Exquisite Synthesis of a Designed PAR-1 Antagonist

by **Hua-Ming Miao**[a])[b]), **Gui-Long Zhao***[b]), **Lin-Shan Zhang**[c]), **Hua Shao**[b]), and **Jian-Wu Wang***[a])

[a]) School of Chemistry and Chemical Engineering, Shandong University, Jinan 250100, P. R. China (phone: +86-531-88362708; e-mail: jwwang@sdu.edu.cn)

[b]) Tianjin Key Laboratory of Molecular Design and Drug Discovery, Tianjin Institute of Pharmaceutical Research, Tianjin 300193, P. R. China (phone: +86-22-23003529; e-mail: zhao_guilong@126.com)

[c]) College of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Qingdao 266042, P. R. China

The synthesis of a designed, sterically congested geminal dimethyl-bearing PAR-1 antagonist was achieved by a route of ten steps, with the oxidation of an electron-rich benzaldehyde, the construction of a tertiary alkyl azide, and the selective hydrogenolysis of a 1,5-fused tetrazole to generate the cyclic amidine with *Raney*-Ni being the key steps. The selective hydrogenolysis of 1,5-fused tetrazole to generate the cyclic amidine with *Raney*-Ni was discovered and may be generally used for the synthesis of structurally unusual cyclic amidines. Several unsuccessful attempts to construct the desired geminal dimethyl-bearing cyclic amidine were also discussed.

Introduction. – Antiplatelet agents constitute an important class of antithrombotic compounds and are now widely used in the therapy of arterial thrombotic diseases such as acute coronary syndrome (ACS). Platelets can be activated by a variety of agonists such as thrombin, ADP, thromboxane A, collagen, epinephrine, *etc.*, among which thrombin was the most potent one [1]. Therefore, the thrombin receptor is a promising target for the discovery of antiplatelet drugs. Since thrombin activates platelets mainly through protease-activated receptor 1 (PAR-1; also known as thrombin receptor) [2], PAR-1 antagonists were considered as a class of attractive antiplatelet agents, and several PAR-1 antagonists such as SCH530348 [3] and E5555 [4] are now in clinical trials (*Fig.*).

During the development of our own PAR-1 antagonists, we designed a derivative of E5555, compound **1**, which has a structurally challenging geminal dimethyl group and was found to be a potent PAR-1 antagonist by *in vitro* evaluation (*Fig.*). Although it appears that only the geminal dimethyl group is additionally present in the molecule of **1** as compared with E5555 (ignoring the F-atom in E5555 in terms of synthetic methodology), it is the sterically congested geminal dimethyl moiety that leads to a great challenge in the construction of this molecule.

Results and Discussion. – In *Scheme 1*, the retrosynthetic analysis of **1** is presented. First, the molecule **1** can be disconnected to the left fragment, a cyclic amidine **A**, and the right fragment, a bromoacetophenone **B**, based on the S_N2 reaction used in the synthesis of E5555 [4b]. Compound **B** can be prepared according to a known procedure

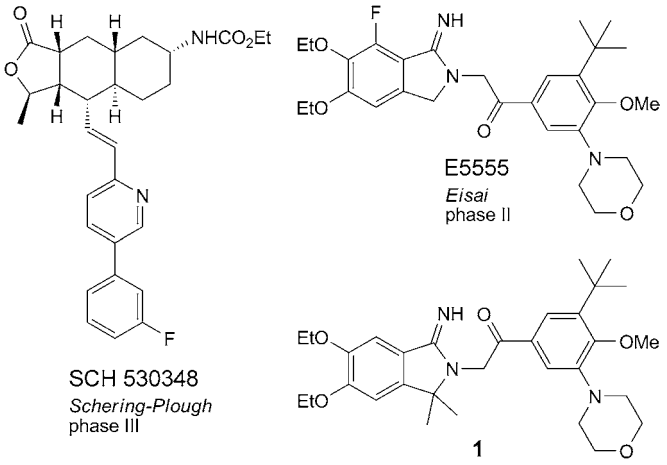


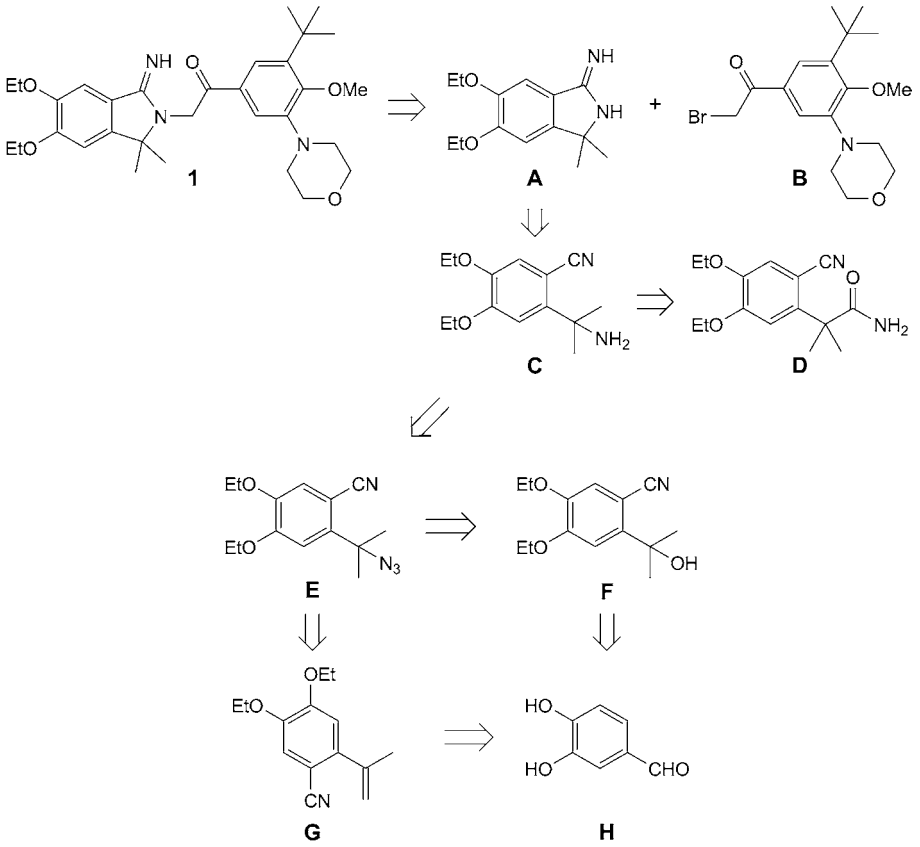
Figure. *PAR-1 Antagonists*

[4b]. Analysis of the cyclic amidine **A** revealed that such an unusual functionality can be constructed by intramolecular nucleophilic addition of a tertiary alkyl amine to the CN group in the *ortho*-position as shown in **C**. Subsequently, an α,α-dimethylbenzylamine **C** was required for this purpose, which bears another structurally challenging functionality, a tertiary alkyl amine. A literature survey revealed that only a few methods are available for the creation of this moiety in this case, including *Hofmann* degradation of **D** [5] or similar reactions [6], and reduction of the corresponding tertiary azido-alkyl derivative **E** [7]. In view of the difficult access to the starting material **D**, used in the *Hofmann* degradation and similar reactions, the other procedure involving reduction of **E** was tentatively selected. The literature search further revealed that the structurally unusual **E** can only be prepared by nucleophilic addition of the N_3^- ion to the corresponding tertiary carbocation [7], which may be generated from the corresponding hydroxy compound **F** [7] or olefin **G** [7a] on treatment with acid. Both the alcohol **F** and the olefin **G** were considered to be accessible starting from 3,4-dihydroxybenzaldehyde **H** by conventional multi-step synthetic routes. As can be seen from the above analysis, there are almost no alternative synthetic approaches available to build compound **1**, since only one or two methods can be used to create such unusual functionalities as cyclic amidine, tertiary alkyl amine, and tertiary alkyl azide involved in the key steps.

