An Improved Method for the *endo*-Fusion of Five-Membered Ring Lactones to the Bornane Ring System

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endo-Fused lactone **3** was obtained in high yield from the camphoracetic acid **2** with thionyl chloride and a subsequent reduction of intermediate **5** with tributyltin hydride. The structure of **5** was elaborated and some aspects of the mechanism of its formation and reactivity were investigated. Lactone **3** serves as key intermediate for lactol **1** which is a useful reagent in racemate resolution and asymmetric synthesis.

The enantiomerically pure lactol **1**[1] is a very versatile anomer-selective protecting group and chiral auxiliary. The advantageous application of **1** in racemate resolution[2][3][4] and asymmetric synthesis[2][5] has been demonstrated many times, and acetals derived from **1** have been used for studies of stereoelectronic effects[6]. In addition, **1** allows the determination of the absolute configuration[2][3][7] and the enantiomeric purity[2][3] of alcohols, cyanohydrins, thiols, acids, and amines.

Despite this broad range of useful applications, a new synthesis was described only recently which allows to manufacture **1** in a high overall yield from *d*-camphor on a multikilogram scale (see Scheme 1)[8]. A key step in this reaction sequence is the sodium tetrahydroborate reduction of the *endo*-camphoracetic acid **2** yielding − rather unselectively − *endo*-lactone **3** and the *trans*-isoborneolacetic acid **4,** which for economical reasons, has to be recycled. This can be done very easily by reoxidation, but, especially on a laboratory scale, this requires at least two more steps. We have thus developed a new two-step sequence for the synthesis of **3** from **2** which avoids the formation of **4**.

Results and Discussion

Our new method takes advantage of chlorolactone **5**. This pseudoacid chloride is obtained as the main product when **2** is treated with thionyl chloride and only about 12% of open-chain isomer **6** is observed. Treating this mixture with *n*-hexane affords colorless crystals of **5** in 94% yield based on **2**. Since the isolated yield of crystalline **5** was higher than was to be expected from the original ratio **5**/**6,** we assumed that during the crystallization a further equilibration had occurred. As a consequence, we decided to concentrate the mother liquor, the residue was dissolved in $CDCl_3$, and the time dependence of the ratio **5**/**6** was measured (Table 1).

Although no crystallization occurred during the experiment, the equilibrium between **5** and **6** was far in advantage of the chlorolactone. Thus, to the product of this reaction should be assigned structure **5** in contrast to earlier assumptions[9].

First hints for the cyclic structure of **5** were obtained from IR[10] and ^{13}C-NMR data[11] which allowed to distinguish between open-chain keto acid chlorides and cyclic pseudoacid chlorides. In the IR spectra only one carbonyl signal was observed whereas **2** showed two absorption bands in this region. In the ^{13}C-NMR spectra there was no recognizable signal for the camphor carbonyl group, but a new signal at a chemical shift, which one would expect for an O,Cl acetal carbon atom, appeared. In our case no definite assignment was possible from ^{1}H-NMR data[12]. Eventually, the structure of **5** was proven by X-ray analysis (Figure 1).

The formation of chlorolactones from γ-keto acids has received considerable attention in the past − especially in the case of laevulinic acid chloride[13] and some 1,2-dicarboxylic acid chlorides[14] − but is now well precedented[15]. However, concerning the mechanism of the chlorolactone formation, it was proposed only at one instance that the carbonyl oxygen atom simply displaces the halogen

