Concise Enantioselective Synthesis and Attribution of the Absolute Configuration of Two-Carbon Bridge Methoxylated Cocaines and Pseudococaines

Daniele Simoni,*[,†] Marinella Roberti,[‡] Vincenza Andrisano,[‡] Monica Manferdini,[†] Riccardo Rondanin,[†] and Alan P. Kozikowski*[,§]

Dipartimento di Scienze Farmaceutiche, Università di Ferrara, Via Fossato di Mortara 17-19, 44100-Ferrara, Italy, Dipartimento di Scienze Farmaceutiche, Università di Bologna, Italy, and Georgetown Institute of Cognitive and Computational Sciences, 3970 Reservoir Road N.W., Washington, D.C. 20007-2197

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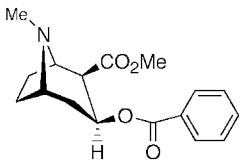
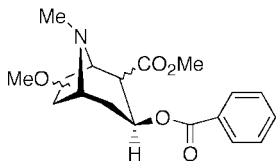
Cocaine (**1**) is currently the focus of intensive studies for reasons relating to both health and social concerns.[1] The discovery of cocaine antagonists or partial agonists may offer a strategy in the quest to identify agents for the treatment of substance abuse.[2]

Our own efforts to acquire a better understanding of the topology of the cocaine receptor with the aim toward identifying a possible cocaine antagonist led us to investigate modifications to various regions of this molecule.[3−6] To this regard, we reported that racemic two-carbon bridge methoxylated cocaines **2** were found to possess interesting pharmacological properties; in particular, some of these methoxylated derivatives were found to antagonize, albeit weakly, cocaine's ability to inhibit dopamine reuptake.[3] Recently, 6- and 7-hydroxy-2-carbomethoxy-3-aryltropanes as well as 6- and 7-methoxy-2-carbomethoxy-3-aryltropanes have been described.[7]



(-)-cocaine **(1)**



6- and 7-methoxylated cocaines and pseudococaines (±)-**2**

Since it has been well-documented by Carroll et al. that stereochemistry affects the binding of cocaine and its analogues and that, for example, the seven stereoisomers of cocaine are less potent than the natural product,[2a] we needed access to the enantiomers, as well as the knowledge of their absolute configuration, of our synthesized methoxycocaines **2**. In this context, we recently reported that pig liver esterase (PLE) allows facile enantioselective hydrolysis of racemic cocaine and cocaine analogues.[4] Herein, we now report a novel enantioselective approach for the preparation of two-carbon bridge methoxylated cocaine which in turn allows concomitant, facile attribution of their absolute configuration. It is noteworthy to observe that the absolute configuration of the majority of chiral tropane alkaloids is not known and most of the syntheses afford racemic mixtures.[8,9]

Results and Discussion

Retrosynthetic analysis suggested (Scheme 1) that chiral (6*R*)- and (6*S*)-2-carbomethoxytropinone derivatives (+)-**3** and (−)-**3** and the corresponding 7-methoxy isomers (+)-**4** and (−)-**4**, possessing the known configuration at the carbon atoms bearing the methoxy functionality, would constitute appropriate starting materials for our purpose. It was anticipated that carbomethoxylation of the known chiral 6-methoxytropinones (−)-**5** and (+)-**5**[10] would allow a facile access to the desired chiral 2-carbomethoxy derivatives **3** and **4**. Moreover, their stereoselective reduction could afford the ecgonine methyl ester derivatives (+)-**7a** and (+)-**8a** and, of course, the corresponding enantiomers (−)-**7a** and (−)-**8a**, together with the pseudoecgonine derivatives (−)-**9a**, (+)-**10a**, (+)-**9a**, and (−)-**10a**.

With this approach in mind, it was easy to imagine that absolute configuration of all the newly synthesized methoxycocaines and methoxypseudococaines could rest upon the known configuration of (−)-**5** and (+)-**5** and therefore could be unambiguously assigned. Thus, carbomethoxylation of (−)-**5** (Scheme 2) afforded in 65% yield the two regioisomers (+)-**3** and (+)-**4** bearing the methoxy function at the 6 and 7 carbon atoms, respectively. The structures of the chiral compounds were compared with those of the racemic methoxycocaines previously prepared by us.[3] Surprisingly, a precise rotation could not be established for the two β-keto esters (+)-**3** and (+)-**4**; this observation is probably the result of enolization.

