Structure assignment of aminoconduritols by ^{15}N NMR correlation spectroscopy; synthesis of a positional isomer of 7-deoxypancratistatin

Stefan Schilling, Uwe Rinner, Collin Chan, Ion Ghiviriga, and Tomas Hudlicky

Abstract: A positional isomer of 7-deoxypancratistatin was synthesized in 12 steps from epoxyaziridines **4** and **5**. An intermolecular opening of the aziridine rather than the epoxide in the early stages of the synthesis led to **13**, which did not match the properties of tetraacetate **10** derived from 7-deoxypancratistatin. At no stage of the synthesis did standard NMR techniques, involving ^{1}H–^{1}H or ^{1}H–^{13}C coupling, prove adequate for the structure assignment. Unambiguous structure was assigned by ^{1}H–^{15}N correlation NMR spectroscopy as well as by the conversion of epoxide **11** to diol **29** synthesized independently by another route. Experimental and spectral details are reported for all new compounds.

Key words: ^{15}N NMR spectroscopy, iso-7-deoxypancratistatin, Lewis acid catalyzed intramolecuar opening of epoxides, aminoconduritols.

Résumé : On a synthétisé un isomère de position de la 7-désoxypancrastistatine en douze étapes à partir des époxyaziridines **4** et **5**. Au cours des premières étapes de la synthèse, une ouverture intermoléculaire de l'aziridine à la place d'une ouverture de l'époxyde a conduit au produit **13** dont les propriétés ne correspondent pas à celles du tétraacétate **10** qui dérive de la 7-désoxypancratistatine. Les techniques normales de RMN impliquant les couplages ^{1}H–^{1}H ou ^{1}H–^{13}C ne se sont avérés adéquates pour faire des attributions de structures. La structure a été attribuée sans ambiguïté par spectroscopie RMN de corrélation ^{1}H–^{15}N ainsi que par conversion de l'époxyde **11** en diol **29** qui a été synthétisé de façon indépendante par une autre voie. On rapporte les détails expérimentaux et les spectres de tous les nouveaux composés.

Mots clés : spectroscopie ^{15}N RMN, iso-7-désoxypancratistatine, ouverture intramoléculaire d'époxydes catalysée par un acide de Lewis, aminoconduritols.

[Traduit par la Rédaction]

Introduction

Several total syntheses of the Amaryllidaceae alkaloids have been recently completed by our research group and by others (1–4). We have reported the first asymmetric synthesis of pancratistatin (1*b*, *c*), as well as brief routes to lycoricidine (4*j*), 7-deoxypancratistatin (2*c*), *ent*-7-deoxypancratistatin (5), and narciclasine (3*b*). Attempting to improve on the 14-step preparation of pancratistatin, which featured an intermolecular aziridine opening by an aryl cuprate (2*c*), we chose to pursue what appeared to be a more efficient strategy based on a novel intramolecular opening of the aziridine in **3**, Fig. 1.

Our strategy, shown in Fig. 1, relies on the availability of epoxyaziridines **4** and **5**, which can be rapidly synthesized from the commercially available diene **8** by established methods (6). Stereoelectronic considerations indicate that the nucleophilic opening of either isomer of epoxide with piperonol **6** followed by alkylation of the resulting alcohol with piperonyl bromide **7** will provide an intermediate in which both oxygens bear identical functionality. Such redundant operations (7) greatly improve the practicality of a synthesis because no attention need be paid either to the control of stereochemistry at the intermediate stage or to the separation of the isomers of epoxides **4** and **5**. Lewis acid catalyzed aziridine opening, oxidation, and recyclization would lead to the phenanthridine core of the alkaloid. We are aware of only three previous examples of intramolecular opening of aziridines (8) before we applied the technique to our synthesis, which is conceptually similar to the opening of the epoxide derived from *myo*-inositol as reported by Bender (9).

In this paper we report the synthesis of tetracetate **13,** a positional isomer of **10**, shown in Fig. 2. The latent func-

Received February 22, 2001. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on November 12, 2001.

Dedicated to Professor Victor A. Snieckus in recognition of his contributions to synthetic organic chemistry.

S. Schilling, U. Rinner, C. Chan,[1] I. Ghiviriga,[2] and T. Hudlicky.[3] Department of Chemistry, University of Florida, Gainesville, Fl 32611, U.S.A.

[1]NSF REU participant, Summer 2000.
[2]Author to whom correspondence regarding NMR work may be addressed (telephone: (352) 846- 3001; fax: (352) 846-3001; e-mail: ion@chem.ufl.edu).
[3]Corresponding author (telephone: (352) 392-9844; fax: (352) 846-1203; e-mail: hudlicky@chem.ufl.edu).

 DOI: 10.1139/cjc-79-11-1659

Fig. 1. Design of synthesis.

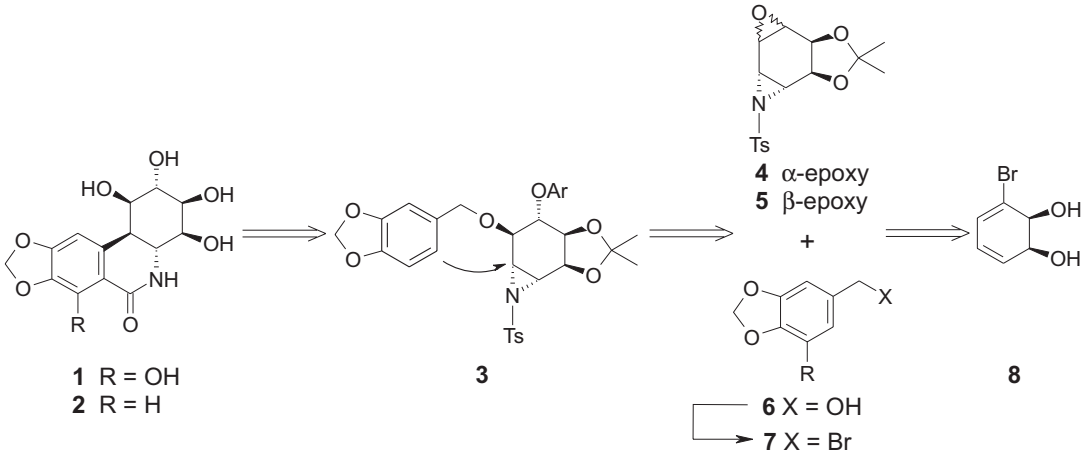
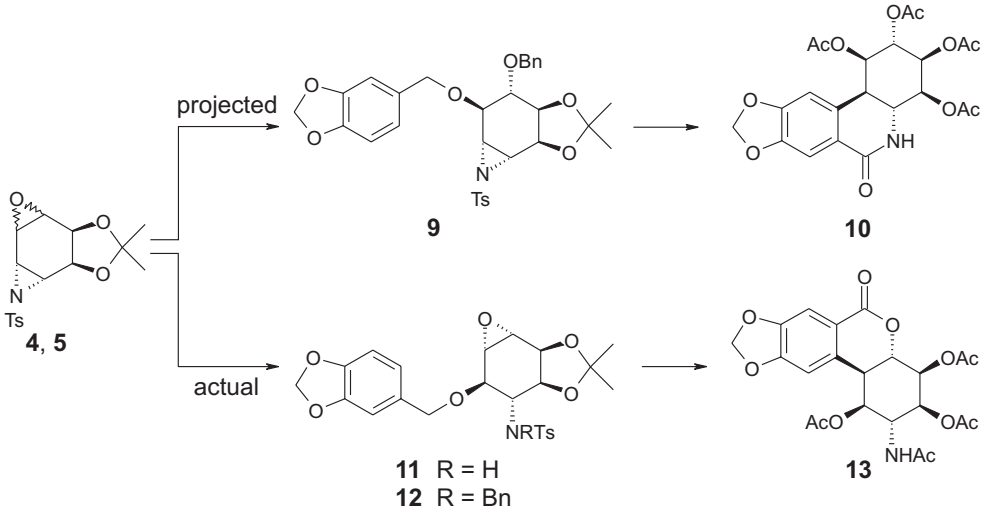


Fig. 2. Pathway to positional isomer of 7-deoxypancratistatin.



