Synthesis of Acenaphthene-1-carboxylic Acid Using Lithiated Tris(methylthio)methane to Carboxylate 1-Bromoacenaphthene

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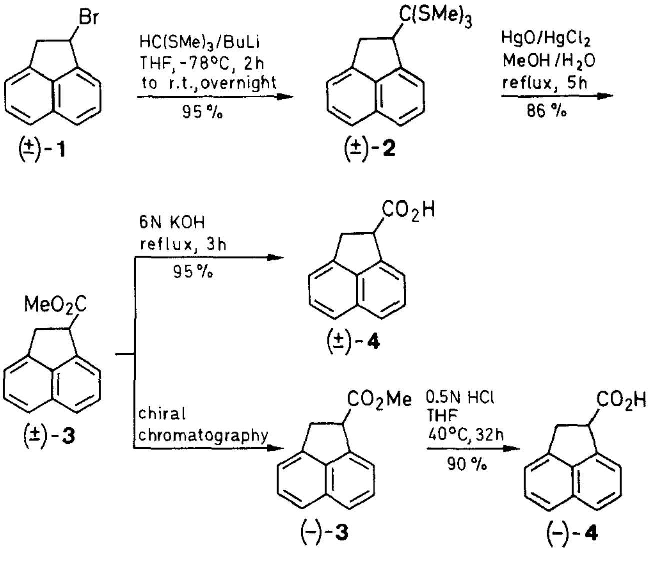
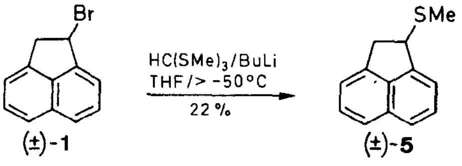
A new synthesis of acenaphthene-1-carboxylic acid (**4**) in 3 steps and 78 % overall yield from 1-bromoacenaphthene (**1**) is described. In the key step, lithiated tris(methylthio)methane is reacted with 1-bromoacenaphthene to give 1-[tris(methylthio)methyl]acenaphthene (**2**). Methanolysis of **2** gives racemic methyl acenaphthene-1-carboxylate **3**, which is resolved by chiral chromatography. The usefulness of tris(methylthio)methyllithium as a carboxyl carbanion equivalent is illustrated by the conversion of three other bromides to the corresponding methoxycarbonyl derivatives.





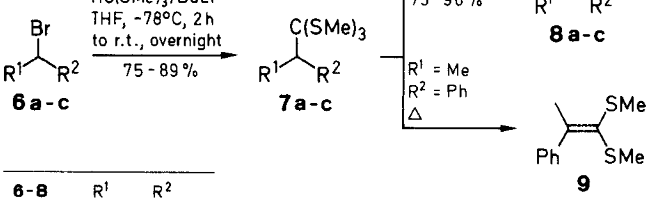
In a recent communication on the synthesis of racemic acenaphthene-1-carboxylic acid (**4**) Salvadori and coworkers[1] report that prior to their work the only routes[2-5] to this plant growth regulator[2,5] suffered from low yields (15–18 %) or inconvenient laboratory procedures. The present communication describes a new short synthesis of **4**, which produces multigram quantities of the racemic target molecule. The (—) enantiomer of **4** was obtained by chiral chromatography.

The first reported synthesis of **4**[5] involved a six step procedure. In this, and subsequent syntheses it was unexpectedly found that the conversion of 1-bromoacenaphthene (**1**) into 1-cyanoacenaphthene could not be effected with cyanide, and so a four-step procedure involving initial reaction with sodium bisethoxycarbonyl methanide was used. In this study we decided to investigate the use of an alternative one-carbon reagent, which possesses the desired oxidation state for a carboxylic acid.

Tris(methylthio)methane was selected for this purpose, because it has been used as a carboxyl carbanion equivalent in 1,4-additions to unsaturated carbonyls,[6] 1,2-additions to ketones,[7] and in one report for the displacement of an alkyl iodide.[8] The bromide **1** was prepared from 1-acenaphthenol with phosphorus tribromide according to the literature method,[5] and when treated with the [tris(methylthio)methyl] lithium at – 78 °C gives the desired adduct **2** in 95% yield. Careful control of the reaction temperature was required because above – 50 °C the anion decomposed to produce methanethiolate,[9,10] which then reacted with the bromide to produce the sulphide **5**. Methanolysis of ortho thioesters has been well described[11] and a mixture of mercury(II) chloride and mercury(II) oxide was used to convert **2** into the racemic methyl ester **3**. The methyl ester **3** was hydrolysed with potassium hydroxide to give racemic acid **4** in three steps and 78% overall yield from the bromide **1**. Attempts to hydrolyse the ortho thioester directly to the carboxylic acid failed.

