127. Synthesis and Odor of Chiral Partial Structures of Khusimone

Part 2[1])

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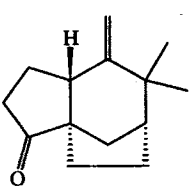
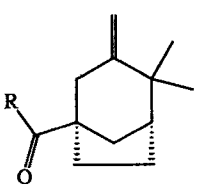
Khusimone (**1**), one of the main odor-donating compounds of vetiver oil, is subject of the following study on structure/odor relationship. Ring opening of the carbonyl-functionalized bridge of the tricyclic khusimone leads to the bicyclic structures **2a/b**. The enantioselective approach to these degraded structures is described, and the olfactory consequences are studied. Starting point of the synthesis is an enantiomerically pure enone ester which is easily obtainable from camphorsulfonic acid.

Introduction. – Vetiver oil is of considerable importance in the cosmetic industry. The harmonious playing together of the heavy-sweet, woody, and earthy notes is unique. Until now, it was not possible to reconstitute the pleasant vetiver aroma by synthetic compounds, as, for example, in the case of sandalwood. Although attempts upon a cheap synthesis starting from the naturally occurring (+)-zizanoic acid reflect economic interests [4], no structure-odor studies on (−)-khusimone (**1**) have been undertaken. In continuation of our studies [1] concerning the question whether it is possible to generate a well-balanced odor also from a bicyclic partial structure of (−)-khusimone, a moderate degradation to partial structures **2a/b** is realized. The consequences of these structural modifications have been studied and the olfactory properties of these compounds discussed. Furthermore, considering the fact that optical antipodes in many cases exhibit different odors, compounds **2a/b** had to be synthesized enantioselectively.



(−)-1

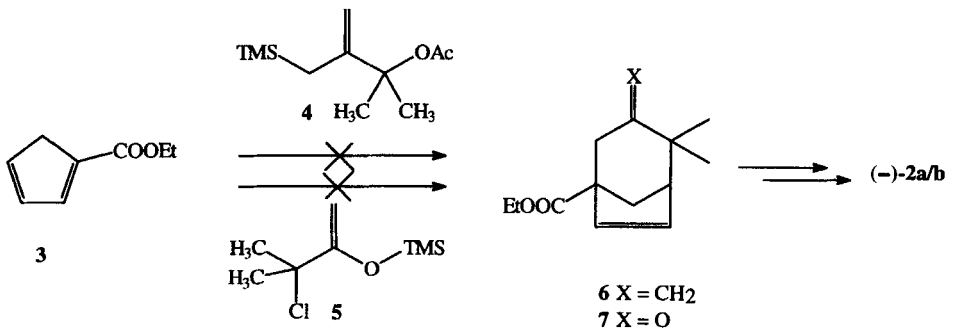


(−)-2a R = Me
(−)-2b R = Et

[1]) Part 1: [1].
[2]) Part of Ph. D. thesis [2].
[3]) Part of Diploma work [3].

Results and Discussion. – A short and promising access to the desired chiral compounds **2a/b** should be achieved *via* [4 + 3] cycloaddition to **6** and **7**, respectively, as depicted in *Scheme 1*. After resolution of the racemic acids two and three steps, respectively, should lead to **2a/b**. Unfortunately, the Pd^0-mediated addition reaction, according to the method of *Trost* and *Nanninga* [5], of **4** [6] with cyclopentadiene ester **3** [7] to **6** was unsuccessful. Employing the method of *Shimizu et al.* [8] led only in poor yields to **7**, the [4 + 3] addition taking place predominantly in the reverse of the desired way.

