The Total Synthesis of Antrimycin D_v

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Antrimycin D_v, a representative of the antrimycin and cirratiomycin classes of tuberculostatic heptapeptide antibiotics containing a tetrahydropyridazinecarboxylic acid unit, has been synthesized.

The closely related (and, in parts, identical) cirratiomycins[1] **1** and antrimycins[2] **2** have been isolated from *Streptomyces xanthocidicus* and *Streptomyces cirratus*. These tuberculostatic peptides contain the non-proteinogenic amino acids β,β-dihydroxy-α-aminoisobutyric acid, didehydrovaline or didehydroisoleucine, (*S*,*S*′)-α,β-diaminobutyric acid and (*S*)-tetrahydropyridazinecarboxylic acid. The latter has now been detected for the first time whereas its 4-hydroxy derivative had been found as a residue of luzopeptin,[3] a DNA intercalating, cancerostatic cyclopeptide.

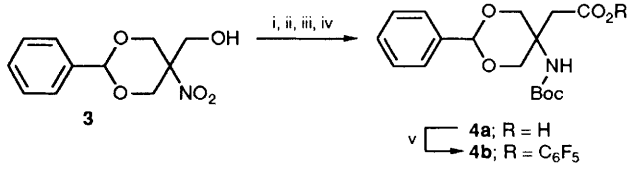
The construction of the completely protected β,β-dihydroxy-α-aminoisobutyric acid is shown in Scheme 1. The nitro alcohol **3** is readily accessible from tris(hydroxymethyl)-nitromethane and was converted to the Boc-protected amino acid **4a** by a two-step oxidation; **4a** can be activated as its pentafluorophenyl ester **4b**.

The masked didehydrotripeptide Boc-Leu-D,D-Val-Ser-OAll **7** was prepared as shown in Scheme 2. The didehydrodipeptide **6** was obtained from the dipeptide **5** by a Horner condensation. Analogous reactions have been reported frequently.[4] When DBU is employed as the base, ketones can also take part in the phosphonic ester condensation.[5]

We have developed two routes for the preparation of the 2,3,4,5-tetrahydropyridazinecarboxylic acid in which the ring is built up through intramolecular hydrazone formation from a 2-hydrazino-4-formylbutyric acid (Scheme 3). The protected 4-formylbutyric acid derivative **9** is metallated and converted to the hydrazine **10** by reaction with an azodicarboxylate according to Evans's method. The latter is converted to the cyclic hydrazone **12** by opening of the cyclic ketal and cleavage of the Boc group. Unfortunately, the free ester is unstable and cannot be acylated.

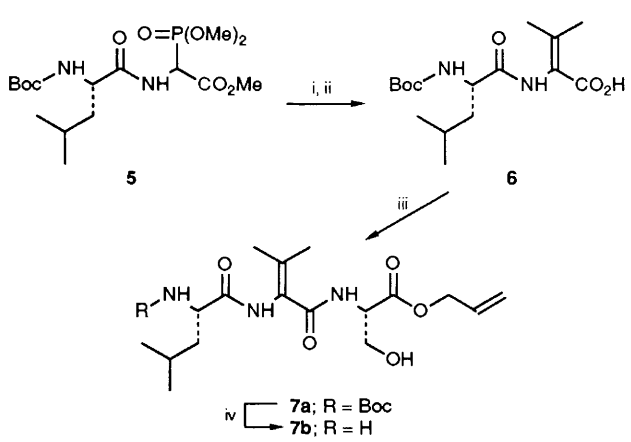
Model experiments, however, have shown that N^{α}-acylated hydrazines (**11**, N^{α}-Ac in place of N^{α}-Boc) form stable *N*-acyl derivatives of tetrahydropyridazinecarboxylic acid in trifluoroacetic acid. This sequence was used to construct the protected diaminobutyryltetrahydropyridazinecarboxylate **15**. A suitably protected diaminobutyric acid derivative was available from a previous synthesis of lavendomycin.[6] The protected 4-formyl-2-oxobutyrate **13** was converted to the Boc-hydrazone which, in turn, was reduced to the hydrazine derivative **14**. Coupling with the α,β-diaminobutyric acid derivative and acid treatment gave rise to the dipeptide **15**. Subsequent cleavage of the Fmoc group, coupling with Boc-alanine to give **16**, and reduction of the azide group furnished the tripeptide **17** as a mixture of diastereoisomers (1 : 1). The diastereoisomers can be separated easily by MPLC at the stages of **16** and **17a**. The assignment was deduced later from a comparison of the NMR spectra of the diastereoisomeric hexapeptides with that of the naturally occurring product. Only in the case of one of the diastereoisomers **18** and *epi*-**18** were the chemical shifts of the signals of the two methyl groups of D,D-valine in agreement with those of the natural product.

