Syntheses of (−)-Isocitric Acid Lactone and (−)-Homoisocitric Acid. A New Method of Conversion of Alkynylsilanes into the Alkynyl Thioether and Corresponding Carboxylic Acids

Carole Schmitz, Anne-Claire Rouanet-Dreyfuss, Marie Tueni, and Jean-François Biellmann*

Laboratoire de Chimie Organique Biologique associé au CNRS, Université Louis Pasteur, Faculté de Chimie, 1 rue Blaise Pascal, 67003 Strasbourg, France

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A simple, stereoselective synthesis of natural isocitric and homoisocitric acids from a common alkynylsilane correlates the stereochemistry of these acids. Starting with dimethyl D-malate dianion, methyl 2-hydroxy-3-carbomethoxy-6-(trimethylsilyl)-5-hexynoate (**6a**) was prepared with a good stereoselectivity (threo/erythro 90/10). Oxidative cleavage of the triple bond provided isocitric acid lactone (**8′**) in 15% overall yield starting from D-malic acid diester **1**. The synthesis of homoisocitric acid relied on a new method of conversion of alkynylsilane to alkynyl thioether, which is converted to the carboxylic acid of the same chain length. Addition of benzenesulfenyl chloride to (trimethylsilyl)alkyne **6b** and elimination of trimethylsilyl chloride gave the corresponding thioether **10**, which by acid hydrolysis gave homoisocitric acid (**11**) in a 24% yield from D-malic acid ester. This novel method of conversion of alkynylsilane to the corresponding acid was illustrated with several other alkynyltrimethylsilanes.

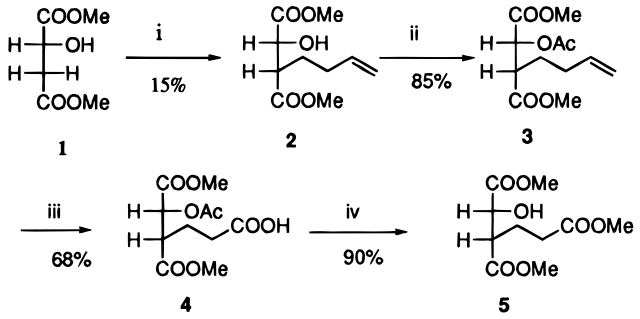
Introduction

Isocitric acid (**8**), which is an intermediate in the Krebs cycle,[1] is produced from citric acid by acotinase[2] and is converted into α-ketoglutaric acid by isocitric acid dehydrogenase. Of the four stereoisomers of isocitric acid, only the (−)-D-threo isomer is a substrate for acotinase and for the $NADP^+$-linked isocitrate dehydrogenase from porcine heart[3] and NAD^+-linked enzyme from bovine heart.[4] Racemic isocitric acid was first prepared by R. Fittig,[5] and two other syntheses of racemic isocitric acid were reported later.[6,7] The absolute configuration of isocitric acid lactone has been established by a stereoselective synthesis based upon the condensation of methyl (−)-*trans*-epoxysuccinate with dimethyl malonate.[8] A stereoselective synthesis of isocitric acid lactone relying on the stereoselective alkylation of L-malic acid[9,10] has been reported.

Homoisocitric acid (**11**) is involved in the α-aminoadipate pathway of lysine synthesis in yeasts and certain fungi. The synthesis of homoisocitric acid from homocitric acid is catalyzed by homoaconitate hydratase.[11] The enzymatic conversion of homoisocitric acid into α-ketoadipic acid is catalyzed by homoisocitric acid dehydrogenase.[12] Racemic homoisocitric acid has been synthesized by condensation of diethyl glutarate with diethyl oxalate to triethyl 2-oxaloglutarate, which was reduced to the corresponding hydroxy ester and saponified to the racemic free acid.[13] The absolute configurations of the four isomers of homoisocitric acid have been established by synthesis from the corresponding 2-hydroxy-3-cyclohexenecarboxylic acids[14] of known absolute configuration.[15] The threo D isomer of homoisocitric acid is a substrate for homoisocitric acid dehydrogenase.[16] However further study of the enzymes involved in this biosynthetic pathway is hampered by the unavailability of the intermediates: homoisocitric and homocitric acids. The enzymes involved in this specific biosynthetic pathway are targets for inhibitors, potential antibiotics, and fungicides.

The aim of our work[17] was to develop a specific synthesis of the (−)-D-threo isomers of isocitric and homoisocitric acids. Our synthesis starts from D-malic acid and correlates the stereochemistry of isocitric and homoisocitric acids. It constitutes the first chiral synthesis of (−)-D-homoisocitric acid and illustrates a novel method of conversion of alkynylsilanes to their carboxylic acids.

