portions of water and a saturated aqueous sodium chloride solution and dried over $MgSO_4$. Removal of solvents under reduced pressure and chromatography on 10 g of silica gel impregnated with 10% silver nitrate (30% ethyl acetate–cyclohexane) afforded 0.037 g (80%) of diplodialide A (**2**) whose characteristics (IR, ^1H NMR, and mass spectra) were identical with those previously reported.[14a]

Registry No. 2, 68296-70-8; **5**, 32357-32-7; **6a**, 5309-98-8; **6b**, 73199-91-4; **6c**, 2832-99-7; **7a**, 73199-92-5; **7b**, 73199-93-6; **7c**, 73199-94-7; **8**, 758-16-7; **9**, 1117-37-9; **10**, 73199-95-8; **11**, 27428-41-7; **12**, 73199-96-9; **13**, 56294-09-8; **14**, 73199-97-0; **15**, 73199-98-1; **16a**, 73199-99-2; **16b**, 73200-00-7; **17a**, 623-48-3; **17b**, 64987-88-8; **18**, 73200-01-8; **19a**, 141-97-9; **19b**, 542-08-5; **20a**, 7737-62-4; **20b**, 73200-02-9; **21**, 73200-03-0; **22**, 5892-65-9; **25**, 40568-55-6; **26a**, 73200-04-1; **26a** acetate (ester), 73200-05-2; **26b**, 73200-06-3; **26b** acetate (ester), 73200-07-4; **27a**, 73200-08-5; **27b**, 73200-09-6; **28**, 73200-10-9; **28** acetate (ester), 73200-11-0; **29a**, 73200-12-1; **29b**, 73200-13-2; **30a**, 73200-14-3; **30b**, 73200-15-4; **31a**, 73200-16-5; **31b**, 73200-17-6; **32a**, 73199-63-0; **32b**, 73199-64-1; **33**, 73199-65-2; **33** acetate (ester), 73199-66-3; **35a**, 73199-67-4; **35b**, 73199-68-5; **35c**, 73199-69-6; **36a**, 73199-70-9; **36b**, 73199-71-0; **36c**, 73199-72-1; **37**, 73199-73-2; **38**, 73199-74-3; **39a**, 73199-75-4; **39a** benzoate (ester), 73199-76-5; **39b**, 73199-77-6; **39b** benzoate (ester), 73199-78-7; **40a**, 73199-79-8; **40b**, 73199-80-1; **41**, 73199-81-2; **42**, 73210-24-9; **43**, 73199-82-3; **43** acetate (ester), 73199-83-4; **44**, 73199-84-5; **45**, isomer I, 73199-85-6; **45**, isomer II, 73245-88-2; methyl pentanedithioate, 55130-99-9; pyrrolidine, 123-75-1; morpholine, 110-91-8; methyl 5,5-(ethylenedioxy)hexanedithioate, 73199-86-7; 5-chloro-2-pentanone ethylene ketal, 5978-08-5; methyl 3-(dimethylcarbamoyl)propanoate, 30891-34-0; 1-[3-(butylthio)propanoyl]azacyclopentane, 73199-87-8; 3-(butylthio)propionic acid, 22002-73-9; ethyl 3-oxoheptanoate, 7737-62-4; *N,N*-dimethylethanethioamide, 631-67-4; phenacyl bromide, 70-11-1; 1-[3-(4-oxothiacyclohexyl)carbonyl]azacyclopentane, 73199-88-9; 3-(carbomethoxy)thian-4-one, 4160-61-6; 1-[3-(*cis*-4-hydroxythiacyclohexyl)carbonyl]azacyclopentane, 73199-89-0; 1-[3-(*trans*-4-hydroxythiacyclohexyl)carbonyl]azacyclopentane, 73199-90-3; 1-[(2*R**,3*S**)-3-hydroxy-2-methylpentanoyl]azacyclopentane, 73200-18-7; 1-[(2*R**,3*S**)-3-acetoxy-2-methylpentanoyl]-azacyclopentane, 73230-62-3; 1-[(2*R**,3*R**)-3-hydroxy-2-methylpentanoyl]azacyclopentane, 73200-19-8; 1-[(2*R**,3*R**)-3-acetoxy-2-methylpentanoyl]azacyclopentane, 73200-20-1; 1-(2-acetoxy-2-phenylacetyl)azacyclopentane, 73200-21-2; acetylmandelyl chloride, 49845-72-9; methyl 7-[(2-oxacyclohexyl)oxy]heptanedithioate, 73200-22-3; 2-[(6-chlorohexyl)oxy]oxacyclohexane, 2009-84-9; 2-[(8-chlorooctyl)oxy]oxacyclohexane, 19754-57-5; 8-chloro-1-octanol, 23144-52-7; methyl 9-[(2-oxacyclohexyl)oxy]nonanedithioate, 73200-23-4; 1-(4-hydroxybutanoyl)azacyclopentane, 73200-24-5; γ-butyrolactone, 96-48-0; 1-(4-acetoxybutanoyl)azacyclopentane, 73200-25-6; 8-[(2-oxacyclohexyl)oxy]oct-4-yn-1-ol, 73200-26-7; 4-pentyn-1-ol, 5390-04-5; 2-(3-bromopropoxy)oxacyclohexane, 33821-94-2; 2-[(8-chloro-4-octynyl)oxy]oxacyclohexane, 73200-27-8; methyl 9-[(2-oxacyclohexyl)oxy]non-5-ynedithioate, 73200-28-9; (*E*)-8-[(2-oxacyclohexyl)oxy]oct-4-en-1-ol, 73200-29-0; 2-[[(*E*)-8-chloro-4-octenyl]oxy]-oxacyclohexane, 73200-30-3; methyl (*E*)-9-[(2-oxacyclohexyl)oxy]-non-5-enedithioate, 73200-31-4; (*Z*)-8-[(2-oxacyclohexyl)oxy]oct-4-en-1-ol, 62422-46-2; 2-[[(*Z*)-8-chloro-4-octenyl]oxy]oxacyclohexane, 73200-32-5; methyl (*Z*)-9-[(2-oxacyclohexyl)oxy]non-5-enedithioate, 73200-33-6; 1-(5-hydroxypentanoyl)azacyclopentane, 1938-53-0; δ-valerolactone, 542-28-9; 1-(5-oxopentanoyl)azacyclopentane, 73200-34-7; 5-chloro-5-oxopentanal, 73200-35-8; 1-[5-hydroxy-9-[(2-oxacyclohexyl)oxy]nonanoyl]azacyclopentane, 73200-36-9; 2-[(4-chlorobutyl)oxy]oxacyclohexane, 41302-05-0; 1-[9-[(2-oxacyclohexyl)-oxy]-5-[(2,2,2-trichloroethoxy)formyloxy]nonanoyl]azacyclopentane, 73200-37-0; trichloroethyl chloroformate, 17341-93-4; 1-[9-hydroxy-5-[(2,2,2-trichloroethoxy)formyloxy]nonanoyl]azacyclopentane, 73200-38-1; 1-[9-(benzoyloxy)-5-[(2,2,2-trichloroethoxy)formyloxy]-nonanoyl]azacyclopentane, 73200-39-2; 1-[9-(benzoyloxy)-5-[(2,2,2-trichloroethoxy)formyloxy]nonanethioyl]azacyclopentane, 73200-40-5; 1-[9-(benzoyloxy)-5-hydroxynonanethioyl]azacyclopentane, 73200-41-6; 1,1-diethoxy-5-[(2,2,2-trichloroethoxy)formyloxy]hexane, 73200-42-7.

