The synthesis of 3*H*-naphthol[1,8-*bc*]thiophene derivatives

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Methods for the synthesis of keto derivatives of the little studied naphtho[1,8-*bc*]thiophene system have been developed. Using the readily available benzothiophene derivative 6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one **4**, a 3-keto-naphtho-[1,8-*bc*]thiophene **14** was synthesized by a tin(IV) chloride catalyzed cyclization of the acid chloride derivative of the saturated acid **13***b*. The bicyclic ketone **4** was also used to prepare the keto-sulfoxide **7**, which was cyclized to the 4-keto-naphtho-[1,8-*bc*]thiophene system **9** in a Pummerer-type rearrangement.

Key words: synthesis, organosulfur, naphtho[1,8-*bc*]thiophenones.

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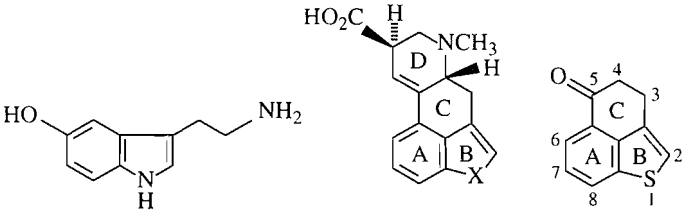
On a mis au point des méthodes de synthétiser les dérivés cétoniques du système naphto[1,8-*bc*]thiophène qui n'a pas été très étudié jusqu'à maintenant. Utilisant comme produit de départ la 6,7-dihydrobenzo[*b*]thiophén-4(5*H*)-one (**4**), un dérivé benzothiophène facilement disponible, on a réalisé la synthèse de la naphto[1,8-*bc*]thiophén-3-one (**14**) en faisant appel à une cyclisation, catalysée par la chlorure d'étain (IV), du chlorure d'acide de l'acide saturé **13***b*. On a utilisé la cétone bicyclique **4** pour préparer ie céto-sulfoxyde **7** qui, par une cyclisation impliquant une transposition du type de Pummerer, conduit au système naphto[1,8-*bc*]thiophón-4-one, **9**.

Mots clés : synthèse, organosulfure, naphto[1,8-*bc*]thiophénones.

[Traduit par la rédaction]

Introduction

Compounds and alkaloids containing the indole nucleus have a wide spectrum of pharmacological activity (1–4). Perhaps the best known examples of these compounds are the natural transmitter 5-hydroxytryptamine **1** (5) and derivatives of the ergoline ring system such as lysergic acid **2***a* (for a general review, see ref. 6). Replacement of the indole nitrogen by sulfur is known (7) to change the pharmacological action of **1** and related compounds and, in some cases, to produce isosteres with useful biological properties (8). Several workers have attempted to prepare the sulfur analogues of ergolines **2***b* but, to our knowledge, none have been successful (9–12). This paper describes the synthesis of naphtho[1,8-*bc*]thiophene derivatives, which should be useful intermediates in the preparation of thia-ergolines **2***b*.



1 **2***a* = NH, **2***b* = S **3**

Very few derivatives of the naphtho[1,8-*bc*]thiophene system have been reported (9–11, 13–15). Most of the syntheses described have been in connection with development of routes of the preparation of thia-ergolines. Considerable effort (9, 10) was put into developing syntheses and the chemistry of the tricyclic ketone **3** as it was expected to be a useful intermediate in constructing ring D of thia-ergoline systems. Unfortunately, this (and related compounds) isomerizes readily to naphthalene derivatives in which the A and C rings become the aromatic nucleus (10). This problem may be overcome by working with derivatives in the early stages of the synthesis in which the A ring is saturated since these compounds would show little tendency to be involved in aromatization processes involving the C ring. Consequently, we have designed syntheses of the novel tricyclic ketones **9** and **14** and report on their preparation here.

Experimental

Melting points were determined using a Thiele tube apparatus containing silicon oil and were uncorrected. The IR spectra were recorded on a Nicolet 5DX spectrometer as neat liquids, thin films, or KBr discs. The ^1H and ^{13}C NMR spectra were recorded on a Bruker ACE 200 or a Bruker AM 400 spectrometer, at 200 and 400 MHz respectively, in $CDCl_3$ solution with either tetramethylsilane or chloroform as the internal standard. Assignments for ^{13}C spectra were made (where possible) on the basis of DEPT, 2D correlation experiments,[2] and chemical shift data. MS and GCMS were recorded on a Hewlett Packard 5970/5890 spectrometer. Elemental analyses were obtained from Canadian Microanalytical Service Ltd., B.C. Column chromatography was performed on Merck silica gel, grade 60, 230–400 mesh. Reagents were obtained from the Aldrich Chemical Company and, unless stated otherwise, were used without purification. Solvents were purified according to procedures described in ref. 16.

*6,7-Dihydro-5*H*-benzo[*b*]thiophen-4-one* **4**

This ketone was prepared either from thiophene or from 2-cyclohexen-1-one using methods described previously (17–20). Both methods are reliable although the preparation from 2-cyclohexen-1-one (20) is preferred for large-scale work.

Preparation of the ene-acetates **5**a *and* **5**b

These compounds were prepared by the following modifications of the literature method (21).

