The Total Synthesis of (+)-Petasin and (+)-Isopetasin

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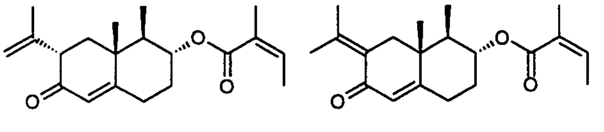
Petasin **1** and isopetasin **2**, anti-inflammatory and analgesic components of the butterbur (*Petasites hybridus*), were prepared for the first time in a short and enantioselective synthesis. The key steps were a Michael addition/alkylation (**7** → **8**), an enamine alkylation to give **9** and a cyclization with *N*-phenyliminoketenylidenetriphenylphosphorane **11** (**10** → **15**).

Extracts of the butterbur (*Petasites hybridus*) have been used for centuries as a cure for inflammations and spasms.[1] Their therapeutic applications were described in the first century by Dioskurides, the physician of Claudius and Nero, in his 'De materia medica'. The major physiological active ingredients were identified[2] in the 1950s as the eremopilane sesquiterpenes (+)-petasin (**1**) and (+)-isopetasin (**2**). In the 1960s degradation and ORD-experiments confirmed the absolute configuration.[3]



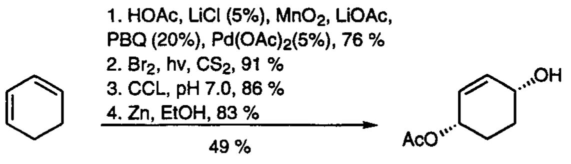
(+)-Petasin 1 (+)-Isopetasin 2

Scheme 1

In recent years several highly interesting pharmacological properties have been attributed to the *Petasites* extracts.[4] Besides analgetic and anti-inflammatory activities the extract exhibits a high cyto- and ulcusprotective activity and a high antiproliferation activity against human T24 bladder carcinoma cells in vitro.[5] Studies of our group in cooperation with K. Brune[6] showed that **1** and **2** also have a strong influence on the biosynthesis of leucotrienes. For further examinations larger amounts of these compounds were necessary. Because of the presence of a variety of similar sesquiterpenes in the extracts, the isolation of sufficient amounts of pure **1** and **2** from plant material was not successful. This prompted us to attempt a practical synthesis of enantiomerically pure **1** and **2**.[7]

The only eremopilane found in the butterbur, that has been synthesized so far, is racemic (±)-isopetasol **18**,[8] the corresponding alcohol to isopetasin **2**. Our synthesis starts with the readily available (1*S*,4*R*)-(−)-1-acetoxycyclohex-2-en-4-ol (**4**). Compound **4** has been synthesized via an enantioselective cleavage of a *meso* diester, prepared from cyclohexa-1,3-diene (**3**), by Kazlauskas and Bäckvall[9] in > 97 % ee. We performed this synthesis on a scale of over 100 mmols of **4** with an optimized total yield of 49 %.

The alcohol **4** was protected as the *tert*-butyldimethylsilyl ether **5** (83 %). The acetate group was cleaved with $MeOH/K_2CO_3$ (86 %) to give **6**. For the determination of the enantiomeric purity of **6** the alcohol was esterified with (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid [(*S*)-MTPA]. The ^1H NMR and ^{19}F NMR spectra showed an enantiomeric eccess of > 90 %. Collins oxidation of the allylic alcohol **6** gave (4*R*)-(+)-*tert*-(butyldimethylsiloxy)cyclohex-2-en-1-one (+)-**7** (82 %). Danishefsky has shown that the enantiomer (−)-**7** is a versatile building block, which was used in several natural product syntheses.[10]



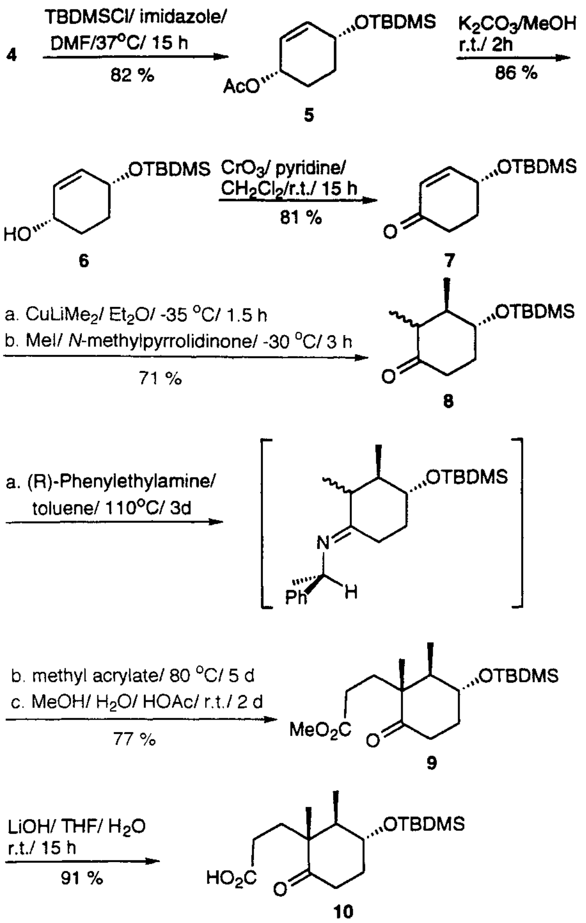
3 4

PBQ = *p*-benzoquinone; CCL = lipase of *Candida cylandrea*
Scheme 2

The success of the subsequent Michael addition/alkylation was highly dependent upon the solvent and the temperature. For the initial dimethylcuprate addition diethyl ether was shown to be a superior solvent. Addition of a polar cosolvent was essential for the subsequent methylation of the intermediate enolate. The carcinogenic hexamethylphosphoramide (HMPA) could be successfully substituted by *N*-methylpyrrolidin-2-one (NMP)[11] with identical yields of **8** (70 %). ^1H NMR spectroscopy of the crude product showed a 9 : 1 epimeric mixture in the 2-position. No 3-epimer could be detected. The relative configuration at C-3 and C-4 of **8** was assigned in analogy to the known antiselective cuprate additions to (−)-**7**[10] and by subsequent transformation to known compounds.