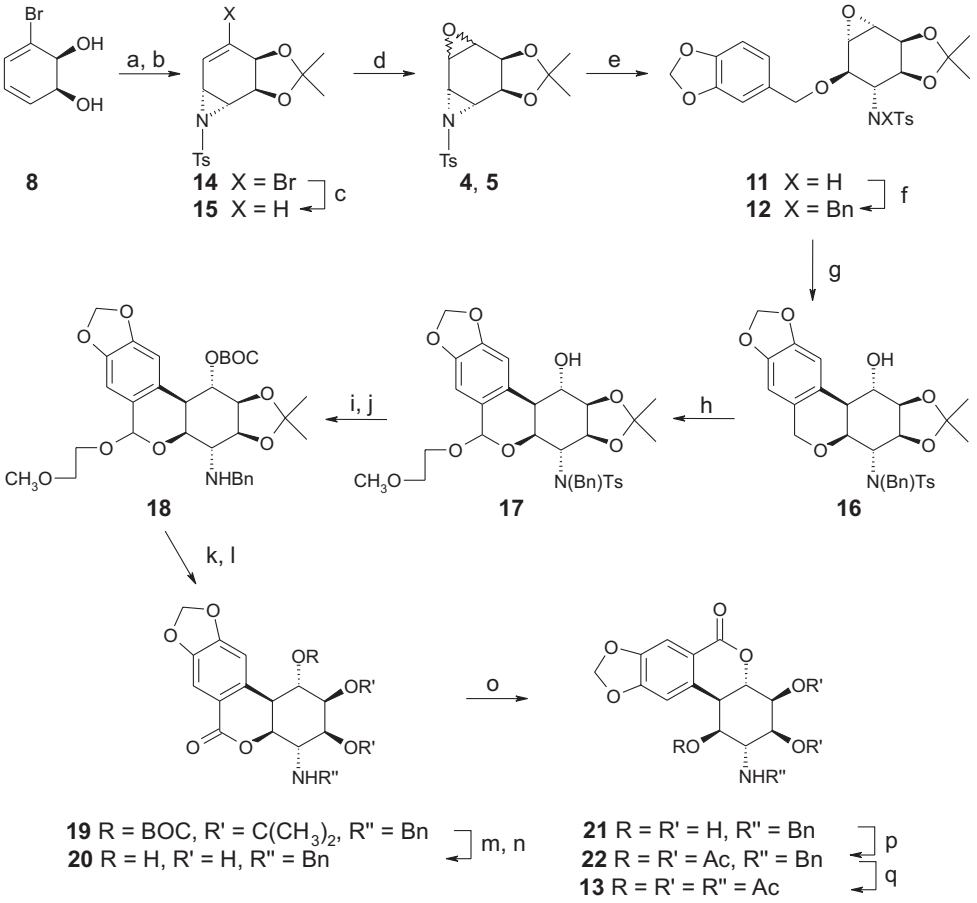
tional symmetry of epoxyaziridines **4** and **5** and their tendency to react with nucleophiles made structural assignment difficult throughout the synthesis. The inherent difficulties in precise stereochemical and regiochemical assignments in all intermediates propagated the errors resulting from the initial incorrect assignment of regiochemistry in the opening of aziridines **4** and **5** under basic conditions. A full structural correlation is reported along with experimental details for the preparation of tetraacetyl aminolactone **13**.

Results and discussion

Enantiomerically pure diol **8** was obtained by whole-cell biooxidation with recombinant *E. coli* JM109 (pDTG601) according to the established procedure (10). Diol **8** was protected as its acetonide and then reacted with (*N*-tosylimino)phenyliodinane according to the protocol established by Evans et al. (11*a*) and Jacobsen and co-workers (11*b*) to produce aziridine **14** in 45% overall yield (1*c*), as shown in Scheme 1. Dehalogenation of **14** with *n*-Bu_3SnH–THF generated vinylaziridine **15** (1*c*), which was subsequently oxidized (*m*CPBA, 1,2-dichloroethane, 85°C) to furnish an inseparable mixture (2.6:1) of α- and β-epoxyaziridines **4** and **5**, respectively. In our group, earlier work on nucleophilic opening of this material indicated that carboxylate salts (12) opened the epoxide under slightly basic conditions and that alcohols (13) under $BF_3{\cdot}Et_2O$ catalysis also opened the epoxide with the aziridine ring intact. Following this precedent, the potassium salt of piperonol was reacted with the epoxyaziridines **4** and **5** and the product subjected to benzylation. Spectroscopic evidence, as presented below, suggested that compound **9** had been obtained, and therefore the rest of the synthesis was carried out. However, the compound, isolated in 71% yield as a single isomer, turned out to be epoxide **12**, ascertained only at the end of the synthesis when tetracetate **13** was identified.

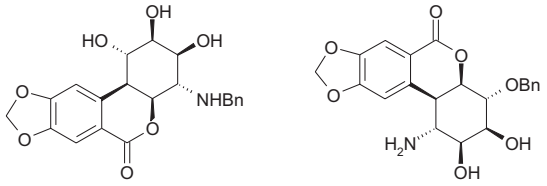
The analysis of ^1H NMR spectra of conduramine and conduritol derivatives is not trivial, viz. the patterns of epoxy vs. aziridinyl methines and the chemical shift differences between *O*-benzyl vs. *N*-benzyl groups in structures where various shielding parameters could lead to pronounced shifts of the benzylic protons. This error in structure assignment was propagated through 12 steps without detection or ambiguity. The functional symmetry of epoxy aziridines **4** and **5** and the difficulty in deciphering the outcome of the first step contributed to the error.

Scheme 1. Reagents and conditions: (*a*) DMP, *p*-TSA (cat.), acetone, rt; (*b*) PhI=NTs, $Cu(acac)_2$, CH_3CN, rt, 63% (over 2 steps); (*c*) Bu_3SnH, AIBN, THF, reflux, 78%; (*d*) *m*CPBA, $C_2H_4Cl_2$, reflux, 80%; (*e*) potassium piperonoxide, 18-C-6, DME, rt; (*f*) (*i*) NaH, THF, (*ii*) BnBr, Bu_4NI, rt, 71% (over 2 steps); (*g*) Me_2AlCl, CH_2Cl_2, –25°C, 77%; (*h*) DDQ, 2-methoxyethanol, CH_2Cl_2, rt, 78%; (*i*) NaH, $(BOC)_2O$, THF, reflux; (*j*) Na–naphthalene, DME, –50°C, 85% (over 2 steps); (*k*) CSA, THF, H_2O, rt; (*l*) PCC, CH_2Cl_2, rt, 72% (over 2 steps); (*m*) $C_6H_5CO_2Na$, MeOH–H_2O, reflux; (*n*) *p*-TsOH, MeOH, 84% (over 2 steps); (*o*) K_2CO_3, MeOH, 44%; (*p*) Ac_2O, DMAP, pyridine, 61%; (*q*) (*i*) H_2, $Pd(OH)_2$, MeOH, (*ii*) Ac_2O, DMAP, pyridine, 55% (over 2 steps).



The actual sequence of steps was as follows: treatment of piperonyl ether **12** with Me_2AlCl resulted in cyclization to pentacycle **16** in 77% yield. Benzylic oxidation of ether **16** by means of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of 2-methoxyethanol gave acetal **17** in 78% yield. Acylation of acetal **17** followed by reductive detosylation (sodium–naphthalene–DME) generated acetal **18** in 85% overall yield. Deprotection of the acetal followed by oxidation of the resulting lactol provided lactone **19** in 72% yield. Removal of the carbamate by thermolysis followed by deketalization gave amino diol **20**, which upon hydrolysis (K_2CO_3–methanol) furnished lactone **21** in 44% yield.

The last stages of the synthesis were reached with what we thought to be lactone **23**, to which the conditions of Paulsen (2*b*) were applied for the final lactone–lactam interconversion, a sequence driven by the greater stability of the *trans*-fused lactam. Following this rearrangement, a protocol for debenzylation was carried out, ultimately leading to the isolation of a compound whose tetraacetate provided ^1H NMR remarkably similar to the ^1H NMR of the known tetraacetate of 7-deoxypancratistatin (2*c*), but whose R_f value in thin layer chromatography was lower by 0.6. The interesting point here is that lactone **20** did isomerize to the more stable lactone **21**, with distinctly different chromatographic and spectral properties; at the time we assumed that we were observing the expected equilibrium-driven transformation to the lactam.

