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A PRACTICAL PROCESS FOR LARGE-SCALE SYNTHESIS OF (S)-5-HYDROXY-6-TRANS-8,11,14-CIS-EICOSATETRAENOIC ACID (5-HETE)

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Summary: (S)-5-Hydroxy-6-trans-8,11,14-cis-eicosatetraenoic acid (5-HETE) (1) and its enantiomer are readily available by a chemical synthesis from arachidonic acid which includes a chromatographic separation of diastereomeric urethanes (3) made from (±)-5-HETE methyl ester and the isocyanate 4 derived from dehydroabietylamine.

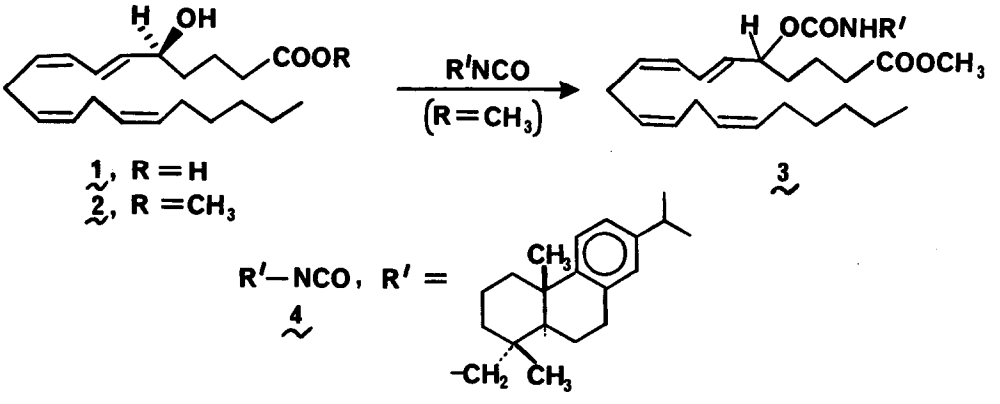
(S)-5-Hydroxy-6-trans-8,11,14-cis-eicosatetraenoic acid (5-HETE) (1) is an important biological mediator which is strongly chemotactic for human eosinophils and neutrophils, displaying a potency greater than 8-,9-,11-,12-, or 15-HETE and comparable in magnitude to the peptide factor C5a derived from the fifth component of human complement.[1,2] The availability of only microgram amounts of 1 from mammalian sources coupled with widespread interest in its role in allergic and inflammatory disease provide incentive to develop an effective synthesis. An enzymic synthesis of 1 using a lipoxygenase of potato and arachidonic acid as substrate which has been developed in these laboratories constitutes a workable method for the preparation of limited quantities (<50 mg), but suffers from scale-up problems arising mainly from the instability of the enzyme.[3] Since an efficient chemical synthesis of (±)-1 from arachidonic acid has already been devised[3] which is well suited to multigram scale preparation, it seemed important to extend this approach for the production of the naturally occurring optically active form of 5-HETE, 1.[4] The successful realization of this objective is described herein.

The methyl ester of (±)-5-HETE (2) was prepared as previously described[3] by (1) iodolactonization of arachidonic acid, (2) elimination of the elements of HI using 1,5-diazabicyclo[5.4.0]undec-5-en, and, (3) treatment of the resulting δ-lactone of (±)-1 with triethylamine in methanol (ca. 60% overall yield). This ester was converted to a mixture of diastereomeric urethane derivatives 3 by reaction with the isocyanate 4 derived from reaction of phosgene with dehydroabietylamine.[5-7] The formation of the urethanes 3 was quantitative using 4-dimethylaminopyridine as catalyst in CH_2Cl_2 solution. The diastereomeric urethanes upon thin layer chromatography (tlc) using silica gel plates with 1:1 ether-hexane for elution were easily separated as indicated by the Rf values of 0.40 and 0.35. The mixture was resolved preparatively by column chromatography

on silica gel using 2.5:1 hexane-ether as eluent.

