Synthetic Studies on the Validamycins. XII. Synthesis of Optically Active Valienamine and Validatol

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Synopsis. (+)-Valienamine and (+)-validatol have been totally synthesized as the peracetyl derivatives starting from a common synthetic intermediate, (1*S*)-(1,3/2)-4-methylene-5-cyclohexene-1,2,3-triol.

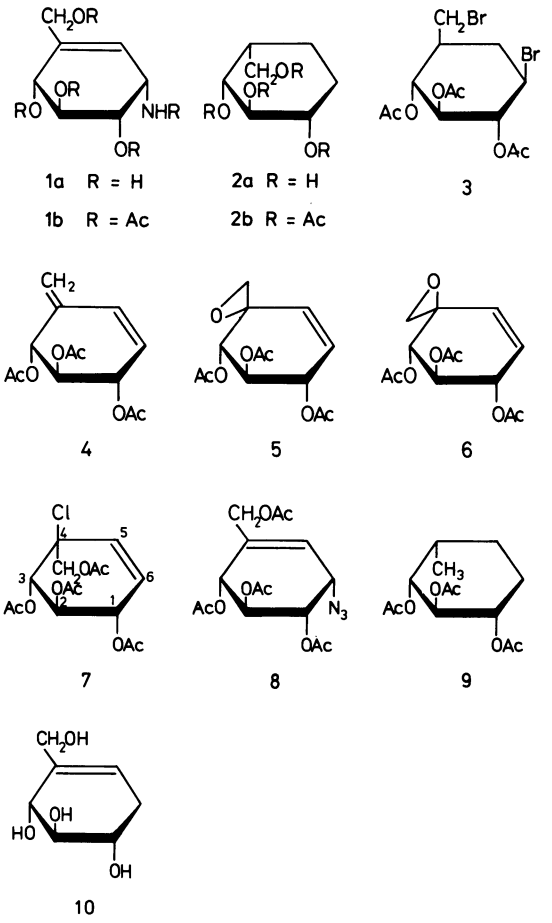
Valienamine (**1a**) is an unsaturated branched-chain aminocyclitol found in the structural unit of the antibiotic validamycins[1] and several pseudo-oligosaccharidic α-glucosidase inhibitors.[2] Later, **1a** itself was shown to be an α-glucosidase inhibitor.[3] Hydrogenolysis of validamycin A produced validatol (**2a**), resulting from a reductive elimination of the imino group of the aminocyclitol part.[4]

We have reported the synthesis of the racemic forms of **1a**[5–7] and **2a**,[8] and Paulsen and Heiker have first synthesized the optically active **1a** starting from quebrachitol (L-2-*O*-methyl-*chiro*-inositol).[9]

We now describe a facile synthesis of the penta-*N*,*O*-acetyl derivative (**1b**) of **1a** from the optically active diene intermediate (**4**), following the route previously used for preparation of its racemate.[6,7] In addition, a new synthesis of the tetra-*O*-acetyl derivative (**2b**) of **2a** is reported.

Dehydrobromination of (1*R*)-(−)-1,2,3-tri-*O*-acetyl-(1,3/2,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol (**3**)[10] with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene afforded exclusively the diene (**4**), which was, without purification, treated with equimolar amount of *m*-chloroperbenzoic acid (MCPBA) in dichloromethane to oxidize the exomethylene group. A mixture of the products was fractionated by a silica-gel column to give the spiro oxiranes **5** (27%) and **6** (12%). Their structures were confirmed by comparison of the ^{1}H NMR spectra with those of the respective racemates.[6,7] Chlorination of **5** with concd hydrochloric acid in tetrahydrofuran (THF) followed by acetylation gave the chloride (**7**) in 92% yield. Treatment of **7** with sodium azide in *N*,*N*-dimethylformamide (DMF) at 60 °C gave selectively the azide (**8**) in a quantitative yield. Reduction of **8** with hydrogen sulfide followed by the conventional acetylation gave **1b**, mp 92.5—95 °C, $[\alpha]_D$ +20° ($CHCl_3$), in 94% yield. The ^{1}H NMR spectrum was superposable on that of an authentic sample.[1,5]

On the other hand, a new synthesis of **2b** was attempted by reduction of **7**. Direct hydrogenolysis of **7** in the presence of Raney nickel and a basic resin gave a complex mixture of products. Therefore, dechlorination was first carried out by treatment of **7** with lithium aluminum hydride (LAH) in THF, and then the product was hydrogenated in the presence of Raney nickel and successively acetylated to give **2b**, $[\alpha]_D$ −16° ($CHCl_3$), in 19% yield, together with tri-*O*-acetyldeoxyvalidatol[4,8] (**9**) (17%). Formation of **9** suggested that the initial dechlorination involved an attack of a hydride ion at C-6 giving an allyl alcohol (**10**). Hydrogenation of **4** with platinum oxide gave only **9** in 56% yield.



Experimental

Melting points were determined on a Büchi 510 capillary melting-point apparatus and are uncorrected. Optical rotations were measured on a Jasco DIP-4 polarimeter. The ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrometer for solutions of chloroform-*d*. The silica gel used for column chromatography was Wakogel C-300 (Wako Co., Osaka). The structures of the optically active compounds synthesized were confirmed by comparison of the ^{1}H NMR spectra with those of the corresponding racemic modifications.

