to undergo cyclization via an intramolecular attack of an amido group.[14] A further support for the mechanism was obtained from the observation that prolinamide (**5**) undergoes a facile conversion to the known dimethylpyrroloimidazolone **12** in the presence of acetone,[15] according to the proposed sequence in Scheme III.

In this case, the obvious reaction intermediate (i.e. acetone adduct **11**) is a direct analogue to **10**, postulated to be the reactive species generating the novel pyrroloimidazolone **6**. Similar condensations (i.e. between acetone and amino/amido functional groups within the same molecule) are rather well established in the field of penicillin chemistry.[16]

Conclusions

This investigation has clearly demonstrated that reacting (*S*)-prolinamide (generated in situ from (*S*)-proline ethyl ester and ammonia) with dichloromethane affords the novel, chiral pyrroloimidazolone **6**. Further explorative work will show if this reaction can be found synthetically useful for the conversion of e.g. easily accessible α-amino acids to a range of substituted 1,3-imidazol-4-ones.

Experimental Section

All utilized chemicals were of reagent grade and were not submitted to any particular treatment (i.e. drying, purification) prior to use. Melting points were determined in capillary tubes on a Büchi SMP 20 melting point apparatus and are uncorrected. IR spectra were taken on a Perkin-Elmer Model 681 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL FX 90 Q (operating at 90 and 22.50 MHz, respectively) or on a JEOL FX 200 (operating at 200 and 50.10 MHz, respectively). Chemical shifts are reported in ppm on the δ scale relative to tetramethylsilane (Me_4Si). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet); br is used as abbreviation for broadened. Mass spectra (electron impact, ionizing voltage 70 eV) were obtained on a Hewlett-Packard Model 5970 A mass-selective detector, equipped with a Hewlett-Packard MS Chem Station, and the chemical ionization (CI) spectra were recorded on a LKB 2091 spectrometer using methane as the ionizing gas. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The optical purity of (*S*)-proline ethyl ester (**4**) was determined on GC after derivatization (ultrasonic bath, room temperature/5 min) with (*R*)-α-(methoxyphenyl)acetyl chloride (prepared from (*R*)-α-(methoxyphenyl)acetic acid; Fluka AG) in CH_2Cl_2/i-Pr_2EtN, using a fused silica capillary column (30 m × 0.32 mm) coated with 1.0 μm of cross-linked phenylcyanopropylmethylsilicone (J&W DB 1701 30W) at 240 °C isothermal oven temperature and a flame-ionization detector. Microanalyses were performed by Mikro Kemi AB, S-750 19 Uppsala, Sweden.

(*S*)-Proline Ethyl Ester (4). (*S*)-Proline (50.0 g, 0.43 mol) was suspended in ethanol (400 mL) and heated to 60 °C. Thionyl chloride (92.1 g, 0.77 mol) was added in one portion, and the resulting solution was allowed to react for 4 h. Excess thionyl chloride and ethanol were evaporated and followed by the addition of dichloromethane (250 mL), water (50 mL), and concentrated ammonia (75 mL). The organic phase was separated off and concentrated in vacuo to afford 63.6 g (97%) of a yellowish oil with a GC purity of ca. 95%: optical purity > 99.8% ee (GC); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.28 (t, 3 H, ester CH_3), 1.74–2.13 (m, 4 H, pyrrolidine CH_2-3 and CH_2-4), 2.88–3.05 (m, 2 H, pyrrolidine CH_2-5), 3.66–3.74 (m, 1 H, pyrrolidine CH-2), 4.19 (q, 2 H, ester CH_2); mass spectrum (EI 70 eV), *m/z* (relative intensity) 143 (M^+, 0.9), 71 (4.9), 70 ($M^+ - COOC_2H_5$, 100), 68 (8.9), 43 (14.2), 41 (15.0).

