Anal. Calcd for $C_{16}H_{17}O_3N_3 \cdot H_2O$: C, 60.55; H, 6.04; N, 13.24. Found: C, 60.52; H, 6.27; N, 13.33.

Hydrolysis of 6b with 3 N NaOH/EtOH. A mixture of **6b** (200 mg, 0.63 mmol), EtOH (4.3 mL), and NaOH (523 mg, 13.1 mmol) (3 N NaOH in EtOH) in an argon-filled pressure tube was stirred at 90 °C. The mixture became a solution in 25 min. Repeated TLC monitoring showed that **6b** disappeared during 110 min, and a single major product formed together with negligible amounts of two far less polar products. After neutralization with AcOH, the mixture was evaporated and repeatedly coevaporated with MeOH. The residue was stirred in acetone (25 mL) for 20 min, and the solid filtered by suction. After washing the filter cake with acetone (12 mL; the filter cake was UV-transparent at this stage), the combined filtrates were evaporated, and the residue subjected to preparative TLC (silica, 20 × 20 cm; $CHCl_3$/MeOH, 9:1, twice developed). The major fraction was eluted with MeOH and recrystallized from a small volume of MeOH to afford 110 mg (55%) of **13c**, identical with the above-obtained product.

Hydrolysis of 2,3′-(Phenylimino)-1-(3′-deoxy-β-D-lyxofuranosyl)uracil (1c) with 3 N NaOH/EtOH. A mixture of NaOH (553 mg, 13.8 mmol) and EtOH (4.5 mL) in an argon-filled pressure tube was stirred at 90 °C for 25 min to give a solution (ca. 3 N NaOH in EtOH). After cooling to room temperature, **1c** (202 mg, 0.67 mmol) was added, and the tube refilled with argon. TLC monitoring of the reaction at 90 °C showed that **1c** disappeared during 70 min and two products formed. The cooled mixture was diluted with MeOH (10 mL), neutralized with AcOH, and then evaporated. After repeated coevaporation with MeOH, the residue was stirred in acetone/MeOH (9:1, 45 mL) for 15 min, and the sparingly soluble solid (UV-transparent) filtered off. The filtrate was evaporated, and the residue heated to reflux in acetone (50 mL) for 10 min to give further UV-transparent solid, which was filtered off. The acetone solution was evaporated, and the residue in hot MeOH was allowed to cool to room temperature to give TLC-pure crystals of **2c**, which were collected by suction (56 mg). Fractionation of the filtrate on a silica plate (20 × 20 cm; $CHCl_3$/MeOH, 85:15, developed three times) gave from the slower moving band an additional crop of **2c**. The combined crops were recrystallized from MeOH to afford 113 mg (50.8%) of the methanolate of **2c**, identical with an authentic sample[1] in terms of IR spectroscopy and mixed melting point determination.

Elution of the less polar fraction with MeOH gave a solid, which was recrystallized from a small volume of MeOH to give 60 mg (28.1%) of **3a**, mp 224–226 °C.

Anal. Calcd for $C_{15}H_{17}N_3O_5$: C, 56.42; H, 5.37; N, 13.16. Found: C, 56.19; H, 5.58; N, 13.17.

The identity of **3a** with an authentic sample[1] was confirmed by IR spectroscopy and mixed melting point determination.

Hydrolysis of 1c with 1 N NaOH/EtOH. A mixture of NaOH (177 mg, 4.4 mmol) and EtOH (4.4 mL) in an argon-filled pressure tube was stirred at 90 °C for 10 min to obtain a ca. 1 N ethanolic solution of NaOH. After the solution cooled, **1c** (91 mg, 0.302 mmol) was added, and argon gas refilled. Under careful TLC control, the mixture was stirred at 90 °C for 3.5 h (at this point, a single major TLC spot for **3a** and two negligibly thin spots corresponding to **1c** and **2c** were observed). After cooling, the mixture was diluted with MeOH, neutralized with AcOH, and thoroughly evaporated. The residue in acetone (20 mL) was stirred at room temperature for 30 min, and the insoluble solid filtered by suction. The filter cake was washed with acetone (10 mL), and the combined acetone solutions evaporated after treatment with Norit. On leaving the residue with a small volume of MeOH, TLC-pure crystals of **3a** (60 mg) were obtained. Preparative TLC (silica, 10 × 20 cm; $CHCl_3$/MeOH, 85:15, developed three times) with the filtrate separated from the major crop gave another crop. The combined crops were recrystallized from a small volume of MeOH to afford 77 mg (79.5%) of **3a**, identical with the above-obtained product.