α-Functionalized Amino Acid Derivatives. A Synthetic Approach of Possible Biogenetic Importance

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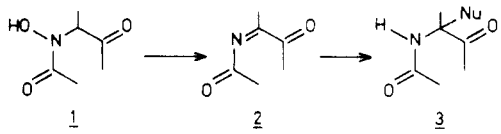
A new and efficient approach of general applicability to the synthesis of α-functionalized α-amino acid derivatives **3** is described. It is based upon the proposal that the biosynthesis of such compounds might occur via oxidation of an N-acylated amino acid to hydroxamic acid **1**, which might then be converted into compound **3** through acylimine **2** (Scheme I). The procedures reported are efficient and can be used for the synthesis of α-oxygenated α-amino acids having an oxidizable function in the side chain. In addition, the method is also applicable for the preparation of peptide analogues with the title compound in their sequence. Starting from the α-oximino acid derivatives **5** and **6**, the O-protected *N*-hydroxy-*N*-acetyl-α-amino esters **9** and **10** were prepared, which could be converted into the *N*-acetyl-α-amino-α-methoxy esters **12** in fair to good overall yields (Scheme II). To extend the scope of this reaction, *N*-hydroxy cyclodipeptides **19** were prepared by reaction of the *N*-benzyloxy-α-amino acid amides **15** with pyruvoyl chloride (**16**) in 54–71% yield (Scheme III). Tosylation of **19a** and subsequent treatment with $(CH_3)_3COK$ in CH_3OH afforded the corresponding *C*(3)-methoxy cyclodipeptide **24a**, whereas **19b** gave a mixture of the *C*(3)- and *C*(6)-methoxy cyclodipeptides **24b** and **25**, respectively (Scheme IV). A mechanism for this isomerization is discussed. It is suggested that **25** arises from the α-lactam intermediate **23b**. This intermediate might also explain the formation of the hydantoin **32**, which is formed when **19b** is tosylated and treated with CH_3SNa in 2-propanol. Under these reaction conditions **19a** gives the reduced cyclodipeptide **30** (Scheme V).

α-Functionalized α-amino acids are known as structural elements in naturally occurring compounds. They are found in the cephamycins,[1] which are of considerable therapeutic significance, and in other physiologically active compounds such as the ergot peptides.[2] In addition, α-hydroxylysine has been mentioned[3] to occur as a free amino acid in plants, whereas ureidoglycine is an example

Scheme I

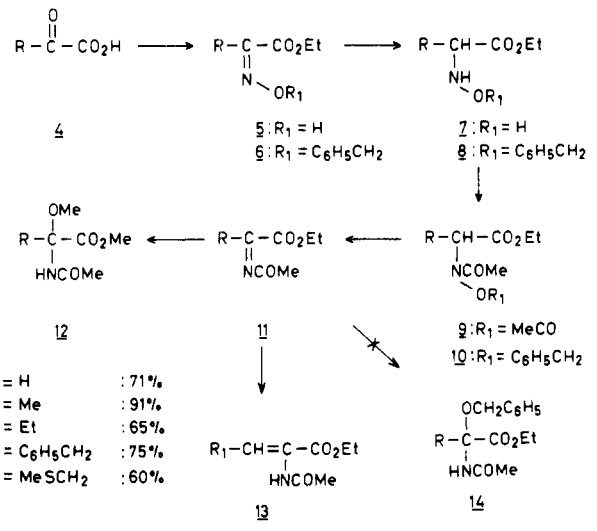


1 2 3

(1) G. Albers-Schönberg, B. H. Arison, and J. L. Smith, *Tetrahedron Lett.*, 2911 (1972).

0022-3263/80/1945-1880$01.00/0

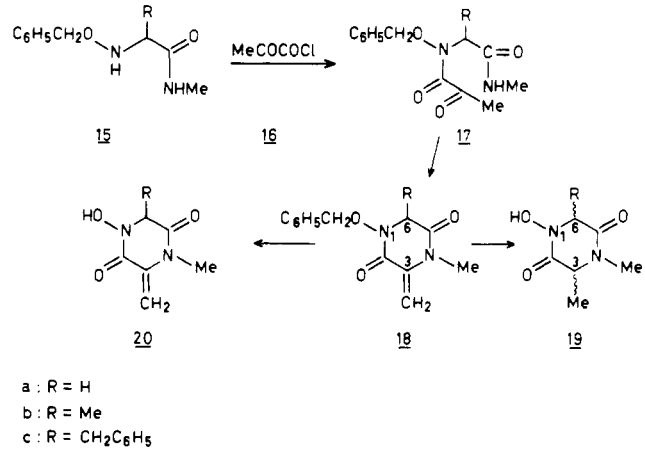
Scheme II



of a naturally occurring α,α-diamino acid.[4] α-Functionalized cyclic dipeptides are also found, e.g., in verruculogen,[5] bicyclomycin,[6,7] and in the fungal metabolites, characterized by a bridge of sulfur atoms across a dioxopiperazine ring.[8]

So far, several methods have been developed for the *synthesis* of α-functionalized α-amino acid derivatives **3**.[9-11] However, little is known about the *biosynthesis* of these compounds. One route might involve direct α-oxidation of amino acid derivatives.[12] Another possible pathway proceeds via the oxidation of an acylamino acid derivative to the corresponding hydroxamic acid of type **1** (Scheme I). Loss of water to yield the acylimine **2** and subsequent addition of a nucleophile should lead to **3**.[8b] The latter proposal is based upon the observation that a large number of metabolites having an *N*-hydroxyamide function are known.[13] In addition, it has been suggested before that *N*-hydroxy peptides play a role in the biosynthesis of β-lactam antibiotics[14] and dehydro amino acids.[9] As to the conversion **1** → **2**, *N*-acylimines[15] and *N*-acylimmonium

Scheme III



ions[16] have recently been documented to allow biogenetic-type syntheses of several catagories of alkaloids.

In this contribution a new synthesis of α-methoxy-α-acylamino acid esters **12** (Scheme II) and α-methoxy cyclic dipeptides **24** (Scheme IV) is described, starting from *N*-hydroxyamino acid derivatives **7** or **8** and **19**, respectively. This approach is based on the exchange of an N substituent for a functionality at C(α) as represented in Scheme I. Our results confirm the usefulness of Scheme I as a possible biosynthetic route for the formation of α-functionalized α-amino acid derivatives.

Synthesis of *N*-Acyl-α-methoxy-α-amino Acid Esters 12. At first we chose the *N*,*O*-diacetyl-*N*-hydroxy-α-amino acid ester **9** as a starting compound[17] in our investigation into preparative methods for compound **12**. Compounds **9a,b,d,e** were prepared from the corresponding oximes **5** by reduction with pyridine–BH_3 complex[18a] and subsequent diacetylation with CH_3COCl and pyridine. Treatment of **9a,b,d,e** with 1 equiv of $(CH_3)_3COK$ in CH_3OH gave the corresponding compounds **12** as desired, albeit in low yields (42, 22, 72, and 38%, respectively). In the reaction mixture *N*-acetyl-*N*-hydroxy-α-amino acid esters were found, which must have been formed by nucleophilic attack at the acetate function of **9**. Therefore, another O-protecting group was searched for.

