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[12] For **4b**: A red plate of **4b** ($0.25 \times 0.2 \times 0.08$ mm) was grown from dichloromethane. Data were obtained on a Bruker SMART APEX CCD diffractometer at 211 K. The structure was solved and refined by the programs SAINT+ and SHELXTX by using heavy atom (Patterson) methods. Hydrogen atoms were localized and refined in the riding mode. The crystal was fixed in a capillary. $CoC_{65}H_{53} \cdot CH_2Cl_2$ ($M_r = 977.93$); $Mo_{K\alpha}$ radiation $\lambda = 0.71073$ Å, graphite monochromator; $2\Theta_{max} = 22.50^\circ$, tetragonal, space group $I4_1$; $a = 19.156(5)$, $b = 19.156(5)$, $c = 15.842(7)$ Å, $V = 5814(3)$ Å^3, $Z = 48$, $\rho_{calcd} = 1.117$ g cm^{-3}, $\mu = 0.424$ mm^{-1}, 12129 reflections were measured and 4807 reflections with $I > 2\sigma(I)$ observed, $R = 0.0491$, $R_w = 0.1031$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-154093. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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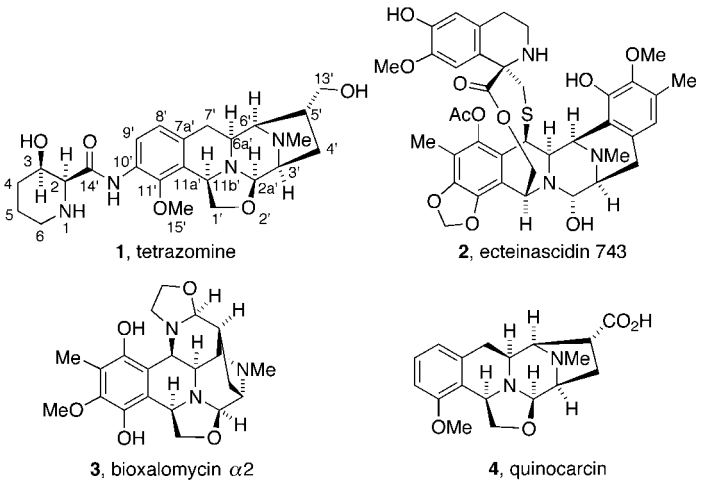
Total Synthesis of (−)-Tetrazomine and Determination of Its Stereochemistry**

Jack D. Scott and Robert M. Williams*

Dedicated to Professor K. Barry Sharpless on the occasion of his 60th birthday

The antitumor antibiotic tetrazomine **1** was isolated from *Saccharothrix mutabilis* at the Yamonouchi Pharmaceutical company by Suzuki et al.[1] Tetrazomine is a member of the tetrahydroisoquinoline family of antitumor antibiotics that



includes ecteinascidin 743 (**2**),[2] bioxalomycin $\alpha 2$ (**3**),[3] and quinocarcin (**4**).[4] Tetrazomine most closely resembles quinocarcin, except for the amino functionality at C10′, the unusual β-hydroxy pipecolic acid moiety, and the oxidation state of C13′. Neither the relative nor the absolute stereochemistry of tetrazomine were determined when the structure was initially reported.[1b] We have since determined that the absolute stereochemistry of the pipecolic acid moiety is 2*S*,3*R*.[5]

Preliminary antitumor/antimicrobial assays of tetrazomine revealed that this substance possesses activity against P388 leukemia in vivo and good antimicrobial activity against both Gram-negative and Gram-positive bacteria.[1a] Tetrazomine exerts its cytotoxic activity through oxidative damage to DNA by the superoxides formed in the auto-redox disproportionation of the fused oxazolidine, and possibly through DNA alkylation.[6]

The total synthesis of tetrazomine has not been reported in the literature,[7] although the synthesis of the AB-ring system of tetrazomine has been discussed by Ponzo and Kaufman.[8] Herein, we describe the first total synthesis of (−)-tetrazo-

