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Selective Catalytic Hydrogenations and Hydrogenolyses VIII [1]: Stereoselective Synthesis of the Stereomeric Pilopyl Alcohols

Eberhard Reimann*, **Manfred Renz** [2], and **Helene Unger**

Department Pharmazie – Zentrum für Pharmaforschung,
Ludwig-Maximilians-Universität München, D-81377 München, Germany

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Summary. The stereoselective synthesis of pilopyl- and isopilopyl alcohol is reported. The reaction of dimethyldioxanone and diethoxyphosphoryl-butyric acid ethyl ester afforded the corresponding dioxanylidenbutyric acid ester as the key intermediate. Upon treatment with mineral acid it cyclized giving 3-ethyl-4-hydroxymethylfuran-2-one which in turn could be converted either to 3-ethyl-4-methylfuranone or pilopyl alcohol with excellent stereoselectivity and quantitative chemical yield. On the other hand, hydrogenation and subsequent cyclization of the same key compound furnished isopilopyl alcohol with good stereomeric purity and yield.

Keywords. *Horner-Wadsworth-Emmons* carbonyl olefination; Selective catalytic hydrogenation; Pilopyl and isopilopyl alcohol.

Introduction

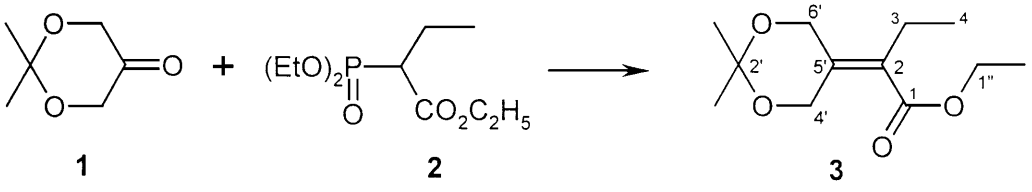
A considerable number of natural products such as pheromones, sesquiterpenes, cardiac glycosides, tetronic acids, or pilocarpine exhibiting important biological activities were found to contain the butyrolactone moiety. Their activities frequently depends on the configuration of this subunit. Thus, in connection with researches concerning structure/activity relationships, extensive work has been devoted to the stereoselective synthesis of differently substituted butyrolactones. Unexpectedly, a corresponding approach to pilopyl alcohol (**6a**) and isopilopyl alcohol (**8a**) has not been reported hitherto [3]. As part of our current interest in the synthesis of protoberberines, we required **6a** and **8a** as starting materials. Herein we present an efficient approach to the title compounds.