(*S*)-Hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (6). (*S*)-Proline ethyl ester (**4**) (31.0 g, 0.21 mol) was dissolved in dichloromethane (150 mL, ca. 2.34 mol) and placed in a stainless steel reactor. Gaseous ammonia (55.0 g, 3.24 mol) dissolved in methanol (150 mL) was added to the reactor, which was then sealed. The reaction mixture was stirred at 50 °C (3.5 bar) for 2 days, after which time the solution was cooled and the precipitated salts were filtered off. Removal of the solvents was performed on a rotary evaporator under reduced pressure to give 33.6 g of a crude, yellowish oil. A portion (15.0 g) of this oil was submitted to a chromatographic purification on a silica gel column (500 g) using methanol/ethanol (10:1) as eluant. The fractions containing the desired product (checked on GC) were combined and concentrated in vacuo to afford 7.0 g of a yellow oil, which subsequently was distilled to give 2.2 g (18%) of product **6** (GC purity >99%): bp 110 °C (0.05 mmHg); mp 95–103 °C; $[\alpha]^{20}_D$ −77.2° (*c* 1, MeOH); IR (KBr) 1690 cm^{-1} (amide C=O); ^{1}H NMR (200 MHz,$CDCl_3$) δ 1.72–2.23 (m, 4 H, CH_2-6, CH_2-7), 2.57–2.74 (m, 1 H, CH-5$_{endo}$), 3.14–3.27 (m, 1 H, CH-5$_{exo}$), 3.62–3.77 (m, 1 H, CH-7a), 4.14 (d, 1 H, CH-3$_{endo}$), 4.59 (d, 1 H, CH-3$_{exo}$), 7.79 (br s, 1 H, NH-2); ^{13}C NMR (50.10 MHz, $CDCl_3$) δ 25.4 and 27.5 (C-6 and C-7), 56.0 (C-5), 64.3 (C-7a), 66.1 (C-3), 179.4 (C-1); mass spectrum (EI 70 eV), *m/z* (relative intensity) 126 (M^+, 39.8), 98 ($M^+ - 28$, 33.5), 83 ($M^+ - CONH$, 78.4), 70 ($M^+ - CHNHCO$, 100), 55 (C_4H_7, 55.6), 41 (C_3H_5, 48.8). Anal. Calcd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.21; O, 12.68. Found: C, 57.1; H, 7.85; N, 21.95; O, 13.1.

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Registry No. **3**, 147-85-3; **4**, 5817-26-5; **6**, 125643-09-6; CH_2Cl_2, 75-09-2.

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Chemical Modification of Paraherquamide. 2. Replacement of the C-14 Methyl Group[1]

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Paraherquamide (**1**) is a toxic metabolite of *Penicillium paraherquei* that was reported several years ago by Yamazaki et al.[2,3] It is structurally related to the marcfortines that were isolated from *P. roqueforti* by Polonsky et al.[4] The unusual structures of these oxindole alkaloids have recently begun to attract the attention of synthetic

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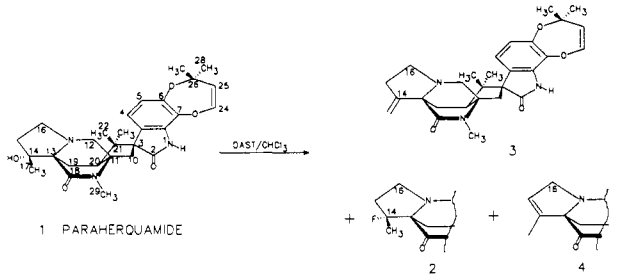
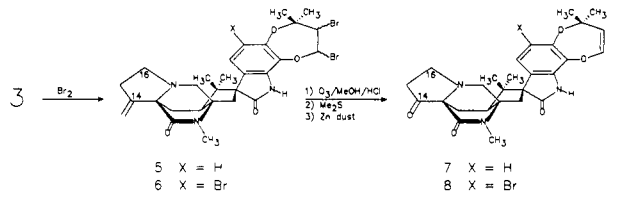
(3) The *Chemical Abstracts* name for paraherquamide is spiro[4*H*,8*H*-[1,4]dioxepino[2,3-*g*]indole-8,7′(8′*H*)-[5*H*,6*H*-5a,9a](iminomethano)[1*H*]cyclopent[*f*]indolizine]-9,10′(10*H*)-dione, 2′,3′,8′a,9′-tetrahydro-1′-hydroxy-1′,4,4,8′,8′,11′-hexamethyl-, (1′α,5′aβ,7′β,8′aβ,9′aβ)-(−). In the interest of brevity and clarity we have used trivial names based on paraherquamide rather than *Chemical Abstracts* names throughout this paper.
(4) (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.

