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Synthetic study toward 17-thiasteroids: synthesis of the 1-thiahydrinden-5-one subunit using a new annulation procedure and investigation of its reduction

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Abstract—The enantioselective syntheses of ketones **6** and **7** featuring the CD subunit of 17-thiasteroid are described. The key bicyclic 1-thiahydrindenone (*S*)-**5** was assembled in three steps from Michael adduct (*S*)-**12** via β-keto ester **15** using a one-pot sequential process involving cleavage of both the ketal group and the *tert*-butyl ester group, decarboxylation, and finally intramolecular aldol condensation. Hydridoalkyl cuprate-induced conjugate reduction of 1-thiahydrindenone (*S*)-**5** and its corresponding sulfone (*S*)-**23** gave 1-thiahydrindanones **6** and **7**, respectively, which display unexpectedly the unnatural cis-ring junctions.

1. Introduction

Heterosteroids have attracted great interest, since it has been recognized that the introduction of a heteroatom in the steroidal framework brings about notable modifications in its biological activities.[1] Despite a recent revival of interest for heterosteroids,[2] there are only few reports on the synthesis of 17-heterosteroids. Thus, in 1964 Rakhit and Gut reported the synthesis of 17-azaprogesterone **1**[3] and 17-oxa-androstan-3-one **2** (Fig. 1).[4] In 1980 Jogdeo and Bhide described the synthesis of 17-thiaestratriene-17-dioxide **3** with the unnatural cis CD ring junction.[5] Unfortunately, no biological data were reported for these compounds. To the best of our knowledge, 17-thiasteroids such as 17-thiaestrone **4** and its corresponding sulfoxides have never been synthesized.

Herein, we report the asymmetric synthesis of 1-thiahydrindenone (*S*)-**5** featuring the CD ring moiety of 17-thiasteroids and our endeavors to reduce this system using the Tsuda–Daniewski conjugate reduction protocol,[6] leading to the unexpected formation of ketones **6** and **7**, which display cis-fused ring junction.

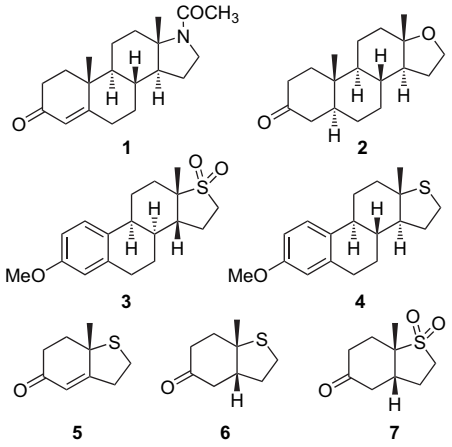

Figure 1.

2. Results and discussion

At the outset of our work we decided to target acid **8**, since C-8 carboxylic acid group is known to direct the stereochemical outcome of the catalytic reduction of the $\Delta^{8(14)}$-double bond (steroidal numbering) to the trans-fused hydrindanone.[7] Keto acid **8** would be prepared from **5**, which in turn is readily available from 2-methyltetrahydrothiophen-3-one **9**, using the 'deracemizing' Michael addition procedure. Indeed, we recently disclosed that chiral imine **10** derived from (*R*)-1-phenylethylamine and **9** gave the

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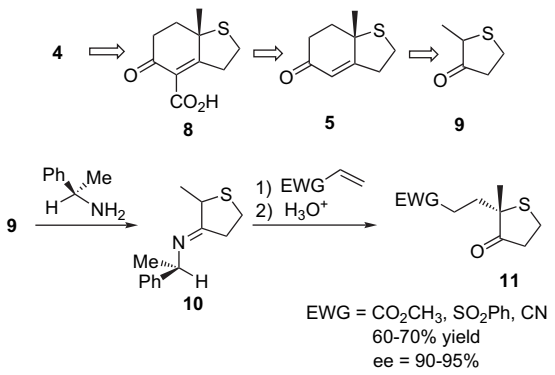
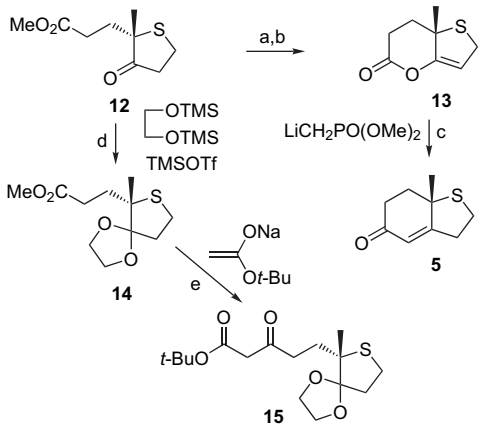
corresponding Michael adducts **11** in 68% yield with a complete regioselectivity and good enantiomeric excesses (ee ≥95%) (Scheme 1).[8]