Scheme 1



(i) LDA, 1-bromo-3-butene; (ii) $(CH_3CO)_2O$; (iii) $NaIO_4/KMnO_4$; (iv) CH_3COCl cat/CH_3OH

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(1) Plaut, G. W. E.; Sung S. C. *J. Biol. Chem.* **1954**, *207*, 305.
(2) Rose, I. A.; O'Connell, E. L. *J. Biol. Chem* . **1967**, *242*, 1870.
(3) Ochoa, S. *Enzymes* **1951**, 929.
(4) Plaut, G. W. E.; Sung, S. C. *Methods Enzymol.* **1955**, *1*, 710.
(5) Fittig, R.; Miller, H. E. *Ann. Chem.* **1889**, *255*, 43.
(6) Wislicenus, W.; Nassauer, M. *Ann. Chem.* **1885,** *285*, 1.
(7) (a) Greenstein, J. P. *J. Biol. Chem.* **1935**, *109*, 529. (b) Greenstein, J. P. *J. Biol. Chem.* **1936**, *116*, 463.
(8) Kaneko, T.; Katsura, H. *Chem. Ind. (London)* **1960**, 1188.
(9) Compound **8**: $[\alpha]_D$ −60 (H_2O, *c* 1.03) (lit. $[\alpha]_D$ +61.7 (H_2O, *c* 0.985) for the enantiomer) Aebi, J. D.; Sutter, M. A.; Wasmuth, D.; Seebach, D. *Liebigs Ann. Chem.* **l983**, 2114.
(10) Seebach, D.; Wasmuth, D. *Helv. Chem. Acta* **1980**, *63*, 197.
(11) Strassman, M.; Ceci, L. N. *J. Biol. Chem.* **1966**, *241*, 5401.
(12) Strassman, M.; Ceci, L. N. *J. Biol. Chem.* **1965**, *240*, 4357.
(13) Yamashita, M. *J. Org. Chem.* **1958**, *23*, 835.
(14) Compound **11**: $[\alpha]_D$ −10 (*c* 2.05, acetone) (lit. $[\alpha]_D$ −8 to −13 (*c* 1.22, acetone). Chilina, K.; Thomas, U.; Tucci, A. F.; McMichael, K. D.; Stevens, C. M. *Biochemistry* **1969**, *8*, 2846.
(15) Febrer, M. A.; Gomis, P.; Pascual, J. *An. R. Soc. Esp. Fis. Quim.* **1964,** *60B*, 671.
(16) Rowley, B.; Tucci, A. F. *Arch. Biochem. Biophys.* **1970**, *141*, 499.
(17) Schmitz, C. Ph.D. Thesis, ULP, 1992.
(18) Schmitz, C.; Rouanet-Dreyfuss, A. C.; Tueni, M.; Biellmann, J. F. *Tetrahedron Lett.* **1992**, *33*, 4911.

0022-3263/96/1961-1817$12.00/0

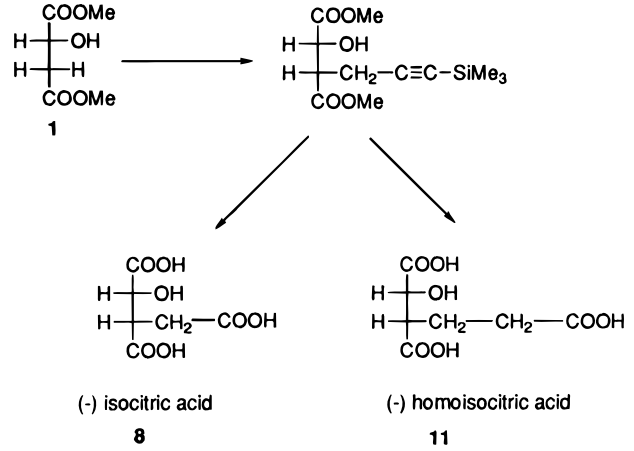


Figure 1.

In a previous paper[18] we reported our preliminary findings on the synthesis of isocitric and homoisocitric acids making use of this method.

Results and Discussion

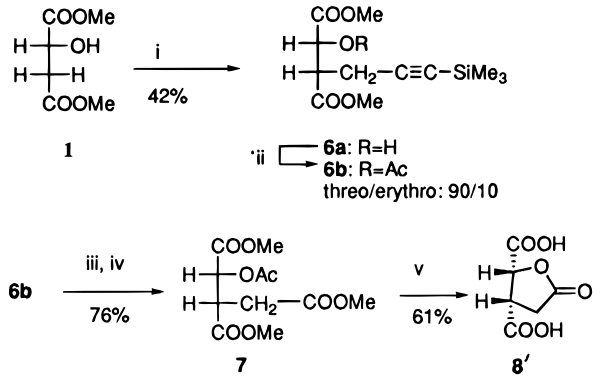
Our approach[19] to homoisocitric acid (**11**) (Scheme 1) is based on the procedure used by Seebach for the synthesis of isocitric acid.[9]

