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SYNTHESIS OF PSYMBERIC ACID

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Dedicated to Prof. Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday

Abstract – A short synthesis of the unique side-chain of psymberin (**1**) – the psymberic acid (**4**) – is presented. Notable features of it include a highly selective aldol addition and an attempted enzymatic resolution step.

Psymberin (or irciniastatin A) (**1**), isolated from marine sponges (*Psammocinia sp.*[1] and *Ircinia ramose*[2]), is a member of the pederin (**2**) family. In contrast to other polyketides of this class,[3] psymberin is potent as well as selective against a number of solid tumors thus triggering considerable synthetic efforts.[4] A common feature to all compounds is the central pyran core (either as a pyran or a related trioxadecalin). The pederic acid (**3**) side chain is invariant; however, psymberic acid (**4**) in psymberin (**1**) is unique. Here we disclose our preliminary results on the synthesis of psymberic acid (**4**).

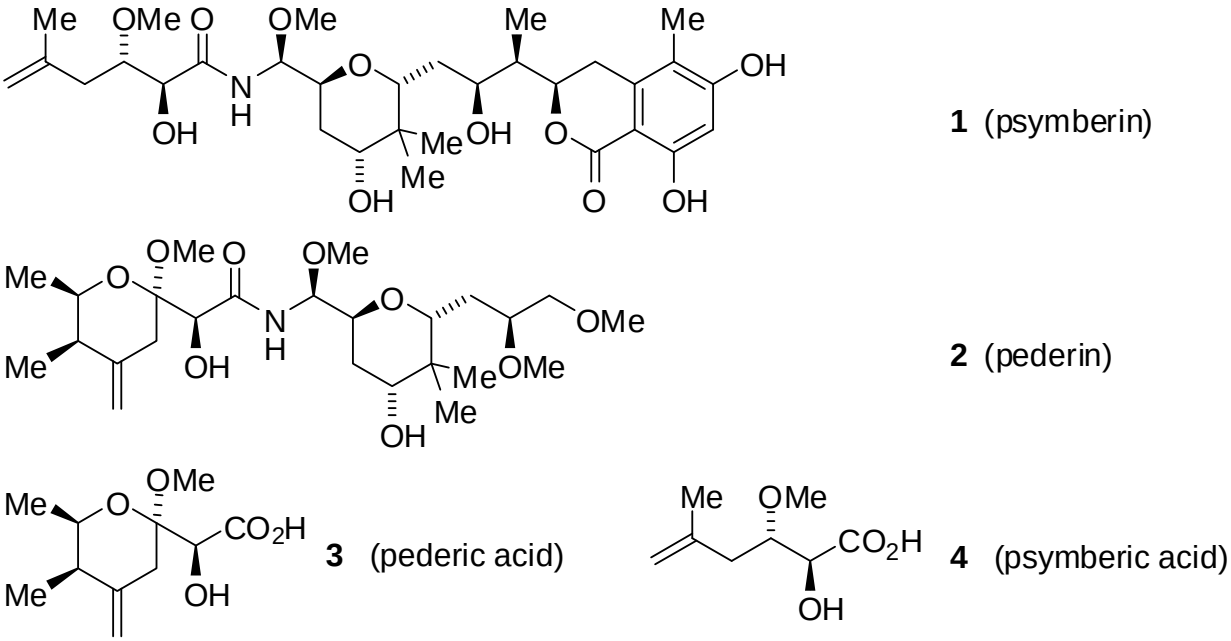
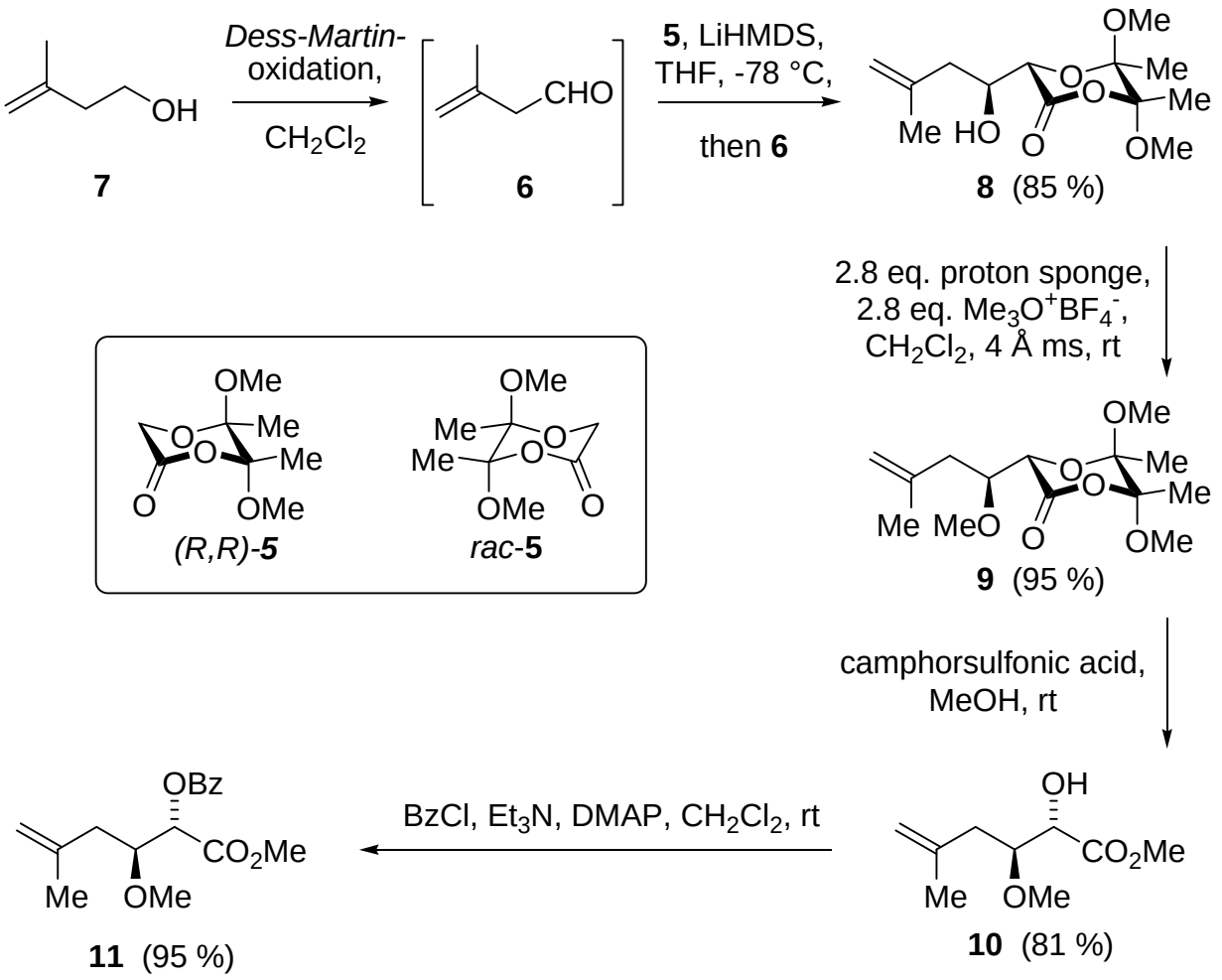