Under a variety of conditions that we have examined to alkylate the thermodynamically more stable enolate of **8**, we observed significant amounts of polyalkylation and low regio- and diastereoselectivity (2 : 1–3 : 1). Alkylations of imines of several achiral amines like benzylamine or cyclohexylamine with methyl acrylate were also not selective. In contrast, the imine with (*R*)-(+)-1-phenylethylamine that is formed, alkylated with methyl acrylate and cleaved in a one-pot procedure according to Pfau,[12] gives **9** in a regio- and diastereoselective manner (selectivity 8 : 1; yield for the one-pot procedure 77 %). The relative orientation of the stereocenters has been proven after the cyclization to **15** and is in accordance with the model of the enamine alkylation proposed by Pfau.[12] Cleavage of the ester with LiOH in water/THF gave the crystalline, diastereomerically pure oxo acid **10** (91 %).

We have previously described the cyclization of γ- and δ-oxo acids with *N*-phenyliminoketenylidenetriphenyl-

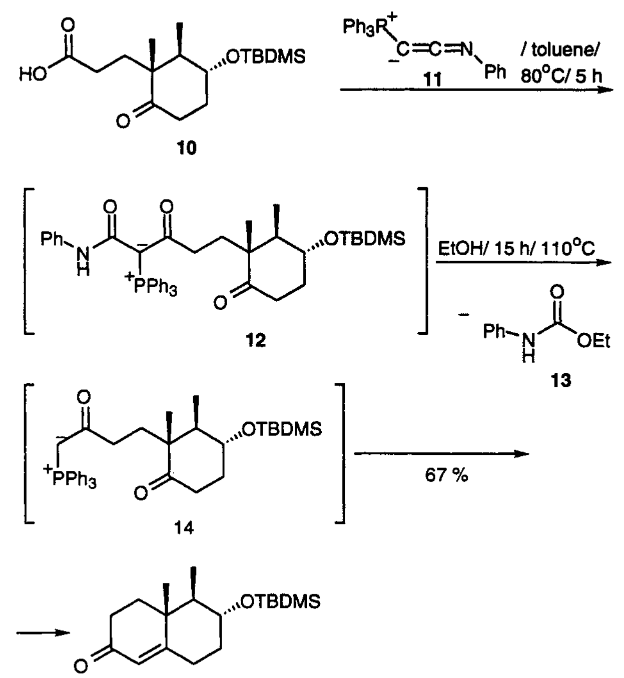


Scheme 3

phosphorane **11**[13] to cyclic enones,[14] e.g. anti-Bredt alkenes. We describe now a one-pot procedure for this reaction. We treated **10** with **11** in toluene at 80 °C, then added ethanol and heated the reaction mixture to reflux to give directly enone **15** in 67 % yield. In this reaction the acid **10** reacts with **11** to form the bis-acyl ylid **12**, which undergoes further reaction with the alcohol to form the acyl ylid **14** and a urethane **13**. The acyl ylid **14** cyclizes in situ to form enone **15**.

Irradiation at the ^{1}H NMR resonance frequencies of the two methyl groups of **15** showed a positive nuclear Overhauser Effect (NOE) for the carbinol proton. This indicates a *cis*-configuration of these groups as depicted in Scheme 4. Compound **15** has been used before as an intermediate in the synthesis of sporogene-AO 1 and related natural products.[8f] In this synthesis **15** was prepared via a different route in 17 steps, compared to 11 steps starting from cyclohexadiene in our aproach (or 7 steps from known **4**).

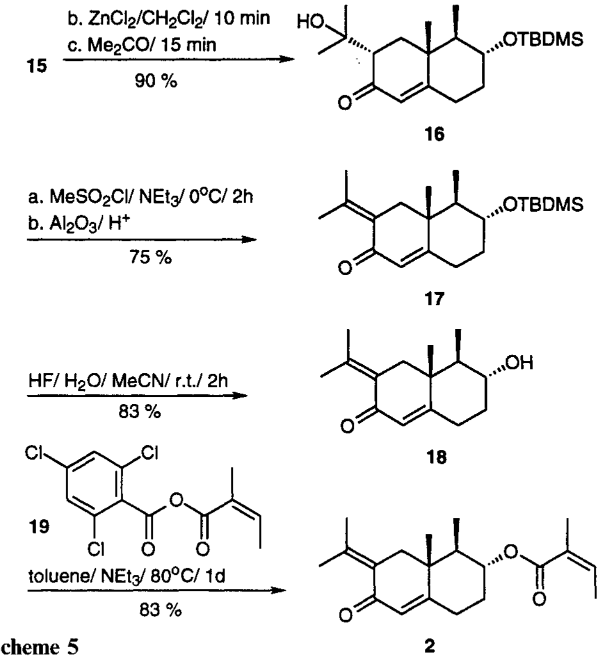
The zinc chloride catalyzed aldol reaction of the lithium enolate of **15** with acetone gave the alcohol **16** (90 %) as a single diastereomer. The relative configuration has been assigned in analogy to the aldol reaction of similar compounds[8a] and by subsequent transformation to (+)-petasin **1**. Elimination of the tertiary alcohol of **16** with methanesulfonyl chloride and triethylamine resulted in a 3 : 1 mixture of products with a terminal and an internal



Scheme 4

double bond. This mixture was directly isomerized with acidic alumina to the more stable isomer with the internal double bond, which is the TBDMS-ether of isopetasol **17** (75 %). Cleavage of the TBDMS ether with aqueous HF/acetonitrile provided isopetasol **18** (83 %).