Reaction of D-malic dimethyl ester (**1**) dianion with 1-bromo-3-butene gave the alkylation product **2** in 15% yield (threo/erythro selectivity of 80/20). Acetylation of the hydroxy function of compound **2** (85%), oxidation of the double bond (68%), and subsequent deprotection of the alcohol and esterification of the free acid functions gave the homoisocitric acid triester **5** (90%). In view of the low overall yield of **5** (<10%) based on D-malic ester **1**, and the low stereoselectivity (threo/erythro:80/20), we planed a more direct approach. Attempts to react the dianion of malic diester with 1-(1′, 3′-dioxolan-2′-yl)-2-bromoethane or with ethyl acrylate were unsuccessful, with starting material being recovered.

Our second approach (Figure 1) made use of a common alkynylsilane, which would be converted to both isocitric and homoisocitric acids. In order to accomplish this, the (trimethylsilyl)propargyl group was chosen. Oxidative cleavage of the triple bond would give isocitric acid; anti-Markovnikov addition of water to the alkyne functionality followed by oxidation would provide homoisocitric acid.

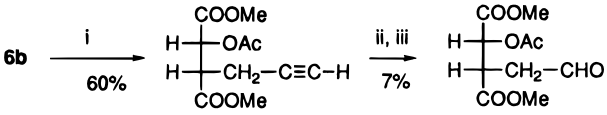
The diastereoselective alkylation of the dianion[9] of the dimethyl ester of D-malic acid (**1**), generated at −78 °C with 2.5 equiv of (trimethylsilyl)propargyl bromide,[20,21] gave the dimethyl 3-[(trimethylsilyl)propynyl]malate (threo **6a**/erythro 90/10) in 51% yield. After acetylation of the hydroxyl group the two C-3 diastereoisomers were separated by column chromatography. The major diastereoisomer (2*R*,3*S*) had the stereochemistry indicated in formula **6b**, as shown by the correlation with isocitric acid. Ruthenium tetroxide[22] oxidation of the silylated triple bond provided the corresponding carboxylic acid with one less carbon atom, which was converted to its methyl ester **7** for purification purposes. Acid hydrolysis of the triester **7** afforded in 61% yield isocitric acid lactone

Scheme 2



(i) LDA, trimethylsilylpropargylbromide,THF; (ii) Ac_2O, Et_3N; (iii) $NaIO_4/RuO_2$; (iv) CH_2N_2, AcOEt; (v) HCl

Scheme 3



(i) nBu_4NF, THF; (ii) disiamylborane; (iii) $H_2O/NaOH$

(**8′**), whose properties[9] corresponded to the natural isomer of the Krebs cycle (Scheme 2).

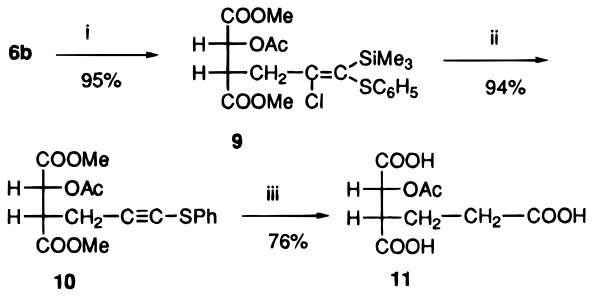
Conversion of the alkynylsilane **6b** to homoisocitric acid required the transformation of the silylated triple bond to the corresponding carboxylic acid **8** without carbon loss. Zweifel reported that hydroboration of (trimethylsilyl)alkynes with dicyclohexylborane followed by oxidation under basic conditions gives the corresponding acid in good yield.[23] However in our hands the use of this method for the transformation of compound **6b** to the corresponding acid failed, starting material being recovered. The bulky trimethylsilyl group may hinder the addition of dicyclohexylborane. Thus the terminal alkyne **12** was obtained by desilylation with tetrabutylammonium fluoride in 60% yield. This intermediate was then hydroborated with disiamylborane, and after oxidation aldehyde **13** was obtained in only 7% yield (Scheme 3).

Several other methods for the preparation of carboxylic acids from acetylenes without loss of a carbon have been described,[24−26] but these methods have only been used on aliphatic or aromatic acetylenes lacking other functional groups and failed when applied to compound **6b**. Thus we had to develop a method for the preparation of the carboxylic acid from a silylated triple bond. Abrams has reported a method of conversion of terminal alkynes into carboxylic acids via an acetylenic thioether.[27] Unfortunately all attempts to obtain the thioether by reaction of diphenyl disulfide on the propargylic carbanion, generated by 1 equiv of LDA, failed.