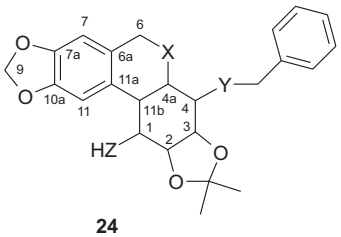


^1H NMR, ^{13}C NMR, and other analytical methods failed to confirm the structure of this material, which had evidently undergone a lactone rearrangement of some kind. An unambiguous assignment was finally made by means of ^{15}N HMQC spectroscopy, described in the next section.

Assignment of regio- and stereochemistry of tosylamide 16

Throughout the synthesis, 2D NMR was employed to confirm the structural integrity of key compounds, namely **16**,

19, and **21**. However, the $^1H–^1H$ couplings and NOE's, and the one-bond and long-range $^1H–^{13}C$ couplings fail to discriminate between compounds from the projected and actual series. In the case of compound **16** for instance, the $^1H–^1H$ and $^1H–^{13}C$ correlations indicate functionalized benzophyranyl system **24**, where X, Y, and Z are two O atoms and one NTs group. Uncertainty arises because there can be no $^1H–^{13}C$ long range coupling between atoms in the tosyl group and atoms at its point of attachment.



24

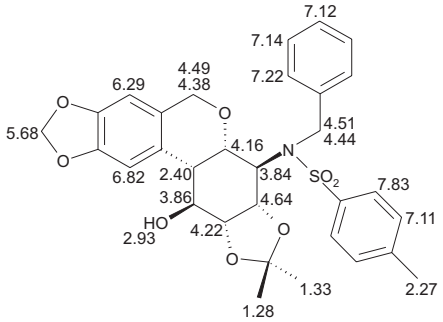
Formula **24** describes a compound in the projected series for X, Y = O and Z = NTs, as well as the actual **16**, for X, Z = O and Y = NTs. The same ambiguity is seen in compound **17**; however, compounds produced after the reductive detosylation step possess a proton attached to nitrogen, which in theory can be used to reveal the location of the trivalent nitrogen. In reality though, fast exchange with residual water in the sample precluded the observation of any coupling of this proton and even of its chemical shift for both **18** and **19**. The peracetylated derivative of **20** (R = R′ = R″ = Ac) displayed coupling of the NH proton with the proton in position 4 and not with the proton in position 1 as expected, thus revealing that the compounds synthesized were different from the projected ones.

Direct evidence for the structure of compound **16** came from the long-range $^1H–^{15}N$ couplings, revealed by the gHMBC spectrum at natural abundance (Fig. 3). Enough sample for the experiment was obtained by repeating the synthesis to provide 100 mg of tosylamide **16**. The nitrogen signal at 277.9 ppm on the nitromethane scale displayed cross-peaks with the benzylic protons (4.44 and 4.51 ppm) and the proton at 4.16 ppm of the cyclohexyl unit.

Chemical proof via structure correlation

In addition to the evidence for the structure of tosylamide **16** based on spectroscopy, including $^1H–^{13}C$ as well as $^1H–^{15}N$ correlation experiments, its structural integrity was confirmed through an independent synthesis. As illustrated in Scheme 2, opening of vinylaziridine **15** with the potassium salt of piperonol generated tosylamide **25**, which was converted to olefin **26** following benzylation. Stereoselective dihydroxylation of the olefin furnished *cis*-diol **27**; moreover, opening of epoxide **12**, derived from opening of the mixture of epoxyaziridines **4** and **5**, with hydroxide provided the *trans*–diol **28**. Cleavage of the diol functionalities in both tosylamides **27** and **28** gave rise to the corresponding dialdehydes, which upon reduction afforded *N*-benzyl tosylamide **29**, whose spectral and physical properties (^1H NMR, R_f, mass spectrum fragmentation pattern) were identical for the materials obtained by two independent synthetic routes.

Fig. 3. Proton assignment of tosylamide **16**.



16

Conclusion

The latent functional symmetry of epoxyaziridines **4** and **5** made it difficult to differentiate clearly the outcome of the initial nucleophilic opening of either of the three-membered rings. Standard structural assignment could not distinguish between the two regioisomers during a 12 step synthesis until a physical match was made. Philosophically, this case should raise interesting questions about the global probability of similar errors, undetected because of limited or nonexisting comparisons of physical properties, in today's literature.

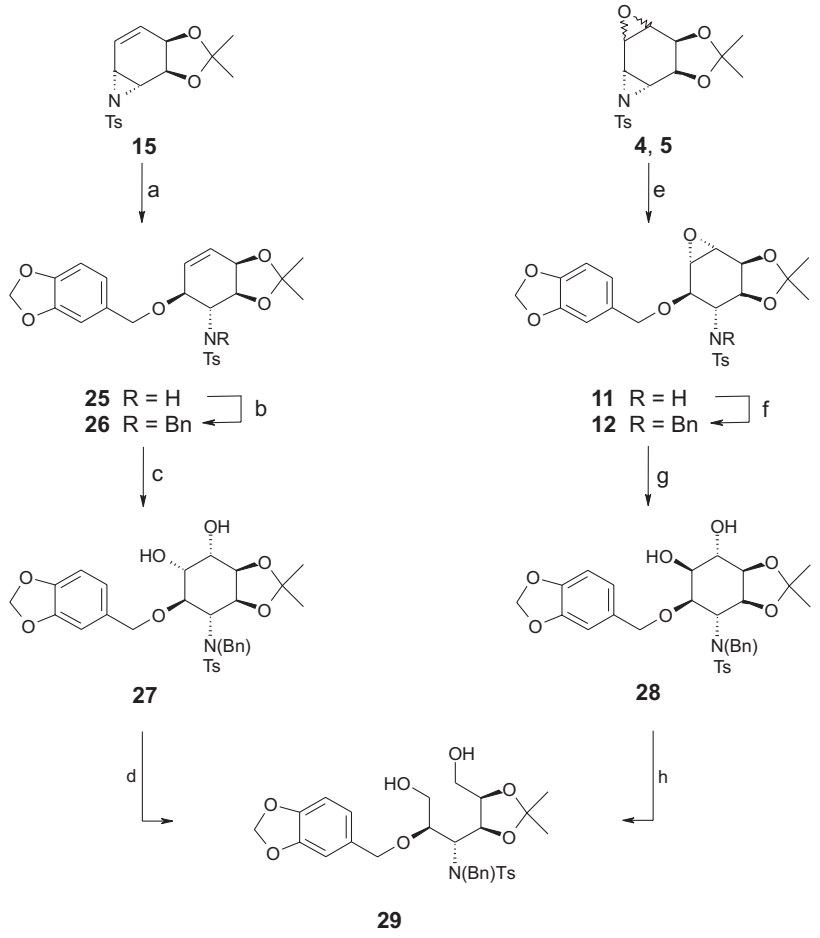
Experimental

All reactions were carried out in an argon atmosphere with standard techniques for the exclusion of air and moisture. Glassware used for moisture-sensitive reactions was flame-dried under vacuum. Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were distilled from sodium benzophenone ketyl. Dichloromethane and 1,2-dichloroethane were distilled from calcium hydride. Reactions were monitored by thin layer chromatography on K6F silica gel (Whatman) plates. Flash column chromatography was performed on Merck silica gel (grade 60, 230–400 mesh). Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared spectra were obtained on a PerkinElmer 1600 Series FT-IR spectrometer. High resolution mass spectra (HRMS) were measured on a Finnigan Mat 95Q mass spectrometer. Nuclear magnetic resonance spectra were recorded on either a Varian VXR-300, Gemini 300, or Inova 500 FT NMR spectrometer in $CDCl_3$ unless otherwise noted. Coupling constants are measured in Hertz and chemical shifts are reported in ppm downfield from tetramethylsilane. Optical rotations were measured on a PerkinElmer model 341 polarimeter.

