Cycloaddition Reactions of Isoquinoline–Pyrroline-2,3-dione and β-Carboline–Pyrroline-2,3-dione with Benzyne. Total Synthesis of 8-Oxypseudopalmatine and Decarbomethoxydihydrogambirtannine

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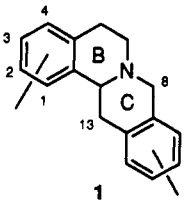
The formation of the skeletons of protoberberines and dehydroyohimbanes by cycloaddition between pyrrolinediones and arynes is described. Total syntheses of 8-oxypseudopalmatine and decarbomethoxydihydrogambirtannine were performed.

Protoberberines are isoquinoline alkaloids characterized by the tetracyclic structure **1**. This group includes more than 100 members[1] whose natural occurrences[1,2] and pharmacological properties[1-4] have been reviewed and continues to attract the interest of several groups.[3] While studying the synthesis of isoquinoline alkaloids by intermolecular benzyne cycloaddition, we observed that pyrrolinediones **3**, which are readily obtained from imines **2**, can act as aza diene equivalents, reacting with arynes **4** to afford oxoprotoberberines **5**.[5] Since oxoprotoberberines **5** can be transformed into protoberberines very efficiently, ready synthesis of the latter was achieved.



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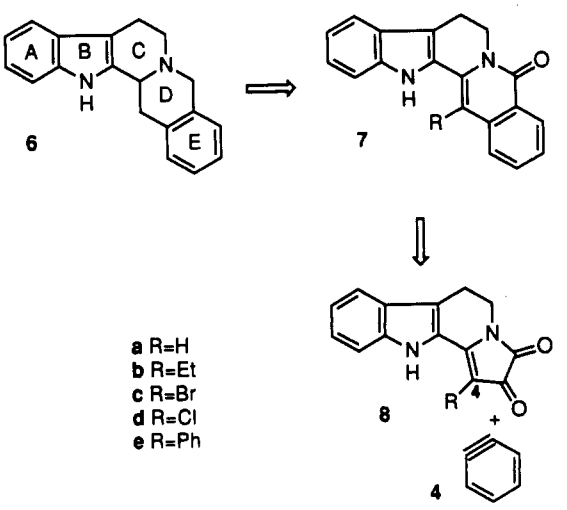
The synthesis of (±)-corydaline showed that the above procedure can be used even for the preparation of ring-D substituted protoberberines.[5] However, we also observed that pyrrolinedione **3a**, which is unsubstituted at position 4 (pyrrolinedione numbering), reacts with 2 equiv of the aryne to afford the 13-(aryloxy)protoberberine **5d**.[5] The introduction of an aryl group at position 13 severely limits this method, since most natural protoberberine alkaloids are unsubstituted at this position.

In order to extend the applicability of this new strategy to most natural protoberberines, we introduced a tactical modification based on the use of chlorine and bromine as protecting groups.[6] These halides were selected with a view to easy synthesis of the protected pyrrolinediones and eventual efficient elimination by hydrogenolysis.

Discussion of Results

Pyrrolinedione **3b** was prepared either by the reaction of 1-(chloromethyl)-3,4-dihydro-6,7-dihydro-6,7-dimethoxyisoquinoline (**2b**)[7] with oxalyl chloride, or by treatment

Scheme I



of pyrrolinedione **3a**[5] with NCS. When pyrrolinedione **3b** was reacted with benzyne (**4a**), which was generated in situ by thermal decomposition of benzenediazonium 2-carboxylate,[8] we obtained the adduct **5b** in 48% yield. Deprotection of position 13 (protoberberine numbering) was carried out by hydrogenolysis (H_2, Pd/C) to afford **5a** in 100% yield.

The brominated pyrrolinedione **3c** was obtained in 98% yield by direct bromination ($Br_2/CHCl_3$) of compound **3a**. Reaction of **3c** with benzyne (**4a**) afforded two products: the oxyprotoberberine **5c** in 67% yield and a small amount (14% yield) of the phenylated product **5d**. Debromination of **5c** as above yielded the 8-oxyprotoberberine **5a** in 88% yield.

The better yield obtained in the cycloaddition of the brominated pyrrolinedione led us to choose this compound as key intermediate for the synthesis of 8-oxypseudopalmatine (**5f**), a natural compound recently isolated from *Stephania suberosa*.[9] The anthranilic acid corresponding to ring D of 8-oxypseudopalmatine is 4,5-dimethoxyanthranilic acid (2-amino-4,5-dimethoxybenzoic acid). When the 4,5-dimethoxybenzenediazonium 2-carboxylate, obtained by aprotic diazotization of 4,5-dimethoxyanthranilic acid as above, was added to a refluxing solution of **3c** in DME, we obtained the adduct **5e** in 44% yield and the arylated product **5g** in very low yield. Hydrogenolysis of **5e** (Pd/C, H_2, 36 psi) yielded 8-oxypseudopalmatine (**5f**) in 96% yield.[10] This total synthesis of 8-oxypseudopal-

(1) Southon, I. W.; Buckingham, J. *Dictionary of Alkaloids*; Chapman and Hall: New York, 1989.
(2) (a) Shamma, M. *The Isoquinoline Alkaloids*; Academic Press: New York, 1972. (b) Shamma, M.; Moniot, J. L. *Isoquinoline Alkaloid Research 1972/1977*; Plenum Press: New York, 1978.
(3) Occurrence, synthesis and pharmacology are periodically reviewed by Bentley, K. W. in *Nat. Prod. Rep.* See, for example: *Nat. Prod. Rep.* **1989**, *6*, 405; *Nat. Prod. Rep.* **1990**, *7*, 245; *Nat. Prod. Rep.* **1991**, *8*, 339.
(4) Suffness, M.; Cordell, G. A. *The Alkaloids*; Brossi, A., Ed., Academic Press: New York, 1985; Vol. 25, pp 1–355.
(5) Saá, C.; Guitián, E.; Castedo, L.; Suau, R.; Saá, J. M. *J. Org. Chem.* **1986**, *51*, 2781.
(6) Cobas, A.; Guitián, E.; Castedo, L.; Saá, J. M. *Tetrahedron Lett.* **1988**, *29*, 2491.
(7) Child, R.; Pyman, F. L. *J. Chem. Soc.* **1931**, 36.
(8) Logullo, F. M.; Seitz, A. H.; Friedman, L. *Org. Synth.* **1968**, *48*, 12.
(9) Patra, A.; Montgomery, C. T.; Freyer, A. J.; Guinaudeau, H.; Shamma, M.; Tantisewie, B.; Pharada, K. *Phytochemistry* **1987**, *26*, 547.