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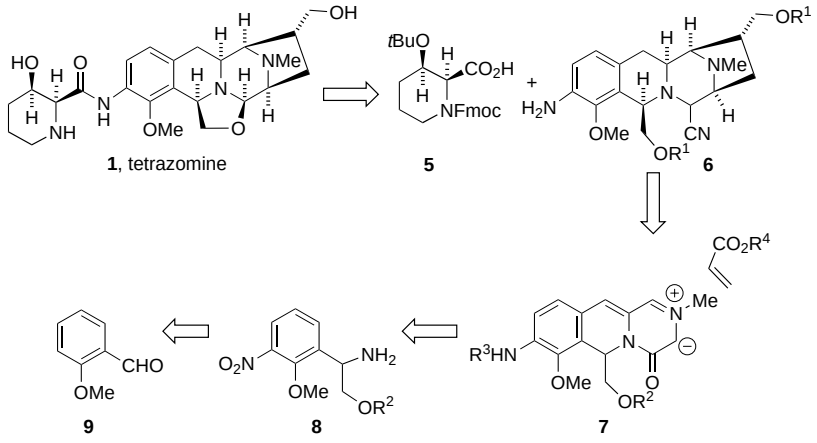
mine and the determination of its relative and absolute stereochemistry.

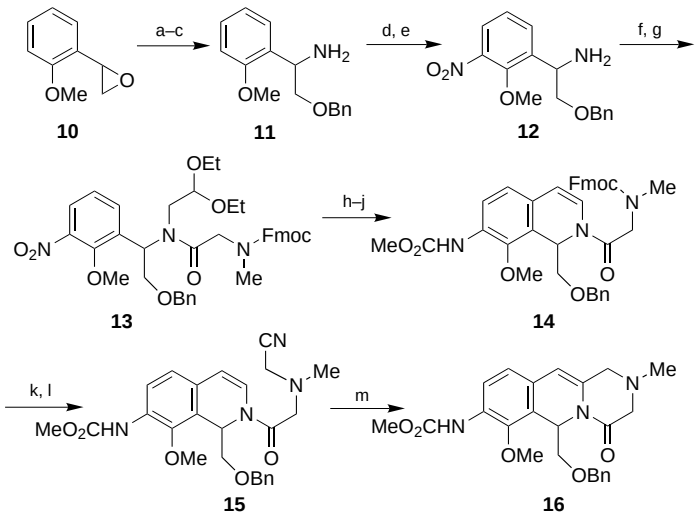
A retrosynthetic disconnection of tetrazomine included the late-stage coupling of the protected β-hydroxypipecolic acid **5**[9] to the aniline **6** (Scheme 1). The aniline was to be derived from a 1,3-dipolar cycloaddition to the azomethine ylide of tricycle **7** using a methodology developed in our laboratories.[7e] Substance **7** could in turn be obtained from the trisubstituted nitroaromatic **8**, which would ultimately be derived from *ortho*-anisaldehyde (**9**).



Scheme 1. Retrosynthesis of tetrazomine (**1**). Fmoc = (9*H*-fluoren-9-ylmethoxy)carbonyl.

The synthesis began with the regioselective opening of the previously described[10] epoxide **10** with sodium azide (Scheme 2). The resulting primary alcohol was protected as the benzyl ether, and the azide was hydrogenated to afford amine **11**. Selective nitration *ortho* to the methoxy group was accomplished at low temperature by using potassium nitrate and trifluoroacetic anhydride (TFAA).[8] Hydrolysis of the trifluoroacetamide afforded amine **12**. Alkylation of the primary amine with bromoacetaldehyde diethylacetal was followed by coupling with *N*-Fmoc-sarcosine acid chloride to yield amide **13** in 82% yield. The nitro group was hydrogenated by using platinum oxide to afford the aniline derivative necessary for acid-promoted cyclization onto the acetal.[7a, 8] The aniline was then protected as the methyl carbamate to afford **14** in 92% yield from **13**. Removal of the Fmoc group was followed by amine alkylation with iodoacetonitrile to yield aminonitrile **15** in 93% yield over the two steps. Attempted iminium cyclization to form tricyclic **16** by using $AgNO_3$[11] or $AgBF_4$[12] afforded no desired product. After extensive experimentation, it was found that treatment of **15** with silver(I) trifluoroacetate in the presence of trifluoroacetic acid (TFA) and trifluoroacetic anhydride afforded the tricycle **16** in 93% yield.