  1434−193X/98/1111−2507 $ 17.50+.50/0

Scheme 1. Synthesis of *endo*-lactol **1**

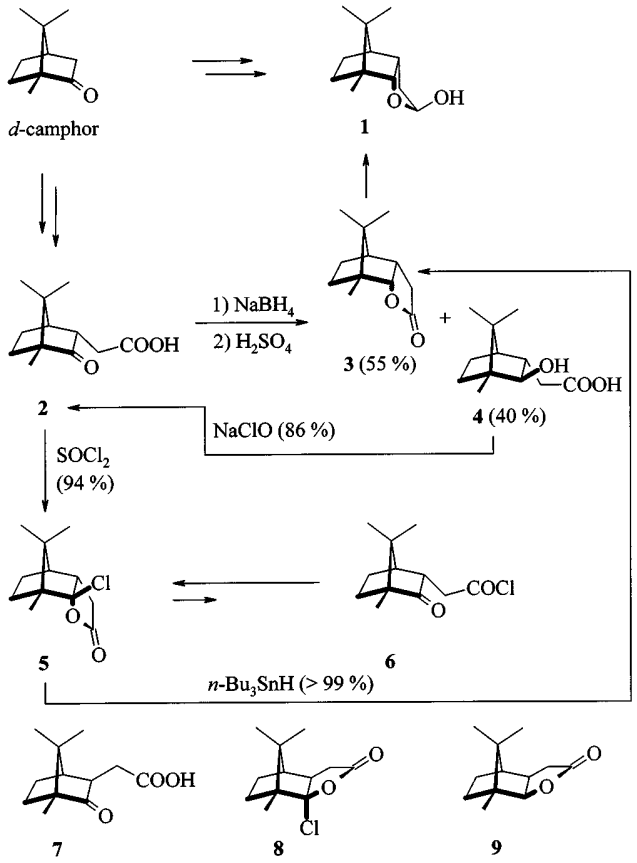


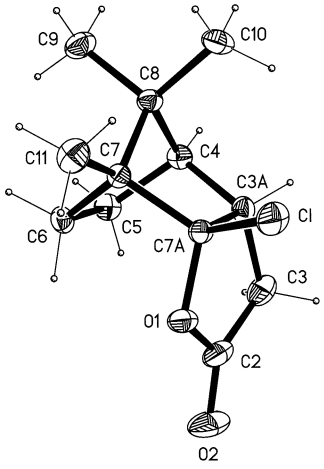
Table 1. Time dependence of the ratio **5**/**6**

time	**5**/**6**
10 min	1:1
1 d	4:1
2 d	6:1
7 d	6:1
54 d (−20°C)	> 95:1

atom[10]. But so far, from the analysis of the investigated substrates we could not rule out that the reaction takes place via the enol form[13f] in cases where an enolization is possible.

For our substrate **2** which gave only *endo*-fused lactone **5** and no *exo* isomer **8** it was obvious that no epimerization had occurred. To exclude the possibility that the lack of formation of **8** was just a result of some high thermodynamic selectivity we carried out the same experiment with a mixture of **2** and the *exo*-camphoracetic acid **7**[8]. From this reaction we obtained a mixture of chlorolactones **5** and **8** in the same ratio as for **2** and **7** (10:1)[16]. These results may be taken as proof that no enol form is involved in the formation of **5** and **8** and this should also be true for other chlorolactones. Thus, it is likely that the formation of pseudoacid chlorides from γ-keto acids does not show any epimerization at the α-carbon atom of the ketone.

Figure 1. Molecular structure of the chlorolactone **5**[a]



[a] Selected distances [Å]: C(7a)−Cl 1.809(2), C(7a)−O(1) 1.427(2), O(1)−C(2) 1.366(2), C(2)−O(2) 1.193(2), C(2)−C(3) 1.488(3), C(3)−C(3a) 1.519(3), C(3a)−C(7a) 1.542(2).