0022-3263/90/1955-2256$02.50/0

Scheme I



Scheme II



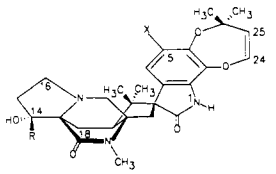
chemists.[5] The discovery that **1** and several natural analogues are potent antiparasitic agents[6] prompted us to begin a program of chemical modification of paraherquamide. We recently described several interesting reactions of **1** and reported its absolute stereochemistry.[1] We have also been studying the replacement of the methyl group at C-14 and in this paper we report a series of reactions that accomplishes this useful transformation.

One of our initial targets for derivatization of paraherquamide was the C-14 hydroxyl group. We treated paraherquamide with (diethylamino)sulfur trifluoride (DAST) in an attempt to replace the hydroxyl group with a fluorine atom. The desired fluoride **2** was isolated as one of the two minor byproducts of the reaction (Scheme I). However, the major product of the reaction was the exo olefin **3**, a natural product previously reported by Ondeyka et al.[6a] and Wichmann et al.[6b] The other minor byproduct of the reaction was the endo olefin **4**. We later found that **4** is the major product of the reaction of paraherquamide with carbonyldiimidazole (CDI).

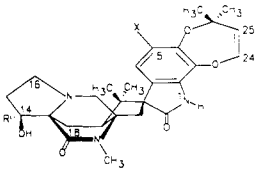
We felt that **3** would be a useful intermediate in the preparation of C-14 substituted analogues of **1** (via oxidative cleavage of the exo olefin followed by addition of a nucleophile to the resulting ketone). We anticipated that these would be especially interesting compounds since some of our other work indicated that C-14 was one of the few portions of the molecule that could be altered without reducing biological activity.

During the oxidative cleavage of the exo olefin it was necessary to protect the vinyl ether double bond. Based on our earlier work,[1] we expected the vinyl ether to be significantly more reactive to bromine than the exo olefin. Indeed, treatment of **3** with 1 equiv of bromine afforded dibromide **5** (mixture of stereoisomers, see Scheme II). Ozonolysis of **5** in *acidic* methanol (to protonate the tertiary amine) solution (methyl sulfide workup) followed by zinc dust reduction (to regenerate the vinyl ether)[1] afforded the desired ketone **7** in very low (ca. 5%) yield. The low yield was probably due to ozone attacking the aromatic ring (ozonolysis of dibromide **5** containing a small amount of 5-bromo olefin **6** resulted in formation of ketone **7** enriched in **8**, suggesting that the 5-bromo substituent was protecting the aromatic ring). Ozonolysis of **6** (from reaction of **3** with 2 equiv of bromine) followed by zinc dust reduction afforded ketone **8** in much higher (although still low) yield (26–36% from **3**). A small amount of **7** was also obtained as a byproduct resulting from incomplete bromination of **3**.

We therefore decided to use ketone **8** as the substrate for nucleophilic addition reactions with the expectation that we would be able to subsequently debrominate. Treatment of **8** with lithium aluminum hydride afforded a 40:60 mixture of the epimeric 17-nor analogues (**9a** and **10a**). However, reaction of **8** with sodium borohydride