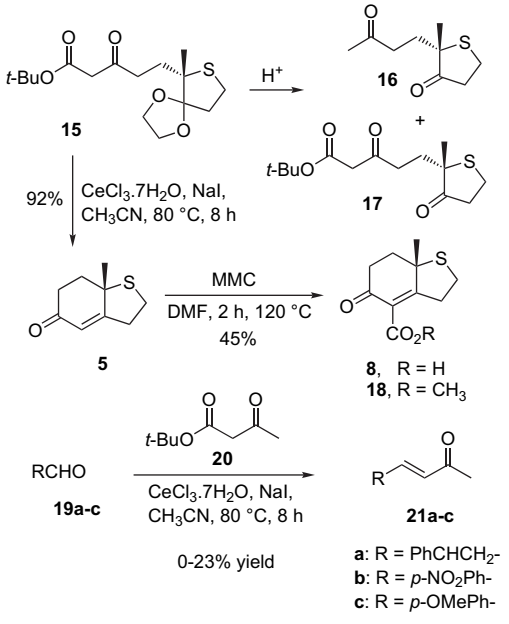
Scheme 1.

However, although efficient with a great variety of electron deficient olefins, this process failed with methyl vinyl ketone, since large amounts of polyalkylated materials were competitively formed. Therefore, an alternative synthetic route to **5** was developed, starting from keto ester (*S*)-**12**. Saponification of latter compound gave the corresponding keto acid, which was then converted into enol lactone **13**. Treatment of **13** with $LiCH_2PO(OMe)_2$ furnished enone (*S*)-**5** with a moderate overall yield of ca. 40% from **12**.[8] Unfortunately, attempts to produce gram quantities of enone **5** according to this procedure encountered unexpected difficulties due to the increasing formation of by-products on scaling up. We thereby decided to access keto acid **8** directly from ester (*S*)-**12**. Accordingly, the keto group of **12** was first protected using the Noyori's ketalization procedure[9] and the resulting ketal **14** was condensed with the sodium enolate of *tert*-butyl acetate[10] to provide β-keto ester **15** in 80% yield (Scheme 2).



Scheme 2. *Reagents and conditions*: (a) 3 N NaOH, THF, 4 h, 20 °C, quantitative; (b) Ac_2O, AcONa, 120 °C, 2 h, 70%; (c) 2 equiv $LiCH_2PO(OMe)_2$, THF, −78 °C, 20 min, then H_3O^+, 57%; (d) 2 equiv $(TMSOCH_2)_2$, 0.2 equiv TMSOTf, CH_2Cl_2, −78 °C, 30 min, then 16 h, 20 °C, 89%; (e) (i) 10 equiv CH_3CO_2t-Bu, 6 equiv NaHMDS, THF, −78 °C, 1 h; (ii) **14**, −78 °C, 1 h, then 2 h, 20 °C; (iii) H_3O^+, 80%.