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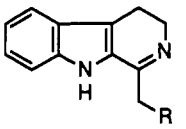
matine also amounts to formal synthesis of xylopinine.[10a]

Since the above procedure allows the synthesis of protoberberines that are unsubstituted at position 13, we belive that it may be used for the synthesis of most natural protoberberine alkaloids.

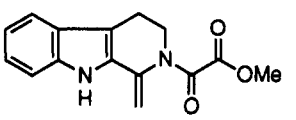
There are a number of indole alkaloids characterized by the basic structure **6**,[11] whose similarity with that of protoberberine alkaloids (**1**) is evident. The similarity of the arrangement of rings CDE of **6** and BCD in **1** suggests that the basic skeleton **6** may be obtained by cycloaddition between pyrrolinediones **8** and arynes **4**. Further, reports of the synthesis of pyrrolinediones **8** by treatment of imines **9** with oxalyl chloride,[12] and of cycloaddition reactions of dienes containing NH-unprotected indoles with benzyne,[13] suggested to us that the synthesis of **7** might be carried out without problems. However, attempts to synthesize pyrrolinedione **8a** by published methods (treatment of imine **9a** with oxalyl chloride)[12] were unsuccessful. When the reaction was carried out in THF/triethylamine, we isolated a compound whose spectroscopic data were in keeping with the dimeric structure **11**. We thought that the use of an oxalyl derivative with an ester group instead of an acid chloride might allow isolation of the intermediate **10**. Treatment of imine **9a** with methyl chlorooxalate yielded a mixture of pyrrolinedione **8a** as minor product and a new compound. All attempts to isolate this compound by chromatography on silica gel plates were unsuccessful, affording samples containing pyrrolinedione **8a**. We concluded that this was due to the transformation of **10** into **8a** on the silica gel plates. Refluxing **10** in the presence of silica gel afforded **8a** in 73% yield.

As expected, when benzyne (**4**) was generated in a refluxing solution of **8a** in DME a mixture containing the phenylated compound, **7e** was obtained. In order to avoid phenylation at position 4 (pyrrolinedione numbering) we synthesized the substituted pyrrolinedione **8b** from **9b**.

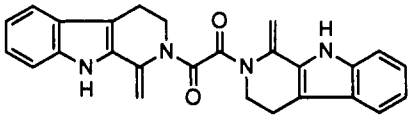


9

a R=H
b R=Et
c R=Cl



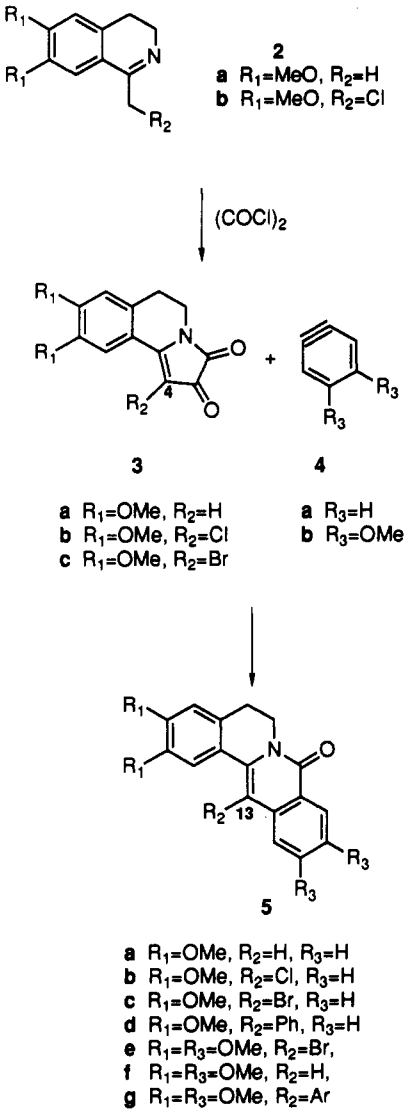
10



11

Acylation of tryptamine with butyryl chloride afforded the amide (80% yield), which was transformed into pyrrolinedione **8b** by Bischler–Napieralski cyclization with $POCl_3$ (76% yield) and reaction of the imine **9b** with oxalyl chloride (44% yield). In view of the satisfactory results obtained in the synthesis of pyrrolinedione **8a** with methyl chlorooxalate, we also prepared **8b** by this procedure (yield 81%). When benzyne (**4**) was generated as above in a refluxing solution of pyrrolinedione **8b** in dichloroethane, the adduct **7b** was obtained in 69% yield.