According to the retrosynthetic analysis described above, the synthesis of **1** was carried out. After considerable experimentation, an exquisite synthetic route to **1** was ultimately established (*Scheme 2*), which turned out to be an optimized version of the initially proposed one shown in *Scheme 1*.

As depicted in *Scheme 2*, the starting material, 3,4-dihydroxybenzaldehyde, was cleanly diethylated to the known diethoxy derivative **2** [8] with excess EtBr in DMF at room temperature in the presence of KI as catalyst and K_2CO_3 as base. Oxidation of the electron-rich benzaldehyde **2** proceeded smoothly to furnish the desired known benzoic acid **3** [9] with freshly prepared Ag_2O in the presence of NaOH in H_2O at room

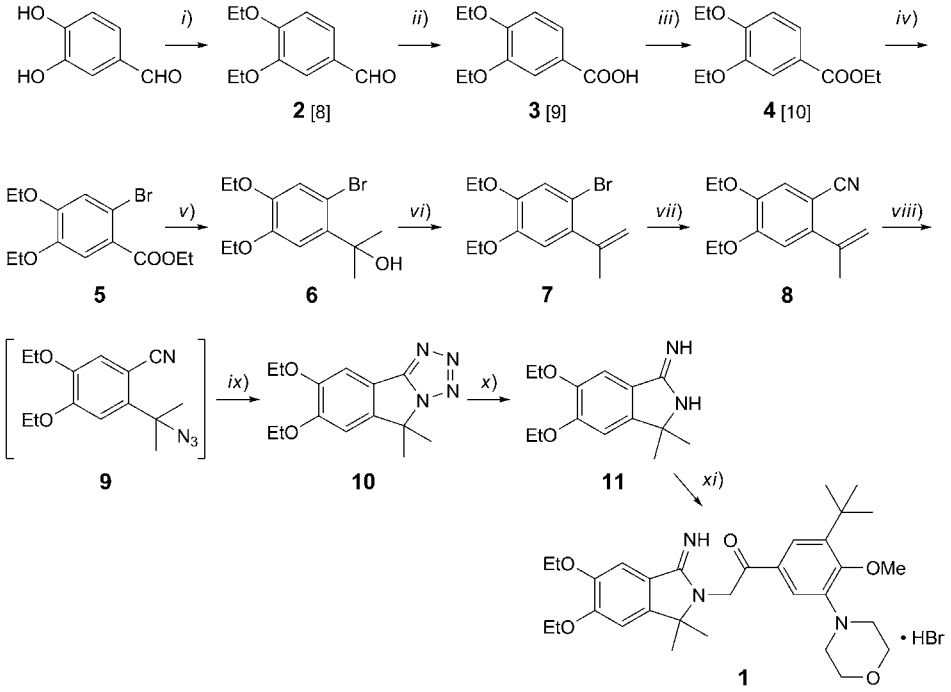
Scheme 1. *The Retrosynthetic Analysis of Compound* **1**



temperature, and the isolated benzoic acid **3** was esterified to the corresponding known ethyl ester **4** [10] with EtOH in the presence of concentrated H_2SO_4 as a catalyst in benzene at reflux with azeotropic removal of H_2O. The ester **4** was brominated to yield **5** with Br_2 in AcOH at 35°, and noteworthy is that the polarities of **4** and **5** were too similar to be discriminated by TLC analysis. Thus, **4** was treated with excess Br_2 in AcOH at 35° for 36 h, and the isolated product was found to be essentially pure **5** almost without contamination by unreacted **4** (^{1}H-NMR), indicating that **4** could be cleanly brominated to **5** under the reaction condition aforementioned[1]). Treatment of **5** with excess MeMgCl at −5° to 0° furnished the desired tertiary alcohol **6** cleanly,

[1]) The reaction conditions described herein were obtained after optimization. Under some unfavorable reaction conditions, the isolated ester **5** was found to be contaminated by appreciable amounts of unreacted starting **4**; the isolated crude product was in turn treated with Br_2 once again until all the starting **4** was consumed and not observed in the isolated product according to ^{1}H-NMR. Attempts to monitor the reaction course on-line by ^{1}H-NMR failed in that the spectrum of the mixture was too complex to draw any meaningful conclusions.

Scheme 2. *The Established Synthetic Route to* **1**



i) KI, K_2CO_3, EtBr, DMF, room temperature (r.t.). *ii*) Ag_2O, NaOH, H_2O, r.t. *iii*) Conc. H_2SO_4, EtOH, benzene, reflux. *iv*) Br_2, AcOH, 35°. *v*) 2 MeMgCl, THF, −5°–0°. *vi*) $MeSO_3H$, CH_2Cl_2, r.t. *vii*) CuCN, DMF, N_2, reflux. *viii*) NaN_3, CF_3COOH (TFA), r.t. *ix*) Spontaneous cyclization. *x*) *Raney*-Ni, ^{i}PrOH, N_2, reflux. *xi*) 2-Bromo-1-[3-(*tert*-butyl)-4-methoxy-5-(morpholin-4-yl)phenyl]ethanone, THF, r.t.

treatment of which with $MeSO_3H$ in CH_2Cl_2 at room temperature led to a rapid dehydration to afford alkene **7**. The alkene functionality is often considered to be labile to high temperature, in particular, in the presence of acidic heavy metal ions; fortunately, however, treatment of **7** with CuCN in refluxing DMF under N_2 successfully furnished the desired benzonitrile **8**. The conversion of **8** to the azido compound **9** with NaN_3 in the presence of CF_3CO_2H (TFA) in $CHCl_3$ at room temperature [7] was found to be rather sluggish, with a conversion of only 20% even after one week. This result may be attributable to the steric hindrance due to the CN group in the *ortho*-position. According to the kinetic theory and the reaction mechanism of this electrophilic addition reaction, the concentrations of both acid and alkene **8** should be increased in this case. Thus, treatment of **8** with a large excess of NaN_3 in minimal pure CF_3CO_2H was adopted, and indeed **8** was rapidly and cleanly consumed. Nonetheless, careful examination of the spectroscopic data, in particular the IR bands, revealed that the isolated product was tetrazole **10** rather than **9**, because an IR absorption band of neither the C≡N group nor the N_3 group was observed,

indicating that **9** spontaneously underwent an intramolecular [3 + 2] cycloaddition to give the isolated tetrazole **10**[2]). Although this cycloaddition can be unambiguously rationalized based on the well-known [3 + 2] cycloaddition, it was almost unpredictable why this cycloaddition occurred so readily in this case. This led to another great challenge: we had to transform tetrazole **10** to the desired cyclic amidine **11**, since, if the synthetic route involving unstable **9** now adopted was bypassed, it seemed difficult, if even possible, to prepare intermediate **C** through an alternative pathway, such as that starting from **D**. Obviously, it also appeared almost impossible to convert tetrazole **10** to the desired cyclic amidine **11**, since it has been shown that the tetrazole ring itself usually does not react with reductants [12], and it is also hard to predict the products even though a suitable reductant is found. Fortunately, however, tetrazole **10** was successfully converted to the desired amidine **11** in high yield after considerable efforts for the search for reagents and reaction conditions (*Table*). Thus, treatment of **10** with freshly prepared *Raney*-Ni under N_2 in refluxing i-PrOH afforded the desired cyclic amidine **11** in 81% yield. Noteworthy is that, under more vigorous conditions, as indicated in *Entry 10* of the *Table*, a complex mixture was obtained, which might contain the over-reduced products. Finally, coupling of **11** with the right fragment bromoacetophenone **B** [4b] in THF at room temperature successfully furnished the desired compound **1** as a hydrobromide salt.

