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Synthesis of Two Precursors of Heterocarbocyclic Nucleoside Analogues

Paula Abeijón,[a] José M. Blanco,*[a] Franco Fernández,[a] Marcos D. García,[a] and Carmen López[a]

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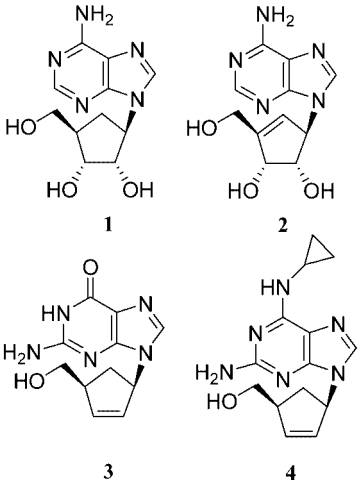
The racemic heterobicyclic amino alcohols **6** and **7**, which are of interest as intermediates in the synthesis of nucleoside analogues with heterobicyclic pseudosugars, were efficiently prepared from 2-thienylsuccinic acid via methyl 4-hydroxyimino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-6-carboxylate [(±)-**14**]. The target compounds were obtained together by direct reduction of (±)-**14** with AlH_3 in refluxing THF, and were separated by flash chromatography of their *N*-acetylated derivatives.

1. Introduction

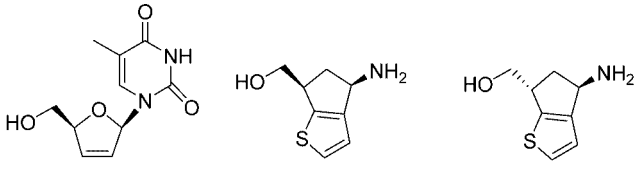
Over the past two decades, several types of nucleoside and nucleoside analogues have been identified as potent, selective inhibitors of the replication of HIV-1, HSV-2, HBV and/or HCMV in vitro and in vivo, and some of these substances now constitute the basis of clinically important therapies.[1] One major class of modified nucleosides comprises the carbocyclic nucleosides, or carbanucleosides, in which the sugar ring oxygen has been replaced by a methylene group.[2]

The first member of this class was the carbocyclic analogue of adenosine described by Shealy in 1966,[3] and interest was spurred by the discovery of the antibiotic and antitumoural activities of the natural carbocyclic nucleosides aristeromycin (**1**)[4] and neplanocin A (**2**).[5] Since then, many synthetic carbanucleosides have been prepared, including the HIV-inhibitors carbovir (**3**)[6] and abacavir (**4**),[7] the latter of which is used therapeutically.

More recently, Mackenzie and co-workers[8] have modified the nucleoside analogue stavudine (**5**) by fusing a benzene ring to the carbasugar, which increases lipophilicity (and hence access to the central nervous system, a major reservoir of HIV[9]) while maintaining the rigidity imposed by the C2′–C3’ double bond, and analogous carbanucleosides have been prepared in which an aromatic heterocycle is fused to the carbasugar of carbovir or abacavir.[10] Here we describe the efficient preparation of the heterobicyclic amino alcohols **6** and **7**, from which the corresponding heteroaromatic nucleosides can be obtained by constructing a purine or pyrimidine base on the amino group, following conventional methods.[11]



1 **2** **3** **4**



5 **6** **7**

2. Results and Discussion

Amino alcohols **6** and **7** were prepared as racemic mixtures awaiting determination of the biological activity of the corresponding nucleoside analogues prior to pursueing enantiomeric separation. As a common intermediate for the two, we first prepared hydroxyimino ester **14**, starting from commercial thiophene-2-carbaldehyde. Knoevenagel condensation of the latter with ethyl malonate afforded the un-

[a] Departamento de Química Orgánica, Facultade de Farmacia, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain
Fax: +34-981-594-912
E-mail: qojb@usc.es

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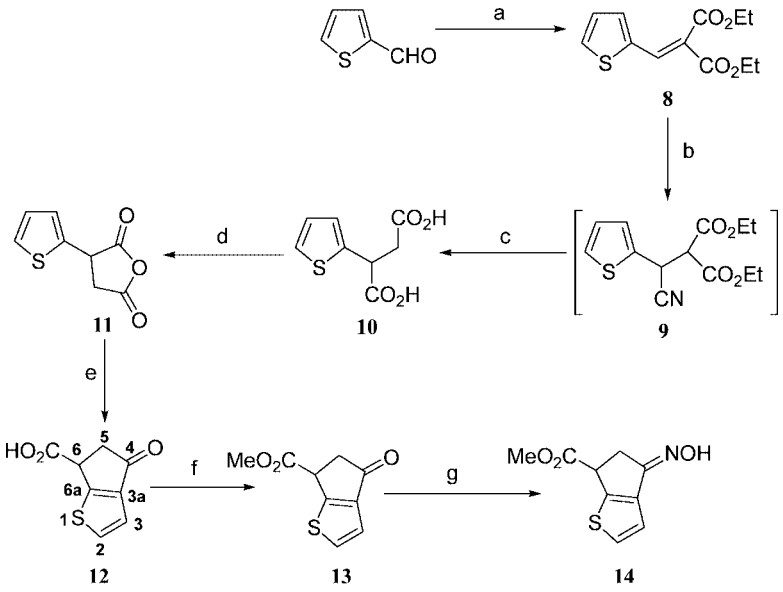
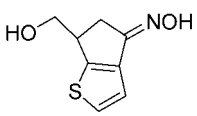


