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A SATURATED ASYMMETRIC ISOPRENE SYNTHON

SYNTHESIS, RESOLUTION AND ABSOLUTE CONFIGURATION

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Abstract—The unknown racemic 3-methyl-4-phenylsulfonylbutanoic acid (**4**) is synthesized by standard procedures. The acid is resolved into its enantiomers by alternating treatment with *l*- and *d*-ephedrine. The *S*-(+)-acid **4** is converted into *R*-(+)-dihydrocitronellol (**7**) in order to determine the absolute configuration and to illustrate its use as a saturated isoprene building block in isoprenoid homologation.

An increasing number of acyclic terpenoids are being synthesized by the condensation of 5-carbon units having the isoprene skeleton. Examples leading to both 1,5-polyenic[1] and conjugated polyenic[2] terpenoids have been recently published from this laboratory.

Many acyclic terpenes possess chirality at the side chain branching of saturated isoprene units and to our knowledge no synthon is available so far which allows the general introduction of saturated isoprene fragments of known configuration.

We wish to report the synthesis of 3-methyl-4-phenylsulfonylbutanoic acid (**4**), its optical resolution and the absolute configuration. The two enantiomeric carboxylic acids **4** may be used in isoprenoid homologation either as such or as a derivative after functional group transformation, e.g. to an alcohol or ether function.

Their application is illustrated by the conversion of the *S*-(+)-acid **4** to *R*-(+)-dihydrocitronellol, a compound of known absolute configuration.[3] Other applications, e.g. in the field of insect pheromones will be published in due course.[4]

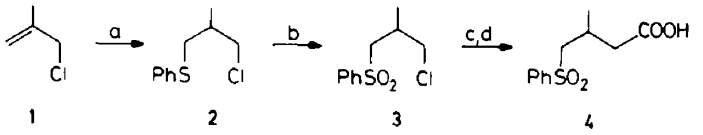
[a]Taken in part from the forthcoming doctorate thesis of C. Bödeker.

Synthesis of racemic **4**. We have tried several schemes for the preparation of **4** or related compounds. Scheme 1 was chosen as the best suited for scaling up to molar quantities. The photoinduced addition of thiophenol to the commercially available methallyl chloride (**1**) gives the chlorosulfide **2**,[5] which was oxidized with m-chloroperbenzoic acid to the corresponding sulfone **3**.

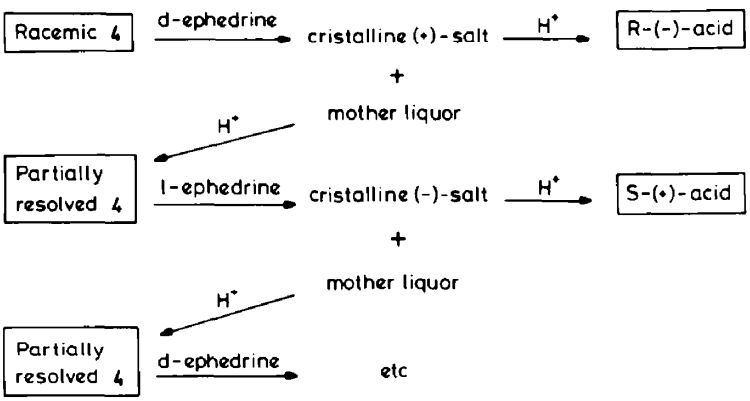
Substitution of the chloride by cyanide ion and hydrolysis of the resulting nitrile[6] furnishes acid **4**, which may be used for resolution purposes in its liquid form without further purification.

Optical resolution of racemic **4**. The optical resolution of 3-methyl-phenylsulfonylbutanoic acid (**4**) is performed as indicated in Scheme 2. When an alcoholic solution containing equimolar amounts of racemic **4** and *d*-ephedrine is diluted with ethyl acetate more than half of the dextrorotary *d*-ephedrinium salt crystallizes. Acidification leads to the levorotary acid with the *R*-configuration as will be shown in the next section.

The partially resolved acid **4** recovered from the acidified mother liquor is then treated with an equimolar quantity of *l*-ephedrine and from the crystallized levorotary salt the *S*-(+)-acid **4** is isolated upon acidification and extraction.



Scheme 1. (a): PhSh, hv, (b): mCIPBA, (c): CN^-, (d): hydrolysis.



Scheme 2.

This procedure has the advantage that both enantiomeric forms are obtained in an optically pure form after each operation.

When the alternating operations using *d*- and *l*-ephedrine are repeated additional crops of the enantiomeric salts are formed. However the relative quantities of crystaline salts gradually diminish, presumably due to the accumulation of water absorbed by the hygroscopic resolving agents.