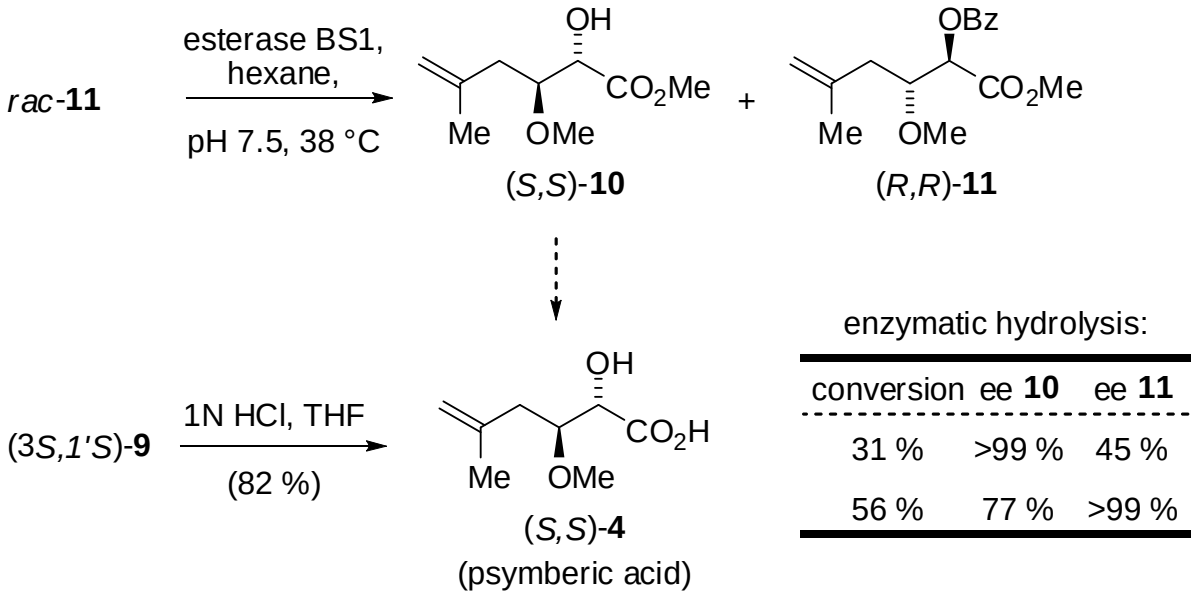
Figure 1 Members of the pederin family.