In view of the fact that sodium amalgam reduction of 2-carbomethoxy-3-tropinone provides hitherto the best route to ecgonine methyl ester, the β-keto esters (+)-**3** and (+)-**4** were reduced with sodium amalgam to generate both the ecgonine-like derivatives (+)-**7a** and (+)-**8a** and the pseudoecgonine-like derivatives (−)-**9a** and (+)-**10a** in 15−32% and 38−60% yields, respectively. Even though this transformation was not stereoselective, the two isomers were readily individualized by TLC, and careful flash chromatography allowed their separation. Benzoylation of (+)-**7a**, (+)-**8a**, (−)-**9a**, and (+)-**10a** was performed using benzoyl chloride, triethylamine, and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) to provide (+)-**7b**, (+)-**8b**, (−)-**9b**, and (+)-**10b**. Interestingly, the (+)-6β-methoxytropinone (+)-**5**, afforded easily, and in the same manner as decribed above for the

† Università di Ferrara.
‡ Università di Bologna.
§ Georgetown Institute.

(1) (a) Woolverton, W. L.; Johnson, K. M. *Trends Pharmacol. Sci.* **1992**, *13*, 193. (b) Woolverton, W. L.; Kleven, M. S. *NIDA Res. Monogr.* **1988**, *88*, 160. (c) Gawin, F. H. *Science* **1991**, *251*, 1580.
(2) (a) Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1992**, *35*, 969 and references therein. (b) Carroll, F. I.; Kotian, P.; Dehghani, A.; Gray, J. L.; Kuzemko, M. A.; Parhan, K. A.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1995**, *38*, 379. (c) Meltzer, P. C.; Liang, A. Y.; Madras, B. K. *J. Med. Chem.* **1994**, *37*, 2001. (d) Newman, A. H.; Allen, A. C.; Izenwasser, S.; Katz, J. L. *J. Med. Chem.* **1994**, *37*, 2258.
(3) Simoni, D.; Stoelwinder, J.; Kozikowski, A. P.; Johnson, K. M.; Bergmann, J. S.; Ball, R. G. *J. Med. Chem.* **1993**, *36*, 3975.
(4) Kozikowski, A. P.; Simoni, D.; Baraldi, P. G.; Lampronti, I.; Manfredini, S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 441.
(5) Kozikowski, A. P.; Simoni, D.; Manfredini, S.; Roberti, M.; Stoelwinder, J. *Tetrahedron Lett.* **1996**, *37*, 5333.
(6) Kozikowski, A. P.; Eddine Saiah, M. K.; Johnson, K. M.; Bergmann, J. S. *J. Med. Chem.* **1995**, *38*, 3086 and references therein.
(7) Chen, Z.; Meltzer, P. C. *Tetrahedron Lett.* **1997**, *38*, 1121.
(8) Lounasmaa, M.; Tamminem, T. *Alkaloids* **1993**, *44*, 1.
(9) Majewski, M.; Lazny, R. *J. Org. Chem.* **1995**, *60*, 5825.
(10) Fodor, G.; Soti, F. *J. Chem. Soc., Perkin Trans. 1* **1965**, 6830.