We next investigated the deprotection of the ketone group to allow the cyclization of the future C-ring. However, this seemingly easy task turned out to be extremely challenging. For example, the treatment of (*S*)-**15** in standard acidic conditions (3 N HCl/MeOH; acetone/PPTS;[11] oxalic acid impregnated SiO_2;[12] 3 N $HClO_4$;[13] Amberlyst 15[14]) let the substrate be unchanged. On the other hand, forcing the conditions gave only a small amount of the desired keto ester **17**, along with diketone **16** and various undefined aldol products arising from **16**. In search for milder conditions to unmask the carbonyl group, we tried to use the $NaI/CeCl_3\cdot 7H_2O/CH_3CN$ mixture according to the procedure of Marcantoni et al.[15] To our surprise, when ketal **15** was subjected to this reaction condition, the enone **5** was obtained in 92% yield (Scheme 3). Formation of **5** could be best explained assuming a sequential process involving concomitant cleavage of both the ketal group and the *tert*-butyl ester group, decarboxylation with formation of the cerium enolate, and finally intramolecular aldol condensation. Interestingly, the cleavage of *tert*-butyl ester with the $NaI/CeCl_3\cdot 7H_2O$ mixture in acetonitrile has been recently reported.[16] In order to examine the scope of this method, we briefly investigated the intermolecular condensation of aldehydes with *tert*-butyl acetoacetate **20** in the presence of $NaI/CeCl_3\cdot 7H_2O$ mixture, reasoning that ketal hydrolysis step could be bypassed. Thus exposure of a mixture of 3-phenylpropanal **19a** and *tert*-butyl acetoacetate **20** to these reaction conditions led to the expected enone **21a**, albeit in a low 23% yield. 4-Nitrobenzaldehyde reacted similarly to give enone **21b** in 14% yields, whereas 4-methoxybenzaldehyde remained unchanged. Attempts to improve the yield using various reaction conditions failed. These results clearly established that entropic factors were crucial for the success of the transformation of **15** into **5**, limiting the usefulness of this sequential process to intramolecular condensations, nevertheless the mildness of this procedure may find further applications to achieve aldol-dehydration sequence with sensitive substrates in neutral conditions.



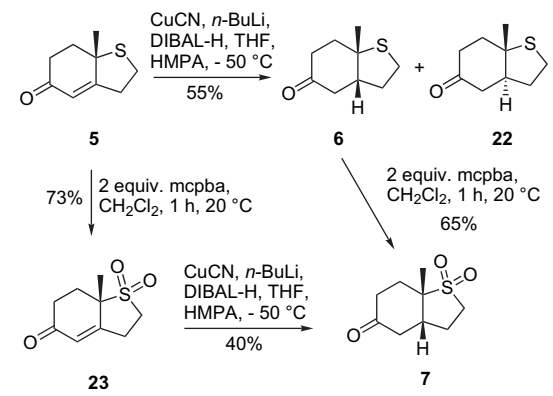
Scheme 3.

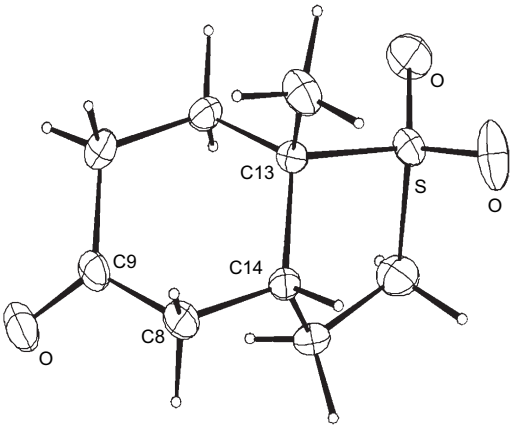
Having secured an efficient access to unsaturated ketone **5**, attention was next given to the installation of the carboxylic acid group at C-8. This task was achieved in a moderate 45%

yield using magnesium methyl carbonate (MMC).[17] We then explored the crucial reduction of the $\Delta^{8(14)}$-double bond.[7] Unfortunately all attempts to reduce this double bond by catalytic hydrogenation, even in forced conditions starting from keto acid **8** or from its corresponding methyl ester **18**, met with failure probably due to poisoning of the catalyst by the sulfur containing substrate. Since attempts at reducing **5** by catalytic hydrogenation were similarly unsuccessful the sulfur atom was clearly implicated in these failures (Scheme 3).