The starting point of our efforts were the chiral glycolic acid anion equivalents **5** that are readily available both in racemic as well as enantiomerically pure form (Scheme 1).[5] The key-step to set-up the 2 stereogenic centers was an aldol reaction between the enolate of the protected glycolic acid **5** and aldehyde **6**. The aldehyde **6** is accessible *via* oxidation of the corresponding alcohol **7**. Although the deconjugated product **6** could be isolated and purified, the yields were usually relatively low (62-64 %). Preferentially, the crude aldehyde **6** was directly added to the preformed enolate (from **5**) at -78 °C. The *anti*-aldol product **8** was isolated in 85 % yield; no *syn*-side-product was detected.[5] Next, *O*-methylation was attempted. As expected, standard deprotonation (e.g. with NaH), but also some less common variants (e.g. using Al_2O_3/Me_2SO_4), did not furnish product **9**. Utilizing a proton sponge [1,8-bis(dimethylamino)naphthalene] – which proved to be superior to $Et(i\text{-}Pr)_2N$ – and Meerwein's salt did finally furnish the desired ether **9** in respectable yield (95 %). Deprotection to the α-hydroxy ester **10** (81 %) and re-protection with benzoyl chloride was straight-forward; the benzoate **11** was obtained in >95 % yield. The sequence described was performed starting from *rac*-**5** as well as (*R,R*)-**5**.[6]



Scheme 1 Synthesis of key intermediates towards psymberic acid (**4**).

With the racemic and enantiomerically pure intermediates **10** and **11** in our hands, we established an analytical base for a kinetic enzymatic resolution {HPLC on Chiracel OD-H stationary phase, 250 x 4.6 mm, heptane:i-PrOH 95:5, 33 bar: t_R [(*S,S*)-**11**] = 10.4 min, t_R [(*R,R*)-**11**] = 11.4 min, t_R [(*S,S*)-**10**] = 14.4 min, t_R [(*R,R*)-**10**] = 16.8 min} which would utilize the cheaper racemic ester *rac*-**11**. Upon screening 24 different hydrolases, only moderate results were observed: While no lipase showed any conversion, some esterases were active. Unfortunately, the selectivity was in most cases not high. As a matter of fact, only 2 esterases (chirazyme E3 from Roche Diagnostics GmbH and esterase BS1 from Julich Chiral Solutions GmbH) were moderately active and sufficiently selective (>96 % ee of the substrate **11**) for our purposes. Best results were obtained with the esterase from *Bacillus subtilis* (BS1; Scheme 2). It was most convenient to optimize the conversion in order to isolate enantiomerically pure starting material (56 % conversion, 31 % yield, >99 % ee); however, the analysis proved that with respect to the desired natural product the wrong enantiomer (*R,R*)-**11** was isolated. Hence we focused on the isolation of the alcohol (*S,S*)-**10** at low conversion. When following the reaction by glc it was shown that the product was indeed enantiomerically pure throughout the enzymatic conversion. Nevertheless, no accumulation of product was observed and only low quantities of alcohol **10** could be detected. We speculated that psymberic acid (**4**) was directly formed in a consecutive step, but in no case considerable amounts could be isolated directly or after derivatisation (esterification with TMS-diazomethane). Instead a considerable number of side-products were detected rendering the biocatalytical approach unpractical at present. A non-enzymatic solution was the convenient hydrolysis of 1,4-dioxan-2-one (3*S,1'S*)-**9** [from (*R,R*)-**5**]. The natural psymberic acid (**4**) was obtained in 82 % yield {$[\alpha]^{22}_D$ = +21.6 (*c* = 0.25, $CHCl_3$); all data in full agreement with those presented in the literature.[4]}.