Secondary β-Aminobenzamide and Heteroatom Directed Lithiation in the Synthesis of 5,6-Dimethoxyanthranilamides and Related Compounds†

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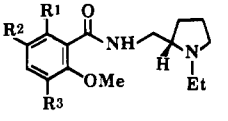
Directed ortho-lithiation strategies have been applied in the synthesis of the dopamine D-2 antagonist (*S*)-6-amino-5-bromo-2,3-dimethoxy-*N*-((1-ethyl-2-pyrrolidinyl)methyl)benzamide (NCQ 318). The secondary β-amino side chain was found to be a powerful ortho directing group which enabled the direct introduction of the amino group after dilithiation with *n*-BuLi. Alternatively, 3,4-dimethoxy-*N*-(*tert*-butoxycarbonyl)aniline was regioselectively metalated with 2 equiv of *n*-BuLi and reacted with carbon dioxide. The methods permit efficient syntheses of the therapeutically important substituted 2-methoxybenzamides also in technical scale. The lithiated secondary β-amino benzamides, e.g. $ArCONHCH_2CH_2NMe_2$, were found to react with various electrophiles with high regioselectivity in contrast to the corresponding ArCONHMe derivative.

The substituted 2-methoxybenzamides (orthopramides) constitute a recently developed class of antipsychotics, which selectively block dopamine D-2 receptors.[1,2] Especially, benzamides with 2-pyrrolidinylmethyl side chains, e.g. sulpiride, remoxipride, and raclopride, display promising features (Chart I).[3] As an extension of our investigations on 6-methoxysalicylamides[4] we required an efficient synthesis of a related anthranilamide NCQ 318 (1).[5]

The directed metalation strategy offers efficient routes for regiospecific synthesis of polysubstituted aromatics.[6,7]

Chart I



	R1	R2	R3
(S)-sulpiride	H	SO_2NH_2	H
remoxipride	OMe	Br	H
raclopride	OH	Cl	Cl
NCQ 318	NH_2	Br	OMe

In the case of NCQ 318, two possibilities are evident (eq 1). In one option, regiocontrol is ascertained by the co-

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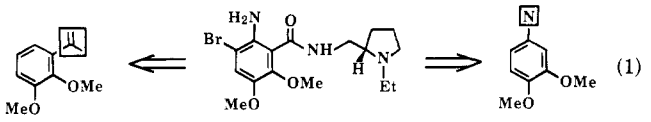
operative ortho directing effects of the meta-related methoxy and suitably protected aniline groups. Pivaloyl[8] and tert-butoxycarbonyl (Boc)[9] derivatization have been used to convert primary anilines into synthetically useful ortho directing groups. The Boc group is more readily removable than pivaloyl, but the dilithiation requires the use of *tert*-butyllithium, which hampers the use in large-scale preparations.



(1)

NCQ 318 (*1*)

The second option resides upon the use of carboxyl-derived directing groups such as secondary amides, tertiary amides, thioamides, or oxazolines.[6,7] The latter group is precluded due to the nucleophilic aromatic substitution of 2-(2-methoxyaryl)oxazolines by organometallics.[10] Bulky tertiary amides ($CONEt_2$) in combination with hindered bases (*sec*-BuLi) have been successfully used to override the competing ortho directing influence of other groups present.[7] The hydrolytic resistance of the tertiary amides and the need for *sec*-butyllithium limits the technical feasibility of this group. Secondary amides are clearly less prone to addition of organolithium reagents, and the hydrolysis is more facile than for tertiary amides.[7]

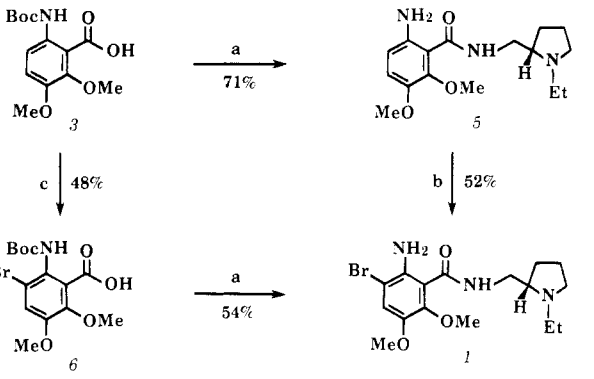
We reasoned that the 2-(aminomethyl)-1-ethylpyrrolidine side chain present in the target compound 1 could serve as an efficient ortho directing moiety. Furthermore, the β-positioned pyrrolidine nitrogen could assist in the chelation and improve the solubility of the dilithio species, which is an inherent problem with many other secondary benzamides.

Results and Discussion

Boc-Aniline Directed Lithiations. The dilithiation of 3,4-dimethoxy-*N*-(*tert*-butoxycarbonyl)aniline (**2**) was anticipated to occur even with *n*-butyllithium due to the combined influence of the ortho directing groups. The lithiation of **2** (2.3 equiv of *n*-BuLi, THF, −20 °C), quenching with solid carbon dioxide, and acidic workup afforded the desired acid **3** in a high yield (eq 2). No other regioisomers could be detected in the reaction mixture. As a control experiment the dilithiation was effected under the standard conditions used for Boc-anilines (2.4 equiv of *tert*-BuLi, THF, −60 to −20 °C).[9] Metalation with this bulkier and stronger base leads to a mixture of **3** and **4** in a 7:3 ratio as judged by the aromatic (**3**, 8.36 and 7.26 (AB); **4**, 7.70 and 7.40 (two s) ppm) and methoxy (**3**, 4.10 and 3.92; **4**, 4.02 and 3.97 ppm) ^1H NMR signals (eq 2). Similarly, lithiation of 3-methoxy-*N*-(*tert*-butoxycarbonyl)-aniline with 2.5 equiv of *tert*-butyllithium has recently been reported to take place in a low yield.[9b] However, no other regioisomers were mentioned.

