Chemical Modification of Paraherquamide. 1. Unusual Reactions and Absolute Stereochemistry

Timothy A. Blizzard,* Gaye Marino, Helmut Mrozik, Michael H. Fisher, Karst Hoogsteen, and James P. Springer

Merck Sharp and Dohme Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065

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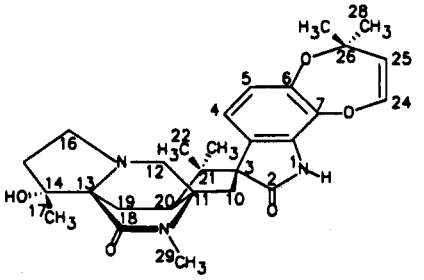
The reaction of paraherquamide (1) with phosgene to form a rearranged cyclic urethane (3) is reported. An unusual Super-Hydride-mediated reductive cyclization of 3 to the interesting analogues 4, 5, and 6 is also described. Conversion of chloride 3 to the corresponding alcohol 12 is discussed. The absolute stereochemistry of 1 is determined by single-crystal X-ray analysis of a brominated derivative of 12. In addition, several other paraherquamide analogues, including 5-bromoparaherquamide (13) and 16-oxoparaherquamide (14c), are reported.

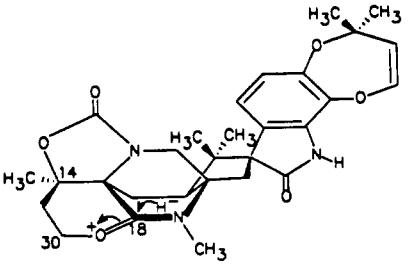
Paraherquamide (1) is a toxic metabolite of *Penicillium paraherquei*, which was reported several years ago by Yamazaki et al.[1] It is structurally related to the marcfortines which were isolated from *Penicillium roqueforti* by Polonsky et al.[2] The unusual structures of these oxindole alkaloids have recently begun to attract the attention of synthetic chemists.[3] During a program of chemical modification of paraherquamide we have noted several interesting reactions of 1 which are described herein.



PARAHERQUAMIDE 1

We decided to focus initially on functionalization of the hydroxyl group at position 14 of paraherquamide. We thus treated 1 with a solution of phosgene in toluene and pyridine, but after quenching the reaction with methanol we obtained a product which was clearly *not* the expected methyl carbonate. We repeated the reaction using a different workup procedure (aqueous base) and obtained a product which was identified by NMR and MS as the cyclic urethane 3 (Scheme I). This interesting product presumably arises by chloride ion opening of the strained intermediate 2. It appears that the formation of such an intermediate is necessary for the reaction to occur since paraherquamide analogues lacking the C-14 hydroxyl group did not undergo ring cleavage under the reaction conditions. A subsequent literature search revealed that there is excellent literature precedent for this reaction.[4]

With urethane 3 in hand we decided to explore its chemical reactivity with the expectation that it would be a valuable intermediate in the preparation of paraherquamide analogues. We were particularly interested in replacing the chlorine atom of 3 with hydrogen. We anticipated that treatment of 3 with Super-Hydride (Aldrich) would smoothly effect the desired displacement of chloride with hydride.[5] However when the reaction was carried out we obtained three unexpected products which we identified by NMR and MS as 4, 5, and 6 (Scheme II). We believe that the major product, 4, results from an unusual reductive cyclization in which intermediate 7 is reduced by Super-Hydride. An alternative mechanism would involve hydride reduction of the lactam carbonyl followed by cyclization to form 4. The other two products might result from a similar reductive cyclization onto the urethane oxygen to form intermediate 8, which is then reduced (with loss of H_2CO) to 5 and subsequently to 6.[6] Again, an alternative mechanism would involve hydride reduction of the urethane followed by cyclization to form 4.



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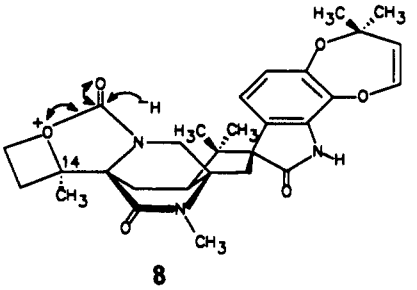

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The observation of this unexpected reductive cyclization prompted us to examine whether a similar reaction could

(1) (a) Yamazaki, M.; Okuyama, E.; Kobayashi, M.; Inoue, H. *Tetrahedron Lett.* **1981**, *22*, 135. (b) Yamazaki, M.; Fujimoto, H.; Okuyama, E.; Ohta, Y. *Maikotokishin (Tokyo)* **1980**, *10*, 27; *Chem. Abstr.* **1981**, *95*, 19321p. (c) The Chemical Abstracts name for paraherquamide is spiro-[4*H*,8*H*-[1,4]dioxepino[2,3-*g*]indole-8,7′(8′*H*)-[5*H*,6*H*-5a,9a](iminomethano)[1*H*]cyclopent[*f*]indolizine]-9,10′(10*H*)-dione, 2′,3′,8′a,9′-tetrahydro-1′-hydroxy-1′,4,4,8′,8′,11′-hexamethyl-(1′α,5′aβ,7′β,8′aβ,9′aβ)-(−). (CAS Registry No. 77392-58-6). In the interest of brevity and clarity we have used trivial names based on paraherquamide rather than Chemical Abstracts names throughout this paper.

(2) (a) Polonsky, J.; Merrien, M. A.; Prange, T.; Pascard, C.; Moreau, S. *J. Chem. Soc., Chem. Commun.* **1980**, 601. (b) Prange, T.; Billion, M. A.; Vuilhorgne, M.; Pascard, C.; Polonsky, J.; Moreau, S. *Tetrahedron Lett.* **1981**, *22*, 1977.

(3) Williams, R. M.; Glinka, T.; Kwast, E. *J. Am. Chem. Soc.* **1988**, *110*, 5927.

(4) Fielden, M. L.; Welstead, W. J., Jr.; Dawson, N. D.; Chen, Y. H.; Mays, R. P.; Davanzo, J. P.; Lunsford, C. D. *J. Med. Chem.* **1973**, *16*, 1124.

(5) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1983**, *95*, 1669.

(6) Isolated 5 is completely (by TLC) converted to 6 upon exposure to the reaction conditions.

