in this regard is the fact that the charges are highly dispersed. The anion has several negatively charged sites competing with each other for binding to the cation. Attenuating this is the fact that the ammonium center is deeply sequestered within the catalyst and its positive charge is significantly delocalized. These delocalized charges give rise, in part, to the broad and shallow minima on the intermolecular potential surfaces, and they cause problems with regard to orientation of the enolate vector when it does bind to catalyst. It is recommended that functionality localizing rather than delocalizing charge on the enolate be considered in future synthetic work.

Fourth, while transition states leading to *R* vs *S* product were not modeled, it was possible to successfully model the facial selectivity of enolate binding to catalyst when the inherently less stable *Z* enolate 12 binds. Thus, it is proposed that the active enolate has the *Z* configuration. By use of our search strategy, it was possible to correctly predict which face binds to the catalyst for the seven *Z* enolates. Furthermore, a linear relationship between ΔE, the energy difference between *si* vs *re* facial selectivity, and experimental ee is found. Hence, theory and experiment are consonant.

Fifth, it was not possible to discern any trends or patterns that explain the origins of enantioselectivity. The reason for this is thought to be the use of single energy-minimized structures rather than those that have been averaged in a statistically meaningful way. Nonetheless, this modeling is now of value because the enantiomeric excess expected for as yet untested enolates can be predicted.

Finally, using a unique energy partitioning algorithm, it was possible to determine what each fragment senses in the ion pair for both catalyst and enolate. For the catalyst, fragments A, C, and E are responsible for most of the binding. The vinyl group is found to play no role in asymmetric induction but the quinoline ring plays a critical role (in spite of not contributing to the binding of enolate) by serving as a platform onto which the enolates rest in their efforts to associate with the other fragments. The catalyst, in turn, is attracted primarily to fragment III and IV in the benzophenone series and to fragment III in the Merck enolate. Overall, the depiction by the Merck group[13b] of the shape and type of ion pairing interactions that takes place with enolates and catalyst are in agreement with the modeling studies presented here.

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Supplementary Material Available: Materials describing the results of MD simulations of catalyst along with contour plots of enolate–catalyst intermolecular potential energy surfaces, tables of conformational energies and torsion angles for *Z* and *E* enolates 3–9, MM2 component energies of the lowest energy ion pairs, and the projected angles of enolate vector 16 onto catalyst (23 pages). Ordering information is given on any current masthead page.

Synthesis of 2,5-Substituted Piperidines and Their Bicyclic Piperazine Analogues: The 2,7-Substituted Octahydro-2*H*-pyrido[1,2-*a*]pyrazines

Frans Compernolle, M.-Ashty Saleh, Suzanne Toppet, and Georges Hoornaert*

Laboratorium voor Organische Synthese, K.U.Leuven, Celestijnenlaan 200 F, B-3030 Leuven-Heverlee, Belgium

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Partial and complete reduction of the key compound 1-benzyl-5-(ethylenedioxy)-2-piperidinecarbonitrile (1) was applied to generate the corresponding aldehyde 2 and primary amine 3. These were transformed into bicyclic 7-(ethylenedioxy)-2(*R*)-octahydro-2*H*-pyrido[1,2-*a*]pyrazines 7 (R = H) and 15 (R = aryl) through the following sequence: (i) chloroacetylation of 3 and of arylamines derived from 2, (ii) cyclization to give the intermediate lactams 5 and 14, and (iii) reduction with $LiAlH_4$. Deprotection of the *N*-aryl compounds 15 yielded the corresponding ketone model compounds 16. From amino acetal 7, a complementary ketone synthon 11 was prepared via N-benzylation and cleavage of the acetal group, providing a general route to piperidine-bridged analogues of 1,4-substituted piperazine drugs.

Recently, we reported[1] the synthesis of 1-benzyl-3-(ethylenedioxy)-2-piperidinecarbonitrile (1), which was obtained via regioselective Hg^{2+} oxidation and trapping of the resulting iminium ion with cyanide. The versatility of synthon 1 in the preparation of 2,5-substituted piperidines was demonstrated by its conversion to the α-anion and further reaction with electrophiles. Here, we describe reduction of 1 to the corresponding aldehyde and primary amine, both of which served as intermediates in the synthesis of bicyclic piperazine analogues of 2,5-substituted piperidines. Whereas some members of the resulting product class, i.e., the octahydro[1,2-*a*]pyrazines have been described already,[2] the 2,7-substituted analogues are reported here for the first time. This 2,7-substitution pattern can be used to define the "active conformations" of monocyclic 1,4-substituted piperazine drugs.

Reduction of aminonitrile 1 with $LiAl(OEt)_3H$ afforded the crude aldehyde 2 in about 70% yield based on weight

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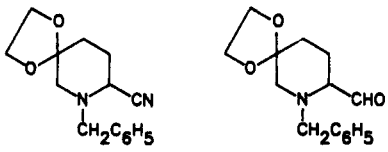
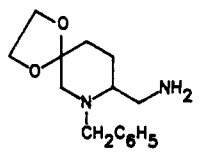
and ^{1}H NMR analysis. The amino aldehyde proved to be sensitive to column chromatography as it could only be isolated in 20% yield. Successful conversion to the aldehyde critically depended on the nature of the reducing agent. When using *i*-Bu_2AlH,[3] an overreduced dimeric product (M^+ 505) was isolated possibly corresponding to the imine structure $RCH_2N{=}CHR$ or aziridine RCHNHCHR. The same compound was formed by using the reagent $LiAl(OEt)_2H_2$ recommended by Rapoport.[4] Reduction of 1 with $LiAlH_4$ gave an almost quantitative yield of primary amine 3.