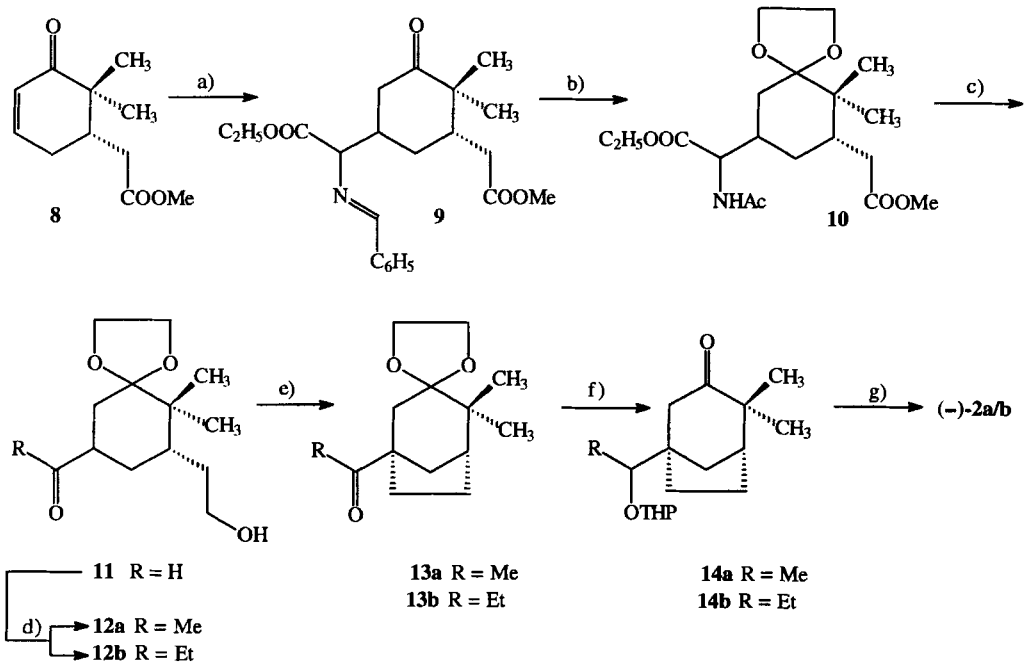
Scheme 1



The enantioselective route to (–)-**2a/b** (*Scheme 2*) started from the enone ester (–)-**8** which can be obtained in a short stereocontrolled reaction sequence from ammonium camphorsulfonate [9]. Since 2-lithio-1,3-dithiane [10] gave no *Michael* addition with **8**, *N*-benzylideneglycinate [11] was chosen as formyl synthon, which underwent regioselectively and quantitatively 1,4-addition to the enone moiety furnishing **9**. Due to the fact that the methylenation of the highly hindered C=O group could be realized neither with compound **9** nor with the *N*-deprotected acetamide derivative of **9** (*Wittig*, *Tebbe*, and a modified *Peterson* olefination failed as did the method of *Takai et al.* with $CH_2Br_2/Zn/TiCl_4$ [12–15]) the C=O group was protected as ethylene ketal **10**. $LiAlH_4$ Reduction and successive treatment with $NaIO_4$ afforded the intermediate **11**. Conversion of the aldehyde function of the methyl and ethyl ketones, **12a** and **12b**, respectively, was realized by reaction with MeLi and EtLi, respectively, followed by selective oxidation of the secondary alcohol (in the presence of the primary alcohol) with $(NH_4)_6Mo_7O_{24}/H_2O_2/K_2CO_3$ [16]. After mesylation of the primary alcohol, cyclization to the bicyclic nucleus, **13a/b**, was accomplished in high yields by successive treatment with *t*-BuOK [17]. The delayed methylenation of the exocyclic C=O group now prevented a straightforward route to **2a/b**. After reduction of **13a/b** to the carbinol, the dioxolane group was cleaved and the carbinol protected as THP-ether (→ **14a/b**). At last, *Tebbe* reagent [14] (*Peterson* olefination failed [18]) was successful in methylenation the highly hindered C=O group of **14a**. In contrast, the established method *via* $MeLi/SOCl_2$ was applied with **14b**, but the $SOCl_2$-induced dehydration to the methylenated product was accompanied by for-

mation of the endocyclic C=C bond. After cleavage of the THP-ether with pyridinium *p*-toluenesulfonate (PPTS) [19] oxidation with pyridinium chlorochromate (PCC) afforded (−)-**2a**/**b**.

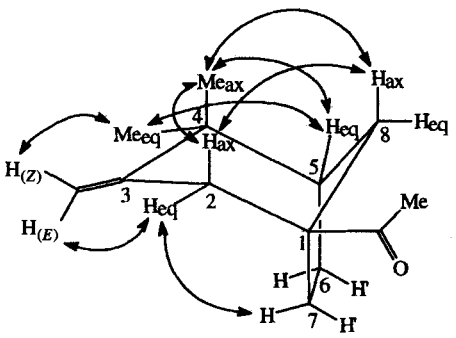
Scheme 2



a) Ethyl *N*-benzylideneglycinate. b) *i. Girard T*, *ii.* Ac_2O, *iii.* $HOCH_2CH_2OH$. c) *i.* $LiAlH_4$, *ii.* $NaIO_4$. d) *i.* MeLi and EtLi, resp., *ii.* $(NH_4)_6Mo_7O_{24}/H_2O_2$. e) *i.* MesCl, *ii. t*-BuOK. f) *i.* $LiAlH_4$, *ii.* H^+/H_2O, DHP; *iii. Tebbe*; reagent and $MeLi/SOCl_2$, resp. g) *i.* H^+/H_2O, *ii.* PCC.

The structures of the target compounds (−)-**2a**/**b** were confirmed by NMR methods. A combination of NOE-difference experiments [20], APT [21], HMQC [22], and long-range INEPT (selective DANTE excitation of suitable proton resonances) experiments [23] enabled us to perform full and unambiguous assignments for all ^1H and ^{13}C signals of (−)-**2a**. The most important through-space connections resulting from a series of NOE-difference experiments are displayed below, clearly indicating chair conformation of the cyclohexane ring. As expected, the homologous ethyl compound (−)-**2b** shows nearly identical chemical shifts for the bicyclic system as its methyl congener (−)-**2a**; assignment of signals was performed by comparison with the latter.

The odorous impression of (−)-**2a** can be summarized as predominantly camphoraceous with a sweet-herbal by-note. The seco-khusimone (−)-**2b** exhibits, above all, a woody cedar-note but with no camphoraceous by-notes. This means the typical odor descriptors of vetiver do not stem from these partial structures. The degradation of the tricyclic khusimone (**1**) to the bicyclic structures (−)-**2a**/**b** leads to a loss of the typical odor.



(–)-2a

We are indepted to Mr. *W. Höppner* and *V. Hausmann*, perfumers of *Dragoco-Vienna*, for the organoleptic analyses of all new compounds.

Experimental Part

General. See [1].