Table. *Reagents and Reaction Conditions Screened to Reduce* **10** *to* **11**

Entry	Reductant	Condition	Outcome
1	$NaBH_4$	r.t., THF	no reaction
2	$NaBH_4$	reflux, THF	no reaction
3	$LiAlH_4$	r.t., THF	no reaction
4	$LiAlH_4$	reflux, THF	no reaction
5	H_2, 10% Pd/C	r.t., THF	no reaction
6	H_2, 10% Pd/C	reflux, THF	4%
7	H_2, 10% Pd/C	reflux, AcOH[a]), THF	15%
8	*Raney*-Ni	r.t., ^{i}PrOH	< 1%
9	*Raney*-Ni	reflux, ^{i}PrOH	81%
10	*Raney* Ni	H_2 (1 mPa), ^{i}PrOH, 50°	complex mixture

[a]) 1% with respect to THF (*v*/*v*).

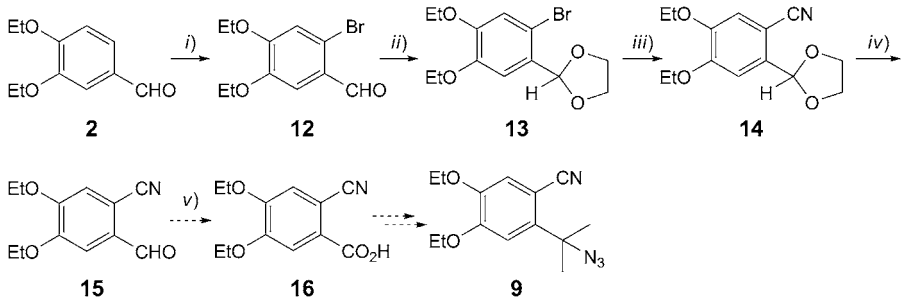
Several unsuccessful approaches have also been attempted before the establishment of the exquisite synthetic route depicted in *Scheme 2*, which will be discussed individually below.

The first unsuccessful attempt is outlined in *Scheme 3*. Analogously to the bromination of **4** shown in *Scheme 2*, **2** was brominated with Br_2 in AcOH at 35° to afford smoothly bromide **12**, and noteworthy was that, unlike **4** and **5**, although the

[2]) A valuable conclusion can then be drawn that the CN and N_3 groups in one molecule can spontaneously and rapidly undergo [3 + 2] cycloaddition even at room temperature if they are sterically favorable; however, under normal circumstances the intermolecular [3 + 2] cycloadditions of CN and N_3 groups to produce 1,5-tetrazole were rather difficult and often carried out at high temperatures in a sealed vessel [11].

polarities of **2** and **12** were similar, they could be readily distinguished by TLC analysis. The aldehyde moiety of **12** was protected as acetal prior to the cyanation, since direct cyanation of **12** with CuCN in refluxing DMF under N_2 led to complete decomposition of **12**. Thus, treatment of **12** with ethylene glycol in the presence of TsOH as catalyst in refluxing benzene with azeotropic removal of H_2O gave the corresponding acetal **13**, and subsequent cyanation with CuCN in refluxing DMF under N_2 smoothly furnished the benzonitrile **14**, which, on treatment with 10% HCl in MeOH at room temperature, yielded the desired *ortho*-formylbenzonitrile **15**. However, all attempts to oxidize **15** with numerous commonly encountered oxidants (see *Scheme 3*) to produce the expected acid **16** failed in that these oxidants were either not sufficiently potent at low temperatures or too potent at elevated temperatures, leading to unidentified over-oxidized products by cleavage of the electron-rich diethoxybenzene ring. The subtle balance, *i.e.*, suitable oxidant under the appropriate reaction condition, has not been found so far. This unsuccessful attempt was initially considered to be rational, since it has been expected that the desired compound **16** could be easily converted to compound **9** by a sequence of conventional functional-group manipulations. Furthermore, all attempts to oxidize the aldehyde **15** to the corresponding acid failed due to the same reasons.

Scheme 3. *The First Unsuccessful Synthetic Route*

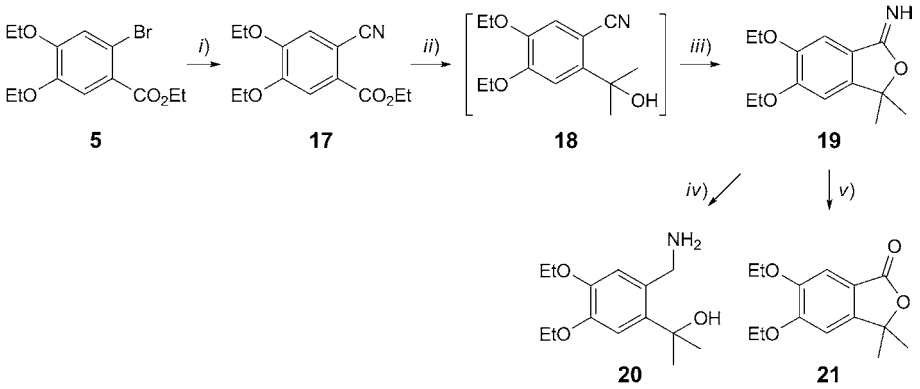


i) Br_2, AcOH, 35°. *ii*) TsOH, $(CH_2OH)_2$, benzene, reflux. *iii*) CuCN, DMF, N_2, reflux. *iv*) 10% HCl, MeOH, r.t. *v*) A variety of oxidants, including Ag_2O, $KMnO_4$, CrO_3, $K_2Cr_2O_7$, and H_2O_2.

Based on the attempted oxidations of the three aldehydes **2**, **12**, and **15** described above, we learned that the substituents in the *ortho*-position (Br in **12** and CN in **15**) posed a significant steric hindrance to the aldehyde function during its oxidation, although neither substituent seems notably bulky, and, therefore, potent oxidants under vigorous reaction conditions were required to bring about the oxidation. However, they were not compatible with and decomposed the electron-rich diethoxy-bearing benzene ring. Fortunately, there is no substituent in *ortho*-position to the aldehyde functionality in **2**, and a mild oxidant was suitable in this case. This valuable conclusion suggests that, in an electron-rich benzaldehyde, the aldehyde functionality should be first oxidized to corresponding acid prior to the introduction of *ortho*-substituents.

The second unsuccessful attempt is outlined in *Scheme 4*. The bromide **5** (see *Scheme 2*) was treated with CuCN as described above to yield the corresponding benzonitrile **17**, which was treated with excess MeMgCl at $-5°$ to $0°$ with anticipation

Scheme 4. *The Second Unsuccessful Synthetic Route*

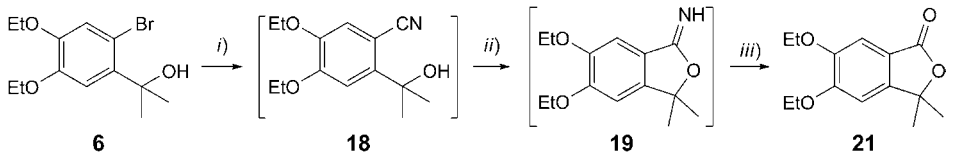


i) CuCN, DMF, N_2, reflux. *ii*) MeMgCl, THF, $-5°$ to $0°$. *iii*) Spontaneous cyclization. *iv*) $LiAlH_4$, THF, $0°$ to r.t. *v*) NaOH, EtOH, H_2O, reflux, and then HCl.

to produce the desired tertiary alcohol **18**. However, the isolated product was the cyclic iminate **19** instead of **18**. It has been initially expected that **18** could be readily converted to **9** by a known method [6b]. Obviously, **18** was indeed formed but spontaneously underwent intramolecular nucleophilic addition in the alkaline reaction media to give **19**. The isolated **19** was derivatized for further structural elucidation. Thus, **19** was treated with $LiAlH_4$ and NaOH to furnish **20** and **21**, respectively.

The last unsuccessful attempt is depicted in *Scheme 5*. The bromide **6** (see *Scheme 2*) was treated with CuCN as described above also with the expectation to furnish **18**, but only the lactone **21** was isolated. Evidently, the desired **18** was produced on treatment of **6** with CuCN; however, **18** underwent spontaneous intramolecular nucleophilic addition to give iminate **19**, which was subsequently hydrolyzed by a trace of H_2O in the mixture to furnish the finally isolated lactone **21**.