1 2

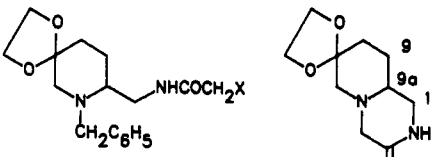


3

A comparison of the ^{1}H NMR spectra of compounds 2 and 3 with that reported[1] for compound 1 revealed a different orientation of the 2-substituent. This varied from exclusively axial for CN[1,5,6] to mainly equatorial for CHO and mixed axial–equatorial for CH_2NH_2, as derived from the coupling between proton H-2 and protons H-3: $\sum^3J_{2,3}$ = 7 Hz for 1,[1] $^3J_{2,3ax}$ = 9.2 Hz and $^3J_{2,3eq}$ = 3.7 Hz for 2, and $\sum^3J_{2,3}$ = 11 Hz for 3. While repulsion with the N lone pair disfavors an equatorial orientation of the linear CN group, the carbonyl dipole can be directed away from this electron pair in the CHO-equatorial conformation. The greater contribution of the axial form for 3 compared with 2 may be ascribed to a stronger gauche interaction of the equatorial aminomethyl group with the N-benzyl substituent.[5]

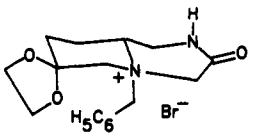
Amine 3 was converted to the key intermediate, bicyclic lactam 5, via the chloroacetyl derivative 4a. Chloroacetylation of 3 was performed by using $ClCH_2COCl$ in dichloromethane without added base. Presumably, formation of the HCl salts of 3 and 4a prevented competing acylation (and debenzylation) of the tertiary benzylamino function. Treatment of the *N*-chloroacetyl derivative 4a with $Bu_4N^+Br^-$ in *o*-dichlorobenzene at high temperature afforded the bicyclic lactam 5 in 84% overall yield from 1. The role of $Bu_4N^+Br^-$ probably is not restricted to displacement of the α-chloro substituent by a better leaving group (4a → 4b), but the reagent may also assist in the dequaternization of intermediate 6.

The polar and water-soluble lactam 5 was fully characterized by spectral and elemental analysis. In the IR spectrum, absorptions at 3440, 3180, and 3070 cm^{-1} can be attributed to ν NH-free, -dimeric, and -associated.[7] Two strong absorption bands at 1690 and 1640 cm^{-1} correspond to the amide I bands. In the ^{1}H NMR spectrum, the proton H-(9a)ax displays two diaxial couplings with H-1ax and H-9ax and two axial–equatorial couplings with H-1eq and H–9eq (tt, $^3J_{(9a)ax-1ax} = {}^3J_{(9a)ax-9ax}$ = 10 Hz and $^3J_{(9a)ax-9eq}$ = 4 Hz). Accordingly, a trans-fused ring conformation was assigned in which the piperidine and piperazinone rings assume a chair and half-chair form, respectively.



4a: X= Cl
4b: X= Br

5



6

Lactam 5 was reduced with $LiAlH_4$ to give secondary amine 7. Further transformation of 7 into 2,7-functionalized octahydro-2*H*-pyrido[1,2-*a*]pyrazines could proceed either by substitution of the 2-amino group (e.g., 7 → 8) or, inversely, via initial protection of the amine followed by deprotection of the 7-ketone group (7 → 9 → 11). Acidic cleavage of amino acetal 7 was not successful due to the unstable nature of amino ketone 10. Conversion of 7 to the *N*-(2-pyridyl) compound 8 with 2-fluoro- or 2-bromopyridine required activation of the secondary amine with $Bu_4N^+F^-$.[8] This activation probably involves (N–H---F^-) H-bridge formation. Protection of the amino group as the *N*-benzyl derivative 9 occurred smoothly (CH_2Cl_2, $C_6H_5CH_2Br$, triethylamine, 0 °C). Unusual vigorous conditions (6 M HCl, reflux) were needed for hydrolysis of the acetal group of 9 to form the ketone 11. This result may be ascribed to the formation of a bis-ammonium salt and the reluctance to further protonation of the acetal O atoms.

The ^{1}H NMR spectra of the acetals 7–9 and ketone 11 were consistent with a trans-fused conformation A. As already observed for lactam 5, proton H-(9a)ax displayed two diaxial couplings with H-1ax and H-9ax and two axial–equatorial couplings with H-1eq and H-9eq (compound 8, tt, $^3J_{(9a)ax-1ax} = {}^3H_{(9a)ax-9ax}$ = 10 Hz and $^3J_{(9a)ax-1eq} = {}^3J_{(9a)-9eq}$ = 3 Hz; similar values were observed for the other compounds). The trans-fused conformation was confirmed by the observation of Bohlmann bands[9] in the IR region 2700–2820 cm^{-1} corresponding to H-atoms adjacent to the angular N atom and oriented anti relative to the free electron pair.

The problem of introducing nonactivated aryl groups at the 2-position of the bicyclic system was solved indirectly by starting from the aldehyde 2. Reductive amination of 2 with aniline or *o*-anisidine ($NaCNBH_3$, MeOH, pH 6) afforded the secondary amines 12. The latter were transformed into the model amino ketones 16 via the sequence 12 → 16, involving cyclization of the *N*-chloroacetyl compounds 13, reduction of the resulting lactams 14, and finally acidic cleavage of amino acetals 15. All of these

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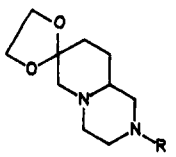
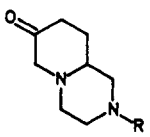
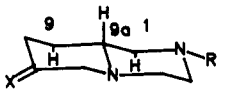


7: R= H
8: R= 2-Pyridyl
9: R= $C_6H_5CH_2$



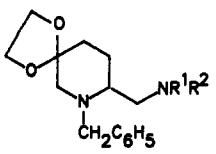
10: R= H
11: R= $C_6H_5CH_2$



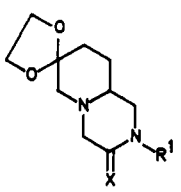
A

X= O, or OCH_2CH_2O

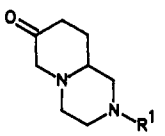
conversions proceeded in satisfactory yield.



12a: R^1= C_6H_5, R^2= H
12b: R^1= 2-$MeOC_6H_4$, R^2= H
13a: R^1= C_6H_5, R^2= $ClCH_2CO$
13b: R^1= 2-$MeOC_6H_4$, R^2= $ClCH_2CO$



14a: R^1= C_6H_5, X= O
14b: R^1= 2-$MeOC_6H_4$, X= O
15a: R^1= C_6H_5, X= H_2
15b: R^1= 2-$MeOC_6H_4$, X= H_2



16a: R^1= C_6H_5
16b: R^1= 2-$MeOC_6H_4$

In conclusion, the versatility of amino nitrile 1, aldehyde 2, and primary amine 3 in the synthesis of 2,5-substituted piperidines is demonstrated in the present paper by their conversion to 2,7-substituted octahydro-2*H*-pyrido[1,2-*a*]pyrazines. A general access to the latter class of compounds is provided by way of the complementary amine and ketone synthons 7 and 11, which should permit the introduction of pharmacophoric 2- and 7-substituents in the strategic order dictated by their chemical properties.

