same configuration as the levorotatory 21-Me analogue 11.[11] A recent X-ray study[12] has revealed that levorotatory 11 has the 21$\alpha$-configuration, contrary to an assignment based on $^1$H NMR data and the Lowe-Brewster rules.[11]

An unambiguous determination of 8 has yet to be performed. On the basis of our configurational assignment to 8, the reaction depicted in eq 2 proceeds with the same stereochemistry as that in eq 1, viz, anti.

## Experimental Section

**General Procedures.** Infrared spectra were recorded on a Perkin-Elmer 457 IR spectrometer. $^1$H NMR spectra were determined on a Varian EM-390 spectrometer by using $CCl_4$ or $CDCl_3$ as the solvent and $Me_4Si$ as the internal standard. $^{13}$C NMR spectra were measured on a Bruker WP-200 spectrometer by using $CDCl_3$ as the solvent and $Me_4Si$ as the internal standard. All reactions were carried out in an atmosphere of dry nitrogen.

**Materials.** THF was distilled from $LiAlH_4$. *n*-Butyllithium was obtained as a 1.50 M solution in *n*-hexane from Metallgesellschaft A.G., Frankfurt am Main; its molarity was determined by using Watson's titration method.[13] Optically enriched 1-phenyl-2-propyn-1-ol was obtained according to the literature;[14] in the presented study the *S* compound (ee 50%) was used. Mestranol was obtained as generous gift from Organon, Oss, The Netherlands; it was converted into the methanesulfonate according to our procedure.[15]

**General Procedure for the Preparation of Optically Active Halides 3a–c.** To a well-stirred solution of 0.66 g of **1** (5.0 mmol) in 15 mL of dry THF were successively added, at −70 °C, 3.4 mL of *n*-butyllithium (1.50 M) in hexane and, at once, 0.63 g of methanesulfonyl chloride (5.5 mmol). After 2 min[16] a solution of cuprate **4** (6.0 mmol) or a suspension of cuprate **5** (3.0 or 6.0 mmol; see Table I) in 5 mL of dry THF was added at once.[17] The mixture was then allowed to warm to 20 °C in 15–20 min. Allenes **3a–c** were isolated by pouring the respective reaction mixtures into 100 mL of a saturated aqueous $NH_4Cl$ solution containing 1 g of NaCN and 0.5 mL of a THF solution of Ionox ($c$ = 1 g/L) in order to prevent decomposition via free radicals, extracting the aqueous layer with pentane (2 × 25 mL), washing the combined extracts with water (5 × 50 mL), and drying the extract with $K_2CO_3$. The solvent was evaporated in vacuo to give **3a-c** in 90–95% yield. The specific rotations of **3a–c** were determined in ethanol; extrapolation of the obtained values to optically pure **1** gave the data as compiled in Table I. For determination of the physical constants of **3a–c**, racemic **1** was converted on a 30.0-mmol scale into **3a–c** by following the procedure described above.

**1-Chloro-3-phenylpropadiene (3a)**: bp 50 °C (0.01 mm Hg); $n^{20}_D$ 1.6147; IR 1945 cm$^{-1}$; $^1$H NMR ($CCl_4$) $\delta$ 6.38 (d, 1 H), 6.50 (d, 1 H), $^4J$(HC=C=CH) = 6.0 Hz; $^{13}$C NMR ($CDCl_3$) $\delta$ 203.3 (=C=).

**1-Bromo-3-phenylpropadiene (3b)**: bp 65 °C (0.001 mm Hg); $n^{20}_D$ 1.6435; IR 1943 cm$^{-1}$; $^1$H NMR ($CCl_4$) $\delta$ 6.21 (d, 1 H), 6.27 (d, 1 H), $^4J$(HC=C=CH) = 5.9 Hz; $^{13}$C NMR ($CDCl_3$) $\delta$ 202.8 (=C=).

**1-Iodo-3-phenylpropadiene (3c)**: bp 70 °C (0.001 mm Hg);[18] $n^{20}_D$ 1.6855; IR 1930 cm$^{-1}$; $^1$H NMR ($CCl_4$) $\delta$ 5.92 (d, 1 H), 6.05 (d, 1 H), $^4J$(HC=C=CH) = 5.9 Hz; $^{13}$C NMR ($CDCl_3$) $\delta$ 205.5 (=C=).