A solution of triethyl phosphonoacetate (22.4 g, 100 mmol) in dry tetrahydrofuran (100 mL) was added dropwise over 45 min to a suspension of sodium hydride (60% in oil, 3.7 g, 90 mmol) in dry tetrahydrofuran (100 mL) under an argon atmosphere. The resulting clear yellow solution was heated under reflux for 15 min and a solution of the ketone **4** (10.0 g, 66 mmol) in tetrahydrofuran (100 mL) was added in one portion. After 36 h at reflux, the resulting orange solution was cooled

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[2]Copies of the homo- and heteronuclear shift correlation spectra for **9** and **14** may be purchased from The Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, Canada K1A 0S2.

and was added to water (300 mL). Organic material was recovered by extraction into dichloromethane (3 × 250 mL). The organic extracts were washed with water (3 × 100 mL), dried ($MgSO_4$), and evaporated. The residual tan colored oil was chromatographed on silica (5% ethyl acetate in hexanes) to remove residual phosphorus compounds and was distilled at reduced pressure to yield a colorless liquid (14.17 g, 97%; bp 105–125°C at 0.05 Torr (1 Torr = 133.3 Pa)). ^{1}H NMR[a] indicated that the product was a 63:37 mixture of *E* and *Z* isomers **5***a* and **5***b*; IR (ν_{max}, neat): 3107, 2933, 1706, 1612, 1174, 1150, and 1049 cm^{-1}; ^{1}H NMR, *E* isomer,[b] δ: 7.20 (d, *J* = 5.4 Hz, -C*H*=CH-), 7.06 (d, *J* = 5.4 Hz, -CH=C*H*), 6.11 (t, *J* = 1.7 Hz, -C=C*H*), 4.19 (q, -C*H*$_2$-CH$_3$), 3.20–3.05 (m, -C*H*$_2$-C=CH-), 2.89 (t, *J* = 6.1 Hz, -C*H*$_2$-S-), 1.95 (m, -CH$_2$-C*H*$_2$-CH$_2$-), 1.31 (t, -CH$_2$-C*H*$_3$); *Z* isomer,[c] δ: 7.81 (d, *J* = 5.5 Hz, -C*H*=CH-), 7.02 (d, *J* = 5.5 Hz, -CH=C*H*-), 5.65 (br, s -C=C*H*-), 4.18 (q, -C*H*$_2$-CH$_3$), 2.93 (t, -C*H*$_2$C=-CH-), 2.50–2.40 (m, -C*H*$_2$-S-), 1.96 (m, -CH$_2$-C*H*$_2$-CH$_2$-), 1.28 (t, -CH$_2$C*H*$_3$); ^{13}C NMR, *E* isomer, δ: 167.17 (*C*=O), 150.32, 144.73, and 134.71 (quaternary C), 123.24, 122.51, and 110.31 (-*C*H=CX), 59.42 (-OC*H*$_2$CH$_3$), 26.18, 25.29, and 23.53 (*C*H$_2$), 14.25 (OCH$_2$*C*H$_2$CH$_3$); Z isomer[c]: 166.45 (*C*=O), 146.81, 145.45, and 132.49 (quaternary C), 128.55, 120.88, and 112.03 (-*C*H=CX), 59.76 (-OC*H*$_2$CH$_3$), 35.51, 25.86, and 24.14 (*C*H$_2$), 14.15 (OCH$_2$*C*H$_3$). Anal. calcd. for $C_{12}H_{14}O_2S$: C 64.84, H 6.35, S 14.42%; found: C 65.22, H 6.55; S, 14.53%.

[a]Determined by integration of vinylic protons in the ^{1}H NMR of the crude reaction mixture.

[b]Remaining isomer after hydrogenation with Wilkinson's catalyst; see Discussion.

[c]Obtained by analysis of spectra for mixture of isomers.

*4′-(4,5,6,7-Tetrahydrobenzo[*b*]thienyl) ethyl ethanoate* **6**

A solution of the ene-acetates **5***a* and **5***b* (20 g, 90 mmol) in toluene (700 mL) was stirred with 10% Pd on charcoal (4.5 g) for 24 h under a hydrogen atmosphere. The mixture was filtered through Celite and the crude product was recovered by evaporation of the solvent. Traces of unhydrogenated material were separated by flash chromatography on silica (5% ethyl acetate in hexanes) and the product was obtained as a colorless liquid (17.75 g, 88%) by distillation (bp 85–92°C at 0.05 Torr); IR (ν_{max}, neat): 2934, 1733, and 1175 cm^{-1}; ^{1}H NMR, δ: 7.01 (d, *J* = 5.2 Hz, -C*H*=CH-), 6.79 (d, *J* = 5.2 Hz, -CH=C*H*-), 4.16 (q, -OC*H*$_2$CH$_3$), 3.35–3.15 (m, -CH$_2$C*H*CH$_2$-), 2.74 (t, -C*H*$_2$-S-), 2.69 and 2.38 (each dd, -CH-C*H*$_2$CO-), 2.05–1.65 and 1.65–1.45 (m, -C*H*$_2$C*H*$_2$-), 1.26 (t, -OCH$_2$C*H*$_3$); ^{13}C NMR, δ: 172.35 (*C*=O), 137.37 and 136.21 (quaternary carbons), 126.13 and 121.73 (-*C*H=*C*H-), 60.11 (-OCH$_2$CH$_3$), 40.84, 28.61, 24.89, and 21.26 (four CH$_2$), 32.48 (-CH-). Anal. calcd. for $C_{12}H_{16}O_2S$: C 64.25, H 7.19, S 14.29%; found: C 64.00, H 7.04, S 14.31%.