F. Cooke reported the addition of arenesulfenyl chlorides to vinyltrimethylsilane.[28] Reaction of benzenesul-

(19) Rouanet-Dreyfuss, A. C. Ph.D. Thesis, ULP, 1989.
(20) Jones, T. K.; Denmark, S. E. *Org. Synth.* **1985**, *64*, 182.
(21) Miller, R. B. *Synth. Commun.* **1972**, *2*, 267.
(22) Zibuck, R.; Seebach, D. *Helv. Chem. Acta* **1988**, *71*, 237.
(23) Zweifel, G.; Backlund, S. J. *J. Am. Chem. Soc.* **1977**, *99*, 3184.
(24) McDonald, R. N.; Schwab, P. A. *J. Am. Chem. Soc.* **1964**, *86*, 4866.
(25) Tamao, K.; Kumada, M. *Tetrahedron Lett.* **1984**, *25*, 321.
(26) Moriarty, R. M.; Vaid, R. K.; Duncan, M. P.; Vaid, B. K. *Tetrahedron Lett.* **1987**, *28*, 2845.
(27) Abrams, S. R. *Can. J. Chem.* **1983**, *61*, 2423.
(28) Cooke, F.; Moerck, R.; Schwindemann, J.; Magnus, P. *J. Org. Chem.* **1980**, *45*, 1046.

Scheme 4



(i) C_6H_5SCl, CH_2Cl_2; (ii) KF, DMSO;
(iii) DOWEX resin H^+ 20% Hg^{2+}

Table 1

	yield, % **14** into **16**	yield, % **16** into **17**	overall yield, % **14** into **17**
14a (R = C_6H_5)	84	70 **A**	59 **A**
		61 **B**	51 **B**
14b (R = $CH_3(CH_2)_5$)	95	50 **A**	47 **A**
		25 **B**	23 **B**
14c (R = $TMSOCH_2(CH_2)_2$)	55	54 **B**	30 **B**

fenyl chloride with compound **6b** gave the vinylic addition product **9** in 92 % yield. β-Elimination with potassium fluoride in dimethyl sulfoxide[29] afforded thioether **10** in 92% yield. To our knowledge, this is the shortest route to alkynyl thioethers reported to date. The last step of the synthesis was the conversion of thioether **10** to the carboxylic acid **11**. Following a published procedure,[30,31] acid hydrolysis of thioether **10** was performed in water in the presence of ion exchange resin DOWEX 50X impregnated with 20% mercuric sulfate. The natural homoisocitric acid (**11**) was isolated as an oil[14] (yield 75%) (Scheme 4).

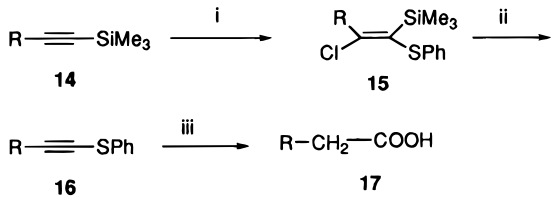
This result encouraged us to extend this method of conversion of a silylated triple bond to the carboxylic acid to other alkynylsilanes, such as phenyl-2-(trimethylsilyl)-ethyne (**14a**), 1-(trimethylsilyl)octyne (**14b**), and 6-[(trimethylsilyl)oxy]-1-(trimethylsilyl)-1-hexyne (**14c**) (Table 1).

Conversion of the (trimethylsilyl)acetylenes **14** to the thioethers **15** was achieved in two steps: benzenesulfenyl chloride addition to the silylated triple bond followed by β-elimination of the chloride and trimethylsilyl groups. In this way alkynyl thioethers **16a**, **16b**, and **16c** were obtained in good yields. Two different sets of conditions were employed for the hydrolysis of thioether **16** to the carboxylic acid: method A, sulfuric acid in the presence of mercuric sulfate, and method B, acid resin impregnated with mercuric ions. Carboxylic acids **17a**, **17b**, and **17c** were isolated in 59, 47, and 30% yields, respectively (Scheme 5).

Conclusion

A new method of conversion of a silylated triple bond to the carboxylic acid of the same chain length is illustrated here. Transformation of the (trimethylsilyl)-alkyne **6b** to the corresponding thioether **10** followed by acid hydrolysis gave homoisocitric acid (**11**) in a 24% yield

Scheme 5



(i) C_6H_5SCl, CH_2Cl_2 ; (ii) KF/DMSO
method A: (iii)2N H_2SO_4 /$HgSO_4$
method B: (iii) Dowex resin H^+ 20% Hg^{2+}

from D-malic acid ester. This novel method of oxidation was applied with success to different trimethylsilanes devoid of functional groups. The facile synthesis of homoisocitric acid will now make studies of homoisocitrate dehydrogenase activity feasible.

Experimental Section

General. Experiments requiring anhydrous conditions were performed in an atmosphere of dry argon. Unless otherwise indicated, all reagents were obtained from commercial suppliers and were used without purification. Solvents were dried according to established protocols:[33] distillation under argon from an appropriate drying agent. THF was distilled from sodium/benzophenone immediatly prior to use. CH_2Cl_2, Et_2O, DMSO, and $CHCl_3$ were distilled from calcium hydride. Glassware was dried at 120 °C in an oven overnight and assembled under a stream of argon.