The 'correct' diastereoisomer of **16b** was converted to the hexapeptide **18** by coupling with the dehydrotripeptide **7b**. Cleavage of the Boc group and acylation with the hydroxymethylserine derivative **4b** gave rise to the completely

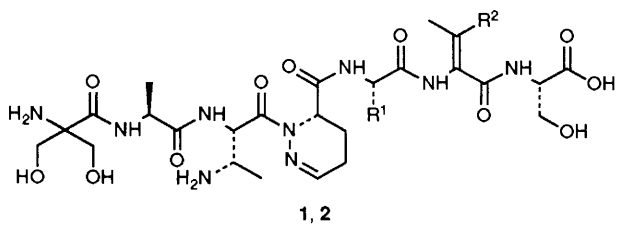


Boc = *tert*-butoxycarbonyl

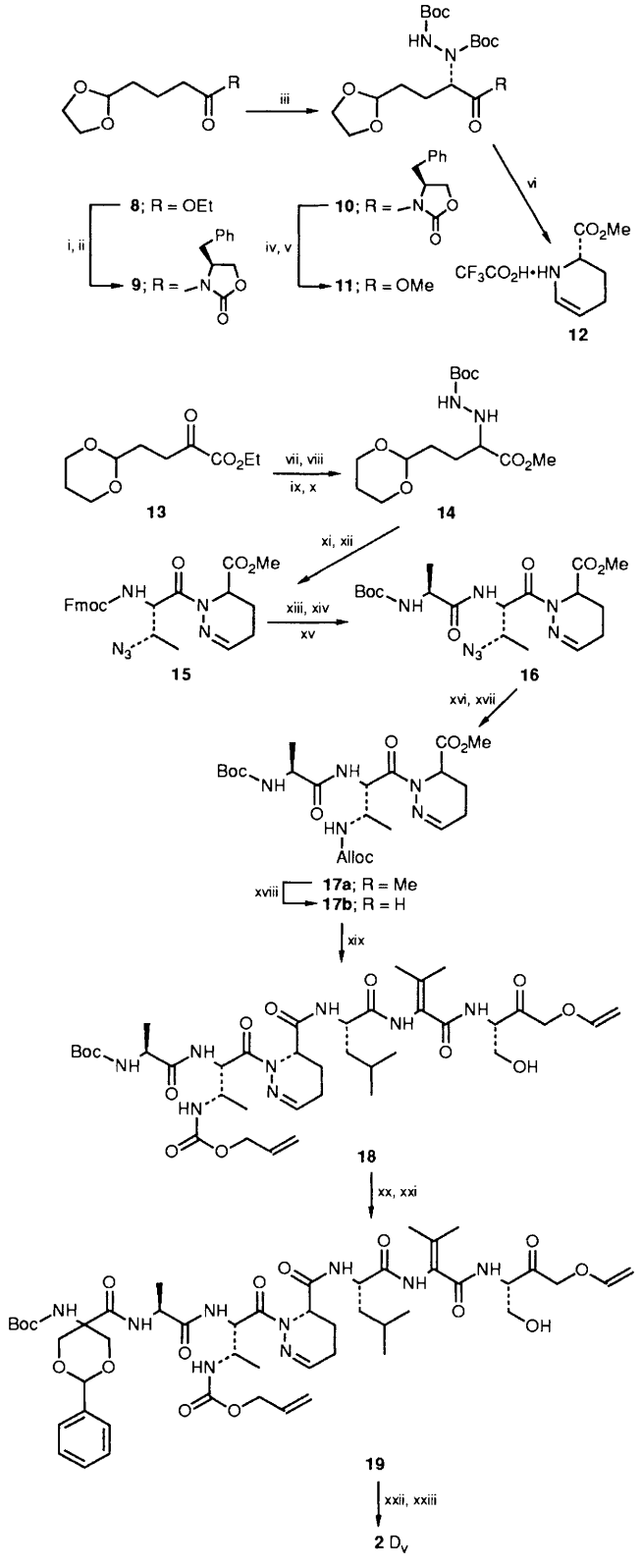
Scheme 1 *Reagents and conditions*: i, H_2, Pd/C, EtOH, room temp., 3 days, 98%; ii, Boc_2O, CH_2Cl_2, room temp., 14 h, 99%; iii, $(COCl)_2$, dimethyl sulfoxide (DMSO), CH_2Cl_2, −60 °C, 10 min, triethylamine (TEA), −60 °C, 15 min, −60 °C to room temp. 1 h, 95%; iv, NH_2SO_3H, $NaHPO_4$, $NaClO_2$, H_2O–dioxane, 5 °C, 30 min, room temp., 30 min, 72%; v, C_6F_5OH, dicyclohexylcarbodiimide (DCC), CH_2Cl_2, −20 to 20 °C, 16 h, 100%