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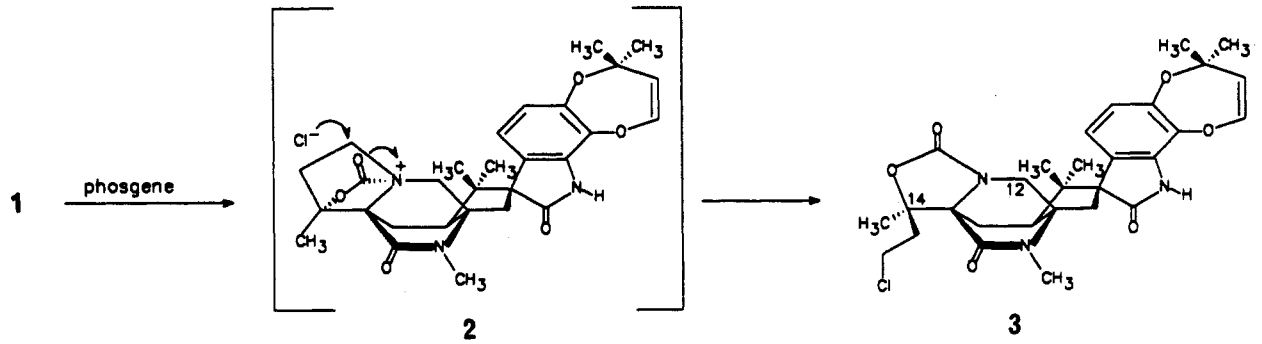
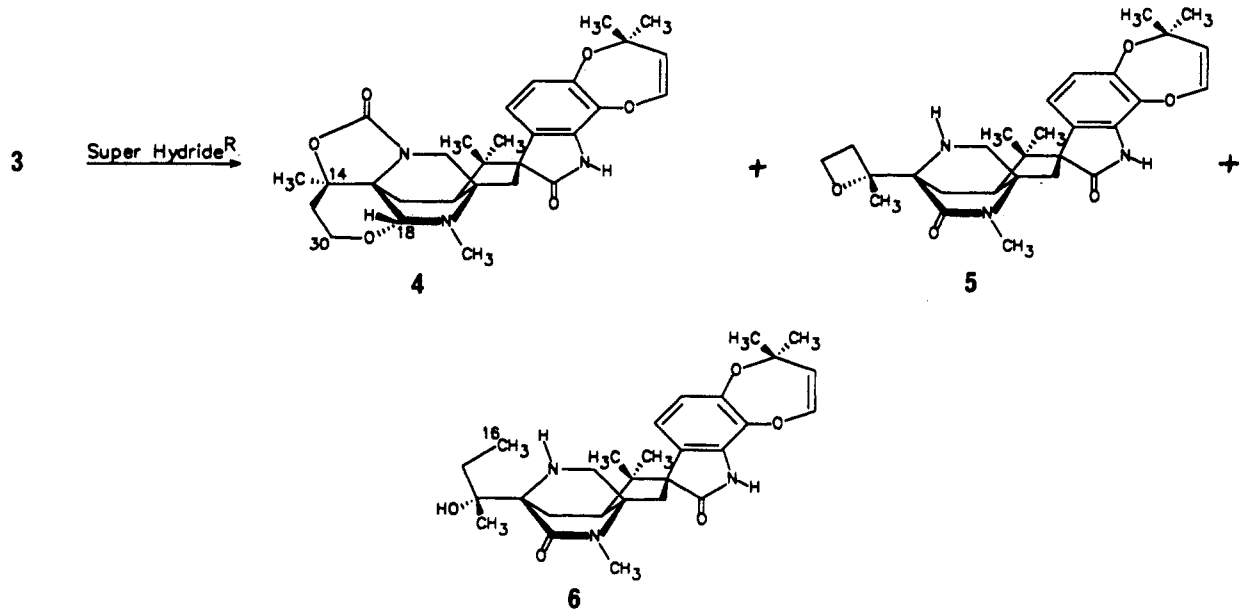
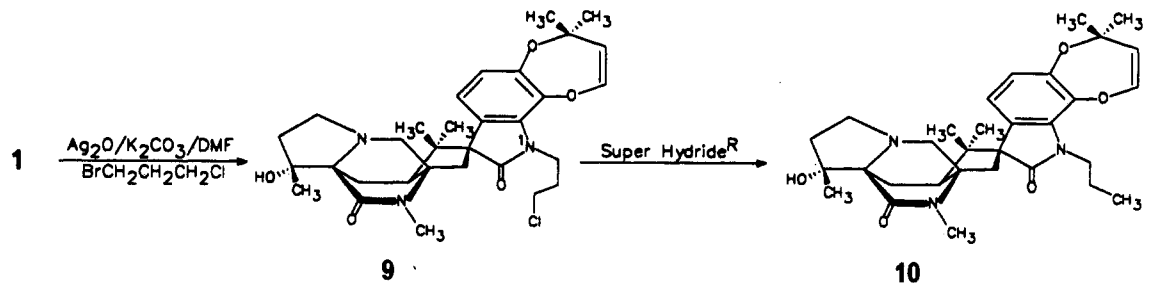
Scheme I



Scheme II



Scheme III



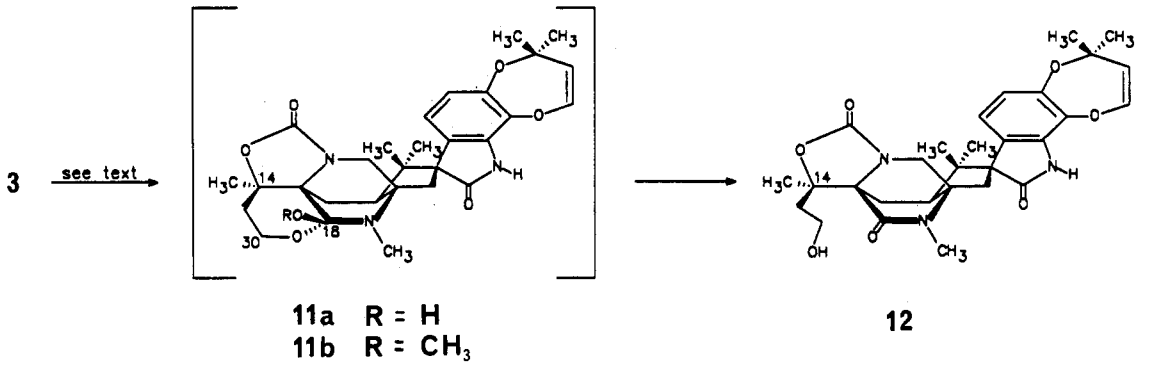
be effected at the other amide group of paraherquamide. We prepared 1-*N*-(3-chloropropyl)paraherquamide (**9**) by treating **1** with silver oxide, potassium carbonate, and 1-bromo-3-chloropropane in DMF[7] (Scheme III). Treatment of **9** with Super-Hydride under the conditions used to reduce **3** led only to the corresponding 1-*N*-propyl derivative (**10**) resulting from hydride displacement of chloride ion. Chloride **9** thus undergoes the normal reaction one would expect with Super-Hydride while chloride **3** undergoes a completely different reaction. Examination of Dreiding models leads us to speculate that this difference in reactivity is due to different constraints imposed on the orientation of the chloromethyl groups in **3** and **9**. In **3** the chloromethyl group is held in relatively close proximity to the lactam carbonyl or the urethane oxygen while in **9** the chloropropyl side chain has much more rotational freedom and the chloromethyl group is located on average farther away from the lactam carbonyl.

While our effort to replace the chlorine atom of **3** with hydrogen was in progress, we were also exploring the possibility of hydroxide displacement of the chlorine atom. We found that the chloride could be easily replaced with a hydroxyl group by treating a solution of **3** in aqueous methanol with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[8] It seems likely that this reaction actually proceeds through a cyclic intermediate (**11a**) rather than by direct displacement of chloride by hydroxide (Scheme IV). This proposed mechanism is supported by the observation that

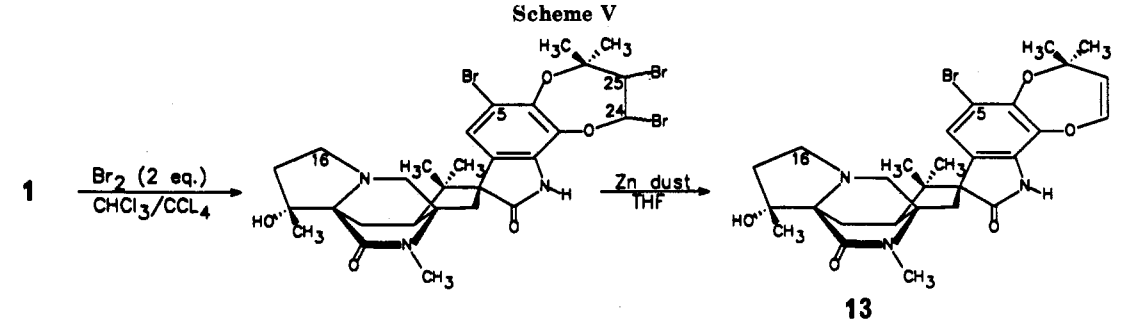
(7) During the course of our work on paraherquamide derivatization we have prepared a large number of 1-N-substituted analogues. The preparation and biological activity of these derivatives will be reported in a subsequent publication.

(8) In fact the chloride is slightly unstable in the presence of moisture and slowly converts to the alcohol on standing at room temperature.