Analytical thin layer chromatography (TLC) was conducted on precoated silica gel plates (Merck Kieselgel $60F_{254}$, 0.25 mm thickness). For visualization, TLC plates were either placed under ultraviolet light or stained with phosphomolybdic acid solution (25% in ethanol). Flash column chromatography was performed using flash grade Merck silica gel 60 (230−400 mesh). Mixtures of hexane and ethyl acetate were used as eluants. Optical rotations were recorded at the sodium D line at ambient temperature.

^1H NMR spectra were taken in $CDCl_3$ unless otherwise noted and are referenced to the appropriate solvent signal. Chemical shifts are reported in ppm units downfield from tetramethylsilane. IR spectra are reported as υ_{max} in cm^{-1}.

Melting points are uncorrected. Elemental analyses were determined by the Analytical Laboratory of the Faculté de Chimie de l'Université Louis Pasteur. Mass spectra were obtained by the chemical ionization technique.

Methyl 2-Hydroxy-3-carbomethoxy-6-(trimethylsilyl)-5-hexynoate (6a). To a solution of 2.1 g of dimethyl D-malate (13 mmol) in 10 mL of anhydrous THF was added dropwise at −78 °C a solution of LDA (26 mmol, 2 equiv) in 20 mL of anhydrous THF. The mixture was warmed up to −20 °C and stirred at this temperature for 30 min. After cooling to −78 °C, (trimethylsilyl)propargyl bromide (6.3 g, 33 mmol) was added dropwise, and the reaction mixture was stirred at −78 °C for 18 h and then was allowed to return to −20 °C over a 3 h period. Acetic acid (3 mL) diluted in ether (6 mL) was added after cooling to −50°C. After warming up to room temperature the reaction mixture was poured into water (100 mL) and the aqueous phase was extracted with ether (3 × 100 mL). The combined organic layers were washed with 50 mL of saturated $NaHCO_3$ and 50 mL of saturated NaCl and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (eluant, hexane/AcOEt 70/30) to afford (trimethylsilyl)propargyl bromide (3.5 g) and (eluant, hexane/AcOEt 60/40) methyl 2-hydroxy-3-carbomethoxy-6-(trimethylsilyl)-5-hexynoate (1.7 g, 51%): ^1H NMR ($CDCl_3$) δ 4.57−4.55 (d, 2H, J = 2.6 Hz), 3.85−3.80 and 3.75−3.69 (2s, 6H) (erythro/threo: 10/90), 3.16−3.12 (m_{ABX}, 1H, J_1 = 10 Hz, J_2 = 2 Hz), 2.84−2.70

(29) Cunico, R. F.; Dexheimer, E. M. *J. Am. Chem. Soc.* **1972**, *94*, 2868.
(30) Newman, M. S. *J. Am. Chem. Soc.* **1953**, *75*, 4740.
(31) Billimoria, J. D.; MacLagan, N. F. *J. Chem. Soc.* **1954,** 3257
(32) Casara, P.; Danzin, C.; Metcalf, B.; Jung, M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2201.
(33) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals,* 3rd. ed.; Pergamon Press: Oxford, 1988.

(m_{ABX}, 2H, J = 14.7 Hz), 0.15 (s, 9H); IR 3600, 2960, 1745, 1440, 1250, 850 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_5Si$: C, 52.92; H, 7.4. Found: C, 52.72; H, 7.31.