1. *Ethyl* N-*Benzylidene-2-{(3S)-4,4-dimethyl-3[(methoxycarbonyl)methyl]-5-oxocyclohexyl}glycinate* (**9**). To a soln. of 1.47 ml (11.19 mmol) of abs. $(i\text{-}Pr)_2NH$ in 20 ml of abs. THF were added, at −78°, slowly 7.0 ml (11.19 mmol) of a 1.6M soln. of BuLi in hexane. Then, the mixture was stirred for 20 min at 0°. Afterwards, it was cooled to −78°, and a soln. of 2.14 g (11.19 mmol) of *N*-benzylideneglycine ethyl ester in 10 ml of abs. THF was added. After stirring for 15 min, a soln. of 2.19 g (11.10 mmol) of *methyl (1S)-6,6-dimethyl-5-oxo-cyclohex-3-ene-1-acetate* (**8**) [9] in 20 ml of abs. THF was added dropwise, and the mixture was stirred for further 3 h at −78°. The mixture was poured into a cooled NH_4Cl soln., and, after extraction, with Et_2O, the combined org. layers were dried and concentrated *in vacuo*. 4.33 g (100%) of **9**. IR (NaCl, liq. film): 2980, 1740, 1710, 1640, 1580, 1180. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.01 (*s*, Me); 1.21 (*s*, Me); 1.27 (*t*, J = 7.2, Me); 1.64 (*m*, H–C(2)); 2.10–2.13 (*m*, H–C(2), 1 H of CH_2COO); 2.33–2.49 (*m*, H–C(2), H–C(3), 1 H of CH_2COO); 2.78 (*m*, H–C(1)); 3.51 (*s*, MeO); 3.84 (*d*, J = 7.2, NCH); 4.20 (*q*, J = 7.2, CH_2O); 7.40 (*m*, H–C(4) of Ph); 7.42 (*m*, H–C(3) and H–C(5) of Ph); 7.79 (*m*, H–C(2) and H–C(6) of Ph); 8.28 (*s*, H–C=N). ^{13}C-NMR (75 MHz, $CDCl_3$): 214.1 (C–(3)); 173.1 (*C*OOMe); 170.6 (*C*OOEt); 164.7 (C=N); 135.5 (arom. C(1)); 131.3 (arom. C(4)); 128.6 (arom. C(2) and C(6)); 128.5 (arom. C(3) and C(5)); 76.1 (NCH); 61.2 (CH_2O); 51.5 (MeO); 47.8 (C(4)); 41.3 (C(3)); 40.1 (C(6)); 37.0 (C(1)); 35.3 (*C*H_2COO); 27.2 (C(2)); 25.2 (Me); 20.8 (Me); 14.1 (Me). MS: 387 (13, M^+), 372 (16), 315 (21), 314 (100), 286 (10), 192 (21), 191 (13), 146 (10), 117 (19), 91 (17).

2. *Ethyl* N-*Acetyl-2-{(5S)-4,4-dimethyl-5-[(methoxycarbonyl)methyl]-3,3-(ethylenedioxy)cyclohexyl}-glycinate* (**10**). 2.1. *Ethyl 2-{(5S)-4,4-Dimethyl-5-[(methoxycarbonyl)methyl]-3-oxocyclohexyl}glycinate.* A soln. of 2.3 g (13.72 mmol) of *Girard T* reagent in 60 ml of abs. MeOH was added to 4.33 g (11.42 mmol) of **9**. After stirring for 2 h at r.t., the mixture was concentrated *in vacuo*, treated with H_2O, and extracted with AcOEt. After drying and concentrating *in vacuo* (at least at 0.3 Torr at 125°), the resulting residue was used without further purification. Yield: 2.87 g (84%). Purification for spectroscopic purposes by recrystallization in Et_2O/hexane. Colorless crystals. M.p. 55°. IR (KBr): 3400, 2980, 1735, 1710, 1190, 1025. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.93 (*s*, Me); 1.18 (*s*, Me); 1.22 (*t*, J = 6.9, Me); 1.38 (*dt*, J = 3.3, 13.5, H–C(6)); 1.42–1.77 (NH_2); 1.93–2.03 (*m*, H–C(6) 1 H of CH_2COO); 2.12–2.19 (*m*, H–C(2)); 2.22–2.36 (*m*, H–C(1), H–C(5)); 2.40 (*m*, 1 H of CH_2COO); 2.64–2.73 (*m*, H–C(2)); 3.28 (*m*, NCH); 3.59 (*s*, MeO); 4.12 (*q*, J = 6.9, CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): 213.7 (C(3)); 174.4/172.8 (2 COO); 60.9 (CH_2O), 57.6 (CNH_2); 51.4 (MeO); 47.4 (Me_2C); 41.8 (C(5)); 40.4 (C(2)); 37.5 (C(1)); 34.9 (*C*H_2COO); 25.8 (C(6)); 25.7 (Me); 20.9 (Me); 14.1 (Me). MS: 299 (1, M^+), 268 (8), 227 (12), 226 (100), 194 (10), 177 (33), 149 (31), 102 (17), 69 (10), 56 (15). Anal. calc. for $C_{15}H_{25}NO_5$ (299.36): C 60.18, H 8.42, N 4.48; found: C 60.13, H 8.34, N 4.66.

2.2. *Ethyl* N-*Acetyl-2-{(5S)-4,4-dimethyl-5-[(methoxycarbonyl)methyl]-3-oxocyclohexyl}glycinate.* The obtained residue (2.87 g, 9.60 mmol) was dissolved in 20 ml of abs. Et_2O and treated with 0.91 ml (9.60 mmol) of freshly distilled Ac_2O. After 3 h, the mixture was concentrated and extracted with CH_2Cl_2. The org. layers were dried and concentrated *in vacuo*: 3.27 g (100%). The crude product can be used without further purification (GC: 94%). Purification for spectroscopic purposes by recrystallization in Et_2O/hexane. Colorless crystals. M.p. 103–