Scheme 1. (a) Diethyl malonate, piperidine, toluene, reflux; (b) KCN/H_2O, EtOH, reflux (c) (1) 1.5 N NaOH, reflux; (2) 6 M HCl, reflux; (d) AcCl, reflux; (e) $AlCl_3$, 1,2-dichloroethane, room temp.; (f) MeOH, TsOH, reflux; (g) $NH_2OH{\cdot}HCl$, NaAc/H_2O, EtOH, reflux.

saturated diester **8**, which was converted into thien-2-ylsuccinic acid (**10**) by addition of KCN and hydrolysis/decarboxylation of the intermediate **9** (Scheme 1). Attempted direct synthesis of 4-oxo-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-6-carboxylic acid (**12**) by heating of **10** with polyphosphoric acid (PPA) at 70 °C achieved a yield of only 4%, and heating with PPA in xylene at 100 °C[12] only increased this value to 12%; in both cases, most of the starting diacid failed to react, and nor was there any reaction when **10** was treated with trimethylsilyl polyphosphate (PPSE, easily prepared from P_2O_5 and hexamethyldisiloxane)[13] in a refluxing mixture of dichloromethane and P_2O_5 (although PPSE has successfully been used for other intramolecular Friedel–Crafts cyclizations in aprotic media for example, to obtain substituted 9*H*-selenoxanthen-9-ones.)[14] Finally, acid **12** was obtained in 57% yield by heating **10** in refluxing acetyl chloride and treating the resulting anhydride **11** with $AlCl_3$ in 1,2-dichloroethane. Esterification of **12** and reaction of the ester **13** with hydroxylamine–hydrochloride then afforded **14** as a mixture of the (*E*)- and (*Z*)-hydroxyimino esters in 46% yield from **12**.

Expecting a simultaneous reduction of the oxime and ester groups,[15] **14** was treated with $LiAlH_4$ for 6 h in refluxing THF, but the product (**19**;[16] yield 23%) was the result of a selective ester reduction (see Supporting Information, Table S1, Entry 1). Increasing the reaction time to 33 h afforded a lower yield of **19** (11%) together with an 11% yield of amino alcohol **20**,[17] presumably the result of Beckmann rearrangement of **19** and subsequent reduction (Entry 2).[18]



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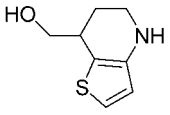

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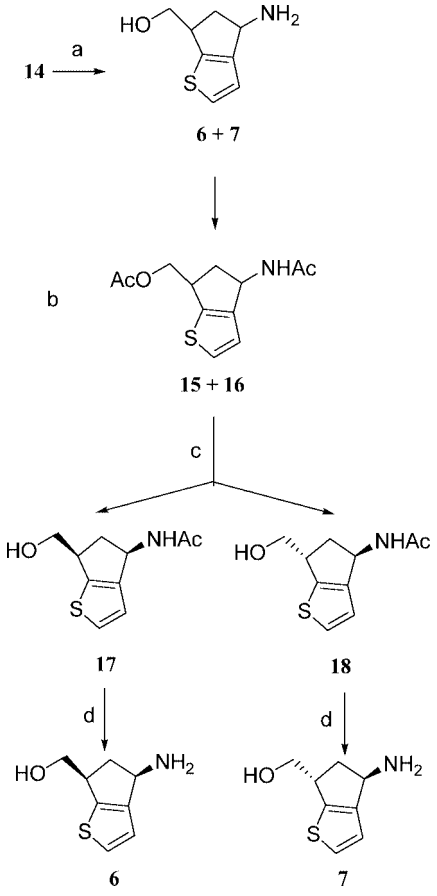
Compound **19** was also the only product when L-selectride was used to investigate the stereoselectivity of the reduction reaction (Entry 3).[19] However, heating **14** for 5 h with AlH_3 in refluxing THF[20] (Entry 4) gave the desired



Scheme 2. (a) AlH_3, THF, reflux; (b) Ac_2O, Et_3N, room temp.; (c) (1) K_2CO_3, MeOH, room temp.; (2) flash chromatography; (d) (1) 2 M HCl, MeOH, reflux; (2) Amberlite IRA-400 (OH).

cis and *trans* amino alcohols **6** and **7** in 55% combined yield and 1:1 ratio as deduced from the ^{1}H NMR spectrum.

After the failure of attempts to separate **6** and **7** chromatographically, they were diacetylated by treatment with Ac_2O in Et_3N at room temperature (Scheme 2). However, the diacetylated derivatives **15** and **16** were also inseparable, except for analytical samples that were obtained by fractional crystallization from 1:1 hexane/EtOAc and were identified by X ray crystallography of a crystal of **16** (Figure S1; see Supporting Information).[21]

Partial saponification of the mixture of **15** and **16** with K_2CO_3 in MeOH at room temperature then afforded the acetamides **17** and **18** in 20% and 17% yield (from **14**) after efficient separation by flash chromatography. Finally, acid hydrolysis of these acetamides with 2 M HCl in MeOH gave the corresponding hydrochlorides, which were converted into the racemic amino alcohols **6** and **7** by ion exchange chromatography on a basic resin. Configurational assignment of **7** as the *trans* isomer (and hence that of **6** as the *cis* isomer) was confirmed by converting **7** into its diacetyl derivative, **16**.