9 (X = Br), 11 (X = H)
a R = H
b R = CH_3
c R = CH_2CH_3
d R = $CH{=}CH_2$



10 (X = Br), 12 (X = H)
a R = H
b R = CH_3
c R = CH_2CH_3
d R = $CH_2C_6H_5$

afforded **10a** almost exclusively with only a trace of the epimeric **9a**. The structures of **9a** and **10a** were assigned by comparison of their NMR spectra with spectra of the products from addition of methyl Grignard to ketone **8**. The epimeric Grignard addition products (**9b** and **10b**) were obtained in a 1:2 ratio by treating **8** with an excess of methylmagnesium iodide. The structure of **9b** was confirmed by comparison with authentic material, which we had prepared previously by bromination of paraherquamide.[1] In the ^1H NMR spectrum of **10b** the singlet for the methyl (C-17) protons was shifted upfield relative to the corresponding signal in the spectrum of **9b**. This upfield shift of H_{17} was observed for all paraherquamide analogues with the 14-epi stereochemistry. In addition, the signal for the OH proton in the spectrum of **10b** (and all other 14-epi analogues) was shifted considerably downfield relative to the corresponding signal for analogues with the natural stereochemistry at C-14. Both of these effects are due to the proximity of the C-14 substituents to the C-18 amide carbonyl group. Inspection of Dreiding models shows that in analogues with the normal stereochemistry the methyl group is close to (and in the plane of) the carbonyl group so the methyl protons are deshielded. In analogues with the 14-epi configuration, the methyl group is away from the carbonyl and the methyl protons are no longer deshielded. Similarly, in analogues with the 14-epi configuration, the 14-OH is hydrogen bonded to the amide carbonyl and is shifted downfield relative to analogues with the natural stereochemistry at C-14 in which the OH group is oriented away from the carbonyl. The C-14 epimers can thus be easily distinguished by ^1H NMR spectroscopy.

We prepared additional analogues by treating **8** with a variety of Grignard reagents. For example, reaction of **8** with ethylmagnesium bromide afforded a 3:1 mixture of the epimeric ethyl adducts (**9c** and **10c**) along with a substantial amount of the reduced product (**10a**). Surprisingly, the corresponding reaction with vinylmagnesium bromide afforded only **9d** (natural stereochemistry at C-14). On the other hand, treatment of **8** with benzylmagnesium chloride afforded only **10d** (epi stereochemistry at C-14). The reason for the differing facial selectivities

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Table I. Activity of Paraherquamide Analogues Against *C. elegans*

analogue	IC_{50} (μg/mL)
unsubstituted (1)	2.5
14-fluoro-14-deoxy- (2)	>100
14,17-anhydro- (3)	70
14,15-anhydro- (4)	80
14-oxo-17-nor- (7)	>100
14-oxo-5-bromo-17-nor- (8)	>100
5-bromo-17-nor- (9a)	>200
5-bromo- (9b)	>100
5-bromo-14-epi-17-nor- (10a)	>100
17-nor- (11a)	60
17-methyl- (11c)	0.75
17-methylene- (11d)	5
14-epi-17-nor- (12a)	>100
14-epi- (12b)	120
14-epi-17-methyl- (12c)	30

of these reagents is unclear but may reflect different states of aggregation and/or different degrees of complexation to the amide carbonyl.

We found that debromination could be accomplished by an adaptation of the method used by Rapoport et al. to effect halogen–metal exchange of brominated indoles.[7] The procedure involves treating the bromide with potassium hydride (to deprotonate OH and NH) followed by *tert*-butyllithium at −78 °C (to effect halogen–metal exchange) and then quenching the resulting alkyllithium derivative with water. Application of this procedure to **9d** afforded **11d** in 65% yield. Similarly, treatment of the other addition products (**9a–c**, **10a–d**) in this manner afforded the corresponding debrominated analogues (**11a–c**, **12a–d**) in yields ranging from 27–80% (see Experimental Section). We have thus been able to prepare a variety of paraherquamide analogues in which the C-14 methyl group has been replaced with other alkyl groups or hydrogen with either configuration at C-14.

The analogues were evaluated in a *Caenorhabditis elegans* motility assay (Table I).[8] The data in Table I indicate that analogues with substitution at C-5 or the 14-epi stereochemistry are substantially less active than paraherquamide. However, C-17 substituted analogues with the natural stereochemistry at C-14 are about as active as the natural product. Thus, it appears that relatively minor structural changes can have a substantial negative impact on the biological activity of paraherquamide. This conclusion is also supported by the biological data for numerous additional paraherquamide analogues that we have prepared and will describe in future publications.

Experimental Section

^1H and ^{13}C NMR spectra were measured at 300 and 75.4 MHz, respectively. All title compounds were judged to be at least 90–95% pure by ^1H NMR. See ref 1 for general experimental conditions and for ^1H and ^{13}C NMR data for paraherquamide.