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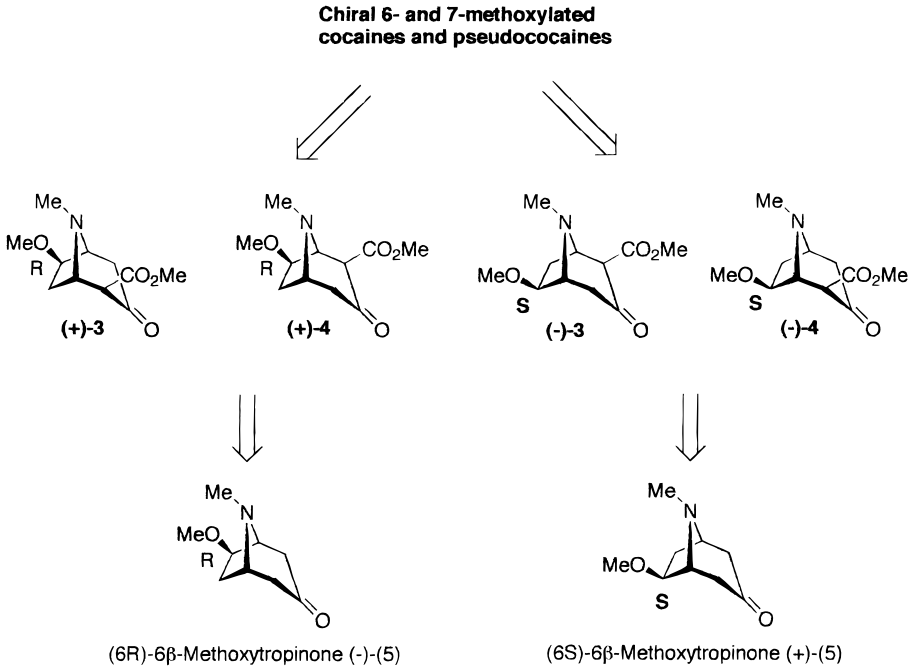
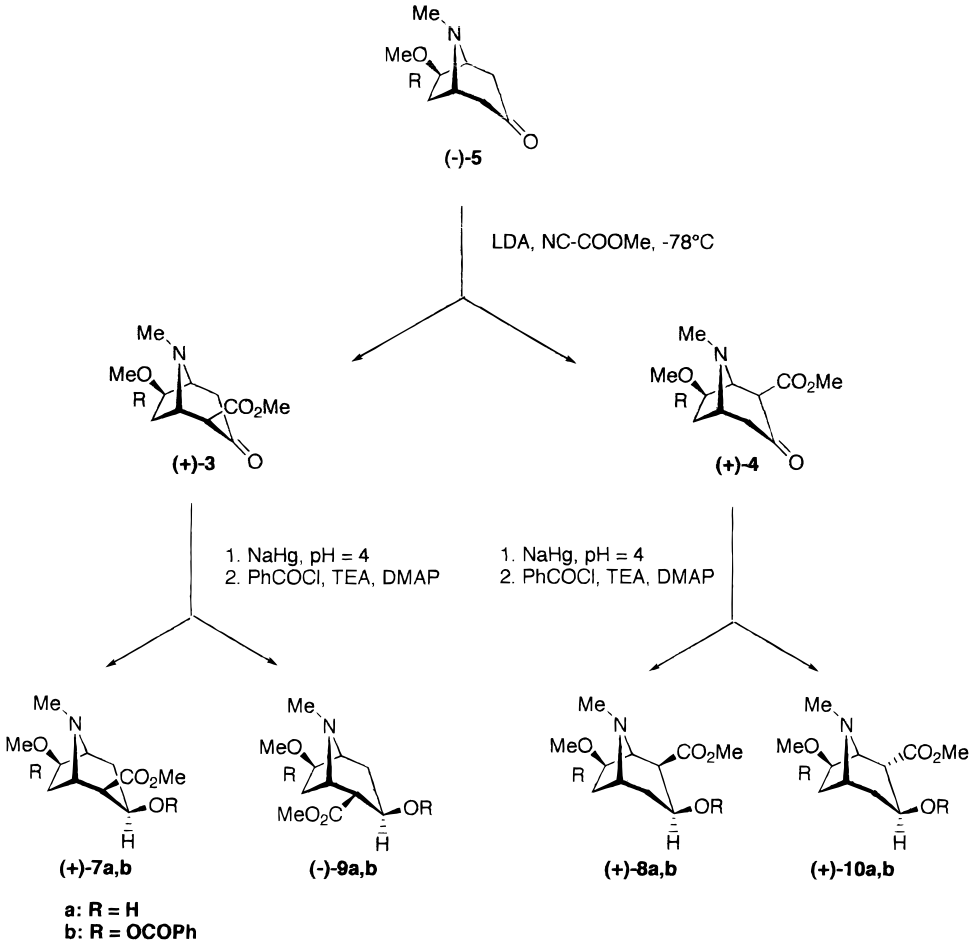
Scheme 1