3. Experimental Section

3.1 General: Melting points are uncorrected and were determined with a Reichert Kofler Thermopan or in capillary tubes in a Büchi 510 apparatus. Infrared spectra were recorded with a Perkin–Elmer 1640 FTIR spectrophotometer. ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded with a Bruker AMX 300 spectrometer using TMS as internal reference (chemical shifts in δ values, J in Hz). Mass spectra were recorded with a Kratos MS-59 spectrometer. HRMS were obtained using MICROMASS AUTOSPEC mass spectrometer. Microanalyses were performed with a Perkin–Elmer 240B elemental analyser by the Microanalysis Service of the University of Santiago. X-ray diffraction data were collected with an Enraf–Nonius CAD4 automatic diffractometer using the program CAD4-EXPRESS. Most of reactions were monitored by TLC on pre-coated silica gel plates (Merck 60 F254, 0.25 mm). Synthesized products were purified by flash column chromatography on silica gel (Merck 60, 230–240 mesh) and crystallized if necessary. Solvents were dried by distillation prior use.

3.1.1 Diethyl (Thien-2-ylmethylene)malonate (8): Diethyl malonate (36.7 g, 0.23 mol) was added dropwise to a mixture of thiophene-2-carbaldehyde (20 g, 0.18 mol), AcOH (5.5 mL), piperidine (5.5 mL) and toluene (150 mL). The mixture was refluxed for 6.5 h in an apparatus with a Dean–Stark trap for removal of water, and was then concentrated under reduced pressure. The residue was taken into dichloromethane (170 mL), and this solution was washed successively with satd. $NaHCO_3$ (3×150 mL), 3 N HCl (3×150 mL) and water (3×150 mL), and then dried with anhydrous Na_2SO_4. Removal of the solvent under reduced pressure afforded **8** as a viscous whitish liquid (44.8 g, 99%). IR (film): $\tilde{\nu}$ = 3105, 2982, 1724, 1617, 1465, 1420, 1254, 1203 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (s, 1 H, CH=C), 7.51 (d, J = 4.9 Hz, 1 H, 5-H_{arom}), 7.35 (d, J = 3.1 Hz, 1 H, 3-H_{arom}), 7.06 (t, J = 4.3 Hz, 1 H, 4-H_{arom}), 4.39 (c, J = 7.1 Hz, 2 H, CH_2CH$_3$), 4.28 (c, J = 7.1 Hz, 2 H, CH_2CH$_3$), 1.36 (t, J = 7.1 Hz, 3 H, CH$_2$CH_3), 1.31 (t, J = 7.1 Hz, 3 H, CH$_2$CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.69 and 164.72 (2 CO), 136.51 (C-2$_{arom}$), 135.04 (*C*H=C), 134.73 (C-5$_{arom}$), 132.03 and 128.17 (C-3, C-4)$_{arom}$, 122.88 (CH=*C*), 62.27 and 61.94 (2 CH$_2$), 14.55 and 14.33 (2 CH$_3$) ppm. EIMS: *m*/*z* (%) = 255 (6) [M + 1]$^+$, 254 (38) [M$^+$], 209 (51) [M$^+$ – OEt], 182 (9), 164 (46) [M$^+$ – 2 OEt], 136 (41) [M$^+$ – $C_5H_{10}O_3$], 108 (100) [C_6H_4S]$^+$, 82 (11), 69 (29). $C_{12}H_{14}O_4S$ (254.30): calcd. C 56.68, H 5.55, S 12.61; found C 56.80, H 5.57, S 12.45.

3.1.2 (±)-(Thien-2-yl)succinic Acid (10): A solution of KCN (1.5 g, 23.1 mmol) in water (10 mL) was added to a solution of **8** (3 g, 11.8 mmol) in EtOH (50 mL), and the mixture was refluxed for 3 h, treated with a solution of NaOH (0.56 g, 14.0 mmol) in water (10 mL), and refluxed for a further 1 h, after which the ethanol was removed under reduced pressure while water was simultaneously added to maintain a constant volume. After cooling to 40 °C, the reaction mixture was brought to pH 1 by addition of 6 N HCl (8 mL) and refluxed for 1 h, after which it was cooled to room temperature and then left overnight in a refrigerator. It was then extracted with EtOAc (3×80 mL), the organic extracts were washed with aqueous Na_2CO_3 (3×50 mL), and the combined aqueous phases were brought to pH 1 with 1 N H_2SO_4 and extracted with EtOAc (3×80 mL). The organic extract was dried with anhydrous Na_2SO_4, and concentration under reduced pressure then afforded a solid that was recrystallized from toluene as pure (±)-**10** (2.19 g, 93%). M.p. 159–161 °C. IR (KBr): $\tilde{\nu}$ = 3028, 2925, 2642, 1693, 1412, 1306, 1282, 1181 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 12.46 (br. s, 1 H, D_2O exch., CO_2H), 12.42 (br. s, 1 H, D_2O exch., CO_2H), 7.40 (dd, J = 4.9, 1.3 Hz, 1 H, 5-H_{arom}), 6.99–6.94 (m, 2 H, 3-H_{arom}, 4-H_{arom}), 4.15 (dd, J = 9.9, 5.2 Hz, 1 H, C*H*CO$_2$H), 2.95 and 2.66 (the AB part of an ABX system, J_{AB} = 16.9, J_{AX} = 9.9, J_{BX} = 5.2 Hz, 2 H, CH$_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.45 and 172.55 (2 CO), 140.93 (C-2$_{arom}$), 127.19, 125.89 and 125.37 (C-3,-4-5)$_{arom}$, 42.57 (*C*HCH$_2$), 38.33 (CH*C*H$_2$) ppm. EIMS: *m*/*z* (%) = 201 (0.02) [M + 1]$^+$, 200 (0.75) [M$^+$], 182 (62) [M$^+$ – H_2O], 154 (100) [M$^+$ – CO_2H], 113 (67), 110 (38) [M$^+$ – 2 CO_2H], 97 (53), 85 (24), 58 (16). $C_8H_8O_4S$ (200.21): calcd. C 47.99, H 4.03, S 16.02; found C 47.89, H 3.91, S 16.22.