14,17-Anhydroparaherquamide (3). (Diethylamino)sulfur trifluoride (DAST, 0.402 mL, 3.03 mmol) was added to a cold (ice bath) solution of paraherquamide (500 mg, 1.01 mmol) in 10 mL of dry chloroform. The cold bath was removed and the orange solution was stirred at room temperature for 1 h. The reaction mixture was cooled in an ice bath as 5 mL of 5% aqueous sodium bicarbonate, 5 mL of water, and 10 mL of dichloromethane were added sequentially. The pH of the aqueous layer was adjusted to ca. pH 10 by additions of 5 N NaOH (required ca. 3 mL). The layers were separated and the aqueous layer extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to an orange oil (915 mg). Analytical TLC (0.25-mm silica gel plate eluted with 50% acetone in hexane) of the crude product showed the presence of one major product (R_f 0.20) and two minor products (R_f 0.29 and 0.44). By comparison, paraherquamide has R_f 0.26 in this system. The crude product was purified by flash chromatography on silica gel eluted with 40% acetone in hexane. After rechromatography of mixed fractions a total of 185 mg (38%) of **3** (R_f 0.20 with 50% acetone in hexane) was obtained as an amorphous white solid. Also obtained were 25 mg (5%) of **4** (white amorphous solid, R_f 0.29 in 50% acetone in hexane) and 51 mg (10%) of **2** (white amorphous solid, R_f 0.44 in 50% acetone in hexane). Note that when the reaction was run on smaller scale in dichloromethane, **3** was obtained in much higher yield (46–62%). The ^1H NMR spectrum of synthetic **3** compared well with a spectrum (provided by Dr. Carol Wichmann of MSDRL) of natural **3**. See ref 6b for spectral data for **3**. ^1H NMR data for **4**: δ 7.39 (1 H, br s, NH), 6.85 (1 H, d, J = 8 Hz, H_4), 6.69 (1 H, d, J = 8 Hz, H_5), 6.31 (1 H, d, J = 8 Hz, H_{24}), 5.68 (1 H, br s, H_{15}), 4.89 (1 H, d, J = 8 Hz, H_{25}), 3.70–3.60 (2 H, m, H_{12a} + H_{16a}), 3.10–3.00 (2 H, m, H_{16b} + H_{20}), 3.05 (3 H, s, NCH_3), 2.81 (1 H, d, J = 11 Hz, H_{12b}), 2.75 (1 H, d, J = 15 Hz, H_{10a}), 2.07 (1 H, t, J = 12 Hz, H_{19}), 1.94 (3 H, br s, H_{17}), 1.93 (1 H, d, J = 15 Hz, H_{10b}), 1.45 and 1.44 (2 × 3 H, 2 s, H_{27} and H_{28}), 1.10 and 0.90 (2 × 3 H, 2 s, H_{22} and H_{23}). FAB-MS: m/z 476 (M + H). ^1H NMR data for **2**: δ 7.61 (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), 6.31 (1 H, d, J = 8 Hz, H_{24}), 4.89 (1 H, d, J = 8 Hz, H_{25}), 3.72 (1 H, d, J = 11 Hz, H_{12a}), 3.32 (1 H, m H_{16b}), 3.09 (1 H, br dd, J = 10, 10 Hz, H_{20}), 3.06 (3 H, s, NCH_3), 2.70 and 1.89 (2 × 1 H, 2 d, J = 15 Hz, H_{10}), 2.59 (1 H, br d, J = 11 Hz, H_{12b}), 2.35–2.15 (4 H, m, H_{15}, H_{16a}, and H_{19a}), 1.94–1.85 (1 H, m, H_{19b}), 1.82 (3 H, d, J = 25 Hz, H_{17}), 1.44 and 1.43 (2 × 3 H, 2 s, H_{27} and H_{28}), 1.12 and 0.86 (2 × 3 H, 2 s, H_{22} and H_{23}). ^{19}F NMR ($CDCl_3$, ppm relative to Freon-11): δ −133.3 to −133.9 (m, F). HRMS: m/z (M^+, $C_{28}H_{34}N_3O_4F$) calcd 495.2533, obsd 495.2535.