**Preparation of 8.** To a stirred solution of cuprate **4** (X = Br; 10.0 mmol) in 10 mL of dry THF was added, at 25 °C, 1.95 g of steroid **7** (5.0 mmol). The resulting mixture was stirred for 90 min at 25 °C. The product was isolated as described for **3** by using a mixture of $Et_2O$/hexane (1:1 v/v) for the extraction. The crude product **8** was obtained in 90% yield together with 10% of enyne **9**. It was purified from **9** by washing twice with 5 mL of boiling pentane. According to $^1$H NMR spectroscopy the remaining crystalline allene **8** was pure (yield after purification 0.90 g; the pentane fraction contained the rest of **8** together with enyne **9**). The following characteristic data were found for **8**: $[\alpha]^{22}_D$ −173° ($c$ 1.2, $CH_2Cl_2$); mp 117 °C; IR 1956 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.90 (s, 13-Me), 5.95 (t, C-21, $\beta$-H), $^5J$(HC=C=C—$CH_2$) = 3.0 Hz; $^{13}$C NMR ($CDCl_3$) $\delta$ 193.7 (=C=).

**Acknowledgment.** The investigations were supported in part by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO).

**Registry No.** (*S*)-(+)-1, 64599-56-0; (*S*)-(+)-**3a**, 81158-17-0; (*S*)-(+)-**3b**, 81158-18-1; (*S*)-(+)-**3c**, 81158-19-2; **7**, 76685-96-6; (−)-**8**, 81158-20-5; **9**, 23640-47-3.

(12) Elsevier, C. J.; Meijer, J.; Westmijze, H.; Vermeer, P.; van Dijck, L. A. *J. Chem. Soc., Chem. Commun.* **1982**, 84.
(13) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
(14) Tadema, G.; Everhardus, R. H.; Westmijze, H.; Vermeer, P. *Tetrahedron Lett.* **1978**, 3935.
(15) Westmijze, H.; Kleijn, H.; Vermeer, P.; van Dijck, L. A. *Tetrahedron Lett.* **1980**, 2665.
(16) Longer reaction times caused a decrease of the optical rotation value of **3** which is most likely due to an interference of lithium chloride liberated during the formation of the ester. Separate experiments showed that ester **2** may undergo a $S_N2$ reaction by lithium chloride.
(17) For the preparation of **5**, 2 molar equiv of CuX was added to a solution of LiX in THF; after a short time a homogeneous solution was obtained which then turned into a suspension.
(18) If distilled at higher pressure, the compound may explode violently.

# Synthesis of Some Dihydroxyphenyl 4,5-Dichloroimidazol-2-yl Ketones: Compounds Related to Pyoluteorin[1]

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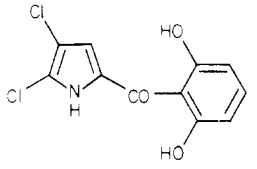
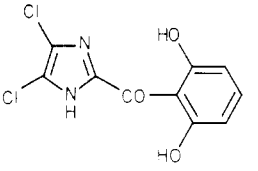
Pyoluteorin (1), a pyrrole antibiotic isolated by Takeda[2]



1



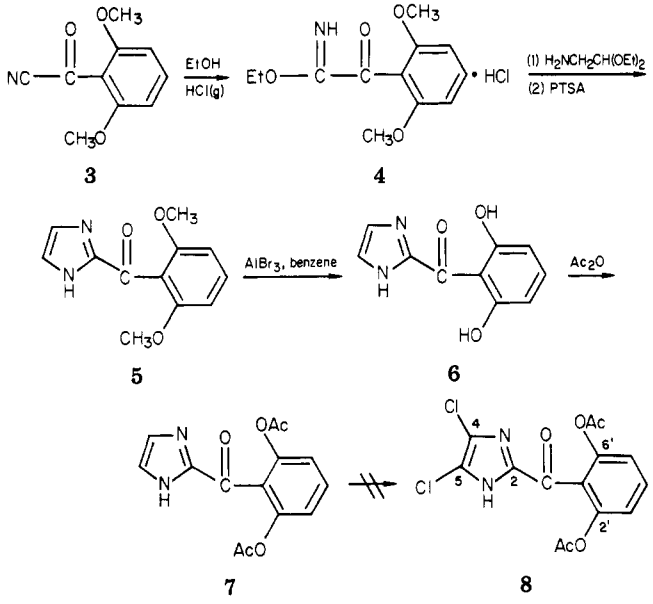
2

from certain strains of *Pseudomonas aeruginosa*, and a wide variety of analogues obtained by total synthesis have been the subject of numerous publications.[3] However, in the analogues reported to date, the pyrrole moiety has always been present. We therefore sought to prepare some compounds similar to pyoluteorin in which the pyrrole ring is replaced with an imidazole ring [e.g., azapyoluteorin (**2**)]. Although 4,5-dibromo and 4,5-diiodo derivatives of imidazoles can be prepared easily and in good yield by halogenation,[4] the corresponding chlorine derivatives are relatively unknown.[5] It was therefore necessary during the