* Corresponding author. E-mail: ebrei@cup.uni-muenchen.de

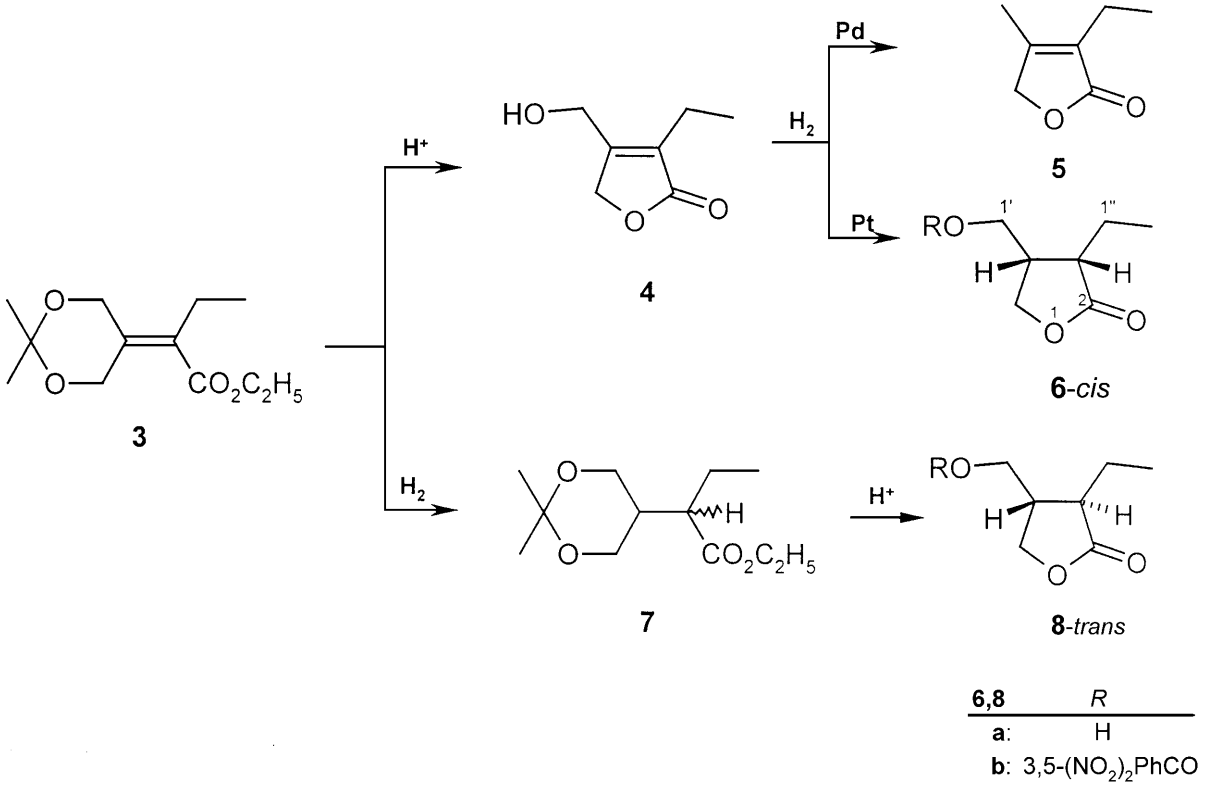
Results and Discussion

The first preparation of pilopyl derivatives was based on a malonic acid ester synthesis with α-bromobutyric acid, affording a mixture of the stereomeric pilopic acid esters as the key compounds (Scheme 2, **6a**, **8a**: CO_2R instead of CH_2OR), which in turn were separated by fractionation and freezing procedures and finally converted to the corresponding pilopyl alcohols [4–6]. However, the use of this route – being the only one to our knowledge – was little attractive especially because of the troublesome separation procedures of the stereomeric acids. This prompted us to develop a more direct and high-yield strategy depicted in Schemes 1 and 2.

The key step involved a *Horner-Wadsworth-Emmons* olefination of the easy available dioxanone **1** [7] with the phosphonate **2** [8], providing the dioxanylidene derivative **3** in good yield which in turn represented the perfect starting material to



Scheme 1



Scheme 2

form our target compounds **6a** and **8a**. Thus, treatment of **3** with dilute mineral acid resulted in cyclization to furnish the unsaturated furanone **4** in quantitative yield. The result of subsequent catalytical hydrogenation depended on the catalyst used. Employing palladium–charcoal, the hydroxy function was smoothly and selectively hydrogenolized, giving the known ethylmethylfuranone **5** [9]. In contrast, the cyclic double bond was hydrogenated by *Adams* catalyst affording the *cis*-configured pilopyl alcohol **6a** in excellent stereoselectivity. Carrying out the hydrogenation under elevated pressure and ambient temperature proved to be the most suitable conditions and afforded a *cis*/*trans* stereomer ratio of $\geq$ 99:1. Normal pressure was found both to decrease the stereomer ratio to about 88:12 and to extend the reaction time.

Using the same reactions, but in an inverted order, the isopilopyl alcohol **8a** could be also prepared in two steps starting from the dioxanylidene derivative. Thus, **3** first was hydrogenated affording the saturated compound **7** in quantitative yield. Then, consecutive treatment with dilute acid caused cyclization, providing mainly the *trans*-configured isopilopyl alcohol **8a**. The ratio of *trans*/*cis* stereomers was 92:8.

Both the configurations and the *cis*/*trans* stereomeric ratios of **6a** and **8a** could be unequivocally assigned by ^{13}C NMR spectroscopy. Because of the more extended mutual sterical hindrance of C-1′ and C-1″ in the *cis*-stereomer, their signals should occur at higher fields compared to those of the *trans*-compound. The δ-values found (59.87/18.17 *vs.* 62.32/22.63 ppm) confirmed this presumption and were in line with those observed in related furanones [10–12].

Separation of the stereomers to upgrade the stereomeric ratio of **8a** was desirable but failed. Using a mixture of the 3,5-dinitrobenzoates **6b** and **8b** and multiple development, however, separation could be achieved by TLC. Thus, the small portions of the opposite stereomers occuring in **6a** and **8a** were detectable.