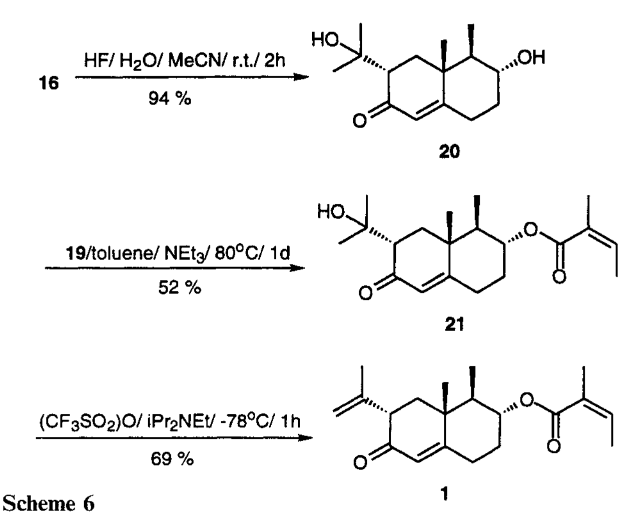
Until recently[15] no successful esterifications of alcohols with (*Z*)-2-methylbut-2-enoic acid (angelic acid) have been described because of the facile isomerisation of angelic esters under nucleophilic esterification conditions to the more stable tiglic esters. Activation of the acid with trichlorobenzoyl chloride[16] and reaction with **18** gave isopetasin **2** (83 %). In the ^{1}H NMR of the crude reaction mixture no isomeric ester could be detected.



Scheme 5

The enantioselective total synthesis of isopetasin **2** has therefore been performed in 11 steps and 9.1 % overall yield starting from **4**.

Cleavage of the silyl ether of **16** with HF/acetonitrile (94 %) gave **20**. The secondary alcohol group of **20** was selectively esterified with the mixed anhydride **19**. Due to the slow simultaneous elimination of the tertiary alcohol under the reaction conditions the reaction was stopped after ca. 75 % conversion. Isopetasin **2** (20 %), **20** (25 %) and the monoester **21** (39 %, 52 % based on recovered **20**) were isolated by chromatography on silica gel. Elimination of the tertiary alcohol of **21** with trifluoromethanesulfonic anhydride and diisopropylethylamine gave, as determined by gas chromatography, a 6 : 1 ratio of petasin **1** and isopetasin **2** in the crude product mixture. Petasin **1** isomerized slowly during workup and purification to isopetasin **2**. Isopetasin **2** (17 %), **21** (32 %) and petasin **1** (48 %, 62 % based on reovered **21**) were finally isolated by careful flash chromatography on silica gel.



Scheme 6

The overall yield of petasin **1** was 4.3 % over 11 steps starting from **4**. The spectroscopical and physical properties of synthetic petasin **1**, isopetasin **2**, and isopetasol **18** were in agreement with those reported for the natural products.

All melting and boiling points are uncorrected. NMR spectra were recorded on a JEOL JNM GX 400 FT spectrometer. IR spectra were recorded on a Beckmann Acculab A8 spectrophotometer. Optical rotations were measured on a Schmidt & Haensch Polartronic E polarimeter. Mass spectra were recorded on a Varian MAT 311 spectrometer at 70 eV. Column chromatography was carried out on columns packed with Merck Kieselgel 60 (Art. Nr. 7734). For all new compounds satisfactory microanalyses (C,H $\pm$ 0.4 %) were obtained from a Hareaus Mikromat C–H–N. All reactions were carried out under N_2. Solvents were purified according to the standard procedures.

Acetic Acid (1*S*,4*R*)-(−)-4-Hydroxycyclohex-2-enyl Ester[9] (4):

The literature procedures[9] have been scaled up without major changes. The workup on a larger scale of the palladium catalyzed oxidation of cyclohexadiene and the enzymatic ester hydrolysis proved to be difficult because of the formation of emulsions. The general problem of the formation of emulsions could be solved by dilution of the crude reaction mixture with the same amount of Et_2O and slow addition of the mixture to half the volume of stirred Na_2SO_4. The resulting slurry was washed five times with Et_2O. The combined organic phases were extracted with sat. $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated in vacuo to give the crude products. Further purification has been performed according to the literature procedures.

Acetic Acid (1*R*,4*S*)-(−)-(*tert*-Butyldimethylsiloxy)cyclohex-2-enyl Ester (5):

To a solution of **4** (16.2 g, 104 mmol) in DMF (70 mL), imidazole (17.9 g, 259 mmol) and TBDMSCl (18.8 g, 124 mmol) were added. The solution was stirred at 37 °C for 15 h. After cooling to r.t. the solution was added to H_2O (400 mL) and the aqueous phase was extracted with Et_2O (3 × 400 mL). The collected organic phases were washed with brine (2 × 100 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was distilled in a Kugelrohr aparatus (0.05 mbar, bath temperature 68–70 °C) to give **5** as a colorless oil; yield 23.3 g (82 %); $[\alpha]_D^{20}$ −35.3 (c = 1.6, $CHCl_3$).

IR (film): ν = 2940, 2900, 2840, 1730, 1240, 1085 cm^{-1}.

^1H NMR ($CDCl_3$, TMS): δ = 5.83 (dd, 1 H, J = 3.6, 10.4 Hz), 5.71 (dd, 1 H, J = 3.7, 10.4 Hz), 5.12 (m, 1 H), 4.14 (m, 1 H), 2.01 (s, 3 H), 169–1.89 (m, 4 H), 0.87 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 170.7, 136.4, 126.2, 67.0, 66.3, 28.4, 25.8, 25.3, 21.3, 18.1, −4.7.

MS: m/z (%) = 270 (M^+, 1), 213 (4), 117 (100), 75 (60).

(1*R*,4*S*)-(+)-4-(*tert*-Butyldimethylsiloxy)cyclohex-2-enol (6):

Compound **5** (23.3 g, 86.2 mmol) was dissolved in MeOH (50 mL) then added to a suspension of K_2CO_3 (35.7 g, 258 mmol) in MeOH (300 mL) and stirred for 2 h at r.t. The suspension was filtered, the filtrate washed with MeOH (3 × 20 mL) and the solution concentrated in vacuo. The residue was dissolved in Et_2O (400 mL) washed with sat. NH_4Cl (2 × 200 mL), brine (2 × 200 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed on silica gel (500 g) with hexanes/EtOAc (6 : 1 → 1 : 1) to give **6** as a colorless oil; yield: 17.0 g (86 %); bp (0.05 mbar, Kugelrohr bath temperature) 72–75 °C; $[\alpha]_D^{20}$ +25.4 (c = 1.3, $CHCl_3$).