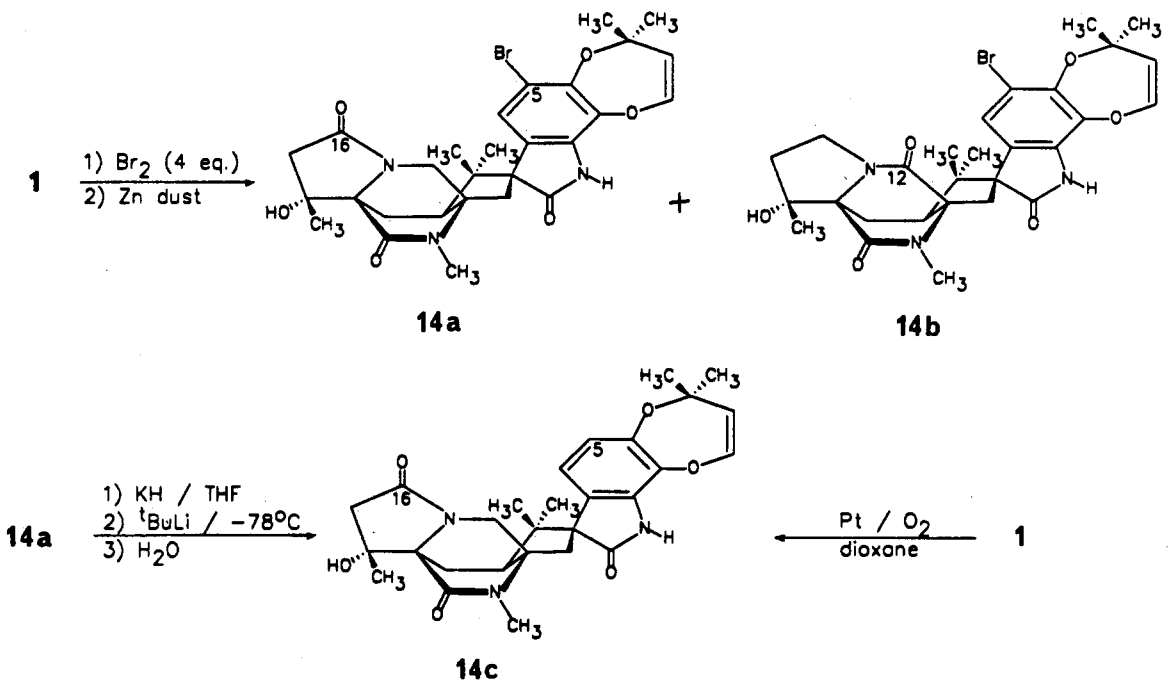
Scheme IV



Scheme V



Scheme VI



when **3** was treated with sodium methoxide in anhydrous methanol we were actually able to isolate the unstable intermediate amide acetal **11b**. Silica gel chromatography of **11b** resulted in its complete conversion to the alcohol (**12**). Note that the isolation of **11b** provides support for our proposed mechanism for the formation of **4** in the reaction with Super-Hydride.

The reaction of **1** with phosgene and the subsequent hydroxide displacement reaction proved to be of great value in our effort to resolve the question of the absolute stereochemistry of paraherquamide. The structure of paraherquamide was determined by Yamazaki et al. by X-ray diffraction analysis, which allowed assignment of the relative stereochemistry but not the absolute stereochemistry of **1**.[1,9] We hoped to be able to determine the absolute stereochemistry of paraherquamide by synthesizing a crystalline *brominated* derivative of **1**. An X-ray analysis of this derivative would then allow us to determine the absolute stereochemistry of **1**.

We prepared 5-bromoparaherquamide (**13**) by treating **1** with 2 equiv of bromine followed by zinc reduction of the intermediate tribromide (Scheme V). We also prepared 5-bromo-16-oxoparaherquamide (**14a**) by treating **1** with 4 equiv of bromine followed by zinc reduction (Scheme VI). A minor byproduct of this reaction was identified as the isomeric 5-bromo-12-oxoparaherquamide

(9) Actually paraherquamide is drawn with one absolute stereochemistry in ref 1a and with the opposite (enantiomeric) absolute stereochemistry in ref 1b.

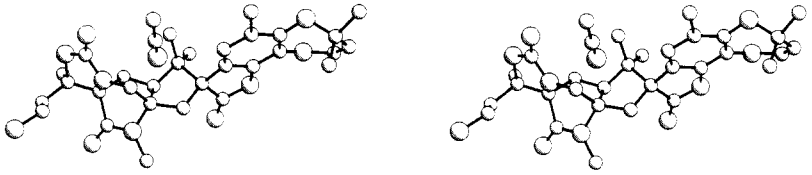
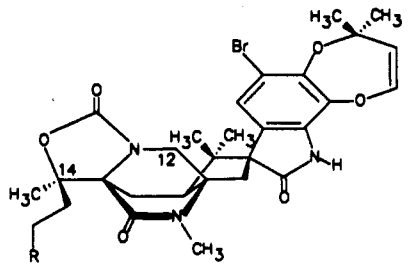


Figure 1. Stereodrawing of **16**.

(**14b**).[10] The structures of **14a** and **14b** were confirmed by debromination (halogen–metal exchange with *tert*-butyllithium followed by water quench) to afford 16-oxoparaherquamide (**14c**) and 12-oxoparaherquamide. The 16-oxoparaherquamide thus obtained was identical in all respects with a sample prepared by platinum-catalyzed air oxidation of paraherquamide. Unfortunately, however, all attempts to crystallize **13** and **14a** were unsuccessful although **14a** appeared to be more amenable to crystallization than **13**. We expected that replacement of the pyrrolidinol ring of **13** with an oxazolidinone ring as in the conversion of **1** to **3** would lead to a derivative which could be more readily crystallized. Accordingly, we treated **13** with phosgene under the conditions used to prepare **3** and obtained the corresponding 5-bromo analogue (**15**). After



15 R = Cl
16 R = OH

several unsuccessful attempts to crystallize **15** we decided to convert it to the corresponding alcohol, anticipating that the presence of additional hydrogen bonding due to the hydroxyl group might lead to a more highly crystalline compound. Reaction of **15** with hydroxide under the conditions used to prepare **12** smoothly afforded the corresponding 5-bromo alcohol **16**. We were able to crystallize **16** from acetonitrile–methanol–methylene chloride to afford crystals suitable for X-ray analysis. The crystals were obtained in the form of prisms (monoclinic, space group $P2_1$) and were enclosed in a capillary with some saturated solvent while the X-ray data was collected. Analysis of the X-ray data allowed the assignment of the absolute stereochemistry of **16** as 3*R*,11*S*,13*R*,14*R*,20*S* (Figure 1, see Experimental Section for details). The assignment of the absolute stereochemistry of **16** by X-ray analysis also allows us to definitely assign the absolute stereochemistry of paraherquamide (**1**) as 3*R*,11*S*,13*R*,14*R*,20*S* since none of the chiral centers are altered in the conversion of **1** to **16**.

In addition to the chemical modifications described in this paper we have also prepared a large number of other paraherquamide analogues with structural changes in different parts of the molecule. The preparation and biological activity of these derivatives will be reported in future publications from this laboratory.

Experimental Section

^1H and ^{13}C NMR spectra were measured at 300 and 75.4 MHz, respectively.[11] All title compounds were judged to be at least 90–95% pure by ^1H NMR analysis. All solvents were HPLC grade or better and were generally dried over activated 3A molecular sieves before use. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl before use. Paraherquamide was obtained from Dr. M. Goetz and J. Ondeyka of MSDRL. Phosgene (1.93 M solution in toluene) was purchased from Fluka Chemical Corp. Super-Hydride (lithium triethylborohydride, 1.0 M solution in THF) was purchased from Aldrich Chemical Co. Analytical thin-layer chromatography (TLC) was performed on 2.5 × 10 cm plates coated with 0.25 mm thickness of silica gel containing PF 254 indicator (Analtech). Preparative TLC was performed on 20 × 20 cm plates coated with 0.5, 1.0, or 1.5 mm of silica gel containing PF 254 indicator (Analtech). Compounds were visualized with shortwave UV light or by staining with iodine vapor. For preparative TLC compounds were eluted from the silica gel with ethyl acetate. All chromatography solvents were HPLC grade or better.