Methyl 2-Acetoxy-3-carbomethoxy-6-(trimethylsilyl)-5-hexynoate (6b). To a mixture of **6a** (3.78 g, 13.9 mmol) and 4-(dimethylamino)pyridine (0.17 g, 1.4 mmol) were consecutively added 2.9 mL (20.8 mmol) of triethylamine and 1.96 mL of acetic anhydride. After being stirred overnight at room temperature the mixture was hydrolyzed by addition of diluted hydrochloric acid (20 mL). This was extracted with 3 × 100 mL of ether, washed with 50 mL of saturated $NaHCO_3$ and 50 mL of saturated NaCl, dried over $MgSO_4$, filtered, and evaporated. The crude mixture of two diastereoisomers was chromatographed on silica gel (eluant, hexane/AcOEt 95/5) to afford minor diastereoisomer II (2*S*,3*S*) (196 mg) and major diastereoisomer I (2*R*,3*S*) (3.12 g). Intermediate fractions were considered for the global yield (3.62 g, 83%). **Diastereoisomer I**: ^{1}H NMR ($CDCl_3$) δ 5.54−5.52 (d, ^{1}H, J = 4 Hz), 3.79−3.72 (2s, 6H), 3.37−3.27 (m_{ABX}, ^{1}H, J_1 = 4 Hz, J_2 = 6 Hz, J_3 = 4 Hz), 2.8−2.47 (m_{ABX}, 2H, J = 14.7 Hz), 2.12 (s, 3H), 0.15 (s, 9H); IR (CCl_4) 2940, 1745, 1440, 1215 cm^{-1}; $[\alpha]_D$ +27.8 (MeOH, c = 1.5 g/100 mL). Anal. Calcd for $C_{14}H_{22}O_6Si$: C, 53.48; H,7.05. Found: C, 53.29; H, 6.88. **Diastereoisomer II**: ^{1}H NMR ($CDCl_3$) δ 5.54−5.52 (d, 1H, J = 5 Hz), 3.77−3.74 (2s, 6H), 3.26−3.16 (m_{ABX}, 1H, J_1 = 4 Hz, J_2 = 7 Hz, J_3 = 7 Hz), 2.85−2.57 (m_{ABX}, 2H, J = 14.7 Hz), 2.15 (s, 3H), 0.15 (s, 9H); IR (CCl_4) 2940, 1745, 1440, 1215 cm^{-1}; $[\alpha]_D$ −5.2 (MeOH, c = 1.5 g/100 mL). Anal. Calcd for $C_{14}H_{22}O_6Si$: C, 53.48; H, 7.05. Found: C, 53.62; H, 7.21

Methyl 2-Acetoxy-3,5-dicarbomethoxypentanoate (7). To a solution of **6b** (dia I) (0.38 g, 1.21 mmol) in a mixture of $CCl_4/CH_3CN/H_2O$ (6/6/10) was added $NaIO_4$ (1.05 g, 4.9 mmol) at room temperature. The mixture was stirred vigorously at room temperature. After two clear phases resulted, $RuO_2{\cdot}H_2O$ (3.8 mg; 0.025 mmol) was added. The mixture turned black followed by pink with formation of a white precipitate. After stirring at room temperature for 20 h, the mixture was poured into 30 mL of H_2O, and the aqueous phase was acidified with a 10% solution of sulfuric acid and extracted with 3 × 10 mL of ether. The combined organic phases were washed by a saturated solution of NaCl, dried over $MgSO_4$ and evaporated to give a colorless oil (0.3 g). A solution of diazomethane (0.74 M) (1.63 mL, 1.21 mmol) was added dropwise to a solution of the crude oil in 10 mL of AcOEt at 0 °C. After stirring for 30 min. at room temperature, the solvent was evaporated and the yellow oil was purified by column chromatography to afford triester **7** (0.25g, 75%): ^{1}H NMR ($CDCl_3$) δ 5.54 (d, 1H, J = 3.8 Hz), 3.76, 3.72, 3.7 (3s, 9H), 3.66−3.57 (m, 1H), 2.94−2.78 (m_{ABX}, 2H, J_1 = 26 Hz, J_2 = 9 Hz, J_3 = 5.4 Hz), 2.14 (s, 3H); IR (CCl_4) 2957, 1750, 1213 cm^{-1}; $[\alpha]_D$: +24.7 (MeOH, c = 1.16 g/100 mL), mass spectrum, m/e 245, 217, 208, 145. Anal. Calcd for $C_{11}H_{16}O_8$: C, 47.82; H, 5.83. Found: C, 47.97; H, 5.67.

Isocitric Acid Lactone (8′). A solution of triester **7** (0.4 g; 1.45 mmol) in 30 mL of 6 N HCl was refluxed for 20 h. After evaporation of the solvent, the residue was crystallized from AcOEt/hexane to give white needles (153 mg, 61%): mp 150−152 °C; ^{1}H NMR (acetone d_6) δ 5.19 (d, 1H, J = 8 Hz), 3.92 (quad, 1H, J = 8 Hz), 2.84 (m_{ABX}, 2H, J = 8 Hz); IR (KBr) 2900, 1810, 1760 cm^{-1}; $[\alpha]_D$ −60.3 (H_2O, c = 1.03 g/100 mL) lit. $[\alpha]_D$ +61.7 (H_2O, c = 0.98 g/100 mL). Anal. Calcd for $C_6H_6O_6$: C, 41.4; H, 3.44 Found: C, 41.31; H, 3.39.