3.1.3 (±)-(Thien-2-yl)succinic Anhydride (11): Acetyl chloride (12.33 mL, 0.17 mol) was added to **10** (2.6 g, 12.99 mmol) under argon, and the mixture was refluxed for 3 h. Concentration under reduced pressure by azeotropic codistillation with toluene then afforded **11** (2.32 g, 98%) as a brownish viscous liquid that crystallized upon cooling. M.p. 50–52 °C (toluene). IR (KBr): $\tilde{\nu}$ = 3099, 3002, 2949, 2879, 1858, 1780, 1408, 1237, 1178 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (dd, J = 5.0, 1.2 Hz, 1 H, 5-H_{arom}), 7.07–7.02 (m, 2 H, 3-H_{arom},4-H)$_{arom}$), 4.63–4.58 (m, 1 H, CHCO), 3.53 and 3.23 (the AB part of an ABX system, J_{AB} = 18.7, J_{AX} = 10.1, J_{BX} = 7.0 Hz, 2 H, CH$_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.31 and 168.22 (2 CO), 135.89 (C-2$_{arom}$), 127.90, 126.72 and 126.57 (C-3,-4,-5)$_{arom}$, 42.23 (*C*HCH$_2$), 37.32 (CH*C*H$_2$) ppm. EIMS: *m*/*z* (%) = 183 (0.91) [M + 1]$^+$, 182 (11) [M$^+$], 168 (2), 154 (4) [M$^+$ – CO], 110 (100) [C_6H_6S]$^+$, 95 (3), 69 (10), 66 (12). $C_8H_6O_3S$ (182.20): calcd. C 52.74, H 3.32, S 17.60; found C 52.68, H 3.42, S 17.48.

3.1.4 (±)-4-Oxo-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-6-carboxylic Acid (12): A solution of **11** (1.88 g, 10.32 mmol) in 1,2-dichloroethane (6 mL) was added dropwise under argon, over 40 min, to a solution of $AlCl_3$ (3.8 g, 28.5 mmol) in 9 mL of the same solvent. The mixture was stirred at room temperature for 5 h, poured into a mixture of ice and hydrochloric acid, and extracted with EtOAc (4×50 mL). The organic phase was extracted with aqueous Na_2CO_3 (3×50 mL), and the aqueous extract was acidified with 1 N HCl and extracted with EtOAc (4×50 mL). The combined organic phases were washed with water (3×60 mL) and dried with anhydrous Na_2SO_4, and concentration under reduced pressure then

yielded 2.1 g of a viscous orange liquid that was chromatographed on silica gel (60 g) using 1:1 hexane/EtOAc (23× 60 mL) as eluent. Recrystallization from EtOAc afforded **12** (1.09 g, 58%) as a white solid. M.p. 174.5–176 °C. IR (KBr): $\tilde{\nu}$ = 3114, 3093, 2973, 2599, 1731, 1639, 1507, 1465, 1391, 1306, 1241, 1216 cm^{-1}. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 9.57 (br. s, 1 H, D_2O exch., CO_2H), 7.70 (d, J = 5.0 Hz, 1 H, 2-H), 7.12 (d, J = 5.1 Hz, 1 H, 3-H), 4.50 (t, J = 5.0 Hz, 1 H, 6-H), 3.12 (d, J = 5.1 Hz, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 195.91 (CO), 171.97 (CO_2H), 167.11 (C-6a), 145.62 (C-3a), 133.94 (C-2), 119.04 (C-3), 44.69 (C-5), 42.66 (C-6) ppm. EIMS: m/z (%) = 183 (6) [M + 1]$^+$, 182 (54) [M$^+$], 164 (42) [M$^+$ – H_2O], 153 (11) [M$^+$ – CO]], 137 (100) [M$^+$ – CO_2H], 109 (34) [C_6H_5S]$^+$, 84 (7), 82 (9), 69 (11), 65 (37), 63 (12). $C_8H_6O_3S$ (182.20): calcd. C 52.74, H 3.32, S 17.60; found C 52.91, H 3.39, S 17.38.