In conclusion, we have established an efficient stereoselective route to the title compounds. In comparison with the first synthesis mentioned above [4–6], the overall yield could be increased from *ca.* 18% to 67 and 76% of the *trans*- and *cis*-product. Furthermore, our method should give an easy access to functional derivatives of **6a** and **8a**, which should be valuable as starting materials in natural product synthesis.

Experimental

Melting points were measured with a Reichert hot-stage microscope and are uncorrected. IR: Perkin Elmer FT-IR Paragon 1000; NMR: Jeol GSX 400 (^1H: 400 MHz, ^{13}C: 100 MHz, $CDCl_3$, *TMS* as internal reference); MS (70 eV): Hewlett Packard MS-Engine. Elemental analyses: Heraeus CHN-Rapid; the results were in good agreement with the calculated values. Thin layer chromatography (TLC): aluminum sheets Kieselgel 60 F_{254} (Merck), thickness of layer 0.2 mm. Flash chromatography (FC): ICN-Silica 32–36 60 A. 2,2-Dimethyl-[1,3]-dioxan-5-one (**1**) and 2-(diethoxyphosphoryl)-butyric acid ethyl ester (**2**) were prepared according to Refs. [7] and [8].

2-(2,2-Dimethyl-[1,3]dioxan-5-ylidene)-butyric acid ethyl ester (**3**; $C_{12}H_{20}O_4$)

To a suspension of 3.1 g NaH (60% in paraffin; 77 mmol) in 150 cm^3 anhydrous *THF*, 29.0 g (115 mmol) **2** [8] were added dropwise under N_2 and stirring at ambient temperature. Stirring was continued until dissolution of NaH was completed. After heating to reflux temperature, 10.0 g

(77 mmol) **1** [7] were added dropwise. The mixture was refluxed for 1 h under N_2, poured into 1000 cm^3 H_2O, and extracted with diethyl ether (3 × 250 cm^3). The combined ether extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue first was destillated *in vacuo* (b.r.: 97–114°C/20 Pa) and then purified by FC (*n*-hexane:EtOAc = 17:3).

Yield: 13.3 g (76%); colourless oil; TLC (eluent: see FC): $R_f = 0.50$; IR (film): $\tilde{\nu} = 1709$ (C=O), 1642 (C=C) cm^{-1}; MS (EI): m/z (%) = 228 ($M^{+\bullet}$, 10), 178 (55), 149 (65), 145 (69), 127 (100), 97 (81); ^{1}H NMR ($CDCl_3$; for numbering of atoms: see formula **3**/Scheme 1): $\delta = 4.60$, 4.30 (each s, 4′-H and 6′-H), 4.12, 2.14 (each q, $J = 6.8/7.3$ and 7.7/7.3 Hz, 1″-H and 3-H), 1.31 (s, 2 CH_3), 1.22, 0.92 (each t, each $J = 7.3$ Hz, 2″-H and 4-H) ppm; ^{13}C NMR ($CDCl_3$): 166.83 (C-1), 149.20 (C-2), 125.92 (C-5′), 99.75 (C-2′), 62.04 (C-1″), 60.34 (C-6′), 59.97 (C-4′), 23.73 (C[CH_3]$_2$), 21.13 (C-3), 14.25 (C-2″), 13.41 (C-4) ppm.

3-Ethyl-4-hydroxymethyl-5H-furan-2-one (**4**; $C_7H_{10}O_3$)

A solution of 3.0 g (13.2 mmol) **3** in 30 cm^3 EtOH was slightly acidified with 2 *N* HCl (*ca.* 3 drops) and stirred at ambient temperature until the reaction was completed (18–20 h; TLC monitoring). After diluting with 50 cm^3 H_2O and saturating with NaCl, the mixture was extracted with $CHCl_3$ (4 × 100 cm^3). The combined organic extracts were dried over Na_2SO_4 and evaporated *in vacuo*.

Yield: 1.8 g (100%); colourless oil which crystallized on cooling in the refrigator (18–20 h); m.p.: 49°C; TLC (EtOAc:$CHCl_3$ = 1:1): $R_f = 0.4$ (educt: $R_f = 0.9$); IR (Film): $\tilde{\nu} = 3438$ (br, OH), 1731 (C=O), 1671 (C=C) cm^{-1}; MS (EI): m/z (%) = 142 ($M^{+\bullet}$, 5), 125 (98), 124 (100), 97 (63); ^{1}H NMR ($CDCl_3$): $\delta = 4.79$ (s, CH_2OCO), 4.56 (s, CH_2OH), 3.41 (br s, OH), 2.21 (q, 2H, $J = 7.7$ Hz, CH_2CH$_3$), 1.05 (t, $J = 7.7$ Hz, CH$_2$CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 175.57$ (CO), 159.70 (C-3), 127.86 (C-4), 70.73 (C-5), 57.30 (CH_2OH), 16.91 (CH_2CH$_3$), 12.59 (CH$_2$CH_3) ppm.