Preparation of the keto-sulfoxide **7**

Dimethyl sulfoxide, freshly distilled from calcium hydride (30 mL, 420 mmol), was added dropwise to a stirred solution of *n*-butyllithium (36 mL of a 1.6 M solution in hexane, 58 mmol) in dry tetrahydrofuran (30 mL) at 0°C under an argon atmosphere. A solution of the ester **6** (5.0 g, 22.3 mmol) in dry tetrahydrofuran (10 mL) was added to the resulting cream colored slurry and the reaction mixture was allowed to warm to room temperature. The orange solution produced was added to water and the mixture was extracted with dichloromethane (3 × 150 mL). The organic extracts were washed with saturated sodium bicarbonate (2 × 100 mL) and with water (3 × 100 mL), dried ($MgSO_4$), and evaporated. The light brown residue was chromatographed on silica (ethyl acetate) to yield a light brown solid (4.8 g, 84%), which was a mixture of diastereomers of **7**. An analytically pure sample of the minor diastereomer was obtained as white crystals, mp 75–77°C, on crystallization from hexanes; IR (ν_{max}, neat): 2930, 1710, and 1035 cm^{-1}; ^{1}H NMR, δ: 7.03 (d, *J* = 5.3 Hz, -C*H*=CH-), 6.75 (d, *J* = 5.3 Hz, -CH=C*H*-), 3.90–3.60 (2 × q,[a] -COC*H*$_2$SO-), 3.45–3.25 (m, -CH$_2$C*H*CH$_2$-), 2.68, 2.66[a] (s, -SOC*H*$_3$), 3.02–2.65 and 2.05–1.40 (unres. m, methylene protons); ^{13}C NMR, δ: 201.39 (*C*=O), 136.95, 136.42 (quaternary carbons), 126.16, 121.94 (-*C*H=*C*H-), 64.55 [63.94][b] (*C*OC*H*$_2$SO), [51.7] 51.51 (*C*HCH$_2$CO), 39.03 [38.78] (SO*C*H$_3$), 30.81 (CH$_2$*C*HCH$_2$), 28.68, 24.76, and 21.18 (3CH$_2$ in six-membered ring). Anal. calcd. for $C_{12}H_{16}O_2S_2$: C 56.22, H 6.29, S 25.01%; found: C 55.86, H 6.21, S 24.87%.

[a]Signals due to diastereomers.

[b]Values for the minor diastereomer given in square brackets.

*3-Methylthio-4,5,5a,6,7,8-hexahydro-3*H*-naphtho[1,8-*bc*]thiophen-4-one* **8**

A solution of *p*-toluenesulfonic acid monohydrate (3.71 g, 19.5 mmol) in 1.2 L of chloroform (distilled from P_2O_5 to remove ethanol) was heated under reflux for 3 h with removal of water via a Dean Stark trap. The sulfoxide **7** (2.5 g, 9.75 mmol) in chloroform (150 mL) was added and resulting orange-brown solution was heated under reflux for 15 min. The cooled reaction mixture was poured into saturated sodium bicarbonate (500 mL) and the organic layer was washed with bicarbonate (500 mL) and with water (2 × 500 mL), and then dried ($MgSO_4$). Evaporation of the chloroform gave a brown oil, which was purified by column chromatography on silica (10% ethyl acetate in hexanes). The pale yellow oil obtained (1.1 g, 47%) was used immediately as it darkened quickly on standing and decomposed on attempted distillation. Spectroscopic analysis indicated that **8** was formed as a mixture of diastereomers; IR (ν_{max}, neat): 3096, 2923, 1704, 1603, and 1435 cm^{-1}; ^{1}H NMR[a], δ: [7.11] 7.00 (s, -C*H*=C-), 4.20 [4.16] (s, -C*H*SCH$_3$-), 3.40–2.65 (unres. m, 5H), [2.15] 2.13 (s, -SCH$_3$), 2.20–1.10 (unres. m, 4H).

[a]Integration of signals at 7.0 and 2.1 ppm suggested that the product was a 2:1 mixture of diastereomers; values for the minor isomer are shown in square brackets.