IR (film): ν = 3300, 2920, 2900, 2850, 1250, 1080, 1020 cm^{-1}.

^1H NMR ($CDCl_3$, TMS): δ = 5.74 (dd, 1 H, J = 3.1, 9.9 Hz), 5.66 (dd, 1 H, J = 2.5, 9.9 Hz), 4.07 (m, 1 H), 4.03 (m, 1 H), 2.54 (br, 1 H), 1.63 − 1.76 (m, 4 H), 0.84 (s, 9 H), 0.02 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 133.6, 130.7, 66.2, 64.6, 28.3, 28.2, 25.8, 18.1, 4.7.

MS: m/z(%) = 228 (M^+, 1), 213 (2), 171 (95), 75 (100).

(4*R*)-(+)-*tert*-Butyldimethylsiloxy)cyclohex-2-enone (7):

CrO_3 (43.6 g, 436 mmol) was added to a stirred solution of pyridine (68.8 g, 871 mmol) in CH_2Cl_2 (1 L) and the red-brown solution was stirred for 30 min at r.t. Compound **6** (16.6 g, 72.6 mmol) in CH_2Cl_2 (100 mL) was added and the resulting suspension was stirred at r.t. for 15 h. To avoid the formation of an emulsion the mixture was added to stirred Na_2SO_4 (400 g) and the flask was washed with additional CH_2Cl_2 (2 × 100 mL) which was added to the slurry. After stirring for 30 min the CH_2Cl_2 was decanted and the Na_2SO_4 was washed with CH_2Cl_2 (4 × 100 mL). The collected organic phases were washed with sat. $NaHCO_3$ (2 × 100 mL), 2 % H_2SO_4 (2 × 100 mL), sat. $NaHCO_3$ (100 mL), brine (2 × 100 mL) and dried (Na_2SO_4). Concentration in vacuo and chromatography (300 g silica gel, 6 : 1 hexanes/EtOAc) gave **7** as a colorless oil; yield 13.4 g (81 %); bp (0.05 mbar, Kugelrohr bath temperature) 60–65 °C; $[\alpha]_D^{20}$ +107.1 (c = 1.3, $CHCl_3$).

IR (film): ν = 3000, 2940, 2840, 1675, 1375, 1250 cm^{-1}.

^1H NMR ($CDCl_3$, TMS): δ = 6.83 (ddd, 1 H, J = 10.2, 2.4, 1.7 Hz), 5.92 (ddd. 1H, J = 10.2, 2.0, 1.0 Hz), 4.53 (m, 1 H), 2.58 (m, 1 H), 2.35 (ddd, 1 H, J = 16.7, 12.4, 4.7 Hz), 2.21 (m, 1 H), 2.00 (m, 1 H), 0.92 (s, 9 H), 0.13, 0.12 (2s, 6 H).

MS: m/z(%) = 226 (M^+, 1), 169 (100), 151 (26).

(2*RS*,3*R*,4*R*)-(−)-4-(*tert*-Butyldimethylsiloxy)-2,3-dimethylcyclohexanone (8):

To a suspension of CuI (7.07 g, 37.1 mmol) in Et_2O (150 mL) at 0 °C MeLi (46.4 mL, 1.6 M in Et_2O, 74.2 mmol) was added. The resulting colorless solution was stirred for 1 h at 0 °C and cooled with a MeOH/dry-ice bath to −60 °C internal temperature. To this solution via a transfer needle a solution of **7** (8.00 g, 35.3 mmol), precooled to 0 °C, in Et_2O (50 mL) was added, so that the internal temperature did not rise above −55 °C (ca. 30 min). The flask was placed into a second ice-bath, precooled to −35 °C, and the resulting yellow suspension was stirred for 100 min at an internal temperature of −35 to −30 °C. The flask was cooled to −70 °C and MeI (17.6 mL, 40.1 g, 282 mmol) in *N*-methylpyrrolidinone (50 mL) was added rapidly (5 min) via a transfer needle to the intensely stirred suspension. During the addition, the internal temperature rose to −30 °C and this temperature (−30 to −35 °C) was maintained for 3 h. During this time the yellow precipitate dissolved and a white precipitate formed. After the reaction was complete (TLC), sat. NH_4Cl/NH_3 (1 : 1)-buffer (20 mL) was added, the suspension was warmed to r.t. and diluted with hexanes/EtOAc (1 : 1, 500 mL). Extraction with NH_4Cl/NH_3 (1 : 1, 2 × 200 mL), H_2O (2 × 50 mL) and brine (2 × 100 mL), drying (Na_2SO_4) and concentration in vacuo gave an oil that was chromatographed over silica gel (200 g; 10 : 1 hexanes/EtOAc) to give **8** (9 : 1 mixture of C-2-epimers according to GC) as a colorless oil. On storage the minor product slowly epimerized to the major; yield 6.41 g (71 %); bp (0.05 mbar, Kugelrohr heating bath) 65–70 °C, $[\alpha]_D^{20}$ (Major) −35.8 (c = 1.06, $CHCl_3$).

IR (major, film): ν = 1940, 1920, 1850, 1840, 1705, 1500, 1245, 1100, 1060, 830, 765 cm^{-1}.

^{1}H NMR (major, $CDCl_3$/TMS): δ = 3.64 (m, 1 H), 2.31-2.46 (m, 2H), 2.03-2.16 (m, 2H), 1.72 (m,1H), 1.48 (m, 1H), 1.07 (d, 3H, J = 6.7 Hz), 1.06 (d, 3H, J = 6.7 Hz), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H).

^{13}C NMR (major, $CDCl_3$); δ = 211,6, 74.2, 48.3, 47.1, 38.4, 34.1, 25.8, 18.0, 17.3, 12.3, −4.2, −4.7.

MS: m/z(%) = 256 (M$^+$, 1), 241 (5), 199 (100), 75 (63).