Scheme II



2
a R_1=MeO, R_2=H
b R_1=MeO, R_2=Cl

$(COCl)_2$

3
a R_1=OMe, R_2=H
b R_1=OMe, R_2=Cl
c R_1=OMe, R_2=Br

4
a R_3=H
b R_3=OMe

5
a R_1=OMe, R_2=H, R_3=H
b R_1=OMe, R_2=Cl, R_3=H
c R_1=OMe, R_2=Br, R_3=H
d R_1=OMe, R_2=Ph, R_3=H
e R_1=R_3=OMe, R_2=Br,
f R_1=R_3=OMe, R_2=H,
g R_1=R_3=OMe, R_2=Ar

The next step was to synthesize pyrrolinediones with protecting groups at position 4. Firstly, we prepared bromopyrrolinedione **8c** in 93% yield by bromination of pyrrolinedione **8a**. The key cycloaddition with benzyne (**4**) afforded 14-bromonorketoyobirine (**7c**) (34% yield) and 14-phenylnorketoyobirine (**7e**) (16% yield), showing that in this case the bromine atom is not so effective as a protecting group.

The preparation of chloropyrrolinedione **8d** from **9c** was attempted using the same procedures, but the Bischler–Napieralski cyclization of the chloroacylated tryptamine led to a complex mixture. As above, we found that **8d** may be obtained by chlorination of **8a** with NCS in 82% yield. The cycloaddition reaction of chloropyrrolinedione **8d** and benzyne (**4**) afforded the 14-chloronorketoyobirine (**7d**) in 63% yield. In this case the phenylated product was not detected.

Compounds **7c** and **7d** were transformed into the natural compound decarbomethoxydihydrogambirtannine (**6**)[14] by

(10) (a) Kametani, T.; Honda, T.; Sugai, T.; Fukumoto, K. *Heterocycles* **1976**, *4*, 927. (b) Ninomiya, I.; Naito, T. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1720. (c) Trifonov, L. S.; Orahovats, A. S. *Tetrahedron Lett.* **1985**, *26*, 3159. Kametani, T.; Sugai, T.; Shoji, Y.; Honda, T.; Satoh, F.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1151.

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(12) Palmisano, G.; Daniele, B.; Lesma, G.; Riva, R. *J. Org. Chem.* **1985**, *50*, 3322.

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(14) Peube-Lucon, N.; Plat, M.; Koch, M. *Phytochemistry* **1973**, *12*, 199.

hydrogenolysis (Pd/C, H_2, 95–98% yield) and reduction of **7a** with $POCl_3/NaBH_4$ (70% yield).

Experimental Section

General Procedures. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at respectively 250 and 62.83 MHz in $CDCl_3$. Low-resolution mass spectra (LRMS) and high-resolution mass spectra (HRMS) were recorded at an ionization voltage of 70 eV. Combustion analyses were performed at the Servei de Microanalisi de la Universitat de Barcelona. Solvents were dried by standard procedures.[15]

1-Chloro-2,3,5,6-tetrahydro-8,9-dimethoxy-2,3-dioxopyrrolo[2,1-*a*]isoquinoline (3b). (a) Pyridine (0.5 mL, 6.32 mmol) was added to a suspension of imine hydrochloride **2b**[7] (400 mg, 1.45 mmol) in dry THF (15 mL) under an Ar atmosphere, the reaction mixture was cooled to 0 °C, and a solution of oxalyl chloride (0.185 mL, 2.15 mmol) in dry THF (7 mL) was added dropwise. The solution was stirred at 0 °C for 20 min and filtered. The precipitate was washed with THF, dissolved in hot CH_2Cl_2, washed twice with 10% HCl and then with H_2O, and dried over anhyd Na_2SO_4. The solvent was evaporated in vacuo to afford **3b** (190 mg, 45%) as a dark violet solid: mp 216–218 °C (CH_2Cl_2–hexane); ^1H NMR δ 8.13 (s, 1 H), 6.83 (s, 1 H), 4.01 (s, 3 H), 3.96 (s, 3 H), 3.83 (t, J = 6.2 Hz, 2 H), 3.07 (t, J = 6.2 Hz, 2 H); UV (EtOH) λ_{max} 268, 322, 385, 492 nm; IR (KBr) 1740, 1705 cm^{-1}; LRMS m/z 295 (M^+, 34), 293 (M^+, 100), 265 (82), 234 (42).

(b) NCS (330 mg, 2.48 mmol) was added to a suspension of **3a**[5] (165 mg, 0.64 mmol) in CH_2Cl_2 (50 mL), and the mixture was stirred for 8 h at rt. After evaporation of the solvent in vacuo without heating, the residue was chromatographed (silica gel, 1:2 hexane–ether) to afford **3b** (161 mg, 89%).

1-Bromo-2,3,4,5-tetrahydro-8,9-dimethoxy-2,3-dioxopyrrolo[2,1-*a*]isoquinoline (3c). A solution of bromine (200 mg, 1.25 mmol) in 10 mL of $CHCl_3$ was added dropwise to a stirred solution of **3a**[5] (321 mg, 1.24 mmol) and dry pyridine (0.097 mL, 1.24 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C. At the end of the addition, stirring was maintained for 5 min. The reaction mixture was washed with a 10% solution of sodium metabisulfite (20 mL), with 10% HCl (2 × 20 mL) and with H_2O (20 mL), dried over Na_2SO_4, and concentrated in vacuo to afford 412 mg (98%) of **3c** as a bright red solid: mp 210–211 °C (CH_2Cl_2–hexane); ^1H NMR δ 8.29 (s, 1 H), 6.82 (s, 1 H), 4.01 (s, 3 H), 3.97 (s, 3 H), 3.83 (t, J = 6.2 Hz, 2 H), 3.06 (t, J = 6.2 Hz, 2 H); ^{13}C NMR δ 178.1, 157.2, 157.1, 154.4, 148.4, 133.7, 116.3, 112.1, 111.5, 85.1, 56.3, 56.2, 36.5, 28.7; UV (EtOH) λ_{max} 264, 324, 390, 494 nm; LRMS m/z 339 (M^+, 99), 337 (M^+, 100), 311 (84), 309 (87), 229 (50), 202 (71).