104°. IR (KBr): 3570, 3390, 2980, 1740, 1710, 1680, 1665, 1525, 1200. ^{1}H-NMR (80 MHz, $CDCl_3$): 0.99 (*s*, Me); 1.22 (*s*, Me); 1.30 (*t*, *J* = 7.1, Me); 2.08 (*s*, MeCO); 3.68 (*s*, MeO); 4.21 (*q*, *J* = 7.1, CH_2O); 4.58–4.69 (*m*, NCH); 6.60 (*d*, *J* = 9.0, NH). ^{13}C-NMR (20 MHz, $CDCl_3$): 213.7 (C(3)); 173.1, 171.0, 170.3 (2 COO, CON); 61.6 (CH_2O); 55.2 (CN); 51.6 (MeO); 47.4 (C(4)); 41.3 (C(5)); 39.7 (C(2)); 36.3 (C(1)); 34.6 (CH_2COO); 26.6 (C(6)); 25.8 (Me); 23.0 (Me); 20.4 (Me); 14.0 (Me). MS: 310 (4), 282 (39), 268 (40), 236 (81), 226 (44), 197 (43), 165 (41), 145 (100), 99 (56), 56 (39). Anal. calc. for $C_{17}H_{27}NO_6$ (341.40): C 59.81, H 7.97, N 4.10; found: C 59.71, H 7.77, N 4.08.

2.3. The obtained residue (3.27 g, 9.6 mmol) was dissolved in 100 ml of toluene and, after treating with 15 ml of ethylene glycol and a catal. amount of *p*-toluenesulfonic acid, the mixture was refluxed in a *Dean* separator. After 20 h the mixture was allowed to cool to r.t. and extracted with sat. $NaHCO_3$ and H_2O. The toluene soln. was dried and concentrated in *vacuo*: 3.09 g. Recrystallization from Et_2O: 2.47 g (67%) colorless crystals of **10**. M.p. 128°. IR (KBr): 3390, 2980, 1735, 1720, 1680, 1530, 1200. ^{1}H-NMR (80 MHz, $CDCl_3$): 0.80 (*s*, Me); 1.03 (*s*, Me); 1.22 (*t*, *J* = 7.1, Me); 1.97 (*s*, MeCO); 3.57 (*s*, MeO); 3.80–3.96 (*m*, OCH_2CH_2O); 4.12 (*q*, *J* = 7.1, CH_2O); 4.58 (*dd*, *J* = 4.8, 9.6, NCH); 6.08 (*d*, *J* = 9.6, NH). ^{13}C-NMR (20 MHz, $CDCl_3$): 171.8, 170.0 (COO, CON); 112.0 (C(3)); 65.2, 64.3 (OCH_2CH_2O); 61.3 (CH_2O); 55.3 (CNH); 51.4 (MeO); 41.0 (C(5)); 40.4 (C(4)); 34.7 (CH_2); 34.1 (C(1)); 33.3 (CH_2); 26.5 (C(6)); 25.1 (Me); 23.1 (Me); 20.1 (Me); 14.1 (Me). MS: 354 (2), 312 (3), 270 (2), 242 (12), 241 (100), 198 (3), 167 (16), 113 (3), 99 (8), 86 (3). Anal. calc. for $C_{19}H_{31}NO_7$ (385.46): C 59.20, H 8.11, N 3.63; found: C 58.99, H 7.98, N 3.42.

3. *(5S)-3,3-(Ethylenedioxy)-5-(2-hydroxyethyl)-4,4-dimethylcyclohexanecarbaldehyde* (**11**). 3.1. *(3S)-5-[1-(Ethylamino)-2-hydroxyethyl]-3-(2-hydroxyethyl)-2,2-dimethylcyclohexanone Ethylene Ketal.* To 56.9 ml (56.9 mmol) of a 1M soln. of $LiAlH_4$ in THF, a soln. of 3.54 g (9.19 mmol) of **10** in 20 ml of THF was added dropwise at 0°. After the addition was complete, the mixture was heated 23 h at 70°. At r.t., 1.5 ml of H_2O, 1.5 ml of 2N NaOH, and 4.5 ml of H_2O were added, and, after filtration by suction, the filtrate was concentrated *in vacuo* (at least at 75° at 0.5 Torr), yielding 2.21 g of crude product. Spectroscopic characterization as triacetate. IR (NaCl, liq. film): 2980, 1740, 1645, 1240. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.82, 0.84 (2*s*, Me); 0.91, 0.95 (2*s*, Me); 1.11, 1.14 (2*t*, *J* = 6.9, 7.2, Me); 1.20–1.66 (*m*, H–C(5)); 1.97 (*s*, 2 MeCO); 2.05 (*s*, MeCO); 1.68–2.38 (*m*, H–C(3)); 2.9–3.41 (*m*, NCH_2); 3.77–4.08 (*m*, 3 CH_2O, NCH); 4.12–4.52 (*m*, CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.1, 170.9, 170.7, 170.5, 170.3 (2 COO, CON); 112.4, 112.3 (C(1)); 65.0, 64.7, 63.64, 63.58, 63.0 (4 OCH_2); 58.8 (NCH); 41.4, 41.1 (C(2)); 39.4, 39.1 (CH); 36.1 (NCH_2); 33.1, 32.3 (CH_2); 32.0, 30.9 (CH); 28.6, 28.0, 27.7, 27.4 (2 CH_2); 23.5, 22.4 (Me); 22.0, 21.7 (Me); 20.73, 20.69 (Me); 20.6, 20.4 (Me); 19.0, 18.3 (Me); 15.2, 13.7 (Me). MS: 428 (2, M^+), 340 (6), 256 (16), 255 (100), 198 (10), 172 (11), 130 (29), 113 (8), 99 (24), 88 (13). Anal. calc. for $C_{22}H_{37}NO_7$ (427.54): C 61.81, H 8.72, N 3.28; found: C 61.51, H 9.01, N 3.49.