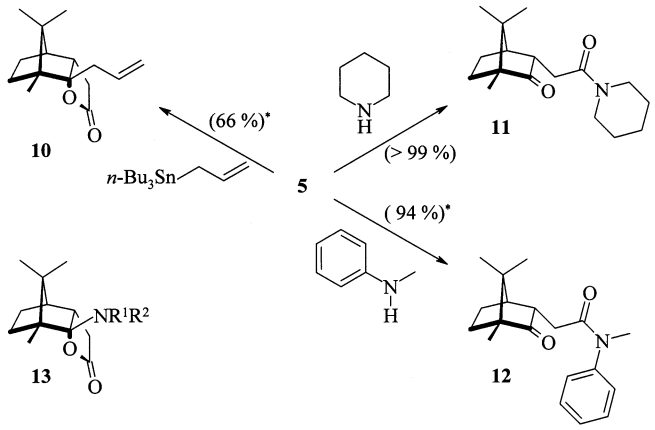
Pseudoacid chloride **5** gave *endo*-lactone **3** in high yield by reductive dehalogenation with tributyltin hydride[17]. In the aforementioned procedure, the diastereomeric purity of **2** was highly important with regard to the isolated yield[8] of lactone **3**. Due to steric reasons (unhindered attack of hydride from the *endo* side of the bornane ring system) *exo* isomer **7** gave almost exclusively *exo*-lactone **9**, whereas **2** yielded **3** and **4** in a ratio of just 55:40 only (see Scheme 1). Because the diastereomeric impurity is thus virtually doubled in this reduction step, careful purification of acid **5** proved far more efficient than the removal of lactone **9** from **3** by recrystallization. In the new synthesis this was no problem at all. The ratio between the *endo* and *exo* isomer was the same throughout the whole sequence from **2** to **3** via **5** and did only depend on the purity of **2**. Thus, no enrichment of *exo*-lactone **9** was observed which is a great advantage, since purification can be done with the same efficacy on each of the compounds **2**, **5**, and **3**.

Finally, the reactivity of pseudoacid chloride **5** towards another stannane and two amines was investigated. When treated with allyltributylstannane[18] **5** gave *C*-allylated lactone **10** as sole product which is a promising starting material for further functionalized derivatives of lactol **1** (Scheme 2). On the other hand in the reaction with piperidine and *N*-methylaniline, respectively, **5** afforded open-chain amides **11** and **12** like any ordinary acid chloride. No aminolactone **13** was formed as was reported for other chlorolactones[14g][19].

The formation of lactones **3** and **10** may be attributed to the stability of the chain reaction carrying radical which is obtained by abstraction of a chlorine atom from chlorolactone **5**. Therefore, no isomerization occurred and no keto aldehyde was formed. The remarkably high stability of a very similar type of radical has been reported earlier[15i].

The reaction of **5** with amines seems to proceed by an addition-elimination mechanism at the lactone carbonyl group and the subsequent elimination of hydrogen chloride[19e]. A displacement at the tetrahedral center (C-7a)

Scheme 2. Reactions of pseudoacid chloride **5** (* yields not optimized and based on recovered starting material)



does not occur, probably due to steric hindrance at this carbon atom.

Thus, it seems to be possible to determine the products to be formed, depending on the reaction conditions. A radical mechanism yields substituted lactones whereas nucleophiles attack the carbonyl group and give ring-opened products.

Experimental Section

General: Melting points are uncorrected. − IR: Perkin-Elmer System 2000 FT-IR. − NMR: Bruker AC 200 (200 MHz and 50 MHz, for ^{1}H and ^{13}C, respectively). For ^{1}H NMR, TMS at δ_H = 0.00 or $CHCl_3$ at δ_H = 7.24 as internal standards; for ^{13}C NMR, TMS at δ_C = 0.00 or $CDCl_3$ at δ_C = 77.0 as internal standards. − Optical rotations were measured with a Perkin−Elmer 241 polarimeter in a 10-cm cell. − TLC: Merck silica gel 60 F_{254}; visualization of the spots with molybdatophosphoric acid (5% in ethanol) and heating. − Column chromatography and vacuum flash chromatography (VFC): Merck silica gel 60 (230−400 mesh). − Allyltributylstannane was synthesized according to ref.[20]. − Abbreviations used: PE = petroleum ether, AIBN = 2, 2′-azobis(2-methylpropionitrile).