*4,5,5a,6,7,8-Hexahydro-3*H*-naphtho[1,8-*bc*]thiophen-4-one* **9**

W-2 Raney nickel (ca. 6 g) was added to a solution of the methylthio ether **8** (1.3 g, 5.5 mmol) in acetone (100 mL) and the mixture was stirred at room temperature for 5 h. The catalyst was removed by filtration through Celite and the crude product was obtained by evaporation of the solvent. Column chromatography on silica (10% ethyl acetate in hexanes) yielded a pale orange solid that crystallized from hexane (charcoal) to yield off-white plates (0.44 g, 43%); mp 60–63°C; IR (ν_{max}, Nujol): 3095, 2930, 1712, 1446, 1393, 1325, 1228, and 1173 cm^{-1}; ^{1}H NMR (400 MHz),[a] δ: 6.79 (d, *J* = 0.9 Hz, -C*H*=C-), 3.59 (d, *J* = 21.0 Hz, 1H of =C-C*H*$_2$-CO), 3.47 (dd, *J* = 21 and 0.9 Hz, 1H of =C-C*H*$_2$CO), 3.05–2.85 (m, -CH$_2$C*H*CH$_2$-), 2.90–2.60 (m, C*H*$_2$S and 1 proton of CHC*H*$_2$CO), 2.20–2.10 (m, 1 proton of CHC*H*$_2$CO, 1 proton of CHC*H*$_2$CH$_2$, and 1 proton of CH$_2$C*H*$_2$CH$_2$S), 1.95–1.80 (m, 1 proton of CH$_2$C*H*$_2$CH$_2$S), and 1.4–1.25 (m, 1 proton of CHC*H*$_2$CH$_2$); ^{13}C NMR, δ: 209.0 (*C*=O), 135.63, 134.86, and 132.71 (quaternary carbons), 116.64 (*C*H=C-), 46.14 (-CHCH$_2$CO), 41.15 (=CCH$_2$CO), 32.22 (-C*H*-), 29.84 (CH$_2$*C*H$_2$CH), 24.64 (SC*C*H$_2$), and 23.45 (CH$_2$CH$_2$CH$_2$). Anal. calcd. for $C_{11}H_{12}OS$: C 68.72, H 6.29, S 16.67%; found: C 68.28, H 6.19, 17.04%.

[a]Assignments were made on the basis of proton–proton and proton–carbon correlation experiments.

*4-Methoxymethylene-6,7-dihydro-5*H*-benzo[*b*]thiophene* **10**a, **10**b

Phenyllithium (22 mL of a 2 M solution in cyclohexane–ether, 44 mmol) was added dropwise to a suspension of (methoxymethyl)-triphenylphosphonium chloride (22) (17.14 g, 50 mmol) in dry ether (100 mL) at 0°C under an argon atmosphere. After stirring the resulting red mixture for 15 min, the temperature was lowered to −65°C and a solution of the ketone **4** (3.04 g, 20 mmol) in anhydrous ether was added over 5 min. The reaction mixture was allowed to warm to room temperature, stirred vigorously for 5 h, and then poured into cold water (100 mL). The ether layer was collected and the aqueous layer was extracted with ether (3 × 25 mL). The combined organic extracts were washed with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated. Column chromatography of the residue on silica (0–2% ethyl acetate in hexanes) gave a mixture (TLC, NMR) of the *E* and *Z* enol ethers **10***a* and **10***b*, which was distilled to yield a colorless liquid (2.7 g, 75%; bp 72–75°C at 0.03 Torr); IR (ν_{max}, neat): 2932, 2832, 1661, 1452, 1223, 1157, and 1124 cm^{-1}; ^{1}H NMR, δ: 7.58[a] (d, *J* = 5.3 Hz, -C*H*=CH-), 7.05–6.94 (unres. m, thiophenic H), 6.45[b] (t, *J* = 1.6 Hz, -C=C*H*OCH$_3$), 5.88[a] (t, *J* = 1.2 Hz, -C=C*H*OCH$_3$), 3.66 (s,

-OCH_3), 2.88–2.75 (m, -CH_2CH_2S-), 2.50–2.44[b] (m, -CH_2CH_2C=), 2.30–2.24[a] (m, -CH_2CH_2C=), 1.95–1.79 (m, -$CH_2CH_2CH_2$-); ms *m/e*: 180 (89).

NOTE: *a* and *b* refer to signals for the *Z* and *E* isomers respectively (see discussion).

*4'-(4,5,6,7-Tetrahydrobenzo[*b*]thienyl) methanal* ***11***

6 M Aqueous hydrochloric acid (6 mL) was added to a solution of the enol ethers **10***a* and **10***b* (8.06 g, 45 mmol) in tetrahydrofuran (100 mL) under argon and the mixture was heated under reflux for 15 h. A further 4 mL of the 6 M acid was added and the solution refluxed for an extra 2 h. The reaction mixture was cooled, evaporated to a small volume, and quenched with water (100 mL). The mixture was extracted with dichloromethane (4 × 20 mL) and the organic extracts were washed with saturated sodium bicarbonate (2 × 10 mL), brine (1 × 50 mL), dried ($MgSO_4$), and evaporated to yield **11** as a pale yellow oil[a] (7.80 g); IR (ν_{max}, neat): 2937, 2858, 2717, and 1725 cm^{-1}; ^1H NMR, δ: 9.66 (d, *J* = 2.2 Hz, -*CH*O), 7.15 and 6.88 (each d, *J* = 5.2 Hz, -*CH*=*CH*-), 3.54 (m, -CH_2*CH*CHO), 2.8 (t, -SCH_2CH_2-), 2.21–1.81 (m, -CH_2CH_2-); ^{13}C NMR, δ: 200.68 (-*C*HO), 138.23 and 129.06 (quaternary C), 126.4 and 122.5 (-*C*H=*C*H-), 48.75 (-*C*HCHO), 24.47, 22.57, and 21.19 (3 × CH_2); ms *m/e*: 166. The aldehyde was characterized as a 2,4-dinitrophenylhydrazone derivative, which crystallized from ethyl acetate as orange crystals, mp 210–213°C. Anal. calcd. for $C_{15}H_{14}N_4O_4S$: C 52.02, H 4.07, N 16.18, S 9.26%; found: C 51.51, H 4.16, N 15.94, S 9.24%.

[a]This product decomposed rapidly unless stored at low temperatures under an inert atmosphere, and was used directly in the next stage.