(1*R*,2*R*,3*R*)-(−)-3-[3-(*tert*-Butyldimethylsiloxy)-1,2-dimethyl-6-oxocyclohexyl]propionic Acid Methyl Ester (9):

Compound **8** (9 : 1 epimeric mixture, 1.80 g, 70.02 mmol) was dissolved in toluene (20 mL) and (*R*)-(+)-1-phenylethylamine (1.09 mL, 8.42 mmol) was added. The solution was heated to reflux under azeotropic removal of H_2O for 3 days. The toluene was evaporated with an oil pump, methyl acrylate (6.30 mL, 6.02 g, 70.2 mmol) was added and the solution was heated for 3 days to 80 °C. The solution was evaporated with an oil pump, MeOH (5 mL) and 20 % HOAc (3 mL) were added and the solution was stirred at r.t. for 48 h. Et_2O (2 mL) was added and the organic phase was extracted with 2 % H_2SO_4 (2 × 50 mL), sat. $NaHCO_3$ (2 × 20 mL), brine (2 × 20 mL) and dried (Na_2SO_4). Concentration in vacuo and chromatography on silica gel (hexanes/EtOAc 6 : 1) gave **9** as a colorless oil that contained less than 5 % (GC, ^{1}H NMR resonance of the singlet at 1.06 ppm) of the C-2-epimer; yield 1.86 g (77 %); $[\alpha]_D^{20}$ −19.5 (c = 2.2, $CHCl_3$).

IR (film): ν = 2920, 2850, 1725, 1695, 1450, 1430, 1245, 1060, 825, 775 cm^{-1}.

^{1}H NMR ($CDCl_3$, TMS): δ = 4.08 (m, 1 H), 3.62 (s, 3 H), 1.60–2.60 (m, 8 H), 0.98 (s, 3 H), 0.91 (d, 3 H, J = 7.2 Hz), 0.87 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 213.8, 174.1, 71.6, 51.5, 50.5, 44.5, 35.5, 33.4, 30.5, 29.2, 25.8, 20.1, 18.0, 12.6, −4.3, −4.8.

MS: m/z(%) = 342 (M$^+$, 1), 327 (4), 311 (20), 285 (100).

(1*R*,2*R*,3*R*)-(−)-3-[*tert*-Butyldimethylsiloxy)-1,2-dimethyl-6-oxocyclohexyl] Propionic Acid (10):

Compound **9** (1.80 g, 5.26 mmol) was dissolved in THF (20 mL), LiOH solution (0.5 M in H_2O, 20 mL) was added and the solution was stirred at r.t. for 15 h. The solution was concentrated in vacuo and Et_2O (100 mL) and 2 % H_2SO_4 (50 mL) were added. Extraction, washing of the organic phase with brine (2 × 20 mL), drying (Na_2SO_4), concentration in vacuo and chromatography over a short column (30 g silica gel, CH_2Cl_2/MeOH 20 : 1) gave **10** as colorless crystals. Compound **10** was recrystallized from hexanes, whereby the small contamination with the minor C-2-epimer remained in solution; yield: 1.58 g (91 %); mp 71–73 °C; $[\alpha]_D^{20}$ −23.3 (c = 5.6, CCl_3).

IR (CCl_4): ν = 2920, 2850, 1700, 1460, 1250, 1090, 1070, 830, 770 cm cm^{-1}.

^{1}H NMR ($CDCl_3$, TMS): δ = 3.75 (m, 1 H), 1.60–2.60 (m, 8 H), 0.99 (s, 3 H), 0.91 (d, 3 H, J = 7.2 Hz), 0.87 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 214.1, 179.8, 71.6, 50.5, 44.5, 35.5, 33.5, 30.5, 29.2, 24.8, 20.1, 18.0, 12.5, −4.3, −4.8.

MS: m/z(%) = 328 (M$^+$, 1), 313 (1), 271 (45), 179 (95), 75 (100).

(4a*R*,5*R*,6*R*)-(+)-6-(*tert*-Butyldimethylsiloxy)-4a,5-dimethyl-4,4a,5,6,7,8-hexahydro-3*H*-naphthalen-2-one (15):

Compounds **10** (2.10 g, 6.39 mmol) and **11** (2.90 g, 7.68 mmol) were dissolved in toluene (60 mL) and heated to 80 °C for 5 h. EtOH (3 mL) was added and the solution was refluxed for 15 h. Et_2O (200 mL) was added, the organic phase was extracted with brine (2 × 20 mL), dried (Na_2SO_4), concentrated in vacuo and filtered with Et_2O through a short silica gel column (10 g). After concentration the residue was chromatographed (150 g silica gel, hexanes/EtOAc 6 : 1) to give **15** as an oil that slowly crystallized. It was recrystallized from hexanes; yield 1.33 g (67 %); mp 30–35 °C; $[\alpha]_D^{20}$ +76.3 (c = 1.14, $CHCl_3$); lit.[8f]: mp 36–37 °C, $[\alpha]_D^{24.5}$ +88.7 (c = 1.1, $CHCl_3$).

IR (film): ν = 1665, 1620, 1255, 1075, 840, 780 cm^{-1}.

^{1}H NMR ($CHCl_3$, TMS): δ = 5.72 (d, 1 H, J = 1.0 Hz), 3.55 (dt, 1 H, J = 4.3, 10.2 Hz), 2.24–2.39 (m, 4 H), 1.99–2.04 (m, 2 H), 1.66–1.71 (m, 2 H), 1.47 (m, 1 H), 1.09 (s, 3 H), 0.96 (d, 3 H, 6.7 Hz), 0.86 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H).

^{13}C NMR ($CHCl_3$): δ = 199.5, 169.3, 124.1, 71.8, 50.0, 39.2, 35.9, 35.7, 33.4, 31.3, 25.8, 18.0, 17.3, 11.1, −4.0, −4.7.

MS: m/z(%) = 308 (M$^+$, 1), 293 (6), 251 (100), 159 (55), 75 (82).