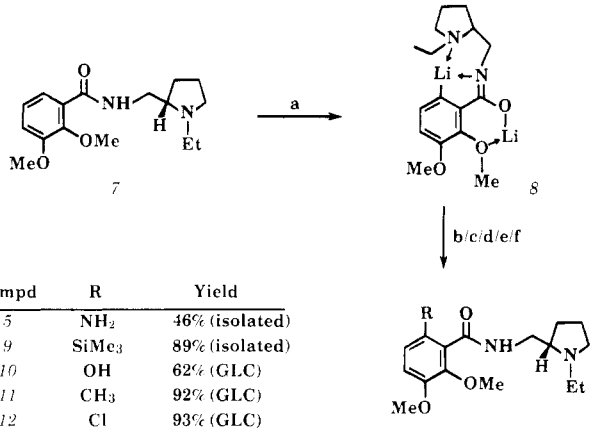
The dilithation of 3-methoxy-*N*-pivaloylaniline also proceeds regiospecificly in high yield with *n*-butyllithium.[8]

Scheme I[a]



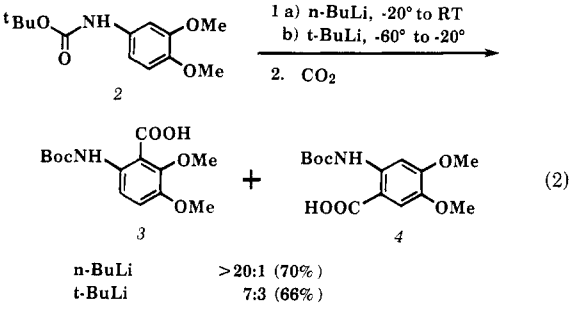
[a] (a) $SOCl_2$, $PhCH_3$; (*S*)-2-(aminomethyl)-1-ethylpyrrolidine, CH_2Cl_2; (b) Br_2, dioxane/HOAc; (c) Br_2, HOAc.

Scheme II[a]



Compd	R	Yield
5	NH_2	46% (isolated)
9	$SiMe_3$	89% (isolated)
10	OH	62% (GLC)
11	CH_3	92% (GLC)
12	Cl	93% (GLC)

[a] (a) 2.3 equiv of *n*-BuLi, THF, −20 °C to room temperature; (b) TsN_3, THF, −15 °C to room temperature; $SnCl_2$, MeOH, room temperature; (c) Me_3SiCl, THF, −15 °C to room temperature; (d) $(n\text{-BuO})_3B$, THF, −30 °C to 0 °C; H_2O_2, NH_4Cl, 0 °C to room temperature; (e) CH_3I, THF, −15 °C to room temperature; (f) Cl_3CCCl_3, THF, −15 °C to room temperature.



(2)

n-BuLi	>20:1 (70%)
t-BuLi	7:3 (66%)

(1) Jenner, P.; Marsden, C. D. *Neuropharmacology* **1981**, *20*, 1285–1293.

(2) de Paulis, T. In *Proceedings from the VIIIth International Symposium on Medicinal Chemistry*; Dahlbom, R., Nilsson, J. L. G., Eds.; Swedish Pharamaceutical Press: Stockholm, 1985; Vol. 1, pp 405–425.

(3) Ögren, S.-O.; Högberg, T. *ISI Atlas of Science: Pharmacology* **1988**, 141–147.

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(5) (a) Bengtsson, K. S.; Högberg, T.; Johansson, L. G.; de Paulis, T.; Ström, H. E. P.; Widman, M. E.; Ögren, S.-O. Eur. Pat. Appl. 85850022, 1985. (b) Bengtsson, S.; Högberg, T.; Rämsby, S.; Ström, P.; Hall, H. The 194th National Meeting of the American Chemical Society, New Orleans, MEDI43, 1987. (c) Högberg, T.; de Paulis, T.; Ström, P.; Bengtsson, S.; Johansson, L.; Hall, H.; Ögren, S.-O. Xth International Symposium on Medicinal Chemistry, Budapest, B12, 1988. (d) Högberg, T.; Bengtsson, S.; de Paulis, T.; Johansson, L.; Ström, P.; Hall, H.; Ögren, S.-O. *J. Med. Chem.*, submitted.

(6) (a) Gschwend, H. W.; Rodrigues, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1–360. (b) Omae, I. *Chem. Rev.* **1979**, *79*, 287–321.

(7) (a) Snieckus, V. *Heterocycles* **1980**, *14*, 1649–1676. (b) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306–312. (c) Snieckus, V. *Lect. Heterocycl. Chem.* **1984**, *7*, 95–106.

(8) Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133–1136.

(9) (a) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798–4801. (b) Reed, J. N.; Rotchford, J.; Strickland, D. *Tetrahedron Lett.* **1988**, *29*, 5725–5728.

