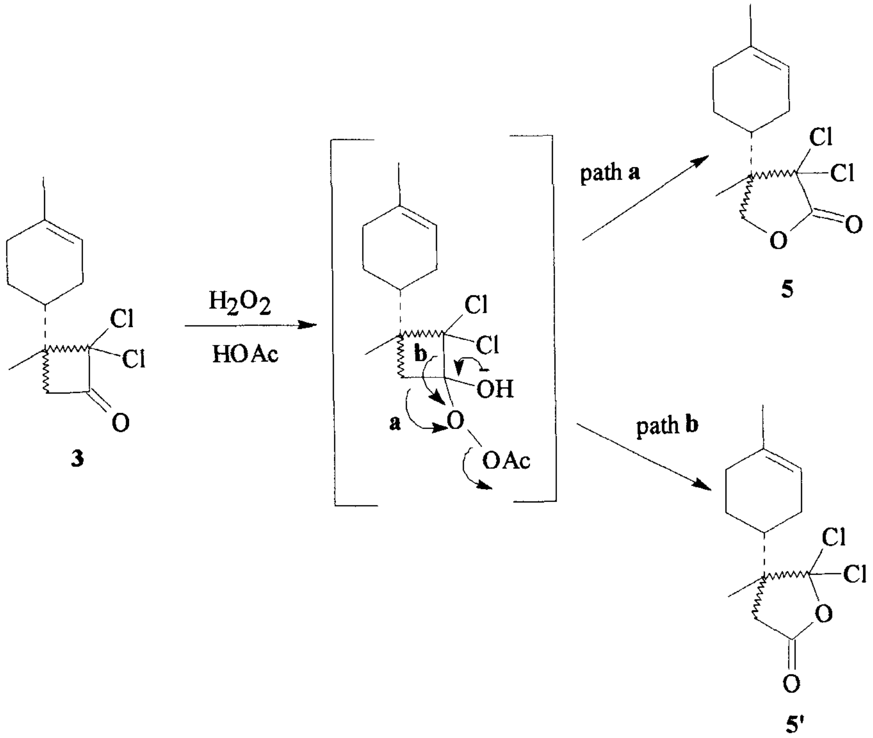
SCHEME 4



To establish that **3** was a mixture of diastereomers, we reduced the C-Cl bonds (Zn/HOAc) to give the cyclobutanone **6** and, consistent with the proposed structures, the product gave only one peak in the HRGC. Baeyer-Villiger oxidation of **6** with CH_3CO_3H gave low yield of **4** after 24 h, but using Petterson's conditions[14] gave, in only 20 min, the same diastereomeric mixture of γ-butyrolactones **4** obtained via the dichlorinated lactones, but now in much better overall yield (92%) from **3** (Scheme 5).

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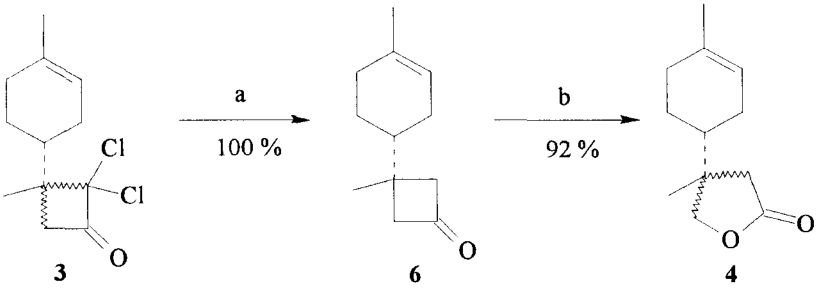
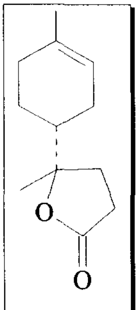
SCHEME 5



a: Zn / HOAc / 70°C / 1 h
b: NaOCl / HOAc (pH 4) / H_2O / r.t. / 20 min

These γ-butyrolactones **4** are analogues of norbisabolide (**7**), a norsesquiterpenoid γ-lactene isolated by Shringapure and Sabata from the root bark of *Atlantia monophylla*,[15] and they can potentially be converted to diverse bisaboloids by further synthetic steps.



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EXPERIMENTAL

Limonene (*R*-(+)-limonene, Dieberger) was distilled twice ($[\alpha]^{20}_{D}$ + 126° (*c* 1.00, $CHCl_3$),[16] lit.[17] $[\alpha]^{20}_{D}$ + 126.8°), $CHCl_2COCl$ was freshly distilled, and NEt_3 was dried over KOH and distilled.[18] The solvents were distilled prior to use and other chemicals were used without further purification.