(3*S*,4a*R*,5*R*,6*R*)-(+)-6-(*tert*-Butyldimethylsiloxy)-3-(1-hydroxy-1-methylethyl)-4a,5-dimethyl-4,4a,5,6,7,8-hexahydro-3*H*-naphthalen-2-one (16):

Hexamethyldisilazane (6.77 mL), 5.18 g, 32.1 mmol) was dissolved in THF (60 mL), cooled to −60 °C, BuLi (12.6 mL, 2.5 M in hexanes, 31.5 mmol) was added and the solution was stirred for 30 min. The solution was cooled to −78 °C and **15** (1.94 g, 6.29 mmol) in THF (20 mL) was added slowly via a transfer needle (ca. 15 min). After stirring for 1 h $ZnCl_2$ (3.15 mL, 2.2 M in CH_2Cl_2, 6.93 mmol) was added. After 10 min, acetone (3.70 mL, 2.93 g, 50.4 mmol) was added and the reaction was quenched after 15 min by the addition of 5 % tartraric acid (20 mL) and warming to r.t. Hexanes/Et_2O (1 : 1, 200 mL) was added, the organic phase was extracted with 5 % tartraric acid (2 × 20 mL), brine (2 × 10 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed (50 g silica gel, hexanes/EtOAc 3 : 2) to give **16** as a colorless oil; yield 2.08 g (90 %); $[\alpha]_D^{20}$ +74.3 (c = 1.1, $CHCl_3$).

IR (film): ν = 3460, 2940, 2929, 2850, 1645, 1460, 1350, 1250, 1070, 830 cm^{-1}.

^{1}H NMR ($CDCl_3$, TMS): δ = 5.65 (d, 1 H, J = 1.7 Hz), 5.10 (br s, 1 H), 3.50 (m, 1 H), 2,22–2.43 (m, 4 H), 1.95–2.00 (m, 2 H), 1.18–1.45 (m, 2 H), 1.15 (s, 6 H), 1.07 (s, 3 H), 0.93 (d, 3 H, J = 6.6 Hz), 0.83 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 203.0, 169.9, 124.6, 72.4, 71.5, 50.5, 50.4, 39.7, 38.9, 35.4, 30.8, 28.2, 25.7, 24.5, 17.9, 17.1, 10.9, −4.1, −4.8.

MS: m/z(%) = 366 (M$^+$, 1), 351 (7), 309 (68), 251 (67), 176 (87), 75 (100).

(+)-Isopetasol-(*tert*-butyldimethylsilyl) Ether (17):

Compound **16** (900 mg, 2.45 mmol) was dissolved in CH_2Cl_2 (15 mL), cooled to 0 °C and Et_3N (4.27 mL, 3.10 g, 30.6 mmol) and methanesulfonyl chloride (1.14 mL, 1.68 g, 14.7 mmol) were added. After stirring for 2 h the white suspension was diluted with CH_2Cl_2

(50 mL), extracted with H_2O (2 × 10 mL), 5 % H_2SO_4 (2 × 10 mL), brine (2 × 10 mL) and dried (Na_2SO_4). The solution was filtered through a column of acidic alumina (WOELM, 20 g), concentrated in vacuo and chromatographed (50 g silica gel, hexanes/EtOAc 6 : 1) to give **17** as a colorless oil; yield: 638 mg (75 %); $[\alpha]_D^{20}$ +29.9 (c = 5.5, $CHCl_3$).

IR (film): ν = 2940, 2920, 2840, 1660, 1620, 1600, 1300, 1070, 830, 770 cm^{-1}.

^{1}H NMR ($CDCl_3$, TMS): δ = 5.68 (d, 1 H, J = 1.5 Hz), 3.47 (m, 1 H), 2.84 (d, 1 H, J = 13.7 Hz), 1.94–2.32 (m, 3 H), 2.03 (d, 3 H, 1.8 Hz), 1.79 (s, 3 H), 1.34–1.45 (m, 2 H), 0.96 (d, 3 H, J = 7.0 Hz), 0.92 (s, 3 H), 0.84 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 191.8, 166.5, 142.7, 127.4, 126.2, 71.9, 49.3, 42.0, 41.3, 35.7, 30.4, 25.8, 22.5, 22.0, 18.0, 17.2, 11.2, −4.1, −4.8.

MS: m/z(%) = 348 (M$^+$, 34), 291 (100), 216 (38), 161 (71), 75 (50).

(+)-Isopetasol (18):

Compound **17** (420 mg, 1.20 mmol) was dissolved in MeCN (20 mL), then ca. 50 % HF (2 mL) was added and the solution was stirred at r.t. for 2 h. Et_2O (100 mL) was added and the organic phase was extracted with sat. $NaHCO_3$ (2 × 20 mL), brine (2 × 10 mL), dried (Na_2SO_4) and concentrated in vacuo. Chromatography (20 g silica gel, hexanes/EtOAc 1 : 1) gave **18** as colorless needles. It was recrystallized from Et_2O/hexanes; yield 232 mg (83 %); mp 116–118 °C; $[\alpha]_D^{20}$ +108.3 (c = 1.3, $CHCl_3$); lit.[17] mp 122–125 °C; $[\alpha]_D$ +116.6 (c = 1.04, $CHCl_3$).

IR (CCl_4): ν = 3400, 2960, 2930, 2870, 1655, 1620, 1440, 1300, 1225, 1040, 885 cm^{-1}.

^{1}H NMR ($CDCl_3$, TMS): δ = 5.70 (d, 1 H, J = 1.5 Hz), 3.51 (m, 1 H), 2.85 (d, 1 H, J = 13.8 Hz), 2.05–2.37 (m, 3 H), 2.02 (d, 3 H, J = 1.7 Hz), 1.79 (d, 3 H, J = 1.0 Hz), 1.30–1.45 (m, 2 H), 1.05 (d, 3 H, J = 6.6 Hz), 0.92 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 191.8, 166.3, 143.1, 127.2, 126.3, 71.0, 49.0, 42.0, 41.1, 35.2, 30.4, 22.5, 22.0, 17.2, 10.7.

MS: m/z(%) = 234 (M$^+$, 87), 201 (33), 161 (100).

(+)-Isopetasin (2):

Angelic acid (256 mg, 2.56 mmol) was dissolved in toluene (4 mL) and 2,4,6-trichlorobenzoyl chloride (0.400 mL, 625 mg, 2.56 mmol) and Et_3N (0.357 mL, 259 mg, 2.56 mmol) were added. The resulting white suspension was stirred at r.t. for 2 h and **18** (300 mg, 1.28 mmol) dissolved in toluene (4 mL) was added. After heating to 80 °C for 24 h Et_2O (20 mL) was added, the crude suspension filtered through silica gel (5 g, Et_2O) and the solution was concentrated in vacuo. The residue was chromatographed (40 g, silica gel, hexanes/EtOAc 10 : 1) to give **2** as colorless crystals that were recrystallized from Et_2O/hexanes; yield: 336 mg (83 %); mp 82–84 °C, $[\alpha]_D^{20}$ +23.8 (c = 0.8, $CHCl_3$); lit.[17] mp 89–91 °C, $[\alpha]_D^{20}$ +28.6 (no concentration stated, $CHCl_3$).