3.2. The residue (2.21 g, 7.34 mmol) was dissolved in 15 ml of abs. Et_2O and treated at 0° with a suspension of 2.1 g (9.82 mmol) of $NaIO_4$ in 7 ml of H_2O. The mixture was stirred vigorously for 1 h at 0° and 2 h at r.t., treated with H_2O, and extracted with Et_2O. After drying, the solvent was removed at r.t. *in vacuo*: 1.66 g (93%) of hygroscopic, at r.t. unstable, yellowish oil (**11**). IR (NaCl, liq. film): 3400, 2950, 1720, 1180. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.81, 0.82 (2*s*, Me); 0.85, 0.86 (2*s*, Me); 2.30 (br. *s*, OH); 3.48–3.72 (*m*, CH_2O); 3.72–4.18 (*m*, OCH_2CH_2O); 9.55 (*s*, HCO). MS: 242 (15, M^+), 213 (100), 211 (15), 183 (12), 141 (24), 113 (17), 99 (36), 86 (21), 69 (11), 55 (16).

4. *1-[(5S)-3,3-(Ethylenedioxy)-5-(2-hydroxyethyl)-4,4-dimethylcyclohexyl]ethanone* (**12a**). 4.1. *(3S)-3-(2-Hydroxyethyl)5-(1-hydroxyethyl)-2,2-dimethylcyclohexanone Ethylene Ketal.* To a soln. of 12.9 ml (20.58 mmol) of MeLi in Et_2O was added, at −30°, a soln. of 1.66 g (6.86 mmol) of **11** in 15 ml of Et_2O. The mixture was allowed to warm up to r.t. and stirred for further 15 h. After addition of H_2O, the mixture was extracted with AcOEt, the org. extracts were dried and concentrated *in vacuo* (at least at 75° at 0.2 Torr): 1.38 g (78%) of a yellowish oil. Spectroscopic characterization as diacetate: IR (NaCl, liquid film): 2980, 1740, 1245. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.87 (*s*, Me); 1.01, 1.03 (2*s*, Me); 1.15 (*d*, *J* = 6.5, *Me*CHO); 2.00 (*s*, MeCO); 3.60–4.16 (*m*, 3 CH_2O); 4.56–5.30 (*m*, OCH). MS: 283 (1), 256 (15), 255 (100), 140 (8), 113 (4), 99 (16), 87 (4), 86 (5), 55 (4). Anal. calc. for $C_{18}H_{30}O_6$ (342.43): C 63.14, H 8.83; found: C 63.01, H 8.81.

4.2. A soln. of 1.38 g (5.35 mmol) of the residue, 4.0 g (3.26 mmol) of ammonium molybdate(VI) tetrahydrate, 0.77 g (2.62 mmol) of Bu_4NCl, and 1.22 g (8.83 mmol) of K_2CO_3 in 45 ml of THF were treated under vigorous stirring with 2.67 ml of aq. H_2O_2 (30%). After stirring for 2 d and 4 d, 0.89 ml of H_2O_2 were added. After 7 d (in total), the mixture was extracted with AcOEt. After drying and concentration *in vacuo* (at least at 75° at 0.1 Torr), 1.06 g (77%) of **12a** were isolated. Purification for spectroscopic purposes with TLC (pentane/acetone 70:30). IR (NaCl, liq. film): 3450, 2960, 1710, 1110. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.91 (*s*, 2 Me); 2.15 (*s*, MeCO); 2.45–2.85 (*m*, CHCO); 3.53–4.3 (*m*, 3 OCH_2). MS: 256 (8, M^+), 214 (13), 213 (100), 155 (18), 113 (23), 99 (51), 86 (17), 73 (16), 69 (19), 55 (10). Anal. calc. for $C_{14}H_{24}O_4$ (256.34): C 65.60, H 9.44; found: C 65.73, H 9.48.

5. *1-[(5S)-3,3-(Ethylenedioxy)-5-(2-hydroxyethyl)-4,4-dimethylcyclohexyl]propan-1-one* (**12b**). 5.1. *(3S)-5-(1-Hydroxyethyl)-3-(hydroxypropyl)-2,2-dimethylcyclohexanone Ethylene Ketal.* A soln. of 1.78 g (7.35 mmol) of **11** was treated with EtLi (instead of MeLi) as described above: 1.9 g (81%). Spectroscopic characterization as diacetate: IR (KBr): 2950, 1750, 1250. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.79 (*t*, *J* = 7.2, *Me*CH_2CHO); 0.83 (*s*, Me); 0.97 (*s*, Me); 1.97 (*s*, MeCO); 1.99 (*s*, MeCO); 3.74–4.20 (*m*, 3 CH_2O); 4.85 (*m*, HCO). MS: 297 (2), 296 (2), 255 (100), 154 (7), 86 (12), 87 (10), 99 (17).

5.2. The crude product (1.9 g, 7 mmol) was oxidized as described above and isolated after purification *via* CC (pentane/acetone 80:20, 1% Et_3N): 830 mg (43.5%) of **12b**. IR (KBr): 3420, 2950, 1710. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.84 (*s*, Me); 0.86 (*s*, Me); 0.98 (*t*, *J* = 7.2, *Me*CH_2CO); 2.39 (*m*, CH_2CO); 2.53 (*m*, CHCO); 3.62–3.92 (*m*, 3 CH_2O). MS: 270 (10, M^+), 225 (4), 213 (100), 169 (12), 156 (9), 113 (17), 99 (35), 57 (15). Anal. calc. for $C_{15}H_{26}O_4$: C 66.63, H 9.68; found: C 66.34, H 9.57.