Experimental Section

IR spectra were recorded as thin films between NaCl plates or as solids in KBr pellets on a Perkin-Elmer 297 grating IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker WM 250 instrument operating at 250 MHz for ^1H and 63 MHz for ^{13}C measurements. The ^1H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane as an internal reference. Mass spectra were run by using a Kratos MS50 instrument and DS90 data system; the ion source temperature was 150–250 °C as required. Exact mass measurements were performed at a resolution of 10 000. Besides the spectral and analytical data mentioned below, the purity of all compounds was checked by TLC.

1-Benzyl-5-(ethylenedioxy)-2-piperidinecarboxaldehyde (2). To a stirred and cooled (0 °C) solution of 1 (650 mg, 2.52 mmol) in 15 mL of anhydrous ether was added a slurry of $LiAl(OEt)_3H$ in ether (12 mL) via syringe. The reagent was prepared by the standard procedure[10] from $LiAlH_4$ (1.00 g, 26.3 mmol) and anhydrous ethyl acetate (3.60 mL, 36.8 mmol) in anhydrous ether (24 mL) at 0 °C. After 15 min, the excess of hydride was decomposed with 2 M HCl. The solution then was made alkaline with aqueous K_2CO_3 and extracted with CH_2Cl_2 (2 × 100 mL). The organic solvent was filtered, and the filtrate was evaporated to dryness to give crude product 2 (585 mg, 89%) as a yellow oil, which was used directly in the next step (estimated purity from ^1H NMR: 80%). Column chromatography of the crude product 2 (500 mg) over silica (gradient elution with 2–10% EtOAc–hexane) afforded pure 2 (100 mg, 20%) as an unstable yellow oil: IR ν 2810, 2720, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.6 (d, 1 H, $^3J_{CHO,2ax}$ = 3.5 Hz, CHO), 7.4 (m, 5 H, aromatic), 3.8–4 (m, 4 H, OCH_2CH_2O), 3.9, 3.6 (AB q, 2 H, ^2J = 13.5 Hz, N-CH_2Ph), 2.9 (dt, 1 H, $^3J_{2ax,3ax}$ = 9.2 Hz, $^3J_{2ax,3e}$ = 3.7 Hz, $^3J_{2ax,CHO}$ = 3.5 Hz, H-2ax), 2.8 (d, 1 H, ^2J = 12 Hz, H-6e), 2.25 (d, 1 H, ^2J = 12 Hz, H-6ax), 1.5–2 (m, 4 H, H-3,4); CIMS *m/z* 262 (MH^+); exact mass calcd for $C_{15}H_{19}NO_3$ 261.1365, found 261.1354.

1-Benzyl-5-(ethylenedioxy)-2-piperidinemethanamine (3). To a stirred solution of 1 (3.0 g, 11.6 mmol) in 50 mL of anhydrous THF (N_2 atmosphere) was added $LiAlH_4$ (1.30 g, 34.2 mmol) portionwise. After 20 min, the excess of hydride was decomposed by dropwise addition of methanol followed by addition of CH_2Cl_2 (300 mL), K_2CO_3 (300 mg), and water (3 mL), respectively. The solvent was evaporated to dryness yielding crude product 3 (3.0 g, 98.6%) as a yellow oil that was used directly in the next step: ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5 H, Ph), 3.85 (m, 4 H, OCH_2CH_2O), 4.04, 3.52 (AB q, 2 H, ^2J = 12 Hz, NCH_2Ph), 2.90 (d, 2 H, ^3J = 5 Hz, CH_2NH_2), 2.74 (dd, 1 H, ^2J = 12.5 Hz, $^4J_{6,4}$ = 1.6 Hz, H-6), 2.24 (dd, 1 H, ^2J = 12.5 Hz, $^4J_{6,4}$ = 1 Hz, H-6), 2.38 (m, 1 H, $^3J_{2,3}$ + $^3J_{2,CH_2NH_2}$ = 21 Hz, H-2), 1.5–1.9 (m, 4 H, H-3,4), 1.5 (br s, 1 H, NH); ^{13}C NMR δ 139 (C-ipso), 128.7 (C-m), 128.1 (C-o), 126.7 (C-p), 106.3 (C-5), 64.1, 64.6 (OCH_2CH_2O), 60.7, (C-2), 57.3 (NCH_2Ph), 55.6 (C-6), 42.5 (CH_2NH_2), 24.9, 32.3 (C-3 and C-4); exact mass calcd for $C_{15}H_{22}N_2O_2$ 262.1681, found 262.1686.