(10) (a) Meyers, A. I.; Mihelich, E. D. *Angew. Chem., Int. Ed. Engl.* **1976**, *5*, 270–281. (b) Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372–1379.

Likewise, 2,3-dimethoxy-*N*-pivaloylaniline has been dilithiated (*n*-BuLi) and converted to 2,3-dimethoxyanthranilic acid after esterification and conversion to the *N*,*N*-diacetyl derivative prior to the cumbersome hydrolysis.[11] However, the present protocol using *N*-Boc has the added advantage of permitting a mild and quantitative one-step deprotection.[5]

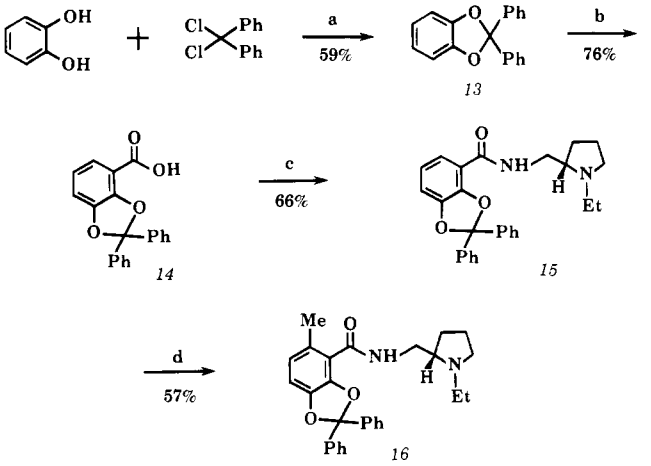
Compound **3** was further elaborated as outlined in Scheme I. Conversion to acid chloride and reaction with an excess of (*S*)-2-(aminomethyl)-1-ethylpyrrolidine furnished the benzamide **5** in a high yield after acidic workup. Bromination gave the target compound **1** in a fair yield. Reversal of the reaction steps gave **5** in a lower overall yield due to a less efficient acylation of the amine with the sterically more encumbered acid chloride derived from **6** (Scheme I). A third way, although less effective, proceeds via deprotection of **6**, conversion to the corresponding isatoic anhydride, and reaction with the pyrrolidine amine.[5]

Benzamide-Directed Lithiations. The benzamide **7** underwent exclusive metalation in the 6-position with 2.3 equiv of *n*-butyllithium (−20 °C to ambient temperature), producing **9** in excellent isolated yield after quenching with trimethylchlorosilane (Scheme II). The high degree of regioselectivity in the reaction is ascertained by the additional coordination of the β-amino nitrogen with the attacking *n*-butyllithium in the rate-determining step. The formation of a tentative bidentate complex **8** with the aryllithium atom and, in the present case, complexation of the amidate lithium with the methoxy oxygen may be envisioned (Scheme II). This type of complex would explain the favorable solubility properties of **8**. The transformation of **8** to **5** was achieved by reaction with tosyl azide followed by hydrolytic workup and reduction of the azide in situ with tin(II) chloride in a reasonable overall yield (46%).[12]

This synthetic scheme complements the previous one, and, importantly, it leads to efficient syntheses of a variety of analogous benzamides of potential therapeutic value from the same key intermediate. Thus, the important antipsychotic group of 2-methoxysalicylamides[3,4,13] can be obtained by this strategy. This reaction scheme gives opportunities for complementary or better regiocontrol than the usual demethylation procedure of the corresponding 2,6-dimethoxybenzamides.[4,5,13] Reaction of **8** with tributyl borate followed by oxidation with hydrogen peroxide furnished the salicylamide **10**,[14] which upon bromination gives a highly potent dopamine D-2 antagonist.[5] The generality of the reaction was shown by the reaction of **8** with other electrophiles, i.e. iodomethane and hexachloroethane, to give **11** and **12**, respectively (Scheme II).

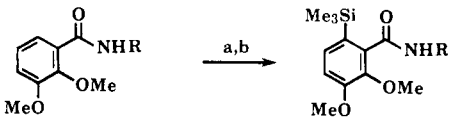
The protocol was applied for the introduction of the contiguous substituents in the related benzamide **16** (Scheme III). Catechol was heated with dichlorodiphenylmethane to give the ketal **13**. Lithiation with *n*-butyllithium and quenching with carbon dioxide gave the acid **14**, which was converted to the benzamide **15** in a good overall yield. The previously used lithiation–methylation sequence gave **16**.

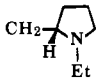
Scheme III[a]



[a] (a) 170 °C, neat; (b) 1.2 equiv of *n*-BuLi, THF, −5 °C to room temperature; CO_2(s); H_3O^+; (c) $SOCl_2$, $PhCH_3$, 60 °C; (*S*)-2-(aminomethyl)-1-ethylpyrrolidine, CH_2Cl_2; (d) 2.3 equiv of *n*-BuLi, THF, −20 °C to room temperature; CH_3I, THF, −15 °C.