Scheme 5. *The Third Unsuccessful Synthetic Route*



i) CuCN, DMF, N_2, reflux. *ii*) DMF, reflux. *iii*) Trace of H_2O, DMF, reflux.

As can be seen from the last two attempts (*Schemes 4* and *5*), the desired key intermediate **18** was indeed formed in both reactions, but it was stable in neither of the mixtures and underwent intramolecular cyclization when exposed to strong base (*Scheme 4*) or high temperature (*Scheme 5*), indicating that it seems considerably hard, if possible, to prepare the key intermediate **E** *via* **F** (*Scheme 1*). Nevertheless, neither the strong base nor high temperature could be avoided, since both unfavorable reaction conditions are necessary for the formation of **18**.

By careful examination of the finally established synthetic route (*Scheme 2*) and the unsuccessful ones (*Scheme 3–5*), it can be concluded that two new functionalities, aryl CN and tertiary N_3, are required to be introduced for the construction of the desired cyclic amidine functionality, and several steps are needed for each introduction. Therefore, a number of synthetic routes resulting from different combinations of these steps exist theoretically. Some valuable conclusions about the strategy for the combination of these steps can be drawn: *1*) the aldehyde functionality should be oxidized prior to the introduction of *ortho*-Br or *ortho*-CN; *2*) the Br-atom should be retained during the manipulation of the other substituent, until an alkene functionality was built; *3*) prior to the introduction of N_3, the CN should be introduced by displacement of the Br-atom.

Compound **1** was found to be a potent PAR-1 antagonist by *in vitro* evaluation model, and the results will be published separately elsewhere.

Conclusions. – In conclusion, the synthesis of a designed potent PAR-1 antagonist **1** was achieved by a ten-step exquisite approach. The strategy for the introduction of the two substituents needed for the construction of the geminal dimethyl-bearing cyclic amidine was intensively explored. Some valuable general conclusions were reached: *1*) as for an electron-rich benzaldehyde, the aldehyde functionality should be first oxidized to the corresponding acid prior to the introduction of the *ortho*-substituents; *2*) like **18**, the *ortho*-cyanobenzylic alcohols were labile to bases and high temperatures in that they often underwent spontaneous intramolecular cycloaddition under the reaction conditions of their formation; *3*) the CN and N_3 groups can undergo intramolecular [3+2] cycloaddition to form a tetrazole moiety spontaneously even at room temperature, if they are sterically permitted in one molecule; *4*) the 1,5-fused tetrazole can be selectively hydrogenolyzed to the corresponding cyclic amidine by *Raney*-Ni in refluxing i-PrOH, which may found wide application in the formation of the structurally challenging cyclic amidines.

Experimental Part

General. M.p.: *XT-4* Microscopic melting-point apparatus; uncorrected. IR: *Thermo Nicolet Avtar FT370* spectrophotometer; KBr discs or thin films. ^{1}H- and ^{13}C-NMR: *Bruker AV400* spectrometer; (D_6)DMSO as solvent; TMS as internal standard; coupling constants *J* in Hz. HR-MS: *Agilent Q-TOF 6510* mass spectrometer; electrospray ionization (ESI) technique.

All the commercially available starting materials and reagents were of anal. grade and used as received unless otherwise noted. Dried THF was distilled from Na/benzophenone ketyl at atmospheric pressure, and DMF was distilled from CaH_2 under reduced pressure.

3,4-Diethoxybenzaldehyde (**2**). A 250-ml round-bottomed flask was charged with 13.81 g (100 mmol) of 3,4-dihydroxybenzaldehyde, 1.66 g (10 mmol) of KI, 32.69 g (300 mmol) of EtBr, 27.64 g (200 mmol) of K_2CO_3, and 150 ml of dried DMF, and the resulting mixture was stirred at r.t. until all 3,4-dihydroxybenzaldehyde was consumed (TLC; typically within 12 h). The mixture was diluted with 200 ml of CH_2Cl_2, stirred for another 5 min and filtered off, and the collected filtrate was washed with three 300-ml portions of sat. brine, dried (Na_2SO_4), and evaporated on a rotary evaporator to afford crude **2** as a deep red oil, which was chromatographed to yield pure **2** as a colorless oil [8]. Yield: 18.06 g (93%). ^{1}H-NMR: 1.32–1.37 (*m*, 2 Me); 4.08 (*q*, *J* = 6.9, CH_2O); 4.14 (*q*, *J* = 6.9, CH_2O); 7.15 (*d*, *J* = 8.4, 1 arom. H); 7.37 (*d*, *J* = 2.0, 1 arom. H); 7.51 (*dd*, *J* = 2.0, 8.4, 1 arom. H); 9.81 (*s*, CHO).

3,4-Diethoxybenzoic Acid (**3**). A 1000-ml beaker was charged with 45.86 g (270 mmol) of $AgNO_3$ and 200 ml of doubly distilled H_2O, and the mixture was stirred to form a clear soln., to which were added portionwise 50 ml of an aq. soln. containing 10.80 g (270 mmol) of NaOH. After addition, the resulting black suspension was stirred, followed by addition of a soln. of 17.48 g (90 mmol) of **2** in 100 ml of MeOH in a portionwise manner. After addition, the mixture thus obtained was stirred at r.t. until all the starting aldehyde **2** was consumed (TLC; typically within ½ h). The mixture was filtered off, and the filter cake was washed with 100 ml of 1% aq. NaOH. The collected filtrate was acidified with conc. HCl to pH 2 and extracted with three 100-ml portions of CH_2Cl_2. The combined extracts were washed with sat. brine, dried (Na_2SO_4), and evaporated on a rotary evaporator to afford crude **3** as a white solid, which was triturated with 100 ml of AcOEt/petroleum ether (PE) 1:9 (*v*/*v*) to give pure **3** as colorless crystals after suction filtration and drying *in vacuo* at r.t. Yield: 15.71 g (83%). M.p. 166–167° ([9]: 164–167°). ^{1}H-NMR: 1.31–1.36 (*m*, 2 Me); 4.02–4.11 (*m*, 2 CH_2O); 7.02 (*d*, *J* = 8.4, 1 arom. H); 7.42 (*d*, *J* = 1.2, 1 arom. H); 7.52 (*dd*, *J* = 1.6, 8.4, 1 arom. H); 12.59 (br. *s*, COOH).

Ethyl 3,4-Diethoxybenzoate (**4**). A 250-ml round-bottomed flask was charged with 15.66 g (74.49 mmol) of **3**, 70 ml of abs. EtOH, and 70 ml of benzene. The mixture was stirred at r.t., followed by dropwise addition of 5 ml of conc. H_2SO_4. The flask was fitted with a *Dean–Stark* trap and a reflux condenser, and the mixture was stirred under reflux with azeotropic removal of H_2O until all **3** was consumed (TLC; typically within 12 h). The mixture was poured into 300 ml of ice-water while stirring, and the resulting mixture thus obtained was extracted with three 100-ml portions of CH_2Cl_2. The combined extracts were washed with sat. brine, dried (Na_2SO_4), and evaporated on a rotary evaporator to give crude **4** as a pale brown solid, which was purified by CC (SiO_2; AcOEt/PE 1:20) to yield pure **4** as colorless crystals. Yield: 16.86 g (95%). M.p. 53–54° ([10]: 52–53°). ^{1}H-NMR: 1.27–1.35 (*m*, 3 Me); 4.02–4.12 (*m*, 2 CH_2O); 4.26 (*q*, *J* = 7.1, $COOCH_2$); 7.04 (*d*, *J* = 8.4, 1 arom. H); 7.42 (*d*, *J* = 2.0, 1 arom. H); 7.54 (*dd*, *J* = 2.0, 8.4, 1 arom. H).