7-(Ethylenedioxy)octahydro-2*H*-pyrido[1,2-*a*]pyrazin-3-one (5). To a stirred solution of the crude product 3 (3.0 g) in dichloromethane (20 mL) was added chloroacetyl chloride (1.30 mL, 16.2 mmol) dropwise. After 15 min, the reaction was worked up by addition of aqueous K_2CO_3 and extraction with CH_2Cl_2 (2 × 100 mL). Evaporation of the organic solution gave the crude product 4a (3.82 g, 98.6%) as a yellow oil, which could be used directly in the next step. Column chromatography with EtOAc on silica gel afforded pure 4a (3.73 g, 96%) as an oil: exact mass calcd for $C_{17}H_{23}N_2O_3Cl$ 338.1635, found 338.1632. A mixture of the crude product 4a (3.82 g), in 200 mL of *o*-dichlorobenzene, and Bu_4NBr (4.0 g, 12.4 mmol) was refluxed gently for 1 h. The solvent then was evaporated under reduced pressure, and the residue was dissolved in 100 mL of water. The aqueous solution was extracted with 40 mL of CH_2Cl_2 after addition of 2 g of K_2CO_3. The aqueous phase was separated, and the dichloromethane layer was further extracted with water (100 mL) containing K_2CO_3 (500 mg). The combined aqueous layers were evaporated to dryness, and the solid residue was treated with CH_2Cl_2 (3 × 200 mL). The CH_2Cl_2 solutions were filtered and evaporated to afford pure 5 (2.08 g, 84% from 1) as a solid with mp 165 °C ($CHCl_3$–hexane): IR ν 3440, 3180, 3070, 1690, 1640, 1295, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (br s, 1 H, NH), 4 (m, 4 H, OCH_2CH_2O), 3.45 (d, 1 H, ^2J = 16.5 Hz, H-4e), 3.23 (dd, 1 H, ^2J = 12 Hz, ^3J = 4.5 Hz, H-1e), 3.19 (t, 1 H, ^2J = 12 Hz, ^3J = 10 Hz, H-1ax), 2.85 (d, 1 H, ^2J = 16.5 Hz, H-4ax), 2.8 (dd, 1 H, ^2J = 11 Hz, $^4J_{6e,8e}$ = 2 Hz, H-6e), 2.31 (tt, 1 H, $^3J_{(9a)ax,1ax}$ = 10 Hz, $^3J_{(9a)ax,9ax}$ = 10 Hz, $^3J_{(9a)ax,1e}$ = 4 Hz, $^3J_{(9a)ax,9e}$ = 4 Hz, H-(9a)ax), 2.14 (d, 1 H, ^2J = 11 Hz, H-6ax), 1.5–1.9 (m, 4 H, H-8,9); ^{13}C NMR δ 168.8 (C=O), 105.2 (C-7), 64.7/64.5 (OCH_2CH_2O), 60.3 (C-6), 57.6 (C-4), 55 (C-9a), 46.6 (C-1), 32.4 (C-8), 26.8 (C-9); exact mass calcd for $C_{10}H_{16}N_2O_3$ 212.1161, found 212.1163. Anal. Calcd for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.26; H, 7.58; N, 13.05.

7-(Ethylenedioxy)-2-(2′-pyridyl)octahydro-2*H*-pyrido-[1,2-*a*]pyrazine (8). To a stirred solution of 5 (3.0 g, 14.1 mmol) in 200 mL of anhydrous THF was added $LiAlH_4$ (1.50 g, 39.5 mmol) portionwise. After 3 h, the excess of hydride was destroyed by dropwise addition of methanol followed by addition of CH_2Cl_2

(10) Brown, H. C.; Tsukamoto, A. *J. Am. Chem. Soc.* **1964**, *86*, 1089.

(300 mL), K_2CO_3 (1 g), and water (4 mL). The organic layer was filtered and concentrated to afford crude product 7 (2.6 g, 93%) as a yellow oil, which was used directly in the next step: MS m/z 198 (M^+). A mixture of the crude product 7, 2-fluoropyridine (3.9 mL, 35 mmol), and $Bu_4NF{\cdot}3H_2O$ (6.5 g, 20.6 mmol) was heated under nitrogen at 75 °C for 8 h. The mixture was chromatographed on silica gel, eluting first with EtOAc then 5% MeOH–EtOAc to afford pure 8 (2.9 g, 74% from 5) as a solid, mp 72 °C (ether): IR ν 3100, 3000, 1593, 1560, 1480 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.2 (dd, 1 H, $^3J_{3',4'}$ = 5 Hz, $^4J_{3',5'}$ = 2.2 Hz, H-3'), 7.5 (td, 1 H, $^3J_{5',6'}$ = 8.5 Hz, $^3J_{5',4'}$ = 8.5 Hz, $^4J_{5',3'}$ = 2 Hz, H-5'), 6.6 (dd, 1 H, $^3J_{4',5'}$ = 7 Hz, $^3J_{4',3'}$ = 5 Hz, H-4'), 6.64 (d, 1 H, $^3J_{6',5'}$ = 8.5 Hz, H-6'), 4 (m, 4 H, OCH_2CH_2O), 4.15 (dm, 2 H, H-1e,3e), 3.13 (td, 1 H, ^2J = 12 Hz, $^3J_{3ax,4ax}$ = 11 Hz, $^3J_{3ax,4e}$ = 3 Hz, H-3ax), 2.85 (dt, 1 H, ^2J = 11 Hz, $^3J_{4e,3ax}$ = 3 Hz, $^3J_{4e,3e}$ = 3 Hz, H-4e), 2.77 (dd, 1 H, ^2J = 11 Hz, $^4J_{6e,8e}$ = 3 Hz, H-6e), 2.65 (dd, 1 H, ^2J = 12 Hz, $^3J_{1ax-(9a)ax}$ = 10 Hz, H-1ax), 2.28 (td, 1 H, ^2J = 11 Hz, $^3J_{4ax,3ax}$ = 11 Hz, $^3J_{4ax,3e}$ = 3 Hz, H-4ax), 2.18 (d, 1 H, ^2J = 11 Hz, H-6ax), 2.02 (tt, 1 H, $^3J_{(9a)ax,1ax}$ = 10 Hz, $^3J_{(9a)ax,9ax}$ = 10 Hz, $^3J_{(9a)ax,1e}$ = 3 Hz, $^3J_{(9a)ax,9e}$ = 3 Hz, H-(9a)ax), 1.55–1.9 (m, 4 H, H-8,9); ^{13}C NMR 158.8 (C-ipso), 147.4 (C-α), 137.1 (C-γ), 112.7, 106.7 (C-β), 105.6 (C-7), 64.5, 64.2 (OCH_2CH_2O), 61.2 (C-6), 59.4 (C-9a), 54.2 (C-4), 49.7 (C-1), 44.2 (C-3), 32.8 (C-8), 26.9 (C-9); exact mass calcd for $C_{15}H_{21}N_3O_2$ 275.1631, found 275.1629. Anal. Calcd for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.40; H, 7.82; N, 15.00.