IR (CCl_4): ν = 2970, 2930, 1705, 1655, 1230, 1160, 1040 cm^{-1}.

^{1}H NMR ($CDCl_3$, TMS): δ = 6.08 (m, 1 H), 5.78 (d, 1 H, J = 1.8 Hz), 4.93 (m, 1 H), 2.94 (d, 1 H, J = 13.8 Hz), 2.51 (m, 1 H), 2.36 (m, 1 H), 2.23 (m, 1 H), 2.20 (d, 1 H, J = 13.5 Hz), 2.10 (d, 3 H, J = 1.8 Hz), 2.00 (dd, 3 H, J = 7.3, 1.5 Hz), 1.90 (s, 3 H), 1.86 (d, 3 H, J = 1.2 Hz), 1.70 (m, 1 H), 1.51 (m, 1 H), 1.06 (s, 3 H), 1.01 (d, 3 H, J = 6.7 Hz).

^{13}C NMR ($CDCl_3$): δ = 191.4, 167.5, 165.0, 143.2, 137.8, 127.8, 127.0, 126.6, 73.1, 46.0, 42.1, 41.0, 31.6, 30.0, 22.4, 22.0, 20.4, 17.0, 15.6, 10.7.

MS: m/z(%) = 316 (83), 216 (54), 201 (31), 161 (100), 147 (12), 83 (22), 55 (44).

(3*S*,4a*R*,5*R*,6R)-(+)-6-Hydroxy-3-(1-hydroxy-1-methylethyl)-4a,5-dimethyl-4,4a,5,6,7,8-hexahydro-3*H*-naphthalen-2-one (20):

Compound **16** (500 mg, 1.36 mmol) was dissolved in MeCN (20 mL), 50 % HF (2 mL) was added and the solution was stirred at r.t. for 2 h. Et_2O (100 mL) was added and the organic phase was extracted with sat. $NaHCO_3$ (2 × 20 mL), brine (2 × 10 mL), dried (Na_2SO_4) and concentrated in vacuo. Chromatography (20 g silica gel, hexanes/EtOAc 1 : 2) gave **20**. It was recrystallized from Et_2O/hexanes to give **20** as colorless crystals; yield: 323 mg (94 %); mp 104–106 °C; $[\alpha]_D^{20}$ +100.0 (c = 1.3, $CHCl_3$).

IR (CCl_4): ν = 3400, 2960, 2920, 2860, 1650, 1640, 1375, 1230, 1030 cm^{-1}.

^{1}H NMR ($CDCl_3$, TMS): δ = 5.71 (d, 1 H, J = 1.8 Hz), 5.10 (br s, 1 H), 3.58 (m, 1 H), 2.31–2.48 (m, 4 H), 2.00–2.15 (m, 2 H), 1.69 (br s, 1 H), 1.25–1.49 (m, 2 H), 1.19 (s, 6 H), 1.11 (s, 3 H), 1.06 (d, 3 H, J = 6.7 Hz).

^{13}C NMR ($CDCl_3$): δ = 203.1, 169.4, 124.9, 72.5, 70.8, 50.6, 50.1, 39.8, 38.8, 35.0, 30.8, 28.2, 24.6, 17.1, 10.5.

MS: m/z(%) = 252 (M$^+$, 1), 237 (6), 234 (7), 194 (57), 176 (32), 121 (100).

2-Methylbut-2-enoic Acid (1*R*,2*R*,7*S*,8a*R*)-7-(1-Hydroxy-1-methylethyl)-1,8a-dimethyl-6-oxo-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl Ester (21):

Angelic acid (159 mg, 1.59 mmol) was dissolved in toluene (4 mL) and 2,4,6-trichlorobenzoyl chloride (0.248 mL, 387 mg, 1.59 mmol) and Et_3N (0.221 mL, 160 mg, 1.59 mmol) were added. The resulting white suspension was stirred at r.t. for 2 h and **20** (200 mg, 0.793 mmol) dissolved in toluene (4 mL) was added. After heating to 80 °C for 24 h Et_2O (20 mL) was added, the crude suspension filtered over silica gel (5 g, Et_2O) and the solution was concentrated in vacuo. The residue was chromatographed (40 g silica gel, hexanes/EtOAc 6 : 1) to give isopetasin **2** (50 mg, 20 %) starting material **20** (50 mg) and the product **21** as colorless crystals, that were recrystallized from Et_2O/hexanes; yield 104 mg (39 %, 52 % based on recovered **20**); mp 83–85 °C, $[\alpha]_D^{20}$ −42.1 (c = 1.6, $CHCl_3$).

IR (CCl_4): ν = 3450, 2960, 2940, 2870, 1700, 1645, 1450, 1375, 1230, 1155, 990 cm^{-1}.

^{1}H NMR ($CDCl_3$, TMS): δ = 6.05 (m, 1 H), 5.71 (d, 1 H, J = 1.8 Hz), 5.05 (br s, 1 H), 4.90 (m, 1 H), 2.33–2.56 (m, 4 H), 2.00–2.23 (m, 2 H), 1.95 (d, 3 H), 1.85 (s, 3 H), 1.20–1.64 (m, 2 H), 1.19 (s, 3 H), 1.17 (s, 3 H), 0.96 (d, 3 H, J = 6.7 Hz).

^{13}C NMR ($CDCl_3$): δ = 203.2, 168.4, 167.5, 138.2, 127.8, 125.0, 72.7, 72.3, 50.8, 50.6, 40.0, 38.8, 37.4, 30.5, 28.2, 24.5, 20.5, 17.0, 15.7, 10.5.

