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M. Gillard, C. T'Kint, E. Sonveaux, L. Ghosez*
Laboratoire de Chimie Organique de Synthèse
Université Catholique de Louvain, Bâtiment Lavoisier
Place L. Pasteur, 1, B, 1348 Louvain-la-Neuve, Belgium
Received March 27, 1979

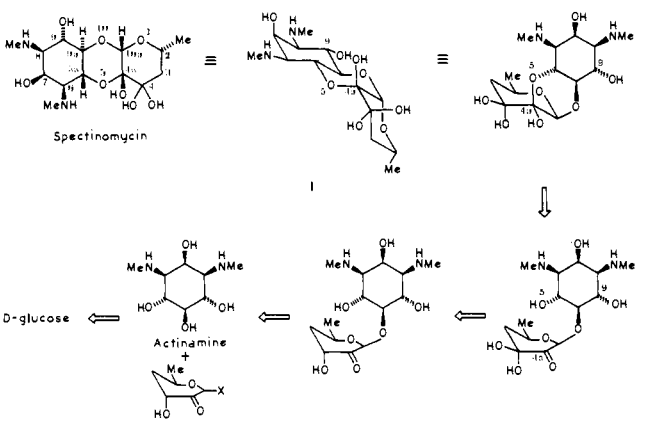
Synthesis of (+)-Spectinomycin

Sir:

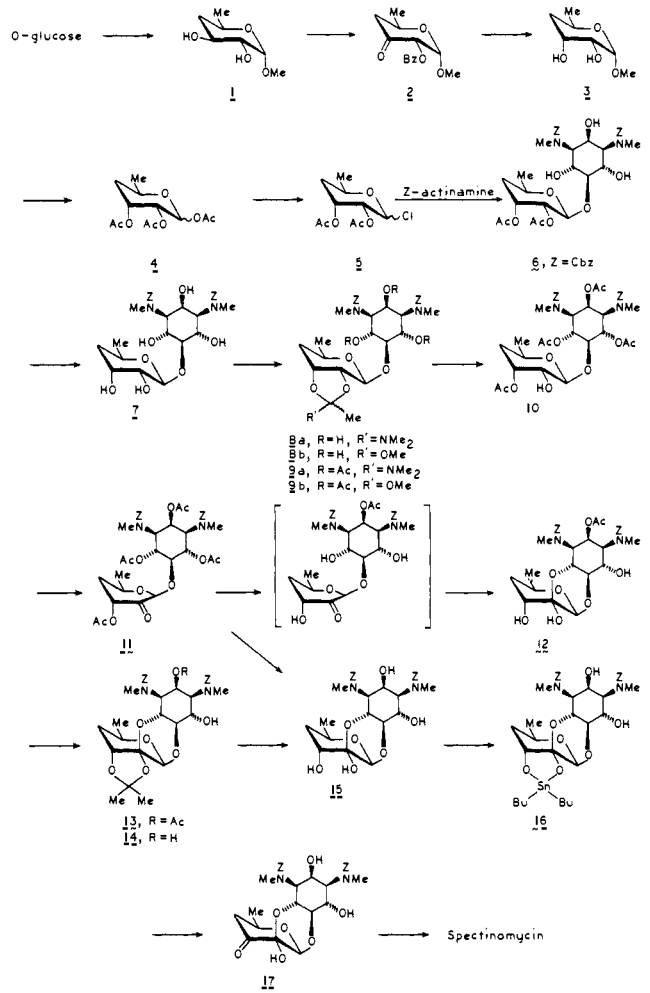
Spectinomycin (actinospectacin), isolated from a fermentation broth of *Streptomyces spectabilis* in 1961,[1] is perhaps structurally the most unique member of the medically important group of aminoglycoside antibiotics.[2] It is also endowed with an unusual biological property in that it exhibits a greater degree of therapeutic effect in infected animals than might be expected on the basis of its in vitro activities.[3] Widely used in the veterinary area, it also possesses potent activity against *Neisseria gonorrhoeae*, the gonorrhoea bacteria that has acquired resistance to penicillin and may be an alternate drug in such cases or for patients allergic to β-lactams.[4] The constitutional structure,[5] stereochemistry, and absolute configuration,[6] as well as the biosynthesis,[7] of spectinomycin have been the subject of elegant studies over the years. Its unique functional, stereochemical, and conformational features are depicted in different perspectives (Scheme I, expression I), where it can be seen that the fused tricyclic ring system contains nine chiral carbon atoms, each of which bears at least one heteroatom. A stereospecific synthesis of spectinomycin was recently disclosed by a group at Upjohn.[8] We now describe a new and stereospecific synthesis of spectinomycin, as well as of its 4(*R*)-dihydro, 4(*R*),4a(*R*)- and 4(*S*),4a(*R*)-tetrahydro derivatives, the first two being chemical precursors in the synthetic scheme leading to the antibiotic.