(1*S*,2*S*,4*R*,5*S*,6*S*,7*S*)-5,6-(Isopropylidenedioxy)-3-(4′-methylphenylsulfonyl)-8-oxa-3-aza-tricyclo[5.1.0.0]octane (4) and (1*R*,2*S*,4*R*,5*S*,6*S*,7*R*)-5,6-(isopropylidenedioxy)-3-(4′-methylphenylsulfonyl)-8-oxa-3-aza-tricyclo[5.1.0.0]-octane (5)

To a degassed solution of aziridine **15** (2.18 g, 6.79 mmol) in 1,2-dichloroethane (70 mL) was added *m*CPBA (8.37 g, 70%, 34.0 mmol) along with 3-*tert*-butyl-4-hydroxy-5-

Scheme 2. Reagents and conditions: (*a*) potassium piperonoxide, 18-C-6, DME, rt, 56%; (*b*) (*i*) NaH, THF, (*ii*) BnBr, Bu_4NI, rt, 84%; (*c*) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, CH_3CN, EtOAc, 0°C, 66%; (*d*) (*i*) $NaIO_4$, CH_3COCH_3, H_2O, (*ii*) $NaBH_4$, MeOH, rt, 52% (over 2 steps); (*e*) potassium piperonoxide, 18-C-6, DME, rt; (*f*) (*i*) NaH, THF, (*ii*) BnBr, Bu_4NI, rt 71%; (*g*) KOH, H_2O, 1,4-dioxane, reflux, 56%; (*h*) (*i*) $NaIO_4$, CH_3COCH_3, H_2O, (*ii*) $NaBH_4$, MeOH, rt, 49% (over 2 steps).



methylphenyl sulfide (1.21 g, 3.40 mmol) as a radical inhibitor. The resulting solution was heated at reflux for 12 h. After allowing the solution to cool to room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed sequentially with saturated $NaHSO_3$ and saturated $NaHCO_3$ solution. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by chromatography (10% deactivated silica gel, hexanes – ethyl acetate, 4:1) to give a mixture of epoxyaziridines **4** and **5** (1.83 g, 80%) as a white solid; mp 107–108°C. $[\alpha]_D^{28}$ –56.5 (*c* 0.8, $CHCl_3$). R_f = 0.43 (hexanes – ethyl acetate, 2:1) FAB-HRMS calcd. for $C_{16}H_{20}NO_5S$: 338.1062; found: 338.1061. IR (neat) (cm^{-1}): 3000, 1595, 1330, 1255, 1158, 1082. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.84 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 4.36 (d, *J* = 5.7 Hz, 1H), 4.24 (d, *J* = 6.3 Hz, 1H), 3.53 (t, *J* = 3.6 Hz, 1H), 3.37 (dd, *J* = 6.8, 3.8 Hz, 1H), 3.12 (dd, *J* = 3.3, 1.2 Hz, 1H), 3.03 (dd, *J* = 6.9, 1.2 Hz, 1H), 2.45 (s, 3H), 1.44 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 144.8, 134.1, 129.6, 127.7, 109.9, 70.6, 69.5, 49.9, 46.5, 37.1, 35.4, 27.2, 25.0, 21.5. Anal. calcd. for $C_{16}H_{19}NO_5S$: C 56.97, H 5.68, N 4.56; found: C 57.37, H 5.96, N 3.72.

N-Benzyl-*N*-[(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-2-(benzo[1,3]dioxolo-5-ylmethoxy)-4,5-(isopropylidenedioxy)-7-oxa-bicyclo-[4.1.0]hept-3-yl]-4′-methylbenzenesulfonamide (12)

To a suspension of KH (757 mg, 18.9 mmol) in DME (12 mL) was added a solution of piperonol (2.51 g, 16.5 mmol) in DME (7 mL), and the mixture was stirred for 20 min. A solution of epoxyaziridine **4**, **5** (1.59 g, 4.72 mmol) in DME (8 mL) was added dropwise followed by the addition of 18-crown-6 (436 mg, 1.65 mmol). The resulting solution was stirred for 20 h. The reaction was quenched with saturated NH_4Cl solution and the reaction mixture was extracted with CH_2Cl_2 (4 × 75 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to provide **11**, which was used without further purification. A solution of the remaining residue in THF (35 mL) was added dropwise to a suspension of NaH (841 mg, 35.0 mmol) in THF (35 mL). The solution was stirred for 20 min, then benzyl bromide (4.30 mL,

36.2 mmol) was added followed by a catalytic amount of tetrabutylammonium iodide. The solution was allowed to stir for 44 h and then quenched with water. The reaction mixture was extracted with ethyl acetate (4 × 60 mL), and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by chromatography (silica gel, hexanes – ethyl acetate, 5:1) to provide epoxide **12** (1.40 g, 71%) as a white solid; mp 63–65°C. $[\alpha]_D^{26}$ –6.9 (*c* 1.0, $CHCl_3$). R_f = 0.27 (hexanes – ethyl acetate, 3:1) FAB-HRMS calcd. for $C_{31}H_{34}NO_8S$: 580.2005; found: 580.2050. IR (KBr) (cm^{-1}): 2987, 1492, 1445, 1251, 1036. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.82 (d, *J* = 8.0 Hz, 2H), 7.18–7.10 (m, 7H), 6.81–6.79 (m, 3H), 5.99 (s, 2H), 4.54–4.48 (m, 2H), 4.31–4.26 (m, 2H), 4.16–4.04 (m, 3H), 3.38 (d, *J* = 3.3 Hz, 1H), 3.30 (d, *J* = 3.0 Hz, 1H), 2.40 (s, 3H), 1.46–1.33 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.7, 147.4, 142.8, 138.0, 136.4, 130.9, 129.0, 128.7, 128.3, 128.2, 127.6, 122.1, 110.1, 109.2, 108.0, 101.0, 72.7, 71.3, 57.2, 52.1, 27.3, 25.6, 21.5. Anal. calcd. for $C_{31}H_{33}NO_8S$: C 64.23, H 5.74, N 2.42; found: C 64.51, H 5.93, N 2.28.

(1*S*,2*R*,3*S*,4*R*,5*S*,6*R*)-1-Hydroxy-2,3-(isopropylidenedioxy)-4-[*N*-benzyl-(4′-methylphenylsulfonyl)amino]-2,3,4,4a,6,11b-hexahydro-1*H*-5,8,10-trioxa-cyclopenta-[*b*]phenanthrene (16)

A solution of epoxide **12** (210 mg, 0.36 mmol) in CH_2Cl_2 (25 mL) at –25°C was treated with a 1.0 M solution of Me_2AlCl in hexanes (400 μL, 0.4 mmol) and stirred at –25°C for 2 h; it was slowly warmed to room temperature. The reaction was quenched with saturated NH_4Cl solution, and the reaction mixture was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure. The remaining residue was purified by chromatography (silica gel, hexanes – ethyl acetate, 4:1) to furnish tosylamide **16** (161 mg, 77%) as a white solid; mp 114–116°C. $[\alpha]_D^{27}$ –49.0 (*c* 1.0, $CHCl_3$). R_f = 0.44 (hexanes – ethyl acetate, 1:1) CI-HRMS calcd. for $C_{31}H_{34}NO_8S$: 580.2005; found: 580.2001. IR (KBr) (cm^{-1}): 3504, 1484, 1329, 1238, 1156, 1038. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.83 (d, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 9.0 Hz, 2H), 7.19 (m, 5H), 6.75 (s, 1H), 6.43 (s, 1H), 5.89 (s, 2H), 4.75 (dd, *J* = 9.7, 7.4 Hz, 1H), 4.58 (d, *J* = 15.1 Hz, 1H), 4.55–4.43 (m, 3H), 4.28 (t, *J* = 7.4 Hz, 1H), 4.21 (dd, *J* = 5.9, 4.5 Hz, 1H), 3.89 (dd, *J* = 11.2, 7.1 Hz, 1H), 3.69 (dd, *J* = 9.4, 6.6 Hz, 1H), 2.47 (dd, *J* = 11.6, 4.2 Hz, 1H), 2.42 (s, 3H), 1.92 (s, 1H), 1.30 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.8, 145.9, 143.2, 137.9, 136.1, 129.3, 128.7, 128.2, 128.1, 127.8, 127.6, 123.4, 111.1, 109.8, 104.1, 100.9, 81.0, 75.9, 73.3, 70.9, 67.4, 64.3, 52.4, 39.8, 27.1, 25.0, 21.5. Anal. calcd. for $C_{31}H_{33}NO_8S$: C 64.23, H 5.74, N 2.42; found: C 63.97, H 5.87, N 2.36.