For this reason, we chose to explore the hydridoalkyl cuprate-induced reduction of thiahydrindenone **5**.[6] This procedure offers an excellent solution to the longstanding problem of the trans-fused hydrindanone synthesis. Thus, the α,β-unsaturated ketone **5** was added to a 10-fold excess of DIBAL/*n*-BuCu (from CuCN and *n*-BuLi) reagent in HMPA at −50 °C.[6h,i] Acidic work up afforded an 8:1 mixture of the two isomeric ketones **6** and **22** in 55% yield. The relative stereochemistry of the major isomer could not be established by NMR spectroscopy, including NOE experiments. Nevertheless, oxidation of **6** with mcpba produced sulfone **7** as a colorless crystalline solid. Single crystal X-ray diffraction analysis of **7** established unambiguously the cis-ring junction of this material and confirmed the (13*S*,14*S*) assignment of the absolute configuration on the basis of the anomalous diffusion of the sulfur atom.

To our knowledge, the preferential formation of the thermodynamically favorable cis-fused hydrindanone using the Tsuda–Daniewski procedure is unprecedented.[6] Since the only difference between the aforementioned examples and enone **5** was the presence of the sulfur atom, we first invoked as plausible explanation a complexation of the copper reagent by the sulfur atom *anti* to the bulky methyl group. The resulting steric hindrance could impede another molecule of reagent from complexing the double bond of **5** on the bottom face. To test the validity of this assumption, we examined the conjugated reduction of the sulfone (*S*)-**23** obtained in 73% yield from (*S*)-**5** upon oxidation with mcpba. Remarkably, treatment of **23** with DIBAL/*n*-BuCu in the conditions previously used for **5**, gave exclusively the same *cis*-fused 1,1-dioxo-1-thiahydrindanone **7**, albeit in a modest 40% yield (Scheme 4).[18]





X-ray crystal structure of sulfone **7**

Scheme 4.

Since copper complexation is unlikely with the sulfone group, we deduced that the stereochemical outcome of the conjugated reduction should be attributed to an increasing destabilization of the *trans*-fused 1-thiahydrindan in respect to the corresponding carbon system due to the longer C–S bond length (1.80 Å in **7**) and increased angle strain. Thus, assuming a late transition state partially reflecting the product, this enhanced torsional strain might override the intrinsic trend of the conjugate reducing process to give trans-hydrindan systems. We shall pursue this intriguing phenomenon with further computational and experimental studies.

3. Conclusions

In summary, we have successfully assembled in optically active form the bicyclic enone (*S*)-**5** in three steps with an overall yield of 64% from Michael adduct (*S*)-**12**. The key step was a new sequential process involving cleavage of both the ketal group and the *tert*-butyl ester group of ketal **15**, followed by decarboxylation, and finally intramolecular aldol condensation, providing 1-thiahydrinden-5-one **5** in 92% yield. Hydridoalkyl cuprate-induced conjugate reduction of either (*S*)-**5** or sulfone (*S*)-**23** with DIBAL/*n*-BuCu in HMPA gave unexpectedly cis-fused ketones **6** and **7**, respectively.

4. Experimental

4.1. General methods

Melting points were measured on a Büchi capillary tube melting point apparatus and are uncorrected. IR spectra were recorded from neat samples on a Fourier Transform Bruker Vector 22 spectrometer. Only significant absorptions are listed. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 589 nm. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200 P (200 and 50 MHz for ^{1}H and ^{13}C, respectively), a Bruker Avance-300 (300 and 75 MHz for ^{1}H and ^{13}C, respectively), or a Bruker ARX 400 (400 and 100 MHz for ^{1}H and ^{13}C, respectively) spectrometer. Recognition of methyl, methylene, methine, and quaternary carbon nuclei in ^{13}C NMR spectra rests on the *J*-modulated spin-echo sequence. Mass spectra were recorded on a Hewlett–Packard G 1019 A (70 eV) or on a Bruker Esquire-LC. Analytical thin-layer chromatography was performed on Merck silica gel $60F_{254}$ glass precoated

plates (0.25 mm layer). Column chromatography was performed on Merck silica gel 60 (230–400 mesh ASTM). Diethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methanol and ethanol were dried over magnesium and distilled. Benzene, toluene, DMF, and CH_2Cl_2 were distilled from calcium hydride, under a nitrogen atmosphere. Chemicals obtained from commercial suppliers were used without further purification. Elemental analyses were performed by the Service de microanalyse, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, France, with a Perkin–Elmer 2400 analyzer.