[3aS-(3aα,4α,7α,7aα)]-3a,4,5,6,7,7a-Hexahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2(3H)-one (**3**): To a solution of **5** (300 mg, 1.31 mmol) in anhydrous, degassed THF (10 ml), tributyltin hydride (390 mg, 1.34 mmol) and AIBN (22 mg, 0.13 mmol) was added and the mixture was stirred for 4 h under reflux. The solution was concentrated in vacuo and the residue was dissolved in Et_2O and extracted with a cold saturated solution of sodium hydrogen carbonate in water (2 × 10 ml). The combined aqueous layers were extracted with Et_2O (1 × 10 ml), and the combined ether solutions were dried with Na_2SO_4 and the solvent was evaporated. The residue was purified by VFC (20 g, PE/Et_2O, 4:1) and yielded after crystallization from *n*-hexane 255 mg of **3** (quant.), colorless crystals, m.p. 45−50°C (ref.[1] 48−50°C).

Analogously the reaction of **5** containing **8** as impurity (300 mg, 1.31 mmol; content of **8**: 9%) with tributyltin hydride (394 mg, 1.31 mmol) and AIBN (22 mg, 0.13 mmol) yielded 194 mg of **3** (77%, content of **9**: 9%)[21].

[3aS-(3aα,4α,7α,7aα)]-7a-Chloro-3a,4,5,6,7,7a-hexahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-one (**5**): A solution of **2** (1.400 g, 6.7 mmol) in freshly distilled thionyl chloride (3.5 ml, 50.0 mmol) was stirred at ambient temperature for 13 h and at 60°C for 1 h. Thionyl chloride was evaporated and the obtained dark oil was distilled in vacuo: b.p. 60−65°C/0.005 Torr (Kugelrohr, ref.[9a] 152−154°C/12 Torr). This colorless oil was treated with *n*-hexane to give colorless crystals which were recrystallized from *n*-hexane to afford 1.436 g of **5** (94%); m.p. 75°C (ref.[9b] 75°C); R_f = 0.38 (PE/Et_2O, 3:1); $[\alpha]_D^{20}$ = −1.5 (*c* = 2.98, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3004, and 2972 cm^{-1} (C−H), 1796 (C=O), 1151, 1030, and 1007 (C−O), 685 (C−Cl). − ^{1}H NMR: δ = 0.99, 1.11, and 1.19 (3 s, 9 H, 3 × CH_3), 1.08−1.25 (m, 1 H, 5-H$_{endo}$), 1.42−1.92 (m, 4 H, 4-H, 5-H$_{exo}$, 6-H), 2.48 (dd, J_1 = 18.9 Hz, J_2 = 2.1 Hz, 1 H, 3-H), 2.90 (dd, J_1 = 18.9 Hz, J_2 = 10.3 Hz, 1 H, 3-H), 3.28 (ddd, J_1 = 10.3 Hz, J_2 = 2.1 Hz, 1 H, 3a-H). − ^{13}C NMR: δ = 13.1 (q, C-11), 19.1 (t, C-5), 19.9/21.0 (2 q, C-9, C-10), 29.5 (t, C-3), 30.6 (t, C-6), 49.2 (d, C-4), 49.4 (d, C-3a), 50.0 (s, C-8), 56.4 (s, C-7), 113.5 (s, C-7a), 175.0 (s, C-2).

Compound **2** containing **7** as impurity (16 g, 76 mmol; content of **7**: 9%) was treated as described above and yielded after distillation 15.339 g (88%) of **5** (content of **8**: 9%)[16] as a colorless oil, b.p. 75°C/0.03 Torr (Kugelrohr). − ^{13}C NMR of **8**: δ = 9.3, 20.8, and 24.6 (3 q, C-9, C-10, C-11), 28.4 (t, C-5), 31.9 (t, C-3), 34.3 (t, C-6), 48.4 (s, C-7), 49.5, and 54.2 (2 d, C-3a, C-4), 55.6 (s, C-8), 116.3 (s, C-7a), 175.6 (s, C-2).