3,4-Dihydro-1-propyl-β-carboline (9b). *N*-[2-(Indol-3-yl)-ethyl]butyrylamide. To a suspension of tryptamine (10 g, 62.5 mmol) in dry $CHCl_3$ (125 mL) cooled at −10 °C was added dropwise a solution of butyryl chloride (8 g, 75.47 mmol) in dry $CHCl_3$ (30 mL), and the mixture was stirred at rt for 12 h. To the resulting suspension was added 10% NaOH (100 mL), and the mixture was stirred until the precipitated dissolved. The organic phase was decanted, washed with H_2O, dried over Na_2SO_4, and concentrated in vacuo. The residue was crystallized from AcOEt–hexane to afford 11.5 g (80%) of amide as white crystals: mp 85–86 °C; ^1H NMR δ 8.56 (bs, 1 H), 7.60–7.57 (m, 1 H), 7.37–7.34 (m, 1 H), 7.24–7.07 (m, 2 H), 6.98–6.97 (m, 1 H), 5.68 (bs, 1 H), 3.58 (m, 2 H), 2.95 (t, J = 6, 7 Hz, 2 H), 2.07 (t, J = 7.5 Hz, 2 H), 1.61 (m, 2 H), 0.89 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 173.2, 136.5, 127.4, 122.1, 119.4, 118.6, 112.8, 111.3, 39.7, 38.7, 25.3, 19.0, 13.6; UV (EtOH) λ_{max} 225, 282, 291 nm; IR (KBr) 3280, 1630 cm^{-1}; LRMS m/z 230 (M^+, 9), 143 (100), 130 (60).

$POCl_3$ (1.42 mL, 15.23 mmol) was added dropwise to a refluxing solution of amide (1.55 g, 6.52 mmol) in toluene (50 mL). The solution was refluxed for 3 h and then cooled to rt, the solvent was decanted, and the residue was dissolved in 10% HCl (80 mL). Remaining organic solvents were decanted off, and the solution was made alkaline with 10% NaOH and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, and the solvent was evaporated. The residue was dissolved in MeOH (20 mL), and the solution was acidified by dropwise addition of a saturated solution of HCl in ether and then diluted with ether to 70 mL. Filtration afforded **9b**·HCl as yellow crystals (1.27 g, 76%), mp 227–228 °C.

Imine: ^1H NMR δ 8.88 (bs, 1 H), 7.62–7.59 (m, 1 H), 7.41–7.37 (m, 1 H), 7.30–7.24 (m, 1 H), 7.18–7.12 (m, 1 H), 3.88 (t, J = 8.2 Hz, 2 H), 2.86 (t, J = 8.3 Hz, 2 H), 2.65 (t, J = 7.6 Hz, 2 H), 1.76 (m, 2 H), 1.00 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 161.0, 136.7, 128.8, 125.7, 124.4, 120.3, 120.0, 116.83, 111.9, 48.2, 37.5, 20.2, 19.3, 13.9; UV (EtOH) λ_{max} 238, 320 nm; IR (KBr) 1620, 1600 cm^{-1}; LRMS m/z 212 (M^+, 30), 211 (16), 197 (29), 184 (100), 183 (23), 155 (33).

Reaction of Imine 9a with Oxalyl Chloride. Synthesis of Dimer 11. Dry Et_3N (0.076 mL, 5.48 mmol) was added to a stirred solution of imine **9a**[12] (505 mg, 2.74 mmol) in dry THF (25 mL) cooled at −50 °C, and a solution of oxalyl chloride (0.024 mL, 2.744 mmol) in THF (15 mL) was then added dropwise. After 15 min at −50 °C, the temperature was slowly raised to 40 °C, and the solution was stirred for 30 min. The solvent was concentrated in vacuo, the residue was dissolved in H_2O–AcOEt, and the organic phase was dried over Na_2SO_4 and evaporated in vacuo. Column chromatography (silica gel, 1:1 AcOEt–$CHCl_3$) of the residue afforded 40 mg (6%) of pyrrolinedione **8a**[12] and 232 mg (40%) of dimer **11**, mp 165–166 °C. Spectroscopic data for dimer **11**: ^1H NMR δ 7.51–7.48 (m, 1 H), 7.25–7.11 (m, 2 H), 6.78–6.75 (m, 2 H), 5.21 (d, J = 1.9 Hz, 1 H), 5.22–5.02 (m, 1 H), 4.69 (d, J = 1.9 Hz, 1 H), 3.25–3.14 (m, 1 H), 3.04–2.91 (m, 1 H), 2.84–2.76 (m, 1 H); ^{13}C NMR δ 164.1, 136.9, 135.4, 129.4, 126.1, 123.8, 120.4, 118.88, 112.5, 112.0, 102.2, 41.9, 20.2; UV (EtOH) λ_{max} 230, 306 nm; IR (KBr) 3320, 1630 cm^{-1}; LRMS (FAB) m/z 423 (M^+ + 1).

2,3,5,6-Tetrahydro-2,3-dioxoindolizino[8,7-*b*]indole (8a). Methyl chlorooxalate (0.5 mL, 5.435 mmol) was added dropwise with a syringe to a solution of 3,4-dihydro-1-methyl-β-carboline (**9a**;[12] 1.00 g, 5.435 mmol) and dry pyridine (429 mL, 5.435 mmol) in dry THF (60 mL) cooled at −20 °C. At the end of the addition the solution was stirred for 20 min at −15 °C, 3 h at rt, and 30 min at 40 °C. The reaction mixture was filtered and concentrated in vacuo, and the residue was column chromatographed (silica gel, 1:1 $CHCl_3$–AcOEt) to afford a red product and a more polar fraction. The latter was evaporated in vacuo, dissolved in toluene (100 mL), mixed with silica gel (4 g), and refluxed for 1 h. The mixture was filtered, the red solid was washed with 20:1 CH_2Cl_2–MeOH, the extracts were added to the red solid obtained by chromatography, and the solvent was evaporated to afford **8a** (940 mg, 73%) as a red solid, mp 238–239 °C (lit.[12] mp 223 °C).