3-Ethyl-4-methyl-5H-furan-2-one (**5**; $C_7H_{10}O_2$)

To a suspension of 285 mg prehydrogenated 10% Pd–C catalyst in 7.0 cm^3 MeOH *p.a.*, 285 mg (2 mmol) **4** were added, and the mixture was hydrogenated at ambient temperature under normal pressure. After 10 min, 50 cm^3 (theory: 44.8 cm^3) H_2 were absorbed. The catalyst was centrifuged off, and the solvent was removed *in vacuo*.

Yield: 240 mg (95%); colourless oil; TLC ($CHCl_3$:EtOAc = 1:1): $R_f = 0.69$ (educt: $R_f = 0.44$); IR (film): $\tilde{\nu} = 2972$, 1744, 1678 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 4.54$ (s, OCH_2), 2.19 (q, $J = 7$ Hz, CH_2), 1.95 (s, =C–CH_3), 0.99 (t, $J = 7$ Hz, CH_3) ppm [8].

(3R,4R/3S,4S)-3-Ethyl-4-hydroxymethyldihydrofuran-2-one
(pilopyl alcohol, **6a**; $C_7H_{12}O_3$)

A mixture of 427 mg (3 mmol) **4**, 220 mg *Adams* catalyst (PtO_2–H_2O), and 65 cm^3 EtOAc *p.a.* was hydrogenated for 2.5 h at ambient temperature and 6.8 × 10^6 Pa initial pressure of H_2. The catalyst was centrifuged off, and the solvent was removed *in vacuo*.

Yield: 426 mg (100%); colourless oil; TLC ($CHCl_3$:EtOAc = 1:1): $R_f = 0.38$ (detection with $KMnO_4$ dissolved in acetone); IR (film): $\tilde{\nu} = 3440$ (OH), 2939, 1757 (C=O) cm^{-1}; MS (CI): m/z (%) = 145 ($M^{+\bullet}$ + 1, 100), 127 (24), 99 (10); ^{1}H NMR ($CDCl_3$): $\delta = 4.43$–4.38 and 4.28–4.23 (each m, 5-H), 3.85–3.76 and 3.65–3.59 (each m, CH_2–O), 2.74–2.64 (m, 4-H), 2.57–2.50 (m, 3-H), 2.23 (br s, OH), 1.91–1.82 and 1.56–1.47 (each m, CH_2), 1.15–0.99 (m, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 179.46$ (C=O), 69.28 (C-5), 59.87 (CH_2OH), 43.11 (C-3), 39.56 (C-4), 18.17 (CH_2), 12.46 (CH_3) ppm.

(R,S)-2-(2,2-dimethyl-[1,3]dioxan-5-yl)-butyric acid ethyl ester (**7**; $C_{12}H_{22}O_4$)

To a suspension of 340 mg 5% Pd–C catalyst, *ca.* 500 mg $NaHCO_3$, and 5 drops of aqueous saturated $NaHCO_3$ in 10 cm^3 EtOH, 15.0 g (66 mmol) **3** were added, and the mixture was hydrogenated for 24 h

at ambient temperature and 8.0×10^6 Pa initial pressure of H_2. The solids were filtered off and washed with EtOH. After removing the solvent *in vacuo*, the remaining colourless oil was used for the next step without further purification.