From the solutions remaining after the isolation of the acid **4** over 80% of optically pure ephedrine can be recovered by the addition of NaOH, extraction with ether and distillation.

The absolute configuration of **4**. The *S*-configuration of the (+)-acid **4** has been established by its conversion to *R*-(+)-dihydrocitronellol (Scheme 3). The *S*-(+)-acid **4** was reduced with LAH to the corresponding alcohol **5**. The alcohol was converted into its dianion by 2 mole *n*-butyllithium and the homologation to the diastereoisomeric monoterpenoid sulfone mixture **6** was performed with isoamylbromide.[b]

The substituted sulfone **6** was purified chromatographically and subsequently desulfurized with lithium in diaminoethane. The resulting alcohol **7** was compared with *R*-(+)-dihydrocitronellol prepared from *R*-(+)-pulegone by a well established literature procedure[3,7] and gave the same rotation within the experimental error.

EXPERIMENTAL

d- and *l*-Ephedrine were obtained from Aldrich and used without further purification. $[\alpha]_D^{22} = +41°$ ($c = 5.1$, 1N HCl), $[\alpha]_D^{22} = -41°$ ($c = 5.1$, 1N HCl), in agreement with the data given by the manufacturer. ^{1}H NMR spectra were recorded on a Varian HA-100 and XL-100 spectrometer and mass spectra on an AEI MS 902 double focussing mass spectrometer with direct insertion probe. The specific rotations were determined on a Carl-Zeiss Lightelectric Polarimeter (LEP). M.ps were determined on a Leitz-Wetzlar apparatus and are not corrected.

Oxidation of **2** *to* **3**. A soln of **2**[5] (200.5 g; 1 mole) in 2 l CH_2Cl_2 was stirred with cooling in ice/water. 85% *m*-Chloroperbenzoic acid (410 g; 2.05 mole) was added in portions of 20 g. Then the mixture was stirred overnight at r.t. and filtered. The filtrate was stirred for 1 hr with a 10% NaOH aq. The CH_2Cl_2 layer was separated and the caustic layer washed with CH_2Cl_2 (500 ml). The combined organic layers were washed with water (250 ml) and saturated brine (100 ml). After drying over $MgSO_4$, filtration and evaporation of the solvent, **3** was obtained as a clear oil (225 g; 96.7%).

^{1}H NMR ($CDCl_3$): 8.0–7.4 (m, 5H), 3.85–2.85 (m, 4H), 2.7–2.3 (m, 1H), 1.2 (d, 3H). (Calc. for $C_{10}H_{13}O_2ClS$ (232.62): C, 51.58; H, 5.63; S, 13.78%. Found: C, 51.67; H, 5.79; S, 13.65).

Conversion of **3** *into* **4**. A mixture of **3** (220 g; 0.95 mole) in 1.6 l EtOH/water was stirred. NaI (142.5 g; 0.95 mole) and NaCN (139.7 g; 2.85 mole) was added and the mixture refluxed for 48 hr. A soln of NaOH (114 g; 2.85 mole) in 400 ml water was added and the mixture refluxed until the NH_3 evolution has ceased (after *ca* 2 hr). The mixture was cooled and extracted three times with 500 ml portions of ether. The water layer containing the Na salt of **4** was acidified and extracted five times with 400 ml portions of ether. The combined ether layers were washed with water and sat. brine. After drying over $MgSO_4$, filtration and evaporation of the solvent acid **4** was obtained as a clear viscous oil (133.6 g; 58%).

^{1}H NMR ($CDCl_3$): 10.8 (s, 1H), 8.1–7.5 (m, 5H), 3.3–3.1 (m, 2H), 2.6–2.4 (m, 2H), 2.9–2.2 (m, 1H), 1.15 (d, 3H). (Calc. for $C_{11}H_{14}O_4S$ (242.17): C, 54.51; H, 5.83; S, 13.24%). Found: C, 54.50; H, 5.70; S, 13.24).