6. *1-[(1R,5R)-3,3-(Ethylenedioxy)4,4-dimethylbicyclo[3.2.1]oct-1-yl]ethanone* (**13a**). To a soln. of 1.73 g (6.75 mmol) of **12a** and 1.5 ml (10.76 mmol) of abs. Et_3N in 25 ml of abs. CH_2Cl_2 were added dropwise, between 0° and −10°, 0.61 ml (7.88 mmol) of freshly distilled methansulfonyl chloride. After stirring for 1 h at 0°, the mixture was diluted with CH_2Cl_2. The mixture was washed with aq. $CuSO_4$ soln., H_2O, dried, and concentrated *in vacuo*. The crude mesylate was dissolved in 15 ml of THF, and a soln. of 0.99 g (8.78 mmol) of *t*-BuOK in 25 ml of abs. THF was added. After stirring for 1 h at r.t., the mixture was poured into an aq. NH_4Cl soln. After extraction with Et_2O and drying, the solvent was distilled off *in vacuo*: 1.64 g (98%) of **13a** as colorless oil. Purification for spectroscopic purposes by TLC (petroleum ether/AcOEt 85:15). IR (NaCl, liq. film): 3000, 1710, 1125, 1090. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.89 (*s*, Me); 1.04 (*s*, Me); 2.14 (*s*, MeCO); 3.70–4.08 (*m*, OCH_2CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): 212.5 (CO); 111.8 (C(3)); 65.1/63.8 (2 CH_2O); 56.6 (C(1)); 48.4 (C(5)); 41.5 (C(4)); 39.5 (CH_2); 36.7 (CH_2); 30.2 (CH_2); 26.0 (*Me*CO); 25.6 (CH_2); 21.6 (2 Me). MS: 196 (13), 195 (100), 107 (5), 99 (4), 87 (8), 86 (5), 73 (8). Anal. calc. for $C_{14}H_{22}O_3$ (238.32): C 70.56, H 9.30; found: C 70.45, H 9.21.

7. *1-[(1R,5R)-3,3-(Ethylenedioxy)-4,4-dimethylbicyclo[3.2.1]oct-1-yl]propan-1-one* (**13b**). Compound **12b** (411 mg, 1.52 mmol) was converted into the mesylate and treated with *t*-BuOK as described above: 198 mg (60%). IR (NaCl, liq. film): 2910, 1710. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.81 (*s*, Me); 0.96 (*t*, *J* = 7.2, *Me*CH_2CO); 0.97 (*s*, Me); 2.42 (*m*, CH_2CO); 3.81–3.29 (*m*, 2 CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): 214.79 (CO); 111.85 (C(3)); 63.75 (CH_2O); 65.06 (CH_2O); 56.26 (C(1)); 48.24 (CH); 41.46 (Me_2C); 39.67 (CH_2); 36.48 (CH_2); 30.59 (CH_2); 30.24 (CH_2); 25.48 (CH_2); 26.02 (Me); 21.57 (Me); 8.06 (Me).

8. *(1R,5R)-4,4-Dimethyl-1-{1-[(tetrahydropyran-2-yl)oxy]ethyl}bicyclo[3.2.1]octan-3-one* (**14a**). 8.1. *(1R,5R)-1-(1-Hydroxyethyl)-4,4-dimethylbicyclo[3.2.1]octan-3-one Ethylene Ketal.* To 6.89 ml (6.89 mmol) of a 1M soln. of $LiAlH_4$ in THF at 0°, a soln. of 1.64 g (6.89 mmol) of **13a**, dissolved in 20 ml of abs. THF, was added. After stirring for 1 h at 0°, 0.27 ml of H_2O, 0.27 ml of 2N NaOH, and 0.78 ml of H_2O were added. After filtration by suction, the filtrate was concentrated *in vacuo*: 1.26 g (76%) yellowish oil.

8.2. *(1R,5R)-1-(1-Hydroxyethyl)-4,4-dimethylbicyclo[3.2.1]octan-3-one.* The crude product (1.26 g, 5.25 mmol) was dissolved in 40 ml of acetone. At 0°, 20 ml of 2N HCl was added dropwise to the soln. After stirring for 1 h at r.t., H_2O was added and the mixture extracted with CH_2Cl_2. The org. extracts were washed with H_2O, dried, and concentrated *in vacuo*. The residue was purified by TLC (pentane/acetone 9:1): 647 mg (66%) of a colorless oil. MS: 196 (29, M^+), 151 (100), 136 (28), 107 (38), 93 (30), 81 (35), 79 (23), 69 (29), 67 (24), 55 (20).

8.3. A soln. of 317 mg (1.62 mmol) of isolated product, 0.3 ml (3.24 mmol) of freshly distilled 3,4-dihydro-2*H*-pyran, and 80 mg (0.32 mmol) of TsOH in 10 ml of abs. CH_2Cl_2 was stirred at r.t. for 6 h. After dilution with Et_2O the mixture was washed with brine, dried, and concentrated *in vacuo*: 446 mg (98%) of **14a** as colorless oil. IR (NaCl liq. film): 2940, 1710, 1025. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.79–1.34 (*m*, 3 Me, aliph. H); 3.42–4.02 (*m*, OCH_2, OCH), 4.56–4.78 (*m*, OCHO). MS: 280 (1, M^+), 196 (9), 179 (12), 151 (37), 109 (8), 95 (38), 85 (100), 81 (13), 67 (17), 55 (9).