1-Ethyl-2,3,5,6-tetrahydro-2,3-dioxoindolizino[8,7-*b*]indole (8b). (a) By Reaction of 9b with Oxalyl Chloride. To a cool (−50 °C) suspension of **9b**·HCl (650 mg, 2.61 mmol) in dry DME (60 mL) was added first pyridine (0.68 mL, 8.72 mmol) and then (dropwise by syringe) oxalyl chloride (0.25 mL, 2.85 mmol); stirring was maintained for 10 min at −50 °C, 30 min at rt, and 15 min at 40 °C. Concentration in vacuo yielded a residue which was dissolved in CH_2Cl_2. The solution was washed with saturated $CuSO_4$ solution and dried over Na_2SO_4, and evaporation of the solvents in vacuo and crystallization of the residue from MeOH afforded **8b** (306 mg, 44%) as red crystals: mp 227–228 °C; ^1H NMR (DMSO-d_6) δ 11.51 (bs, 1 H), 7.73–7.70 (m, 1 H), 7.60–7.56 (m, 1 H), 7.41–7.35 (m, 1 H), 7.18–7.12 (m, 1 H), 3.75 (t, J = 6.3 Hz, 2 H), 3.18 (t, J = 6.3 Hz, 2 H), 2.54 (q, J = 7.5 Hz, 2 H), 1.06 (t, J = 7.4 Hz, 3 H); UV (EtOH) λ_{max} 222, 255, 289, 354, 447 nm; IR (KBr) 3360, 1710, 1685 cm^{-1}; LRMS m/z 266 (M^+, 100), 251 (33), 223 (28), 210 (32), 195 (30).

(b) By Reaction of 9b with Methyl Chlorooxalate. Pyridine (0.26 mL, 3.27 mmol) was added by syringe to a solution of imine **9b** (630 mg, 2.97 mmol) in dry THF (40 mL). The mixture was cooled (−40 °C), treated dropwise with methyl chlorooxalate (0.3 mL, 3.269 mmol), allowed to reach rt, and stirred for a further 8 h. Evaporation and chromatography (silica gel column, 1:1 $CHCl_3$–AcOEt) afforded a red solid (**8b**) and a residue. Silica gel (4 g) was added to a solution of this residue in toluene (100 mL), and the mixture was refluxed for 3 h. After cooling to rt and filtration, the collected solid was washed with 20:1 CH_2Cl_2–MeOH until the red color had disappeared. Evaporation in vacuo afforded a red solid (**8b**) which was pooled with that isolated by chromatography (joint yield 640 mg, 81%).

1-Bromo-2,3,5,6-tetrahydro-2,3-dioxoindolizino[8,7-*b*]indole (8c). To a cooled (0 °C), stirred solution of **8a**[12] (1.95 g, 8.19 mmol) in CH_2Cl_2 (150 mL) and MeOH (10 mL) was added dropwise a

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solution of bromine (2.00 g, 12.5 mmol) in CH_2Cl_2 (20 mL). Stirring was continued for 5 min. The reaction mixture was washed with 20% sodium metabisulfite, $CuSO_4$ saturated solution, and water and was dried over Na_2SO_4. The solvent was then evaporated in vacuo to afford **8c** (2.41 g, 93%) as a dark solid: mp >325 °C dec; ^1H NMR (DMSO-d_6) δ 11.56 (s, 1 H), 7.75–7.65 (m, 2 H), 7.44–7.38 (m, 1 H), 7.19–7.13 (m, 1 H), 3.79 (t, J = 6.4 Hz, 2 H), 3.20 (t, J = 6.4 Hz, 2 H); UV (EtOH) λ_{max} 222, 256, 366, 452, 488 nm; IR (KBr) 3360, 1740, 1705, 1610 cm^{-1}; LRMS m/z 318 (M^+, 100), 316 (M^+, 93), 290 (19), 288 (17).

1-Chloro-2,3,5,6-tetrahydro-2,3-dioxoindolizino[8,7-*b*]indole (8d). NCS (123 mg, 0.924 mmol) was added to a suspension of **8a**[12] (200 mg, 0.840 mmol), CH_2Cl_2 (50 mL), and MeOH (5 mL), and the mixture was stirred for 2 h at rt. After evaporation of the solvent in vacuo without heating, the residue was crystallized from AcOEt to afford **8d** (187 mg, 82%): mp >320 °C; ^1H NMR (DMSO-d_6) δ 11.74 (s, 1 H), 7.78–7.74 (m, 1 H), 7.65–7.62 (m, 1 H), 7.46–7.40 (m, 1 H), 7.20–7.15 (m, 1 H), 3.80 (t, J = 6.4 Hz, 2 H), 3.23 (t, J = 6.4 Hz, 2 H); ^{13}C NMR (DMSO-d_6) δ 175.7, 158.1, 150.7, 141.8, 128.0, 124.7, 124.6, 121.4, 121.2, 121.1, 113.5, 94.7, 36.8, 20.2; UV (EtOH) λ_{max} 254, 366, 450, 488 nm; IR (KBr) 3390, 1730, 1695, 1580 cm^{-1}; LRMS m/z (%) 274 (M^+, 32), 272 (M^+, 100), 244 (64).