Reaction of Paraherquamide (1) with Phosgene. A solution of phosgene in toluene (2.0 mL of a 1.93 M toluene solution, 3.86 mmol) was added dropwise to a solution of paraherquamide (80 mg, 0.16 mmol) and (dimethylamino)pyridine (10 mg, 0.08 mmol) in 2 mL of pyridine, and then 2 mL of toluene was added. The mixture (voluminous precipitate) was stirred vigorously at room temperature for 26 h and then diluted with 4 mL of ether. The mixture was cooled in an ice bath as 4 mL of 5% aqueous sodium bicarbonate was added followed by sufficient 50% aqueous sodium hydroxide to raise the pH to 10. The layers were separated, and the aqueous layer was extracted with ether (4 × 3 mL). The combined extracts were dried with magnesium sulfate, filtered, and evaporated under vacuum. Preparative layer chromatography of the residue on a 1.0 mm silica gel plate eluted with 50% acetone in hexane afford 70 mg of a yellow oil, which was not completely pure by analytical layer chromatography. Preparative layer chromatography of this impure material on a 1.0 mm silica gel plate eluted with ether afforded 61 mg (68%) of a colorless oil, which was identified by NMR and MS as cyclic urethane **3**. ^1H NMR (300 MHz, $CDCl_3$): δ 7.70 (1 H, br s, NH), 6.81 (1 H, d, J = 8 Hz, H_4), 6.71 (1 H, d, J = 8 Hz, H_5), 6.32 (1 H, d, J = 7 Hz, H_{24}), 4.91 (1 H, d, J = 7 Hz, H_{25}), 3.98 and 3.48 (2 × 1 H, 2 d, J = 11 Hz, H_{12}), 3.74–3.56 (2 H, m, CH_2Cl), 3.24 (1 H, br dd, J = 10, 10 Hz, H_{20}), 3.09 (3 H, s, NCH_3), 2.81 and 2.00 (2 × 1 H, d, J = 15 Hz, H_{10}), 2.87–2.75 and 2.65–2.53 (2 × 1 H, m, CH_2CH_2Cl), 1.95 and 1.79 (2 × 1 H, dd, J = 10, 12 Hz, H_{19}), 1.55 (3 H, s, $C_{14}CH_3$), 1.45 and 1.43 (2 × 3 H, s, H_{27} and H_{28}), 1.10 and 0.88 (2 × 3 H, s, H_{22} and H_{23}). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 181.9, 168.9, 155.2, 146.4, 138.8, 135.4, 132.2, 124.0, 120.4, 117.8, 115.3, 83.9, 79.9, 66.7, 64.9, 62.8, 52.3, 49.9, 46.1, 39.5, 39.1, 36.8, 30.0, 29.8, 27.0, 25.0, 23.9, 20.7, 20.4. FAB-MS: 556, 558 (M + H). Anal. Calcd for $C_{29}H_{34}ClN_3O_6$: C, 62.64; H, 6.16; N, 7.56. Found: C, 62.41; H, 6.34; N, 7.88.

Reduction of 3 with Super-Hydride. A solution of lithium triethylborohydride in tetrahydrofuran (1.1 mL of a 1.0 M THF solution, 1.1 mmol) was added under nitrogen to a cold (0 °C) solution of cyclic urethane **3** (60 mg, 0.1 mmol) in 3 mL of dry tetrahydrofuran. The resulting solution was stirred at room

(10) The conversion of cyclic amines to lactams by oxidation with bromine is a known reaction: Picot, A.; Lusinchi, X. *Synthesis* **1975**, 109.

(11) For comparison the ^1H NMR and ^{13}C NMR spectra of paraherquamide are summarized below. ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (1 H, br s, NH), 6.80 (1 H, d, J = 8 Hz, H_4), 6.68 (1 H, d, J = 8 Hz, H_5), 6.31 (1 H, d, J = 8 Hz, H_{24}), 4.89 (1 H, d, J = 8 Hz, H_{25}), 3.60 (1 H, d, J = 11 Hz, H_{12a}), 3.21 (1 H, ddd, J = 4, 9, 9 Hz, H_{16b}), 3.05 (3 H, s, NCH_3), 3.03 (1 H, br dd, J = 10, 10 Hz, H_{20}), 2.69 and 1.86 (2 × 1 H, 2 d, J = 15 Hz, H_{10}), 2.66 (1 H, br s, OH), 2.56 (1 H, br d, J = 11 Hz, H_{12b}), 2.40–2.20 (2 H, m, H_{15b} and H_{16a}), 1.94–1.74 (3 H, m, H_{15a} and H_{19}), 1.65 (3 H, s, H_{17}), 1.45 and 1.44 (2 × 3 H, 2 s, H_{27} and H_{28}), 1.10 and 0.86 (2 × 3 H, 2 s, H_{22} and H_{23}). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 183.4, 172.0, 146.6, 139.5, 135.8, 133.0, 125.5, 120.8, 117.7, 115.5, 80.3, 78.6, 71.8, 65.8, 63.6, 59.6, 52.3, 52.0, 46.9, 38.6, 37.5, 30.4, 30.3, 26.4, 24.2, 22.6, 20.9, 19.6.