Racemic methyl ester **3** was resolved chromatographically using a commercially available (*R*)-*N*-(3,5-dinitrobenzoyl)-α-phenylglycine derivatised amino propyl 10 μm silica[12] support on an analytical HPLC column. This procedure was utilised on a preparative scale to provide a sample of (–) **3**, which when assayed on the analytical column had an enantiomeric excess (ee) of > 95%. This sample was converted into optically active carboxylic acid (–) **4** by mild acidic hydrolysis. Comparison of the optical rotation obtained with this acid versus the literature value indicated an ee of 91%.

To investigate the usefulness of [tris(methylthio) methyl]lithium for the carboxylation of alkyl bromides, three other substrates, the primary and secondary bromides **6a–c** were treated as for **1** to form the tris(methylthio)derivatives **7a–c** in 82%, 89% and 75% yield respectively. There was no evidence (by TLC or ^{1}H-NMR analysis) for the elimination of hydrogen bromide from phenylethyl bromide (**6b**). Methanolysis of these crude products into the methyl esters **8a–c** was achieved using the mercury salts as for **2**. The overall yields for conversion of the bromides **6a–c** to the methyl esters **8a–c** were 79%, 81%, 56% respectively. Attempts to purify the intermediate **7c** by distillation resulted in formation of the dithioketene **9**.[13] Therefore elemental analyses were obtained for **7a** and **b** but not **7c**.



6-8	R^1	R^2
a	H	Ph
b	H	$PhCH_2$
c	Me	Ph

Table. Compounds **7a–c** and **8a–c** Prepared

Product	Yield (%)	bp (°C)	Molecular Formula[b] or Lit. bp (°C)	^{1}H-NMR ($CDCl_3$/TMS) δ, *J*(Hz)
7a	82	166 (0.3 mbar)	$C_{11}H_{16}S_3$ (244.4)	2.11 (s, 9H), 3.28 (s, 2H), 7.35 (m, 5H)
7b	89	195 (0.1 mbar)	$C_{12}H_{18}S_3$ (258.5)	2.08 (s, 9H), 2.10 (m, 2H), 2.92 (m, 2H), 7.20 (m, 5H)
7c	75	–[a]	$C_{12}H_{18}S_3$ (258.5)	1.60 (d, 3H, *J* = 7), 2.00 (s, 9H), 3.26 (q, 1H, *J* = 7), 7.5–7.73 (m, 5H)
8a	96	216–218	215[13]	
8b	91	235–238	232[13]	
8c	75	223–225	98–100[14] (16 mbar)	

[a] Attempts to distill compound **7a** produced 1-methyl-2,2-bis(methylthio)ethenylbenzene (**9**); bp 96–98 °C (0.3 mbar) [Lit.[15] bp 78–80 °C (0.13 mbar)].

[b] Satisfactory microanalyses obtained: C ±0.07, H ±0.02, S ±0.06.

All reagents were of commercial quality from freshly opened containers. Tris(methylthio)methane, acenaphthenol, mercury(II) chloride, mercury(II) oxide and the alkyl bromides **6a–c** were purchased from Aldrich Chemical Co.

Melting points were determined using a Reichart Thermovar hot-stage apparatus or a Mettler FP800 automatic mp apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker AM 300 spectrometer at 300 MHz and ^{13}C-NMR spectra at 90 MHz. IR spectra were recorded using a Perkin-Elmer 1750 FT spectrophotometer. Optical rotations were determined in CH_2Cl_2 solution using a Perkin-Elmer 241 polarimeter. Silica gel used for chromatography of racemic compounds was Kieselgel-60 (230–400 mesh) purchased from E. Merck A.G., Darmstadt, Germany. (*R*)-*N*-(3,5-Dinitrobenzyl)-α-phenylglycine derivatised amino propyl 10 μm silica was purchased from Regis Chromatography. Elemental microanalyses were performed by Mr. B. Oliver at C.H.N. Analysis Ltd., Leicester, England.