General Procedure for the Reaction of Pyrrolinediones with Benzyne.[8] This procedure has been described previously.[16]

Reaction of Chloroisoquinoline–Pyrrolinedione 3b with Benzyne. A suspension of benzenediazonium 2-carboxylate prepared from anthranilic acid (274 mg, 2 mmol) and isoamyl nitrite (370 mg, 3.6 mmol) was added dropwise to a refluxing solution of **3b** (100 mg, 0.34 mmol) in DME (30 mL) via the general procedure. The solvent was evaporated in vacuo and the residue chromatographed on silica gel (100:1, CH_2Cl_2–MeOH) to afford 56 mg (48%) of 13-chloro-2,3-dimethoxy-8-oxyprotoberberine (**5b**): mp 181–182 °C (MeOH); ^1H NMR δ 8.51–8.47 (m, 1 H), 8.12–8.08 (m, 1 H), 7.90 (s, 1 H), 7.78–7.75 (m, 1 H), 7.59–7.55 (m, 1 H), 6.79 (s, 1 H), 4.29 (t, J = 5.8 Hz, 2 H), 3.97 (s, 3 H), 3.95 (s, 3 H), 2.90 (t, J = 5.8 Hz, 2 H); UV (EtOH) λ_{max} 336 nm; IR (KBr) 1635, 1600 cm^{-1}; LRMS m/z 343 (M^+, 35), 341 (M^+, 100), 328 (32), 326 (93).

Reaction of Bromoisoquinoline–Pyrrolinedione 3c with Benzyne. To a refluxing solution of **3c** (108 mg, 0.32 mmol) in dichloroethane (500 mL) was added a suspension of benzenediazonium 2-carboxylate in DME prepared from anthranilic acid (400 mg, 2.92 mmol) and isoamyl nitrite (644 mg, 5.5 mmol) via the general procedure, until **3c** had disappeared (TLC). The reaction mixture was concentrated in vacuo and chromatographed in silica gel (100:5, CH_2Cl_2–Et_2O) to afford 87 mg (67%) of 13-bromo-2,3-dimethoxy-8-oxyprotoberberine (**5c**) and 17 mg (14%) of 2,3-dimethoxy-13-phenyl-8-oxyprotoberberine (**5d**), which had the same spectroscopic characteristics as an authentic sample.[5] Data for **5c**: mp 146–148 °C (MeOH); ^1H NMR δ 8.50–8.46 (m, 1 H), 8.16–8.12 (m, 1 H), 7.91 (s, 1 H), 7.80–7.73 (m, 1 H), 7.58–7.51 (m, 1 H), 6.77 (s, 1 H), 4.29 (t, J = 5.7 Hz, 2 H), 3.97 (s, 3 H), 3.96 (s, 3 H), 2.89 (t, J = 5.8 Hz, 2 H); ^{13}C NMR δ 161.3, 150.4, 146.5, 136.4, 133.1, 132.6, 128.1, 127.3, 127.0, 124.9, 122.3, 115.1, 109.8, 99.4, 56.3, 56.0, 42.0, 29.2; UV (EtOH) λ_{max} 336 nm; IR (KBr) 1635, 1600 cm^{-1}; LRMS m/z 387 (M^+, 100), 385 (M^+, 98), 372 (84), 370 (85).

Reaction of Bromoisoquinoline–Pyrrolinedione 3c with 4,5-Dimethoxybenzyne (4b). To a refluxing suspension of **3c** (117 mg, 0.35 mmol) in dichloroethane (20 mL) was added a suspension of 4,5-dimethoxybenzenediazonium 2-carboxylate prepared from 2-amino-4,5-dimethoxybenzoic acid (517 mg, 2.71 mmol) and isoamyl nitrite (498 mg, 4.25 mmol) via the procedure described for benzenediazonium 2-carboxylate, with the same precautions. After 2 h at reflux the reaction mixture was concentrated in vacuo, and the residue was chromatographed in silica gel (100:0.3 CH_2Cl_2–MeOH) to afford 13-bromo-8-oxypseudopalmatine (**5e**) (68 mg, 44%) and 13-(3,4-dimethoxyphenyl)-8-oxypseudopalmatine (**5g**) (23 mg, 13%). Data for **5e**: mp 184–185 °C (MeOH); ^1H NMR δ 7.89 (s, 1 H), 7.87 (s, 1 H), 7.51 (s, 1 H), 6.77 (s, 1 H), 4.28 (m, 2 H), 4.07 (s, 3 H), 4.05 (s, 3 H), 3.96 (s, 6 H), 2.88 (t, J = 5.9 Hz, 2 H); ^{13}C NMR δ 160.6, 153.9, 150.1, 149.6, 146.5, 135.1, 132.4, 131.9, 122.5, 118.8, 115.0, 109.8, 108.1, 107.7, 99.0, 56.3, 56.3, 56.2, 56.0, 42.1, 29.3; UV (EtOH) λ_{max} 236, 262, 340 nm; IR (KBr) 1625, 1600 cm^{-1}; LRMS m/z 447 (M^+, 100), 445 (M^+, 98), 432 (46), 430 (45).

Data for **5g**: mp 226–228 °C (MeOH); ^1H NMR δ 7.91 (s, 1 H), 6.95 (d, J = 7.1 Hz, 1 H), 6.86–6.84 (m, 2 H), 6.72 (s, 1 H), 6.68 (s, 1 H), 6.53 (s, 1 H), 4.60–4.45 (m, 1 H), 4.27–4.18 (m, 1 H), 4.04 (s, 3 H), 3.93 (s, 3 H), 3.89 (s, 3 H), 3.80 (s, 3 H), 3.75 (s, 3 H), 3.26 (s, 3 H), 2.91 (m, 2 H); ^{13}C NMR δ 161.0, 153.2, 149.9, 149.1, 148.8, 148.6, 146.4, 133.7, 133.2, 132.2, 131.1, 124.3, 122.8, 118.8, 115.8, 115.0, 113.9, 112.1, 109.7, 107.8, 105.8, 56.2, 56.2, 56.0, 55.8, 55.3, 41.5, 29.1; UV (EtOH) λ_{max} 234, 254, 336 nm; IR (KBr) 1624, 1605 cm^{-1}; LRMS m/z 503 (M^+, 100), 488 (51).