Methyl 2-Acetoxy-3-carbomethoxy-5-chloro-6-(phenylthio)-6-(trimethylsilyl)-5-hexynoate (9). To a solution of **6b** (0.5 g, 1.59 mmol) in 5 mL of anhydrous CH_2Cl_2 was added dropwise a solution of benzenesulfenyl chloride (0.23 g; 1.59 mmol) at −78 °C. After stirring at room temperature for 16 h, the solvent was evaporated and the residue was purified by column chromatography (eluant, hexane/AcOEt 90/10) to give compound **9** (0.68 mg, 95%) as white needles: mp 88−89 °C; ^{1}H NMR ($CDCl_3$) δ 7.41−7.21 (m, 5H), 5.23−5.21 (d, 1H, J = 4 Hz), 3.76−3.72 (2s, 6H), 3.7−3.58 (m_{ABX}, J_1 = 6 Hz, J_2= 10 Hz), 3.07−2.78 (m_{ABX}, 2H, J = 14.7 Hz), 2.17 (s, 3H), 0.38 (s, 1H); IR (CCl_4) 2958, 1750, 1640, 1580, 1250 cm^{-1}; $[\alpha]_D$ −23.37 (MeOH, c = 1.5 g/100 mL). Anal. Calcd for $C_{20}H_{27}O_6SiSCl$: C, 52.3; H, 5.53. Found: C, 52.33; H, 5.77.

Methyl 2-Acetoxy-3-carbomethoxy-6-(phenylthio)-5-hexynoate (10). To a solution of **9** (500 mg, 1.08 mmol) in 15 mL of anhydrous DMSO was added anhydrous KF (62 mg, 1.08 mmol). After stirring 4 h at room temperature, the solvent was removed and the residue was purified by column chromatography (eluant, hexane/AcOEt 90/10) to yield compound **10** as an oil (280 mg, 94%): ^{1}H NMR ($CDCl_3$) δ 7.43−7.19 (m, 5H, SPh), 5.58−5.56 (d, 1H, J = 4 Hz), 3.8, 3.75 (2s, 6H), 3.45−3.35 (m_{ABX}, 1H, J = 14.7 Hz), 2.14 (s, 3H); $[\alpha]_D$ +5.18 (MeOH, c = 1.6 g/100 mL); IR (CCl_4) 2960, 2196, 1750, 1582, 1210 cm^{-1}; mass spectrum, m/e 350 (M^+), 307, 291, 241, 217, 147, 121. Anal. Calcd for $C_{17}H_{18}O_6S$: C, 58.27; H, 5.17. Found: C, 58.19; H, 5.2.

Homoisocitric Acid (11). A suspension of **10** (0.4 g, 1.13 mmol) and DOWEX 50 × 8[30,31] 20% Hg^{2+} resin (2 g) in 20 mL of water was heated at 100 °C for 72 h. After cooling, the solution was filtered and the aqueous phase was washed with CH_2Cl_2 (2 × 50 mL). After evaporation of the water, compound **11** was isolated as a yellow oil (177 mg, 76%): ^{1}H NMR (CD_3OD) δ 4.3−4.28 (d, 1H, J = 3 Hz), 2.91−2.84 (m_{ABX}, 1H), 2.47−1.9 (m, 4H), $[\alpha]_D$ −10 (acetone, c = 2 g/100 mL).

Homoisocitric Acid Triester. To a solution of homoisocitric acid (**11**) (0.177 g, 0.85 mmol) in 10 mL of AcOEt was added dropwise a solution of diazomethane (0.74 M) (1.15 mL) at 0 °C. After stirring for 1 h at room temperature, the solvent was evaporated and the crude product was purified by column chromatography (eluant, hexane/AcOEt 90/10) to yield homoisocitric acid trimethyl ester as an oil (0.138 g, 66%): ^{1}H NMR ($CDCl_3$) δ 4.37−4.36 (d, 1H, J = 3 Hz), 3.81, 3.77, 3.67 (s, 9H), 3.16−3.04 (m, 1H), 2.53−1.96 (m, 4H); IR (CCl_4) 3537, 2987, 1740 cm^{-1}; $[\alpha]_D$ −7.4 (MeOH, c = 1.2 g/100 mL); mass spectrum, m/e 217, 189, 161, 157, 87. Anal. Calcd for $C_{10}H_{16}O_7$: C, 48.38; H, 6.49. Found: C, 48.19; H, 6.3.

General Procedure for the Addition of Benzenesulfenyl Chloride to the Alkynylsilane. To a solution of (trimethylsilyl)alkyne (8.61 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise a solution of benzenesulfenyl chloride (8.61 mmol) at −78 °C. After stirring for 16 h at room temperature, the solvent was evaporated and the residue was purified by column chromatography.

1-Chloro-1-phenyl-2-(phenylthio)-2-(trimethylsilyl)-ethene (15a) was prepared from **14a**[32] and purified by column chromatography (eluant, hexane): 86% yield; ^{1}H NMR ($CDCl_3$) δ 7.41−7.08 (m, 5H), 0.42 (s, 9H).

1-(Phenylthio)-1-(trimethylsilyl)-2-chloro-1-octene (15b) was prepared from **14b**[32] and purified by column chromatography (eluant, hexane): 95% yield; ^{1}H NMR ($CDCl_3$) δ 7.32−7.18 (m, 5H), 2.44−2.36 (t, 2H, J = 5.8), 1.27−1.20 (m, 8H), 0.85 (t, 3H, J = 6.4), 0.31 (s, 9H).