Scheme IV[a]



R		Yield (GLC)	
	*7*	97%	*9*
$CH_2CH_2NMe_2$	*17*	93%	*18*
CH_3	*19*	76%	*20*

[a] (a) 2.3 equiv of *n*-BuLi, THF, −20 °C to room temperature; (b) 2.5 equiv of Me_3SiCl, THF, −15 °C to room temperature.

In order to facilitate the hydrolysis of tertiary benzamides a number of β-amino derivatives have been developed as ortho directing moieties.[15] This class of benzamides is closely related to the secondary benzamides **7** and **15** used in this study. The attractiveness to use secondary benzamides in directed metalation in general lies in the resistance to carbonyl addition of the organolithium reagents. This permits lithiation with *n*-butyllithium at higher temperatures (>−78 °C) in contrast to the case of tertiary amides,[16] which is of advantage in large-scale production. In order to expand the scope of secondary β-aminobenzamides to less esoteric side chains than *N*-[(1-ethyl-2-pyrrolidinyl)methyl]benzamides, we have also prepared the corresponding *N*-[2-(dimethylamino)ethyl]-benzamide **17** (Scheme IV). Dilitiation and quenching with trimethylchlorosilane produced the ortho-silylated derivative **18** in an excellent yield. The importance of the

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(14) ArMgX to ArOH: (a) Hawthorne, M. F. *J. Org. Chem.* **1957**, *22*, 1001. (b) Kidwell, R. L.; Darling, S. D. *Tetrahedron Lett.* **1966**, 531–535. ArLi to ArOH: (c) Lumma, W. C.; Dutra, G. A.; Voeker, C. A. *J. Org. Chem.* **1970**, *35*, 3442–3444. (d) Bondesson, G.; Hedbom, C.; Högberg, T. Magnusson, O.; Stjernström, N. E. *J. Med. Chem.* **1974**, *17*, 108–112. (e) Bondesson, G.; Högberg, T.; Misiorny, A.; Stjernström, N. E. *Acta Pharm. Suec.* **1976**, *13*, 97–106.

(15) Commins, D. L.; Brown, J. D. *J. Org. Chem.* **1986**, *51*, 3566–3572.

(16) The competition between ortho metalation and carbonyl addition as a function of the cumulative steric properties of the *N*-alkyl and organolithium alkyl groups has recently been discussed: Bindal, R. D.; Katzenellenbogen, J. A. *J. Org. Chem.* **1987**, *52*, 3181–3185.

additional complexation to the β-nitrogen is evident when comparing the result with the same reaction sequence applied to the corresponding *N*-methylbenzamide **19** (Scheme IV). In the latter case, another regioisomer was detected, whereas no other regioisomers were found on lithiation of **7** or **17**.

Conclusions

The present work describes the powerful ortho directing properties of secondary β-amino benzamides, which allows for the use of *n*-butyllithium at moderately low temperatures. Besides, we have found that Boc-protected *m*-methoxyanilines can be regioselectively metalated with *n*-butyllithium. These methods permit effective syntheses of the therapeutically important substituted 2-methoxybenzamides also in technical scale. The $CONHCH_2CH_2NMe_2$ and related groups complement the commonly used carbon based ortho directing groups.[6,7,10,15]

Experimental Section

Melting points were determined in open capillary tubes on a Mettler FP 61 apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian EMS 360A or a JEOL FX 200 spectrometer with Me_4Si as internal standard. Mass spectra were obtained on an LKB 9000 (EI, 70 eV) or an LKB 2091 (EI, 70 eV, or CI, CH_4) instrument. GLCs were run on an SE 30 capillary column, and the amounts determined by a Hewlett-Packard 3390A integrator. Preparative, centrifugally accelerated TLCs were conducted on a Chromatotron from Harrison Research. Elemental analyses were performed by Analytische Laboratorium, Elbach, West Germany, and are within ±0.4% of the theoretical values.

2-Carboxy-3,4-dimethoxy-*N*-(*tert*-butoxycarbonyl)aniline (3). *n*-Butyllithium (43 mL of 1.6 M in hexane, 69 mmol) was added to a solution of 3,4-dimethoxy-*N*-(*tert*-butoxycarbonyl)-aniline[17] (**2**, 7.60 g, 30 mmol) in 80 mL of anhydrous tertrahydrofuran (THF) under N_2 at −20 °C. After stirring for 2 h at −10 to −20 °C, the reaction mixture was poured into solid carbon dioxide in THF. The mixture was allowed to reach room temperature and was then partitioned between water and Et_2O. Drying (Na_2SO_4) and evaporation of the organic solvent gave a crude acid **3**, which contained no detectable amounts of the regioisomer **4** (NMR, TLC). Recrystallization of the residue from *i*-Pr_2O gave 6.2 g (70%) of pure **3**: mp 137–138 °C; ^1H NMR ($CDCl_3$) δ 10.6 (br, 1), 8.36 and 7.26 (AB, 2), 4.10 (s, 3), 3.92 (s, 3), 1.53 (s, 9). Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; O, 32.29. Found: C, 56.73; H, 6.49; O, 32.23.