Recently, we reported a facile and general method for the synthesis of the *N*-(benzyloxy)-α-amino acid esters **8**: the α-oximino esters **6a–e**, which in most cases can be prepared quantitatively from the corresponding α-keto acids **4** and *O*-benzylhydroxylamine, can be reduced in good yields to the corresponding amines **8** with pyridine–BH_3.[18a] Treatment of **8a–e** with acetyl chloride in the presence of pyridine afforded **10a–e**, which were indeed converted quantitatively into the desired **12a–e** by reaction with 1 equiv of $(CH_3)_3COK$ in CH_3OH. The overall yields for the conversion **6** → **12** varied after purification by high-pressure LC from 60 to 91%.

The acylimine **11** is proposed as an intermediate in the conversion of **9** or **10** into **12**. As will be reported else-

(2) For recent reviews see: (a) H. G. Floss, *Tetrahedron*, **32**, 873 (1976); (b) P. A. Stadler and P. Stütz in "The Alkaloids", Vol. 15, R. H. F. Manske, Ed., Academic Press, New York, 1975, p 1.
(3) C. H. Brieskorn and J. Glasz, *Naturwissenschaften*, **51**, 216 (1964).
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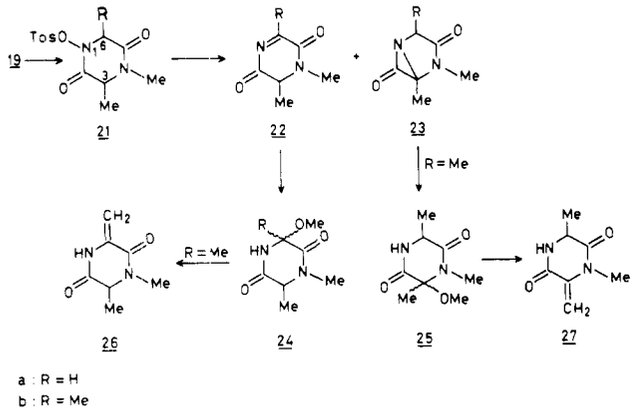
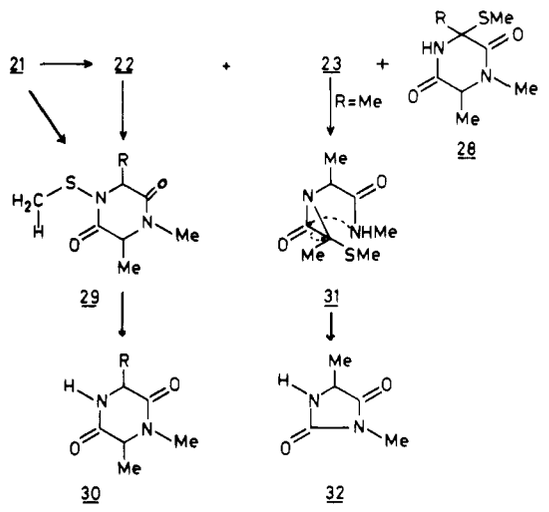
(5) J. Fayos, D. Lokensgard, J. Clardy, R. J. Cole, and J. W. Kirksey, *J. Am. Chem. Soc.*, **96**, 6785 (1974).
(6) Y. Tokuma, S. Koda, T. Miyoshi, and Y. Morimoto, *Bull. Chem. Soc. Jpn.*, **47**, 18 (1974).
(7) H. Maag, J. F. Blount, D. L. Coffen, T. V. Steppe, and F. Wong, *J. Am. Chem. Soc.*, **100**, 6786 (1978).
(8) For recent reviews see: (a) A. Taylor in "Microbial Toxins", Vol. VII, S. Kadis, A. Ciegler, and S. J. Ajl, Eds., Academic Press, New York, 1971, p 337; (b) P. G. Sammes, *Fortschr. Chem. Org. Naturst.*, **32**, 87 (1975); (c) C. Leigh and A. Taylor, *Adv. Chem. Ser.*, **No. 133**, 228 (1976); (d) S. Johne and D. Gröger, *Pharmazie*, **32**, 1 (1977); (e) B. Ganem, *Tetrahedron*, **34**, 3375 (1978).
(9) For a review see: U. Schmidt, J. Häusler, E. Öhler, and H. Poisel, *Fortschr. Chem. Org. Naturst.*, **37**, 251 (1979).
(10) Y. Ozaki, T. Iwasaki, H. Horikawa, M. Miyoshi, and K. Matsumoto, *J. Org. Chem.*, **44**, 391 (1979); T. Iwasaki, H. Horikawa, K. Matsumoto, and M. Miyoshi, *Bull. Chem. Soc. Jpn.*, **52**, 826 (1979).
(11) K. Ogura and G. Tsuchihashi, *J. Am. Chem. Soc.*, **96**, 1960 (1974).
(12) Direct α-oxidation of α-amino acid derivatives has been discussed before with regard to the biosynthesis of α,β-dehydro-α-amino acids **10**; see, e.g., ref 9.
(13) J. H. Weisburger and E. K. Weisburger, *Pharmacol. Rev.*, **25**, 1 (1973); H. Maehr, *Pure Appl. Chem.*, **28**, 603 (1971); J. B. Neilands, *Science*, **156**, 1443 (1967); J. B. Bapat, D. S. C. Black, and R. F. C. Brown, *Adv. Heterocycl. Chem.*, **10**, 199 (1969).
(14) A. I. Scott, S. E. Yoo, S. K. Chung, and J. A. Lacadie, *Tetrahedron Lett.*, 1137 (1976).
(15) (a) H. E. Zaugg and W. B. Martin, *Org. React.*, **14**, 52 (1965); (b) R. K. Olsen and A. J. Kolar, *Tetrahedron Lett.*, 3579 (1975).
(16) (a) V. Bacchi, G. Casnati, and G. P. Gardini, *Tetrahedron Lett.*, 683 (1971); (b) J. C. Hubert, W. N. Speckamp, and H. O Huisman, *ibid.*, 4493 (1972); (c) J. B. P. A. Wijnberg and W. N. Speckamp, *ibid.*, 4035 (1975); (d) S. Blechert, *Nachr. Chem. Tech.*, **27**, 400 (1979).
(17) Compound **9** has been used before for the synthesis of acyl enamino compounds: C. Shin, K. Nanjo, E. Ando, and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, **47**, 3109 (1974). See also: S. Nakatsuka, H. Tanino, and Y. Kishi, *J. Am. Chem. Soc.*, **97**, 5008 (1975).
(18) (a) J. D. M. Herscheid and H. C. J. Ottenheijm, *Tetrahedron Lett.*, 5143 (1978); (b) J. D. M. Herscheid, M. W. Tijhuis, and H. C. J. Ottenheijm, submitted for publication in *Synthesis*.

Scheme IV



Scheme V



where,[19] the reaction of **10** with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in the nonnucleophilic solvent dioxane gave the α,β-dehydro-α-amino acid derivative **13**, whereas none of the α-benzyloxy derivative **14** could be detected. This indicates that the acylimine **11** reacts with an alcohol only when present in excess[20] and otherwise rearranges into the *N*-acyl enamine **13**.