temperature for 7 h and then cooled in an ice bath as 5% aqueous $NaHCO_3$ (3 mL) was added slowly (foaming). The aqueous layer was extracted with ether (7 mL) and dichloromethane (4 × 7 mL). The combined organic extracts were dried with magnesium sulfate, filtered, and evaporated under vacuum. Preparative layer chromatography of the residue on a 1.5 mm silica gel plate eluted with 5% methanol in dichloromethane afforded one pure compound (R_f 0.26, 13 mg) and another band, which was a mixture of two compounds (R_f 0.37, 38 mg). The pure compound was identified by NMR and MS as 14-*O*,16-cyclo-16,*N*-secoparaherquamide (**5**, 13 mg = 25%). The impure band was rechromatographed on a 0.5 mm silica gel plate eluted with 50% acetone in hexane to afford two new derivatives. The first (R_f 0.32, 23 mg = 41%) was identified by NMR and MS as the cyclized analogue **4**. The second product obtained (R_f 0.44, 13 mg = 25%) was identified by NMR and MS as 16,*N*-secoparaherquamide (**6**). ^1H NMR data (300 MHz, $CDCl_3$) for **4**: δ 7.68 (1 H, br s, NH), 6.79 (1 H, d, J = 8 Hz, H_4), 6.68 (1 H, d, J = 8 Hz, H_5), 6.28 (1 H, d, J = 8 Hz, H_{24}), 4.87 (1 H, d, J = 8 Hz, H_{25}), 4.02–3.94 and 3.52–3.44 (2 × 1 H, m, H_{30}), 4.00 (1 H, s, H_{18}), 3.88 (1 H, d, J = 10 Hz, H_{12a}), 3.60 (1 H, d, J = 10 Hz, H_{12b}), 3.16 (1 H, dd, J = 10, 10 Hz, H_{20}), 2.61 and 1.68 (2 H, 2 d, J = 15 Hz, H_{10}), 2.70 (3 H, s, NCH_3), 2.59 and 1.68 (2 × 1 H, d, J = 15 Hz, CH_2CH_2OCHN), 1.60–1.80 (2 H, m, H_{19}), 1.45, 1.43 and 1.41 (3 × 3 H, 3 s, $C_{14}CH_3$, H_{26}, and H_{28}), 1.10 and 0.91 (2 × 3 H, 2 s, H_{22} and H_{23}). ^{13}C NMR (75.4 MHz, $CDCl_3$) data: δ 182.0, 156.6, 146.0, 138.8, 135.2, 132.0, 125.5, 120.7, 117.6, 115.2, 94.5, 80.0, 79.8, 62.5, 62.4, 60.8, 60.6, 53.0, 45.8, 44.2, 36.9, 35.2, 34.3, 30.0, 29.7, 25.1, 24.5, 21.9, 21.0. HRMS: m/z (M^+, $C_{29}H_{35}N_3O_6$) calcd 521.2525, obsd 521.2526. ^1H NMR data (300 MHz, $CDCl_3$) for 14-*O*,16-cyclo-16,*N*-secoparaherquamide (**5**): δ 7.60 (1 H, br s, NH), 6.82 (1 H, d, J = 8 Hz, H_4), 6.68 (1 H, d, J = 8 Hz, H_5), 6.32 (1 H, d, J = 8 Hz, H_{24}), 4.89 (1 H, d, J = 8 Hz, H_{25}), 4.65–4.45 (2 H, m, H_{16}), 3.54 (1 H, d, J = 11 Hz, H_{12a}), 3.12–3.00 and 2.42–2.30 (2 × 1 H, m, H_{15}), 3.07 (3 H, s, NCH_3), 3.06 (1 H, dd, J = 10, 10 Hz, H_{20}), 3.04 (1 H, d, J = 11 Hz, H_{12b}), 2.71 and 1.82 (2 × 1 H, 2 d, J = 15 Hz, H_{10}), 1.85 and 1.57 (2 × 1 H, 2 dd, J = 10, 12 Hz, H_{19}), 1.70 (3 H, s, H_3CCO), 1.43 and 1.41 (2 × 3 H, 2 s, H_{27} and H_{28}), 1.08 and 0.82 (2 × 3 H, 2 s, H_{22} and H_{23}). ^{13}C NMR (75.4 MHz, $CDCl_3$) data: δ 182.0, 172.4, 146.9, 138.9, 135.2, 132.3, 124.8, 120.5, 117.3, 115.1, 88.1, 79.8, 66.3, 64.1, 63.3, 63.0, 53.4, 50.9, 46.8, 37.2, 30.2, 30.0, 29.8, 26.5, 25.4, 23.9, 23.6, 20.7. HRMS: m/z (M^+, $C_{28}H_{35}N_3O_5$) calcd 493.2576, obsd 493.2575. ^1H NMR data (300 MHz, $CDCl_3$) for 16,*N*-secoparaherquamide (**6**): δ 7.90 (1 H, br s, NH), 6.81 (1 H, d, J = 8 Hz, H_4), 6.68 (1 H, d, J = 8 Hz, H_5), 6.33 (1 H, d, J = 8 Hz, H_{24}), 4.90 (1 H, d, J = 8 Hz, H_{25}), 3.38 (1 H, d, J = 11 Hz, H_{12a}), 3.08 (3 H, s, NCH_3), 3.02 (1 H, dd, J = 10, 10 Hz, H_{20}), 2.90 (1 H, d, J = 11 Hz, H_{12b}), 2.69 and 1.92 (2 × 1 H, 2 d, J = 15 Hz, H_{10}), 1.95 and 1.93 (2 × 3 H, 2 s, H_{27} and H_{28}), 1.25 (3 H, s, H_{17}), 1.12 and 0.84 (2 × 3 H, 2 s, H_{22} and H_{23}), 1.02 (3 H, t, J = 7 Hz, H_{16}). HRMS: m/z (M^+, $C_{28}H_{37}N_3O_5$) calcd 495.2733, obsd 495.2733.

1-*N*-(3-Chloropropyl)paraherquamide (9). Silver oxide (47 mg, 0.20 mmol), potassium carbonate (28 mg, 0.20 mmol), and 1-bromo-3-chloropropane (0.10 mL, 1.0 mmol) were added sequentially to a solution of paraherquamide (50 mg, 0.10 mmol) in 2 mL of dry DMF. The resulting mixture was stirred at 55 °C for 7 h. Analytical TLC indicated that the reaction was not complete, so an additional 0.10 mL of 1-bromo-3-chloropropane was added and the mixture was stirred at 55 °C for an additional 18 h. The reaction mixture was diluted with ether (5 mL), and then 2 mL of 5% aqueous $NaHCO_3$ was added. The aqueous layer was extracted with ether (3 × 5 mL) and methylene chloride (2 × 5 mL). The combined extracts were dried with magnesium sulfate, filtered, and evaporated under vacuum (high vacuum to remove DMF). Preparative layer chromatography of the residue on a 0.5 mm silica gel plate eluted with 50% acetone in hexane afforded 35 mg (61%) of an amorphous white solid (R_f 0.39), which was identified by NMR and MS as 1-*N*-(3-chloropropyl)paraherquamide (**9**): ^1H NMR (300 MHz, $CDCl_3$): δ 6.81 (1 H, d, J = 8 Hz, H_4), 6.69 (1 H, d, J = 8 Hz, H_5), 6.37 (1 H, d, J = 8 Hz, H_{24}), 4.86 (1 H, d, J = 8 Hz, H_{25}), 4.15–3.90 (2 H, m, NCH_2), 3.62–3.52 (2 H, m, CH_2Cl), 3.57 and 2.53 (2 × 1 H, 2 d, J = 11 Hz, H_{12}), 3.18 (1 H, ddd, J = 4, 9, 9 Hz, H_{16b}), 3.02 (3 H, s, NCH_3), 3.02 (1 H, br dd, J = 10, 10 Hz, H_{20}), 2.63 and 1.81 (2 × 1 H, 2 d, J = 15 Hz, H_{10}), 2.61 (1 H, s, OH), 2.36–2.00 (4 H, m, H_{15b} + H_{16a} + $NCH_2CH_2CH_2Cl$), 1.90–1.72 (3 H, m, H_{19} and H_{15a}), 1.61 (3 H, s, H_{17}), 1.43 and 1.40 (2 × 3 H, 2 s, H_{27} and H_{28}), 1.02 and 0.72 (2 × 3 H, 2 s, H_{22} and H_{23}). FAB-MS (M + H) 570. Anal. Calcd for $C_{31}H_{40}ClN_3O_5$: C, 65.31; H, 7.07; N, 7.37. Found: C, 65.14; H, 7.28; N, 7.23.

Reduction of 1-*N*-(3-Chloropropyl)paraherquamide with Super-Hydride. A solution of lithium triethylborohydride in THF (0.37 mL of a 1.0 M THF solution, 0.37 mmol) was added under nitrogen to a cold (0 °C) solution of chloride **9** (35 mg, 0.06 mmol) in 2 mL of dry THF. The resulting solution was stirred at room temperature for 2 h, and then an additional 0.37 mL of the 1.0 M lithium triethylborohydride solution was added. The solution was stirred at room temperature for an additional 4 h and then cooled in an ice bath as water (1 mL) and 5% aqueous $NaHCO_3$ (1 mL) were added slowly (foaming). The aqueous layer was extracted with ether (4 × 5 mL) and dichloromethane (2 × 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated under vacuum. Preparative layer chromatography of the residue on a 0.5 mm silica gel plate eluted with ethyl acetate afforded 25 mg (76%) of a colorless oil (R_f 0.26), which was identified by NMR and MS as 1-*N*-propylparaherquamide (**10**). ^1H NMR (300 MHz, $CDCl_3$): δ 6.81 (1 H, d, J = 8 Hz, H_4), 6.67 (1 H, d, J = 8 Hz, H_5), 6.29 (1 H, d, J = 8 Hz, H_{24}), 4.85 (1 H, d, J = 8 Hz, H_{25}), 3.94–3.68 (2 H, m, NCH_2), 3.58 and 2.53 (2 × 1 H, 2 d, J = 11 Hz, H_{12}), 3.17 (1 H, ddd, J = 4. 9, 9 Hz, H_{16b}), 3.03 (3 H, s, NCH_3), 3.03 (1 H, br d, J = 10, 10 Hz, H_{20}), 2.61 and 1.80 (2 × 1 H, 2 d, J = 15 Hz, H_{10}), 2.61 (1 H, br s, OH), 2.37–2.15 (2 H, m, H_{15b} and H_{16a}), 1.90–1.50 (5 H, m, H_{15a} + H_{19} + $CH_2CH_2CH_3$), 1.62 (3 H, s, H_{17}), 1.43 and 1.40 (2 × 3 H, 2 S, H_{27} and H_{28}), 1.02 and 0.73 (2 × 3 H, 2 s, H_{22} and H_{23}), 0.93 (3 H, t, J = 8 Hz, $CH_2CH_2CH_3$). HRMS: m/z (M^+, $C_{31}H_{41}N_3O_5$) calcd 535.3046, obsd, 535.3048.