Ethyl 2-Bromo-4,5-diethoxybenzoate (**5**). A 250-ml round-bottomed flask was charged with 16.72 g (70.17 mmol) of **4**, 100 ml of glacial AcOH, and 15.98 g (100 mmol) of Br_2, and the mixture was stirred at 35° for 36 h. On cooling, the mixture was poured into 500 ml of ice-water, and the mixture was extracted with three 100-ml portions of CH_2Cl_2. The combined extracts were washed sequentially with 300 ml of sat. $NaHCO_3$ and 200 ml of sat. brine, dried (Na_2SO_4), and evaporated on a rotary evaporator to afford crude **5** as a pale yellow oil, which was purified by CC (SiO_2; AcOEt/PE 1:20) to furnish pure **5** as a white solid. Yield: 20.25 g (91%). M.p. 48–49°. IR: 3095*w*, 1724*s* (C=O), 1592*s*, 1509*s*, 1470*s*, 1395*s*. ^{1}H-NMR: 1.28–1.34 (*m*, 3 Me); 4.03 (*q*, *J* = 6.9, CH_2O); 4.09 (*q*, *J* = 6.9, CH_2O); 4.27 (*q*, *J* = 7.2, $COOCH_2$); 7.20 (*s*, 1 arom. H); 7.32 (*s*, 1 arom. H). ^{13}C-NMR: 13.97 (Me); 14.33 (Me); 14.45 (Me); 60.93 (CH_2O); 64.18 (CH_2O); 64.35 (CH_2O); 112.30 (arom. C); 115.05, 117.64 (2 arom. CH); 123.09, 146.93, 151.27 (3 arom. C); 164.92 (C=O). HR-MS (TOF-ES$^+$): 317.0401 ([M(^{79}Br) + H]$^+$, $C_{13}H_{18}{}^{79}BrO^+$; calc. 317.0388); 319.0380 ([M(^{81}Br) + H]$^+$, $C_{13}H_{18}{}^{81}BrO^+$; calc. 319.0368).

2-(2-Bromo-4,5-diethoxyphenyl)propan-2-ol (**6**). A dried 500-ml round-bottomed flask was charged with 20.17 g (63.59 mmol) of **5**, 200 ml of dried THF, and a magnetic stirring bar, flushed with N_2, and sealed with a rubber septum. The flask was cooled with a cooling bath held at −5°, and 50 ml (150 mmol) of 3M MeMgCl in THF were added dropwise through syringe. After addition, the mixture was stirred at 0° for another ½ h. The mixture was poured into 500 ml of ice-water while stirring, and to the mixture thus obtained were added 200 ml of CH_2Cl_2, followed by stirring for 10 min. The mixture was filtered through a pad of *Celite*, and the org. phase was separated from the filtrate. The aq. phase was back-extracted with another 100 ml of CH_2Cl_2. The combined org. phases were washed with sat. brine, dried (Na_2SO_4), and evaporated on a rotary evaporator to furnish crude **6** as a colorless oil, which was purified by CC (SiO_2; AcOEt/PE 1:10) to afford pure product **6** as a waxy white solid. Yield: 16.77 g (87%). M.p. 62–63°. IR: 3518*s* (OH), 3117*w*, 3094*w*, 1598*m*, 1499*s*, 1473*s*, 1391*s*, 1369*s*. ^{1}H-NMR: 1.27–1.33 (*m*, 2 Me); 1.57 (*s*, Me_2C); 3.96–4.03 (*m*, 2 CH_2O); 5.19 (*s*, OH); 7.05 (*s*, 1 arom. H); 7.43 (*s*, 1 arom. H). ^{13}C-NMR: 14.62 (Me); 14.72 (Me); 29.06 (Me_2C); 63.94 (CH_2O); 64.19 (CH_2O); 71.26 (C–OH); 109.06 (arom. C); 113.09, 119.22 (2 arom. CH); 140.41, 146.95, 147.07 (3 arom. C). HR-MS (TOF-ES$^+$): 285.0488 ([M(^{79}Br) − H_2O + H]$^+$, $C_{13}H_{18}{}^{79}BrO_2^+$; calc. 285.0490); 287.0466 ([M(^{81}Br) − H_2O + H]$^+$, $C_{13}H_{18}{}^{81}BrO_2^+$; calc. 287.0470).

1-Bromo-4,5-diethoxy-2-(1-methylethenyl)benzene (**7**). A 250-ml round-bottomed flask was charged with 16.59 g (54.72 mmol) of **6** and 100 ml of CH_2Cl_2, and the soln. was stirred at r.t., followed by addition of 0.96 g (10 mmol) of $MeSO_3H$. The mixture thus obtained was stirred at r.t., until all the starting **6** was consumed (TLC; typically within 1 h). The mixture was poured into 200 ml of sat. brine while stirring, and the org. phase was separated. The aq. phase was back-extracted with another 100 ml of CH_2Cl_2. The combined extracts were washed with sat. brine, dried (Na_2SO_4), and evaporated on a rotary evaporator to afford crude **7** as a pale yellow oil, which was purified by CC (SiO_2; AcOEt/PE 1:15) to furnish pure **7** as a colorless oil. Yield: 14.36 g (92%). IR: 3082*w*, 1641*w* (C=C), 1596*w*, 1500*s*, 1390*s*. ^{1}H-NMR: 1.28–1.32 (*m*, 2 Me); 2.01 (*s*, =CMe); 3.98–4.04 (*m*, 2 CH_2O); 4.87 (*s*, =CH); 5.19–5.20 (*m*, =CH); 6.79 (*s*, 1 arom. H); 7.09 (*s*, 1 arom. H). ^{13}C-NMR: 14.54 (Me); 14.57 (Me); 23.45 (Me); 64.02 (CH_2O); 64.21 (CH_2O); 110.48 (=C); 114.25 (=CH_2); 116.06, 117.06 (2 arom. CH); 136.01, 144.77, 147.47, 147.87 (4 arom. C). HR-MS (TOF-ES$^+$): 285.0494 ([M(^{79}Br) + H]$^+$, $C_{13}H_{18}{}^{79}BrO_2^+$; calc. 285.0490); 287.0473 ([M(^{81}Br) + H]$^+$, $C_{13}H_{18}{}^{81}BrO_2^+$; calc. 287.0470).

4,5-Diethoxy-2-(1-methylethenyl)benzonitrile (**8**). A dried 250-ml round-bottomed flask was charged with 14.23 g (49.90 mmol) of **7**, 5.37 g (60 mmol) of CuCN, and 70 ml of dried DMF, and the mixture was stirred at reflux under N_2, until starting **7** was consumed (TLC; typically within 5 h). On cooling, the mixture was poured into 300 ml of sat. brine, and the mixture was extracted with three 100-ml portions of CH_2Cl_2. The combined extracts were washed with sat. brine, dried (Na_2SO_4), and evaporated on a rotary evaporator to afford the crude product as a deep brown oil, which was purified by CC (SiO_2; AcOEt/PE 1:7) to yield pure **8** as a white solid. Yield: 10.39 g (90%). M.p. 83–85°. IR: 3088*w*, 2212*s* (C≡N), 1598*s*, 1560*m*, 1516*s*, 1475*m*, 1457*m*, 1388*s*, 1356*s*. ^{1}H-NMR: 1.30–1.35 (*m*, 2 Me); 2.11 (*s*, =CMe); 4.06 (*q*, J = 7.1, CH_2O); 4.12 (*q*, J = 7.1, CH_2O); 5.16 (*s*, =CH); 5.31–5.32 (*m*, =CH); 6.97 (*s*, 1 arom. H); 7.29 (*s*, 1 arom. H). ^{13}C-NMR: 14.33 (Me); 14.40 (Me); 22.90 (Me); 64.07 (CH_2O); 64.21 (CH_2O); 100.10 (=C); 111.89 (=CH_2); 116.30, 117.04 (2 arom. CH); 118.81 (CN); 140.64, 141.72, 147.11, 151.63 (4 arom. C). HR-MS (TOF-ES$^+$): 232.1345 ([M + H]$^+$, $C_{14}H_{18}NO_2^+$; calc. 232.1338); 249.1607 ([M + NH_4]$^+$, $C_{14}H_{21}N_2O_2^+$; calc. 249.1603).