6-[(Trimethylsilyl)oxy]-2-chloro-1-(trimethylsilyl)-1-(phenylthio)-1-hexene (15c) was prepared from **14c**[30] and purified by column chromatography (eluant, hexane): 91% yield; ^{1}H NMR ($CDCl_3$) δ 7.37−7.19 (m, 5H), 3.60−3.53 (t, 2H, J = 6.4 Hz), 2.52−2.43 (t, 2H, J = 6.8 Hz), 1.64−1.49 (m, 4H), 0.35 (s, 9H), 0.1 (s, 9H).

General Procedure for the Preparation of Thioalkynes. To a solution of 2-(phenylthio)-2-(trimethylsilyl)-1-chloroalkene (3.76 mmol) in 3 mL of anhydrous DMSO was added anhydrous KF (4.41 mmol). The reaction mixture was heated at 100 °C for 2 h, then the crude reaction mixture was purified by column chromatography.

1-Phenyl-2-(phenylthio) ethyne (16a) was prepared from 1-phenyl-2-(phenylthio)-2-(trimethylsilyl)-1-chloroethene (**15a**) and purified by column chromatography (eluant, hexane: 100%): 98% yield; ^{1}H NMR δ 7.55−7.13 (m, 10H).

1-(Phenylthio)-1-octyne (16b) was prepared from **15b** and purified by column chromatography (eluant, hexane): 95% yield; ^{1}H NMR ($CDCl_3$) δ 7.43−6.96 (m, 5H), 2.48−2.41 (t, 2H, J = 6.8 Hz), 1.67−1.25 (m, 8H), 0.91−0.85 (t, 3H, J = 6.4).

6-[(Trimethylsilyl)oxy]-1-(phenylthio)-1-hexyne (16c) was prepared from **15c** and purified by column chromatography (eluant, hexane 100%): 57% yield; ^{1}H NMR; δ 7.43−7.18 (m, 5H), 3.65−3.59 (t, 2H, J = 4.1 Hz), 2.48−2.44 (t, 2H), 1.70−1.54 (m, 4H), 0.11 (s, 9H).

General Procedure for the Hydrolysis of Alkynyl Thioethers. Method A. A suspension of thioether (2.37

mmol) and mercuric sulfate in 2 N sulfuric acid (10 mL) and acetic acid (30 mL) was heated at 80 °C for 24 h. The aqueous phase was extracted with chloroform (3 × 50 mL), and the combined organic phases were washed with water (50 mL) and a saturated solution of NaCl (20 mL). After evaporation of the solvant, the crude product was dissolved in ether and extracted by a saturated solution of $NaHCO_3$ (3 × 50 mL). The combined basic phases were acidified by HCl and then extracted with chloroform (3 × 50 mL). The combined organic phases were washed with a saturated solution of NaCl and dried over Na_2SO_4. After evaporation of the solvent the crude product was purified by column chromatography.

Method B. A solution of 1-alkynyl thioether (1.66 mmol) in a mixture of water (1 mL) and acetic acid (5 mL) was heated at 80−90 °C in the presence of DOWEX 50 × 8[30,31] 20% Hg^{2+} resin for 72 h. After cooling the solution was filtered and the resin washed with water. The aqueous phase was washed with CH_2Cl_2 (20 mL), and the water was evaporated to give the crude compound which was purified by column chromatography.

Phenylacetic acid (17a) was prepared from **16a** and purified by column chromatography (eluant, hexane/AcOEt 70/30) to give white crystals: 70% yield for method A, 61% yield for method B. Mp 77−78 °C. ^{1}H NMR ($CDCl_3$): δ 7.37−7.24 (m, 5H), 3.65 (s, 2H).

Octanoic acid (17b) was prepared from 1-(phenylthio)-1-octyne (**16b**) and purified by column chromatography (eluant, hexane/AcOEt 70/30): 50% yield for method A, 25% yield for method B. ^{1}H NMR ($CDCl_3$): δ 2.38−2.31 (t, 2H, J = 7.2 Hz), 1.66−1.56 (t, 2H, J = 7.5 Hz), 1.34−1.25 (m, 8H), 0.91−0.84 (t, 3H, J = 7 Hz).

6-Hydroxyhexanoic acid (17c) was prepared from 6-[(trimethylsilyl)oxy]-1-(phenylthio)-1-hexyne (**16c**) and purified by column chromatography (eluant, hexane/AcOEt 70/30): 54% yield for method B: ^{1}H NMR ($CDCl_3$) δ 4.06−4.02 (t, 2H, J = 6.6 Hz), 2.39−2.32 (t, 2H, J = 7.2), 1.71−1.35 (m, 6H).

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