The reactions were monitored by TLC using Merck silica gel 60 HF_{254}. Column chromatography performed using Merck silica gel 60, 350-

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70 mesh, and flash chromatography (as described by Still[19]) using Merck silica gel 60, 400-230 mesh.

"Usual work-up" means, drying over Na_2SO_4, filtration, concentration at reduced pressure, column chromatography of the residue (same eluent as used on TLC), and solvent evaporation (reduced pressure).

Melting points were determined on a Mel-Temp apparatus and are uncorrected.

^1H NMR spectra of $CDCl_3$ solutions (TMS as internal standard) were recorded on a Varian XL-100 (100 MHz) or Varian EM-360 (60 MHz) spectrometers. ^{13}C NMR spectra of a $CDCl_3$ solution (TMS as internal standard) was recorded on a Varian Gemini 300 (75 MHz) spectrometer.

HRGC analyses were performed on a HP 5890 gas chromatograph with FID by using a 20 m, 0.3 mm (i.d.), and 0,25 μm (phase thickness) SE-54 glass capillary column and H_2 (rate flow: 50 cm/s) as carrier gas (split: 1/20). Oven temp.: 120°C to 220°C, 8°C/min; injector temp.: 180°C, detector temp.: 250°C.

IR spectra were obtained using a Perkin Elmer 257 spectrometer.

UV spectra were obtained in EtOH solutions using a Beckman DU-6 spectrometer.

MS spectra were determined on a HP 5986-A HRGC-MS spectrometer using electron impact (70 eV).

(1'R, 3RS)-2,2-dichloro-3-methyl-3-(4'-methyl-3'-cyclohexenyl)-cyclobutanone (3)

A 200 ml six-necked flask equipped with a reflux condenser, two addition funnels, a thermometer, mechanical stirrer, and dry N_2 inlet was

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charged with limonene (80 ml). The olefin was stirred under N_2 at 60°C while $CHCl_2COCl$ (9.7 ml, 0.10 mmol) and NEt_3 (7.2 ml, 0.10 mmol) were added dropwise simultaneously and independently over 1 h.[20] When the addition was completed, the brown suspension was heated (60°C) with stirring for 3 h. After cooling, H_2O (25 ml) was added to the reaction mixture, the organic layer was separated and washed with 5% HCl (3 x 25 ml), 5% $NaHCO_3$ (3 x 25 ml), H_2O (25 ml), and dried (Na_2SO_4). After distillation of excess limonene at reduced pressure, the brownish residue was purified by column chromatography (eluent: CCl_4). The solvent was removed at reduced pressure to leave 13.82 g (56%) of **3** (diastereomers unseparated) as a white solid (mp 67°C), R_f 0.91 (CCl_4 unresolved), t_r 7.7 and 7.8 min.

^{1}H NMR (100 MHz): δ 5.40 (br, 1H); 3.40-3.16 (m, 2H): 3.24 (d, *J* 16 Hz), 3.20 (d, *J* 16 Hz); 2.80-2.58 (m, 2H): 2.72 (d, *J* 16 Hz), 2.66 (d, *J* 16 Hz); 2.40-1.20 (m, 11H): 1.68 (br), 1.24 (s), 1.22 (s) ppm.

^{13}C NMR (75 MHz): δ 192.41, 192.35 (s); 134.47, 133.66 (s); 120.01, 119.79 (d); 92.9, 92.5 (s); 54.37, 53.68 (t); 47.76, 47.74 (s); 40.62, 40.10 (d); 30.80, 30.46 (t); 27.22, 26.81 (t); 25.61, 25.39 (t); 23.36, 23.31 (q), 18.69, 18.63 (q) ppm.

IR (KBr): ν 2960, 2920, 1805, 1435, 1380, 805, 770 cm^{-1}.

MS (%): m/z 250 (0.4) $[M^{+}+4]$, 248 (1) $[M^{+}+2]$, 246 (3) $[M^{+}]$, 208 (2), 206 (7), 204 (12), 171 (3), 169 (9), 136 (100), 93 (24).

Derivative 2,4-DNPH: diastereomeric 2,4-DNPH separated by flash chromatography ($CHCl_3$ /.hexane: 1 / 10), mp 114°C and 126-27°C, UV λ_{max} 351 nm, log ε 4.47.