Reaction of Ethyl-β-carboline–Pyrrolinedione (8b) with Benzyne. **8b** (112 mg, 0.42 mmol), benzenediazonium 2-carboxylate prepared from anthranilic acid (500 mg, 3.65 mmol), and isoamyl nitrite (640 mg, 5.48 mmol) afforded 81 mg (69%) of **7b**, which crystallized from MeOH as white crystals: mp 258–260 °C; ^1H NMR δ 8.54–8.50 (m, 1 H), 8.39 (bs, 1 H), 7.79–7.61 (m, 3 H), 7.49–7.43 (m, 2 H), 7.33–7.16 (m, 2 H), 4.49 (t, J = 6.1 Hz, 2 H), 3.20 (q, J = 7.6 Hz, 2 H), 3.07 (t, J = 6.2 Hz, 2 H), 1.56 (t, J = 7.6 Hz, 3 H); UV (EtOH) λ_{max} 232, 348 nm; IR (KBr) 3400, 1630 cm^{-1}; LRMS m/z (%) 314 (M^+, 67), 299 (100).

Reaction of Bromo-β-carboline–Pyrrolinedione (8c) with Benzyne. **8c** (100 mg, 0.32 mmol), anthranilic acid (250 mg, 1.82 mmol), and isoamyl nitrite (319 g, 2.73 mmol) afforded 14-bromonorketoyobirine (**7c**; 39 mg, 34%), 14-phenylnorketoyobirine (**7e**; 16 mg, 16%), and starting **8c** (10 mg, 10%). Data for **7c**: mp 165–166 °C (darkening); ^1H NMR δ 11.30 (s, 1 H), 8.31–8.28 (m, 1 H), 8.05–8.01 (m, 1 H), 7.89–7.82 (m, 1 H), 7.64–7.56 (m, 3 H), 7.28–7.22 (m, 1 H), 7.12–7.07 (m, 1 H), 4.39 (t, J = 5.7 Hz, 2 H), 3.06 (t, J = 5.8 Hz, 2 H); UV (EtOH) λ_{max} 352, 368, 386 nm; IR (KBr) 3400, 1635, 1605 cm^{-1}; LRMS m/z 366 (M^+, 92), 364 (M^+, 100), 285 (80).

Data for **7e**: mp 230–231 °C (EtOH); ^1H NMR δ 8.55–8.51 (m, 1 H), 7.67–7.64 (m, 3 H), 7.55–7.45 (m, 5 H), 7.14–7.07 (m, 2 H), 7.02–6.99 (m, 1 H), 6.92–6.89 (m, 1 H), 6.80 (bs, 1 H), 4.65 (t, J = 6.5 Hz, 2 H), 3.14 (t, J = 6.5 Hz, 2 H); ^{13}C NMR δ 162.27, 137.31, 136.90, 136.53, 132.21, 131.75, 129.83, 129.18, 128.97, 128.13, 128.00, 126.46, 124.87, 124.71, 123.87, 120.12, 118.96, 115.35, 111.08, 41.41, 19.85; UV (EtOH) λ_{max} 232, 348, 364, 382 nm; IR (KBr) 3440, 1653 cm^{-1}; LRMS m/z 362 (M^+, 100), 347 (29), 285 (34).

Reaction of Chloro-β-carboline–Pyrrolinedione (8d) with Benzyne. From **8d** (204 mg, 0.75 mmol) in dichloroethane (60 mL), anthranilic acid (1.00 g, 7.30 mmol), and isoamyl nitrite (1.280 g, 10.95 mmol)) as above. After chromatography (20:1, CH_2Cl_2–AcOEt), **7d** (74 mg, 63%) was isolated as a yellow solid: ^1H NMR (DMSO-d_6) δ 11.35 (s, 1 H), 8.33–8.30 (m, 1 H), 8.04–8.00 (m, 1 H), 7.90–7.83 (m, 1 H), 7.65–7.57 (m, 3 H), 7.28–7.22 (m, 1 H), 7.13–7.07 (m, 1 H), 4.42 (t, J = 6.4 Hz, 2 H), 3.09 (t, J = 6.3 Hz, 2 H); UV (EtOH) λ_{max} 234, 352, 338, 386 nm; IR (KBr) 3400, 1640, 1605 cm^{-1}; LRMS m/z 322 (M^+, 32), 320 (M^+, 100), 285 (41).

Synthesis of 2,3-Dimethoxy-8-oxyprotoberberine (5a). (a) By Hydrogenolysis of 13-Chloro-8-oxyprotoberberine (5b). NaOH (20 mg, 0.5 mmol) and 10% Pd–C (3 mg) were added to a solution of **5b** in MeOH (10 mL). The reaction flask was evacuated and connected to a balloon with hydrogen, and the reaction mixture was stirred for 3 h and then filtered through Celite. The filtrate was concentrated in vacuo, and the resulting residue was dissolved in CH_2Cl_2–H_2O. The organic phase was decanted and dried over Na_2SO_4, and the solvent was evaporated to afford **5a** in quantitative yield.

(b) By Hydrogenolysis of 13-Bromo-8-oxyprotoberberine (5c). A mixture of **5c** (40 mg, 0.10 mmol), NaOH (80 mg, 2 mmol), and 10% Pd–C (10 mg) in 40 mL of MeOH was stirred under H_2 (36 psi, 1 h). Workup as above afforded 28 mg (88%) of 2,3-dimethoxy-8-oxyprotoberberine (**5a**), which crystallized from MeOH (white crystals): mp 184–185 °C (lit.[10d] mp 181–182 °C).