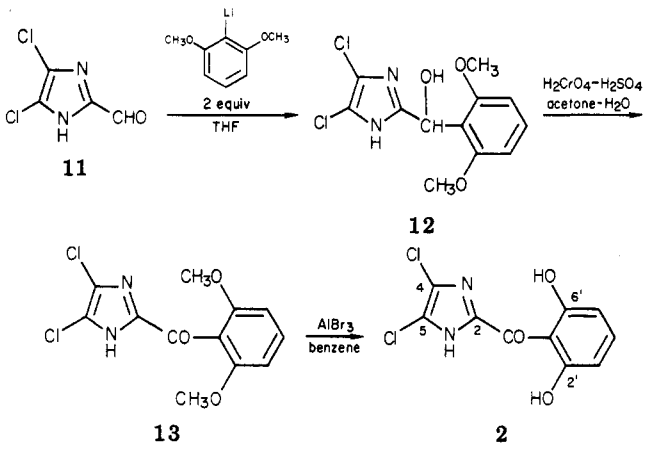
(1) This paper has been presented in part. See "Abstracts of Papers", 178th National Meeting of the American Chemical Society, Washington, DC, Sept 1979; American Chemical Society: Washington, DC, 1979; Abstr Medi 71.
(2) Takeda, R. *J. Am. Chem. Soc.* **1958**, *80*, 4749.
(3) (a) Durham, D. G.; Hughes, C. G.; Rees, A. H. *Can. J. Chem.* **1972**, *50*, 3223. (b) Hughes, C. G.; Rees, A. H. *J. Med. Chem.* **1973**, *16*, 574. (c) Bailey, D. M.; Johnson, R. E.; Salvador, U. J. *Ibid.* **1973**, *16*, 1298. (d) Cue, B. W., Jr.; Dirlam, J. P.; Czuba, L. J.; Windisch, W. W. *J. Heterocycl. Chem.* **1981**, *18*, 191. (e) Cue, B. W., Jr.; Chamberlain, N. *Ibid.* **1981**, *18*, 667, and references cited therein.
(4) K. Hofmann *Chem. Heterocycl. Compd.* **1953**, *6*, 111 ff.
(5) (a) Baldwin, J. J.; Lumma, P. K.; Novello, F. C.; Ponticello, G. S.; Sprague, J. M.; Duggan, D. E. *J. Med. Chem.* **1977**, *20*, 1189. (b) Lutz, A. W.; DeLorenzo, S. *J. Heterocycl. Chem.* **1967**, *4*, 399. (c) Beck, G.; Sasse, K.; Heitzer, H.; Eue, H.; Schmidt, R.; Scheinpflug, H. German Offen. 2 610 527, 1977; *Chem. Abstr.* **1978**, *88*, P6886*g*. (d) Günther, D.; Bosse, D. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 130. (e) Dirlam, J. P.; James, R. B.; Shoop, E. V. *J. Heterocycl. Chem.* **1980**, *17*, 409.

0022-3263/82/1947-2196$01.25/0 

Scheme I

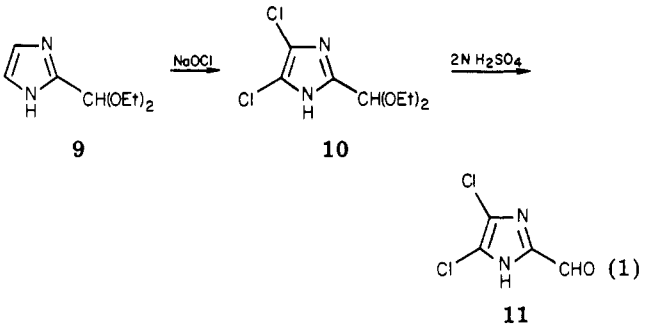


Scheme II



course of this work to develop new methods applicable for the synthesis of **2** and related compounds, which are the topic of this paper.

Using procedures analogous to those employed previously for the synthesis of 2-substituted imidazoles from imidates,[6] we prepared 2′,6′-dimethoxyphenyl imidazol-2-yl ketone (**5**) from ethyl 2,6-dimethoxybenzoylimidate[7] (**4**) by treatment with aminoacetaldehyde diethyl acetal, followed by acid-promoted cyclization of the resulting amidine[8] (Scheme I). Unfortunately, the diacetate **7** could not be converted to the corresponding 4,5-dichloro derivative **8** by chlorination with elemental chlorine, *N*-chlorosuccinimide, *tert*-butyl hypochlorite, or sodium hypochlorite. Starting material or in some cases a complex mixture of products was obtained in these reactions. The conversion of **6** to the diacetate **7** with acetic anhydride was necessary to prevent chlorination of the phenyl ring. In sharp contrast, the diacetate **7** was very easily dibrominated in the 4,5-positions using bromine–acetic acid to afford the 4,5-dibromo derivative of **8** in 60% yield.[9] This result is consistent with previous studies regarding the bromination of imidazoles.[4] The failure to obtain compound **8** (via Scheme I) necessitated introduction of the 4,5-dichloro substituents at an earlier stage in the synthetic sequence. In this regard, 4,5-dichloroimidazole-2-carboxaldehyde (**11**) was considered as a potential synthetic intermediate. This compound was synthesized in a straightforward manner by chlorination of imidazole-2-carboxaldehyde diethyl acetal (**9**) with sodium hypochlorite,[10] under conditions similar to those used by others to prepare 4,5-dichloro-2-methylimidazole.[5b] Acid hydrolysis of **10** yielded the aldehyde **11** (eq 1). Compound **11** was indeed converted to azapyoluteorin (**2**) in three steps as illustrated in Scheme II (method A). The lithiation of *m*-dimethoxybenzene with *n*-butyllithium was carried out in dry THF.[11] It is most remarkable that no formal protecting group for the imidazole nitrogen was required[12] for the addition of the resulting (2,6-dimethoxyphenyl)lithium to afford the alcohol **12**. Two equivalents of the aryllithium was used, and it is assumed that the imidazole NH is removed by 1 equiv of this base. Oxidation of the alcohol **12** to the ketone **13**, followed by demethylation of the 2′,6′-dimethoxy groups, gave rise to azapyoluteorin (**2**). Some 3′-alkyl-, 4′-alkyl-, and 3′,4′-dialkylazapyoluteorin analogues were synthesized using alkyl-substituted *m*-dimethoxybenzenes[13] as listed in Table I (i.e., **16–19**).[14]