Synthesis of *N*-Hydroxydioxopiperazines 19 and 20. *N*-Hydroxydioxopiperazines are structural features of several natural products such as aspergillic acid, pulcherriminic acid, and mycelianamide.[8b,13]

So far, two syntheses of di-*N*-hydroxydioxopiperazines have been reported,[21] which have, however, the disadvantage of limited applicability. Recently, Shin and coworkers[22] described the synthesis of some unsymmetric *N*-hydroxydioxopiperazines, which proceeded only in low yield, however.

We studied the syntheses of **19** and **20** by a modification of the known and efficient reaction[23] of α-amino acid amides with pyruvoyl chloride. The reaction sequence is depicted in Scheme III.

The *N*-(benzyloxy)-α-amino acid amides **15** were prepared by reduction of the corresponding oximes with the trimethylamine–BH_3 complex; with pyridine–BH_3 the reaction did not proceed completely.[18b] Reaction of **12** with pyruvoyl chloride[24] (**16**) and triethylamine at room temperature gave the acylated compound **17**. Due to the lower nucleophilicity of the (benzyloxy)amino function, this acylation proceeds slower than that with the corresponding *N*-alkyl-α-amino acid amides.[23b] Ring closure of **17** and subsequent dehydration were catalyzed by CF_3COOH. The resulting *N*-(benzyloxy)dioxopiperazines **18a–c** were isolated in good overall yields (58, 71, and 54%, respectively).

Treatment of **18a–c** with H_2 and Pd/C caused not only removal of the benzyl group[26] but also reduction of the *exo*-methylene function to give, quantitatively, the *N*-(hydroxy)dioxopiperazines **19a–c**. This reduction proceeded with high chiral induction: the ^1H NMR spectra of **19b** and **19c** showed the presence of only one isomer, the stereochemistry of which has not been determined.[25]

The benzyl group in **18a** could be removed selectively by using $(CF_3CO_2)_3B$[26] to give **20a** in 79% yield. However, reaction of **18c** with this reagent yielded an intractable reaction mixture. All compounds **19** and **20** gave the characteristic deep red color for hydroxamic acids with $FeCl_3$.

Synthesis of α-Functionalized Dioxopiperazines from 19. Compounds **19a** and **19b** were converted into the tosyl derivatives **21** by a standard procedure. Treatment of **21a** with 1 equiv of $(CH_3)_3COK$ in CH_3OH gave, quantitatively, a mixture of the two stereoisomers of **24a** (Scheme IV).

However, under these reaction conditions **21b** gave at least three products, all of which contained a methoxy function according to ^1H NMR spectroscopy. It was assumed that, besides **24b**, compound **25**, having a methoxy function at C(6), also had been formed. This could be confirmed by treatment of the reaction mixture with CF_3COOH: the newly formed mixture consisted of only two products, to which the structures **26** and **27** could be assigned.

The formation of **25** from **21b** might be explained by proton abstraction at C(3) to give the bicyclic intermediate **23b**. The occurrence of α-lactams in reactions of cyclic hydroxamic acids with a base has been discussed before.[27] Nucleophilic attack of CH_3OH may then convert **23b** into **25**. Compound **24b** must have been formed from **21b** by deprotonation at C(6) to give the acylimine **22b**, and subsequent addition of CH_3OH. In case of **21a**, the latter pathway is the only one to occur, as in this compound the C(3) proton is less acidic than the C(6) proton.

We also studied the introduction of a methylmercapto function at C(6) by reaction of **21** with mercaptides. Again, a striking difference in reactivity between **21a** and **21b** was

(19) J. D. M. Herscheid, H. P. H. Scholten, M. W. Tijhuis, and H. C. J. Ottenheijm, to be submitted for publication.

(20) Recently, Miyoshi and co-workers[10] reported the efficient conversion of *N*-acyl-α-acetoxy-α-amino acid esters into the corresponding α-methoxy esters **12** by treatment with base and 1 equiv of MeOH, for which **11** has been proposed as an intermediate. However, our results indicate that this acylimine should rearrange to **13** under the reaction conditions used, so that an S_N2-type reaction is more likely for Miyoshi's reaction.

(21) (a) A. H. Cook and C. A. Slater, *J. Chem. Soc.*, 4130 (1956); (b) A. Ohta, *Chem. Pharm. Bull.*, **12**, 125 (1964).

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(24) H. C. J. Ottenheijm and J. H. M. de Man, *Synthesis*, 163 (1975); H. C. J. Ottenheijm and M. W. Tijhuis, submitted for publication in *Org. Synth.*

(25) In heterogeneous catalytic hydrogenation of cyclodipeptides with dehydro amino acid subunits, it has been observed before that the chiral center induces asymmetry at the sp^2 carbon atom. On basis of the low δ value for the C(3)-methyl group in **19c** (0.43 ppm), we are inclined to assign a cis stereochemistry to this compound, which is in accordance with the mechanism proposed for similar conversions; see, e.g., T. Kanmera, S. Lee, H. Aoyagi, and N. Izumiya, *Tetrahedron Lett.*, 4483 (1979).

(26) T. Kolasa and A. Chimiak, *Tetrahedron*, **33**, 3285 (1977).

(27) J. C. Sheenan and I. Lengyel, *J. Org. Chem.*, **31**, 4244 (1966); H. E. Baumgarten, J. F. Feurholzer, R. D. Clark, and R. D. Thompson, *J. Am. Chem. Soc.*, **85**, 3303 (1963).

found. Treatment of **21a** with excess CH_3SNa in 2-propanol did not give the expected product **28a** but gave the reduced dioxopiperazine **30a** in 75% yield. This compound might have been formed by a 1,5 hydride shift and extrusion of CH_2S in **29a**, an intermediate whose formation can be explained either by an attack of CH_3S^- on the N atom of the acylimine **22a** or, more likely, by a nucleophilic displacement of the tosylate group in **21a** (see Scheme V).

One might argue that initially the α-substituted product **28a** might have been formed but that it decomposed to **22** due to the strong alkaline reaction conditions.[28] However, treatment of **21a** with only 1 equiv of $(CH_3)_3COK$ in CH_3SH/CH_3OH (1:19 v/v) gave **30a** again in 74% yield. Careful product analysis showed the presence of **28a** and **24a** as side products in 21 and 5% yield, respectively.

Treatment of **21b** with an excess of CH_3SNa in 2-propanol gave the dimethylhydantoin **32** in 70% yield; the reduced compound **30b** could not be detected. Although we have no evidence about the mechanism of this remarkable ring contraction, structure **31** is proposed as an intermediate which might have been formed from the bicyclic compound **23**. The same argument used above to explain the difference in behavior between **21a** and **21b** toward $(CH_3)_3COK$ and CH_3OH might be advanced to interpret the formation of **30a** and **32** from **21a** and **21b**, respectively.

Discussion

We have shown here that *N*-hydroxyamino acid derivatives **1** can be converted easily into α-functionalized α-amino acid derivatives **3**. The procedures are efficient and seem to be of general applicability: they can be used where others fail, e.g., for the synthesis of α-substituted α-amino acids having an oxidizable function in the side chain[29] (see **12e**). In addition, the method described for the synthesis of **12** from **8** might also be applicable for the preparation of peptide analogues with α-functionalized α-amino acids in their sequence.[30]

We feel that *N*-hydroxyamino acids deserve further attention both as biosynthetic precursors and as chemosynthetic synthons for a wide range of natural products. In the following paper it is shown that they can be used in the synthesis of sulfur-bridged dioxopiperazine.[31] In addition, compounds of type **1** can be converted into α,β-dehydro-α-amino acid derivatives,[17,19] the structural components of various other natural products.[9] Recently the biological importance of the β-addition of thiols to dehydropeptides and the reversible conversion of the latter in α-keto acids and amides have been discussed in detail.[9]

Work is in progress to use *N*-hydroxy-α-amino acid derivatives in a biomimetic synthesis of penicillin derivatives and other fungal metabolites.