X-ray-Crystal Structure Analysis of **5**: A colorless rounded block (0.5 × 0.5 × 0.6 mm, epoxy-coated) of **5**, $C_{12}H_{17}ClO_2$, formula weight 228.71, orthorhombic, space group $P2_12_12_1$ (No. 19), *a* = 13.367(3), *b* = 12.079(3), *c* = 7.185(2) Å, *V* = 1155.7(5) Å^3, *Z* = 4, *d*(calcd.) = 1.314 g/cm^3, was used for data collection with a Philips PW1100 four-circle diffractometer and graphite-monochromatized Mo-K_α radiation. Cell dimensions from ± ω scans of 13 reflections (Θ = 17−24°). The intensities of 2832 reflections (two octants) with Θ < 27°, $-17 \le h \le 17$, $0 \le k \le 15$, $0 \le l \le 9$, were measured with Θ−2Θ scans. The data were corrected for LP and system instability. Absorption was small and therefore neglected. No. of unique reflections 2513 (R_{int} = 0.0313). The structure was solved by direct methods[22]. Structure refinement by full-matrix least squares on F^2[23] with anisotropic temperature factors for all non-hydrogen atoms. Hydrogen atoms were located by Fourier methods and were refined unrestrained. The final full-matrix least-squares refinement varied 205 parameters and used all 2513 independent reflections. Final R_1 = 0.0326, for all data, and R_1 = 0.0288 for the 2331 reflections with $F_o \ge 4\sigma(F_o)$. Excursions in final Fourier map between −0.11 and 0.19 eÅ^{-3}. The Flack absolute structure parameter of 0.02(6) was consistent with the known absolute configuration of the compound[24].

[3aS-(3aα,4α,7α,7aα)]-3a,4,5,6,7,7a-Hexahydro-7,8,8-trimethyl-7a-(2-propenyl)-4,7-methanobenzofuran-2(3H)-one (**10**): To a solution of **5** (300 mg, 1.3 mmol) in anhydrous, degassed benzene (1.3 ml) allyltributylstannane (868 mg, 2.6 mmol) and AIBN (32 mg, 0.2 mmol) were added. The reaction mixture was stirred under reflux for 16 h, cooled to room temp., diluted with Et_2O (10 ml), and washed with saturated sodium bicarbonate solution (3 × 15 ml) and water (1 × 15 ml). The aqueous layers altogether were extracted with Et_2O (1 × 40 ml) and the combined ether solutions were dried with sodium sulfate, and the solvent was evaporated. The residual yellow oil was purified by MPLC (150 g, PE/Et_2O, 5:1) and gave 142 mg of **10** (46%) and 90 mg of recovered **5** (30%). − **10**: Colorless crystals, m.p. 63−65°C (*n*-hexane), R_f = 0.46 (PE/Et_2O, 3:1), $[\alpha]_D^{20}$ = +40.04 (*c* = 0.45, CH_2Cl_2). − ^{1}H NMR: δ = 0.89, 0.95, and 0.98 (3 s, 9 H, 3 × CH_3), 1.14−1.90 (m, 5 H, 4-H, 5-H, 6-H), 2.22−2.79 (m, 5 H, 3-H, 3a-H, $-CH_2CH=CH_2$), 5.09−5.23 (m, 2 H, $-CH_2CH=CH_2$), 5.60−5.80 (m, 1 H, $-CH_2CH=CH_2$). − ^{13}C NMR: δ = 12.0 (q, C-11), 19.6 (t, C-5),

20.2 (q, C-10), 21.1 (q, C-9), 29.9 (t, C-6), 32.3 (t, C-3), 39.8 (d, C-3a), 40.9 (t, $-CH_2CH=CH_2$), 48.0 (d, C-4), 49.6 (s, C-8), 52.9 (s, C-7), 95.7 (s, C-7a), 120.1 (t, $-CH_2CH=CH_2$), 131.5, (d, $-CH_2CH=CH_2$), 177.5 (s, C-2). – $C_{15}H_{22}O_2$ (234.34): calcd. C 76.88, H 9.46; found C 77.12, H 9.72.