3.1.5 (±)-Methyl 4-Oxo-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-6-carboxylate (13): A solution of **12** (1.38 g, 7.58 mmol) in dry MeOH (40 mL) containing *p*TsOH (0.1 g, 0.53 mmol) was refluxed for 5 h under argon. Concentration to dryness then afforded 1.5 g of a viscous liquid residue that when chromatographed on silica gel (50 g) with hexane/EtOAc, 6:1 (33× 40 mL) as eluent yielded a whitish liquid that crystallized in the refrigerator. Recrystallization from hexane/EtOAc afforded **13** (1.37 g, 92%) as a white solid. M.p. 58.5–61 °C. IR (KBr): $\tilde{\nu}$ = 3566, 3085, 2953, 1750, 1706, 1517, 1458, 1436, 1394, 1321, 1252, 1206 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39 (d, J = 5.1 Hz, 1 H, 2-H), 7.13 (d, J = 5.1 Hz, 1 H, 3-H), 4.38–4.35 (m, 1 H, 6-H), 3.80 (s, 3 H, OCH_3), 3.39 and 3.17 (the AB part of an ABX system, J_{AB} = 18.5, J_{AX} = 7.4, J_{BX} = 3.0 Hz, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.89 (CO), 170.92 (CO_2CH_3), 166.14 (C-6a), 137.83 (C-3a), 132.94 (C-2), 119.82 (C-3), 53.36 (CH_3), 44.77 (C-5), 42.67 (C-6) ppm. EIMS: m/z (%) = 197 (4) [M + 1]$^+$, 196 (37) [M$^+$], 164 (20) [M$^+$ – OCH_3], 153 (18), 137 (100) [M$^+$ – CO_2CH_3], 136 (56), 119 (16), 109 (30) [C_6H_5S]$^+$, 97 (7), 69 (10), 65 (23). $C_9H_8O_3S$ (196.22): calcd. C 55.09, H 4.11, S 16.34; found C 55.00, H 3.99, S 16.52.

3.1.6 (±)-Methyl 4-Hydroxyimino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-6-carboxylate (14): A solution of hydroxylamine hydrochloride (0.55 g, 7.91 mmol) and sodium acetate (1.2 g, 8.82 mmol) in water (3 mL) was added to the keto ester **13** (0.87 g, 4.43 mmol), and EtOH was added until dissolution was complete (20 mL). This solution was refluxed for 5 h and cooled to room temperature, and after removal of EtOH under reduced pressure the solution was extracted with Et_2O (3× 30 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, and concentration under reduced pressure then afforded **14** (a mixture of *E* and *Z* isomers) as a white solid (0.90 g, 96%). M.p. 148–151 °C. IR (KBr): $\tilde{\nu}$ = 3200, 3078, 2940, 2865, 1742, 1654, 1508, 1435, 1401, 1329, 1271, 1207 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) (two isomers apparent): δ = 8.12 (br. s, 1 H, D_2O exch., NOH), 7.36 (d, J = 4.9 Hz, 1 H, 2-H), 7.10 (d, J = 5.1 Hz, 1 H, 3-H), 4.27 (dd, J = 8.0, 3.6 Hz, 1 H, 6-H) 3.79 (s, 3 H, OCH_3), 3.69 and 3.54 (the AB part of an ABX system, J_{AB} = 18.5, J_{AX} = 8.1, J_{BX} = 3.6 Hz, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.14 (CO_2Me), 157.83 (C=N), 150.97 (C-6a), 142.83 (C-3a), 132.37 (C-2), 119.05 (C-3), 53.13 (CH_3), 44.57 (C-6), 35.27 (C-5) ppm. EIMS: m/z (%) = 212 (15) [M + 1]$^+$, 212 (73) [M$^+$], 195 (8), 162 (13), 152 (100) [M$^+$ – CO_2CH_3], 135 (75) [M$^+$ – $C_2H_4O_3$], 121 (14) [M$^+$ – $C_2H_4NO_3$], 108 (20), 97 (8), 69 (10), 63 (15). $C_9H_9NO_3S$ (211.24): calcd. C 51.17, H 4.29, N 6.63, S 15.18; found C 51.06, H 4.35, N 6.76, S 15.03.