Resolution[c] *of acid* **4**. *d*-Ephedrine (22 g; 133 mmole) dissolved in 80 ml EtOH was added to a soln of racemic **4** (30 g; 124 mmole) in 80 ml EtOH. After refluxing for 15 min 640 ml EtOAc was added to the hot soln and the mixture left overnight at r.t. under stirring. The crystals were filtered off and washed with 50 ml EtOAc followed by 100 ml ether. 14 g *d*-Ephedrinesalt with $[\alpha]_D^{22} = +10.7°$ ($c = 5.0$, H_2O) was obtained. The filtrate was concentrated as far as possible and refluxed with 10% HCl (1.1 mole eq) during 0.5 hr, cooled and extracted with three portions of ether (200 ml). The combined ether extracts were washed with 10% HCl, water and sat. brine. After drying over $MgSO_4$ and evaporation of the solvent 21 g (92 mmole) of the partially resolved acid **4** remained. This acid was treated with 16.5 g (100 mmole) *l*-ephedrine as described above and so on. Ultimately 4 crystal fractions were isolated and the corresponding ones combined. 20.5 g *d*-Ephedrine salt and 15.1 g *l*-ephedrine salt were obtained with m.p. 140–143° and specific rotations of $[\alpha]_D^{22} = +10.7°$ ($c = 5$, H_2O) and $-10.7°$ ($c = 5$, H_2O) respectively.[d]

The salts were treated with 10% HCl as described. From 20.0 g *d*-ephedrine salt 11.9 g *R*-(−)-acid **4** was obtained; $[\alpha]_D^{22} = -2.0°$ ($c = 14$, EtOH). The *S*-(+)-acid **4** (8.9 g) was obtained from the *l*-ephedrine salt (15.1 g); $[\alpha]_D^{22} = +2.0°$ ($c = 14$, EtOH).

The acids failed so far to crystallize.

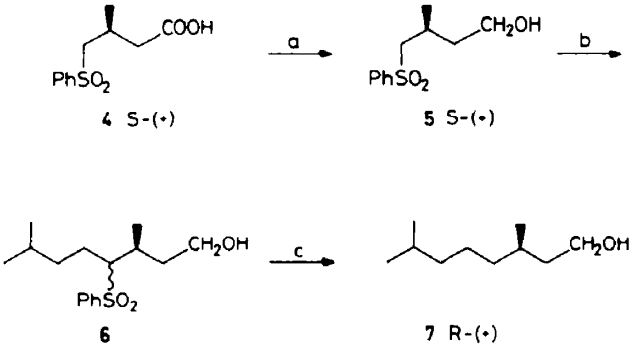
R-(−)-acid **4**: ^{1}H NMR ($CDCl_3$: 9.4 (s, 1H), 8.1–7.5 (m, 5H) 3.3–3.1 (m, 2H), 2.6–2.4 (m, 2H), 2.9–2.2 (m, 1H), 1.15 (d, 3H). (Calc. for $C_{11}H_{14}O_4S$ (242.17): C, 54.51; H, 5.83; S, 13.24%. Found: C, 54.50; H, 5.70; S, 13.24).

S-(+)-acid **4**: ^{1}H NMR ($CDCl_3$); identical with the above. (Found: C, 54.57; H, 5.81; S, 13.27%).

[b] We have indications that this homologation step proceeds with some stereo-selectivity.

[c] On a larger scale the resolution can be carried out exactly as described, but longer crystallization times and/or additional cooling may be necessary.

[d] Recrystallization from water (1 g salt in 5 ml) furnished salts with specific rotation of $[\alpha]_D^{22} = 8.0°$ ($c = 6.0$, H_2O) and $-8°$ ($c = 6.0$, H_2O) respectively. The m.ps of both salts were 148–149°. The lowering of the specific rotation is presumably due to crystal water.



Scheme 3. (a): LAH, (b): 2 mole n-BuLi, isoamylbromide, (c): Li, diaminoethane.

Reduction of S-(+) **4** to S-(+) **5**. A soln of *S*-(+) **4** (8.5 g; 35 mmole) in 25 ml THF was added under cooling (ice/water) in 0.5 hr to a suspension of 1.5 g LAH in 100 ml THF. After all the acid was added the mixture was refluxed during 1 hr: Upon cooling and acidfying with conc. HCl the clear soln was decanted from the salt slurry. The slurry was washed twice with 100 ml ether. The combined organic layers were washed with dil. HCl, $NaHCO_3$aq and sat. brine respectively and dried over $MgSO_4$. Evaporation of the solvent gave the alcohol *S*-(+) **5** (7.5 g; 33 mmole, 94%) as an oil; $[\alpha]_D^{22} = +7.6°$ ($c = 7.6$, EtOH).