Experimental Section

Infrared spectra were measured with a Perkin-Elmer spectrophotometer, Model 397. Proton magnetic resonance spectra were measured on a Varian Associates Model T-60 or a Bruker WH-90 spectrometer. Chemical shifts are reported as δ values (parts per million, relative to tetramethylsilane as an internal standard); deuteriochloroform was used as solvent unless stated otherwise. Mass spectra were obtained with a double-focusing Varian Associates SMI-B spectrometer. Melting points were taken on a Köfler hot stage (Leitz-Wetzlar) and are uncorrected. Thin-layer chromatography (TLC) was carried out by using Merck precoated silica gel F-254 plates (thickness 0.25 mm). Spots were visualized with a UV hand lamp or iodine vapor. For high-pressure LC the Miniprep LC (Jobin Yvon) was used.

***N*-(Benzyloxy)-α-amino Acid Esters 8a–c.** A stirred solution of 10 mmol of the corresponding oxime **6a–c** and 30 mmol of pyridine–BH_3 complex (3 mL) in 20 mL of dry ethanol was treated with 14 mL of a ca. 7 N HCl solution in ethanol at room temperature at such a rate that the temperature of the mixture remained below 40 °C. Stirring was continued at room temperature for 16 h after which the solvent was evaporated. Then CH_2Cl_2 was added together with Na_2CO_3 in order to neutralize the suspension. After being stirred for several hours, the mixture was filtered and the solvent evaporated to yield **8a–c**. The reaction products, which were homogeneous on TLC (CH_2Cl_2), except for the presence of a trace of pyridine, were used for the next reaction without further purification. **8a**: NMR δ 7.34 (s, 5 H, Ph), 6.0 (m, 1 H, NH), 4.73 (s, 2 H, OCH_2Ph), 4.22 (q, 2 H, CH_3CH_2), 3.59 (s, 2 H, $C_\alpha H_2$), 1.29 (t, 3 H, CH_3CH_2). **8b**: NMR δ 7.33 (s, 5 H, Ph), 5.90 (m, 1 H, NH), 4.71 (s, 2 H, OCH_2Ph), 4.22 (q, 2 H, CH_3CH_2), 3.71 (q, 1 H, $C_\alpha H$), 1.29 (t, 3 H, CH_3CH_2), 1.19 (d, 3 H, $C_\alpha CH_3$). **8c**: NMR δ 7.31 (s, 5 H, Ph), 5.95 (m, 1 H, NH), 4.67 (s, 2 H, OCH_2Ph), 4.20 (q, 2 H, OCH_2CH_3), 3.51 (t, 1 H, $C_\alpha H$), 1.55 (m, 2 H, CH_3CH_2), 1.28 (t, 3 H, OCH_2CH_3), 0.92 (t, 3 H, CH_3CH_2).

***N*-(Benzyloxy)-α-amino Acid Esters 8d,e.** A 10-mL sample of a ca. 7 N HCl solution in ethanol was added at room temperature at once to a stirred solution of 10 mmol of oxime **6d** or **6e** and 20 mmol of $(CH_3)_3N{\cdot}BH_3$ complex (1.46 g) in 20 mL of dry ethanol. The temperature of the reaction mixture increased only slightly. Stirring was continued at room temperature for 16 h after which the solvent was evaporated. The remainder was suspended in CH_2Cl_2 and supplied with Na_2CO_3. The resulting suspension was stirred for several hours. Filtration and evaporation of the solvent gave a reaction product that was chromatographed (high-pressure LC) on silica gel H (Merck 60) with CH_2Cl_2 as eluent. The resulting compounds were homogeneous on TLC (CH_2Cl_2). **8d**: 80% yield; NMR δ 7.30 (s, 5 H, $PhCH_2O$), 7.20 (m, 5 H, $PhCH_2$), 5.90 (m, 1 H, NH), 5.68 (s, 2 H, $PhCH_2O$), 4.13 (q, 2 H, OCH_2CH_3), 3.85 (t, 1 H, $C_\alpha H$), 2.87 (d, 2 H, $PhCH_2$), 1.16 (t, 3 H, CH_3CH_2O). **8e**: 66% yield; NMR δ 7.30 (s, 5 H, Ph), 6.10 (m, 1 H, NH), 4.70 (s, 2 H, $PhCH_2O$), 4.20 (q, 2 H, OCH_2CH_3), 3.70 (m, 1 H, $C_\alpha H$), 2.70 (d, 2 H, SCH_2), 2.05 (s, 3 H, SCH_3), 1.30 (t, 3 H, OCH_2CH_3).

***N*-Acetyl-*N*-(benzyloxy)-α-amino Acid Esters 10a–e.** A stirred solution of 10 mmol of the corresponding amine **8a–e** in 25 mL of CH_2Cl_2 (dried and freed of alcohol) was at room temperature subsequently treated with 1.1 equiv of freshly distilled acetyl chloride and pyridine (dried and stored over 4-Å molecular sieves). Stirring was continued at room temperature for 16 h, after which the reaction mixture was washed with 0.1 N aqueous HCl, water, and brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to yield, quantitatively, the acetylamines **10a–e**, which were homogeneous by TLC (2% CH_3OH/CH_2Cl_2). **10a**: NMR δ 7.26 (s, 5 H, Ph), 4.69 (s, 2 H, $PhCH_2O$), 4.23 (s, 2 H, $C_\alpha H_2$), 4.10 (q, 2 H, CH_3CH_2), 2.10 (s, 3 H, $COCH_3$), 1.23 (t, 3 H, CH_3CH_2). **10b**: NMR δ 7.20 (s, 5 H, Ph), 4.88 (q, 1 H, $C_\alpha H$), 4.87 (s, 2 H, $PhCH_2$), 4.13 (q, 2 H, CH_3CH_2), 2.13 (s, 3 H, $COCH_3$), 1.53 (d, 3 H, $C_\alpha CH_3$), 1.26 (t, 3 H, CH_3CH_2). **10c**: NMR δ 7.26 (s, 5 H, Ph), 4.60–4.82 (m, 1 H, $C_\alpha H$), 4.20 (q, 2 H, CH_3CH_2O), 2.35–1.72 (m, 2 H, CH_3CH_2), 2.17 (s, 3 H, $COCH_3$), 1.27 (t, 3 H, CH_3CH_2O), 1.0 (t, 3 H, CH_3CH_2). **10d**: NMR δ 7.0–7.40 (m, 5 H, $PhCH_2$), 7.17 (s, 5 H, $PhCH_2O$), 4.97, (m, 1 H, $C_\alpha H$), 4.66 (s, 2 H, $PhCH_2O$), 4.20 (q, 2 H, CH_3CH_2), 3.33 (m, 2 H, $PhCH_2$), 2.0 (s, 3 H, $COCH_3$), 1.26 (t, 3 H, CH_3CH_2). **10e**: NMR δ 7.17 (s, 5 H, Ph), 4.76–5.0 (m, 1 H, $C_\alpha H$), 4.86 (s, 2 H, $PhCH_2$), 4.13 (q, 2 H, CH_3CH_2), 2.92–3.17 (m, 2 H, $S-CH_2$), 2.13 (s, 3 H, SCH_3), 2.06 (s, 3 H, $COCH_3$), 1.26 (t, 3 H, CH_3CH_2).