3.1.7 (±)-*cis*-[4-Acetylamino-5,6-dihydro-4*H*-cyclopenta[*b*]thien-6-yl]-methyl Acetate (15) and (±)-*trans*-[4-Acetylamino-5,6-dihydro-4*H*-cyclopenta[*b*]thien-6-yl]methyl Acetate (16): AlH_3 was prepared by adding concentrated H_2SO_4 (99.99%, 0.8 mL, 15 mmol) dropwise at 0 °C to a 1 M solution of $LiAlH_4$ in THF (30 mL) and stirring the mixture vigorously for 1 h at room temperature.[20] Once prepared, 11.5 mL (22.7 mmol) of AlH_3 was added dropwise at 0 °C under argon to a solution of **14** (0.5 g, 2.37 mmol) in dry THF (20 mL), and the mixture was stirred under reflux for 5 h. After addition of THF/H_2O (1:1, 15 mL) and water (20 mL) at 0 °C, stirring was continued while the mixture reached room temperature. The organic solvent was removed under reduced pressure, and the solid formed was filtered off and washed with EtOAc (3× 40 mL). The aqueous filtrate was extracted with EtOAc (3× 40 mL), and the combined organic phases were dried with anhydrous Na_2SO_4. Removal of the solvent under reduced pressure left 0.27 g of an oily residue that when chromatographed on silica gel (10 g) with 2:5 CH_2Cl_2/*i*PrOH as eluent afforded a 1:1 yellowish pasty mixture of **6** and **7** (0.22 g, 55%). This mixture (0.22 g, 1.3 mmol) was stirred with Ac_2O (3 mL) and dry Et_3N (3 mL) for 6 h under argon at room temperature, the resulting mixture was concentrated to dryness, and the solid residue was washed successively with saturated $NaHCO_3$ (3× 20 mL) and water (3× 40 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting pasty residue was chromatographed on silica gel (20 g) with hexane/EtOAc (1:2) as eluent, affording a mixture of the acetates **15** and **16** as a yellow oil that crystallized upon standing at 5 °C (0.27 g, 83%). A sample subjected to fractional crystallization from hexane/EtOAc (1:1) afforded pure **15** and pure **16** for analysis.

15: Reddish white solid, m.p. 123–125 °C. IR (KBr): $\tilde{\nu}$ = 3282, 3072, 2961, 1743, 1638, 1557, 1371, 1234 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.21 (d, J = 5.0 Hz, 1 H, 2-H), 6.85 (d, J = 5.0 Hz, 1 H, 3-H), 6.01 (d, J = 7.3 Hz, D_2O exch., 1 H, NH), 5.33–5.26 (m, 1 H, 4-H), 4.21 and 4.04 (AB part of an ABM system, J_{AB} = 10.6, J_{AM} = 8.13, J_{BM} = 6.25 Hz, 2 H, OCH_2), 3.50–3.46 (m, 1 H, 6-H), 3.10 (dt, J = 13.8, J = 8.0 Hz, 1 H, 5-H), 2.08 (s, 3 H, CH_3), 1.96 (s, 3 H, CH_3), 1.87 (dt, J = 13.8, J = 5.2 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.27 and 169.98 (2 CO), 146.72 and 144.99 (C-3a,-6a), 130.43 (C-2), 121.80 (C-3), 68.12 (CH_2O), 50.44 (C-4), 42.08 (C-5), 40.19 (C-6), 23.68 and 21.30 (2× CH_3) ppm. EIMS: m/z (%) = 254 (7) [M + 1]$^+$, 253 (6) [M$^+$], 210 (9) [M$^+$ – Ac], 193 (89), 167 (31) [M$^+$ – 2 Ac], 150 (99), 137 (16) [M$^+$ – $C_5H_8O_3$], 133 (100), 122 (15) [M$^+$ – $C_5H_9NO_3$] ppm. $C_{12}H_{15}NO_3S$ (253.32): calcd. C 56.90, H 5.79, N 5.53, S 12.66; found C 56.78, H 6.04, N 5.68, S 12.57.

16: Yellowish white solid, m.p. 100–102 °C. IR (KBr): $\tilde{\nu}$ = 3306, 3050, 2943, 2889, 1731, 1638, 1538, 1385, 1252 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, J = 5.0 Hz, 1 H, 2-H), 6.86 (d, J = 5.0 Hz, 1 H, 3-H), 5.85 (d, J = 7.3 Hz, D_2O exch., 1 H, NH), 5.38–5.31 (m, 1 H, 4-H), 4.18 and 3.99 (AB part of an ABM system, J_{AB} = 10.5, J_{AM} = 8.3, J_{BM} = 6.3 Hz, 2 H, OCH_2), 3.68–3.63 (m, 1 H, 6-H), 2.63 (ddd, J_{gem} = 13.9, J_{vic} = 8.1, J_{vic} = 5.5 Hz, 1 H, 5-H), 2.39 (ddd, J_{gem} = 13.9, J_{vic} = 7.9, J_{vic} = 3.9 Hz, 1 H, 5-H), 2.07 (s, 3 H, CH_3), 1.95 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.24 and 170.02 (2 CO), 146.58 and 145.62 (C-3a, -6a), 130.53 (C-2), 121.85 (C-3), 67.81 (CH_2O), 50.58 (C-4), 42.45 (C-5), 40.14 (C-6), 23.67 and 21.27 (2 CH_3) ppm. EIMS: m/z (%) = 254 (2) [M + 1]$^+$, 253 (1) [M$^+$], 210 (3) [M$^+$ – Ac], 193 (53), 167 (4) [M$^+$ – 2 Ac], 151 (30) [M$^+$ – $C_4H_6O_3$], 137 (17) [M$^+$ – $C_5H_8O_3$], 134 (100), 122 (25) [M$^+$ – $C_5H_9NO_3$]. $C_{12}H_{15}NO_3S$ (253.32): calcd. C 56.90, H 5.97, N 5.53, S 12.66; found C 57.07, H 6.06, N 5.42, S 12.50.