(1*S*,2*R*,3*S*,4*R*,5*S*,6*R*)-1-Hydroxy-2,3-(isopropylidenedioxy)-6-(2′-methoxyethoxy)-4-[*N*-benzyl-(4′-methylphenyl-sulfonyl)-amino]-2,3,4,4a,6,11b-hexahydro-1*H*-5,8,10-trioxa-cyclopenta[*b*]phenanthrene (17)

A degassed solution of tosylamide **16** (320 mg, 0.55 mmol) in CH_2Cl_2 (25 mL) and 2-methoxyethanol (0.33 mL, 4.2 mmol) was treated with DDQ (188 mg, 0.828 mmol). The resulting solution was stirred at room temperature for 23 h. The solvent was removed under reduced pressure and the remaining residue was purified by chromatography (silica gel, hexanes – ethyl acetate – triethylamine, 2.5:2:1) to afford acetal **17** (282 mg, 78%) as a white solid ; mp 87–90°C. $[\alpha]_D^{27}$ +2.7 (*c* 1.0, $CHCl_3$). R_f = 0.31 (hexanes – ethyl acetate, 1:1) FAB-HRMS calcd. for $C_{34}H_{40}NO_{10}S$: 654.2373; found: 654.2409. IR (KBr) (cm^{-1}): 3448, 1485, 1328, 1242, 1039. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.83 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.19–7.13 (m, 5H), 6.72 (s, 1H), 6.69 (s, 1H), 5.91 (m, 2H), 5.46 (s, 1H), 4.73–4.62 (m, 2H), 4.44 (ABq, *J* = 15.3 Hz, 2H), 4.30 (t, *J* = 7.3 Hz, 1H), 3.93–3.86 (m, 3H), 3.71–3.59 (m, 3H), 3.43 (s, 3H), 2.42 (s, 3H), 2.38 (d, *J* = 12.0 Hz, 1H), 2.07 (s, 1H), 1.35–1.33 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.2, 146.9, 143.1, 137.8, 135.7, 129.2, 129.0, 128.2, 128.0, 127.7, 127.3, 124.5, 110.5, 109.8, 107.1, 101.0, 96.8, 81.1, 73.7, 72.0, 69.7, 68.3, 67.2, 63.6, 59.0, 52.5, 39.6, 27.1, 24.9, 21.5.

(1*S*,2*R*,3*S*,4*R*,5*S*,6*R*)-4-Benzylamino-1-(*tert*-butoxy-carbonyloxy)-2,3-(isopropylidenedioxy)-6-(2′-methoxy-ethoxy)-2,3,4,4a,6,11b-hexahydro-1*H*-5,8,10-trioxa-cyclopenta[*b*]phenanthrene (18)

To a suspension of NaH (12 mg, 0.50 mmol) in THF (5 mL) was added a solution of acetal **17** (208 mg, 0.319 mmol) in THF (8 mL). The resulting solution was stirred at room temperature for 20 min after which a solution of di-*tert*-butyl dicarbonate (105 mg, 0.481 mmol) in THF (2 mL) was added dropwise. The solution was heated at reflux for 5 h. After the solution cooled to room temperature, the reaction was quenched with water, and the mixture extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. A solution of the remaining residue in DME (5 mL) cooled to –50°C was treated with a 0.6 M solution of Na–naphthalene in DME until a dark color persisted. The resulting solution was stirred at –50°C for 30 min, and then the reaction was quenched with water. After it had warmed to room temperature, the reaction mixture was extracted with ethyl acetate (3 × 25 mL), and the combined organic extracts were dried over $MgSO_4$. Removal of the solvent under reduced pressure and purification of the residue by chromatography (hexanes – ethyl acetate – triethylamine, 3:1:1) gave carbonate **18** (163 mg, 85%) as a white foam; $[\alpha]_D^{25}$ +21.5 (*c* 1.0, $CHCl_3$). R_f = 0.24 (hexanes – ethyl acetate, 1:1). FAB-HRMS calcd. for $C_{32}H_{42}NO_{10}$: 600.2809; found: 600.2813. IR (KBr) (cm^{-1}): 3448, 1751, 1508, 1490, 1243, 1039. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.34–7.32 (m, 5H), 6.74 (s, 1H), 6.63 (s, 1H), 5.86 (d, *J* = 18.0 Hz, 2H), 5.64 (s, 1H), 5.09 (dd, *J* = 11.7, 7.8 Hz, 1H), 4.43–4.38 (m, 2H), 4.20 (t, *J* = 5.9 Hz, 1H), 4.01–3.82 (m, 4H), 3.58 (m, 2H), 3.34 (s, 3H), 3.23 (dd, *J* = 6.7, 3.3 Hz, 1H), 2.64 (dd, *J* = 11.6, 2.9 Hz, 1H), 1.69 (br s, 1H), 1.45 (s, 3H), 1.35 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.8, 147.7, 147.3, 140.3, 128.9, 128.7, 127.6, 126.6, 112.6, 110.2, 109.9, 108.1, 101.3, 98.0, 82.6, 78.0, 77.9, 76.4, 72.4, 69.9, 68.0, 59.4, 59.2, 52.7, 38.8, 28.3, 27.9, 26.4.

(1*S*,2*R*,3*S*,4*R*,5*S*,6*R*)-4-Benzylamino-1-(*tert*-butoxycarbonyloxy)-2,3-(isopropylidenedioxy)-2,3,4,4a,6,11b-hexahydro-1*H*-5,8,10-trioxa-cyclopenta[*b*]phenanthrene-6-one (19)

A solution of acetal **18** (204 mg, 0.340 mmol) in 30% aqeous THF (13 mL) was treated with CSA (395 mg, 1.70 mmol) and stirred at room temperature for 21 h. The solution was then diluted with ethyl acetate and washed successively with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried over Na_2SO_4 and then concentrated in vacuo. To a solution of the remaining residue in CH_2Cl_2 (9 mL) and molecular sieves (3 Å) was added PCC (112 mg, 0.520 mmol). The resulting solution was stirred at room temperature for 3 h. The reaction mixture was then filtered over silica and was subsequently washed with several portions of CH_3OH. Removal of the solvent under reduced pressure and purification of the residue by chromatography (silica gel, hexanes – ethyl acetate, 1:1) provided lactone **19** (131 mg, 72%) as a white solid; mp 201–203°C. $[\alpha]_D^{27}$ –28.1 (*c* 1.0, $CHCl_3$). R_f = 0.23 (hexanes – ethyl acetate, 1:1) FAB-HRMS calcd. for $C_{29}H_{34}NO_9$: 540.2234; found: 540.2238. IR (KBr) (cm^{-1}): 3318, 1733, 1702, 1501, 1485, 1260, 1038. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.55 (s, 1H), 7.33–7.26 (m, 5H), 6.72 (s, 1H), 6.05 (m, 1H), 5.96 (m, 1H), 5.07 (dd, *J* = 11.5, 7.5 Hz, 1H), 4.72 (t, *J* = 3.5 Hz, 1H), 4.40 (dd, *J* = 7.5, 5.8 Hz, 1H), 4.22 (t, *J* = 5.4 Hz, 1H), 3.94 (ABq, *J* = 12.9 Hz, 2H), 3.48 (dd, *J* = 5.0, 3.4 Hz, 1H), 2.99 (dd, *J* = 11.5, 3.4 Hz, 1H), 1.63 (br s, 1H), 1.43 (s, 3H), 1.36 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.5, 152.2, 152.1, 148.1, 139.6, 134.6, 128.8, 128.4, 127.6, 118.9, 110.3, 110.2, 108.7, 102.2, 82.9, 79.3, 77.4, 76.9, 75.2, 58.3, 52.7, 38.8, 28.1, 27.6, 26.2.