4.2. (*R*)-(2-Methyl-dihydrothiophen-3-ylidene)-(1-phenyl-ethyl)-amine (10)

A mixture of 5 Å molecular sieves (7.3 g), basic alumina (1.8 g), and silica (0.9 g) was activated by heating for a few minutes at 0.05 Torr with a free flame. After cooling, freshly distilled cyclohexane (25 mL) and 2-methyltetrahydrothiophen-3-one (4.15 g, 35.7 mmol) were added under inert atmosphere. The solution was degassed with azote, and (*R*)-1-phenylethylamine (4.72 g, 39.0 mmol) was added. After stirring for 6 days at room temperature, the mixture was filtered, washed with anhydrous Et_2O, and concentrated to yield crude imine **10** as a pale yellow oil (7.8 g, quantitative), which was used without further purification in the next step; IR (neat, cm^{-1}) 1663, 1492, 1448.

4.3. (*S*)-3-(2-Methyl-3-oxo-tetrahydrothiophen-2-yl)-propionic acid methyl ester (12)

To a solution of crude imine **10** (9.40 g, 42.9 mmol) in distilled cyclohexane (5 mL), methyl acrylate (27 g, 0.31 mol) and few crystals of hydroquinone (35 mg, 0.3 mmol) were added. The resulting mixture was stirred at 45 °C for 70 h under nitrogen. The mixture was cooled to room temperature and diluted with THF (300 mL). Aqueous acetic acid of 20% (50 mL) was then added and the resulting mixture was stirred at 20 °C for 3 h. The solvents were removed under reduced pressure and 15 mL of 3 N HCl was added. The mixture was extracted with Et_2O (4×25 mL), the organic layers were then washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography over silica gel (cyclohexane/ethyl acetate, 4:1) to yield keto ester **12** (5.8 g, 68% yield). Colorless oil, bp 80–85 °C/0.1 Torr (oil bath); $[\alpha]_D$ −31 (*c* 13, EtOH); IR (neat, cm^{-1}) 2956, 1733, 1713, 1436, 1349, 1248; ^1H NMR ($CDCl_3$, 200 MHz) δ: 3.64 (s, 3H), 2.95–2.85 (m, 2H), 2.71–2.64 (m, 2H), 2.44–2.30 (m, 2H), 2.15–1.85 (m, 2H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 219.2 (C), 172.6 (C), 55.8 (C), 51.4 (CH_3), 38.1 (CH_2), 32.2 (CH_2), 29.4 (CH_2), 23.5 (CH_3), 21.1 (CH_2); MS (EI) *m*/*z* (%): 203 (M+1, 46), 202 (M, 55), 184 (23), 171 (15), 170 (42), 146 (34), 143 (30), 116 (25), 115 (37), 114 (100), 86 (76). Anal. Calcd for $C_9H_{14}O_3S$: C, 53.44; H, 6.98. Found: C, 53.41; H, 7.01.

4.4. (*S*)-3-(6-Methyl-1,4-dioxa-7-thiaspiro[4.4]non-6-yl)-propionic acid methyl ester (14)