5-Bromo-14-oxo-17-norparaherquamide (8). A solution of bromine (74 mg, 0.46 mmol) in 1 mL of carbon tetrachloride was added to a cold (−20 °C) solution of **3** (110 mg, 0.23 mmol) in 4 mL of chloroform. The yellow solution was allowed to warm to room temperature and the solvent was evaporated under vacuum. The yellow solid residue was dissolved in 10 mL of 9:1 methanol/2 N HCl and the resulting yellow solution cooled to −78 °C (dry ice/acetone bath). A stream of ozone in oxygen gas was bubbled through the solution for 80 s followed by a stream of nitrogen gas for 1 min. Methyl sulfide (0.11 mL, 1.5 mmol) was then added and the mixture allowed to warm to 5 °C. Zinc dust (90 mg, 1.4 mmol) was added and the mixture was stirred at room temperature for 1 h. The mixture was then concentrated under vacuum and the residual oil partitioned between ether (5 mL) and water (3 mL). The pH was adjusted to 10 by careful addition of 5 N aqueous sodium hydroxide; then the mixture was filtered to remove the white precipitate. The layers were separated and the aqueous layer extracted with ether (2 × 3 mL) and ethyl acetate (3 × 3 mL). The combined extracts were dried, filtered, and evaporated under vacuum. Preparative TLC of the residue on a 0.5-mm silica gel plate eluted with ethyl acetate afforded 46 mg (36%) of **8** as a light yellow oil (R_f 0.35). ^1H NMR: δ 7.48 (1 H, br s, NH), 7.12 (1 H, s, H_4), 6.32 (1 H, d, J = 8 Hz, H_{24}), 4.95 (1 H, d, J = 8 Hz, H_{25}), 3.74 (1 H, d, J = 11 Hz, H_{12a}), 3.35 (1 H, t, J = 8 Hz, H_{16b}), 3.13 (1 H, br dd, J = 10, 10 Hz, H_{20}), 3.07 (3 H, s, NCH_3), 2.70 and 1.89 (2 × 1 H, 2 d, J = 15 Hz, H_{10}), 2.69 (1 H, br d, J = 11 Hz, H_{12b}), 2.68–2.4 (3 H, m, H_{15} + H_{16}a), 2.20 (1 H, t, J = 12 Hz, H_{19a}), 1.62 (1 H, dd, J = 11, 12 Hz, H_{19b}), 1.52 (6 H, s, H_{27} and H_{28}), 1.11 and 0.86 (2 × 3 H, 2 s, H_{22} and H_{23}). HRMS: m/z (M^+, $C_{27}H_{30}BrN_3O_5$) calcd 555.1369, obsd 555.1367.

17-Methylparaherquamide (11c) and 14-Epi-17-methylparaherquamide (12c). A solution of 2 M ethylmagnesium bromide in THF (0.39 mL, 0.78 mmol) was added to a cold (−78 °C) solution of **8** (29 mg, 0.052 mmol) in 2 mL of dry methylene chloride. The resulting solution was stirred at −78 °C for 30 min and then at room temperature for 2 h. Water (2 mL) was then added slowly and the mixture centrifuged to separate the layers. The aqueous layer was extracted with dichloromethane (3 × 4 mL) and the combined extracts were dried, filtered, and evaporated under vacuum. Preparative TLC of the residual oil on a

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(8) The *C. Elegans* motility assay was carried out as described in ref 6a.