Our strategy called for the synthesis of one of the four[9] possible tetrahydrospectinomycins (4(*R*),4a(*R*) isomer), which

Scheme I



Scheme II



by virtue of a predisposed arrangement of hydroxyl groups was expected to provide the necessary regio- and stereocontrol in subsequent operations leading to a pivotal 4a-keto derivative of 4(*R*)-tetrahydrospectinomycin, and eventually to spectinomycin itself. With such a precursor in hand, we further expected the critical intramolecular ketalization[8] to be diastereoselective, owing primarily to a process of anomeric stereoselection.[10,11] These expectations were duly rewarded.

D-Glucose was transformed via a high-yielding sequence into the known[12] dideoxy derivative **1** (Scheme II). Sequential monobenzoylation ($(Bu_3Sn)_2O$, toluene, reflux 1 h; BzCl, room temperature, 30 min)[13] gave the known 2-benzoate, mp 103-105 °C (94%),[14] which was oxidized with pyridinium chlorochromate[15] (CH_2Cl_2, room temperature) to the 3-keto

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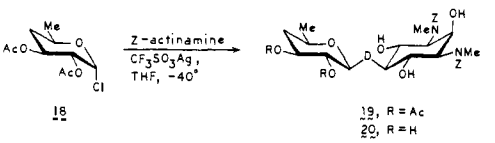
derivative **2** (quantitative), $[\alpha]_D$ +65.2°,[14,16] Borohydride reduction followed by debenzoylation gave the diol **3** (syrup), in over 70% yield. Acetolysis (Ac_2O, BF_3Et_2O)[17] gave a mixture of triacetates **4** (75%) from which the β anomer could be crystallized, mp 131.5–134 °C, $[\alpha]_D$ −53.3°. Treatment of the mixture of **4** with gaseous HCl in ether (0 °C, 2 h) gave the chloride **5** as a syrup (quantitative). Glycosidation[18] with *N,N'*-dibenzyloxycarbonylactinamine[19] (1.5 equiv; CF_3SO_3Ag, 1.5 equiv; THF, −40 °C, 4 h), followed by chromatographic separation on silica gel, gave the 1,2-trans glycoside **6** (60–65%, amorphous solid), $[\alpha]_D$ − 8.2°. Only minor quantities of stereoisomeric glycosides were formed. Deacetylation (NaOMe, MeOH, pH 8.5, room temperature) gave crystalline 5-*O*-(4,6-dideoxy-α-D-*ribo*-hexopyranosyl)-*N,N'*-dibenzyloxycarbonylactinamine (**7**, 85%), mp 190–192 °C, $[\alpha]_D$ − 31.2° (MeOH), identical with a sample prepared by conventional N-benzyloxycarbonylation of authentic 4(*R*),4a(*R*)-tetrahydrospectinomycin[9] (melting point, mixture melting point, α_D, IR, NMR, X-ray powder diffraction diagram).