Keto ester **12** (4.65 g, 23.0 mmol) was taken into anhydrous CH_2Cl_2 (80 mL), 1,2-bis(trimethylsilyloxy)ethane (9.5 g, 46.0 mmol) was added and the solution was cooled to −78 °C. TMSOTf (1.0 g, 4.5 mmol) was added dropwise and the mixture was stirred at −78 °C. After 30 min, the mixture was allowed to warm to 20 °C and kept at this temperature for 16 h. The reaction was quenched with aqueous sodium bicarbonate (20 mL) and the mixture was extracted with CH_2Cl_2 (4×20 mL). After drying over $MgSO_4$, the combined organic layers were concentrated. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate/Et_3N, 4:1:0.005) to give 5.03 g of ketal **14** (89%) as a colorless oil; $[\alpha]_D$ −36.8 (*c* 5.4, EtOH); IR (neat, cm^{-1}) 2950, 2885, 1733, 1435, 1373, 1308, 1218, 1169, 1069; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.98–3.95 (m, 4H), 3.64 (s, 3H), 2.85–2.30 (m, 4H), 2.14 (t, *J*=7.2 Hz, 2H), 2.12–1.90 (m, 2H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 174.1 (CO), 118.5 (C), 65.5 (CH_2), 65.2 (CH_2), 56.6 (C), 51.4 (CH_3), 34.8 (CH_2), 33.6 (CH_2), 30.8 (CH_2), 23.6 (CH_2), 22.9 (CH_3). Anal. Calcd for $C_{11}H_{18}O_4S$: C, 53.64; H, 7.37. Found: C, 53.99; H, 7.47.

4.5. (*S*)-5-(6-Methyl-1,4-dioxa-7-thiaspiro[4.4]non-6-yl)-3-oxo-pentanoic acid *tert*-butyl ester (15)

A solution of *tert*-butyl acetate (23.2 g, 200 mmol) in anhydrous THF (10 mL) was added dropwise at −78 °C to a mixture of sodium hexamethyldisilazane (2 M in THF, 61 mL, 122 mmol) in THF (200 mL) under nitrogen. The resulting mixture was stirred at −78 °C for 1 h and a solution of ketal **14** (5.0 g, 20.3 mmol) in THF (100 mL) was added dropwise. The reaction mixture was stirred for 1 h at −78 °C and the temperature was then slowly raised to 20 °C over a 1 h period of time. A saturated aqueous NH_4Cl solution (200 mL) was then added and the solvent was removed under reduced pressure. The aqueous residue was extracted with diethyl ether (4×100 mL). After drying over $MgSO_4$, the combined organic layers were concentrated. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate/Et_3N, 4:1:0.005) to give 5.3 g of keto ester **15** (80%) as a colorless oil; $[\alpha]_D$ −35.9 (*c* 2.6, EtOH); IR (neat, cm^{-1}) 2977, 2887, 1734, 1714, 1456, 1369, 1310, 1256, 1149; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.88–3.82 (m, 4H), 3.25 (s, 2H), 2.70–2.46 (m, 4H), 2.04 (t, *J*=7.3 Hz, 2H), 2.00–1.70 (m, 2H), 1.33 (s, 9H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 202.5 (CO), 166.0 (CO), 118.1 (C), 81.3 (C), 65.2 (CH_2), 64.9 (CH_2), 56.6 (C), 50.4 (CH_2), 39.3 (CH_2), 34.4 (CH_2), 31.6 (CH_2), 27.6 ($3CH_3$), 23.3 (CH_2), 23.1 (CH_3). Anal. Calcd for $C_{16}H_{26}O_5S$: C, 58.16; H, 7.93. Found: C, 57.86; H, 8.09.

4.6. (*S*)-7a-Methyl-2,3,7,7a-tetrahydro-6*H*-benzo[*b*]-thiophen-5-one (5)

A mixture of keto ester **15** (530 mg, 1.6 mmol), $CeCl_3 \cdot 7H_2O$ (1.0 g, 2.6 mmol), and sodium iodide (67 mg, 0.44 mmol) in acetonitrile (20 mL) was stirred at reflux temperature for 16 h. After cooling, the mixture was concentrated under reduced pressure. The residue was taken into 0.5 N HCl and the mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with aqueous sodium thiosulfate and brine. After drying over $MgSO_4$, the organic layer was concentrated. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate, 2:1) to give 248 mg of ketone **5** (92%) as a pale yellow oil; $[\alpha]_D$ +148 (*c* 1.5, EtOH); IR (neat, cm^{-1}) 2929,

2860, 1667, 1445, 1417, 1337, 1316, 1222, 1180; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.65 (s, 1H), 3.05–2.72 (m, 4H), 2.50–2.10 (m, 4H), 1.51 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 197.6 (CO), 170.8 (C), 120.4 (CH), 51.6 (C), 36.8 (CH_2), 35.1 (CH_3), 33.6 (CH_2), 27.0 (CH_2), 26.6 (CH_3). Anal. Calcd for $C_9H_{12}OS$: C, 64.24; H, 7.19. Found: C, 64.01; H, 7.34.