2-Benzyl-7-(ethylenedioxy)octahydro-2*H*-pyrido[1,2-*a*]pyrazine (9). To an ice-cooled stirred mixture of the crude product 7 (5.5 g), prepared from the lactam 5 (6.0 g, 28.3 mmol) as described for the preparation of 8, in 50 mL of CH_2Cl_2 was added Et_3N (4.5 mL, 30 mmol) and then dropwise benzyl bromide (4.2 mL, 35 mmol). After 1 h the reaction mixture was allowed to come to room temperature and was stirred further for 1 h. The mixture was diluted with CH_2Cl_2 (300 mL). The CH_2Cl_2 solution was washed with water (50 mL), filtered, and evaporated. Column chromatography of the residue on silica with 5% MeOH–EtOAc yielded pure 9 (6.05 g, 74% from 5), mp 90 °C (EtOAc): IR ν 3100, 3030, 1600, 1490, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3 (m, 5 H, Ph), 3.9 (m, 4 H, OCH_2CH_2O), 3.53, 3.49 (AB q, 2 H, ^2J = 13 Hz, NCH_2Ph), 2.65–2.8 (m, 4 H, H-1e,3e,4e,6e), 2.35 (td, 1 H, ^2J = 11 Hz, $^3J_{3ax-4ax}$ = 11 Hz, $^3J_{3ax,4e}$ = 3 Hz, H-3ax), 2.29 (td, 1 H, ^2J = 11 Hz, $^3J_{4ax,3ax}$ = 11 Hz, $^3J_{4ax,3e}$ = 3 Hz, H-4ax), 2.15 (d, 1 H, ^2J = 11 Hz, H-6ax), 2.03 (m, 1 H, H-(9a)ax), 1.94 (t, 1 H, ^2J = 10 Hz, $^3J_{1ax,(9a)ax}$ = 10 Hz, H-1ax), 1.78 (ddd, 1 H, ^2J = 10 Hz, $^3J_{8e,9ax}$ = 4 Hz, $^3J_{8e,9e}$ = 2.5 Hz, H-8e), 1.4–1.6 (m, 3 H, H-9, 8ax); ^{13}C NMR δ 138.1 (C-ipso), 129.1 (C-m), 128.1 (C-o), 126.9 (C-p), 106.2 (C-7) 64.7, 64.4 (OCH_2CH_2O), 62.9 (CH_2Ph), 61.5 (C-6), 60.1 (C-9a), 58.4 (C-1), 54.9 (C-4), 52.4 (C-3), 33.3 (C-8), 27.5 (C-9); exact mass calcd for $C_{17}H_{24}N_2O_2$ 288.1836, found 288.1839. Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.65; H, 8.45; N, 9.62.

2-Benzyloctahydro-2*H*-pyrido[1,2-*a*]pyrazin-7-one (11). A solution of 9 (6.0 g, 20.8 mmol) in 80 mL of 6 M HCl was refluxed gently for 3 h. After evaporation, the residue was dissolved in water (30 mL), and the cooled solution was made alkaline with K_2CO_3 after addition of CH_2Cl_2 (300 mL). The water phase was extracted further with CH_2Cl_2 (300 mL), and the combined organic layers were filtered and evaporated, yielding crude 11 (5 g). Column chromatography on silica with 5% MeOH–EtOAc yielded pure 11 (4.7 g, 92%) as a yellow oil: IR ν 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3 (m, 5 H, Ph), 3.55, 3.5 (AB q, 2 H, ^2J = 13.5 Hz, CH_2Ph), 3.25 (dd, 1 H, ^2J = 14.3 Hz, $^4J_{6e,8e}$ = 2.3 Hz, H-6e), 2.65–2.9 (m, 3 H, H-1e,3e,4e), 2.78 (d, 1 H, ^2J = 14.3 Hz, H-6ax), 2.3-2.5 (m, 4 H, H-(9a)ax, 8ax, 8e, 3ax), 2.2 (td, 1 H, ^2J = 11 Hz, $^3J_{4ax,3ax}$ = 11 Hz, $^3J_{4ax,3e}$ = 3 Hz, H-4ax), 1.86 (t, 1 H, ^2J = 11 Hz, $^3J_{1ax,(9a)ax}$ = 11 Hz, H-1ax), 1.8 (m, 1 H, H-9e), 1.6 (dtd, 1 H, ^2J = 13 Hz, $^3J_{9ax,(9a)ax}$ = 11 Hz, $^3J_{9ax,8ax}$ = 11 Hz, $^3J_{9ax,8e}$ = 5 Hz, H-9ax); ^{13}C NMR δ 205.6 (C=O), 137.6 (C-ipso), 128.9 (C-m), 128.1 (C-o), 126.9 (C-p), 65.1 (C-6), 62.6 (CH_2Ph), 58.3 (C-1), 58.2 (C-9a), 54.6 (C-4), 52.2 (C-3), 38.2 (C-8), 28.4 (C-9); exact mass calcd for $C_{15}H_{20}N_2O$ 244.1575, found 244.1577.

1-Benzyl-5-(ethylenedioxy)-*N*-phenyl-2-piperidinemethanamine (12a). To a stirred solution of the crude product 2 (585 mg) in anhydrous methanol (5 mL) were added aniline (0.4 mL) and $NaCNBH_3$ (230 mg). The solution was adjusted to pH 6 by dropwise addition of 2 M HCl in MeOH and stirred for 15 min at room temperature and then at reflux temperature for 30 min. The cooled solution was treated with 2 M HCl (1 mL), made alkaline with aqueous K_2CO_3, and extracted with CH_2Cl_2 (2 × 100 mL). The organic solvent was evaporated, and the residue was chromatographed on a column of silica gel. Elution with $CHCl_3$ then EtOAc–$CHCl_3$ (1:9) afforded pure 12a (427 mg, 50%) as a yellow oil: IR (CCl_4) ν 3380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (m, 5 H, CH_2Ph), 7.15 (dd, 2 H, ^3J = 9 and 7 Hz, H-m PhNH), 6.65 (tt, 1 H, ^3J = 7.5 Hz, ^4J = 2 Hz, H-p PhNH), 6.57 (dd, 2 H, ^3J = 8 Hz, ^4J = 2 Hz, H-o PhNH), 4.5, 3.53 (AB q, 2 H, ^2J = 13 Hz, NCH_2Ph), 3.85 (m, 4 H, OCH_2CH_2O), 3.25 (dd, 2 H, ^2J = 12 Hz, ^3J = 5 Hz, CH_2NHPh), 2.75 (m, 1 H, H-2), 2.73 (dd, 1 H, ^2J = 12 Hz, $^4J_{6e,4e}$ = 2 Hz, H-6e), 2.3 (d, 1 H, ^2J = 12 Hz, H-6ax), 1.54–1.95 (m, 4 H, H-3,4); exact mass calcd for $C_{21}H_{26}N_2O_2$ 338.1992, found 338.1990.