***N*-Acetyl-α-amino-α-methoxy Acid Esters 12a–e.** To a stirred solution of 1 mmol of the corresponding compound **10a–e** in 100 mL of dry CH_3OH was added at room temperature at once 112 mg (1 mmol) of $(CH_3)_3COK$. Stirring was continued at room

(28) The base-catalyzed conversion of thioaminales into imines is a known reaction: G. W. Stacy, R. I. Day, and R. J. Morath, *J. Am. Chem. Soc.*, **77**, 3869 (1955).

(29) Most of the methods used for the preparation of **3** employ α-addition of nucleophiles to either acylimines **2** or α,β-dehydro-α-amino acids **13**, which are made by oxidation of amides or β-elimination of sulfonium salts, respectively; see ref 9.

(30) Acylation of a free *N*-hydroxy-α-amino acid gives a mixture of N- and O-acylated products; see, e.g., T. Kolasa and A. Chimiak, *Tetrahedron*, **30**, 3591 (1974).

(31) J. D. M. Herscheid, R. J. F. Nivard, M. W. Tijhuis, and H. C. J. Ottenheijm, *J. Org. Chem.*, following paper in this issue.

temperature for 24 h, after which the reaction mixture was neutralized with NH_4Cl. The solvent was evaporated, after which CH_2Cl_2 was added. The salts were removed by filtration, and the filtrate was evaporated to dryness. The residue was subjected to column chromatography on silica gel H (Merck 60) with the aid of high-pressure LC using 2% CH_3OH/CH_2Cl_2 as eluent. The isolated compounds were homogeneous on TLC (8% CH_3OH/CH_2Cl_2); yields are given on basis of **6**. **12a**: 71% yield; NMR δ 7.06 (m, 1 H, NH), 5.43 (d, J = 9 Hz, 1 H, $C_\alpha H$), 3.69 (s, 3 H, $COOCH_3$), 3.34 (s, 3H, $C_\alpha OCH_3$), 2.04 (s, 3 H, $COCH_3$); mp (CCl_4/hexane) 46–47.5 °C. **12b**: 91% yield; NMR δ 7.30 (br s, 1 H, NH), 3.76 (s, 3 H, $COOCH_3$), 3.26 (s, 3 H, $C_\alpha OCH_3$), 2.03 (s, 3 H, $COCH_3$), 1.66 (s, 3 H, $C_\alpha CH_3$); mp (CH_2Cl_2/hexane) 140–143 °C. **12c**: 65% yield; NMR δ 6.60 (br s, 1 H, NH), 3.80 (s, 3 H, $COOCH_3$), 3.23 (s, 3 H, $C_\alpha OCH_3$), 1.50–2.80 (m, 2 H, CH_3CH_2), 2.06 (s, 3 H, $COCH_3$), 0.82 (t, 3 H, CH_3CH_2); oil. **12d**: 75% yield; NMR δ 7.0–7.30 (m, 5 H, Ph), 6.37 (br s, 1 H, NH), 3.88 (d, J = 13 Hz, 1 H, CHPh), 3.85 (s, 3 H, $COOCH_3$), 3.26 (s, 3 H, $COCH_3$), 3.22 (d, 1 H, CHPh), 2.06 (s, 3 H, $COCH_3$); mp (CH_2Cl_2/hexane) 98–100 °C. **12e**: 60% yield; NMR δ 6.80 (br s, 1 H, NH), 3.72 (s, 3 H, CO_2CH_3), 3.36 (d, J = 14 Hz, 1 H, $CH_\alpha S$), 3.20 (s, 3 H, $COCH_3$), 2.90 (d, 1 H, $CH_\beta S$), 2.13 (s, 3 H, SCH_3), 2.06 (s, 3 H, $C(O)CH_3$); oil.

1-(Benzyloxy)-3-methylene-4-methyl-2,5-dioxopiperazine (18a). To a stirred solution of 3.2 g (16.5 mmol) of **15a**[18b] in 50 mL of dry CH_2Cl_2 were added 1.8 g (17.5 mmol) of triethylamine and 35 mL of a 0.5 M solution of pyruvoyl chloride[24] (**16**) in CCl_4 (17.5 mmol). After being stirred for 16 h at room temperature, the reaction mixture was concentrated to a final column of 25 mL; then 2 mL of CF_3COOH was added. Stirring was continued for 8 h, after which ring closure was completed (TLC, 3% $MeOH/CH_2Cl_2$). The solution was washed with 1 N NaOH, and the organic layer was dried (Na_2SO_4) and concentrated to give a solid mass. Recrystallization from CCl_4/*n*-hexane afforded **18a**: 58% yield; mp 108–110 °C; IR (KBr) 1689 (CO), 1612 cm^{-1} (C=C); NMR δ 7.30 (s, 5 H, Ph), 5.85 (d, 1 H, $C{=}CH_\alpha$), 5.0 (s, 2 H, CH_2O), 4.91 (d, 1 H, $C{=}CH_\beta$), 4.09 (s, 2 H, $C(6)H_2$), 3.12 (s, 3 H, NMe); mass spectrum, m/e 246 (M^+). Anal. ($C_{13}H_{14}N_2O_2$) C, H, N.

1-(Benzyloxy)-3-methylene-4,6-dimethyl-2,5-dioxopiperazine (18b). Reaction of **15b**[18b] with pyruvoyl chloride (**16**) was performed as described for the synthesis of **18a**. Column chromatography on silica gel (Merck 60) with CH_2Cl_2/EtOH (98:2 v/v) gave **18b**: 71% yield; mp ($CHCl_3$) 90–92 °C; IR (KBr) 1680 (CO), 1610 cm^{-1} (C=C); NMR δ 7.23 (s, 5 H, Ph), 5.81 (d, 1 H, $C{=}CH_\alpha$), 4.93 (s, 2 H, CH_2O), 4.88 (d, 1 H, $C{=}CH_\beta$), 4.13 (q, 1 H, C(6)H), 3.13 (s, 3 H, NMe), 1.50 (d, 3 H, C(6)Me); mass spectrum, m/e 260 (M^+). Anal. ($C_{14}H_{16}N_2O_3$) C, H, N.

1-(Benzyloxy)-3-methylene-4-methyl-6-benzyl-2,5-dioxopiperazine (18c). Reaction of **15c**[18b] with pyruvoyl chloride (**16**) was performed as described for the synthesis of **18a**. Column chromatography on silica gel (Merck 60) with CH_2Cl_2/MeOH (98:2 v/v) gave **18c**: 54% yield (besides 13% of **15c**); NMR δ 7.43 (s, 5 H, $PhCH_2O$), 7.13 (m, 5 H, $C(6)CH_2Ph$), 5.30 (d, 1 H, $C{=}CH_\alpha$), 5.14 (d, J = 10 Hz, 1 H, $CH_\alpha O$), 5.0 (d, 1 H, $CH_\beta O$), 4.36 (m, 2 H, $C{=}CH_\beta$ and C(6)H), 3.23 (8 lines, 2 H, $C(6)CH_2$), 2.90 (s, 3 H, NMe).