(1*S*,2*R*,3*S*,4*R*,5*S*,6*R*)-4-Benzylamino-1,2,3-trihydroxy-2,3,4,4a,6,11b-hexahydro-1*H*-5,8,10-trioxa-cyclopenta-[*b*]phenanthrene-6-one (20)

A solution of carbonate **19** (17.5 mg, 0.0295 mmol) in MeOH–H_2O (3:2, 3.5 mL) was treated with a catalytic amount of sodium benzoate and then heated at reflux for 17 h. After the solution cooled to ambient temperature, the reaction mixture was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was dissolved in MeOH (1.2 mL) to which *p*-toluenesulfonic acid (95 mg, 0.50 mmol) was added. The resulting solution was stirred at room temperature for 38 h. The reaction mixture was diluted with ethyl acetate, and the organic phase was washed with saturated $NaHCO_3$ solution. Following separation of the aqueous and organic phases, the aqueous phase was extracted with ethyl acetate (4 × 25 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was purified by chromatography (silica gel, $CHCl_3$–MeOH, 9:1) to give diol **20** (9.9 mg, 84% over two steps) as a white solid; mp 173–176°C (dec.). $[\alpha]_D^{26}$ –81.0 (*c* 1.0, $CHCl_3$). R_f = 0.28 ($CHCl_3$–MeOH, 9:1) FAB-HRMS calcd. for $C_{21}H_{22}NO_7$: 400.1396; found: 400.1312. IR (KBr) (cm^{-1}): 3417, 1703, 1503, 1482, 1260, 1034. ^1H NMR (500 MHz, acetone) δ: 7.38 (d, *J* = 7.4 Hz, 2H), 7.32 (s, 1H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 6.89 (s, 1H), 6.10 (m, 2H), 4.75 (td, *J* = 2.9, 1.3 Hz, 1H), 4.14 (m, 1H), 3.91 (ABq, *J* = 14.0 Hz, 2H), 3.85 (m, 2H), 3.68–3.38 (m, 4H); 3.32 (t, *J* = 2.6 Hz, 1H), 3.11 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.8, 152.0, 147.5, 137.8, 129.8, 128.5, 128.3, 128.1, 117.2, 109.7, 108.9, 101.9, 78.7, 72.8, 69.8, 59.4, 52.3, 41.1.

(1*S*,2*R*,3*S*,4*R*,4a*S*,11b*R*)-2-Benzylamino-1,3,4-trihydroxy-1,2,3,4,4a,11b-hexahydro-1*H*-5,8,10-trioxa-cyclopenta[*b*]-phenanthrene-6-one (21)

A solution of triol **20** (43 mg, 0.11 mmol) in MeOH (4 mL) was treated with K_2CO_3 (31 mg, 0.22 mmol) and subsequently heated at reflux for 13 h. The reaction was diluted with ethyl acetate and quenched with saturated NH_4Cl solution. The organic and aqueous phases were separated and the aqueous phase was extracted with ethyl acetate (4 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The remaining residue was purified by chromatography (silica gel, $CHCl_3$–MeOH, 9:1) to give triol **21** (19 mg, 44%) as a thin film: $[\alpha]_D^{25}$ –60.4 (*c* 1.0, $CHCl_3$). R_f = 0.42 ($CHCl_3$–MeOH, 9:1). FAB-HRMS calcd. for $C_{21}H_{22}NO_7$: 400.1396; found: 400.1379. IR (neat) (cm^{-1}): 3410, 1690, 1484, 1261, 1026. ^1H NMR (500 MHz, acetone) δ: 7.40 (d, *J* = 7.2 Hz, 2H), 7.36 (s, 1H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.94 (d, *J* = 0.8 Hz, 1H), 6.10 (m, 2H), 4.68 (s, 1H), 4.58 (dd, *J* = 12.2, 9.4 Hz, 1H), 4.37 (s, 1H), 4.27 (td, *J* = 3.2, 1.3 Hz, 1H), 4.22 (dd, *J* = 9.4, 3.2 Hz, 1H), 3.91 (s, 2H), 3.45 (ddd, *J* = 12.3, 2.6, 0.7 Hz, 1H), 3.38 (t, *J* = 2.8 Hz, 1H), 3.0–2.62 (m, 3H). ^{13}C NMR (126 MHz, acetone) δ: 163.8, 152.5, 147.0, 140.8, 138.0, 128.3, 126.9, 120.1, 108.7, 105.6, 102.3, 78.5, 74.2, 70.3, 69.1, 60.3, 52.0, 39.7.

(1*S*,2*R*,3*S*,4*R*,4a*S*,11b*R*)-2-Benzylamino-1,3,4-triacetoxy-1,2,3,4,4a,11b-hexahydro-1*H*-5,8,10-trioxa-cyclopenta-[*b*]phenanthrene-6-one (22)

A solution of triol **21** (8.2 mg, 0.016 mmol) in pyridine (0.25 mL) was treated with neat acetic anhydride (58 μL, 0.61 mmol) and a catalytic amount of DMAP. The reaction was allowed to stir for 32 h. The solvent was removed and the remainder purified by chromatography (silica gel, hexanes – ethyl acetate, 1:1) to give triacetate **22** (6.6 mg, 61%) as an oil: $[\alpha]_D^{26}$ –16.2 (*c* 1.0, $CHCl_3$). R_f = 0.44 (hexanes – ethyl acetate, 1:1). FAB-HRMS calcd. for $C_{27}H_{28}NO_{10}$: 526.1713; found: 526.1718. IR (neat) (cm^{-1}): 3441, 1742, 1505, 1485, 1372, 1230, 1040. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.54 (s, 1H), 7.38–7.28 (m, 5H), 6.40 (s, 1H), 6.06 (m, 2H), 5.61–5.56 (m, 2H), 5.52 (m, 1H), 4.91 (dd, *J* = 20.7, 12.2 Hz, 1H), 3.96 (ABq, *J* = 13.2 Hz, 2H), 3.77 (dd, *J* = 12.3, 3.0 Hz, 1H), 3.30 (t, *J* = 2.6 Hz, 1H), 2.10 (s, 3H), 2.05 (s, 3H), 1.98 (s, 3H), 1.7 (br s, 1H).

(1*S*,2*R*,3*S*,4*R*,4a*S*,11b*R*)-2-Acetylamino-1,3,4-triacetoxy-1,2,3,4,4a,11b-hexahydro-1*H*-5,8,10-trioxa-cyclopenta-[*b*]phenanthrene-6-one (13)

A solution of triacetate **22** (5.7 mg, 0.011 mmol) and $Pd(OH)_2$ (25 mg) in MeOH (1.5 mL) was subjected to an atmosphere of hydrogen for 40 min. The reaction mixture was

filtered over Celite, and the filtrate concentrated in vacuo. The remaining residue was dissolved in pyridine to which acetic anhydride (15 μL, 0.16 mmol) was added followed by a catalytic amount of DMAP. The reaction was stirred for 19 h. The solvent was removed and the residue purified by chromatography (hexanes – ethyl acetate, 1:1) to provide tetraacetate **13** (2.8 mg, 55%) as a film. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44 (s, 1H), 6.99 (d, J = 8.1 Hz, 1H), 6.62 (s, 1H), 6.06 (m, 2H), 5.71 (s, 1H), 5.53–5.46 (m, 2H), 4.89 (dd, J = 12.2, 10.1 Hz, 1H), 4.54 (m, 1H), 3.53 (dd, J = 10.5, 1.8 Hz, 1H), 2.08 (m, 9H), 1.98 (s, 3H).