Treatment of allylic amine **16** with *N*-bromosuccinimide (NBS) in refluxing chloroform[7e] yielded the corresponding iminium ion species that upon deprotonation with triethylamine afforded the azomethine ylide **17** (see **7**, Scheme 1), which was trapped by *tert*-butyl acrylate to afford a 3.9:1 mixture of separable cycloadducts **18** and **19**, respectively (Scheme 3).



Scheme 2. Synthesis of tricyclic precursor **16**. Reagents and conditions: a) NaN_3, acetone/H_2O, Δ; b) NaH, THF; BnBr, KI (94%, two steps); c) H_2, Pd/C, EtOH (87%); d) KNO_3, TFAA, CH_2Cl_2, $-20\,^{\circ}C$; e) LiOH (2M), EtOH,(56%, two steps); f) bromoacetaldehyde diethylacetal, K_2CO_3, MeCN, Δ (74%); g) *N*-Fmoc-sarcosine-Cl, DMAP, pyridine, CH_2Cl_2 (82%); h) H_2 (60 psi (414 kPa)), PtO_2, EtOH/THF; i) HCl (6M), dioxane, $90\,^{\circ}C$; j) MeOCOCl, pyridine, CH_2Cl_2, $4\,^{\circ}C$ (92%, three steps); k) pyrrolidine, MeCN (94%); l) ICH_2CN, iPr$_2$NEt (99%); m) $AgOCOCF_3$, TFA, TFAA, $ClCH_2CH_2Cl$, Δ (93%).

Tetracycle **19** was hydrogenated in the presence of Raney-nickel at a moderate pressure, which resulted in the removal of the benzyl group and reduction of the benzylic olefin from the least hindered face to afford **20**. The major product from the cycloaddition, **18**, possessed the undesired configuration at C11b′, thus an epimerization at C11b′ was executed. After hydrogenation, the resulting alcohol was oxidized to the aldehyde. Treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded a 1.4:1 mixture of epimers at C-11b′ with the desired isomer as the predominant product. These aldehydes were easily separated by column chromatography, thus allowing the undesired epimer to be recycled. Sodium borohydride reduction of the desired epimer afforded alcohol **20**.

The simultaneous reduction of the *tert*-butyl ester group and partial reduction of the lactam were fortuitously accomplished in a single step by using $LiAlH_3OEt$ in THF at $0\,^{\circ}C$. The resulting methanolamine was trapped with potassium cyanide under acidic conditions[13] to afford the corresponding stable aminonitrile. The relative stereochemistry of this product was determined by extensive 2D NMR studies. The two primary alcohols were protected as their triisopropylsilyl (TIPS) ethers, and the methyl carbamate was hydrolyzed to afford aniline **21**. The optically active acid chloride of **5**[9] was prepared by using oxalyl chloride, and was coupled to **21** in the presence of 4-dimethylaminopyridine to afford the corresponding pipecolamide (plus a separable diastereomer, which was identified as the *ent*-tetrahydroisoquinoline portion; obtained as a 1:1 mixture of optically active diaster-