MS: m/z% = 334 (M$^+$, 1), 319 (4), 316 (7), 219 (6), 176 (100), 121 (80).

(+)-Petasin (1):

Compound **21** (120 mg, 0.359 mmol) was dissolved in CH_2Cl_2 (5 mL), cooled to − 78 °C and diisopropylethylamine (0.188 mL), 140 mg, 1.08 mmol) and trifluoromethanesulfonic anhydride (0.091 mL, 152 mg, 0.539 mmol) were added. After stirring for 60 min sat. NH_4Cl (2 mL) was added and the suspension was warmed to r.t. CH_2Cl_2 (50 mL) was added and the organic phase was extracted with sat. NH_4Cl (2 × 10 mL), brine (2 × 5 mL), dried (Na_2SO_4) and concentrated in vacuo. Chromatography (20 g silica gel, hexanes/EtOAc 10 : 1) gave isopetasin **2** (19 mg, 17 %), **21** (36 mg) and product **1** as a colorless oil; yield 55 mg (48 %, 69 % based on recovered **21**); $[\alpha]_D^{20}$ +34.1 (c = 0.7, $CHCl_3$); lit.[2]: $[\alpha]_D$ = 39.6 (no concentration, temperature and solvent stated).

IR (film): ν = 2940, 2870, 1700, 1665, 1625, 1455, 1380, 1230, 1160, 1045, 985, 890, 850 cm^{-1}.

^{1}H NMR ($CDCl_3$, TMS): δ = 6.08 (m, 1 H), 5.79 (d, 1 H, J = 2.2 Hz), 5.00 (s, 1 H), 4.96 (m, 1 H), 4.83 (s, 1 H), 3.13 (dd, 1 H, J = 14.8, 4.4 Hz), 2.54 (m, 1 H), 2.39 (m, 1 H), 2.26 (m, 1 H), 2.04 (dd, 1 H, 13.2, 4.4 Hz), 2.00 (dd, 3 H, J = 7.3, 1.5 Hz), 1.94 (d, 1 H, J = 13.2 Hz), 1.89 (s, 3 H), 1.86 (s, 3 H), 1.69 (m, 1 H), 1.52 (m, 1 H), 1.25 (s, 3 H), 0.98 (d, 3 H, J = 6.6 Hz).

^{13}C NMR ($CDCl_3$): δ = 198.5, 167.6, 166.8, 143.3, 138.1, 127.9, 124.6, 114.4, 72.9, 50.3, 47.2, 41.6, 40.0, 31.6, 30.6, 20.6, 20.0, 17.1, 15.7, 10.5.

MS: m/z(%) = 316 (M$^+$, 27), 216 (22), 161 (15), 148 (100), 105 (20).

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(1) see also Fuchs, L., "Von Pestilenzwurz", *New Kreuterbuch*, **1543**, Kap. 248; Camerarium, *Kreutterbuch*, Nürnberg, **1626**, p. 149.

(2) Aebi, A.; Büchi, J.; Waaler, T.; Eichberger, E. *Pharm. Acta Helv.* **1955**, *29*, 277.
Stoll, A.; Morf, R.; Rheiner, A.; Renz, J. *Experientia* **1956**, *12*, 360.

(3) Aebi, A.; Djerassi, C. *Helv. Chim. Acta* **1959**, *42*, 1785.
Herbst, D.; Djerassi, C. *J. Am. Chem. Soc.* **1960**, *82*, 4337.

(4) Meier, B. *Z. Phytochem.* **1994**, *15*, 268.

(5) Debrunner, B.; Neuenschwander, M. *Chimia* **1994**, *48*, 564.

(6) Pichel, D.; Röder, T.; Bestmann, H. J.; Brune, K. *Planta Medica* **1994**, *60*, 318.

(7) preliminary communication: Witschel, M. C.; Bestmann, H. J. *Tetrahedron Lett.* **1995**, *36*, 3325.

(8) a) Yamakawa, K.; Izuta, I.; Oka, H.; Sakaguch, R.; Kobajash, M.; Satoh, T. *Chem. Pharm. Bull.* **1979**, *27*, 331.
b) Torii, S.; Inokuchi, T.; Kawai, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 861.
c) Bohlmann, F.; Otto, W. *Liebigs Ann. Chem.* **1982**, 186.
d) Mühle, H.; Neuenschwander, M. *Chimia* **1983**, *37* 41.
See for related syntheses.
e) Mori, K.; Tamura, H. *Liebigs Ann. Chem.* **1988**, 97.
f) Kitahara, T.; Kurata, H.; Mori, K. *Tetrahedron* **1988**, *44*, 4339.

(9) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *58*, 2656.
Bäckvall, J.-E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619.

(10) Danishefsky, S. J.; Simoneau, B. *J. Am. Chem. Soc.* **1989**, *111*, 2599.
Jeroncic, J. O.; Cabal, M.-P.; Danishefsky, S. J.; Shulte, G. M. *J. Org, Chem.* **1991**, *56*, 387.

(11) Koga, M.; Kageyama, H.; Tanaka, T.; Fujii, T. *Synth. Commun.* **1994**, *24*, 1447.

(12) Pfau, M.; Jabin, I.; Revial, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1935.

(13) Bestmann, H. J.; Schmid, G. *Chem. Ber.* **1980**, *113*, 3369.
Bestmann, H. J.; Hotz, M.; Witschel, M.; Roth, C. *Chem. Ber.* **1993**, *126*, 2151.

(14) Bestmann, H. J.; Schade, G.; Schmid, G. *Angew. Chem.* **1980**, *92*, 856; *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 822.
Bestmann, H. J.; Schade, G.; Lütke, H.; Mönius, T. *Chem. Ber.* **1985**, *118*, 2640.
Bestmann, H. J.; Schade, G. *Tetrahedron Lett.* **1982**, *23*, 3543.

(15) Hartmann, B.; Kanazawa, A. M.; Depres, J.-D.; Green, A. E. *Tetrahedron Lett.* **1991**, *32*, 5077.

(16) Inanaga, J.; Hitara, K.; Saeki, H.; Kasuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(17) Neuschwander, M.; Neuschwander, A.; Steinegger, E. *Helv. Chim. Acta* **1979**, *62*, 627.