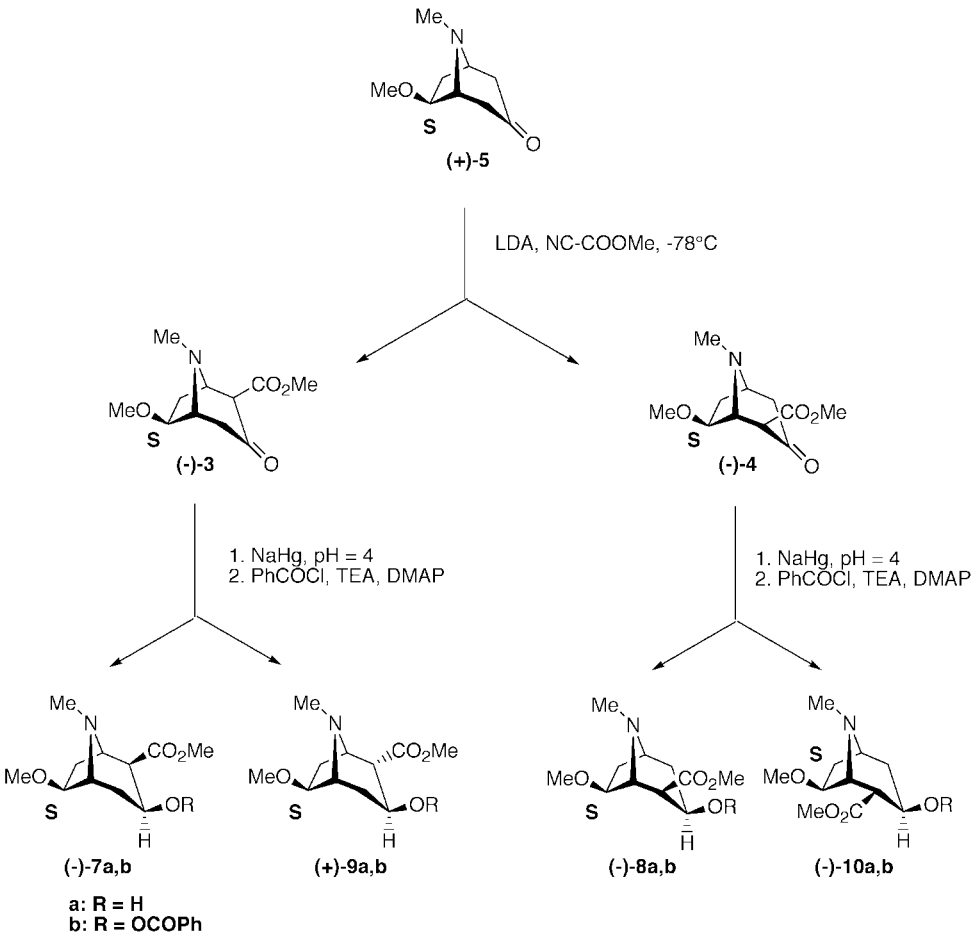


Scheme 2



methoxytropinone (−)-**5** (Scheme 3), the new 6*S* and 7*S* enantiomers (−)-**7b**, (−)-**8b**, (+)-**9b**, and (−)-**10b**. Structural assignments of the new analogues were made by analysis of their ^{1}H and ^{13}C NMR spectra and by comparison with the spectral data of the racemic compounds previously reported by us.[3] Briefly, positions of all protons in the tropane ring were assigned on the basis of proton-decoupling experiments, starting from the diagnostic C-3 proton that appears as a multiplet in the 4.4−5.5 ppm region. The stereochemical relationship between H-2 and H-3 was assigned on the basis of the coupling between these protons. In all cases the chiral

Scheme 3



methoxycocaines were found to have coupling constants very similar to those reported by Carroll for cocaine and its isomers.[11] All new synthetic enantiomers showed enantiomeric excess in the range of 92−99%.[12]

Expectedly, the optical rotations of (+)-6β-methoxypseudococaine (**7b**) and (+)-7β-methoxycocaine (**8b**) in the positive direction were of equal magnitude to those of (−)-6β-methoxycocaine (**7b**) and (−)-7β-methoxycocaine (**8b**) which have values in the negative direction. Similarly, optical rotations of compounds (−)-**9b** and (+)-**10b** showed absolute values of equal magnitude as those of their enantiomers (+)-**9b** and (−)-**10b**. This observation alone serves to establish the optical purity of the enantiomers, as well as the optical purity of the 6- and 7-methoxy-2-carbomethoxy-3-tropinones **3** and **4**. Compounds (+)-**7b**, (+)-**10b**, (−)-**7b**, and (−)-**10b** showed optical rotations very similar to those reported by us previously.[4]

Thus, combining elements of the chemistry developed recently by us on methoxycocaines[3−5] and chemistry described by Carrol et al.[11] for the preparation of cocaine and its stereoisomers, we were able to gain facile access to both enantiomers of 6- and 7-methoxycocaines and 6- and 7-methoxypseudococaines.