N-[(1*R*,2*S*,5*R*,6*S*)-2-(Benzo[1,3]dioxol-5-ylmethoxy)-5,6-(isopropylidenedioxy)cyclohex-3-enyl]-4′-methylbenzenesulfonamide (25)

To a suspension of KH (108 mg, 2.69 mmol) in DME (3 mL) was added a solution of piperonol (378 mg, 2.49 mmol) in DME (5 mL). The resulting solution was stirred for 20 min, then a solution of vinylaziridine **15** (228 mg, 0.710 mmol) in DME (3 mL) was added dropwise followed by 18-crown-6 (66 mg, 0.25 mmol). The reaction mixture was stirred for 24 h and then the reaction quenched with saturated NH_4Cl solution. The reaction mixture was extracted with CH_2Cl_2 (4 × 50 mL) and the combined organic extracts dried over Na_2SO_4. The solvent was removed under reduced pressure and the remainder purified by chromatography (silica gel, hexanes – ethyl acetate, 2:1) to furnish tosylamide **25** (223 mg, 56%) as a white foam; $[\alpha]_D^{29}$ –10.5 (*c* 1.0, $CHCl_3$). R_f = 0.38 (hexanes – ethyl acetate, 1:1). FAB-HRMS calcd. for $C_{24}H_{28}NO_7S$: 474.1586; found: 474.1587. IR (neat) (cm^{-1}): 3269, 1503, 1599, 1492, 1445, 1326, 1251, 1156, 1094, 1039. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.80 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 6.73 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 1.6 Hz, 1H), 6.68 (dd, J = 7.9, 1.8 Hz, 1H), 5.94 (s, 2H), 5.88 (dd, J = 10.3, 1.0 Hz, 1H), 5.84 (ddd, J = 10.1, 3.2, 1.8 Hz, 1H), 5.10 (d, J = 7.4 Hz, 1H), 4.53 (dd, J = 6.3, 3.4 Hz, 1H), 4.36 (d, J = 11.6 Hz, 1H), 4.27 (d, J = 11.5 Hz, 1H), 4.05 (dd, J = 9.4, 6.1 Hz, 1H), 3.80 (dq, J = 9.2, 1.6 Hz, 1H), 3.55 (td, J = 9.2, 7.4 Hz, 1H), 2.37 (s, 3H), 1.36 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 147.9, 147.2, 142.9, 139.0, 132.6, 131.9, 129.3, 127.6, 124.5, 121.6, 110.8, 109.0, 108.2, 101.0, 76.4, 75.7, 72.2, 70.8, 57.3, 27.8, 26.0, 21.7.

N-Benzyl-*N*-[(1*R*,2*S*,5*R*,6*S*)-2-(benzo[1,3]dioxol-5-ylmethoxy)-5,6-(isopropylidenedioxy)cyclohex-3-enyl]-4′-methylbenzenesulfonamide (26)

To a suspension of NaH (10.8 mg of 60% reagent, 0.270 mmol) in THF (2 mL) was added a solution of tosylamide **25** (117 mg, 0.208 mmol) in THF (5 mL). The resulting solution was stirred for 20 min then benzyl bromide (36 μL, 0.28 mmol) was added, followed by a catalytic amount of tetrabutylammonium iodide. The solution was stirred for 18 h and then quenched with water. The reaction was diluted with ethyl acetate and the aqueous and organic layers separated. The aqueous phase was extracted with ethyl acetate (4 × 40 mL) and the combined organic extracts dried over Na_2SO_4. Removal of the solvent in vacuo provided a residue which was purified by chromatography (silica gel, hexanes – ethyl acetate, 3:1) generating tosylamide **26** (114 mg, 84%) as a solid; mp 157–160°C. $[\alpha]_D^{25}$ +3.2 (*c* 1.0, $CHCl_3$). R_f = 0.21 (hexanes – ethyl acetate, 5:1). FAB-HRMS calcd. for $C_{31}H_{34}NO_7S$: 564.2056; found: 564.2099. IR (neat) (cm^{-1}): 1599, 1503, 1492, 1445, 1330, 1251, 1156, 1040. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.86 (d, J = 8.1 Hz, 2H), 7.22–7.15 (m, 7H), 6.81–6.78 (m, 3H), 5.97–5.94 (m, 3H), 5.80 (d, J = 9.9 Hz, 1H), 4.57–4.31 (m, 6H), 2.40 (s, 3H), 1.32–1.25 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.6, 142.9, 138.1, 136.4, 133.0, 131.7, 129.1, 128.9, 128.2, 127.5, 123.0, 121.6, 112.0, 110.3, 108.9, 107.9, 100.9, 73.6, 72.7, 70.6, 27.5, 25.7, 21.5.

(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-3,4-Dihydroxy-5,6-(isopropylidenedioxy)-2-(3′,4′-methylenedioxyphenylmethyl)-1-cyclohexylbenzenesulfonamide (27)

A solution of tosylamide **26** (16.2 mg, 0.0288 mmol) in CH_3CN–EtOAc (1:1, 0.80 mL) at 0°C was treated with a solution of $NaIO_4$ (10.1 mg, 0.0432 mmol) and a catalytic amount of $RuCl_3 \cdot 3H_2O$ in water (0.5 mL). The resulting solution was stirred at 0°C for 3 min and then quenched with saturated $Na_2S_2O_3$ solution. The reaction mixture was extracted with CH_2Cl_2 (4 × 10 mL) and the combined organic extracts dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by chromatography (silica gel, hexanes – ethyl acetate, 1:2) to provide diol **27** (11.3 mg, 66%) as a film; $[\alpha]_D^{26}$ –27.9 (*c* 1.0, $CHCl_3$). R_f = 0.34 (hexanes – ethyl acetate, 1:2). FAB-HRMS calcd. for $C_{31}H_{36}NO_9S$: 598.2111; found: 598.2108. IR (neat) (cm^{-1}): 3460, 1504, 1492, 1445, 1328, 1251, 1156, 1040. ^{1}H NMR (300 MHz, acetone) δ: 7.75 (d, J = 7.8 Hz, 2H), 7.24–7.15 (m, 7H), 6.88 (s, 1H), 6.80–6.78 (m, 2H), 6.00 (s, 2H), 4.60 (d, J = 11.1 Hz, 1H), 4.45–4.38 (m, 3H), 4.28–4.14 (m, 4H), 4.03–3.79 (m, 3H), 3.93 (br s, 1H), 2.38 (s, 3H), 1.28–1.24 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.7, 147.3, 142.8, 138.3, 136.2, 131.8, 129.1, 128.8, 128.2, 128.0, 127.5, 122.1, 109.3, 109.2, 108.1, 101.0, 76.5, 73.0, 69.7, 27.4, 25.4, 21.4.

(1*R*,2*R*,3*R*,4*S*,5*S*,6*S*)-3,4-Dihydroxy-5,6-(isopropylidenedioxy)-2-(3′,4′-methylenedioxyphenylmethyl)-1-cyclohexylbenzenesulfonamide (28)

A solution of epoxide **12** (17.2 mg, 0.0297 mmol) in a mixture of 1,4-dioxane–H_2O (1:1, 1 mL) was treated with KOH (16.7 mg, 0.297 mmol) and then heated at reflux for 48 h. The reaction mixture was diluted with ethyl acetate and the organic and aqueous layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 20 mL) and the combined organic extracts dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded a residue that was purified by chromatography (silica gel, hexanes – ethyl acetate, 1:4) to give diol **28** (9.9 mg, 56%) as a film; $[\alpha]_D^{27}$ –35.4 (*c* 1.0, $CHCl_3$). R_f = 0.36 (hexanes – ethyl acetate, 1:24). FAB-HRMS calcd. for $C_{31}H_{35}NO_9S$ + Na: 620.1930; found: 620.1910. IR (neat) (cm^{-1}): 3478, 1493, 1445, 1326, 1246, 1156, 1038. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.82 (d, J = 8.1 Hz, 2H), 7.24–7.20 (m, 7H), 6.76–6.75 (m, 3H), 5.97 (s, 2H), 4.48 (m, 2H), 4.38–4.24 (m, 3H), 4.10–4.06 (m, 2H), 3.98–3.90 (m, 2H), 3.73 (t, J = 6.0 Hz, 1H), 2.42 (s, 3H), 1.35 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.7, 147.4, 143.1, 137.8, 136.3, 131.2, 129.2, 128.8, 128.4, 128.0, 127.7, 122.0,

109.5, 109.1, 108.1, 101.0, 77.8, 75.3, 74.1, 72.5, 70.5, 69.4, 61.0, 50.9, 27.4, 25.2, 21.5.