Scheme 2 *Reagents and conditions*: i, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), acetone, room temp., 48 h, 75%; ii, NaOH, H_2O–dioxane, room temp., 16 h, 83%; iii, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC), Et_3N, hydroxybenzotriazole, dimethylformamide (DMF), H-Ser-OAll·*x*HCl, −20 °C to room temp., 16 h, 52%; iv, 6 mol dm^{-3} HCl–dioxane, 5 to 20 °C, 2 h, 100%



		R¹	R²			R¹	R²
1	A	Bu^{i}	Et	**2**	B	Et	Et
1	B	Me	Et	**2**	C_v	Pr^{n}	Me
2	A_v	Me	Me	**2**	C	Pr^{n}	Et
2	A	Me	Et	**2**	D_v	Bu^{i}	Me
2	B_v	Et	Me	**2**	D	Bu^{i}	Et



Abbreviations: Fmoc = fluoren-9-ylmethoxycarbonyl; Alloc = allyloxy-carbonyl; All = allyl; Succ = succinimido

Scheme 3 *Reagents and conditions*: i, NaOH, H_2O–dioxane, room temp., 14 h, 93%; ii, 1-chloro-*N*,*N*,2-trimethylprop-1-en-1-amine, CH_2Cl_2, 0 °C, 10 min, lithium salt of (4*S*)-4-benzyl-2-oxazolidinone, tetrahydrofuran (THF), −80 °C, 15 min, −80 to 0 °C, 2 h, 76%; iii, $NaN(SiMe_3)_2$, THF, −80 °C, 30 min, di-*tert*-butoxycarbonyl azocarboxylate, CH_2Cl_2–THF, 3 min, 67%; iv, LiOH, H_2O–THF, 0 °C, 2 h, v, CH_2N_2, CH_2Cl_2, room temp., 2 min, iv + v: 99%; vi, CF_3CO_2H, room temp., 15 min, 90%; vii, Boc-$NHNH_2$, hexane, reflux, 3 h, 64%, viii, NaOH, H_2O–dioxane, room temp., 4 h, 86%; ix, CH_2N_2, CH_2Cl_2, room temp., 5 min, 98%; x, $NaCNBH_3$, HOAc, MeCN, room temp., 24 h, 98%; xi, Fmoc-NH-CH($CHMeN_3$)COCl, collidine, THF, 0 °C, 2 h, room temp., 16 h; xii, CF_3CO_2H, room temp., 2 h, xi + xii: 52%; xiii, NaOH, H_2O–dioxane, room temp., 14 h, xiv, H_2SO_4, dioxane–H_2O, room temp., 5 min, xv, $NaHCO_3$, Boc-Ala-OSucc, H_2O–dioxane, room temp., 16 h, xiii + xiv + xv: 74%; xvi, H_2, Pd/C, dioxane, room temp., 3 h, xvii, Alloc-Cl, pyridine, CH_2Cl_2, 0 °C, 1 h, room temp., 14 h, xvi + xvii: 84%; xviii, NaOH, H_2O–dioxane, room temp., 14 h, 100%; xix, **7b**, $EtNPr^i_2$, diphenyl phosphorylazide, CH_2Cl_2, −20 °C, 1 h, 4 °C, 3 days, 68%; xx, 6 mol dm^{-3} HCl–dioxane, 5 to 20 °C, 2 h, 100%; xxi, **4b**, dimethylaminopyridine (DMAP), THF, room temp., 16 h, 47%; xxii, $Pd(PPh_3)_4$, morpholine, THF, room temp., 2 h, xxiii, 6 mol dm^{-3} HCl–H_2O, room temp., 2 h, xxii + xxiii: 56%

protected antrimycin D_v **19**.† The two allyl protecting groups were cleaved by[7] Pd^0 while the protecting groups on the hydroxymethylserine unit were removed by acid treatment. The thus synthesized compound was identical with the natural product.

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† ^1H NMR (250 MHz, $CDCl_3$): δ 8.22 (d, *J* 6.7 Hz, 1H), 8.17 (s, 1H), 7.35–7.51 (m, 7H), 7.23 (d, *J* 6.7 Hz, 1H), 7.09 (s, 1H), 5.82–5.98 (m, 2H), 5.60–5.63 (m, 1H), 5.57 (s, 1H), 5.16–5.38 (m, 4H), 5.0 (s, 1H), 4.59–4.68 (m, 4H), 4.42–4.52 (m, 2H), 4.22–4.39 (m, 5H), 3.84–4.02 (m, 2H), 3.37–3.72 (m, 1H), 2.17–2.23 (m, 2H), 2.11 (s, 3H), 1.80–1.85 (m, 1H), 1.76 (s, 3H), 1.55–1.71 (m, 4H), 1.50 (s, 9H), 1.35 (d, *J* 7.0 Hz, 3H), 1.09 (d, *J* 6.8 Hz, 3H), 0.94 (d, *J* 6.7 Hz, 3H), 0.90 (d, *J* 5.5 Hz, 3H).