Synthesis of crystalline (±)-A58365B—an inhibitor of angiotensin-converting enzyme

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A58365B 1, an inhibitor of angiotensin-converting enzyme, is synthesized from two subunits, spiro lactone 5 and ε-hydroxynorleucine methyl ester 6, by a process based on enyne radical cyclization (9a,b → 11a,b).

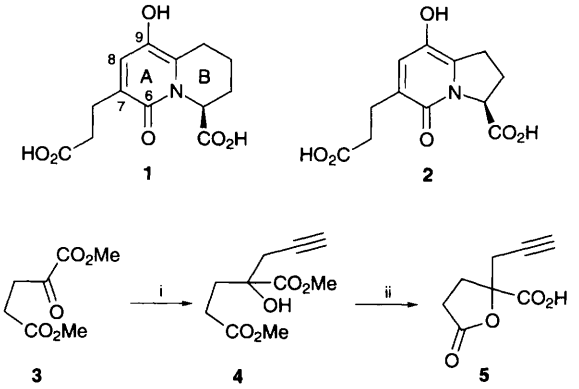
A58365B **1** and the related pyridone **2** are water-soluble metabolic products of *Streptomyces chromofuscus* NRRL 15098.[1] Both substances inhibit angiotensin-converting enzyme, and so the development of synthetic approaches might be of use in the further refinement of drugs to control hypertension.

The structures of **1** and **2** do not appear to be especially complicated, but synthetic work—both our own and that done earlier[2]—revealed a number of unexpected difficulties. In particular, generation of the C(7)–C(8) double bond of **1** (and the corresponding double bond of **2**) is not at all straightforward,[2] because ring B is also susceptible to desaturation. After appreciable exploratory work, we were led to an approach in which the C(7)–C(8) unsaturation is introduced early—but in the disguised form of a spirolactone (*cf.* **5**). This compound, which was prepared as shown in Scheme 1, represents all the carbons that make up the C(6)–C(9) segment of the natural product, including the propionic side chain.

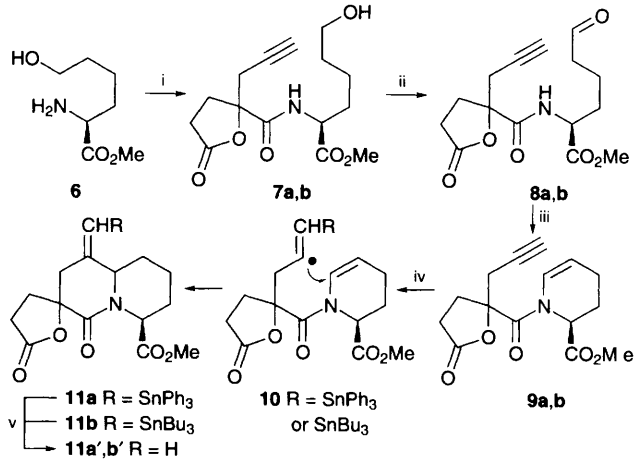
Condensation of dimethyl 2-ketoglutarate[3] with prop-2-ynyl aluminum sesquibromide[4] gave the desired addition product **4** (95%). Ester hydrolysis (LiOH, THF, water, room temperature, overnight), liberation of the free hydroxy diacid by ion-exchange chromatography using Amberlite IR-120 (acid form), followed by evaporation of the resulting aqueous solution,† converted the hydroxy diester **4** into lactone acid **5** (95%).

The ring B portion of **1** was constructed[5] (Scheme 2) from ε-hydroxynorleucine methyl ester **6**,[5] which not only has all of the required atoms, but also could be used without prior hydroxy protection. Coupling of the ring A (**5**) and ring B (**6**) subunits under standard conditions [*N*-methyl morpholine, 1-hydroxybenzotriazole, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, DMF][5,6]‡ gave a mixture (*ca.* 6 : 4) of diastereoisomeric amides **7a** (major) and **7b** (minor) in 65% yield (based on **6**). Isomers **7a** and **7b** were individually oxidized (PCC) to the corresponding aldehydes (**7a** → **8a**, 73%; **7b** → **8b**, 87%), and these were cyclized[5] [**8a** → **9a**, 82%; **8b** → **9b**, 65%, after correction for recovered starting material (14%)] by exposure to freshly distilled TFA (1 mol dm^{-3} in CH_2Cl_2, 10 equiv., 4 Å molecular sieves, 4 h for **8a**, and 1 h for **8b**). The stage was then set for closure of ring B (**9a,b** → **11a,b**) by stannane addition to the alkyne, followed by cyclization of the resulting vinyl radical onto the proximal terminus[7] of the enamine double bond (see **10**). Treatment§ of **9a** in refluxing toluene with AIBN and Ph_3SnH led to the desired products **11a**, while cyclization of **9b**, under similar conditions, but using Bu_3SnH, gave **11b**.¶ Thorough purification of **11a** and **11b** was difficult because of persistent tin species, but protodestannylation gave **11a′** (TFA, THF, 12 h at room temperature, 2 h at 60 °C; 62% from **9a**) and **11b′** (TFA, THF, 5 h at room temperature; 89% from **9b**). Both cyclization–destannylation products **11a′** and **11b′** were single compounds although, of course, of different stereochemistry; however, both served equally well for the last steps of the synthesis (Scheme 3).