9. *(1R,5R)-4,4-Dimethyl-1-{1-[(tetrahydropyran-2-yl)oxy]propyl}bicyclo[3.2.1]octan-3-one* (**14b**). 9.1. *(1R,5R)-1-(1-Hydroxypropyl)-4,4-dimethylbicyclo[3.2.1]octan-3-one Ethylene Ketal and (1R,5R)-1-(1-Hydroxypropyl)-4,4-dimethylbicyclo[3.2.1]octan-3-one.* Reduction of 529 mg (2.1 mmol) of **13b** with $LiAlH_4$ and cleavage of the ketal as well as workup were done as described above: 328 mg (76%). MS: 210 (17, M^+), 181 (5), 151 (100), 150 (51), 121 (26), 107 (60), 81 (60), 67 (42).

9.2. The isolated product (328 mg, 1.56 mmol) was treated with 3,4-dihydro-2*H*-pyran: 457 mg (100%). IR (NaCl, liq. film): 2940, 1710, 1025. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.92–1.16 (*m*, 3 Me); 3.18–3.62 (*m*, CH_2O); 3.96 (*m*, OCH); 4.48–4.72 (*m*, OCHO). MS: 294 (2, M^+), 265 (4), 236 (9), 210 (8), 193 (15), 165 (19), 123 (8), 85 (100), 67 (24).

10. *1-[(1R,5R)-4,4-Dimethyl-3-methylidenebicyclo[3.2.1]oct-1-yl]ethanone* (**2a**). 10.1. *(1R,5R)-4,4-Dimethyl-3-methylidene-1-{1-[(tetrahydropyran-2-yl)oxy]ethyl}bicyclo[3.2.1]octane*. To a soln. of 535 mg (1.91 mmol) of **14a** in 10 ml of abs. THF were added, at 0°, 3.82 ml (1.91 ml) of 0.5M *Tebbe* reagent in toluene. After stirring at r.t. for 2 d, the same quantity of *Tebbe* reagent was added again. After stirring for further 2 d, the mixture finally was warmed up for 5 h to 50°. Then, the mixture was cooled to 0° and diluted with Et_2O, and treated with 1 ml of MeOH. The precipitate was filtered off with *Celite* and the filtrate concentrated in *vacuo*. The residue was purified by TLC (petroleum ether/AcOEt 9:1, addition of 1% Et_3N): 43 mg (15%) of colorless oil (252 mg of educt could be recovered). MS: 278 (4, M^+), 194 (9), 177 (37), 176 (31), 121 (37), 107 (23), 91 (20), 85 (100), 67 (24), 55 (22).

10.2. *[(1R,5S)-4,4-Dimethyl-3-methylidenebicyclo[3.2.1]oct-1-yl]ethanol*. A soln. of 58 mg (0.21 mmol) of product and 5 mg (0.02 mmol) of pyridinium *p*-toluenesulfonate (PPTS) in 4.0 ml of EtOH was stirred for 3 h at 55°. After the mixture was allowed to cool or r.t., the CH_2Cl_2 extracts were washed with H_2O, dried, and concentrated cautiously *in vacuo* at r.t.: 41 mg (100%) of colorless oil. MS: 177 (12), 176 (80), 161 (100), 148 (29), 119 (65), 107 (68), 105 (76), 91 (82), 79 (71), 67 (96).

10.3. To a well-stirred suspension of 73 mg (0.34 mmol) of pyridinium chlorochromate (PCC) in 3.0 ml of abs. CH_2Cl_2 a soln. of 41 mg of product in 3 ml of abs. CH_2Cl_2 was added, and the mixture was stirred for 2 h at r.t. After addn. of Et_2O, the precipitate was filtered off and the filtrate cautiously concentrated. The crude product was subjected to TLC (CH_2Cl_2): 17 mg (42%) of (–)-**2a** as colorless oil. $[\alpha]_D^{20} = -39.68$ ($c = 1$, EtOH). IR (NaCl, liq. film): 3085, 2960, 1705, 1640. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.06 (*s*, Me_{ax}); 1.07 (*s*, Me_{eq}); 1.48 (*m*, H–C(7)); 1.59 (*m*, CH_2(6)); 1.63 (*m*, H_{eq}–C(6)); 1.71 (*m*, H′–C(7)); 1.84 (*m*, H–C(5)); 2.05 (*dt*, $J = 1.5$, 11.8, H_{ax}–C(8)); 2.15 (*s*, MeCO); 2.20 (*dd*, $J = 2.8$, 13.7 H_{eq}–C(2)); 2.53 (*dq*, $J = 2.0$, 13.7, H_{ax}–C(2)); 4.76 (*m*, = $CH_{(E)}$); 4.78 (*m*, = $CH_{(Z)}$). ^{13}C-NMR (75 MHz, $CDCl_3$): 212.6 (CO); 151.8 (C(3)); 109.9 (H_2C=); 57.7 (C(1)); 48.5 (C(5)); 41.7 (C(2)); 39.7 (C(4)); 36.9 (C(8)); 30.6 (C(7)); 27.3 (Me_{ax}); 26.2 (C(6)); 26.1 (Me_{eq}); 25.8 (*Me*CO). MS: 192 (58, M^+), 177 (40), 149 (43), 136 (100), 121 (45), 107 (61), 93 (52), 91 (59), 79 (50), 67 (53). HR-MS: calc. for $C_{13}H_{20}O^+$: 192.1514; found: 192.1498 ± 0.0019.