In order to prepare various isomers of azapyoluteorin in which the dihydroxy groups are in different positions on the phenyl ring (i.e., 2′,3′; 2′,5′; 3′,4′; etc.), it was necessary to develop another synthetic route for derivatives of **2**. An attractive new synthesis (method B) was conceived that has proven useful, starting from the readily available 2-bromo-4,5-dichloroimidazole[15] (**14**, eq 2). The

(6) Berkelhammer, G.; Gastrock, W. H.; Remers, W. A.; Tomcufcik, A. S. U.S. Patent 3 600 399, 1971; *Chem. Abstr.* **1971**, *75*, 118322*h*.

(7) Although the imidate formed from benzoyl cyanide using the Pinner reaction is reported to be unstable, compound **4** could be isolated and characterized (see Experimental Section). The sterically hindered ethyl *o*-toluoylimidate hydrochloride has been suggested as the intermediate in the preparation of ethyl o-toluoylformate: Roger, R.; Neilson, D. G. *Chem. Rev.* **1961**, *61*, 179.

(8) English, J. P.; Berkelhammer, G. U.S. Patent 3 812 189, 1974; *Chem. Abstr.* **1974**, *81*, 49293.

(9) The 4,5-dibromo derivative of **8** melts at 262–264 °C. Anal. Calcd for $C_{14}H_{10}BrN_2O_5$: C, 37.67; H, 2.24; N, 6.28. Found: C, 37.59; H, 2.36; N, 6.15.

(10) In contrast to this result, we were unable to chlorinate imidazole-2-carboxaldehyde without decomposition of the starting material, and thus the use of the diethyl acetal **10** was required for the synthesis of **11**.

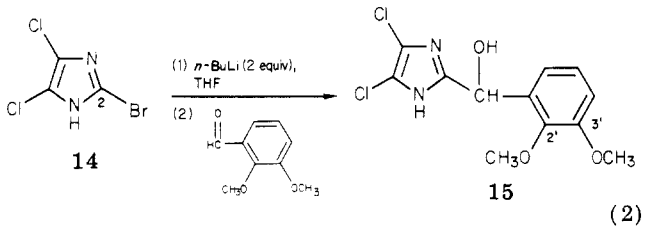
(11) Adams, R.; Mathieu, J. *J. Am. Chem. Soc.* **1948**, *70*, 2120.

(12) Many different N-protected imidazoles have been used in order to prepare a variety of 2-substituted imidazoles: Curtis, N. J.; Brown, R. S. *J. Org. Chem.* **1980**, *45*, 4038, and references cited therein.

(13) The requisite alkyl-substituted *m*-dimethoxybenzenes were synthesized in collaboration with Dr. B. W. Cue, Jr., of these laboratories. For experimental details, see Cue, B. W., Jr.; Chamberlain, N. C.; Girard, A. E.; Pezzullo, R. M. *J. Med. Chem.*, submitted for publication.

(14) Azapyoluteorin (**2**) was found to possess an in vitro spectrum of activity very similar to that reported for pyoluteorin (1)[3c] and was approximately equipotent compared with 1 against *E. coli* and *Pasteurella multocida*. Compounds **16–19** listed in Table I were found to have comparable activity to that observed for azapyoluteorin, whereas the analogues **20–22** were less active (Dr. A. E. Girard, unpublished results).

(15) 2-Bromo-4,5-dichloroimidazole was conveniently prepared in 74% yield by bromination of 4,5-dichloroimidazole[5b] at 25 °C using 1 equiv of bromine in acetic acid: mp 221–222 °C (lit.[5b] mp 219–220 °C).