(±)-1-[Tris(methylthio)methyl]acenaphthene (2); Typical Procedure for 7a–c:

Tris(methylthio)methane (22.4 g, 0.168 mol) is dissolved in THF (100 mL), and cooled to – 78 °C under N_2. A 1.6 M solution of BuLi in hexane (95 mL, 0.15 mol) is added over 2 h keeping the temperature of the solution below – 70 °C. A solution of 1-bromoacenaphthene (**1**)[5] (31.4 g, 0.135 mol) in THF (100 mL) is added dropwise and stirring is continued at – 78 °C for a further 2 h. The mixture is allowed to warm to r.t. overnight and the resulting black solution is evaporated *in vacuo* and the residue dissolved in boiling hexane (500 mL). The hot solution is filtered to remove lithium salts and the resulting black filtrate cooled to – 25 °C to give **2** as orange prisms; yield: 39.3 g (95%); mp 72.0–72.5 °C.

		C	H	S
$C_{16}H_{18}S_3$	calc.	62.70	5.92	31.38
(306.5)	found	62.72	5.87	31.11

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.97 (s, 9H), 3.51 (dd, 1H, *J* = 17, 7 Hz), 3.98 (dd, 1H, *J* = 17, 2 Hz), 4.26 (dd, 1H, *J* = 7, 2 Hz), 7.29 (d, 1H, *J* = 7 Hz), 7.43 (m, 2H), 7.59 (d, 1H, *J* = 5 Hz), 7.68 (d, 1H, *J* = 7 Hz), 7.89 (d, 1H, *J* = 5 Hz).

^{13}C-NMR, ($CDCl_3$/TMS): $\delta = 14.15, 36.35, 52.5, 75.35, 119.0, 122.4, 123.55, 124.24, 127.3, 128.0, 131.55, 139.8, 143.4, 144.0$.

(±)-1-(Methylthio)acenaphthene (5):

The procedure is as described for **2** using the same quantities as is described above except that temperature control is not rigorously maintained. After dissolving the residue in boiling hexane and filtering the hot solution to remove lithium salts compound **5** is purified by column chromatography using CH_2Cl_2 as eluent; yield: 8.2 g (22 %); bp 103 °C (10 mbar).

$C_{13}H_{12}S$	calc.	C 77.95	H 6.04	S 16.01
(200.3)	found	77.99	6.09	16.33

IR (neat): ν = 2915, 1604, 1426 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.82 (s, 3 H), 3.31 (dd, 1 H, J = 17, 2 Hz) 3.73 (dd, 1 H, J = 17, 7 Hz), 4.57 (dd, 1 H, J = 7, 2 Hz), 7.13 (d, 1 H, J = 7 Hz), 7.40 (m, 3 H), 7.52 (m, 2 H).

^{13}C-NMR ($CDCl_3$/TMS): $\delta = 12.1, 39.4, 46.2, 119.8, 120.1, 122.2, 123.7, 128.1, 128.2, 131.0, 137.9, 142.8, 145.2$.

(±)-Methylacenaphthene-1-carboxylate (3); Typical Procedure for 8a–c:

A solution of **2**, (18.6 g, 60.7 mmol), $HgCl_2$ (68.7 g, 145 mmol) and HgO (23.2 g, 107 mmol) in MeOH/H_2O (12 : 1, 1.6 L) is refluxed for 5 h. The resulting suspension is cooled to r. t., filtered and the filter cake washed with CH_2Cl_2 (500 mL). The filtrate is poured into H_2O (1 L), separated and extracted with CH_2Cl_2 (2 × 1 L). The combined organic fractions are washed with 75 % aq NH_4OAc (2 × 500 mL), sat. NH_4Cl (500 mL) and dried ($MgSO_4$). The solvent is removed *in vacuo* to leave an orange oil (12.5 g). This material is purified by medium pressure column chromatography with CH_2Cl_2 as eluent. The resulting oil is recrystallised from hexane to give **3** as orange prisms; yield: 11.1 g (86 %); mp 33.5–34 °C.

$C_{14}H_{12}O_2$	calc.	C 79.22	H 5.70
(212.2)	found	79.02	5.72

IR (neat): ν = 1738 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.58 (dd, 1 H, J = 17, 7 Hz), 3.76 (s, 3 H), 3.78 (dd, 1 H, J = 17, 2 Hz), 4.55 (dd, 1 H, J = 7, 2 Hz), 7.28 (d, 1 H, J = 5 Hz), 7.43 (m, 3 H), 7.63 (m, 2 H).