4.7. (*S*)-7a-Methyl-hexahydrobenzo[*b*]thiophen-5-one (6)

Copper cyanide (2.15 g, 24 mmol) was suspended in THF (100 mL) and chilled to −20 °C. A 2.5 M solution of *n*-BuLi in hexanes (8.65 mL, 21.6 mmol) was added dropwise. The brown solution was stirred at −20 °C for 30 min, and then the temperature was lowered to −50 °C. A 1.1 M solution of DIBAL in hexanes (43 mL, 47 mmol) was added slowly dropwise. The dark brown solution was allowed to stir at −50 °C for 1 h before the enone **5** (400 mg, 2.38 mmol) was added as a solution in 1:1 THF/HMPA (36 mL). The temperature was raised to −20 °C over the next 10 min and then the mixture was allowed to stir at −20 °C for 1 h. The reaction was quenched with a solution of 1:1 saturated aqueous NH_4Cl and 3 M aqueous HCl (100 mL) at −20 °C and allowed to warm to ambient temperature over 30 min. The mixture was filtered and extracted with diethyl ether (4×50 mL). The organic layer was dried over $MgSO_4$, concentrated, and then washed sequentially with 1 M aqueous HCl, water, and brine. The organic layer was dried, filtered through silica gel, and evaporated to yield a pale yellow oil. Purification by silica gel chromatography eluting with cyclohexane/ethyl acetate, 4:1, gave pure ketone **6** as a colorless oil, 222 mg, 55%, bp 75 °C/0.5 Torr (oil bath); $[\alpha]_D$ +44.5 (*c* 2.6, EtOH); IR (neat, cm^{-1}) 2948, 2867, 1711, 1447, 1418, 1378, 1229; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.00 (t, *J*=6.7 Hz, 2H), 2.62–2.50 (m, 1H), 2.40–2.11 (m, 6H), 2.03–1.92 (m, 1H), 1.84–1.70 (m, 1H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 211.2 (CO), 54.1 (C), 50.6 (CH), 41.6 (CH_2), 37.2 (CH_2), 36.3 (CH_2), 35.8 (CH_2), 30.3 (CH_3), 29.7 (CH_2). Anal. Calcd for $C_9H_{14}OS$: C, 63.48; H, 8.29. Found: C, 63.23; H, 8.43.

4.8. (*S*)-7a-Methyl-1,1-dioxo-1,2,3,6,7,7a-hexahydrobenzo[*b*]thiophen-5-one (23)

To an ice-cooled solution of enone **5** (672 mg, 4.0 mmol) in CH_2Cl_2 (4 mL) was added dropwise a solution of mcpba (70%, 2.0 g, 8.1 mmol) in CH_2Cl_2 (6 mL). The reaction mixture was stirred for 1 h at 20 °C. CH_2Cl_2 of 20 mL was added and then the reaction mixture was filtered over a pad of Celite, and the filtrate was washed with saturated aqueous $NaHSO_3$ and saturated aqueous $NaHCO_3$. The organic layer was dried and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate, 1:1) to give 590 mg of sulfone **23** (73%) as a colorless oil; $[\alpha]_D$ +27.9 (*c* 5.2, EtOH); IR (neat, cm^{-1}) 2959, 1705 (weak), 1668, 1448, 1418, 1300, 1229, 1191, 1139; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.02 (s, 1H), 3.41 (ddd, *J*=14.1, 10.4, 7.8 Hz, 1H), 3.26 (ddd, *J*=14.1, 9.1, 5.3 Hz, 1H), 3.13–2.93 (m, 2H), 2.68–2.42 (m, 3H), 2.06 (m, 1H), 1.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 195.8 (CO), 159.5 (C), 127.0 (CH), 60.1 (C), 45.5 (CH_2), 31.5 (CH_2), 25.1 (CH_2), 24.9 (CH_2), 19.3 (CH_3); MS (+APCI) *m*/*z* (%): 201 (M+1, 100), 183 (33), 137 (82), 109 (45).