Conversion of Chloride 3 to Alcohol 12. 1,8-Diazabicyclo-[5.4.0]undec-7-ene (DBU, 0.050 mL, 0.33 mmol) was added to a solution of chloride **3** (35 mg, 0.063 mmol) in 1.5 mL of 9:1 methanol–water. The solution was stirred at 55 °C for 4 h. The mixture was diluted with ether (2 mL), and then 1 mL of 5% aqueous sodium bicarbonate was added. The layers were separated, and the aqueous layer was extracted with ether (3 × 3 mL) and methylene chloride (2 × 2 mL). The combined extracts were dried with magnesium sulfate, filtered, and evaporated under vacuum. Preparative layer chromatography of the residue on a 1.0 mm silica gel plate eluted with 7% methanol in methylene chloride afforded 22 mg (65%) of an amorphous white solid (R_f 0.29), which was identified by NMR and MS as alcohol **12**. ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (1 H, br s, NH), 6.82 (1 H, d, J = 8 Hz, H_4), 6.72 (1 H, d, J = 8 Hz, H_5), 6.32 (1 H, d, J = 8 Hz, H_{24}), 4.90 (1 H, d, J = 8 Hz, H_{25}), 3.87 and 3.52 (2 × 1 H, 2 d, J = 11 Hz, H_{12}), 3.98–3.86 and 3.82–3.66 (2 × 1 H, 2 m, CH_2OH), 3.20 (1 H, br dd, J = 10, 10 Hz, H_{20}), 3.07 (3 H, s, NCH_3), 3.10–2.96 and 2.20–2.10 (2 × 1 H, m, CH_2CH_2OH), 2.81 and 2.20 (2 × 1 H, 2 d, J = 15 Hz, H_{10}), 2.34 (1 H, br s, OH), 2.12 and 1.83 (2 × 1 H, dd, J = 10, 12 Hz, H_{19}), 1.55 (3 H, s, $C_{14}CH_3$), 1.46 and 1.44 (2 × 3 H, 2 s, H_{27} and H_{28}), 1.11 and 0.88 (2 × 3 H, 2 s, H_{22} and H_{23}). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 182.1, 170.9, 155.5, 146.4, 138.9, 135.4, 132.3, 124.0, 120.3, 117.7, 115.2, 85.3, 79.9, 66.7, 64.9, 62.8, 58.8, 52.3, 49.7, 46.2, 38.0, 36.6, 29.9, 29.8, 27.1, 24.9, 23.7, 21.4, 20.6. HRMS: m/z (M^+, $C_{29}H_{35}N_3O_7$) calcd 537.2475, obsd 537.2476.

5-Bromoparaherquamide (13). A solution of bromine in carbon tetrachloride (2.0 mL of a 0.12 M solution, 0.24 mmol) was added to a cold (ice bath) solution of paraherquamide (60 mg, 0.12 mmol) in 6 mL of chloroform. The yellow solution was stirred at room temperature for 70 min, and then 5 mL of 5% aqueous sodium bicarbonate was added. The layers were separated, and the aqueous layer was extracted with methylene chloride (4 mL). The combined organic layers were dried with magnesium sulfate, filtered, and evaporated under vacuum. The residue was dissolved in 5 mL of THF, and then zinc dust (80 mg, 1.2 mmol) was added followed immediately by 1 mL of 1 M aqueous potassium dihydrogen phosphate. The mixture was stirred at room temperature for 15 h, and then 4 mL of 5% aqueous sodium bicarbonate was added. The mixture was extracted with ether (3 × 5 mL), and the combined extracts were dried with magnesium sulfate, filtered, and evaporated under vacuum. Preparative layer chromatography of the residue on a

1.5 mm silica gel plate eluted with 50% acetone in hexane afforded 37 mg (53%) of an amorphous white solid (R_f 0.33), which was identified by NMR and MS as 5-bromoparaherquamide (**13**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (1 H, br s, NH), 7.10 (1 H, s, H_4), 6.34 (1 H, d, J = 8 Hz, H_{24}), 4.95 (1 H, d, J = 8 Hz, H_{25}), 3.59 and 2.58 (2 × 1 H, 2 d, J = 11 Hz, H_{12}), 3.21 (1 H, ddd, J = 4, 9, 9 Hz, H_{16b}), 3.03 (3 H, s, NCH_3), 3.03 (1 H, dd, J = 10, 10 Hz, H_{20}), 2.70 (1 H, br s, OH), 2.67 and 1.85 (2 × 1 H, 2 d, J = 15 Hz, H_{10}), 2.40–2.18 (2 H, m, H_{15b} and H_{16a}), 1.95–1.72 (3 H, m, H_{15a} and H_{19}), 1.64 (3 H, s, H_{17}), 1.51 (3 H, s, H_{27} and H_{28}), 1.11 and 0.84 (2 × 3 H, 2 s, H_{22} and H_{23}). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 182.1, 171.4, 143.6, 138.6, 136.0, 132.0, 125.5, 124.0, 115.4, 110.7, 81.7, 78.1, 71.4, 65.3, 63.2, 59.1, 51.9, 51.6, 46.8, 38.2, 37.2, 29.6 (2C), 26.0, 23.8, 22.3, 20.6, 19.2. FAB-MS: m/z 572, 574 (M + H).