11. *1-[(1R,5R)-4,4-Dimethyl-3-methylidenebicyclo[3.2.1]oct-1-yl]propan-1-one* (**2b**). *(1R,5R)-4,4-Dimethyl-3-methylidene-1-{1-[(tetrahydropyran-2-yl)oxy]propyl}bicyclo[3.2.1]octane*. An ethereal soln. of 457 mg (1.56 mmol) of **14b** was treated at 0° with 1.42 ml (2.84 mmol) of MeLi in Et_2O and stirred for further 90 h. The mixture was worked up as usual and the residue was dissolved in 11 ml of CH_2Cl_2 and 0.9 ml of pyridine. After addition of 0.22 ml (0.12 mmol) of freshly distilled $SOCl_2$ and stirring for 30 min at r.t., H_2O was added and worked up as usual. The resulting residue (327 mg, 1.12 mol) was treated with PPTS and with PCC as described above: 166 mg (72%) of **2b** and dihydro-isomer (50:50). Purification of **2b** was performed with a sample of 35 mg by TLC (petroleum ether/Et_2O 95:5; plates pretreated with aq. 10% $AgNO_3$ soln.). $[\alpha]_D^{20} = -41.55°$ ($c = 0.3$, EtOH). IR (NaCl, liq. film): 3095, 2980, 1705, 1640. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.04 (*t*, $J = 7.2$, *Me*CH_2); 1.06 (*s*, Me_{ax}); 1.07 (*s*, Me_{eq}); 1.48 (*m*, H–C(7)); 1.58 (*m*, CH_2(6)); 1.63 (*m*, H_{eq}–C(8)); 1.67 (*m*, H′–C(7)); 1.83 (*m*, H–C(5)); 2.05 (*dt*, $J = 1.5$, 11.8, H_{ax}–C(8)); 2.21 (*dd*, $J = 2.8$, 13.7 H_{eq}–C(2)); 2.51 (*dq*, $J = 4.0$, 7.2, $COCH_2$); 2.53 (*m*, H_{ax}–C(2)); 4.76 (*m*, = $CH_{(E)}$); 4.78 (*m*, = $CH_{(Z)}$). ^{13}C-NMR (75 MHz, $CDCl_3$): 215.0 (CO); 151.9 (C–(3)); 109.8 (CH_2=); 57.4 (C(1)); 48.4 (C(5)); 41.9 (C(2)); 39.7 (C(4)); 36.8 (C(8)); 30.9 ($COCH_2$); 30.6 (C(7)); 27.3 (Me_{ax}); 26.2 (C(6)); 26.1 (Me_{eq}); 8.0 (*Me*CH_2). MS: 206 (94, M^+), 191 (35), 177 (52), 150 (91), 149 (86), 121 (52), 107 (100), 93 (72), 79 (44), 57 (4). HR-MS: calc. for $C_{14}H_{22}O^+$: 206.1671; found: 206.1675 ± 0.0020.

REFERENCES

[1] H. Spreitzer, A. Pichler, W. Holzer, I. Toth, B. Zuchart, *Helv. Chim. Acta* **1997**, *80*, 139.
[2] A. Pichler, Ph. D. thesis, University of Vienna, 1996.
[3] M. Shahabi, Diploma work, University of Vienna, 1997.
[4] B. Maurer, *Seifen-Öle-Fette-Wachse* **1980**, *13*, 34.
[5] B. M. Trost, T. N. Nanninga, *J. Am. Chem. Soc.* **1985**, *107*, 1293.
[6] R. Henning, H. M. R. Hoffmann, *Tetrahedron Lett.* **1982**, *23*, 2305.
[7] G. L. Grunewald, D. P. Davies, *J. Org. Chem.* **1978**, *43*, 3074.
[8] N. Shimizu, M. Tanaka, Y. Tsuno, *J. Am. Chem. Soc.* **1982**, *104*, 1330.
[9] H. J. Liu, W. H. Chan, *Can. J. Chem.* **1982**, *60*, 1081.
[10] C. A. Brown, A. Yamaichi, *J. Chem. Soc., Chem. Commun.* **1979**, 100.
[11] G. Stork, A. Y. W. Leong, A. M. Touzin, *J. Org. Chem.* **1976**, *41*, 3491.

[12] G. Wittig, D. Lichtenberg, *Liebigs Ann. Chem.* **1957**, *606*, 1.
[13] S. H. Pine, R. J. Pettit, G. D. Geib, S. G. Cruz, C. H. Gallego, T. Tijerina, R. D. Pine, *J. Org. Chem.* **1985**, *50*, 1212.
[14] C. R. Johnson, B. D. Tait, *J. Org. Chem.* **1987**, *52*, 281.
[15] K. Takai, Y. Hotta, K. Oshima, H. Nozaki, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1698.
[16] B. M. Trost, Y. Masuyama, *Tetrahedron Lett.* **1984**, *25*, 173.
[17] K. Sakurai, T. Kitahara, K. Mori, *Tetrahedron* **1988**, *44*, 6581.
[18] T. H. Chan, E. Chang, *J. Org. Chem.* **1974**, *39*, 3264.
[19] M. Miyashita, A. Yoshikoshi, P. A. Grieco, *J. Org. Chem.* **1977**, *42*, 3772.
[20] D. Neuhaus and M. P. Williamson, 'The Nuclear Overhauser Effect in Structural and Conformational Analysis', VCH Publishers, New York – Weinheim – Cambridge, 1989.
[21] S. Patt, N. Shoolery, *J. Magn. Reson.* **1982**, *46*, 535.
[22] A. Bax, S. Subramanian, *J. Magn. Reson.* **1986**, *67*, 565.
[23] A. Bax, *J. Magn. Reson.* **1984**, *57*, 314.