1-Benzyl-5-(ethylenedioxy)-*N*-(2-methoxyphenyl)-2-piperidinemethanamine (12b). To a stirred solution of the crude product 2 (400 mg) in anhydrous methanol (5 mL) were added o-anisidine (0.30 mL, 2.23 mmol) and then $NaCNBH_3$ (180 mg, 2.87 mmol). The solution was adjusted to pH-6 with 2 M HCl in MeOH and stirred for 30 min at room temperature followed by workup as described for 12a. The product was purified by column chromatography on silica gel. Elution with EtOAc–$CHCl_3$ (3:97) afforded 12b (310 mg, 55%) as an oil: ^1H NMR ($CDCl_3$) δ 7.2–7.5 (m, 5 H, Ph), 6.82 (td, 1 H, ^3J = 8.4 H, ^4J = 2 Hz, H-4' ArNH), 6.73 (d, 1 H, ^3J = 8.4 Hz, H-6' ArNH), 6.62 (td, 1 H, ^3J = 8.4 Hz, $^4J_{5',3'}$ = 2 Hz, H-5' ArNH), 6.52 (d, 1 H, ^3J = 8.4 Hz, H-3' ArNH), 4.8 (br s, 1 H, NH), 3.7–4.0 (m, 4 H, OCH_2CH_2O), 3.85 (s, 3 H, OCH_3), 4.05, 3.59 (AB q, 2 H, ^2J = 13 Hz, NCH_2Ph), 3.26 (m, 2 H, CH_2NH), 2.81 (quintet, 1 H, ^3J = 6 Hz, H-2), 2.72 (d, 1 H, ^2J = 13 Hz, H-6e), 2.3 (d, 1 H, ^2J = 13 Hz, H-6ax), 1.6–2 (m, 4 H, H-3,4); CIMS m/z 369 (MH^+); exact mass calcd for $C_{22}H_{28}N_2O_3$ 368.2100, found 368.2090.

7-(Ethylenedioxy)-2-phenyloctahydro-2*H*-pyrido[1,2-*a*]pyrazin-3-one (14a). To a solution of 12a (647 mg, 1.91 mmol) in 20 mL of CH_2Cl_2 was added chloroacetyl chloride (0.20 mL, 2.5 mmol) dropwise. After 10 min, aqueous K_2CO_3 was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The CH_2Cl_2 solution was filtered and concentrated to afford crude 13a (650 mg) as an oil. This was dissolved in 20 mL of toluene, and after addition of Bu_4NBr (600 mg, 1.86 mmol), the solution was stirred at reflux temperature for 2 h. The solvent was evaporated, and the residue was chromatographed on a column of silica gel. Elution with EtOAc–MeOH (95:5) gave 14a (410 mg, 74%) as an oil: IR ν 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.0–7.45 (m, 5 H, Ph), 4.2 (m, 4 H, OCH_2CH_2O), 3.67 (dd, 1 H, ^2J = 11.5 Hz, $^3J_{1ax,(9a)ax}$ = 10.5 Hz, H-1ax), 3.66 (d, 1 H, ^2J = 16.5 Hz, H-4e), 3.50 (dd, 1 H, ^2J = 11.5 Hz, $^3J_{1e,(9a)ax}$ = 3.5 Hz, H-1e), 3.06 (d, 1 H, ^2J = 16.5 Hz, H-4ax), 2.85 (dd, 1 H, ^2J = 11.5 Hz, $^4J_{6e,8e}$ = 3 Hz, H-6e), 2.55 (tt, 1 H, $^3J_{(9a)ax,1ax}$ = 10.5 Hz, $^3J_{(9a)ax-9ax}$ = 11 Hz, $^3J_{(9a)ax,1e}$ = 3 Hz, $^3J_{(9a)ax,9e}$ = 3 Hz, H-(9a)ax), 2.17 (d, 1 H, ^2J = 11.5 Hz, H-6ax), 1.75 (m, 4 H, H-8,9); ^{13}C NMR δ 27 (C-9), 32.7 (C-8), 55.7 (C-1), 56.2 (C-9a), 58.9 (C-4), 60.2 (C-6), 64.8, 65 (OCH_2CH_2O), 105.4 (C-7), 125.9 (C-o Ph), 127.1 (C-p Ph), 129.2 (C-m Ph), 141.6 (C-ipso Ph), 166 (C=O); exact mass calcd for $C_{16}H_{20}N_2O_3$ 288.1472, found 288.1472.

7-(Ethylenedioxy)-2-(2-methoxyphenyl)octahydro-2*H*-pyrido[1,2-*a*]pyrazin-3-one (14b). To a stirred solution of 12b (310 mg, 0.84 mmol) in 15 mL of CH_2Cl_2 was added chloroacetyl chloride (0.08 mL, 1 mmol) dropwise at 0 °C. After 15 min, the mixture was allowed to come to room temperature and to react further for 10 min. Workup as described for intermediate 13a in the preparation of 14a afforded crude product 13b as an oil, which was used directly in the next step: CIMS m/z 445, 447 (MH^+). A mixture of the crude 13b in 15 mL of o-dichlorobenzene and Bu_4NBr (350 mg, 1.09 mmol) was refluxed gently for 15 min. The solvent was evaporated, and the residue was chromatographed on a column of silica gel with MeOH–EtOAc (5:95) to afford pure 14b (205 mg, 77% from 12b) as an oil: IR (CCl4) ν 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (m, 1 H, H-4' Ar), 7.14 (dd, 1 H, $^3J_{6',5'}$ = 8 Hz, $^4J_{6',4'}$ = 1.5 Hz, H-6' Ar), 6.97 (td, 1 H, $^3J_{5',6'}$ = 4 Hz, $^3J_{5',4'}$ = 4 Hz, $^4J_{5',3'}$ = 1 Hz, H-5' Ar), 6.94 (dd, 1 H, $^3J_{3',4'}$ = 4 Hz, $^4J_{3',5'}$ = 1 Hz, H-3' Ar), 4.01 (m, 4 H, OCH_2CH_2O), 3.82 (s, 3 H, OCH_3), 3.66 (d, 1 H, ^2J = 16 Hz, H-4e), 3.57 (t, 1 H, ^2J = 12 Hz, $^3J_{1ax,(9a)ax}$ = 11 Hz, H-1ax), 3.37 (dd, 1 H, ^2J = 12 Hz, $^3J_{1e,(9a)ax}$ = 3 Hz, H-1e), 3.05 (d, 1 H, ^2J = 16 Hz, H-4ax), 2.87 (dd, 1 H, ^2J = 11 Hz, $^3J_{6e,8e}$