5-Bromo-16-oxoparaherquamide (14a). A solution of bromine (260 mg, 1.60 mmol) in 1 mL of carbon tetrachloride was added to a cooled (ice bath) solution of paraherquamide (200 mg, 0.40 mmol) in 5 mL of chloroform. The mixture (orange precipitate) was stirred at room temperature for 75 min, and then 4 mL of 5% aqueous sodium bicarbonate was added followed by enough 1 N NaOH to raise the pH to 10. The layers were separated, and the aqueous layer was extracted with methylene chloride (3 × 3 mL). The combined organic layers were dried with magnesium sulfate, filtered, and evaporated under vacuum. The residue was dissolved in 10 mL of tetrahydrofuran, and then zinc dust (265 mg, 4.0 mmol) was added followed immediately by 2 mL of 1 M aqueous potassium dihydrogen phosphate. The mixture was stirred at room temperature for 17 h, and then 4 mL of 5% aqueous sodium bicarbonate was added. The pH of the aqueous layer was adjusted to 10 by addition of 1 N NaOH. The aqueous layer was extracted with ether (4 × 3 mL), and the combined extracts were dried ($MgSO_4$), filtered, and evaporated under vacuum. Flash chromatography of the residue on silica gel (18 cm of 230–400 mesh silica gel in a 40-mm column) eluted with 50% acetone in hexane afforded two fractions. The major fraction (R_f 0.22) was a white solid (103 mg, 43%, mp >210 °C dec), which was identified by NMR and MS as 5-bromo-16-oxoparaherquamide (**14a**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (1 H, br s, NH), 7.12 (1 H, s, H_4), 6.13 (1 H, d, J = 8 Hz, H_{24}), 4.96 (1 H, d, J = 8 Hz, H_{25}), 3.67 and 3.55 (2 × 1 H, 2 d, J = 12 Hz, H_{12}), 3.23 (1 H, dd, J = 10, 10 Hz, H_{20}), 3.02 (3 H, s, NCH_3), 2.80 and 2.03 (2 × 1 H, 2 d, J = 15 Hz, H_{10}), 2.78 and 2.53 (2 × 1 H, 2 d, J = 16 Hz, H_{15}), 2.10–1.95 (2 H, m, H_{19}), 1.84 (3 H, s, H_{17}), 1.53 and 1.51 (2 × 3 H, 2 s, H_{27} and H_{28}), 1.13 and 0.89 (2 × 3 H, 2 s, H_{22} and H_{23}). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 181.5, 172.8, 170.1, 143.8, 138.5, 136.1, 131.9, 124.7, 124.1, 115.5, 111.1, 81.8, 74.8, 69.8, 64.9, 63.2, 52.8, 48.7, 47.2, 46.8, 36.8, 29.7, 29.4, 27.0, 23.7, 22.3, 21.9, 20.5. HRMS (M^+, $C_{28}H_{32}BrN_3O_6$): calcd 585.1474, obsd 585.1475. The second fraction (R_f 0.42) was an impure oil. Preparative layer chromatography of this second fraction on a 0.5 mm silica gel plate eluted with ethyl acetate afforded 14 mg (6%) of an amorphous white solid (R_f 0.36), which was identified by NMR and MS as 5-bromo-12-oxoparaherquamide (**14b**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (1 H, br s, NH), 7.32 (1 H, s, H_4), 6.31 (1 H, d, J = 8 Hz, H_{24}), 4.94 (1 H, d, J = 8 Hz, H_{25}), 3.70–3.53 (2 H, m, H_{16}), 3.25 and 2.51 (2 × 1 H, 2 d, J = 15 Hz, H_{10}), 2.14–1.96 (4 H, m, H_{15} and H_{19}), 1.83 (3 H, s, H_{17}), 1.52 and 1.50 (2 × 3 H, 2 s, H_{27} and H_{28}), 0.88 and 0.83 (2 × 3 H, 2 s, H_{22} and H_{23}). FAB-MS: m/z 586 (M + H).

16-Oxoparaherquamide (14c). A. By Debromination of 14a. Potassium hydride (6 drops of a 25% oil dispersion) was added to a solution of 5-bromo-16-oxoparaherquamide (*14a*, 41 mg, 0.070 mmol) in 2 mL of dry THF. The mixture was stirred at room temperature for 30 min and then cooled to −78 °C. A solution of *tert*-butyllithium (0.175 mL of 2 M pentane solution, 0.35 mmol) was added, and the yellow mixture was stirred at −78 °C for 90 min. Water (2 mL) was then added cautiously, and the mixture was allowed to warm to 0 °C. Ether (2 mL) was added, and the layers were separated. The aqueous layer was extracted with ether (2 mL) and ethyl acetate (2 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated to a yellow oil. Preparative layer chromatography of this crude product on a 1.0 mm plate eluted three times with 50% acetone in hexane afforded 27 mg (76%) of a colorless oil identified by NMR and MS as 16-oxoparaherquamide. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (1 H, br s, NH), 6.81 (1 H, d, J = 8 Hz, H_4), 6.70 (1 H, d, J = 8 Hz, H_5), 6.32 (1 H, d, J = 8 Hz, H_{24}), 4.90 (1 H, d, J = 8 Hz, H_{25}), 3.68 and 3.54 (2 × 1 H, 2 d, J = 12 Hz, H_{12}), 3.14 (1 H, dd, J = 10, 10 Hz, H_{20}), 3.04 (3 H, s, NCH_3), 2.78 and 2.52 (2 × 1 H, 2 d, J = 16 Hz, H_{15}), 2.76 and 2.04 (2 × 1 H, 2 d, J = 15 Hz, H_{10}), 2.08–1.96 (2 H, m, H_{19}), 1.83 (3 H, s, H_{17}), 1.46 and 1.44 (2 × 3 H, 2 s, H_{27} and H_{28}), 1.11 and 0.88 (2 × 3 H, 2 s, H_{22} and H_{23}). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 181.8, 172.9, 170.1, 146.3, 138.9, 135.3, 132.2, 124.2, 120.4, 117.6, 115.2, 79.9, 74.9, 69.7, 64.9, 63.0, 52.6, 48.7, 47.1, 46.4, 36.7, 30.0, 29.7, 26.9, 23.6, 22.2, 21.7, 20.5. HRMS: m/z (M^+, $C_{28}H_{33}N_3O_6$) calcd 507.2369, obsd 507.2369.

B. By Air Oxidation of 1. Platinum black (21 mg) was added to a solution of paraherquamide (30 mg, 0.06 mmol) in 3 mL of 50% aqueous dioxane. Air was bubbled through the mixture as it was stirred at room temperature for 5 h. Additional platinum black was then added, and air was bubbled through the mixture for an additional 3 h. The mixture was stored in the freezer overnight and then rewarmed to room temperature. Additional platinum black was again added, and air was bubbled through the mixture for an additional 3 h (total reaction time 11 h). The mixture was then filtered through Celite and evaporated under vacuum. Preparative layer chromatography of the residue on a 1.5 mm silica gel plate eluted with 7% methanol in methylene chloride afforded 26 mg of an amorphous white solid (R_f 0.48), which was not completely pure by analytical layer chromatography. Preparative layer chromatography of this impure material on a 0.25 mm silica gel plate eluted with 50% acetone in hexane afforded 6 mg (19%) of an amorphous white solid (R_f 0.24), which was identical by TLC and NMR with material prepared by debromination of 5-bromo-16-oxoparaherquamide (see above).

12-Oxoparaherquamide by Debromination of 14b. Application of the debromination procedure described above to 11 mg of 5-bromo-12-oxoparaherquamide (**14b**) and preparative layer chromatography of the crude product on a 0.5 mm plate eluted with 40% acetone in hexane afforded 7 mg (77%) of a colorless oil (R_f 0.32), which was identified by NMR and MS as 12-oxoparaherquamide. ^{1}H NMR: δ 7.45 (1 H, br s NH), 7.00 (1 H, d, J = 8 Hz, H_4), 6.70 (1 H, d, J = 8 Hz, H_5), 6.30 (1 H, d, J = 8 Hz, H_{24}), 4.88 (1 H, d, J = 8 Hz, H_{25}), 3.70–3.52 (2 H, m, H_{16}), 3.37 (1 H, t, J = 9 Hz, H_{20}), 3.25 and 2.52 (2 × 1 H, 2 d, J = 15 Hz, H_{10}), 2.97 (3 H, s, NCH_3), 2.12–1.85 (4 H, m, H_{15} and H_{19}), 1.84 (3 H, s, H_{17}), 1.45 and 1.43 (2 × 3 H, 2 s, H_{27} and H_{28}), 0.85 and 0.83 (2 × 3 H, 2 s, H_{22} and H_{23}). HRMS: m/z (M^+, $C_{28}H_{33}N_3O_6$) calcd 507.2369, obsd 507.2369.