^{1}H NMR ($CDCl_3$): 8.07–7.4 (m, 5H), 3.7–3.5 (t, 2H), 3.3–2.8 (m, 2H), 2.5 (broad s, 1H), 2.5–2.0 (m, 1H) 1.9–1.3 (m, 2H), 1.05 (d, 3H). (Calc. for $C_{11}H_{16}O_3S$ (228.19): C, 57.84; H, 7.06; S, 14.04. Found: C, 57.68; H, 7.16; S, 13.85%). MS (70 eV) *m/e*: 229 (M + H), 211 (229–H_2O), 198, 183. The reduction of 11.1 g (46 mmole) *R*-(−) **4** gave 9.9 g (43 mmole, 94%) *R*-(−) **5**: $[\alpha]_D^{22} = -7.6°$ ($c = 8.8$, EtOH). ^{1}H NMR and MS were identical with those of the enantiomer. (Found: C, 57.55; H, 7.06; S, 13.85%).

Coupling of S-(+) **5** *to a mixture of disastereoisomers* **6**. A soln of *S*-(+) **5** (2.29 g; 10 mmole) in 20 ml dry THF and 2 ml HMPA was stirred and cooled to 0° in ice/water. Addition of 20 mmole *n*-BuLi (15 ml, 1.33 M soln in hexane) gave a yellow soln. After 15 min a soln of isoamylbromide (1.51 g; 10 mmole) in 5 ml THF was added. The soln was left overnight at r.t. with stirring. The mixture was acidified with dil. HCl and extracted twice with 150 ml ether. The organic layer was washed with a $NaHCO_3$ aq, sat. brine and dried over $MgSO_4$. Filtration and evaporation of the solvent gave 2.5 g crude product. Chromatography on a Merck Lobar column (type B) with ether as eluens furnished 2.0 g (67%) **6** as an oil. $[\alpha]_D^{22} = -5.0°$ ($c = 2.5$, EtOH).

^{1}H NMR ($CDCl_3$): 8.0–7.4 (m, 5H), 3.8–3.4 (m, 2H), 3.0–2.8 (m, 1H), 2.43 (s, 1H), 2.5–2.0 (m, 1H), 2.0–1.2 (m, 4H), 1.1–1.0 (two d, 3H), 0.78 (d, 3H), 0.76 (d, 3H). (Calc. for $C_{16}H_{26}O_3S$: C, 64.37; H, 8.78; S, 10.75. Found: C, 64.48; H, 8.85; S, 10.44%). MS (70 eV) *m/e*: 299 (M + H), 298 (M^+, $C_{16}H_{26}O_3S$, 281 (M + H − H_2O), 157.

R-(−) **5** was converted into the corresponding mixture **6** following the same procedure in 60% yield; $[\alpha]_D^{22} = +5.0°$ ($c = 2.5$, EtOH). ^{1}H NMR and MS data were identical with those given above. (Found: C, 64.17; H, 8.91; S, 10.45%).

Reductive cleavage of the levorotary mixture **6** *to* R-(+) **7**

A soln of **6** (1.49 g; 5 mmole) in 15 ml ethylenediamine was stirred at r.t. Then 15 ml heptane[e] was added and Li in a slight excess. As soon as the mixture had become dark blue, 4 g NH_4Cl was added. After the reaction had subsided a soln of 50 ml sat. NH_4Cl was added and the mixture stirred until all the Li had disappeared. The mixture was extracted twice with 100 ml ether and the etherial layer washed with 25 ml 25% KOH soln and 25 ml sat. brine respectively. After drying over K_2CO_3, filtration and evaporation of the solvent 1 g crude product was obtained. Short path distillation furnished 500 mg (62%) *R*-(+) **7**; b.p. 130–135°/12 mm, $[\alpha]_D^{22} = +4.1°$ ($c = 4.9$, EtOH), which proved to be identical with *R*(+)-dihydrocitronellol synthesized from *R*(+)-pulegon according to Plešek;[7] $[\alpha]_D^{22} = +5.28°$ (neat) and $[\alpha]_D^{22} = +4.1°$ ($c = 5.0$, EtOH).

^{1}H NMR ($CDCl_3$): 3.8–3.6 (m, 2H), 2.52 (s, 1H), 2.3–1.0 (m, 10H), 0.89 (d, 3 × 3H). (Calc. for $C_{10}H_{22}O$ (158.17): C, 75.86; H, 14.02. Found: C, 76.05; H, 13.84%). MS (70 eV) *m/e*: 158 (M^+ not obs), 140 (M–H_2O).

The dextrorotatory mixture **6** was converted into *S*-(−) **7** as described. The same yield was obtained; $[\alpha]_D^{22} = 4.1°$ ($c = 5.0$, EtOH). ^{1}H NMR and MS data were identical with those above. (Found: C, 75.93; H, 13.96%).

[e]Without addition of heptane stirring becomes impossible due to excessive foaming.

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