1-Hydroxy-3,4-dimethyl-2,5-dioxopiperazine (19a). A catalytic amount of Pd/C was added to a methanolic solution of 1.17 g (5 mmol) of **18a**, which was kept in a N_2 atmosphere. After replacement of the N_2 by H_2, the reaction mixture was shaken for 3 h, after which the calculated amount of H_2 had been consumed. The catalyst was filtered off and the filtrate concentrated to give **19a** quantitatively: NMR δ 4.43 (d, J = 14 Hz, 1 H $C(6)H_\alpha$), 4.23 (d, 1 H, $C(6)H_\beta$), 4.06 (q, 1 H, C(3)H), 3.0 (s, 3 H, NMe), 1.50 (d, 3 H, C(3)Me).

1-Hydroxy-3,4,6-trimethyl-2,5-dioxopiperazine (19b). Reduction of **18b** was carried out as described for the synthesis of **19a**. For **19b**: NMR δ 4.33 (q, 1 H, C(6)H), 4.03 (q, 1 H, C(3)H), 3.0 (s, 3 H, NMe), 1.66 (d, 3 H, C(6)Me), 1.50 (d, 3 H, C(3)Me).

1-Hydroxy-3,4-dimethyl-6-benzyl-2,5-dioxopiperazine (19c). Reduction of **18c** was carried out as described for the synthesis of **19a**. For **19c**: NMR δ 7.30 (m, 5 H, Ph), 4.70 (m, 1 H, C(6)H), 3.77 (q, 1 H, C(3)H), 3.50 (m, 2 H, CH_2Ph), 2.83 (s, 3 H, NMe), 0.43 (d, 3 H, C(3)Me).

1-Hydroxy-3-methylene-4-methyl-2,5-dioxopiperazine (20a). To a solution of 526 mg (2.14 mmol) of **18a** in 8 mL of CF_3COOH was added at 0 °C 8 mL of a 1 M solution of $B(CF_3COO)_3$ in CF_3COOH. After the mixture was stirred for 2 h at room temperature, the CF_3COOH was evaporated and 100 mL of $EtOH/H_2O$ (1:1 v/v) was added to the residue. The precipitate was filtered off and the filtrate concentrated to dryness. Column chromatography on Sephadex LH-20 using $MeOH/H_2O$ (85:15 v/v) as eluent yielded 265 mg (79%) of **20a**: NMR (CD_3OD) δ 5.62 (d, 1 H, $C{=}CH_\alpha$), 4.97 (d, 1 H, $C{=}CH_\beta$), 4.30 (s, 2 H, $C(6)H_2$), 3.10 (s, 3 H, NMe).

1-(Tosyloxy)-3,4-dimethyl-2,5-dioxopiperazine (21a). To a stirred solution of 790 mg (5 mmol) of **19a** in 30 mL of dry CH_3CN were added 953 mg (5 mmol) of tosyl chloride and 506 mg (5 mmol) of triethylamine. Stirring was continued at room temperature for 16 h, after which the solvent was evaporated. To the residue was added CH_2Cl_2, and the resulting suspension was washed with H_2O. Drying (Na_2SO_4) of the organic layer and evaporation of the solvent gave **21a** in quantitative yield: NMR δ 7.94–7.17 (AB spectrum, 4 H, Ph), 4.39 (d, J = 14 Hz, 1 H, $C(6)H_\alpha$), 4.23 (d, 1 H, $C(6)H_\beta$), 3.83 (q, 1 H, C(3)H), 2.90 (s, 3 H, NMe), 2.55 (s, 3 H, PhMe), 1.40 (d, 3 H, C(3)Me).

1-(Tosyloxy)-3,4,6-trimethyl-2,5-dioxopiperazine (21b). The conversion of **19b** into **21b** was performed as described for the synthesis of **21a**. For **21b**: NMR δ 7.93–7.13 (AB spectrum, 4 H, Ph), 4.36 (q, H, C(6)H), 3.90 (q, 1 H, C(3)H), 2.87 (s, 3 H, NMe), 2.50 (s, 3 H, PhMe), 1.56 (d, 3 H, C(6)Me), 1.39 (d, 3 H, C(3)Me).

1,6-Dimethyl-3-methoxy-2,5-dioxopiperazine (24a). To a stirred solution of 270 mg (0.87 mmol) of **21a** in 100 mL of MeOH was added at room temperature 98 mg (0.87 mmol) of *t*-BuOK at once. Stirring was continued for 15 min at room temperature, after which the solvent was evaporated. To the residue was added CH_2Cl_2, and the resulting suspension was filtered. After concentration of the filtrate **24a** was obtained in quantitative yield. According to TLC (7% $MeOH/CH_2Cl_2$) and ^1H NMR spectroscopy, a mixture of two diastereomers had been formed: NMR δ 4.93 and 4.74 (2 s, 1 H, C(3)H), 4.07 and 3.87 (2 q, 1 H, C(6)H, 3.50 (2 s, 3 H, CH_3O), 3.07 and 3.03 (2 s, 3 H, NMe), 1.66 and 1.53 (2 d, 3 H, C(6)Me).

1,6-Dimethyl-3-methylene-2,5-dioxopiperazine (26) and 1,3-Dimethyl-6-methylene-2,5-dioxopiperazine (27). Compound **21b** was treated as described for the synthesis of **24a**. According to TLC (7% $MeOH/CH_2Cl_2$) and ^1H NMR spectroscopy, the reaction mixture consisted of at least three products. After treatment with CF_3COOH in CCl_4, the newly formed mixture consisted of only two products. These were separated by column chromatography on silica gel H (Merck 60) with 2% CH_3OH/CH_2Cl_2 as eluent. On the basis of the ^1H NMR spectra, structures **26** and **27** were assigned to the more and less polar component, respectively. **26**: NMR δ 8.14 (br s, 1 H, NH), 5.62 (d, 1 H, $C{=}CH_\alpha$), 4.84 (d, 1 H, $C{=}CH_\beta$), 4.04 (q, 1 H, C(6)H), 3.07 (s, 3 H, NMe), 1.58 (d, 3 H, C(6)Me). **27**: NMR δ 6.65 (br s, 1 H, NH), 5.80 (d, 1 H, $C{=}CH_\alpha$), 4.93 (d, 1 H, $C{=}CH_\beta$), 4.22 (dq, 1 H, C(3)H, irradiation on the NH-proton leaves only one quartet), 3.21 (s, 3 H, NMe), 1.56 (d, 3 H, C(3)Me).