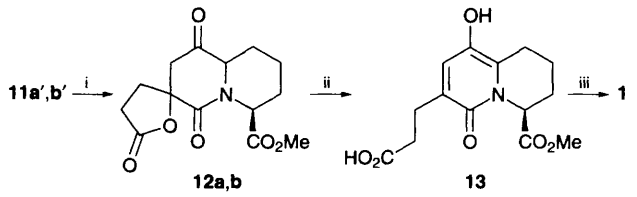
Ozonolysis (**11a′** → **12a**; **11b′** → **12b**; O_3, CH_2Cl_2, −78 °C; Ph_3P, −78 °C to room temperature) gave the corresponding ketones, and, without isolation, exposure to Et_3N (THF, 60 °C, 2 h) served both to introduce the critical C(7)–C(8) double bond and release the propionic acid side chain (63% overall yield from either **11a′** or **11b′**). Finally, ester hydrolysis, using $(Bu_3Sn)_2O$[8] in refluxing PhH (3 d), gave crystalline‖ (±)-A58365B (67%) (mp 209–213 °C, from water).



Scheme 1 *Reagents and conditions*: i, prop-2-ynyl bromide, Al, $HgCl_2$, 40 °C, then add to dimethyl 2-ketoglutarate at −78 °C, 95%; ii, LiOH, THF–H_2O, room temp., Amberlite IR-120 (H^+), evaporate at bath temperature of 60 °C, 95%



Scheme 2 *Reagents and conditions*: i, **6**, DMF, *N*-methyl morpholine, 1-hydroxybenzotriazole **5**, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, room temp., 12 h, 65%; ii, PCC, 4 Å molecular sieves, CH_2Cl_2, room temp., 1.5 h, 73% for **8a**, 87% for **8b**; iii, TFA, 4 Å molecular sieves, CH_2Cl_2, room temp., 4 h for **8a**, and 1 h for **8b**, 82% for **8a**, 65% for **8b**; iv, Ph_3SnH, AIBN, PhMe, reflux for **8a**, Bu_3SnH, AIBN, PhMe, reflux for **8b**; v, TFA, THF, 12 h at room temp., 2 h at 60 °C for **9a**, TFA, THF, 5 h at room temperature for **9b**, 62% overall for **11a′** and 89% overall for **11b′**



Scheme 3 *Reagents and conditions*: i, O_3, CH_2Cl_2, −78 °C, Ph_3P, −78 °C to room temp; ii, Et_3N, THF, 60 °C, 2 h, 63% overall for each isomer; iii, $(Bu_3Sn)_2O$, PhH, reflux, 3 d, 67%

All new compounds, except **11a,b** and **12a,b**, were fully characterized by spectroscopic methods, including accurate mass measurements.

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Footnotes

† Evaporation should be done using a rotary evaporator and a bath temperature of 65–70 °C. We did not establish the stage at which lactonization occurs.

‡ This was the best of several standard coupling methods we tried.

§ A toluene solution of AIBN (0.043 mmol, 0.043 mol dm^{-3}) and Ph_3SnH (0.422 mmol, 0.422 mol dm^{-3}) was added over 2 min to a refluxing solution of **9a** (0.158 mmol, 0.079 mol dm^{-3}) in the same solvent, and refluxing was continued for 4 h.

¶ Use of Bu_3SnH with **9a** was much less efficient in either refluxing PhMe or PhH. It may be significant that **9a** exists as two rotamers at room temperature,while **9b**, which closes efficiently (Bu_3SnH, refluxing PhMe), does not. The ^1H NMR spectrum of **9a** shows broad signals at 85 °C, but coalesced signals at 100 °C.

‖ Natural **1** is reported as an amorphous powder: J. S. Mynderse, S. K. Samlaska, D. S. Fukuda, R. H. Du Bus and P. J. Baker, *J. Antibiot.*, 1985, **38**, 1003. Our data (s = quaternary carbon, d = CH, t = CH_2): (^{13}C NMR, 100.64 MHz, D_2O) δ 16.12 (t), 23.70 (t), 26.07 (t), 26.46 (t), 33.38 (t), 57.55 (d), 126.79 (s), 132.73 (s), 133.46 (d), 137.63 (s), 161.82 (s), 176.24 (s), 178.59 (s). Data from ref. 1: (67.9 MHz, D_2O) δ 16.05 (t), 23.40 (t), 26.05 (t), 26.35 (t), 33.44 (t), 58.10 (d), 126.54 (s), 132.99 (d), 132.89 (s), 137.11 (s), 161.70 (s), 177.10 (s) and 178.60 (s). Data from ref. 2*a*: (75 MHz, D_2O): δ 15.1, 22.7, 25.0, 25.5, 32.4, 56.5, 125.8, 131.7, 132.5, 136.7, 160.8, 175.2 and 177.6.

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