E-*3-(4'-(4,5,6,7-Tetrahydrobenzo[*b*]thienyl)) ethyl propenoate* ***12***

A solution of triethyl phosphonoacetate (16.08 g, 71.8 mmol) in dry tetrahydrofuran (100 mL) was added dropwise to a suspension of sodium hydride (60% in oil, 2.88 g, 72 mmol) in tetrahydrofuran (100 mL) under an argon atmosphere. The mixture was cooled to −60°C and a solution of the aldehyde **11** in tetrahydrofuran (100 mL) was added over a period of 10 min. The reaction mixture was allowed to warm to room temperature and was stirred for 1.5 h. Solvent was removed by rotary evaporation, the residue was quenched with water (100 mL), and the resulting mixture was extracted with dichloromethane (4 × 20 mL). Evaporation of the washed (brine, 1 × 50 mL) and dried ($MgSO_4$) extracts yielded an oil that was distilled (bp 116–119°C at 0.03 Torr) to give **12** as a clear liquid (9.50 g, 90% from **10***a* and **10***b*); IR (ν_{max}, neat): 2936, 1718, and 1652 cm^{-1}; ^1H NMR, δ: 7.05 (d, *J* = 5.2 Hz, S-*CH*=CH-), 7.0 (dd, -CHC*H*=CHCO$_2$-), 6.73 (d, *J* = 5.2 Hz, SCH=C*H*-), 5.79 (dd, *J* = 15.6 and 1.2 Hz, -CHCH=C*H*CO$_2$-), 4.18 (q, -OCH_2CH_3), 3.56 (m, -CH_2*CH*(C=)CH=), 2.78 (t, SCH_2CH_2-), 1.70–1.90 (m, -$CH_2CH_2CH_2$CH-), 1.29 (t, -OCH_2CH_3); ^{13}C NMR, δ: 166.64 (-*C*O$_2$CH$_2$CH$_3$), 151.49 (=*C*HCO$_2$CH$_2$CH$_3$), 136.87 and 134.59 (quaternary C), 127.28, 122.02, and 121.54 (thiophenic *C*H and remaining olefinic C), 60.23 (-OCH_2CH$_3$), 39.1 (-CH_2CH(C=)CH=), 28.64, 24.90, and 21.16 (3 × CH_2), 14.24 (-OCH_2CH_3); ms *m/e*: 236 (M^+). Anal. calcd. for $C_{13}H_{16}O_2S$: C 66.07, H 6.83, S 13.57%; found: C 66.01, H 6.72, S 12.95%.

*3-(4'-(4,5,6,7-Tetrahydrobenzo[*b*]thienyl)) ethyl propionate* ***13***a

Tris(triphenylphosphine)rhodium(I) chloride (0.86 g, 9.3 mmol) was added to benzene (270 mL) that had been presaturated with hydrogen. After stirring the resulting orange solution for 15 min, a solution of the ester **12** (8.72 g, 36.6 mmol) in benzene (30 mL) was added and the reaction mixture was stirred under a hydrogen atmosphere for 50 h at 20°C. After removal of solvent, the residue was purified by flash chromatography on silica (5% ethyl acetate in hexanes) and the oil obtained was distilled (bp 117–121°C at 0.07 Torr), yielding **13***a* as a clear liquid (8.62 g, 98%); IR (ν_{max}, neat): 2933, 1733, and 1174 cm^{-1}; ^1H NMR, δ: 7.03 and 6.86 (two d, *J* = 5.1 Hz, SC*H*=C*H*-), 4.13 (q, -OCH_2CH_3), 2.75 (t, -SCH_2CH_2-), 2.37 (dd, -$CH_2CH_2CO_2$-), 2.12 (m, -CH_2*CH*CH_2-), 1.98–1.22 (m, 3 × CH_2); ^{13}C NMR, δ: 173.73 (-*C*O$_2$-), 138.38 and 136.11 (quaternary C), 126.59 and 121.61 (-*C*H=*C*H-), 60.26 (-CH_2CO$_2$-), 35.01 (-CH_2*C*HCH_2-), 31.89, 30.73, 27.79, 25.10, and 21.59 (5 × CH_2), 14.21 (-$CO_2CH_2CH_3$); ms *m/e*: 238 (M^+). Anal. calcd. for $C_{13}H_{18}O_2S$: C 65.51, H 7.61, S 13.43%; found: C 65.74, H 7.64, S 13.12%.

*3-(4'-(4,5,6,7-Tetrahydrobenzo[*b*]thienyl))propanoic acid* ***13***b

A mixture of the ester **13***a* (6.96 g, 29 mmol) and 1:1 absolute ethanol and 20% aqueous sodium hydroxide solution (140 mL) was heated under reflux for 2 h. The cooled reaction mixture was extracted with dichloromethane (2 × 20 mL), acidified with concentrated hydrochloric acid, and extracted with dichloromethane (3 × 20 mL). Evaporation of the washed (water) and dried ($MgSO_4$) extracts gave a solid residue that was recrystallized as pale yellow plates (5.26 g, 86%), mp 78–80°C from aqueous ethanol; IR (ν_{max}, KBr): 3000 (br) and 1704 cm^{-1}; ^1H NMR, δ: 10.10 (br s, -O*H*), 7.05 and 6.86 (two, d, *J* = 5.2 Hz, -SC*H*=C*H*-), 2.76 (t, -SCH_2CH_2-), 2.43 (dd, -$CH_2CH_2CO_2$H), 2.12 (m, -CH_2*CH*CH_2-), 2.0–1.41 (m, 3 × CH_2); ^{13}C NMR, δ: 180.13 (-*C*O$_2$H), 138.17 and 136.25 (quaternary C), 126.49 and 121.49 (-SC*H*=C*H*-), 34.97 (-CH_2*C*HCH_2-), 31.59, 30.47, 27.86, 25.10, and 21.65 (5 × CH_2); ms *m/e*: 210. Anal. calcd. for $C_{11}H_{14}O_2S$: C 62.83, H 6.71, S 15.22%; found: C 63.22, H 6.79, S 14.95%.