3.1.8 (±)-*cis*-*N*-[(6-Hydroxymethyl)-5,6-dihydro-4*H*-cyclopenta[*b*]-thien-4-yl]acetamide (17) and (±)-*trans*-*N*-[(6-Hydroxymethyl)-5,6-dihydro-4*H*-cyclopenta[*b*]thien-4-yl]acetamide (18): Potassium car-

bonate (1.88 g, 13.60 mmol) was added to a 1:1 solution of **15/16** (0.92 g, 3.64 mmol) in MeOH (12 mL), and the mixture was stirred for 2.5 h at room temperature and brought to pH 7 by addition of saturated NH_4Cl solution (40 mL). The organic solvent was removed under reduced pressure, and the solid formed was redissolved in water (60 mL). This solution was extracted with EtOAc (3× 60 mL), and the combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The solid residue so obtained was chromatographed on silica gel (22 g) with CH_2Cl_2/*i*PrOH (15:1) as eluent, it afforded first **17** (0.33 g, 43%) and then **18** (0.29 g, 38%).

17: M.p. 155–157 °C. IR (KBr): $\tilde{\nu}$ = 3276, 2964, 1635, 1553, 1372, 1041 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.23 (d, J = 4.9 Hz, 1 H, 2-H), 6.87 (d, J = 4.9 Hz, 1 H, 3-H), 6.35 (d, J = 7.6 Hz, 1 H, NH), 5.31 (dt, J = 8.4, J = 3.1 Hz, 1 H, 4-H), 3.86 and 3.69 (AB part of an ABM system, J_{AB} = 10.4, J_{AM} = 4.3, J_{BM} = 3.5 Hz, 2 H, OCH_2), 3.42–3.36 (m, 1 H, 6-H), 3.11 (dt, 1 H, J = 13.8, J = 8.4 Hz, 5-H), 2.21 (br. s, D_2O exch., 1 H, OH), 1.99 (dt, J = 13.8, J = 3.3 Hz, 1 H, 5-H), 1.92 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.72 (CO), 147.98 and 145.14 (C-3a,-6a), 130.26 (C-2), 122.21 (C-3), 66.16 (CH_2O), 49.79 (C-4), 43.50 (C-6), 42.09 (C-5), 23.82 (CH_3) ppm. EIMS: *m*/*z* (%) = 152 (0.23) [$C_8H_{10}SN$], 138 (11) [C_7H_8SN], 122 (16), 58 (100). $C_{10}H_{13}NO_2S$ (211.28): calcd. C 56.85, H 6.20, N 6.63, S 15.18; found C 57.11, H 6.11, N 6.68, S 15.07.

18: M.p. 94–96 °C. IR (KBr): $\tilde{\nu}$ = 3531, 3254, 2925, 1612, 1562, 1261, 1057 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, J = 5.0 Hz, 1 H, 2-H), 6.88 (d, J = 5.0 Hz, 1 H, 3-H), 5.77 (d, J = 6.4 Hz, 1 H, NH), 5.39–5.33 (m, 1 H, 4-H), 3.79–3.52 (m, 3 H, OCH_2, 6-H), 2.67 (ddd, J_{gem} = 13.8, J_{vic} = 7.8, J_{vic} = 4.7 Hz, 1 H, 5-H), 2.35 (ddd, J_{gem} = 13.8, J_{vic} = 7.8, J_{vic} = 4.1 Hz, 1 H, 5-H), 2.02 (br. s, D_2O exch., 1 H, OH), 1.97 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.98 (CO), 147.87 and 146.98 (C-3a,-6a), 130.26 (C-2), 121.98 (C-3), 66.83 (CH_2O), 50.80 (C-4), 43.61 (C-6), 42.30 (C-5), 23.76 (CH_3) ppm. EIMS: *m*/*z* (%) = 193 (33) [$M^+ - H_2O$], 168 (3) [M^+ – Ac], 152 (46) [$C_8H_{10}SN$], 138 (100) [C_7H_8SN], 122 (66) ppm. $C_{10}H_{13}NO_2S$ (211.28): calcd. C 56.85, H 6.20, N 6.63, S 15.18; found C 56.94, H 6.26, N 6.59, S 15.09.

3.1.9 (±)-*cis*-(4-Amino-5,6-dihydro-4*H*-cyclopenta[*b*]thien-6-yl)methanol (6): A solution of **17** (0.132 g, 0.78 mmol) in a mixture of MeOH (3 mL) and 2 N HCl (3 mL) was refluxed for 8 h and then reduced to dryness by evaporation under reduced pressure followed by azeotropic distillation with EtOH (2× 20 mL). The solid residue was dissolved in MeOH (4 mL), loaded on a 10 mL Amberlite IRA-400(OH) column, and eluted with MeOH (100 mL). Concentration of the eluate under reduced pressure left an oily residue that afforded **6** (0.042 g, 40%) as an orange oil after chromatography on silica gel (8 g) with dichloromethane/methanol (1:1) as eluent . IR (film): $\tilde{\nu}$ = 3346, 2923, 1841, 1587, 1503, 1438, 1037 cm^{-1}. ^1H NMR (300 MHz, [D_4]MeOH): δ = 7.30 (d, J = 4.9 Hz, 1 H, 2-H), 6.97 (d, J = 4.9 Hz, 1 H, 3-H), 4.34–4.29 (m, 1 H, 4-H), 3.78–3.52 (m, 3 H, OCH_2, 6-H), 3.16–2.88 (m, 1 H, 5-H), 1.98–1.81 (m, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D_4]MeOH): δ = 149.05 and 145.08 (C-3a,-6a), 129.05 (C-2), 121.04 (C-3), 65.72 (CH_2O), 52.09 (C-4), 43.59 (C-6), 43.14 (C-5) ppm. EIMS: *m*/*z* (%) = 168 (0.62) [M – 1]$^+$, 152 (6) [M^+ – OH], 138 (100) [C_7H_8SN], 123 (19), 122 (95). HMRS *m*/*z* calcd. for [$C_8H_{11}NOS$] 169.0561, found 169.0569.