(2)

selective lithiation at C-2 and deprotonation of the imidazole NH was accomplished with 2 equiv of *n*-butyllithium in THF. The addition of various benzaldehydes to this resulting intermediate, presumably a dianion of 4,5-dichloroimidazole, afforded the corresponding phenyl-4,5-dichloroimidazol-2-carbinol derivatives (e.g., **15**). Oxidation and demethylation reactions, respectively, gave rise to analogues of azapyoluteorin (**2**) (Table I; **20–22**).[14] As was the case in method A, no N-protecting group was needed under the above reaction conditions.

The use of the 4,5-dichloroimidazole intermediates **11** and **14** should allow the simple preparation of a variety of other 2-substituted 4,5-dichloroimidazoles. The procedures described herein offer the unique advantage over existing imidazole methodology[12] in that no N-protecting group is required when the 4,5-dichloroimidazolyl ring system is used.

## Experimental Section

Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus or a Mel-Temp capillary hot-stage apparatus (for compounds melting higher than 250 °C). NMR spectra were recorded on a Varian T-60 spectrometer with $Me_4Si$ as in internal standard. IR spectra were determined with a Perkin-Elmer Model 21 spectrophotometer, and mass spectra were obtained with a Perkin-Elmer RMU-6E mass spectrometer. Microanalyses were performed by the Pfizer Analytical Department. All evaporations were conducted in vacuo using either a water aspirator or a vacuum pump.

**Ethyl 2,6-Dimethoxy-α-oxobenzeneacetimidate (4).** To a solution of 2,6-dimethoxybenzoyl cyanide[16] (5.00 g, 26 mmol) in chloroform (15 mL) and ethanol (1.6 mL) at 0 °C was bubbled dry HCl gas for 5 min. The reaction mixture was stored at 0 °C for 3 days. Following the addition of diethyl ether (20 mL), **4** crystallized out of solution: yield 5.5 g (77%); mp 115–116 °C; mass spectrum, *m/e* 237 ($M^+$), 165 (base peak, 2,6-dimethoxybenzoyl).

Anal. Calcd for $C_{12}H_{15}NO_4$·HCl: C, 52.70; H, 5.90; N, 5.12. Found: C, 52.56; H, 5.61; N, 4.93.

**2′,6′-Dimethoxyphenyl Imidazol-2-yl Ketone (5).** To a solution of compound **4** (1.20 g, 4.38 mmol) in ethanol (8 mL) at room temperature was added aminoacetaldehyde diethyl acetal (0.61 g, 4.38 mmol). The mixture was allowed to stir for 3 h, and then the ethanol was removed in vacuo. The resulting amidine[8] was heated at 110 °C with stirring for 0.5 h following the addition of a catalytic amount of *p*-toluenesulfonic acid (50 mg). The dark reaction mixture was allowed to cool to room temperature and was added to a saturated solution of sodium bicarbonate (25 mL). The product was filtered and triturated with ether to afford **5**: yield 0.80 g (79%); mp 272–274 °C; IR (KBr) 1680 (C=O) $cm^{-1}$; NMR ($Me_2SO$-$d_6$) δ 3.66 (6, s, $OCH_3$), 6.70 (2, d, $H_{3'}$, $H_{5'}$), 7.20 (2, br s, $H_4$, $H_5$; this peak becomes a singlet at δ 7.60 upon addition of 1 drop of $CF_3CO_2H$), 7.40 (1, d of d, $H_{4'}$); mass spectrum, *m/e* 232 ($M^+$). An analytical sample of **5** was obtained following recrystallization in methanol (mp 275–276 °C).

Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.07; H, 5.17; N, 12.07. Found: C, 61.71; H, 5.26; N, 11.96.

**2′,6′-Dihydroxyphenyl Imidazol-2-yl Ketone (6).** To a solution of ketone **5** (1.00 g, 4.3 mmol) in dry benzene (200 mL) at temperature was added aluminum bromide (4.2 g, 15.5 mmol, 99.9% pure) all at once.[3d] The mixture, under a nitrogen atmosphere, was allowed to stir vigorously for 16 h and was then poured into cold water (200 mL) and extracted with diethyl ether. The combined ether extract was dried over anhydrous $MgSO_4$ and evaporated in vacuo to give **6** as a red solid: yield 0.42 g (48%); mp 190–192 °C dec; NMR ($Me_2SO$-$d_6$) δ 6.35 (2, d, $H_{3'}$, $H_{5'}$), 7.15 (1, d of d, $H_{4'}$), 7.40 (2, s, $H_4$, $H_5$); IR (KBr) 1640 (C=O) $cm^{-1}$; mass spectrum, *m/e* 204 ($M^+$).

Anal. Calcd for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.46; H, 4.25; N, 13.45.