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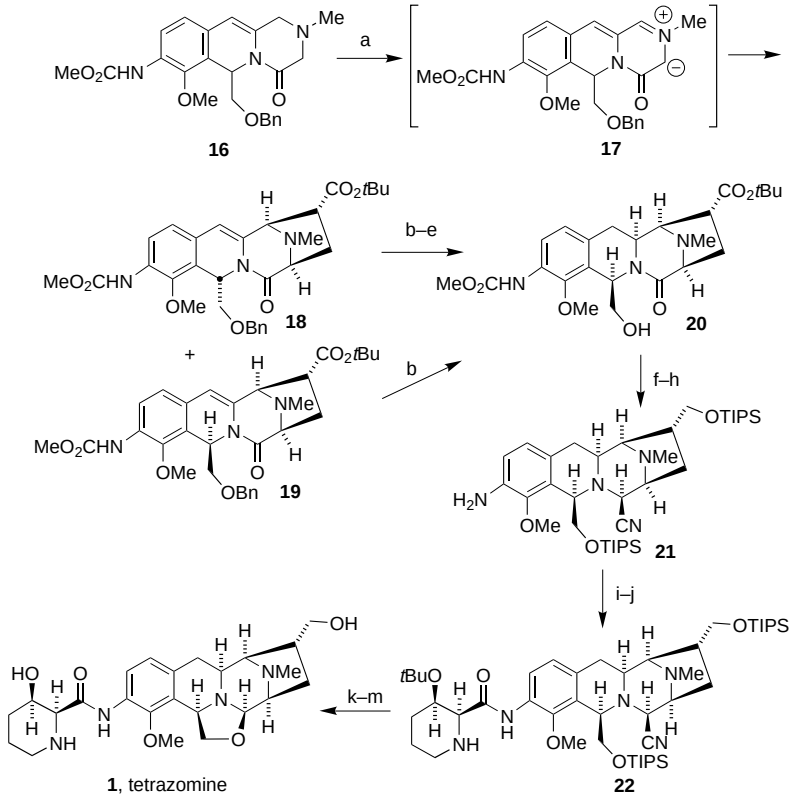

Scheme 3. Synthesis of tetrazomine (**1**). Reagents and conditions: a) NBS, $CHCl_3$, Δ; *tert*-butyl acrylate, Et_3N, 0 °C to room temperature, **18** (35 %), **19** (9 %); b) H_2 (100 psi (689 kPa)), Raney-Ni, EtOH (90 %); c) Swern oxidation (98 %); d) DBU, THF, (55 % + 38 % starting material); e) $NaBH_4$, EtOH (89 %); f) $LiAlH_3OEt$, THF, 0 °C; KCN, AcOH, 0 °C to room temperature (69 %); g) TIPSCl, imidazole, DMF (92 %); h) 2 M LiOH, EtOH, Δ, (63 %); i) **5**, oxalyl chloride, DMF, CH_2Cl_2; **21**, DMAP, CH_2Cl_2; j) DBU, CH_2Cl_2 (72 %, two steps); k) TFA, 4 °C, (53 %); l) HF, MeCN (82 %); m) $AgOCOCF_3$, TFA, $MeOH/H_2O$; Dowex (Cl^-) (61 %).

eomers). The intermediate pipecolamide was treated with DBU to cleave the Fmoc group, thus furnishing **22**.

To determine which diastereomer would lead to tetrazomine, natural tetrazomine was treated with sodium cyanide to afford 2a′-α-cyanotetrazominol, which was compared to the synthetic diastereomeric products of the cleavage of the *tert*-butyl ether and silyl ethers of **22** and its diastereomer. As expected, one diastereomer afforded a product that had identical spectral data to the naturally derived substance. With this comparison, the relative stereochemistry of the pentacyclic core of tetrazomine was established. Based on biosynthetic considerations, the absolute configuration of the tetrahydroisoquinoline core is assumed to be that depicted in structure **1**, since quinocarcin, bioxalomycin, and ecteinascidin possess the same absolute configuration of the tetrahydroisoquinoline moiety.

After removal of the protecting groups, precursor **22** was treated with silver(I) trifluoroacetate in the presence of TFA for four hours to furnish the intact oxazolidine ring. The addition of Dowex (Cl^-), followed by filtration and lyophilization afforded (−)-tetrazomine · 2 HCl, which after purification by HPLC exhibited identical spectral characteristics to those of the natural product. The chemistry described herein is currently being extended to the preparation of several mechanistically inspired analogues for biochemical and biological evaluation, and will be reported in due course.

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