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(1'R)-3-methyl-3-(4'-methyl-3'-cyclohexenyl)-cyclobutanone (6)

To a mechanically stirred suspension of Zn (5 g) in HOAc (25 ml) at 70°C, a solution of **3** (2.47 g, 10 mmol) in HOAc (5 ml) was added dropwise over 5 min. After 1 h heating at 70°C, the suspension was cooled, filtered through a Celite pad, and unreacted Zn was washed with HOAc (10 ml). The combined HOAc solutions were diluted with H_2O (50 ml) and extracted with $CHCl_3$ (5 x 20 ml). The organic layer was washed with H_2O (4 x 50 ml), 5% $NaHCO_3$ (2 x 20 ml), and H_2O (20 ml). After usual work-up, 1.78 g (100%) of **6** was obtained as a colorless liquid, R_f 0.67 (CCl_4), t_r 4.6 min.

^{1}H NMR (100 MHz): δ 5.40 (br); 3.04-2.50 (m, 4H): 2.90 (d, J 16 Hz); 2.64 (d, J 16 Hz); 2.20-1.20 (m, 13 H): 1.66 (br); 1.22 (s) ppm.

IR (neat): ν 2950, 2900, 1450, 1360, 800 cm^{-1}.

MS (%): m/z 178 (4) [M^+], 163 (5), 150 (22), 136 (11), 121 (16), 107 (36), 93 (100), 68 (24).

Derivative 2,4-DNPH: mp 110-11°C, UV λ_{max} 360 nm, log ε 3.96.

(1'R, 3RS)-3-methyl-3-(4'-methyl-3'-cyclohexenyl)-γ-butyrolactone (4)

- from cyclobutanone (6)

To a solution of *ca.* 6% NaOCl (5 ml), glacial HOAc was added to pH 4, followed by H_2O (3 ml), and **6** (100 mg, 0.56 mmol). After stirring at room temp. for 20 min, the solution was extracted with Et_2O (5 x 4 ml) and the ethereal layer washed with saturated $NaHSO_3$ (3 x 3 ml), and H_2O (3 ml). After usual work-up, 100.3 mg (92%) of 4 (diastereomers unseparated)

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was obtained as a colorless liquid, *R*f 0.40 ($CHCl_3$/EtOAc: 10/1, not resolved), t_r 6.5 and 6.6 min.

^{1}H NMR (60 MHz): δ 5.4 (br); 3.9 (m, 2H); 2.5 (m, 2H); 2.1-1.0 (m, 13H): 1.7 (br), 1.2 (s), 1.1 (s) ppm.

IR (neat): ν 2950, 2900, 1770, 1450, 1430, 1030, 1020, 800 cm^{-1}.

MS (%): m/z 194 (25) [M^+], 179 (10), 165 (10), 152 (9), 136 (40), 121 (15), 107 (19), 93 (100), 43 (55).

- from dichlorocyclobutanones 3

A solution of **3** (50 mg, 0.20 mmol) and 30% H_2O_2 (100 mg) in HOAc (2 ml) was stirred at 0°C for 48 h. Then, H_2O (3 ml) was added and the solution extracted with Et_2O (5 x 2 ml). The ethereal layer was washed with saturated $NaHSO_3$ (3 x 2 ml), 5% $NaHCO_3$ (3 x 2 ml), H_2O (5 ml), and dried (Na_2SO_4).[21] To the ethereal solution were added HOAc (2 ml) and Zn (50 mg) and the suspension mechanically stirred at room temp. for 3 h. The suspension was filtered through a pad of Celite and the unreacted Zn washed with HOAc (2 ml). The combined HOAc solutions were diluted with H_2O (5 ml) and extracted with $CHCl_3$ (3 x 5 ml). The combined $CHCl_3$ solutions were washed with H_2O (5 x 3 ml), 5% $NaHCO_3$ (2 x 3 ml), and H_2O (5 ml). After usual work-up, 12.0 mg (31%) of **4** was obtained.

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20. The reaction is exothermic and a white solid ($NHEt_3Cl$) immediately appeared when the reactants were added.

21. Evaporation of the solvent at reduced pressure left a colorless liquid (**5**) that turned brown quickly, R_f 0.32 (hexane, unresolved), t_r 7.3 and 7.4 min. **IR** (neat): ν 1785, 1180, 1140, 805, 790 cm^{-1}. **MS** (%): m/z 266 (0.3) [M^++4], 264 (1.2) [M^++2], 262 (3) [M^+], 152 (20), 136 (40), 93 (100).

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