**2′,6′-Dihydroxyphenyl Imidazol-2-yl Ketone *O,O*-Diacetate (7).** The reaction of **6** (0.58 g, 2.8 mmol) and acetic anhydride (1.5 g, 16 mmol) in benzene under reflux for 5.5 h afforded **7** as white crystals: yield 0.32 g (40%); mp 249–250 °C; NMR ($CDCl_3$) δ 2.05 (6, s, $OCOCH_3$), 7.30 (5, m, $H_{4-5}$, $H_{3'-5'}$); IR (KBr) 1755, 1670 (C=O) $cm^{-1}$; mass spectrum, *m/e* 288 ($M^+$). Anal. Calcd for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.17; N, 9.72. Found: C, 58.09; H, 3.89; N, 9.57.

**Imidazole-2-carboxaldehyde Diethyl Acetal (9).** A solution of sodium methoxide (2.50 g, 0.046 mol) in dry methanol (180 mL) was added dropwise over 30 min to diethoxyacetonitrile (60 g, 0.46 mol) under nitrogen atmosphere. This reaction was mildly exothermic, and the temperature was maintained at 35 °C with an ice bath. The mixture was allowed to stir at room temperature for 2.5 h. To the thus-formed methyl diethoxyacetimidate[8] was added aminoacetaldehyde diethyl acetal (61.8 g, 0.46 mol), followed by the portionwise addition, with exterior ice cooling, of 56 mL of saturated ethanolic hydrogen chloride. The temperature was kept below 35 °C during the addition of the acid, and the final solution was acidic to pH indicator paper. The reaction mixture was allowed to stand at room temperature for 1 h and filtered. The filtrate was evaporated under reduced pressure, leaving 131.6 g (96% yield) of *N*-(2,2-diethoxyethyl)-2,2-diethoxyacetamidine hydrochloride[8] as a light yellow viscous oil. A mixture of the acetamidine hydrochloride and *p*-toluenesulfonic acid (0.5 g) was heated at 115 °C for 1 h. The reaction mixture was cooled to 50 °C and was poured into a saturated sodium bicarbonate solution (800 mL). The pH was adjusted to pH 7.0 with the addition of solid sodium carbonate. The aqueous layer was extracted with ethyl acetate, and the combined extract was dried over anhydrous magnesium sulfate and evaporated to afford a solid. The solid was triturated with ether to give **9**: yield 48.1 g (63%); mp 111–112 °C (lit.[17] mp 112–113 °C).

**4,5-Dichloroimidazole-2-carboxaldehyde Diethyl Acetal (10).** Compound **9** (30.5 g, 0.18 mol) was added in one portion to a stirred solution of sodium hydroxide (7.2 g, 0.18 mol) in 5.25% sodium hypochlorite (630 mL). The resulting reaction was *exothermic*, and the temperature was maintained at 45 °C with an ice bath. After the mixture was allowed to stir an additional 10 min, it was then cooled with an ice bath, and the pH (9–10) was adjusted to 4 with concentrated hyrochloric acid. The white precipitate was collected, washed with water, and dried under vacuum to give 40.0 g (93% yield) of crude **10**: mp 107–108 °C. An analytical sample was prepared by recrystallization from water: mp 110–111 °C; NMR ($Me_2SO$-$d_6$) δ 1.20 (3, t, $CH_3$), 3.60 (4, m, $CH_2$), 6.40 (1, s, CH); mass spectrum, *m/e* 242, 240, 238 ($M^+$). Anal. Calcd for $C_8H_{12}Cl_2N_2O_2$: C, 40.20; H, 5.06, N, 11.72. Found: C, 40.06; H, 5.45; N, 11.42.

**4,5-Dichloroimidazole-2-carboxaldehyde (11).** A mixture of 4,5-dichloroimidazole-2-carboxaldehyde diethyl acetal (**10**; 14.2 g, 59 mmol) and 2 N sulfuric acid (225 mL) was heated at 90 °C for 1.5 h. While the mixture was cooling to 0 °C, the product crystallized out of solution to afford **11**: yield 6.3 g (64%); mp 190–191 °C; IR (KBr) 1670 $cm^{-1}$. Anal. Calcd for $C_4H_2Cl_2N_2O$: C, 29.12; H, 1.22, N, 16.98. Found: C, 29.09, H, 1.21, N, 16.97.

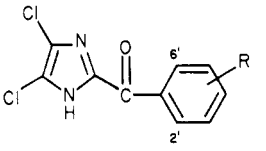
**(2,6-Dimethoxyphenyl)lithium.**[11] To 40 mL of dry THF under $N_2$ at 0 °C and containing *m*-dimethoxybenzene (14.3 g, 10.4 mmol) was added via syringe 10.4 mmol of *n*-BuLi in hexane (Ventron). After the addition, the solution was warmed to room temperature for 15 min before use.