0.5-mm silica gel plate eluted with ethyl acetate afforded 17 mg of a mixture of **9c** and **10c** as a colorless oil (R_f 0.41) along with 8 mg of reduction product **10a** (R_f 0.15) and 8 mg of recovered ketone **8** (R_f 0.29). The mixture of **9c** and **10c** was rechromatographed on a 0.25-mm silica gel plate eluted twice with 3.5% methanol in methylene chloride. Two bands were extracted from the plate. The first (R_f 0.42) afforded 9 mg (20%) of **9c** as a colorless oil. The second band (R_f 0.30) afforded 3 mg (7%) of **10c** as a colorless oil. Potassium hydride (6 drops of a 25% oil dispersion) was added to a solution of **9c** (15 mg, 0.025 mmol) in 1 mL of dry THF. The mixture was stirred at room temperature for 15 min and then cooled to −78 °C. A solution of *tert*-butyllithium in pentane (0.15 mL of 2 M pentane solution, 0.30 mmol) was added and the yellow mixture was stirred at −78 °C for 2 h. Water (1 mL) was then added cautiously and the mixture was allowed to warm to ca. 5 °C. Ether (2 mL) was added and the layers were separated. The aqueous layer was extracted with ether (2 × 2 mL) and ethyl acetate (2 × 2 mL). The combined extracts were dried, filtered, and evaporated under vacuum. Preparative TLC of the oily residue on a 0.5-mm silica gel plate eluted with ethyl acetate afforded 9 mg (69%) of **11c** as a colorless oil (R_f 0.30). ^{1}H NMR data: δ 7.84 (1 H, br s, NH), 6.79 (1 H, d, J = 8 Hz, H_4), 6.66 (1 H, d, J = 8 Hz, H_5), 6.30 (1 H, d, J = 8 Hz, H_{24}), 4.87 (1 H, d, J = 8 Hz, H_{25}), 3.59 and 2.53 (2 × 1 H, 2 d, J = 11 Hz, H_{12}), 3.22–3.14 (1 H, m, H_{16b}), 3.03 (3 H, s, NCH_3), 3.00 (1 H, br dd, J = 10, 10 Hz, H_{20}), 2.68 and 1.85 (2 × 1 H, 2 d, J = 15 Hz, H_{10}), 2.59 (1 H, br s, OH), 2.30–2.15 (2 H, m, H_{15b} and H_{16}a), 1.92–1.70 (5 H, m, H_{15}a + H_{17} + H_{19}), 1.43 and 1.42 (2 × 3 H, 2 s, H_{27} and H_{28}), 1.08 and 0.83 (2 × 3 H, 2 s, H_{22} and H_{23}), 1.02 (3 H, t, J = 8 Hz, 17-CH_3). HRMS: m/z (M^+, $C_{29}H_{37}N_3O_5$) calcd 507.2733, obsd 507.2733. Application of the procedure described above to 5 mg of **10c** afforded a yellow oil, which was chromatographed on a 0.25-mm silica gel plate eluted with ethyl acetate to afford 3 mg (70%) of**12c** as a colorless oil (R_f 0.35). ^{1}H NMR data: δ 7.51 (1 H, br s, NH), 6.78 (1 H, d, J = 8 Hz, H_4), 6.66 (1 H, d, J = 8 Hz, H_5), 6.50 (1 H, br s, OH), 6.30 (1 H, d, J = 8 Hz, H_{24}), 4.87 (1 H, d, J = 8 Hz, H_{25}), 3.60 and 2.59 (2 × 1 H, 2 d, J = 11 Hz, H_{12}), 3.05–2.95 (2 H, m, H_{16b} and H_{20}), 3.08 (3 H, s, NCH_3), 2.68 and 1.85 (2 × 1 H, 2 d, J = 15 Hz, H_{10}), 2.50–2.40 and 2.22–2.10 (2 × 1 H, 2 m, H_{15b} and H_{16a}), 2.02–1.80 (3 H, m, H_{15a} and H_{19}), 1.74–1.54 (2 H, m, H_{17}), 1.43 and 1.42 (2 × 3 H, 3 s, H_{27} and H_{28}), 1.08 and 0.84 (2 × 3 H, 2 s, H_{22} and H_{23}), 1.02 (3 H, t, J = 8 Hz, 17-CH_3). HRMS: m/z (M^+, $C_{29}H_{37}N_3O_5$) calcd 507.2733, obsd 507.2733.