(*S*)-6-Amino-2,3-dimethoxy-*N*-[(1-ethyl-2-pyrrolidinyl)-methyl]benzamide (5). Method A. A solution of the acid **3** (1.19 g, 4.0 mmol), thionyl chloride (0.48 mL, 5.6 mmol), and 3 drops of DMF in 30 mL of toluene was stirred at 60 °C for 1.5 h. The solvent was evaporated, and the residue was dissolved in 50 mL of CH_2Cl_2 and evaporated again. The residual acid chloride was dissolved in 60 mL of CH_2Cl_2, and a solution of (*S*)-2-(aminomethyl)-1-ethylpyrrolidine[18] (0.79 g, 6.0 mmol) in 15 mL of CH_2Cl_2 was added with cooling. After being stirred overnight the solvent was evaporated and the residue was partitioned between 0.5 M HCl and Et_2O. The ether phase was extracted with water, and the combined water phase was made alkaline and extracted repeatedly with Et_2O. Drying (Na_2SO_4) and evaporation of the solvent gave 0.88 g (71%) of pure amide **5**: ^1H NMR ($CDCl_3$) δ 8.0 (br, 1), 6.85 and 6.41 (AB, 2), 5.4 (br, 2), 3.82 (s, 3), 3.80–3.68 (m, 1), 3.80 (s, 3), 3.30–1.69 (multiplets, 10), 1.10 (t, 3). Anal. Calcd for $C_{16}H_{25}N_3O_3$: C, 62.52; H, 8.20; N, 13.67; O, 15.61. Found: C, 62.49; H, 8.05; N, 13.62; O, 15.78.

Method B. *n*-Butyllithium (3.3 mL of 1.6 M in hexane, 5.3 mmol) was added to a solution of (*S*)-2,3-dimethoxy-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide[19] (**7**, 0.68 g, 2.3 mmol) in 12 mL of dry THF under N_2 at −20 °C. The reaction mixture was stirred for 20 min at ambient temperature to allow for the formation of the dilithio derivative. After cooling to −15 °C, *p*-toluenesulfonyl azide[20] (0.83 g, 4.2 mmol) dissolved in 5 mL of anhydrous THF was added dropwise at −15 °C. After 20 min at room temperature the reaction mixture was worked up as described for compound **9**. The crude 6-azido benzamide was dissolved in 2 mL of MeOH and added dropwise to a solution of tin(II) chloride hydrate (0.50 g, 2.2 mmol) in 3 mL of MeOH at 0 °C. After 1.5 h at room temperature the solvent was evaporated, and the residue was partitioned between 0.5 M NaOH and Et_2O. The organic layer was dried (Na_2SO_4) and evaporated. Purification of the residue on a SiO_2 column with *i*-Pr_2O/THF/MeOH/NH_3 (50:10:5:1) as eluent afforded 0.33 g (46% from compound **7**) of benzamide **5** having spectroscopic and chromatographic properties as above.

6-Bromo-2-carboxy-3,4-dimethoxy-*N*-(*tert*-butoxycarbonyl)aniline (6). A solution of bromine (0.93 mL, 18 mmol) in 5 mL of acetic acid was added to a stirred mixture of compound **3** (2.97 g, 10 mmol) dissolved in 45 mL of acetic acid and sodium acetate (3.0 g, 36 mmol). The reaction mixture was stirred overnight and partitioned between water and Et_2O. The organic layer was washed five times with water, dried (Na_2SO_4), and evaporated to afford 1.93 g of an oily residue, which crystallized after addition of EtOH/hexane. Recrystallization from *i*-Pr_2O gave 1.79 g (48%) of pure product: mp 171–172 °C; ^1H NMR ($CDCl_3$) δ 10.7 (br, 1), 7.33 (s, 1), 3.88 (s, 3), 3.77 (s, 3), 1.42 (s, 9). Anal. Calcd for $C_{14}H_{18}BrNO_6$: C, 44.70; H, 4.82; Br, 21.24; O, 25.52. Found: C, 44.67; H, 4.81; Br, 21.38; O, 25.37.

(*S*)-6-Amino-5-bromo-2,3-dimethoxy-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide (1). Method A. To a stirred solution of compound **5** (0.74 g, 2.4 mmol) in 5 mL of dioxane and 1 mL of acetic acid was added dropwise a solution of bromine (0.14 mL, 2.7 mmol) in 5 mL of dioxane at 0 °C during 10 min. The reaction mixture was stirred for 1 h at room temperature and then partitioned between CH_2Cl_2 and 0.5 M NaOH. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was dried (Na_2SO_4) and evaporated to give 0.48 g (52%) after chromatography on SiO_2 with *i*-Pr_2O/MeOH/NH_3 (100:5:0.5): ^1H NMR ($CDCl_3$) δ 7.9 (br, 1), 7.14 (s, 1), 5.8 (br, 2), 3.82 (s, 3), 3.90–3.67 (m, 1), 3.80 (s, 3), 3.35–1.70 (multiplets, 10), 1.11 (t, 3). Anal. Calcd for $C_{16}H_{24}BrN_3O_3$: C, 49.75; H, 6.26; N, 10.88. Found: C, 49.90; H, 6.31; N, 10.69.