Having thus obtained this essential intermediate and secured the stereochemical identity of the glycosidic linkage, we proceeded to chemically manipulate the hydroxyl groups in this molecule in such a way so as to preferentially protect all but the 4a(*R*) position (C-2 in the sugar), thereby setting the stage for oxidation and eventual intramolecular ketalization. The cis-diol unit in **7** and, more importantly, the specific axial–equatorial orientation of hydroxyl groups at the 4,4a positions proved to be a judicious choice for the synthetic operations yet to be performed, which relied on a regiospecific ring opening of the corresponding ortho amide or ortho ester derivatives to give the axial ester-equatorial alcohol.[20] Indeed, treatment of **7** with *N,N*-dimethylacetamide dimethyl acetal (CH_2Cl_2, room temperature, 4 h) or trimethyl orthoacetate (TsOH, benzene, room temperature, 1 h) gave the corresponding 1-(*N,N*-dimethylamino)ethylidene and -methoxyethylidene derivatives **8a** and **8b** respectively (quantitative), which were individually acetylated (Ac_2O, pyr DMAP, room temperature) to give the respective acetates **9a** and **9b**. Without isolation, these were subjected to mild hydrolysis (aqueous 80% AcOH, room temperature, 15 min)[20,21] to give, in either case, the crystalline tetraacetate **10**; mp 185–187 °C (85% overall from **7**); $[\alpha]_D$ −22.4°; ^1H NMR δ 1.99 (O-5, O-9 equatorial acetates), 2.05, 2.11 (O-4, O-7 axial acetates). Oxidation of **10** by an adaptation[22] of the Corey-Suggs procedure[15] (pyridinium chlorochromate, benzene, reflux, 1 h) gave the keto derivative **11**, isolated as a chromatographically homogenous amorphous solid (77%),[23] $[\alpha]_D$ −26.7°, which was used without further purification. Controlled deacetylation of **11** (NaOMe, MeOH, pH 8.5, room temperature, 2 h) gave the monoacetate **12**[11] (amorphous solid, 41%), $[\alpha]_D$ + 12.8°. Acetonation (2,2-dimethoxypropane, benzene, TsOH, 25 °C, 30 min) gave the corresponding known[11] 4,4a-acetonide **13** (quantitative) as a solid, $[\alpha]_D$ + 16°, M^+ 684, thus conclusively demonstrating the presence of the tricyclic ring structure as well as establishing the correct stereochemistry of its precursors.[24] Deacetylation (NaOMe, MeOH, pH ~12, room temperature, 3.5 h), followed by chromatographic separation from minor quantities of carbamate byproducts, gave the known[11,25] *N,N'*-dibenzyloxycarbonyl-4(*R*)-dihydrospectinomycin 4,4a-acetonide (**14**) in >85% yield (amorphous), $[\alpha]_D$ + 29.6°, reported[11] $[\alpha]_D$ + 31.17° (identical by IR, NMR). Controlled acid hydrolysis (MeOH, aqueous HCl, reflux) gave the known[25] *N,N'*-dibenzyloxycarbonyl-4(*R*)-dihydrospectinomycin (**15**) in >90% yield (amorphous solid), $[\alpha]_D$ + 25.4°, identical with an authentic specimen kindly provided by Dr. Rosenbrook (Abbott Laboratories) (α_D, IR, NMR). Alternatively, it was more expedient to subject the keto intermediate **11** to base-catalyzed deacetylation (NaOMe, MeOH, pH ~8.5, room temperature, 18 h; pH ~10, 3–4 h), where the formation of **12** and its conversion into **15** could be monitored by TLC ($CHCl_3$–MeOH, 9:1). The dihydro derivative **15**, isolated after chromatographic separation from carbamate byproducts, was identical in all respects with the material obtained via the above-described route.[26]

Scheme III



18

19, R = Ac
20, R = H

We were now in a position to address the next critical step in the sequence, namely the oxidation of **15** into *N,N'*-dibenzyloxycarbonylspectinomycin. The challenge here was to effect preferential oxidation of the 4(*R*) axial hydroxyl group in the presence of a pair of axially (C-7) and equatorially (C-9) disposed hydroxyl groups, while maintaining the structural integrity of the molecule. After exploring a number of methods, the mild oxidative conversion of alkyltin derivatives of alcohols[27] and diols[28] into carbonyls compounds was found to be admirably adaptable to our needs.[29] Treatment of **15** with dibutyltin oxide (MeOH, reflux, 1.5 h) gave the 4,4a-*O*-dibutylstannylidene derivative (syrup, quantitative) **16** which, upon treatment with a dilute solution of bromine in the presence of tributyltin methoxide (CH_2Cl_2, −10 °C, dropwise over 1 h, TLC monitoring), followed by addition of cyclohexene to destroy traces of residual bromine and precipitation with excess hexane, gave *N,N'*-dibenzyloxycarbonylspectinomycin (**17**) as an amorphous solid (92%) contaminated with traces of unreacted **15** and a compound[30] slightly less polar than **17** ($CHCl_3$–MeOH, 9:1). Purification by column chromatography gave pure **17** (70%) as an amorphous solid identical with an authentic sample (α_D, IR, NMR, ^{13}C, NMR, MS). Vital to this achievement was the original choice of a 4(*R*) axial alcohol, since, by its very nature, the cyclic stannylidene derivative **16** could only be oxidized at C-4 which has a favorably disposed equatorial hydrogen.[31] Finally, hydrogenation of **17** (5% Pd/C, H_2, 2-propanol–H_2O, room temperature, CO_2 monitoring), followed by acidification and crystallization from acetone–water, gave spectinomycin dihydrochloride pentahydrate (90%), mp 205–207 °C dec, $[\alpha]_D$ + 14.8° (H_2O), identical with an authentic sample[32] (mixture melting point, α_D, IR, NMR, X-ray powder diffraction diagram).

Our studies in this area also led us to the synthesis of *N,N'*-dibenzyloxycarbonyl-4(*S*),4a(*R*)-tetrahydrospectinomycin (**20**, Scheme III).