17-Norparaherquamide (11a) and 14-Epi-17-norparaherquamide (12a). A solution of 1 M lithium aluminum hydride in ether (0.14 mL, 0.14 mmol) was added to a cold (ice bath) solution of **8** (39 mg, 0.07 mmol) in 2 mL of dry THF. The mixture was stirred at 0 °C for 20 min and then water (1 mL) and ether (2 mL) were added and the layers separated. The aqueous layer was extracted with ether (2 × 2 mL) and ethyl acetate (2 × 2 mL). The combined extracts were dried, filtered, and evaporated under vacuum. Preparative TLC of the residue on a 0.5-mm silica gel plate eluted with 7% methanol in methylene chloride afforded 10 mg (26%) of **9a** as a colorless oil (R_f 0.20). A second band (R_f 0.36) afforded 15 mg (38%) of **10a** as a colorless oil. Application of the debromination procedure described above to 17 mg of **9a** and preparative TLC of the crude product on a 0.5-mm silica gel plate eluted with 7% methanol in methylene chloride afforded 4 mg (27%) of **11a** as a colorless oil (R_f 0.24). ^{1}H NMR data: δ 7.54 (1 H, br s, NH), 6.80 (1 H, d, J = 8 Hz, H_4), 6.66 (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}), 4.72 (1 H, br t, J = Hz, H_{14}), 3.63 and 2.61 (2 × 1 H, 2 d, J = 11 Hz, H_{12}), 3.18 (1 H, br t, J = 9 Hz, H_{16b}), 3.05 (1 H, br dd, J = 10, 10 Hz, H_{20}), 3.05 (3 H, s, NCH_3), 2.68 and 1.86 (2 × 1 H, 2 d, J = 15 Hz, H_{10}), 2.51–2.39 (1 H, m, H_{15b}), 2.22–2.10 (1 H, m, H_{16a}), 1.94–1.74 (4 H, m, H_{15a} + H_{19} + OH), 1.53 and 1.52 (2 × 3 H, 2 s, H_{27} and H_{28}), 1.11 and 0.85 (2 × 3 H, 2 s, H_{22} and H_{23}). HRMS: m/z (M^+, $C_{27}H_{33}N_3O_5$) calcd 479.2420, obsd 479.2420. Application of the debromination procedure described above to 21 mg of **10a** and preparative TLC of the crude product on a 0.5-mm silica gel plate eluted with 50% acetone in hexane afforded 9 mg (50%) of **12a** as a colorless oil (R_f 0.25). ^{1}H NMR data: δ 7.62 (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), 6.31 (1 H, d, J = 8 Hz, H_{24}), 5.53 (1 H, d, J = 11 Hz, OH), 4.90 (1 H, d, J = 8 Hz, H_{25}), 4.10–4.00 (1 H, m, H_{14}), 3.59 and 2.57 (2 × 1 H, 2 d, J = 11 Hz, H_{12}), 3.15–3.04 (2 H, m, H_{16b} and H_{20}), 3.09 (3 H, s, NCH_3), 2.69 and 1.87 (2 × 1 H, 2 d, J = 15 Hz, H_{10}), 2.48–2.32 (2 H, m, H_{15b} and H_{16a}), 2.21 (1 H, d, J = 11, 12 Hz, H_{19a}), 1.98–1.85 (1 H, m, H_{15a}), 1.52 (1 H, d, J = 11, 12 Hz, H_{19b}), 1.46 and 1.45 (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}). HRMS: m/z (M^+, $C_{27}H_{33}N_3O_5$) calcd 479.2420, obsd 479.2420.

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Supplementary Material Available: Experimental procedures for **11d**, **12b**, and **12d** and an alternative procedure for **4**; ^{1}H NMR spectra (300 MHz) of all title compounds and isolated intermediates; and ^{13}C NMR data for **2**, **3**, **8**, and **11d** (21 pages). Ordering information is given on any current masthead page.

Two Rings in One Step: A Novel 1,2,4-Triazolo[1,5-*a*]pyridone with an Unusual Crystal Structure

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Although the title molecules are reported to be useful compounds,[1] they are not easy to obtain.

The known methods for the synthesis of 1,2,4-triazolo[1,5-*a*]pyridines require several steps, with separate formation of each ring. The key step usually involves the construction of a triazole ring on a pyridine compound,[2-8] although syntheses starting from a triazole derivative have also been reported.[9] Triazolo[1,5-*a*]pyridines have also been prepared by ring transformation of isomeric triazolo[4,3-*a*]pyridines[10] and from 2-thioxopyrones.[11]

We report in this paper a one-step synthesis of a triazolo[1,5-*a*]pyridine, in anion form, involving the simultaneous generation of the two heterocyclic rings from acyclic starting materials.[12]

The reaction is very simple to carry out. It is performed in ethanol solution, using piperidine as the intended basic catalyst. A crystalline solid is thus obtained in moderate yield.

Structural assignment of this compound could not be unambiguously made from analytical and spectral data, showing the presence of a molecule of piperidine per molecule of each reactant, in disagreement with the mo-

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