The carbamate $\underset{\sim}{3}_8$ of R_f 0.40, $[\alpha]_{\underline{D}}^{23}$ +14.9° (c = 2.3 in C_6H_6), with triethylamine and trichlorosilane at 23° afforded after chromatographic purification R-(-)-5-HETE methyl ester (62%) as a colorless oil, $[\alpha]_{\underline{D}}^{23}$ -13.5° (c = 2.0 in C_6H_6), $[\alpha]_{\underline{D}}^{23}$ -13.9° (c = 1.75 in C_2H_5OH), spectroscopically and chromatographically identical with an authentic sample. In an identical way the carbamate $\underset{\sim}{3}$ of R_f 0.35, $[\alpha]_{\underline{D}}^{23}$ +58.4° (c = 2.4 in C_6H_6), was converted to the methyl ester of S-(+)-5-HETE, $[\alpha]_{\underline{D}}^{23}$ +14.0° (c = 2.0 in C_6H_6). Basic hydrolysis of the methyl ester of 5-HETE provides the free acid, 5-HETE ($\underset{\sim}{1}$) as reported earlier.

The isocyanate $\underset{\sim}{4}$ derived from dehydroabietylamine was far more effective as a resolving agent than a number of others which were studied including the isocyanates from α-phenylethylamine and α-1-napthylethylamine. Although the diastereomers prepared from the last two reagents and $\underset{\sim}{2}$ could be separated by preparative tlc on small scale, larger scale tlc or column chromatographic resolution was impractical. Diastereomeric esters of (±)-5-HETE with optically active alcohols such as (-)-methanol were not readily separated. In addition the amide of (±)-5-HETE with optically active α-phenylethylamine also resisted separation.



In the following sections experimental information is provided on (1) the preparation of (±)-5-HETE methyl ester from the least expensive grade of arachidonic acid (ca. 50% purity) which is commercially available (Nu-Chek Prep, Inc.), (2) the preparation of the mixture of diastereomeric carbamates $\underset{\sim}{3}$ and their chromatographic separation, and (3) the conversion of $\underset{\sim}{3}$ to (S)-5-HETE.

Racemic 5-HETE Methyl Ester: To a stirred solution of arachidonic acid (purity ca. 50%, 7.0 g) in 90 ml of tetrahydrofuran (THF) and 45 ml of aq. potassium bicarbonate (8.7 g) at 0° was added sequentially 11.45 g of potassium iodide and 33.2 g of iodine. The mixture was stirred in the dark (aluminum foil-covered flask at 0-5° for 15 hr), poured into ice cold sodium thiosulfate solution (120 g in 140 ml of water), and extracted with 3:2 pentane-ether (3 x 160 ml). After washing of the extract (ice-cold 3.5% Na_2CO_3 solution then sat. NaCl), drying (Na_2SO_4), concentration in vac., and rapid (<40 min) chromatography on 100 g of silica gel (3:1 ether-hexane as eluent), 5.64 g of essentially pure (±)-6-iodo-1,5-lactone was obtained as a pale yellow oil (yield ca. 100%).

To a stirred solution of iodo lactone (2.15 g) in 70 ml of dry benzene was gradually added a solution of 1.37 g (1.8 equiv) of 1,5-diazabicyclo[5.4.0]undec-5-ene in 15 ml of benzene at 23° under argon. After 17 hr at 23°, 8.0 g of powdered $CuSO_4 \cdot 5H_2O$ was added, stirring was continued for 30 min and the mixture was diluted with 80 ml of hexane and filtered rapidly through 20 g of silica gel (Merck 60 G) (suction; further washing with 4 x 50 ml of 3:1 ether-hexane). Evaporation in vac. gave 1.38 g (91%) of the δ-lactone of (±)-5-HETE as a pale yellow oil which was stirred with 25 ml of methanol containing 3 g of triethylamine under argon at 23° for 45 min. Concentration in vac. and chromatography on 110 g of silica gel deactivated with 2.5 w/w% of water using 1:1 ether-hexane gave 1.02 g of (±)-5-HETE methyl ester (67%, ca. 61% overall from arachidonic acid).

Isocyanate 4: Dehydroabietylamine (tech. grade, Aldrich Chemical Co.) was purified by three recrystallizations of its acetate salt from toluene.[5] Purified material, showing $[\alpha]_D^{23}$ +31.9° (c = 6.4 in methanol) (cf. ref. 5c), (4.28 g) was dissolved in 70 ml of dry toluene, and treated with a slight excess of dry hydrogen chloride (white ppt.). The mixture was heated at reflux for 1.5 hr during which time phosgene was bubbled into the mixture. Removal of toluene in vac. afforded 4.58 g (98%) of isocyanate 4 as a colorless, viscous oil, homogeneous by tlc analysis (silica gel, 1:1 ether-hexane).