**2′,6′-Dimethoxyphenyl-4,5-dichloroimidazol-2-ylcarbinol (12). Method A.** To 10.4 mmol of the solution of 2,6-dimethoxyphenyllithium in THF/hexane (prepared as above) at 0 °C was added dropwise, over 15 min, 4,5-dichloroimidazole-2-carboxaldehyde (8.4 g, 50 mmol) in THF (40 mL). After the

(16) Birchall, G. R.; Rees, A. H. *Can. J. Chem.* **1971**, *49*, 919.

(17) Iversen, P. E.; Lund, H. *Acta. Chem. Scand.* **1966**, *20*, 2649.

Table I



| no.[a] | R | method | mp, °C (dec) | formula | ($M_r$) |
|---|---|---|---|---|---|
| 2 | 2′,6′-$OH_2$ | A, B | 239–241 | $C_{10}H_6Cl_2N_2O_3$ | (273) |
| 16 | 2′,6′-$OH_2$, 3′-Me | A | 193–195 | $C_{11}H_8Cl_2N_2O_3$ | (287) |
| 17 | 2′,6′-$OH_2$, 3′-*n*-Pr | A, B | 153–155 | $C_{13}H_{12}Cl_2N_2O_3$ | (315) |
| 18 | 2′,6′-$OH_2$, 4′-*n*-Pr | A | 125–128 | $C_{13}H_{12}Cl_2N_2O_3$ | (315) |
| 19 | 2′,6′-$OH_2$, 3′,5′-$Me_2$ | A | 198–200 | $C_{12}H_{10}Cl_2N_2O_3$ | (301) |
| 20 | 2′,3′-$OH_2$ | B | 247–248 | $C_{10}H_6Cl_2N_2O_3$ | (273) |
| 21 | 2′,5′-$OH_2$ | B | 238–240 | $C_{10}H_6Cl_2N_2O_3$ | (273) |
| 22 | 3′,4′-$OH_2$ | B | 256–258 | $C_{10}H_6Cl_2N_2O_3$ | (273) |

[a] The compounds listed had spectral properties and mass spectral data for the molecular ion fully compatible with the assigned structures. The C, H, and N analyses were within ±0.3% of the calculated values.

mixture was allowed to stir at room temperature for 2.5 h, 300 mL of 1 N sulfuric acid was added, and the mixture was extracted with ethyl acetate. Removal of solvent in vacuo yielded a solid, which after trituration with ether gave **12** as a white solid: yield 10.0 g (70%); mp 157–158 °C; NMR ($Me_2SO$-$d_6$) δ 3.65 (6, s, $OCH_3$), 5.55 (1, br s, OH), 6.00 (1, m, CH), 6.55 (2, d, $H_{3'}$ and $H_{5'}$), 7.20 (1, d of d, $H_{4'}$); mass spectrum, *m/e* 306, 304, 302 ($M^+$). Anal. Calcd for $C_{12}H_{12}Cl_2N_2O_3$: C, 47.57; H, 3.99, N, 9.25. Found: C, 47.54; H, 3.98; N, 9.31.

**2′,6′-Dimethoxyphenyl 4,5-Dichloroimidazol-2-yl Ketone (13).** To a solution of 2′,6′-dimethylphenyl-4,5-dichloroimidazolylcarbinol (**12**; 8.7 g, 29 mmol) in acetone (75 mL) at 5 °C was added dropwise 2.7 M Jones reagent[18] (11 mL; the standard solution was prepared by dissolving 26.7 g of chromic trioxide in 23 mL of concentrated sufuric acid diluted with water to a volume of 100 mL). The mixture was allowed to stir at room temperature for 1.5 h and then 2-propanol (2 mL) was added. The solvent layer was separated from a green gum by filtration. The solvent was evaporated in vacuo, and the resulting solid was triturated with water and then dried to afford **13**: yield 6.4 g (74%); mp 201–202 °C dec; NMR ($Me_2SO$-$d_6$) δ 3.62 (6, s, $OCH_3$), 6.70 (2, d, $H_{3'}$, $H_{5'}$), 7.35 (1, d of d, $H_{4'}$); IR (KBr) 1681 (C=O) $cm^{-1}$; mass spectrum, *m/e* 304, 302, 300 ($M^+$).

**2′,6′-Dihydroxyphenyl 4,5-Dichloroimidazol-2-yl Ketone (2).** To a solution of ketone **13** (2.23 g, 7.4 mmol) in dry benzene (400 mL) at room temperature was added aluminum bromide (7.9 g, 29.6 mmol, 99.9% pure) all at once. The mixture, under a nitrogen atmosphere, was allowed to stir vigorously for 1.5 h and was then poured into cold water and extracted with diethyl ether. The combined ether extract was dried over anhydrous $MgSO_4$ and evaporated in vacuo to give a red solid. The solid was recrystallized from aqueous methanol to afford **2** as red crystals: yield 1.18 g (58%); mp 239–241 °C; NMR ($Me_2SO$-$d_6$) δ 6.35 (2, d, $H_{3'}$, $H_{5'}$), 7.05 (1, m, $H_{4'}$); IR (KBr) 1640 (C=O) $cm^{-1}$; mass spectrum, *m/e* 276, 274, 272 ($M^+$). Anal. Calcd for $C_{10}H_6Cl_2N_2O_3$: C, 44.00; H, 2.22; N, 10.26. Found: C, 44.08; H, 2.31; N, 10.05.[19]