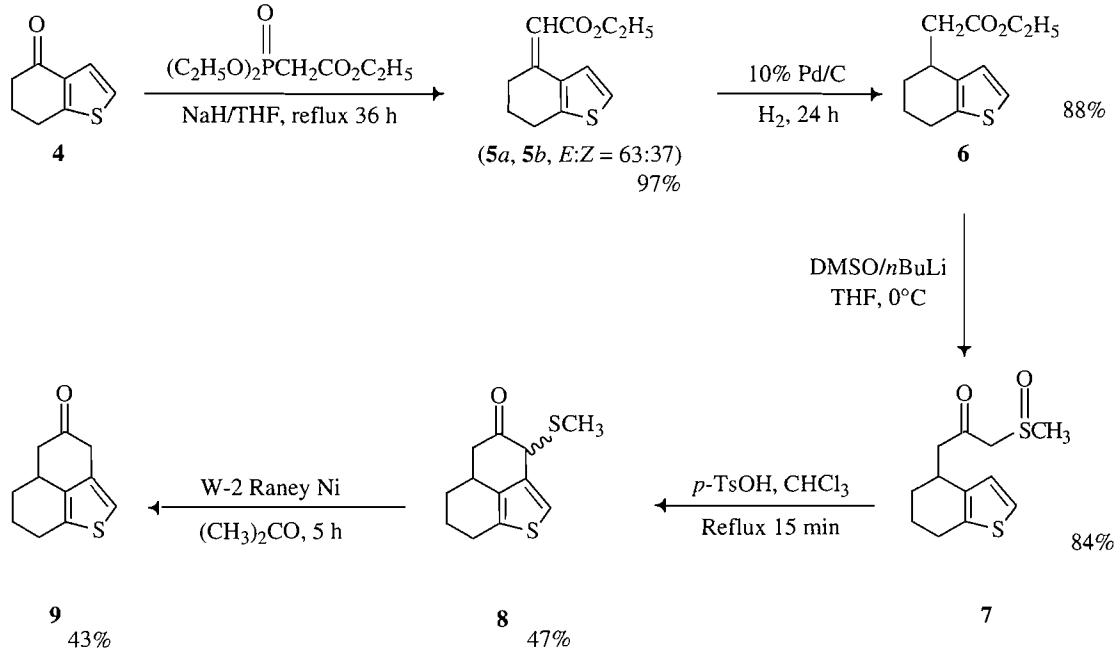
*4,5,5a,6,7,8-Hexahydro-3*H*-naphtho[1,8-*bc*]thiophen-3-one* ***14***

A solution of the acid **13***b* (1.05 g, 5 mmol) in dichloromethane (10 mL) was gently heated under reflux with thionyl chloride (1.19 g, 10 mmol) and pyridine (25 μL) under argon for 3 h. The mixture was concentrated by rotary evaporation and the crude acid chloride (IR 1798 cm^{-1}) was dissolved in carbon disulfide (5 mL). Under argon, the solution was cooled to 0°C, and tin tetrachloride (0.70 mL, 6 mmol) in carbon disulfide (15 mL) was added dropwise over 10 min. After carefully stirring the dark green mixture for 20 min at this temperature, it was heated under reflux for 2.5 h. The contents were cooled, evaporated to near dryness, and taken up into chloroform (50 mL). Ice (20 g) and hydrochloric acid (3 mL) were added, the organic layer was separated off, and the aqueous layer extracted with chloroform (3 × 10 mL). Organic extracts were combined, washed with brine (25 mL), dried ($MgSO_4$), evaporated down, and the residue was purified by flash column chromatography on silica (20% ethyl acetate in hexanes) to yield 0.74 g (77%) of **14** as a yellow solid. Recrystallization from hexanes produced pale yellow needles; mp 67–68°C; IR (ν_{max}, KBr): 3082, 2903, and 1681 cm^{-1}; ^1H NMR (400 MHz), δ: 7.92 (C*H*=C), 2.95–2.84 (dd, 1 proton of SCCH*H*$_2$), 2.80–2.62 (m, 1 proton of CH_2CO, 1 proton of SCCH_2 and CH_2*CH*CH_2), 2.55–2.44 (td, 1 proton of *CH*$_2$CO), 2.20–2.02 (m, 1 proton of $CH_2CH_2CH_2$, 1 proton of CHCH_2CH_2CO, and 1 proton of CHC$H_2CH_2CH_2$), 1.92–1.80 (m, 1 proton of $CH_2CH_2CH_2$), 1.66–1.52 (qd, 1 proton of CHCH_2CH_2CO), and 1.36–1.20 (m, 1 proton of CHC$H_2CH_2CH_2$); ^{13}C NMR, δ: 194.39 (-*C*=O-), 140.95, 136.01, and 135.92 (quaternary C), 128.02 (-SC*H*=), 40.12 (-CH_2CO-), 35.66 (-CH_2*C*HCH_2-), 31.08 (CH*C*H$_2$CH$_2$CO), 29.02 (CH*C*H$_2$CH$_2$CH$_2$), 24.15 (SC*C*H$_2$), and 23.36 (CH_2*C*H$_2$CH$_2$); ms *m/e*: 192 (M^+). Anal. calcd. for $C_{11}H_{12}OS$: C 68.71, H 6.29, S 16.68%; found: C 68.87, H 6.17, S 16.99%.