Conversion of 5-Bromoparaherquamide (13) to Alcohol 16. A solution of phosgene in toluene (2.0 mL of a 1.93 M toluene solution 3.86 mmol) was added dropwise to a solution of 5-bromoparaherquamide (**13**, 70 mg, 0.12 mmol) and (dimethylamino)pyridine (10 mg, 0.08 mmol) in 2 mL of pyridine, and then 2 mL of toluene was added. The mixture (voluminous precipitate) was stirred vigorously at room temperature for 65 h and then diluted with 4 mL of ether. The mixture was cooled in an ice bath as 4 mL of 5% aqueous sodium bicarbonate was added followed by sufficient 50% aqueous sodium hydroxide to raise the pH to 10. The layers were separated, and the aqueous layer was extracted with ether (4 × 3 mL) and methylene chloride (2 × 3 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated under vacuum. Preparative layer chromatography of the residue on a 1.0 mm silica gel plate eluted with 50% acetone in hexane afforded 35 mg of a yellow oil, which was not completely pure by analytical layer chromatography. Preparative layer chromatography of this impure material on a 0.5 mm silica gel plate eluted with 50% ethyl acetate in hexane afforded 30 mg (39%) of a colorless oil, which was identified by NMR and MS as cyclic urethane **15**. This material was dissolved in 2 mL of 90% aqueous methanol, and then 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.050 mL) was added. The solution was stirred at 55 °C for 19 h and then partitioned between ether (4 mL) and 5% aqueous $NaHCO_3$ (2 mL). The aqueous layer was extracted with ether (3 × 3 mL), and the combined organic layers were dried with magnesium sulfate, filtered, and evaporated under vacuum. Preparative layer chromatography of the residue on a 0.5 mm silica gel plate eluted with 7% methanol in methylene chloride afforded 20 mg (69%) of a colorless oil, which was identified by NMR and MS as **16**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (1 H, br s, NH), 7.12 (1 H, s, H_4), 6.32 (1 H, d, J = 8 Hz, H_{24}), 4.96 (1 H, d, J =

8 Hz, H_{25}), 3.97-3.87 and 3.80-3.70 (2 H, m, CH_2OH), 3.86 (1 H, d, J = 11 Hz, H_{12a}), 3.54 (1 H, d, J = 11 Hz, H_{12b}), 3.20 (1 H, br dd, J = 10, 10 Hz, H_{20}), 3.07 (3 H, s, NCH_3), 3.08-2.95 and 2.21-2.10 (2 × 1 H, m, CH_2CH_2OH), 2.80 and 2.02 (2 × 1 H, 2 d, J = 15 Hz, H_{10}), 2.39 (1 H, dd, J = 3, 8 Hz, OH), 2.12 and 1.84 (2 × 1 H, dd, J = 10, 12 Hz, H_{19}), 1.57 (3 H, s, $C_{14}CH_3$), 1.53 and 1.51 (2 × 3 H, 2 s, H_{27} and H_{28}), 1.13 and 0.89 (2 × 3 H, 2 s, H_{22} and H_{23}). FAB-MS: m/z 616, 618 (M + H).

Single-Crystal X-ray Diffraction Analysis of 16. Crystals grown from acetonitrile-methanol-methylene chloride were obtained in the form of prisms ($C_{29}H_{32}N_3O_7Br \cdot CH_3CN$; M_r = 655.51; monoclinic; space group $P2_1$; a = 13.187 (1), b = 7.743 (1), c = 14.871 (3) Å; β = 97.33 (1); V = 1506 Å^3; Z = 2; D_{calcd} = 1.341 g/cm; $F(000)$ = 680; μ = 23.08 cm^{-1}; R= 0.036; R_w = 0.052; S = 2.50). The crystal was enclosed in a capillary with some saturated solvent. A CAD4 diffractometer was used for data collection. The unit cell constants and their standard deviations were determined by least-squares analysis of diffractometer setting angles of 23 reflections with 30° ≤ 2θ < 40°. The intensities of 2203 reflections with 2° < 2θ < 120° were measured with 1.5° ω scans; of these, 2121 reflections had $I > 3\sigma(I)$. The intensities of three standard reflections were monitored during the data collection, and no significant deterioration of the crystal was observed. The data were corrected for Lorentz, polarization factors and for absorption. Scattering factors for neutral atoms with f' and f'' contributions for anomalous dispersion were used. The structure was solved by determining the Br position with a vector density map; all other non-hydrogen atoms were found subsequently by a series of difference Fourier analyses. One molecule of acetonitrile was found during these calculations. The structure was refined by a full-matrix least-squares procedure[12] using F^2 magnitudes with $w = [4F_o^2/\sigma(F_o^2)^2]$. When the refinement for the scale factor, the positional coordinates, and the anisotropic temperature factor of the 43 non-hydrogen atoms had converged, the absolute stereochemistry was determined. For one enantiomer R = 0.05357, R_w = 0.07963, and S = 3.644 while for the other enantiomer R = 0.05469, R_w = 0.08161, and S = 3.891, a difference which is statistically significant.[13] Centrosymmetrically related pairs of 16 enantiomer sensitive reflections were remeasured, and all data confirmed the assignment of the absolute configuration. Figure 1 shows a stereodrawing of the correct enantiomer with the configurations at the chiral carbon atoms established as 3R,11S,13R,14R,20S. The refinement was completed with hydrogen atoms assigned calculated positional coordinates and one overall isotropic temperature factor; these parameters were not adjusted during the final calculations. There were no significant deviations in the molecular dimensions from their expected values.

(12) All calculations were performed with the Enraf-Nonius Structure Determination Package, Revision 3-B, April 1980, on a DEC 11/60 computer.

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Supplementary Material Available: Tables of atomic positional parameters, anisotropic temperature factors, interatomic distances, and angles for **16**, ^{1}H NMR spectra (300 MHz) of all title compounds, and ^{1}H-^{1}H COSY NMR spectra of **1** and **4**. (21 pages). Ordering information is given on any current masthead page.

(13) Hamilton, W. C. *Acta. Crystallogr.* **1965**, *18*, 502.

Stereoselective Reactions of Lithium and Zinc *tert*-Butyl Phenylmethyl Sulfoxide with Carbonyl Compounds and Imines[1]

Stephen G. Pyne*[2,4] and Gernot Boche[3]

Department of Chemistry, University of Wollongong, P.O. Box 1144, Wollongong, NSW 2500, Australia, and Fachbereich Chemie der Philipps-Universität, Hans-Meerwein Strasse, D-3550 Marburg, Federal Republic of Germany

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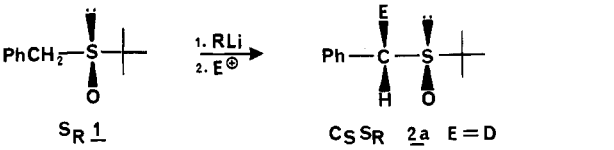
Racemic lithium *tert*-butyl phenylmethyl sulfoxide **1A** when quenched with benzophenone gives $C_{R*}S_{R*}$-2-(*tert*-butylsulfinyl)-1,1,2-triphenylethanol as determined by single-crystal X-ray analysis. The diastereoselection in the reaction of **1A** with various aldehydes and imines as a function of aldehyde and imine structure and metal cation (Li^+ or Zn^{2+}) is reported. Both substrates show a preference for anti diastereoselection. Transition-state structures are proposed to account for this diastereoselection.

In 1971, Durst[5] reported that the lithium carbanion of S_R-*tert*-butyl phenylmethyl sulfoxide (**1**) underwent highly diastereoselective reactions with deuterium oxide (D_2O), methyl iodide, and acetone. Methylation of the lithium carbanion of S_R-**1** gave C_SS_R-*tert*-butyl 1-phenylethyl sulfoxide (**2b**). In 1986, Iitaka[6] unequivocally showed by neutron diffraction crystallography that quenching the

Scheme I



S_R **1**

C_SS_R **2a** E = D
C_SS_R **2b** E = CH_3
C_RS_R **2c** E = $Ph_2C(OH)$—
C_RS_R **2d** E = RCH(OH)—

(1) Chiral Sulfur Compounds. 7. Part 6: Pyne, S. G.; Griffith, R.; Edwards, M. *Tetrahedron Lett.* **1988**, *29*, 2089.
(2) University of Wollongong.
(3) Philipps-Universität.
(4) This work was performed by S.G.P. while on sabbatical leave at Marburg in 1988.
(5) Durst, T.; Viau, R.; McClory, M. R. *J. Am. Chem. Soc.* **1971**, *93*, 3077.

0022-3263/89/1954-2663$01.50/0