Method B. The acid **6** was converted to the corresponding acid chloride, aminated, and worked up analogous to the preparation of **5**. The benzamide **1**, having identical properties with the one obtained by method A, was achieved in a yield of 54%.

(*S*)-2,3-Dimethoxy-6-(trimethylsilyl)-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide (9). To a stirred solution of 2,3-dimethoxy-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide[19] (**7**, 0.29 g, 1.0 mmol) in 5 mL of anhydrous THF kept under N_2 at −20 °C was added *n*-butyllitium (1.62 mL of 1.6 M in hexane, 2.3 mmol) dropwise. The reaction mixture was stirred at room temperature for 20 min to allow for a complete formation of the orange dilithio intermediate **8** and then cooled to −15 °C. Distilled trimethylsilyl chloride (0.32 mL, 2.5 mmol) was added dropwise, and the stirred reaction mixture was allowed to reach room temperature. After 1 h water was added dropwise followed by partitioning between Et_2O and 0.5 M NaOH. To the organic layer, which contained more than 99% of the title compound (GLC), 0.5 M HCl was added followed by back extraction from the aqueous phase by Et_2O after alkalization. Drying (Na_2SO_4) and evaporation of the solvent afforded 0.36 g (89%) of the pure title compound: mp 68–70 °C. ^1H NMR ($CDCl_3$) δ 7.31 and 6.94 (AB, 2), 3.88 (s, 3), 3.84 (s, 3), 3.80–3.69 (m, 1), 3.35–1.71 (multiplets, 10), 1.09 (t, 3), 0.28 (s, 9). An analytical sample of the HCl salt was prepared, mp 184–185 °C. Anal. Calcd for $C_{19}H_{32}N_2O_3Si$·HCl: C, 56.91; H, 8.29; N, 6.99; Cl, 8.84. Found: C, 56.90; H, 8.21; N, 7.05; Cl, 8.69.

The compounds **10–12** were prepared in analogy with the above procedure by reaction of the dilithio intermediate **8** with the indicated electrophiles followed by standard workup.

10: (1) tributyl borate (3 equiv); (2). H_2O_2/NH_4Cl;[14] yield 62% (GLC); ^1H NMR ($CDCl_3$) δ 7.06 and 6.74 (AB, 2), 3.96 (s, 3), 3.86

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(s, 3), 3.80–3.62 (m, 1), 3.37–1.70 (multiplets, 10), 1.10 (t, 3).

11: methyl iodide (1.2 equiv); yield 92% (GLC); ^{1}H NMR ($CDCl_3$) δ 6.89 and 6.81 (AB, 2), 3.84 (s, 3), 3.83 (s, 3), 3.85–3.73 (m, 1), 3.40–1.74 (multiplets, 10), 2.27 (s, 3), 1.11 (t, 3).

12: hexachloroethane (1.1 equiv);[21] yield 93% (GLC); ^{1}H NMR ($CDCl_3$) δ 7.08 and 6.85 (AB, 2), 3.87 (s, 3), 3.86 (s, 3), 3.88–3.75 (m, 1), 3.35–1.83 (multiplets, 10), 1.11 (t, 3).

2,3-[(Diphenylmethylene)dioxy]benzene (13). Catechol (7.15 g, 65 mmol) and dichlorodiphenylmethane (17.10 g, 70 mmol) was heated at 170 °C for 5 min.[22] The reaction mixture was recrystallized from EtOH to give 10.5 g (59%) of **13**, mp 87–89 °C (lit.[23] mp 94–95 °C).

2,3-[(Diphenylmethylene)dioxy]benzoic Acid (14). 2,3-[(Diphenylmethylene)dioxy]benzene (**13**, 10.0 g, 36.5 mmol) in anhydrous THF under N_2 was treated with *n*-butyllithium (27.5 mL of 1.6 M in hexane, 44 mmol) at −5 °C followed by 2 h at room temperature. The reaction mixture was poured into solid carbon dioxide in Et_2O. After reaching room temperature the reaction mixture was partitioned between water and Et_2O. The alkaline aqueous layer was repeatedly extracted with Et_2O while the pH was continuously adjusted with HCl to 8.0–8.5. Drying and evaporation of the solvent gave 8.86 g (76%) of acid **14** (one spot on TLC). An analytical sample was prepared by recrystallization from *i*-Pr_2O/MeOH (6:1): mp 188–189 °C (lit.[24] mp 188–190 °C); IR (KBr) 1680 cm^{-1}. Anal. Calcd for $C_{20}H_{14}O_4$: C, 75.46; H, 4.43; O, 20.10. Found: C, 75.44; H, 4.55; O, 19.88.

(*S*)-2,3-[(Diphenylmethylene)dioxy]-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide (15) was prepared from the acid **14** in analogy with the amide **5** (method A). Recrystallization of the solid residue from *i*-Pr_2O/MeOH gave the title compound in 66% yield: mp 142–144 °C; ^{1}H NMR ($CDCl_3$) δ 7.64–6.87 (multiplets, 13), 3.90–3.78 (m, 1), 3.40–1.62 (multiplets, 10), 1.02 (t, 3). Anal. Calcd for $C_{27}H_{28}N_2O_3$: C, 75.68; H, 6.59; N, 6.53. Found: C, 75.75; H, 6.73; N, 6.52.