3.1.10 (±)-*trans*-(4-Amino-5,6-dihydro-4*H*-cyclopenta[*b*]thien-6-yl)-methanol (7): A solution of **18** (0.104 g, 0.49 mmol) in a mixture of EtOH (2.5 mL) and 2 N HCl (2.5 mL) was refluxed for 24 h. Compound **7** (0.034 g, 41%) was obtained as a brown oil by a procedure analogous to that by which **6** was obtained from **17**. IR (film): $\tilde{\nu}$ = 3344, 2925, 1654, 1560, 1504, 1458, 1040 cm^{-1}. ^1H NMR (300 MHz, [D_4]MeOH): δ = 7.36 (d, J = 5.02 Hz, 1 H, 2-H), 7.01 (d, J = 5.02 Hz, 1 H, 3-H), 4.49–4.41 (m, 1 H, 4-H), 3.68–3.49 (m, 3 H, OCH_2+6-H), 2.61–2.49 (m, 1 H, 5-H), 2.42–2.31 (m, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D_4]MeOH): δ = 147.05 and 146.11 (C-3a,-6a), 129.48 (C-2), 121.09 (C-3), 65.86 (CH_2O), 51.79 (C-4), 43.55 (C-6), 42.23 (C-5) ppm. EIMS: *m*/*z* (%) = 169 (12) [M^+], 168 (3) [M – 1]$^+$, 152 (7) [M^+ – OH], 138 (100) [C_7H_8SN], 123 (6), 122 (24). HMRS *m*/*z* calcd. for [$C_8H_{11}NOS$] 169.0561, found 169.0571.

Supporting Information (see footnote on the first page of this article): The ORTEP plot of the structure of (±)-**16** and the details of the reduction of hydroxyimino ester **14** is available.

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[16] (±)-(4-Hydroxyimino-5,6-dihydro-4*H*-cyclopenta[*b*]thien-6-yl)-methanol (**19**). Viscous liquid. IR (film): $\tilde{\nu}$ = 3383, 2937, 2810, 1654, 1559, 1399, 1269 cm^{-1}. ^1H NMR (300 MHz, [D_6]-DMSO): δ = 10.45 (s, D_2O exch., 1 H, NOH), 7.50 (d, J = 4.9 Hz, 1 H, 2-H), 7.00 (d, J = 4.9 Hz, 1 H, 3-H), 5.04 (t, J = 4.9 Hz, D_2O exch., 1 H, OH), 3.57–3.52 (m, 1 H, 6-H), 3.43–3.27 (m, 2 H, CH_2O), 3.21–3.13 (m, 1 H, 5-H), 2.74–2.67 (m, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 156.20 (C=N), 155.21 (C-6a), 141.93 (C-3a), 131.55 (C-2), 118.33 (C-3), 65.01 (CH_2O), 42.24 (C-6), 34.94 (C-5) ppm. EIMS: *m*/*z* (%) = 184 (4) [M + 1]$^+$, 183 (33) [M$^+$], 152 (100) [M$^+$ – NOH], 135 (70) [M$^+$ – H_2NO_2]. HMRS *m*/*z* calcd. for [$C_8H_9NO_2S$] 183.0354, found 183.0346.
[17] (±)-(4,5,6,7-Tetrahydrothieno[3,2-*b*]pyridin-7-yl)methanol (**20**). M.p. 145–147 °C. IR (KBr): $\tilde{\nu}$ = 3238, 2920, 1569, 1490, 1331, 1027 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 6.98 (d, J = 5.2 Hz, 1 H, 2-H), 6.41 (d, J = 5.2 Hz, 1 H, 3-H), 5.08 (br. s, D_2O exch., 1 H, OH), 4.72 (t, J = 5.3 Hz, D_2O exch., 1 H, NH), 3.49–3.34 (m, 2 H, CH_2O), 3.09–3.03 (m, 2 H, 2× 5-H), 2.88–2.81 (m, 1 H, 7-H), 1.88–1.79 (m, 1 H, 6-H), 1.72–1.63 (m, 1 H, 6-H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 144.88 (C-3a), 122.67 (C-2), 118.97 (C-3), 111.65 (C-7a), 66.88 (CH_2O), 39.11 (C-5), 36.79 (C-7), 26.07 (C-6). EIMS: *m*/*z* (%) = 170 (12) [M + 1]$^+$, 169 (31) [M$^+$], 151 (21) [M$^+$ – H_2O], 138 (2) [M$^+$ – CH_2OH], 123 (48) [M$^+$ – CH_4NO], 108 (100). HMRS *m*/*z* calcd. for [$C_8H_{11}NOS$] 169.0561, found 169.0552.
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[21] CCDC-268240 (**16**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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