4.9. (7a*S*,*cis*)-7a-Methyl-1,1-dioxo-octahydrobenzo[*b*]-thiophen-5-one (7)

Copper cyanide (895 mg, 10 mmol) was suspended in THF (40 mL) and chilled to −20 °C. A 2.0 M solution of *n*-BuLi in hexanes (4.5 mL, 9.0 mmol) was added dropwise. The brown solution was stirred at −20 °C for 30 min, and then the temperature was lowered to −50 °C. A 1.1 M solution of DIBAL in hexanes (18 mL, 19.8 mmol) was added slowly dropwise. The dark brown solution was allowed to stir at −50 °C for 1 h before the enone **23** (200 mg, 1.0 mmol) was added as a solution in 1:1 THF/HMPA (15 mL). The temperature was raised to −20 °C over the next 10 min and then the mixture was allowed to stir at −20 °C for 1 h. The reaction was quenched with a solution of 1:1 saturated aqueous NH_4Cl and 3 M aqueous HCl (50 mL) at −20 °C and allowed to warm to ambient temperature over 30 min. The mixture was filtered and extracted with diethyl ether (4×20 mL). The organic layer was dried over $MgSO_4$, concentrated, and then washed sequentially with 1 M aqueous HCl, water, and brine. The organic layer was dried, filtered through silica gel, and evaporated to yield a pale yellow oil. Purification by silica gel chromatography eluting with cyclohexane/ethyl acetate, 4:1, gave pure ketone **7** as a colorless crystals, 80 mg, 40%; $[\alpha]_D$ +28.0 (*c* 2.7, $CHCl_3$); mp 145 °C (MeOH); IR (neat, cm^{-1}) 2968, 1703, 1471, 1453, 1417, 1292, 1161, 1131, 1095, 1040; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.22 (ddd, *J*=13.7, 9.9, 3.6 Hz, 1H), 3.09 (dt, *J*=13.7, 9.1 Hz, 1H), 2.63 (dd, *J*=14.7, 5.7 Hz, 1H), 2.60–2.55 (m, 1H), 2.50–2.16 (m, 5H), 1.98 (dtd, *J*=13.9, 4.8, 1.4 Hz, 1H), 1.82–1.70 (m, 1H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 208.0 (CO), 58.4 (C), 47.9 (CH_2), 42.5 (CH), 41.5 (CH_2), 36.5 (CH_2), 27.9 (CH_2), 24.3 (CH_2), 18.1 (CH_3). Crystal data: crystal of size 0.19×0.20×0.22 mm. Orthorhombic, space group *P* 21 21 21, *Z*=4, *a*=7.201(2), *b*=7.399(7), *c*=18.483(4) Å, $\alpha=\beta=\gamma=90°$, *V*=982.4(18) Å^3, *d*=1.160 g cm^{-3}, *F*(000)=432, λ=0.710693 Å (Mo Kα), μ=0.302 mm^{-1}; 6078 reflections measured ($-10\leq h\leq 10, 0\leq k\leq 10, 0\leq l\leq 25$) on a Nonius CAD4 diffractometer. The structure was solved with SIR92 and refined with CRYSTALS with hydrogen atoms riding. Refinement converged to *R*(*gt*)=0.0285 for the 1742 (119 parameters) reflections having $I\geq 3\sigma(I)$, and *wR*(*gt*)=0.0348, goodness-of-fit *S*=1.0986. Residual electron density: −0.14 and 0.17 e Å^3. Flack parameter=0.07(12). Crystallographic results have been deposited (CIF file) in the Cambridge Crystallographic Data Centre, UK, and allocated the deposition number CCDC 625028.

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References and notes

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18. 1,1-Dioxo-1-thiahydrindanone **7** was also obtained in 80% yield upon catalytic hydrogenation of **23** (Pd/C, AcOEt, EtOH, 4 bars H_2, 22 °C, 48 h).