= 3 Hz, H-6e), 2.57 (tt, 1 H, $^3J_{(9a)ax,1ax}$ = 11 Hz, $^3J_{(9a)ax,9ax}$ = 11 Hz, $^3J_{(9a)ax,1e}$ = 3 Hz, $^3J_{(9a)ax,9e}$ = 3 Hz, H-(9a)ax), 1.5-1.9 (m, 4 H, H-8,9); ^{13}C NMR δ 165.9 (C=O), 154.5 (C-ipso), 129.5, 128.9, 128.7, 120.8, 112 (C-Ar), 105.3 (C-7), 64.8, 64.5 (OCH_2CH_2O), 60.2 (C-6), 58.4 (C-4), 55.8 (C-9a), 55.4 (C-OCH_3), 54.6 (C-1), 32.5 (C-8), 26.5 (C-9); exact mass calcd for $C_{17}H_{22}N_2O_4$ 318.1577, found 318.1573.

7-(Ethylenedioxy)-2-phenyloctahydro-2*H*-pyrido[1,2-*a*]pyrazine (15a). To a stirred solution of **14a** (293 mg, 1.02 mmol) in 20 mL of anhydrous ether was added $LiAlH_4$ (100 mg, 2.64 mmol) portionwise. After 1 h, the excess of hydride was destroyed by dropwise addition of methanol followed by addition of CH_2Cl_2 (200 mL), K_2CO_3 (100 mg), and water (2 mL). The organic solvent was evaporated, and the residue was chromatographed on a silica column (gradient elution 5-20% EtOAc-$CHCl_3$) to give **15a** (200 mg, 72%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.3 (dd, 2 H, Ph), 6.9 (dd, 2 H, Ph), 6.89 (tt, 1 H, Ph), 4 (m, 4 H, OCH_2CH_2O), 3.63 (dd, 1 H, ^2J = 12 Hz, $^3J_{1ax,(9a)ax}$ = 10 Hz, H-1ax), 3.5 (dm, 1 H, ^2J = 12 Hz, H-1e), 3.5 (dm, 1 H, ^2J = 11 Hz, H-3e), 3.05 (td, 1 H, ^2J = 11 Hz, $^3J_{3ax,4ax}$ = 11 Hz, $^3J_{3ax,4e}$ = 3 Hz, H-3ax), 2.89 (dt, 1 H, ^2J = 11 Hz, $^3J_{4e,3ax}$ = 3 Hz, $^3J_{4e,3e}$ = 2.5 Hz, H-4e), 2.8 (dd, 1 H, ^2J = 11.5 Hz, $^4J_{6e,8e}$ = 2.5 Hz, H-6e), 2.4 (td, 1 H, ^2J = 11 Hz, $^3J_{4ax,3ax}$ = 11 Hz, $^3J_{4ax,3e}$ = 3 Hz, H-4ax), 2.22 (d, 1 H, ^2J = 11.5 Hz, H-6ax), 2.15 (m, 1 H, H-(9a)ax), 1.87 (m, 1 H, H-8e), 1.65 (m, 3 H, H-9, 8ax); exact mass calcd for $C_{16}H_{22}N_2O_2$ 274.1680, found 274.1677.

2-Phenyloctahydro-2*H*-pyrido[1,2]pyrazin-7-one (16a). A mixture of **15a** (500 mg, 1.82 mmol) and 6 M HCl (20 mL) was refluxed for 2 h. The solution was evaporated, and the residue was dissolved in water (10 mL). The aqueous solution was cooled to 0 °C and made alkaline with K_2CO_3 after the addition of CH_2Cl_2 (100 mL). The aqueous layer was further extracted with CH_2Cl_2 (50 mL), and the combined organic layers were evaporated. Column chromatography of the residual oil on silica (gradient elution 5-15% EtOAc-$CHCl_3$) afforded pure **16a** (395 mg, 94%) as a yellow oil (stored as the HCl salt since it was oxidized in its basic form): IR ν 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$ + C_6D_6) δ 7.22 (dd, 2 H, Ph), 6.85 (t, 1 H, Ph), 6.75 (dd, 2 H, Ph), 3.38 (dt, 1 H, ^2J = 11.3 Hz, $^3J_{1e,(9a)ax}$ = 2.5 Hz, $^4J_{1e,3e}$ = 2.5 Hz, H-1e), 3.32 (dq, 1 H, ^2J = 11.5 Hz, $^3J_{3e,4ax}$ = 3 Hz, $^3J_{3e,4e}$ = 2.5 Hz, $^4J_{3e,1e}$ = 2.5 Hz, H-3e), 3.17 (dd, 1 H, ^2J = 14 Hz, $^4J_{6e,8e}$ = 2 Hz, H-6e), 2.71 (td, 1 H, ^2J = 11.5 Hz, $^3J_{3ax,4ax}$ = 11.5 Hz, $^3J_{3ax,4e}$ = 3 Hz, H-3ax), 2.56 (dt, 1 H, ^2J = 11 Hz, $^3J_{4e,3ax}$ = 3 Hz, $^3J_{4e,3e}$ = 2.5 Hz, H-4e), 2.54 (dd, 1 H, ^2J = 14 Hz, $^4J_{6ax,8ax}$ = 1 Hz, H-6ax), 2.35 (dd, 1 H, ^2J = 11.3 Hz, $^3J_{1ax,(9a)ax}$ = 10.2 Hz, H-1ax), 2.21 (td, 1 H, ^2J = 11 Hz, $^3J_{4ax,3ax}$ = 11.5 Hz, $^3J_{4ax,3e}$ = 3 Hz, H-4ax), 2.12-2.38 (m, 2 H, H-8e,(9a)ax), 2.04 (dddd, 1 H, ^2J = 15 Hz, $^3J_{8ax,9ax}$ = 13 Hz, $^3J_{8ax,9e}$ = 7 Hz, $^4J_{8ax,6ax}$ = 1 Hz, H-8ax), 1.57 (ddt, 1 H, ^2J = 13 Hz, $^3J_{9e,8ax}$ = 7 Hz, $^3J_{9e,(9a)ax}$ = 3 Hz, $^3J_{9e,8e}$ = 2.5 Hz, H-9e), 1.45 (tdd, 1 H, ^2J = 13 Hz, $^3J_{9ax,8ax}$ = 13 Hz, $^3J_{9ax,(9a)ax}$ = 10.5 Hz, $^3J_{9ax,8e}$ = 5 Hz); exact mass calcd for $C_{14}H_{18}N_2O$ 230.1419, found 230.1417.