(*S*)-2,3-[(Diphenylmethylene)dioxy]-6-methyl-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide (16). Preparation from compound **15**, by the procedure used for compound **9**, gave the desired product in 57% yield after recrystallization from *i*-Pr_2O: mp 143–145 °C; ^{1}H NMR ($CDCl_3$, 22 °C) δ 7.80–6.89 (multiplets, 12), 3.86–3.76 (m, 1), 3.34–1.70 (multiplets, 10), 2.23 and 2.24 (2 s, atropisomers, 3), 1.04 and 0.88 (2 t, atropisomers, 3). Anal. Calcd for $C_{28}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33; O, 10.85. Found: C, 76.03; H, 6.60; N, 6.26; O, 10.81.

2,3-Dimethoxy-*N*-[2-(dimethylamino)ethyl]benzamide (17) was obtained as an oil in 71% yield by preparation from 2,3-dimethoxybenzoic acid and 2-(dimethylamino)ethylamine in analogy with compound **5** (method A): ^{1}H NMR ($CDCl_3$) δ 7.69, 7.15 and 7.03 (ABX, 3), 3.90 (s, 3), 3.89 (s, 3), 3.55 (dt, 2), 2.51 (t, 2), 2.28 (s, 6). An analytical sample of the oxalate hydrate was recrystallized from EtOH/Et_2O, mp 127–128 °C. Anal. Calcd for $C_{13}H_{20}N_2O_3 \cdot C_2H_2O_4 \cdot H_2O$: C, 50.00; H, 6.72; N, 7.77; O, 35.52. Found: C, 50.07; H, 6.84; N, 7.73; O, 35.24.

2,3-Dimethoxy-6-(trimethylsilyl)-*N*-[2-(dimethylamino)-ethyl]benzamide (18) was prepared from compound **17** in analogy with compound **9**: yield 93% (GLC), 71% (isolated); ^{1}H NMR ($CDCl_3$) δ 7.30 and 6.93 (AB, 2), 3.87 (s, 3), 3.84 (s, 3), 3.51 (q, 2), 2.49 (t, 2), 2.23 (s, 6), 0.28 (s, 9). An analytical sample of the HCl salt was prepared, mp 126–128 °C. Anal. Calcd for $C_{16}H_{30}N_2O_4Si \cdot HCl$: C, 50.71; H, 8.25; N, 7.39; Cl, 9.35. Found: C, 50.72; H, 8.03; N, 7.47; Cl, 9.23.

2,3-Dimethoxy-6-(trimethylsilyl)-*N*-methylbenzamide (20) was prepared from 2,3-dimethoxy-*N*-methylbenzamide[25] (**19**) in analogy with compound **9**. An analytical sample of **20** was crystallized from *i*-Pr_2O: mp 151–152 °C; yield 76% of **20** and 9% of the 4-trimethylsilyl isomer (GLC–MS); ^{1}H NMR ($CDCl_3$) δ 7.30 and 6.93 (AB, 2), 3.87 (s, 3), 3.82 (s, 3), 2.99 (d, 3), 0.27 (s, 9). Anal. Calcd for $C_{13}H_{21}NO_3Si$: C, 58.39; H, 7.92; N, 5.24. Found: C, 58.34; H, 7.84; N, 5.29.

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Studies in Biomimetic Alkaloid Syntheses. 17. Syntheses of Iboxyphylline and Related Alkaloids

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A synthesis of the amino ketal **16** and its condensation with formaldehyde provided, after hydrolysis, a biomimetic formation of the iboxyphylline ketones **18c,d**. The major methyl epimer, **18d**, obtained on equilibration, was reduced to iboxyphylline (**4**). The condensation also provided D/E trans products **18a,b** and the five-membered ring D ketones **19a,b**. For alternative syntheses of the iboxyphylline skeleton, a *D-homo*-secodine intermediate **40a** was generated, leading specifically to the *D/E-cis*-demethyliboxyphylline ketone **50**. Attempts to extend this approach to an iboxyphylline synthesis provided, instead, the spirocyclopentanones **53a–d**. Generation of dehydroibophyllidine (**12**) and its autoxidation gave 20-oxodeethylibophyllidine (**34**). Alternative syntheses of that lactam and its reduction to the alkaloid deethylibophyllidine (**35**) and a synthesis of the corresponding D/E trans epimer **37** are described.

The powdered root of *Tabernanthe iboga* has been used in West Africa, in small doses, as a stimulant to keep hunters alert for days and, in larger doses, as a ceremonial hallucinogen.[1] Its alkaloidal components (Scheme I) include the isoquinuclidines ibogaine (**1b**, with established analogous uses in Western drug culture), ibogamine (**1a**), and tabernanthine (**1c**),[2–5] as well as the ψ-vincadifformine

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