(2*R*,3*R*,4*S*,5*R*)-[2-(Benzo[1,3]-dioxol-5-ylmethoxy)-3-(*N*-benzyl-(4′-methylphenylsulfonyl)amino)-1,6-dihydroxy-4,5-(isopropylidenedioxy)]hexane (29)

A solution of diol **27** (21.1 mg, 0.0353 mmol) in a 40% aqueous acetone solution (2 mL) was treated with a solution of $NaIO_4$ (10.2 mg, 0.0477 mmol) in water (0.2 mL) and stirred at room temperature for 3 h. The reaction mixture was concentrated in vacuo and the resulting solution was extracted with ethyl acetate (4 × 25 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The remaining residue was dissolved in MeOH (1 mL), cooled to 0°C, and treated with neat $NaBH_4$. The solution was slowly warmed to room temperature and stirred for 18 h. The reaction mixture was treated with water and then concentrated in vacuo. The remaining solution was extracted with ethyl acetate (4 × 20 mL) and the combined organic extracts dried over Na_2SO_4. Removal of the solvent under reduced pressure gave a residue, which was purified by chromatography (silica gel, hexanes – ethyl acetate, 1:2) furnishing diol **29** (11.1 mg, 52%) as a film; $[\alpha]_D^{25}$ +66.8 (*c* 1.0, $CHCl_3$). R_f = 0.30 (hexanes – ethyl acetate, 1:2). FAB-HRMS calcd. for $C_{31}H_{38}NO_9S$: 600.2267; found: 600.2264. IR (neat) (cm^{-1}): 3501, 1503, 1491, 1445, 1332, 1251, 1157, 1039. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.56 (d, *J* = 8.1 Hz, 2H), 7.36–7.34 (m, 2H), 7.21–1.15 (m, 5H), 6.73 (d, *J* = 8.7 Hz, 1H), 6.62–6.60 (m, 2H), 5.93 (m, 2H), 4.60 (d, *J* = 15.9 Hz, 1H), 4.39–4.27 (m, 4H), 4.13 (d, *J* = 11.7 Hz, 1H), 3.93 (m, 1H), 3.69–3.58 (m, 2H), 3.44–3.40 (m, 4H), 2.37 (s, 3H), 2.03 (br s, 1H), 1.13 (s, 3H), 1.0 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.8, 147.5, 143.0, 138.1, 137.0, 131.2, 128.8, 128.0, 127.7, 126.8, 121.9, 108.8, 108.0, 107.9, 101.1, 78.5, 73.2, 72.3, 61.2, 58.9, 55.2, 49.6, 27.7, 25.0, 21.4. (Note: an analagous procedure can be applied to diol **28** which also affords diol **29**).

Acknowledgments

The authors thank the National Science Foundation (CHE-9 615 112), TDC Research, Inc., and the University of Florida for financial support.

References

1. Pancratistatin: (*a*) S. Danishefsky and J.Y. Lee. J. Am. Chem. Soc. **111**, 4829 (1989); (*b*) X. Tian, T. Hudlicky, and K. Königsberger. J. Am. Chem. Soc. **117**, 3643 (1995); (*c*) T. Hudlicky, X. Tian, K. Königsberger, R. Maurya, J. Rouden, and B. Fan. J. Am. Chem. Soc. **118**, 10752 (1996); (*d*) B.M. Trost and S.R. Pulley. J. Am. Chem. Soc. **117**, 10143 (1995).(*e*) T.J. Doyle, M. Hendrix, D. VanDerveer, S. Javanmard, and J. Haseltine. Tetrahedron, **53**, 11153 (1997); (*f*) P. Magnus and I.K. Sebhat. J. Am. Chem. Soc. **120**, 5341 (1998); (*g*) J.H. Rigby, U.S.M. Maharoof, and M.E. Mateo. J. Am. Chem. Soc. **122**, 6624 (2000).
2. 7-Deoxypancratistatin: (*a*) S. Ohta and and S. Kimoto. Chem. Pharm. Bull. **24**, 2977 (1976); (*b*) G.E. Keck, S.F. McHardy, and J.A. Murry. J. Am. Chem. Soc. **117**, 7289 (1995); (*c*) X. Tian, R. Maurya, K. Königsberger, and T. Hudlicky. Synlett, 1125 (1995); (*d*) N. Chida, M. Jitsuoka, and Y. Yamamoto. Heterocycles, **43**, 1385 (1996); (*e*) G.E. Keck, T.T. Wager, and S.F. McHardy. J. Org. Chem. **63**, 9164 (1998); (*f*) G.E. Keck, S.F. McHardy, and J.A. Murry. J. Org. Chem. **64**, 4465 (1999); (*g*) J.L. Acena, O. Arjona, M.L. Leon, and J. Plumet. Org. Lett. **2**, 3683 (2000).
3. Narciclasine: (*a*) J.H. Rigby and M.E. Mateo. J. Am. Chem. Soc. **119**, 12655 (1997); (*b*) D. Gonzalez, T Martinot, and T. Hudlicky. Tetrahedron Lett. **40**, 3077 (1999); (*c*) G.E. Keck, T.T. Wager, and J.F.D. Rodriguez. J. Am. Chem. Soc. **121**, 5176 (1999).
4. Lycoricidine: (*a*) S. Ohta and S. Kimoto. Tetrahedron Lett. **23**, 2279 (1975); (*b*) S. Ohta and S. Kimoto. Chem. Pharm. Bull. **24**, 2969, (1976); (*c*) S. Ohta and S. Kimoto. Chem. Pharm. Bull. **24**, 2977 (1976); (*d*) H. Paulsen and M. Stubbe. Tetrahedron Lett. **23**, 3171 (1982); (*e*) H. Paulsen and M. Stubbe. Liebigs Ann. Chem. 535 (1983); (*f*) S. Ogawa, M. Ohtsuka, and N. Chida. Tetrahedron Lett. **32**, 4525 (1991); (*g*) T. Hudlicky and H.F. Olivo. J. Am. Chem. Soc. **114**, 9694 (1992); (*h*) S.F. Martin and H.H. Tso. Heterocycles, **35**, 85 (1993); (*i*) S. Ogawa, M. Ohtsuka, and N. Chida. J. Org. Chem. **58**, 4441 (1993); (*j*) T. Hudlicky, H.F. Olivo, and B. McKibben. J. Am. Chem. Soc. **116**, 5108 (1994).
5. H. Akgun amd T. Hudlicky. Tetrahedron Lett. **40**, 3081 (1999).
6. (*a*) H.G. Viehe amd J.L. Vaerman. Tetrahedron, **45**, 3183 (1989); (*b*) H.G. Viehe, J.L. Vaerman, F.P. Schmidtchen, G. Kresze, W. Burger, and H. Braun. Tetrahedron: Asymmetry, **1**, 403 (1990).
7. For definitions of redundant operations, see T. Hudlicky. Chem. Rev. **96**, 3 (1996).
8. (*a*) S.C. Bergmeier, W.K. Lee, and H. Rapoport. J. Org. Chem. **58**, 5019 (1993); (*b*) S.C. Bergmeier, and P.P. Seth. Tetrahedron Lett. **36**, 3793 (1995); (*c*) S.C. Bergmeier and P.P. Seth. J. Org. Chem. **64**, 3237 (1999); (*d*) S.C. Bergmeier, S.L. Fundy, and P.P. Seth. Tetrahedron, **55**, 8025 (1999).
9. D.R. Gauthier and S.L. Bender. Tetrahedron Lett. **37**, 13 (1996).
10. (*a*) T. Hudlicky, E.E. Boros, and C.H. Boros. Tetrahedron: Asymmetry, **4**, 1365, (1993); (*b*) T. Hudlicky, E.E. Boros, and C.H. Boros. Synthesis, 174 (1992); (*c*) T. Hudlicky, M.R. Stabile, D.T. Gibson, and G.M. Whited. Org. Syn. **76**, 77 (1999).
11. (*a*) D.A. Evans, M.M. Faul, and M.T. Bilodeau. J. Org. Chem. **56**, 6744 (1991); (*b*) Z. Li, K.R. Conser, and E.N. Jacobsen. J. Am. Chem. Soc. **115**, 5326 (1993); (*c*) J.G. Knight and M.P. Muldowney. Synlett, 949 (1995).
12. (*a*) S. Miah. Unpublished results. 1995; (*b*) R.D. Guthrie, I.D. Jenkins, S. Thang, J. Watters, and R. Yamasaki. Carbohydr. Res. **103**, 1 (1982).
13. S. McLamore. Studies directed towards the total synthesis of *ent*-7-deoxypancratistatin. PhD thesis. University of Florida. 1997.