Results and discussion

*4,5,5a,6,7,8-Hexahydro-3*H*-naphtho[1,8-*bc*]thiophen-4-one* ***9***

Synthesis of the naphthol[1,8-*bc*-]thiophenones requires benzo[*b*]thiophene compounds functionalized at the 3- and 4-positions. The bicyclic ketone **4** satisfies this requirement if both the carbonyl and the aromatic centres are viewed as substituents, and is readily available from either thiophene or from 2-cyclohexen-1-one (17–20). Our general strategy was to introduce a side chain at the 4-position, incorporating the carbonyl group of the target ketone and containing a functional group that could be cyclized onto the thiophene ring in an electrophilic process. This approach avoids using direct oxidation procedures to introduce the carbonyl group that could also oxidize the thiophenic sulfur.



SCHEME 1. Synthesis of 4,5,5a,6,7,8,-hexahydro-3*H*-naphtho[1,8-*bc*]thiophe-4-one.

Functionalization of the bicyclic ketone **4** at the 4-position using Wittig chemistry afforded the unsaturated ester **5** as a mixture of *E* and *Z* isomers (67:33) in almost quantitative yield. The reaction mixutre was readily analysed using ^{1}H NMR spectroscopy because the proximity of the ester function to the thiophenic proton H-3 in the *Z* isomer caused a considerable downfield shift of the resonance for H-3. The *E* to *Z* ratio was dependent on the base used to form the ylid; butyllithium produced the 67:33 *E*/*Z* mixture, and sodium hydride and potassium *tert*-butoxide produced 63:37 and 56:44 mixtures respectively. Various solvents and other reaction conditions were tried but it was not possible to produce either isomer as a major product.

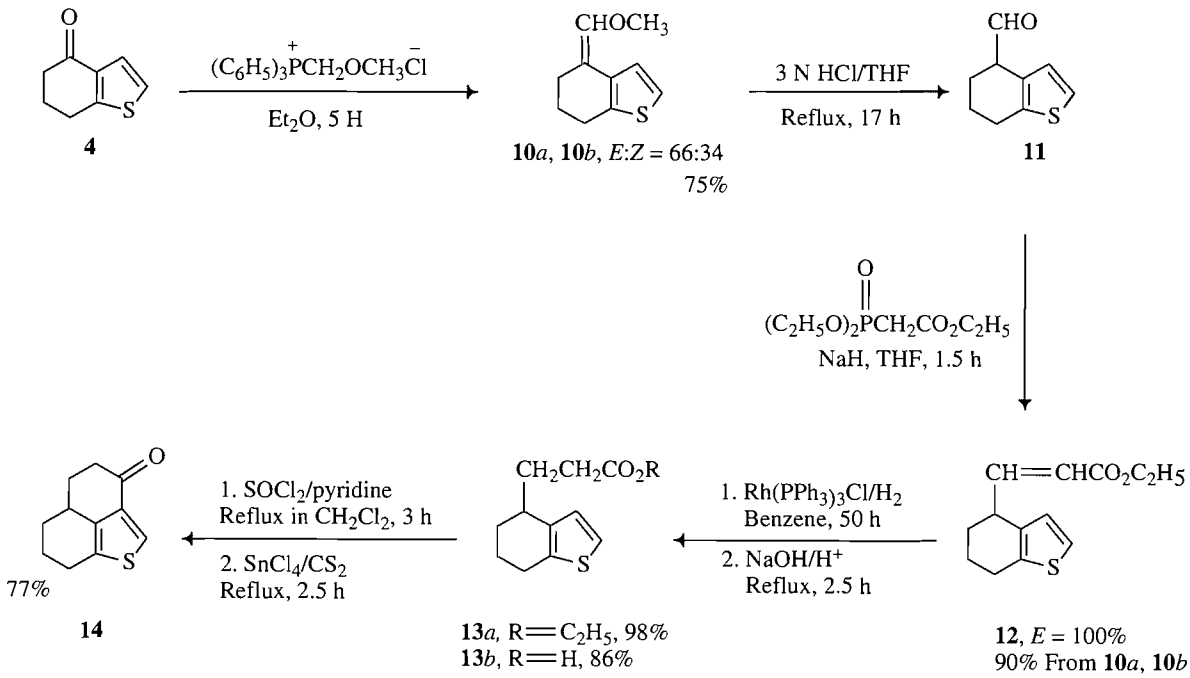
A key step in the overall synthesis was the reduction of the double bond in **5** to produce the saturated ester **6**. Thiophenic compounds are difficult to reduce using conventional heterogeneous catalysts because of catalyst poisoning caused by adsorption of the sulfur to the active sites (23). In addition, high activity catalysts can desulfurize thiophenic systems. In general, homogeneous hydrogenation catalysts such as Wilkinson's catalyst are less susceptible to poisoning by aromatic sulfur compounds but often will not saturate hindered double bonds (24). In this case, hydrogenation using Wilkinson's catalyst resulted in rapid reduction of the *Z* isomer of **5** but left the *E* isomer, containing the more hindered double bond, unreduced. Since the *Z* isomer was the minor product of the Wittig reaction, this approach to the saturated ester **6** was not practical. After consideration of a number of other hydrogenation catalysts, it was found that both isomers of **5** were reduced quite conveniently (24 h, 88% yield) employing a standard Pd-on-carbon catalyst in a somewhat larger compound/catalyst ratio (5:1) than is usual.