^{13}C-NMR ($CDCl_3$/TMS): $\delta = 34.3, 48.5, 52.2, 119.7, 120.5, 122.7, 124.65, 127.9, 128.2, 131.7, 136.25, 142.25, 143.3, 173.4$

(±)-Acenaphthene-1-carboxylic Acid (4):

A solution of **3**, (3.2 g, 15 mmol) in 6 N KOH solution (40 mL) is refluxed for 3 h. The mixture is then cooled and washed with Et_2O (50 mL). The aqueous layer is cooled to 5 °C and 10 N HCl is added slowly until the solution is acidic to litmus paper. The acidic solution is extracted with EtOAc (2 × 50 mL) and the combined EtOAc fractions are washed with H_2O (25 mL), dried ($MgSO_4$) and evaporated to leave an orange solid (2.9 g). This is recrystallised from toluene to give off-white needles; yield: 2.85 g (95 %); mp 164 °C (Lit.[5] mp 164 °C).

$C_{13}H_{10}O_2$	calc.	C 78.77	H 5.09
(198.2)	found	78.94	5.21

IR (neat): ν = 3412 (OH); 1698 (CO) cm^{-1}

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.59 (dd, 1 H, J = 17, 7 Hz), 3.84 (dd, 1 H, J = 17, 2 Hz), 4.58 (dd, 1 H, J = 7, 2 Hz), 7.29 (d, 1 H, J = 7 Hz), 7.50 (m, 3 H), 7.65 (m, 2 H), 11.70 (br s, 1 H).

^{13}C-NMR ($CDCl_3$/TMS): $\delta = 33.95, 48.2, 119.6, 120.55, 122.7, 124.1, 127.8, 128.0, 131.5, 138.0, 141.3, 142.6, 179.3$.

(−)-Methylacenaphthene-1-carboxylate ((−)-3):

Racemic ester **3** is dissolved in hexane/*i*-PrOH (99 : 1) to give a solution of 10 mg/mL^{-1}. This solution is then injected onto a 40 × 500 mm i. d. medium pressure column packed with (*R*)-*N*-(3,5-dinitrobenzoyl)-α-phenylglycine derivatised amino propyl silica of particle size 10 μm. At each injection 10 mL of the ester solution is introduced onto the column. The elution is performed using hexane/*i*-PrOH (99 : 1) as eluent with a flow rate of 25 mL min^{-1}. Those fractions where the ee of the first eluent exceeded 95 % are combined as are the remaining fractions with the ee exceeding 50 %; yield for a single injection: > 95 % ee, 5 mg, > 50 % ee, 30 mg. The process is repeated 10 times after which 47 mg of > 95 % ee, material and 280 mg of > 50 % ee material is collected. The > 50 % ee material is then rechromatographed in 3 aliquots to give a further 46 mg of > 95 % ee material; total yield from 10 injections: > 95 % ee, 93 mg (19 %), mp 32–34 °C; $[\alpha]_D^{20}$ − 200° (c = 0.04, CH_2Cl_2).

$C_{14}H_{12}O_2$	calc.	C 79.22	H 5.70
(212.2)	found	78.98	5.74

IR (neat): ν = 1737 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.66 (dd, 1 H, J = 17, 7 Hz), 3.73 (s, 3 H), 3.90 (dd, 1 H, J = 17, 2 Hz), 4.61 (dd, 1 H, J = 7, 2 Hz), 7.31 (d, 1 H, J = 5 Hz), 7.50 (m, 3 H), 7.65 (m, 2 H).

(−)-Acenaphthene-1-carboxylic Acid ((−)-4).

(−)-Methyl acenaphthene-1-carboxylate (**(−)-3**) (70 mg, 0.32 mmol) is dissolved in THF/0.5 N aq HCl (1 : 1, 10 mL), and the resulting solution is stirred at 40 °C for 32 h. The THF is evaporated *in vacuo* and the carboxylic acid (**(−)-4**) solidifies on standing. The solid is isolated by filtration and recrystallisation from toluene to give off-white needles; yield: 59 mg (90 %); mp 163.4 °C; $[\alpha]_D^{25}$ − 110° (c = 0.04, EtOH) [Lit.[2] $[\alpha]_D^{25}$ − 120.1° (c = 2, EtOH)].

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