2-(1-Azido-1-methylethyl)-4,5-diethoxybenzonitrile (**9**) and *7,8-diethoxy-5,5-dimethyl-5*H-*tetrazolo[5,1-*a*]isoindole* (**10**). A 250-ml round-bottomed flask was charged with 13.00 g (200 mmol) of NaN_3 and 130 ml of CF_3COOH (TFA), and the slurry thus obtained was stirred at r.t., followed by addition of 10.18 g (44.01 mmol) of **8**. The stirring was continued at r.t. until all **8** was consumed (TLC; typically within 12 h). The mixture was poured into 500 ml of ice-water, and the resulting mixture was extracted with three 100-ml portions of CH_2Cl_2. The combined extracts were washed with sat. brine, dried (Na_2SO_4), and evaporated on a rotary evaporator to afford crude **10** as a brown solid, which was purified by CC (SiO_2; AcOEt/PE 1:10) to yield pure **10** as a white solid. Yield: 10.50 g (87%). M.p. 125–126°. IR: 3055*w*, 1624*m*, 1587*w*, 1550*w*, 1495*s*, 1472*s*, 1448*s*, 1393*m*. ^{1}H-NMR: 1.34–1.39 (*m*, 2 Me); 1.76 (*s*, Me_2C); 4.12–4.19 (*m*, 2 CH_2O); 7.50 (*s*, 1 arom. H); 7.52 (*s*, 1 arom. H). ^{13}C-NMR: 14.45 (Me); 14.50 (Me); 25.75 (Me_2C); 64.29 (CH_2O); 64.32 (CH_2O); 65.51 (C–N); 106.36, 107.79 (2 arom. CH); 112.35, 147.40, 148.87, 151.11 (4 arom. C); 158.31 (C=N). HR-MS (TOF-ES$^+$): 275.1529 ([M + H]$^+$, $C_{14}H_{19}N_4O_2^+$; calc. 275.1508); 549.2943 ([2M + H]$^+$, $C_{28}H_{37}N_8O_4^+$; calc. 549.2938).

*5,6-Diethoxy-2,3-dihydro-3,3-dimethyl-1*H-*isoindol-1-imine* (**11**). A 1000-ml beaker was charged with 50 g of Ni–Al alloy (containing 0.927 mol of Al) and 200 ml of H_2O, and the mixture was stirred, followed by portionwise addition of 150 ml (1.125 mol) of 30% aq. NaOH at such a rate that the evolution of gas (H_2) was in control. Cooling of the beaker with an ice-water bath may be necessary during the addition. Then, the beaker was heated in a H_2O bath held at 70° for another ½ h. The stirring was ceased, and the mixture was left to stand at r.t. The supernatant was decanted carefully, and H_2O was added. The mixture was stirred and left to stand, and the supernatant was decanted once again. This procedure was repeated until the pH value of the supernatant was in the range of 7–9. The *Raney*-Ni thus obtained was stored at r.t. in H_2O and used within one week. A 250-ml round-bottomed flask was charged with 10.37 g (37.80 mmol) of **10**, 150 ml of i-PrOH, and the *Raney*-Ni prepared above (*ca.* 20 g), and the mixture was stirred at reflux under N_2 until all **10** was consumed (TLC; typically within 12 h). On cooling, the mixture was filtered with suction in such a manner that the *Raney*-Ni was always covered with liquid. The collected filtrate was evaporated on a rotary evaporator to afford crude **11** as a pale yellow oil, which was purified by CC (SiO_2; MeOH) to yield pure **11** as a white solid. Yield: 7.60 g (81%).

M.p. 85–87°. IR: 3440*s* (NH), 3336*m* (NH), 3099*m*, 1668*s*, 1601*s*, 1569*s*, 1498*s*, 1448*s*, 1389*s*. ^{1}H-NMR: 1.33–1.37 (*m*, 2 Me); 1.39 (*s*, Me_2C); 4.04 (*q*, *J* = 6.9, CH_2O); 4.11 (*q*, *J* = 6.9, CH_2O); 7.22 (*s*, 1 arom. H); 7.60 (*s*, 1 arom. H); 8.79 (br. *s*, 2 NH). ^{13}C-NMR: 14.69 (Me); 14.77 (Me); 27.55 (Me_2); 63.94 (CH_2O); 64.08 (CH_2O); 68.49 (C–N); 105.62, 105.76 (2 arom. CH); 125.44, 147.32, 149.27, 151.59 (4 arom. C); 160.26 (C=NH). HR-MS (TOF-ES$^+$): 249.1631 ($[M+H]^+$, $C_{14}H_{21}N_2O_2^+$; calc. 249.1603).

*1-[3-(*tert*-Butyl)-4-methoxy-5-(morpholin-4-yl)phenyl]-2-(5,6-diethoxy-1,3-dihydro-3-imino-1,1-dimethyl-2*H*-isoindol-2-yl)ethanone Hydrobromide* (**1**). A dried 100-ml round-bottomed flask was charged with 7.41 g (29.84 mmol) of **11**, 11.05 g (29.84 mmol) of 2-bromo-1-[3-(*tert*-butyl)-4-methoxy-5-(morpholin-4-yl)phenyl]ethanone [4b] and 100 ml of dried THF, and the mixture was stirred at r.t. until all the starting materials were consumed (TLC; typically within 12 h), when a pale yellow slurry was obtained. The mixture was filtered with suction, and the collected crystals were washed with 20 ml of dried THF and dried *in vacuo* at r.t. to furnish pure **1** in the form of hydrobromide as a white solid. Yield: 17.17 g (93%). M.p. 154–156°. IR: 3435(*w*), 3357*w* (NH), 3220*w* (NH), 3038*s*, 1693*s* (C=O), 1671*s* (C=N), 1603*m*, 1494*s*, 1471*m*. ^{1}H-NMR: 1.36–1.41 (*m*, Me_3C, 2 Me); 1.48 (*s*, Me_2C); 3.04 (*s*, 2 CH_2O); 3.83 (*s*, 2 CH_2N); 3.97 (*s*, MeO); 4.11 (*q*, *J* = 7.1, CH_2O); 4.20 (*q*, *J* = 6.9, CH_2O); 5.40 (*s*, CH_2N); 7.44 (*s*, 1 arom. H); 7.60 (*s*, 1 arom. H); 7.68 (*s*, 1 arom. H); 7.84 (*s*, 1 arom. H); 9.15 (br. *s*, 1 arom. H); 9.47 (br. *s*, NH). ^{13}C-NMR: 14.37 (Me); 14.45 (Me); 23.69; 30.18; 34.85; 48.01; 50.22; 58.51; 64.25 (CH_2O); 64.51 (CH_2O); 66.38; 70.18; 105.57; 106.36; 116.55; 117.59; 121.18; 129.01; 143.13; 145.01; 146.58; 148.65; 153.72; 156.86; 160.77 (C=NH); 190.35 (C=O). HR-MS (TOF-ES$^+$): 538.3285 ($[M+H]^+$, $C_{31}H_{44}N_3O_5^+$; calc. 538.3281).