Yield: 15.0 g (100%); TLC ($CHCl_3$:*n*-hexane:MeOH = 1:1:0.1): $R_f = 0.8$ (detection with $KMnO_4$ dissolved in acetone); IR (film): $\tilde{\nu} = 1731$ (C=O) cm^{-1}; MS (CI): m/z (%) = 231 ($M^{+\bullet} + 1$, 2), 173 (100), 79 (49); ^1H NMR ($CDCl_3$; for numbering of atoms see formula **3**/Scheme 1): $\delta = 4.09$ (q, $J = 7.1$ Hz, 1″-H), 3.86–3.82, 3.77–3.72, 3.67–3.59 (each m, 4′-H and 6′-H), 2.15 (dt, $J = 2.4/6.2$ Hz, 2-H), 2.00 (m, 5′-H), 1.53 (m, 3-H), 1.34, 1.32 (each s, 2 CH_3), 1.20 (t, $J = 7.1$ Hz, 2″-H), 0.82 (t, $J = 7.3$ Hz, 4-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 174.39$ (C=O), 97.99 (C-2′), 62.82, 62.53 (C-4′ and C-6′), 60.41 (C-1″), 46.56 (C-2), 35.88 (C-5′), 26.46 (acetal–CH_3), 22.53 (C-3), 21.36 (acetal–CH_3), 14.36 (C-2″), 11.61 (C-4) ppm.

(3R,4S/3S,4R)-3-Ethyl-4-hydroxymethyldihydrofuran-2-one
(isopilopyl alcohol, **8a**; $C_7H_{12}O_3$)

To a solution of 15.0 g (65.2 mmol) **7** in 50 cm^3 EtOH, 1 cm^3 2 *N* HCl and 3 cm^3 H_2O were added. The mixture was stirred at ambient temperature for 5.5 h and then rendered alkaline by addition of solid $NaHCO_3$. After evaporating the EtOH *in vacuo*, the mixture was diluted with 250 cm^3 H_2O and extracted with $CHCl_3$ (3×200 cm^3). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by FC (silica gel, *n*-hexane:$CHCl_3$:EtOH = 5:5:1).

Yield: 8.36 g (88%); colourless oil; TLC (eluent: see FC): $R_f = 0.5$ (detection with $KMnO_4$ dissolved in acetone; one spot, no separation of the stereomer **6a**; educt: $R_f = 0.95$); IR (film): $\tilde{\nu} = 3431$ (OH), 2968, 1758 (C=O), 1182, 1017 cm^{-1}; MS (EI): m/z (%) = 116 (28), 85 (100); (CI): 145 ($M^{+\bullet} + 1$, 100); ^1H NMR ($CDCl_3$): $\delta = 4.39$, 4.14 (each dd, $J = 7.8/1.5$ and $7.1/2.2$ Hz, CH_2OH), 3.78–3.72, 3.69–3.61 (each m, CH_2OCO), 3.40 (*pseudo*-t, $J = 5.0$ Hz, OH), 2.56–2.46 (m, 4-H), 2.44–2.38 (m, 3-H), 1.83–1.62 (m, CH_2), 1.02 (t, $J = 7.4$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 180.15$ (C=O), 69.33 (C-5), 62.32 (CH_2OH), 42.75 (C-3), 42.29 (C-4), 22.63 (CH_2), 11.06 (CH_3) ppm (the spectrum contained small peaks revealing *ca.* 8% of the *cis*-stereomer **6a**).

3,5-Dinitrobenzoic acid (3R,4S/3S,4R)-4-ethyl-5-oxo-tetrahydrofuran-3-ylmethyl ester
(pilopyl 3,5-dinitrobenzoate, **6b**; $C_{14}H_{14}N_2O_8$)

To a solution of 110 mg (0.76 mmol) **6a** in 0.35 cm^3 anhydrous pyridine, a solution of 250 mg (1.09 mmol) 3,5-dinitrobenzoyl chloride in 1.5 cm^3 pyridine was added. The mixture was heated for 10 min at 60°C, then diluted with 6 cm^3 H_2O and cooled in an ice bath for 4 h. The crystalline product was filtered off, washed with ice-cold H_2O, dried *in vacuo*, and recrystallized from MeOH.

Yield: 216 mg (84%); colourless platelets; m.p.: 111–112°C; TLC ($CHCl_3$:EtOAc:petroleum ether = 11:4:1, developing twice over a path of 6 cm): $R_f = 0.65$ (an additional very small spot at $R_f = 0.74$ indicated the presence of **8b**).

3,5-Dinitrobenzoic acid (3R,4R/3S,4S)-4-ethyl-5-oxo-tetrahydrofuran-3-ylmethyl ester
(isopilopyl 3,5-dinitrobenzoate, **8b**; $C_{14}H_{14}N_2O_8$)

Preparation from 110 mg **8a** according to **6b**.

Yield: 229 mg (89%); m.p.: 101–102°C (MeOH); TLC (see **6b**): $R_f = 0.74$ (a small spot at $R_f =$ 0.65 indicated the presence of **6b**).

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