[1R-endo]-1-[(4,7,7-Trimethyl-3-oxobicyclo[2.2.1]hept-2-yl)-acetyl]piperidine (**11**): A mixture of **5** (200 mg, 0.9 mmol), piperidine hydrochloride (213 mg, 1.8 mmol), and triethylamine (0.5 ml, 3.5 mmol) in anhydrous THF (10 ml) was stirred at ambient temperature for 15 h. The solvent was evaporated, and the residue was dissolved in diethyl ether (20 ml) and extracted with 2 N HCl (2 × 10 ml). The organic layer was dried with sodium sulfate, and the solvent was removed under diminished pressure. Recrystallization from PE gave 243 mg of **11** (quant.) as colorless crystals, m.p. 78°C (PE), R_f = 0.13 (PE/Et_2O, 3:1), $[\alpha]_D^{20}$ = +70.1 (c = 1.38, CH_2Cl_2). – ^{1}H NMR: δ = 0.88–1.04 (m, 9 H, 3 × CH_3), 1.11–1.90 (m, 10 H, 5-H, 6-H, 3′-H, 4′-H, 5′-H), 2.13–2.36 (m, 2 H, 1-H, 2-H), 2.69–3.05 (m, 2 H, α-H), 3.25–3.70 (m, 4 H, 2′-H, 6′-H). – ^{13}C NMR: δ = 9.4 (q, C-10), 19.2, and 19.5 (2 q, C-8, C-9), 20.3 (t, C-6), 24.5 (t, C-4′), 25.5, and 26.4 (2 t, C-3′, C-5′), 30.1, and 31.2 (2 t, C-5, C-α), 42.8 (t, C-6′), 45.9 (s, C-7), 46.5 (t, C-2′), 46.8, and 46.9 (2 d, C-1, C-2), 58.5 (s, C-4), 169.3 (s, CON), 221.2 (s, C-3). – $C_{17}H_{27}NO_2$ (277.41): calcd. C 73.61, H 9.81, N 5.05; found C 73.67, H 10.04, N 4.99.

[1R-endo]-N,4,7,7-Tetramethyl-3-oxo-N-phenylbicyclo-[2.2.1]heptan-2-acetamide (**12**): A mixture of **5** (4.673 g, 20.4 mmol), *N*-methylaniline (6.604 g, 61.4 mmol), and triethylamine (6.210 g, 61.2 mmol) in anhydrous benzene (70 ml) was stirred for 48 h under reflux, and washed with 2 N HCl (3 × 30 ml) and saturated sodium bicarbonate solution (30 ml). The organic layer was dried with sodium sulfate and the solvent was evaporated. The residue yielded after VFC (80 g, PE/Et_2O, 5:1) 2.630 g of **12** (44%) and 2.463 g of recovered **5** (53%). – **12**: Colorless oil, b.p. 75°C/0.005 Torr (Kugelrohr), R_f = 0.13 (PE/Et_2O, 3:1), $[\alpha]_D^{20}$ = +80.1 (c = 0.88, CH_2Cl_2). – ^{1}H NMR: δ = 0.76–1.30 (m, 11 H, 5-H_{endo}, 6-H_{endo}, 3 × CH_3), 1.43–1.81 (m, 2 H, 5-H_{exo}, 6-H_{exo}), 1.85–2.28 (m, 2 H, 1-H, 2-H), 2.40–2.66 (m, 1 H, α-H), 2.81–3.04 (m, 1 H, α-H), 3.27 (s, 3 H, NCH_3), 7.08–7.50 (m, 5 H, phenyl-H). – ^{13}C NMR: δ = 9.3 (q, C-10), 19.1, and 19.4 (2 q, C-8, C-9), 20.3 (t, C-6), 30.8, and 31.4 (2 t, C-5, C-α), 37.3 (q, NCH_3), 45.7 (s, C-7), 46.5, and 47.0 (2 d, C-1, C-2), 58.3 (s, C-4), 127.1 (d, 2 *ortho*-C), 127.8 (d, *para*-C), 129.7 (d, 2 *meta*-C), 143.6 (s, *ipso*-C), 171.1 (s, CON), 220.5 (s, C-3). – $C_{19}H_{25}NO_2$ (299.42): calcd. C 76.22, H 8.42, N 4.68; found C 76.07, H 8.61, N 4.71.

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