Thus glycosidation of 2,3-di-*O*-acetyl-4,6-dideoxy-α-D-*xylo*-hexopyranosyl chloride[33] (**18**) essentially as described for the synthesis of **6** gave, after chromatographic separation from minor periodate-sensitive products, crystalline 5-*O*-(2,3-diacetyl-4,6-dideoxy-β-D-*xylo*-hexopyranosyl)-*N,N'*-dibenzyloxycarbonylactinamine (**19**, 67%, mp 143–147 °C, $[\alpha]_D$ 0° ± 1°. Deacetylation (NaOMe, MeOH, pH 8.5, 1 h) gave crystalline **20** (87%), mp 260–265 °C, $[\alpha]_D$ −3.2° (pyr), reported[18] mp 244–246 °C, $[\alpha]_D$ −1.1° (pyr), for material obtained in 7.8% yield via a Koenigs-Knorr reaction.

The stereospecific sequence leading to spectinomycin as described in this paper can also be adapted to the synthesis of analogues, either directly or by chemical modification of intermediates at varying levels of functional and structural development.

Acknowledgment. We thank the National Research Council of Canada and le Ministère de L'Education du Québec for a fellowship to R.R. and for financial support. We also thank Daniel Delorme for skillful technical assistance and Dr. W.

Rosenbrook Jr. (Abbott Laboratories, North Chicago) for samples of dihydrospectinomycin and spectinomycin for comparison. Thanks are due to R. Mayer for recording the 90-MHz NMR spectra.

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(30) The identity of this substance (IR 1750 cm^{-1} (KBr); compare 1740 cm^{-1} for **17**) is under study. It is also formed from **15** and **17** with longer reaction times.
(31) Vicinal trans-disposed stannylidene acetals are also subject to oxidation by bromine.[28] In our case however, this would involve an axially oriented hydrogen atom at C-4 (4(*S*) isomer of **15**). Also, it is not ruled out that the C-7 and/or C-9 hydroxyl groups are transformed into alkoxytin derivatives in the treatment of **15** with Bu_2SnO, since dimeric and intermolecular structures are possible (see ref 28). Oxidation at these centers appears to be slower under our conditions presumably owing to steric reasons (at least at C-7).
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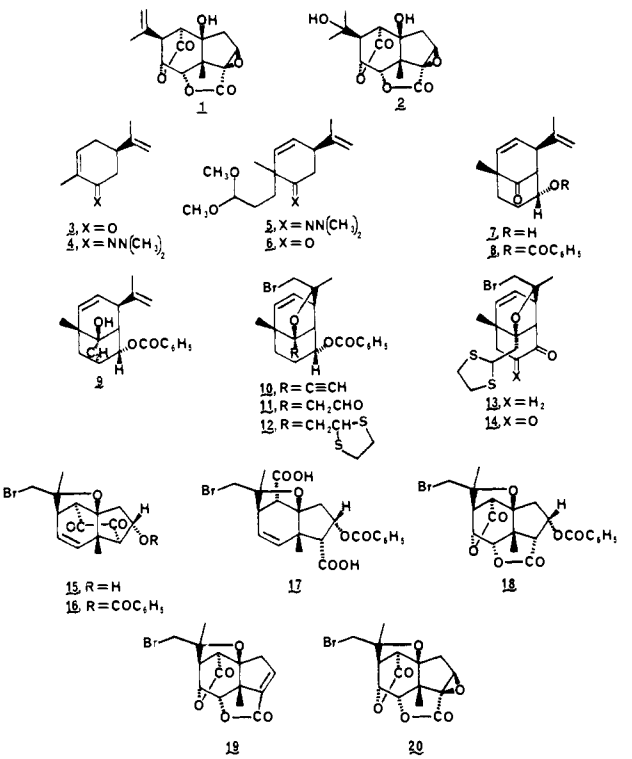
(34) NRCC and Quebec Education Ministry predoctoral fellow.

Stephen Hanessian,* René Roy[34]
Department of Chemistry, University of Montreal
Montreal, Quebec, Canada H3C 3V1
Received April 23, 1979

Total Synthesis of Picrotoxinin

Sir:

Picrotoxin, first isolated in 1811 from the berries of the plant *Menispermum cocculus*,[1] upon purification yields two closely related components, picrotoxinin (**1**) and picrotin (**2**). Despite intensive investigations, the molecular architecture of these substances remained obscure for almost 150 years, until the advent of modern techniques of structural analysis and, in particular, the brilliant and now classical investigations of Conroy,[2,3] whose conclusions were later confirmed by an X-ray crystallographic study.[4] In this report, we describe the first total synthesis of **1**, which is currently of considerable interest



because of its utility as an investigational tool in neuroscience (e.g., in antagonism of the inhibitory action of γ-aminobutyric acid (GABA) at synapses).[5] It is remarkable that there seem to have been no reports of progress toward the synthesis of picrotoxins in the literature of the past 25 years.[6]

The first step in our synthetic plan required an α-alkylation of the γ-extended enolate derived from commercially available (−)-carvone (**3**).[7] In accord with past experience,[8] we found that this type of transformation of carvone could not be realized

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