Diastereomeric Carbamates 3: To a solution of 340 mg of (±)-5-HETE methyl ester in 5 ml of CH_2Cl_2 was added 250 mg of 4-dimethylaminopyridine and a solution of 950 mg of isocyanate 4 in 3 ml of CH_2Cl_2 and the whole was heated at reflux for 40 hr under argon. Removal of solvent in vac., and rough chromatography on silica gel (1:10 → 1:3 ether-hexane) afforded 670 mg (100%) of urethane 3 along with 540 mg of recovered 4.

5-HETE: The diastereomeric carbamates 3 (670 mg) were separated by column chromatography on silica gel using ether-hexane 1:2.5 as eluent to give each isomer in pure condition.

Less polar carbamate 3 (240 mg, 73%); tlc (SiO_2): ether-hexane 1:1 R_f = 0.40; $[\alpha]_D^{23}$ +14.9° (c = 2.32, benzene). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460, 1720, 980, 950; NMR (in $CDCl_3$) δ: 0.91 (6H, s+t, $-CH_3$), 1.22 (9H, s+d, J=7Hz, $-CH_3$ + $-CH(CH_3)_2$), 3.64 (3H, s, $COOCH_3$), 4.45-4.75 (1H, m, $-CHO-C=O$), 5.90 (1H, d of d, Jeach=10.5Hz, C(8)-H), 6.50 (1H, d of d, J=10.5, 15Hz, C(7)-H). More polar carbamate 3 (263 mg, 80%). TLC(SiO_2): ether-hexane(1:1) Rf=0.35, $[\alpha]_D^{23}$ +58.4° (c = 2.42, benzene); IR and NMR spectra were identical with those of the less polar carbamate.

To a stirred solution of the less polar carbamate (220 mg, 0.341 mmol) and triethylamine (172 mg, 1.70 mmol, 5 equiv) in 3 ml of benzene was added dropwise a solution of trichlorosilane (115 mg, 0.853 mmol, 2.5 equiv) in 1.5 ml of benzene at 23° under argon. After stirring at 23° for 18 hr, this mixture was treated with a small amount of water (~0.1 ml), and subjected to rough chromatography on silica gel (solvent system: 3:4 ether-hexane) followed by careful column chromatography on silica gel with 3:4 ether-hexane as eluent to afford (R)-(-)-5-HETE methyl ester (71 mg, 62%) as a colorless oil, $[\alpha]_D^{23}$ -13.5°, $[\alpha]_{436}^{23}$ -35.0° (c = 2.00, benzene), $[\alpha]_D^{23}$ -13.9°, $[\alpha]_{436}^{23}$ -35.9° (c = 1.75, ethanol). Spectral (NMR) and chromatographic (tlc) behavior of this sample were identical with that of the authentic sample.

The same treatment of the more polar carbamate (240 mg, 0.372 mmol) as above produced (S)-(+)-5-HETE methyl ester (90 mg, 72%) as a colorless oil, $[\alpha]_D^{23}$ +14.0°, $[\alpha]_{436}^{23}$ +35.7° (c = 2.02, benzene).[9]

References and Notes

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5. See, (a) B. Sjöberg and K. Sjöberg, Arkiv. För Kemi, 22, 447 (1964); (b) W. J. Gottstein and L. C. Cheney, J. Org. Chem., 30, 2072 (1965); (c) G. Bellucci, G. Berti, A. Borraccini and F. Macchia, Tetrahedron, 25, 2979 (1969) for the purification and use of dehydroabietylamine as a resolving agent.
6. W. H. Pirkle and M. S. Hoekstra, J. Org. Chem., 39, 3904 (1974).
7. Satisfactory spectroscopic data were obtained on chromatographically purified and homogeneous samples of each new substance.
8. (a) W. H. Pirkle and J. R. Hauske, J. Org. Chem., 42, 2781 (1977); (b) G. Greber and H. R. Kricheldorf, Ang. Chem. Int. Ed. Eng., 7, 941 (1968).

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