In conclusion, the use of the optical antipodes of the 6β-methoxytropinone permits the synthesis of all enantiomers of the 6β- and 7β-methoxycocaines as well as of the diastereoisomers 6β- and 7β-methoxypseudococaines. The described approach is amenable for multigram-scale preparation in the laboratory. It is noteworthy that the synthetic methodology described above also allowed the assignment of absolute configuration of each synthetic enantiomer with ease. As well, owing to the easy manipulation of the methoxy functionality as well as the simplicity of the developed methodology, one may expect its broad application for the preparation of a variety of chiral cocaines derivatized on the two-carbon bridge.

Experimental Section

General Procedures. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 250 MHz. Chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane. IR spectra of samples were measured as thin films on NaCl plates or in KBr pressed disks for crystalline samples. Gas chromatography was performed on a commercially available chiral column: the chromatographic column was a Chiral OD (250- × 4.6-mm i.d.), Daicel Chemical Industries, Ltd. Optical rotations were measured at ambient temperature, in methanol solution, at the sodium line. Column chromatography was performed on 230−400 mesh silica gel. Thin-layer chromatography (TLC) was performed with Merck F-254 silica gel plastic sheets.

General Procedure for the Preparation of the Carbomethoxytropinone Derivatives (+)-3, (−)-3, (+)-4, and (−)-4. A solution of *n*-BuLi in hexane (1.76 mL, 1.4 M concentrated, 2.46 mmol) was added to a solution of diisopropylamine (0.35 mL, 2.46 mmol) in THF (5 mL) at 0 °C, and the mixture stirred for 25 min. After the mixture cooled to −78 °C, the appropriate tropinone derivative **5** (0.378 g, 2.24 mmol) dissolved

(11) (a) Lewin, A. H.; Naseree, T.; Carrol, F. I. *J. Heterocycl. Chem.* **1987**, *24*, 19. (b) Carroll, F. I.; Lewin, A. H.; Abraham, P.; Parham, K.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1991**, *34*, 883.

(12) The enantiomeric excess for the newly synthesized ecgonine and pseudoecgonine methyl ester derivatives was determined by their conversion to the corresponding α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) esters by treatment with (+)-MTPA chloride as described in the literature. For the cocaine- and pseudococaine-like derivatives, enantiomeric excess was determined by ^{1}H NMR studies employing the chiral shift reagent Eu(Tfc)$_3$ (3−5% molar concentration) and by gas chromatography on a commercially available chiral column.

in THF (10 mL) was added dropwise, and the resulting mixture stirred for a further 45 min at −78 °C. Methyl cyanoformate (0.231 mL, 2.91 mmol) was added quickly to the enolate, the mixture was stirred at −78 °C for 30 min, and then the reaction was quenched with a solution of $AgNO_3$ (0.33 g, 1.94 mmol) in THF (2 mL), water (1 mL), and AcOH (0.5 mL). The mixture was warmed to room temperature, treated with concentrated ammonia (5 mL) to dissolve Ag salts, and extracted with $CHCl_3$ (3 × 15 mL). The combined extracts were dried (Na_2SO_4), the solvent was removed in vacuo, and the residue was purified by flash chromatography (9.5:0.5 EtOAc−MeOH).[13]

Optical rotations for derivatives (+)-**3**, (−)-**3**, (+)-**4**, and (−)-**4** were imprecise probably due to enolization. Some observed values are as follows. (+)-**3**: $[\alpha]^{25}_D = +5.5$ (*c* 2). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.91; H, 7.58; N, 6.05. (−)-**3**: $[\alpha]^{25}_D = -5.5$ (*c* 1.8). (+)-**4**: $[\alpha]^{25}_D = +14.0$ (*c* 2). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.97; H, 7.78; N, 6.16. (−)-**4**: $[\alpha]^{25}_D = -14.5$ (*c* 1.5).