Hydrogenolysis of 13-Bromo-8-oxypseudopalmatine (5e). From **5e** (19 mg, 0.043 mmol), NaOH (40 mg, 1 mmol), Pd–C (10%) (10 mg), MeOH (30 mL), and H_2 (36 psi, 1 h) was obtained 8-oxypseudopalmatine (**5f**) (15 mg, 96%), which was crystallized from MeOH as white crystals: mp 195–197 °C (lit.[9] mp 196–198 °C).

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Norketoyobirine (7a). (a) Hydrogenolysis of 7c. From **7c** (26 mg, 0.0721 mmol), NaOH (100 mg, 2.5 mmol), 10% Pd–C (10 mg), CH_2Cl_2 (3 mL), MeOH (40 mL), and H_2 (3 h) was obtained **7a**[17] (20 mg, 98% yield): mp 299–300 °C (MeOH) (Lit.[17] mp 299–300 °C).

(b) Hydrogenolysis of 7d. From **7d** (13 mg, 0.0405 mmol), NaOH (50 mg, 1.25 mmol), Pd–C (30 mg), CH_2Cl_2 (3 mL), MeOH (40 mL), and H_2 (balloon, 3 h) was obtained **7a**[17] (11 mg, 95% yield).

Decarbomethoxydehydrogambirtannine (6a). A solution of **7a** (15 mg, 0.05 mmol) in $POCl_3$ (2 mL) was refluxed for 2 h. Volatile materials were evaporated in vacuo, the residue was dissolved in MeOH (5 mL), and the solution was treated with $NaBH_4$ (150 mg, 3.95 mmol) at 0 °C. The mixture was stirred for a further 30 min at rt and then concentrated in vacuo. The residue was dissolved in H_2O and CH_2Cl_2, the organic phase was decanted and dried with Na_2SO_4, and the solvent was evaporated. Chromatography of the residue (20:1, CH_2Cl_2–ether) afforded (±)-decarbomethoxydihydrogambirtannine (**6a**) (10 mg, 70%), which was crystallized from MeOH–H_2O as white crystals: mp 191–192 °C (lit.[18] mp 193–195 °C).

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Registry No. **2b**, 91494-65-4; **3a**, 102421-38-5; **3b**, 119219-84-0; **3c**, 119219-85-1; **4a**, 462-80-6; **4b**, 54632-05-2; **5a**, 32255-47-3; **5b**, 119219-83-9; **5c**, 119219-86-2; **5d**, 15495-36-0; **5e**, 119219-88-4; **5f**, 10211-78-6; **5g**, 144181-88-4; (±)-**6a**, 61825-78-3; **7a**, 51598-75-5; **7b**, 144181-84-0; **7c**, 144181-85-1; **7d**, 144181-87-3; **7e**, 144181-86-2; **8a**, 96165-61-6; **8b**, 144181-81-7; **8c**, 144181-82-8; **8d**, 144181-83-9; **9a**, 525-41-7; **9b**, 68796-67-8; **11**, 144181-80-6; EtCOCl, 141-75-3; ClCOCOCl, 79-37-8; ClCOCOOMe, 5781-53-3; *N*-[2-(indol-3-yl)-ethyl]butyramide, 76049-36-0; tryptamine, 61-54-1; benzenediazonium 2-carboxylate, 1608-42-0; 4,5-dimethoxybenzenediazonium 2-carboxylate, 119219-87-3.

Supplementary Material Available: HRMS for compounds **3b**, **3c**, **5a**, **5d**, **5e**, **5g**, **7b**, **7d**, **7e**, and **8d** and elemental analyses for compounds **3b**, **3c**, **5b**, **5d**, **5g**, **7b**, **7c**, **7d**, **7e**, **8b**, **8c**, **8d**, **9b**, *N*-[2-(indol-3-yl)ethyl]butyrylamide, and **11** (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthesis of Racemic α-Amino Carboxamides via Lewis Acid-Mediated Reactions of α-Methoxyglycinamide Derivatives with Allylsilanes: Enzymatic Resolution to Optically Active α-Amino Acids

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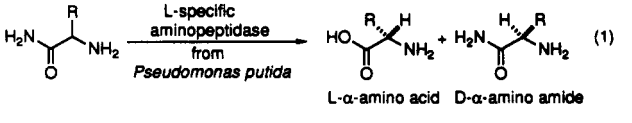
A short and expedient synthetic route to optically active, saturated and γ,δ-unsaturated α-amino acids is reported. The key step is a $BF_3{\cdot}OEt_2$-mediated reaction of allylsilanes with *N*-(alkoxycarbonyl)-α-methoxyglycinamides **11–15**, leading to the corresponding γ,δ-unsaturated α-aminocarboxamides. The genuine S_N1-character of this process with iminium ion **6** as intermediate is proven in the case of the glycine ester **10**. Thus, reaction of enzymatically resolved **10** with π-nucleophiles leads to racemic products. The most useful iminium precursors are the *N*-methoxyamides **12–14** providing good yields of coupling products. The most convenient N-protective group is the allyloxycarbonyl group. Deprotection proceeds via a Pd(0)-catalyzed transprotection to the corresponding BOC-protected analogues. Four examples of the enzymatic resolution of α-amino carboxamides, by using an L-specific aminopeptidase from *Pseudomonas putida*, are described in detail. Most notably, secondary *N*-methoxyamides are good substrates for the enzyme to provide the desired α-amino acids in high optical purity.

Introduction

The synthesis of α-amino acids remains a topic of considerable interest because of the ever growing importance of both natural and unnatural amino acids.[1] It is crucial that such compounds are available in enantiomerically pure form due to the divergent biological activities of the enantiomers.

Of the several methods known to obtain α-amino acids as pure enantiomers,[2] a particularly attractive method involves the use of an L-specific aminopeptidase to perform an enzymatic kinetic resolution of a racemic mixture of α-amino amides (eq 1).[3] This enzymatic reaction has been



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