**2′,6′-Dihydroxyphenyl 4,5-Dichloroimidazol-2-yl Ketone *O,O*-Diacetate (8).** The reaction of **2** (0.50 g, 1.8 mmol), acetic anhydride (1.4 g, 14 mmol), and 4-(dimethylamino)pyridine (10 mg) in benzene (15 mL) under reflux for 2.5 h gave **8** as a white crystalline material: yield 0.44 g (69%); mp 229–230 °C; NMR ($Me_2SO$-$d_6$) δ 2.03 (6, s, $OCOCH_3$), 7.20 (2 H, m, $H_{3'}$, $H_{5'}$), 7.60 (1 H, d of d, $H_{4'}$); IR (KBr) 1770, 1680 (C=O) $cm^{-1}$; mass spectrum, *m/e* 360, 358, 356 ($M^+$).

**2′,3′-Dimethoxyphenyl-4,5-dichloroimidazol-2-ylcarbinol (15). Method B.** To a solution of 2-bromo-4,5-dichloroimidazole[15] (4.5 g, 21 mmol) in tetrahydrofuran (75 mL) at −70 °C was added dropwise 2.4 M *n*-butyllithium in hexane (17.3 mL, 42 mmol) over 1 h. To this mixture was added dropwise a solution of 2,3-dimethoxybenzaldehyde (3.44 g, 21 mmol) in tetrahydrofuran (30 mL) while the temperature was maintained at −70 °C. The mixture was then allowed to warm to room temperature and was poured into ice-cold 1 N sulfuric acid solution. The aqueous mixture was extracted with ethyl acetate. The combined extracts were dried and evaporated to afford a residue, which was then triturated with diethyl ether to give **15**: yield 2.73 (44%); mp 269–270 °C dec; NMR ($Me_2SO$-$d_6$) δ 3.70 (3, s, $OCH_3$), 3.85 (3, s, $OCH_3$), 5.97 (1, d, $J$ = 5 Hz, CH), 6.18 (1, d, $J$ = 5 Hz, OH), 7.10 (3, m, $H_{4'-6'}$); mass spectrum, *m/e* 306, 304, 302 ($M^+$). Anal. Calcd for $C_{12}H_{12}Cl_2N_2O_3$: C, 47.57; H, 3.99; N, 9.25. Found: C, 47.73; H, 3.71; N, 9.16.

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**Registry No. 2**, 81293-92-7; **3**, 31709-80-5; **4**·HCl, 81293-93-8; **5**, 81293-94-9; **6**, 81293-95-0; **7**, 81293-96-1; **8**, 81315-58-4; **9**, 13750-84-0; **10**, 81315-59-5; **11**, 81293-97-2; **12**, 81293-98-3; **13**, 81293-99-4; **14**, 16076-27-0; **15**, 81294-00-0; **16**, 81294-01-1; **17**, 81294-02-2; **18**, 81294-03-3; **19**, 81294-04-4; **20**, 81294-05-5; **21**, 81294-06-6; **22**, 81294-07-7; (2,6-dimethoxyphenyl)lithium, 2785-97-9; 2,3-dimethoxybenzaldehyde, 86-51-1; *N*-(2,2-diethoxyethyl)-2,2-diethoxyacetamidine hydrochloride, 53981-62-7.

(18) Djerassi, C.; Engle, R. R.; Bowers, A. *J. Org. Chem.* **1956**, *21*, 1547.
(19) The demethylation of **13** was also accomplished, albeit in lower (47%) yield, by heating an intimate mixture of **13** and 10 equiv of freshly purified pyridine hydrochloride at 210 °C for 3 h.

## Concerning the Preparation of Optically Pure *N*-(Thiocarboxy)-L-aspartic Anhydride

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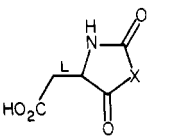
In the course of work directed toward a new synthesis of the dipeptide sweetener, aspartame, we wished to prepare *N*-thiocarboxy-L-aspartic anhydride **1** (L-Asp-NTA).[1]



**1**, X = S
**2**, X = O

(1) Dewey, R. S.; Schoenewaldt, E. F.; Joshua, H.; Paleveda, W. J., Jr.; Schwam, H.; Barkemeyer, H.; Arison, B. H.; Veber, D. F.; Strachan, R. G.; Milkowski, J.; Denkewalter, R. G.; Hirschmann, R. *J. Org. Chem.* **1971**, *36*, 49. This paper provides an elegant and definitive account of the use of NTA's in peptide synthesis.

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