General Procedure for the Preparation of the Methoxyecgonine Derivatives (+)-7a, (−)-7a, (+)-8a, and (−)-8a and the Methoxypseudoecgonine Derivatives (−)-9a, (+)-9a, (+)-10a, and (−)-10a. The appropriate methoxytropinone **3** or **4** (2.3 g, 10.1 mmol) was dissolved in 32 mL of aqueous sulfuric acid (pH 3−4) and treated portionwise in 3.5 h with 330 g of sodium amalgam (1.5%) at 0 °C. The pH of the reaction mixture was maintained between 3 and 4 by the periodic addition of 30% sulfuric acid. Water was also added during the reaction in order to solubilize the sodium sulfate. The mixture was poured in a separatory funnel, the mercury was recovered, the aqueous solution was basified with concentrated ammonium hydroxide (pH = 9), and the resulting mixture was extracted with chloroform (3 × 100 mL). The aqueous layer was concentrated to a small volume and extracted again with chloroform (2 × 100 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo. The crude mixture obtained after evaporation of the solvent was subjected to flash column chromatography.

(+)-7a: oil, $[\alpha]^{25}_D = +24.5$ (*c* 2), ee 94%, 15% yield, flash chromatography (silica gel/ethyl acetate−diethyl ether−methanol, 1/1/0.1 v/v; IR 3420, 2947, 1732, 1440, 1377, 1199, 1167 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87−1.97 (m, 3H), 2.10−2.18 (m, 1H), 2.42 (s, 3H), 2.70 (m, 1H), 3.24 (m, 1H), 3.27 (s, 3H), 3.61 (br, 1H), 3.75 (s, 3H), 3.75−3.82 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 32.4, 34.5, 37.5, 41.8, 50.5, 51.8, 56.9, 64.4, 66.1, 86.4, 174.2. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.81; H, 8.31; N, 6.17.

(−)-7a: oil, $[\alpha]^{25}_D = -24.3$ (*c* 2), ee 93%, 19% yield; IR, ^1H NMR, and ^{13}C NMR spectra are the same as reported for (+)-**7a**.

(+)-8a: oil, $[\alpha]^{25}_D = +50.5$ (*c* 1.5), ee 99%, 32% yield, flash chromatography (silica gel/ethyl acetate−diethyl ether−methanol, 1/1/0.4 v/v); IR (neat) 3400, 1730, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87−2.15 (m, 4H), 2.40 (s, 3H), 2.85 (m, 1H), 3.31 (s, 3H), 3.32 (m, 1H), 3.52−3.64 (m, 2H), 3.76 (s, 3H), 3.73−3.78 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 32.3, 34.8, 37.5, 41.6, 50.3, 52.1, 56.9, 66.0, 66.1, 84.3, 174.1. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.68; H, 8.39; N, 6.11.

(−)-8a: oil, $[\alpha]^{25}_D = -50.1$ (*c* 1.8), ee 98%, 25% yield; IR, ^1H NMR, and ^{13}C NMR spectra are the same as reported for (+)-**8a**.

(−)-9a: oil, $[\alpha]^{25}_D = -7.45$ (*c* 2), ee 97%, 53% yield, flash chromatography (silica gel/ethyl acetate−diethyl ether−methanol, 1/1/0.2 v/v); IR (neat) 3450, 1735, 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (m, 2H), 1.95 (m, 2H), 2.55 (s, 3H), 2.71 (dd, 1H, $J_1 = 3.2$ Hz, $J_2 = 10.7$ Hz), 2.96 (br, 1H), 3.29 (s, 3H), 3.32 (m, 1H), 3.61 (m, 2H), 3.73 (s, 3H), 3.90 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 30.8, 34.7, 35.8, 48.1, 52.1, 56.6, 61.1, 63.9, 64.5, 84.2, 174.1. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.79; H, 8.28; N, 6.05.

(+)-9a: oil, $[\alpha]^{25}_D = +7.05$ (*c* 2), ee 92%, 62% yield; IR, ^1H NMR, and ^{13}C NMR spectra are the same as reported for (−)-**9a**.