2-Bromo-4,5-diethoxybenzaldehyde (**12**). A 250-ml round-bottomed flask was charged with 14.62 g (75.27 mmol) of **2** and 100 ml of glacial AcOH, and the mixture was stirred at r.t., followed by addition of 15.98 g (100 mmol) of Br_2. The resulting mixture was stirred at 35°, until all **2** was consumed (TLC; typically within 24 h). On cooling, the mixture was poured into 500 ml of ice-water, and the resulting mixture was extracted with three 100-ml portions of CH_2Cl_2. The combined extracts were washed sequentially with 200 ml of sat. $NaHCO_3$ and 200 ml of sat. brine, dried (Na_2SO_4), and evaporated on a rotary evaporator to afford crude **12** as a red oil, which was triturated with 100 ml of AcOEt/PE 1:9 (*v*/*v*) to furnish pure **12** as colorless crystals after suction filtration and drying *in vacuo* at r.t. Yield: 18.09 g (88%). M.p. 68–69°. IR: 3080*w*, 1675*s* (C=O), 1589*s*, 1507*s*, 1472*s*, 1396*s*. ^{1}H-NMR: 1.31–1.36 (*m*, 2 Me); 4.07 (*q*, *J* = 7.1, CH_2O); 4.17 (*q*, *J* = 6.9, CH_2O); 7.28 (*s*, 1 arom. H); 7.30 (*s*, 1 arom. H); 10.04 (*s*, CHO). ^{13}C-NMR: 14.28 (Me); 14.37 (Me); 63.99 (CH_2O); 64.71 (CH_2O); 111.55, 116.54 (2 arom. CH); 119.10, 125.51, 147.74, 153.90 (4 arom. C); 190.02 (CHO). HR-MS (TOF-ES$^+$): 273.0124 ($[M(^{79}Br)+H]^+$, $C_{11}H_{14}{}^{79}BrO_3^+$; calc. 273.0126); 275.0104 ($[M(^{81}Br)+H]^+$, $C_{11}H_{14}{}^{81}BrO_3^+$; calc. 275.0106).

2-(2-Bromo-4,5-diethoxyphenyl)-1,3-dioxolane (**13**). A 250-ml round-bottomed flask was charged with 18.02 g (65.98 mmol) of **12**, 13.40 g (200 mmol) of ethylene glycol, 1.90 g (10 mmol) of $TsOH \cdot H_2O$, and 150 ml of benzene, and fitted with a *Dean–Stark* trap and a reflux condenser. The mixture was stirred at reflux with azeotropic removal of H_2O, until all the aldehyde **12** was consumed (TLC; typically within 12 h). On cooling, the mixture was poured into 500 ml of ice-water containing 3.02 g (20 mmol) of Na_2CO_3 while stirring, and the resulting mixture was extracted with three 100-ml portions of CH_2Cl_2. The combined extracts were washed with sat. brine, dried (Na_2SO_4), and evaporated on a rotary evaporator to give crude **13** as a pale brown oil, which was purified by CC (neutral Al_2O_3; AcOEt/PE 1:15) to yield pure **13** as a colorless oil. Yield: 17.16 g (82%). IR: 3080*w*, 1600*s*, 1510*s*, 1477*s*, 1395*s*. ^{1}H-NMR: 1.29–1.32 (*m*, 2 Me); 3.92–4.09 (*m*, 4 CH_2O); 5.82 (*s*, H–C–NO); 7.03 (*s*, 1 arom. H); 7.11 (*s*, 1 arom. H). ^{13}C-NMR: 14.45 (Me); 14.54 (Me); 64.07 (CH_2O); 64.19 (CH_2O); 64.81 (OCH_2CH_2O); 101.79 (OCHO); 112.26 (arom. CH); 112.48 (arom. C); 116.61 (arom. CH); 128.08, 147.48, 149.56 (3 arom. C). HR-MS (TOF-ES$^+$): 317.0398 ($[M(^{79}Br)+H]^+$, $C_{13}H_{18}{}^{79}BrO_4^+$; calc. 317.0388); 319.0379 ($[M(^{81}Br)+H]^+$, $C_{13}H_{18}{}^{81}BrO_4^+$; calc. 319.0368).

2-(1,3-Dioxolan-2-yl)-4,5-diethoxybenzonitrile (**14**). A 250-ml round-bottomed flask was charged with 17.02 g (53.66 mmol) of **13**, 6.27 g (70 mmol) of CuCN, and 100 ml of dried DMF, and mixture was refluxed under N_2, until all **13** was consumed (TLC analysis; typically within 5 h). On cooling, the mixture was poured into 300 ml of sat. brine, and the mixture was extracted with three 100-ml portions of CH_2Cl_2. The combined extracts were washed with sat. brine, dried (Na_2SO_4), and evaporated on a rotary evaporator to afford crude **14** as a black oil, which was purified by CC (neutral Al_2O_3; AcOEt/PE 1:7) to

yield pure **14** as a colorless oil. Yield: 12.29 g (87%). IR: 3096*w*, 3069*w*, 2222 (C≡N, *s*), 1600*s*, 1517*s*, 1475*s*, 1393*s*. ^{1}H-NMR: 1.30–1.37 (*m*, 2 Me); 3.96–4.02 (*m*, CH_2O); 4.06–4.14 (*m*, 3 CH_2O); 5.81 (*s*, H–C–NO); 7.16 (*s*, 1 arom. H); 7.38 (*s*, 1 arom. H). ^{13}C NMR: 14.30 (Me); 14.33 (Me); 64.18 (CH_2O); 64.33 (CH_2O); 65.31 (OCH_2CH_2O); 101.19 (OCHO); 101.42 (CN); 111.75, 116.69 (2 arom. CH); 117.31, 134.84, 148.46, 151.53 (4 arom. C). HR-MS (TOF-ES$^+$): 264.1233 ($[M+H]^+$, $C_{14}H_{18}NO_4^+$; calc. 264.1236).

4,5-Diethoxy-2-formylbenzonitrile (**15**). A 250-ml round-bottomed flask was charged with 12.16 g (46.18 mmol) of **14** and 100 ml of MeOH, and the mixture was stirred at r.t., followed by addition of 1 ml of 10% HCl. The stirring was continued, until all **14** was consumed (TLC; typically within 5 h). The mixture was poured into 300 ml of sat. brine, and the mixture was extracted with three 100-ml portions of CH_2Cl_2. The combined extracts were washed with sat. brine, dried (Na_2SO_4), and evaporated on a rotary evaporator to afford crude **15** as a colorless oil, which was purified by CC (SiO_2; AcOEt/PE 1:12) to yield pure **15** as a white solid. Yield: 9.42 g (93%). M.p. 116–117°. IR: 2225*m* (C≡N), 1697*s* (C=O), 1585*s*, 1516*m*, 1359*m*. ^{1}H-NMR: 1.30–1.38 (*m*, 2 Me); 4.16–4.22 (*m*, 2 CH_2O); 7.55 (*s*, 1 arom. H); 7.57 (*s*, 1 arom. H); 10.00 (*s*, CHO). ^{13}C-NMR: 14.34 (2 Me); 64.49 (CH_2O); 64.93 (CH_2O); 104.51 (CN); 113.23, 116.76 (2 arom. CH); 116.93, 130.88, 151.50, 152.33 (4 arom. C); 188.53 (CHO). HR-MS (TOF-ES$^+$): 220.0968 ($[M+H]^+$, $C_{12}H_{14}NO_3^+$; calc. 220.0974).

Ethyl 2-Cyano-4,5-diethoxybenzoate (**17**). A dried 250-ml round-bottomed flask was charged with 19.96 g (62.93 mmol) of **5**, 7.16 g (80 mmol) of CuCN, and 150 ml of dried DMF, and the mixture was stirred at reflux under N_2, until all **5** was consumed (TLC; typically within 5 h). On cooling, the mixture was poured into 500 ml of sat. brine, and the mixture was extracted with three 100-ml portions of CH_2Cl_2. The combined extracts were washed with sat. brine, dried (Na_2SO_4), and evaporated on a rotary evaporator to afford crude **17** as a deep brown oil, which was purified by CC (SiO_2; AcOEt/PE 1:7) to furnish pure **17** as a white solid. Yield: 14.75 g (89%). M.p. 138–140°. IR: 2227*m* (C≡N), 1707*s* (C=O), 1591*s*, 1528*s*, 1473*w*, 1393*m*, 1367*s*. ^{1}H-NMR: 1.31–1.37 (*m*, 3 Me); 4.13–4.20 (*m*, 2 CH_2O); 4.34 (*q*, J = 7.2, $COOCH_2$); 7.48 (*s*, 1 arom. H); 7.50 (*s*, 1 arom. H). ^{13}C-NMR: 14.08 (Me); 14.43 (Me); 62.01 (CH_2O); 64.91 (CH_2O); 65.07 (CH_2O); 105.15 (CN); 114.28, 117.11 (2 arom. CH); 118.08, 126.05, 151.41, 151.52 (4 arom. C); 164.03 (C=O). HR-MS (TOF-ES$^+$): 264.1232 ($[M+H]^+$, $C_{14}H_{18}NO_4^+$; calc. 264.1236); 281.1501 ($[M+NH_4]^+$, $C_{14}H_{21}N_2O_4^+$; calc. 281.1501); 286.1055 ($[M+Na]^+$, $C_{14}H_{17}NNaO_4^+$; calc. 286.1047).