Scheme 2 Syntheses of psymberic acid (**4**).

To conclude a short synthesis of the title compound was presented. In only 3 steps and 66 % overall yield from (*R,R*)-**5** (or 4 steps from alcohol **7**) psymberic acid (**4**) could be obtained. An alternative biocatalytical route was also devised: However, the only practical protocol for a kinetic enzymatic resolution *via* an esterase would unfortunately yield the enantiomer of the natural product. Further studies are in progress to adopt the current results for a total synthesis of psymberin (**1**) and related analogues.

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6. Selected data of key intermediates; (*3S,5R,6R,1'S*)-**9**: R_f = 0.37 (PE:EA 90:10); MS (ESI): m/z (%) = 311 (100) [M + Na^+]; IR (film): 1748 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): 1.43, 1.49 (2 s, 6 H, 5- and 6-Me), 1.78 (s, 3 H, 3'-Me), 2.12 (dd, *J* = 14.7 Hz and 3.4 Hz, 2'-H_a), 2.57 (dd, *J* = 14.7 Hz and 9.4 Hz, 2'-H_b), 3.33, 3.41 (2 s, 6 H, 5- and 6-OMe), 3.46 (s, 3 H, 1'-OMe), 3.88 (ddd, *J* = 9.4, 3.4 Hz and 2.6 Hz, 1'-H) 4.45 (d, *J* = 2.6, 3-H), 4.82 (br, 2 H, 4'-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): 16.94, 17.94 (5- and 6-Me), 22.70 (3'-Me), 38.81 (C-2'), 49.14, 49.81 (5- and 6-OMe), 58.17 (1'-OMe), 71.03 (C-3), 80.79 (C-1'), 98.32, 105.23 (C-5 and C-6), 112.79 (C-4'), 142.49 (C-3'), 167.78 (C-2); $[\alpha]_D^{20}$ = –179 (c = 0.11, $CHCl_3$). (*2S,3S*)-**11**: R_f = 0.15 (PE:EA 98:2); MS (ESI): m/z (%) = 315

(100) [M + Na^+]; IR (film): 1724 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): 1.80 (s, 3 H, 5-Me), 2.41 (dd, *J* = 14.4 Hz and 4.9 Hz, 4-H_a), 2.52 (dd, *J* = 14.4 Hz and 7.9 Hz, 4-H_b), 3.50 (s, 3 H, 3-OMe), 3.79 (s, 3 H, CO_2Me), 3.92 (ddd, *J* = 7.9, 4.9 Hz and 2.6 Hz, 3-H), 4.85, 4.87 (2 br, 2 H, 6-H), 5.55 (d, *J* = 2.6 Hz, 2-H), 7.47-8.10 (m, 5 H, arom. H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): 22.70 (5-Me), 39.09 (C-4), 52.44 (CO_2Me), 58.27 (3-OMe), 73.30 (C-2), 79.50 (C-3), 113.48 (C-6), 128.48, 129.33, 129.96, 133.47 (arom. C), 141.50 (C-5), 165.84 (C=O), 168.59 (C-1); $[\alpha]_D^{20}$ = +15 (c = 0.16, $CHCl_3$).