2-(2-Methoxyphenyl)octahydro-2*H*-pyrido[1,2-*a*]pyrazin-7-one (16b). To a stirred solution of **14b** (200 mg, 0.63 mmol) in 15 mL of anhydrous ether was added $LiAlH_4$ (50 mg, 1.32 mmol). After 1 h, the excess of hydride was destroyed with MeOH and the mixture worked up as for **15a** to give the crude product **15b** (176 mg, 92%) as an oil, which was used directly in the next step: MS *m/z* 304 (M^+). A mixture of the crude product **15b** (176 mg) and 6 M HCl (10 mL) was refluxed for 2 h. After workup as described for **16a**, column chromatography using silica gel with EtOAc as eluent afforded pure **16b** (107 mg, 65% from **15b**) as a pale yellow crystalline product, mp 106-108 °C: IR ν 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.85-7.1 (m, 4 H, Ar), 3.9 (s, 3 H, OCH_3), 3.49 (dt, 1 H, ^2J = 11 Hz, $^3J_{1e,(9a)ax}$ = 3 Hz, $^4J_{1e,3e}$ = 3 Hz, H-1e), 3.43 (dq, 1 H, ^2J = 12.5 Hz, $^3J_{3e,4ax}$ = 3 Hz, $^3J_{3e,4e}$ = 3 Hz, $^4J_{3e,1e}$ = 3 Hz, H-3e), 3.33 (dd, 1 H, ^2J = 14 Hz, $^4J_{6e,8e}$ = 2 Hz, H-6e), 2.84-2.9 (m, 1 H, H-4e), 2.88 (d, 1 H, ^2J = 14 Hz, H-6ax), 2.84 (td, 1 H, ^2J = 12.5 Hz, $^3J_{3ax,4ax}$ = 12.5 Hz, $^3J_{3ax,4e}$ = 3 Hz, H-3ax), 2.46-2.7 (m, 3 H, H-(9a)ax,8e,4ax), 2.47 (t, 1 H, ^2J = 10.5 Hz, $^3J_{1ax,(9a)ax}$ = 10.5 Hz, H-1ax), 2.38 (ddd, 1 H, ^2J = 15 Hz, $^3J_{8ax,9ax}$ = 11.7 Hz, $^3J_{8ax,9e}$ = 7 Hz, H-8ax), 1.95 (ddt, 1 H, ^2J = 13 Hz, $^3J_{9e,8ax}$ = 7 Hz, $^3J_{9e,(9a)ax}$ = 3 Hz, $^4J_{9e,1e}$ = 3 Hz, H-9e), 1.7 (tdd, 1 H, ^2J = 13 Hz, $^3J_{9ax,8ax}$ = 11.7 Hz, $^3J_{9ax,(9a)ax}$ = 10 Hz, $^3J_{9ax,8e}$ = 5.5 Hz, H-9ax); ^{13}C NMR δ 205.8 (C=O), 152.3 (C-2' Ar), 140.8 (C-1' Ar), 123.1, 121, 118.2, 111.4 (C-3',4',5',6' Ar), 65.3 (C-6), 58.6 (C-9a), 56.1 (C-1), 55.4 (OCH_3), 55 (C-4), 49.9 (C-3), 38.3 (C-8), 28.4 (C-9); exact mass calcd for $C_{15}H_{20}N_2O_2$ 260.1523, found 260.1525. Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.21; H, 7.74; N, 10.76. Found: C, 69.25 H, 7.70; N, 10.80.

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Registry No. **1**, 132462-23-8; **2**, 134334-33-1; **3**, 134334-34-2; **4a**, 134334-35-3; **5**, 134334-36-4; **7**, 134334-37-5; **8**, 134334-38-6; **9**, 134334-39-7; **11**, 134334-40-0; **12a**, 134334-41-1; **12b**, 134334-42-2; **13a**, 134334-45-5; **13b**, 134334-46-6; **14a**, 134334-43-3; **14b**, 134334-44-4; **15a**, 134334-47-7; **15b**, 134334-48-8; **16a**, 134334-49-9; **16b**, 134334-50-2; $LiAl(OEt)_3H$, 17250-30-5; $ClCH_2COCl$, 79-04-9; $C_6H_5CH_2Br$, 100-39-0; $C_6H_5NH_2$, 62-53-3; 2-$MeOC_6H_4NH_2$, 90-04-0; 2-fluoropyridine, 372-48-5.

Supplementary Material Available: ^{1}H and/or ^{13}C NMR spectra for compounds **2**, **3**, **11**, **12a**, **12b**, **14a**, **14b**, **15a**, and **16a** (10 pages). Ordering information is given on any current masthead page.

Asymmetric Total Synthesis of (+)-Jasplakinolide

Kent S. Chu, George R. Negrete, and Joseph P. Konopelski*,†

Department of Chemistry and Biochemistry, University of California, Santa Cruz, California 95064

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A convergent synthesis of the marine cyclodepsipeptide (+)-jasplakinolide has been realized. The synthesis of the required (*R*)-β-tyrosine unit is accomplished via the stereospecific palladium-catalyzed arylation of an enantiomerically pure dihydropyrimidinone. The overall yield of the synthesis, based on the longest linear sequence, is 6.6%.

In 1986, two papers documenting the isolation, structure, and biological activity of a novel cyclodepsipeptide of marine origin appeared in the literature.[1] This metabolite, which is composed of both peptide and polypropionate portions, was named jasplakinolide (1) by the Crews group[1a] and jaspamide by the Ireland-Faulkner team.[1b]

Along with the common acid (*S*)-alanine, jasplakinolide contains two unusual amino acids, β-tyrosine[2] and 2-

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