*5,6-Diethoxy-3,3-dimethyl-2-benzofuran-1(3*H*)-imine* (**19**). A dried 250-ml round-bottomed flask was charged with 14.51 g (55.11 mmol) of **17**, a magnetic stirring bar, and 150 ml of dried THF, sealed with a rubber septum, and cooled with a bath held at −5°. The mixture was stirred, followed by dropwise addition of 40 ml (120 mmol) of 3M MeMgCl in THF through syringe. After addition, the mixture was stirred at 0° for another 1/2 h. The mixture was poured into 500 ml of ice-water, and to the mixture were added 200 ml of CH_2Cl_2, followed by stirring for 10 min. The mixture thus obtained was filtered through a pad of *Celite*, and the filtrate was collected, from which the org. phase was separated. The aq. phase was back-extracted with another 100 ml of CH_2Cl_2. The combined extracts were washed with sat. brine, dried (Na_2SO_4) and evaporated on a rotary evaporator to furnish crude **19** as a pale yellow oil, which was purified by CC (SiO_2; AcOEt) to afford pure **19** as a waxy white solid. Yield: 11.54 g (84%). M.p. 88–90°. IR: 3280*s* (NH), 1676*s* (C=N), 1605*m*, 1505*s*, 1478*s*, 1445*s*. ^{1}H-NMR: 1.32–1.36 (*m*, 2 Me); 1.50 (*s*, Me_2C); 4.02–4.13 (*m*, 2 CH_2O); 7.12 (*s*, 1 arom. H); 7.28 (*s*, 1 arom. H); 7.74 (br. *s*, NH). ^{13}C-NMR: 14.47 (Me); 14.54 (Me); 27.61 (Me_2C); 54.82 (C–O); 64.00 (CH_2O); 64.10 (CH_2O); 85.11, 104.60, 106.36, 119.33, 145.26, 148.74 (6 arom. C); 152.07 (C=N). HR-MS (TOF-ES$^+$): 250.1451 ($[M+H]^+$, $C_{14}H_{20}NO_3^+$; calc. 250.1443).

2-[2-(Aminomethyl)-4,5-diethoxyphenyl]propan-2-ol (**20**). A dried 100-ml round-bottomed flask was charged with 5.12 g (20.54 mmol) of **19** and 50 ml of dried THF, and the mixture was stirred on an ice-water bath, followed by portionwise addition of 0.76 g (20 mmol) of $LiAlH_4$. The resulting mixture was stirred at r.t., until all **19** was consumed (TLC; typically within 3 h). The mixture were *carefully* poured into 300 ml of ice-water while stirring, and to the resulting mixture were added 200 ml of CH_2Cl_2. The mixture thus obtained was stirred for 5 min and filtered through a pad of *Celite* with suction. The org. phase was separated from the filtrate, and the aq. phase was back-extracted with another 100 ml of CH_2Cl_2. The combined org. phases were washed with sat. brine, dried (Na_2SO_4), and evaporated on a

rotary evaporator to afford crude **20** as a colorless oil, which was purified by CC (SiO_2; MeOH) to give pure **20** as a waxy white solid. Yield: 4.37 g (84%). M.p. 28°. IR: 3440 (OH, *w*), 3182*s* (NH), 3136*s* (NH), 3026*s*, 1581*s*, 1517*s*, 1466*s*, 1393*s*. ^{1}H-NMR: 1.26–1.31 (*m*, 2 Me); 1.47 (*s*, Me_2C); 3.65 (*s*, CH_2N); 3.96–4.00 (*m*, 2 CH_2O); 6.85 (*s*, 1 arom. H); 6.89 (*s*, 1 arom. H). ^{13}C-NMR: 14.74 (Me); 14.80 (Me); 32.12 (Me_2); 41.40 (C–N); 63.91 (CH_2O); 64.02 (CH_2O); 72.54 (C–OH); 112.02, 118.06 (2 arom. CH); 123.87, 140.65, 146.35, 147.36 (4 arom. C). HR-MS (TOF-ES$^+$): 236.1646 ($[M-H_2O+H]^+$, $C_{14}H_{22}NO_2^+$; calc. 236.1651).

*5,6-Diethoxy-3,3-dimethyl-2-benzofuran-1(3*H*)-one* (**21**). A 100-ml round-bottomed flask was charged with 4.76 g (19.09 mmol) of **19** and 20 ml of EtOH, and the mixture was stirred at r.t., followed by addition of 20 ml of 20% aq. NaOH. The stirring was continued at reflux, until all **19** was consumed (TLC). On cooling, the mixture was poured into 200 ml of H_2O, and the mixture was acidified by conc. HCl to pH 2, stirred for another 10 min, and extracted with three 50-ml portions of CH_2Cl_2. The combined extracts were washed with sat. brine, dried (Na_2SO_4), and evaporated on a rotary evaporator to furnish crude **21** as a pale yellow solid, which was purified by CC (SiO_2; AcOEt/PE 1:30) to afford pure **21** as a white solid. Yield: 3.82 g (80%). M.p. 98–99°. ^{1}H-NMR: 1.33 (*t*, $J=7.0$, Me); 1.37 (*t*, $J=7.0$, Me); 1.56 (*s*, Me_2C); 4.08 (*q*, $J=6.9$, CH_2O); 4.16 (*q*, $J=6.9$, CH_2O); 7.16 (*s*, 1 arom. H); 7.29 (*s*, 1 arom. H).

*5,6-Diethoxy-3,3-dimethyl-2-benzofuran-1(3*H*)-one* (**21**). A dried 50-ml round-bottomed flask was charged with 1.77 g (5.84 mmol) of **6**, 0.52 g (7 mmol) of CuCN, and 15 ml of dried DMF, and the mixture was stirred at reflux under N_2, until all **6** was consumed (TLC; typically within 5 h). On cooling, the mixture was poured into 200 ml of H_2O, and the mixture was extracted with three 50-ml portions of CH_2Cl_2. The combined extracts were washed with sat. brine, dried (Na_2SO_4), and evaporated on a rotary evaporator to give crude **21** as a deep brown oil, which was purified by CC (SiO_2; AcOEt/PE 1:30) to yield pure **21** as a waxy white solid. Yield: 1.18 g (81%). M.p. 98–99°. IR: 3077*w*, 1731*s* (C=O), 1598*m*, 1503*m*, 1477*m*, 1364*m*. ^{1}H-NMR: 1.31–1.38 (*m*, 2 Me); 1.56 (*s*, Me_2C); 4.08 (*q*, $J=6.9$, CH_2O); 4.16 (*q*, $J=6.9$, CH_2O); 7.16 (*s*, 1 arom. H); 7.29 (*s*, 1 arom. H). ^{13}C-NMR: 14.33 (Me); 14.42 (Me); 26.94 (2 Me); 64.09 (CH_2O); 64.35 (CH_2O); 84.28 (C–O); 104.50, 106.77 (2 arom. CH); 115.65, 149.08, 149.47, 154.03 (4 arom. C); 168.93 (C=O). HR-MS (TOF-ES$^+$): 251.1302 ($[M+H]^+$, $C_{14}H_{19}O_4^+$; calc. 251.1283); 273.1105 ($[M+Na]^+$, $C_{14}H_{18}NaO_4^+$; calc. 273.1103).

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