(2R)-(+)-2,3,4-Tri-O-acetyl-1,7-anhydro-(1,2,4/3)- (5) and (1,3/2,4)-1-C-Hydroxymethyl-5-cyclohexene-1,2,3,4-tetrol (6). Treatment of (1*R*)-(−)-1,2,3-tri-*O*-acetyl-(1,3/2,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol[9] (**3**) (1.0 g, 2.3 mmol) with DBU in toluene similarly as described in the preparation of the racemate[8] gave a diene (**4**) (574 mg), which was, without isolation, subjected to an oxidation

with MCPBA in dichloromethane.[6,7] A crystalline mixture of the products (540 mg) was fractionated by a silica-gel column (18 g) with 1:10 2-butanone–toluene as an eluant to give 82 mg (12%) of **6** as plates (from ethanol): mp 114—115 °C; $[\alpha]_D^{24}$ +147° (*c* 1.03, $CHCl_3$). The second fraction gave 179 mg (27%) of **5** as plates (from ethanol): mp 102—103 °C; $[\alpha]_D^{22}$ +65° (*c* 1.0, $CHCl_3$).

Found for **5**: C, 54.78; H, 5.46%, and for **6**: C, 54.64; H, 5.73%. Calcd for $C_{13}H_{16}O_7$: C, 54.93; H, 5.67%.

(2S)-(+)-1,2,3-Tri-O-acetyl-(1,3/2,4)-4-C-acetoxymethyl-4-chloro-5-cyclohexene-1,2,3-triol (7). Treatment of **5** (119 mg, 0.42 mmol) with concd hydrochloric acid (0.044 ml) in THF (4.8 ml) similarly as described in the preparation of the racemate.[6,7] The product was crystallized from ethanol to give 141 mg (92%) of **7** as thin needles: mp 103.5—105 °C; $[\alpha]_D^{18}$ +60° (*c* 1.02, $CHCl_3$).

Found: C, 49.71; H, 5.48%. Calcd for $C_{15}H_{19}ClO_8$: C, 49.66; H, 5.28%.

(1S)-1,2,3-Tri-O-acetyl-(1,3,6/2)-4-acetoxymethyl-6-azido-4-cyclohexene-1,2,3-triol (8). The chloride (**7**) (67 mg, 0.18 mmol) was treated with sodium azide in DMF similarly as described in the preparation of the racemate[6,7] to give 68 mg (99%) of **8** as a syrup: $[\alpha]_D^{20}$ +40° (*c* 1.0, $CHCl_3$).

Found: C, 48.79: H, 5.25; N, 11.44%. Calcd for $C_{15}H_{19}N_3O_8$: C, 48.78; H, 5.19; N, 11.38%.

(1S)-1,2,3-Tri-O-acetyl-(1,3,6/2)-6-acetamido-4-acetoxymethyl-4-cyclohexene-1,2,3-triol [penta-N,O-acetyl-(+)-valienamine] (1b). The azide (**8**) (90 mg, 0.24 mmol) was reduced with hydrogen sulfide and then acetylated similarly as described in the preparation of the racemate[6,7] to give 88 mg (94%) of **1b** as needles (from ethanol–toluene): mp 92.5—95 °C; $[\alpha]_D^{21}$ +20° (*c* 1.04, $CHCl_3$) [lit.[1] mp 95 °C, $[\alpha]_D^{23}$ +30.2° ($CHCl_3$)].

Found: C, 53.27; H, 6.01; N, 3.42%. Calcd for $C_{17}H_{23}NO_9$: C, 52.98; H, 6.02; N, 3.63%.

(3R)-1,2,3-Tri-O-acetyl-(1,3,4/2)-4-acetoxymethyl-1,2,3-cyclohexanetriol [tetra-O-acetyl-(−)-validatol] (2b) and (3R)-1,2,3-Tri-O-acetyl-(1,3,4/2)-4-methyl-1,2,3-cyclohexanetriol [tri-O-acetyl-(−)-deoxyvalidatol] (9). A mixture of **7** (66 mg, 0.18 mmol), lithium aluminum hydride (42 mg), and THF (7.5 ml) was refluxed for 9 h. To a cooled mixture was added water (1.5 ml), and an insoluble material was removed by filtration and the filtrate was concentrated. The residue was treated with acetic anhydride (0.6 ml) and pyridine (0.6 ml) at room temperature overnight. The product was then hydrogenated in ethyl acetate (10 ml) in the presence of Raney nickel T-4[11] (0.5 ml) at room temperature overnight (initial hydrogen pressure of 3.4 kg cm^{-2}). The products were separated by a silica-gel column with 1:8 2-butanone-toluene to give first 8.7 mg (17%) of **9** as a syrup: $[\alpha]_D^{23}$ −7.9° (*c* 0.37, $CHCl_3$).

Found: C, 57.38; H, 7.13%. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40%.

The second fraction gave 12 mg (19%) of **2b** as a syrup: $[\alpha]_D^{25}$ −16° (*c* 0.52, $CHCl_3$).

Found: C, 54.84; H, 6.79%. Calcd for $C_{15}H_{22}O_8$: C, 54.54; H, 6.71%.

Catalytic Hydrogenation of 4. The crude **4** (139 mg) was hydrogenated in ethyl acetate (10 ml) in the presence of platinum oxide (10 mg) at room temperature overnight (initial hydrogen presure of 3.4 kg cm^{-2}). The product was purified by a silica-gel column with 1:10 2-butanone–toluene to give 91 mg (56%) of **9** as a syrup: $[\alpha]_D^{21}$ −8.6° (*c* 1.0, $CHCl_3$).

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