Reaction of the saturated ester **6** with the lithium anion of dimethyl sulfoxide gave a good yield (85%) of the keto-sulfoxide **7** as a mixture of diastereoisomers. Treatment of **7** under acidic conditions resulted in a Pummerer-type rearrangement and cyclization to the keto-sulfide **8**. Raney nickel treatment of this product under mild conditions removed the thioether sulfur to give the desired tricyclic ketone **9** without desulfurization of the thiophenic ring. Despite the moderate yield for the cyclization, this synthesis has the advantage of introducing a carbonyl substituent directly into the 4-position of the naphtho[1,8-*bc*]thiophene ring system.

Clear evidence that the tricyclic product had been obtained was given by the observation of only one thiophenic proton in the ^{1}H NMR spectrum. Spectra recorded at 400 MHz showed that the signal for the thiophenic proton of **9** was a doublet (J = 0.9 Hz). Two of the lines of the quartet representing the signal for the methylene sandwiched between the carbonyl and the thiophene ring showed the same small coupling, and double irradiation experiments confirmed that the thiophenic proton was coupled to one of the protons of the methylene group at the 3-position. This coupling is similar to those observed in alkylaromatics (25). Using chemical shift arguments and shift correlation spectra[2] it was possible to assign all of the signals in the ^{1}H NMR spectrum of **9**. Perhaps the most interesting feature of this spectrum is the large difference in chemical shift for the methylene protons at C-6 (1.3 and 2.15 ppm). Examination of molecular models of **9** shows that one possible conformation of the B and C rings results in close contact between C-6 and the carbonyl group at C-4, thus explaining why one of the protons at C-6 is deshielded.

*4,5,5a,6,7,8-Hexahydro-3*H*-naphtho[1,8-*bc*]thiophen-3-one* ***14***

It should be possible to synthesize the 3-keto-substituted naphthothiophene **14** by cyclization of the acid chloride derivative of the carboxylic acid **13***b* under Friedel–Crafts-type conditions. Introduction of the appropriate substituent to the 4-position of the bicyclic ketone **4** was accomplished in three basic stages. Firstly, **4** was converted to the aldehyde derivative **11** by reaction with (methoxymethyl)triphenylphosphonium chloride and hydrolysis of the resultant mixture of enol ethers **10***a* and **10***b*. A satisfactory analysis for the enol ethers could not be



SCHEME 2. Synthesis of 4,5,5a,6,7,8,-hexahydro-3*H*-naphtho[1,8-*bc*]thiophen-3-one.

obtained. The enol ethers were formed as an *E*/*Z* mixture that hydrolyzed readily to the aldehyde **11**. Extension of the 4-substituent by two carbons and introduction of an ester functional group was accomplished by reaction of the aldehyde with triethyl phosphonoacetate under standard Wittig conditions in an overall yield of 90% from the enol ether mixture. This reaction yielded the unsaturated ester **12** as a single isomer, which was assigned as the *E* isomer on the basis of the value of the coupling constant for the olefinic protons (J = 15.6 Hz). Also, the observation that the resonance due to the thiophenic proton on C-3 had not been shifted appreciably (as might have been expected if the ester group was in close proximity, as it would be in the *Z* isomer and as was observed for the *Z* isomer of **5**) supports the conclusion that **12** was formed as the *E* isomer.

Saturation of the double bond in **12** using palladium-on-carbon was very slow and difficult to force to completion unless large quantities of catalyst were used. However, reduction using Wilkinson's catalyst, although slow, gave an almost quantitative yield of the saturated ester **13**. This reduction and the reduction of the *Z* isomer of **5** indicate the general utility of Wilkinson's catalyst for reducing double bonds in thiophene derivatives as long as the double bond is relatively unhindered. Standard chemistry involving saponification of **13***a*, conversion of the resulting carboxylic acid **13***b* to its acid chloride, and treatment of the acid chloride with $SnCl_4$ gave the 3-keto naphthothiophene **14** in an overall yield of 77%. It was difficult to maintain this yield for large-scale preparations (>2 g).

^{1}H NMR spectra of **14** confirmed that cyclization had taken place, as only one uncoupled singlet was observed in the aromatic region. The rest of the ^{1}H NMR spectrum of **14** was complex although a reasonable assignment was possible using shift correlation spectra[2] and from chemical shift arguments. Interestingly, as was observed in the ^{1}H NMR spectra of **9**, the signals for the two protons on C-6 occur at quite different chemical shifts, one being considerably more downfield than would be expected (2.08 and 1.28 ppm). Inspection of molecular models indicates that when overlap of the carbonyl substituent and the π-system of the thiophene ring is maximized, one of the protons on C-6 is in close contact with the carbonyl group and thus is shifted downfield.

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