1,6-Dimethyl-2,5-dioxopiperazine (30a). To a stirred solution of 624 mg (2 mmol) of **28a** in 75 mL of MeOH/MeSH (19:1 v/v) was added at room temperature 220 mg (1.95 mmol) of *t*-BuOK. After the mixture was stirred for 3 h at room temperature, the solvent was evaporated, and CH_2Cl_2 was added; the precipitated potassium tosylate was then filtered off. Column chromatography on silica gel (Merck 60) with 3% CH_3OH/CH_2Cl_2 as eluent gave the following fractions: (a) 30 mg of **28**, (b) 50 mg of the second isomer of **28** together with **24a** (in a ratio of 7:3, respectively), (c) 220 mg (74%) of **30**. **28a**: NMR δ 7.20 (br s, 1 H, NH), 4.94 (br s, 1 H, C(3)H), 4.03 (q, 1 H, C(6)H), 3.06 (s, 3 H, NMe), 2.20 (s, 3 H, SMe), 1.61 (d, 3 H, C(6)Me). **28b**: NMR δ 7.87 (br s, 1 H, NH), 4.87 (d, 1 H, C(3)H), 3.89 (q, 1 H, C(6)H), 3.00 (s, 3 H, NMe), 2.30 (s, 3 H, SMe), 1.67 (d, 3 H, C(6)Me). **30a**: NMR δ 7.80 (br s, 1 H, NH), 3.94 (br s, 2 H, $C(3)H_2$), 3.87 (q, 1 H, C(6)H), 2.97 (s, 3 H, NMe), 1.53 (d, 3 H, C(6)Me); mass spectrum, m/e 142 (M^+).

2,4-Dioxo-3,5-dimethylimidazolidine (32). To a stirred solution of 326 mg (1 mmol) of **21b** in 25 mL of $(CH_3)_2CHOH$ was added at room temperature 210 mg (3 mmol) of $NaSCH_3$. After the mixture was stirred for 3 h at room temperature, the solvent was evaporated. Column chromatography of the residue on silica gel (Merck 60) with 2% C_2H_5OH/CH_2Cl_2 as eluent gave 105 mg

(70%) of compound **32**: NMR δ 6.87 (br s, 1 H, NH), 4.10 (dq, 1 H, C(5)H, irradiation on the NH proton leaves only one quartet), 3.00 (s, 3 H, NMe), 1.47 (d, 3 H, C(5)Me); mass spectrum, *m/e* 128 (M^+); mp (hexane/CH_2Cl_2) 110–112 °C.

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Registry No. 6a, 70771-85-6; **6b**, 70771-86-7; **6c**, 73198-47-7; **6d**, 70771-87-8; **6e**, 73198-48-8; **8a**, 70771-89-0; DL-**8b**, 21653-11-2; **8c**, 73198-49-9; DL-**8d**, 70771-90-3; DL-**8e**, 73198-50-2; **10a**, 73198-51-3; DL-**10b**, 73198-52-4; **10c**, 73198-53-5; DL-**10d**, 73198-54-6; DL-**10e**, 73198-55-7; **11a**, 73198-56-8; **12b**, 41839-79-6; **12c**, 57294-55-0; **12d**, 62927-27-9; **12e**, 73198-57-9; **15a**, 73198-58-0; **15b**, 73198-59-1; **15c**, 73198-60-4; **18a**, 73198-61-5; **18b**, 73198-62-6; **18c**, 73198-63-7; **19a**, 73198-64-8; **19b**, 73198-65-9; *cis*-**19c**, 73198-66-0; **20a**, 73198-67-1; **21a**, 73198-68-2; **21b**, 73198-69-3; *cis*-**24a**, 73198-70-6; *trans*-**24a**, 73198-71-7; **26**, 73198-72-8; **27**, 52785-16-7; **28a**, 73198-73-9; **28b**, 73198-74-0; **30a**, 50627-39-9; **32**, 6851-79-2; pyruvoyl chloride, 5704-66-5.

Biosynthesis of Gliotoxin. Synthesis of Sulfur-Bridged Dioxopiperazines from *N*-Hydroxyamino Acids

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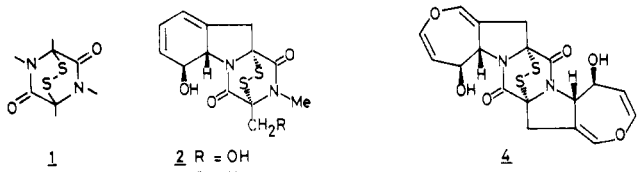
A biomimetic approach to the synthesis of sulfur-bridged dioxopiperazines **1** is described. It is postulated that the biosynthesis of this type of compound progresses by oxidation of dioxopiperazines **12** to the corresponding di-*N*-hydroxy compounds **13**, which might be converted into acylimmonium ions of type **14**. These could react with sulfur nucleophiles to give the sulfur-bridged compounds **15** (Scheme II). The biosynthesis of gliotoxin (**2**) might thus proceed as depicted in Scheme III, which features the stereochemically controlled cis addition of a disulfide. Support of this biosynthetically hypothetic scheme was come by as follows: the *N*-hydroxydioxopiperazines **23** and **24** could be converted efficiently into the sulfur-bridged dioxopiperazines **30** and **31** (Scheme IV). The key step in this scheme is the migration of the N functionality in **23** to a C(3)-position in **27**, a reaction that proceeds through the acylimine **26**. N-Methylation of **27a** followed by treatment with liquid H_2S in the presence of $ZnCl_2$ gave the dithiol **29a**. Surprisingly, under these reaction conditions **27b** afforded a mixture of dithiol **29b** and the monosulfide **31b**, whereas **27c** gave only the monosulfide **31c**. It is proposed (Scheme V) that from **28** a mixture of cis and trans dithiol **29** is formed, the ratio of which depends upon the ring substituent R. The trans dithiol is, in contradistinction to the cis dithiol, not stable under the reaction conditions and is converted by a transanular thiol attack into the monosulfide **31**.

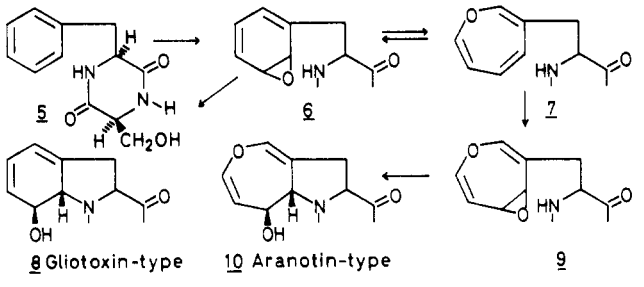
The epidithiodioxopiperazine moiety **1** is a common feature of a substantial number of natural products, exhibiting antiviral, antifungal, or antibacterial activity.[1] The best known representative of this class of compounds is gliotoxin (**2**), a metabolite of various *Fungi imperfecti*.



1 **2** R = OH; **3** R = H **4**

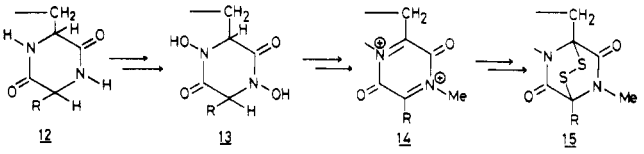
During the last decades several new specimens of this class have been isolated, one of which is aranotin (**4**). The structural resemblance of **4** to **2** has led to considerable speculation on their biosynthesis. Cyclo-L-Phe-L-Ser (**5**)[2] has been shown to be an efficient precursor of gliotoxin (**2**), and further labeling studies have demonstrated that the *N*-methyl group is derived from methionine,[3] whereas the sulfur atoms are delivered by cystine.[4] The most likely explanation for the formation of the dihydro aromatic systems has been provided by Neuss et al.,[5] who invoked the intermediacy of benzene oxides **6**. This system is in equilibrium with the isomeric oxepin **7** (Scheme I). Nucleophilic attack by the dioxopiperazine amide group of **6** would produce a substituted cyclohexadienol **8** of the

Scheme I



8 Gliotoxin-type **10** Aranotin-type **9**

Scheme II



12 **13** **14** **15**

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