(+)-10a: oil, $[\alpha]^{25}_D = +39.5$ (*c* 1.2), ee 99%, 38% yield, flash chromatography (silica gel/ethyl acetate−chloroform−ethanol, 1/1/0.5 v/v); IR (neat) 3450, 1730, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68 (m, 2H), 1.98 (m, 2H), 2.52 (s, 3H), 2.61 (br, 1H), 2.73 (dd, 1 H, $J_1 = 3.2$ Hz, $J_2 = 10.5$ Hz), 3.24 (s, 3H), 3.35 (m, 1H), 3.52 (d, 1H, $J = 3.2$ Hz), 3.62 (m, 1H), 3.77 (s, 3H), 3.94 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 32.0, 35.7, 37.5, 47.2, 52.1, 56.6, 58.7, 64.5, 65.2, 82.2, 174.2. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.63; H, 8.33; N, 6.25.

(−)-10a: oil, $[\alpha]^{25}_D = -38.5$ (*c* 2), ee 97%, 45% yield; IR, ^1H NMR, and ^{13}C NMR spectra are the same as reported for (+)-**10a**.

General Procedure for the Preparation of the Methoxycocaine Derivatives (+)-7b, (−)-7b, (+)-8b, and (−)-8b and the Methoxypseudococaine Derivatives (−)-9b, (+)-9b, (+)-10b, and (−)-10b. The appropriate ecgonine derivative (+)-**7a** or (+)-**8a** or the pseudoecgonine derivative (−)-**9a** or (+)-**10a** (0.6 g, 2.6 mmol) was dissolved in methylene dichloride and the solution cooled at 0 °C. Triethylamine (1.45 mL, 10 mmol), benzoyl chloride (0.45 mL, 3.9 mmol), and a catalytic amount of 4-(dimethylamino)pyridine were added. The reaction mixture was stirred for 10 min at 0 °C and then for 3 h at room temperature. The solution was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residual oil was subjected to flash chromatography eluting with ethyl acetate/methanol.

(+)-7b: oil, $[\alpha]^{25}_D = +18.3$ (*c* 2), ee 93%, yield 66%; IR (neat) 2955, 1753, 1714, 1458, 1284, 1130, 1091 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.91 (m, 1H), 2.14 (dd, 1H, $J_1 = 6.7$ Hz, $J_2 = 14.3$ Hz), 2.22 (m, 1H), 2.39 (dd, 1H, $J_1 = 5.5$ Hz, $J_2 = 14.1$ Hz), 2.47 (s, 3H), 2.94 (m, 1H), 3.30 (s, 3H), 3.35 (m, 1H), 3.71 (s, 3H), 3.78 (m, 1H), 3.96 (dd, 1H, $J_1 = 3.2$ Hz, $J_2 = 6.8$ Hz), 5.02 (m, 1H), 7.43 (m, 2H), 7.54 (m, 1H), 8.01 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 32.9, 34.8, 41.7, 49.1, 51.2, 56.7, 64.9, 66.1, 66.6, 86.0, 128.2, 129.5, 130.0, 132.8, 165.9, 170.3. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 65.09; H, 7.22; N, 4.47.

(−)-7b: oil, $[\alpha]^{25}_D = -17.8$ (*c* 2), ee 90%, 55% yield; IR, ^1H NMR, and ^{13}C NMR spectra are the same as reported for (+)-**7b**.

(+)-8b: oil, $[\alpha]^{25}_D = +14.0$ (*c* 1), ee 99%, yield 78%; IR (neat) 2947, 1755, 1722, 1454, 1284, 1116 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (m, 1H), 2.12−2.18 (m, 2H), 2.38 (dd, 1H, $J_1 = 3.2$ Hz, $J_2 = 11.9$ Hz), 2.48 (s, 3H), 3.10 (m, 1H), 3.34 (s, 3H), 3.47 (m, 1H), 3.63 (m, 1H), 3.72 (s, 3H), 3.97 (dd, 1H, $J_1 = 3.9$ Hz, $J_2 = 6.6$ Hz), 4.99 (m, 1H), 7.43 (m, 2H), 7.55 (m, 1H), 8.03 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 34.4, 35.2, 41.8, 48.3, 51.5, 57.2, 61.7, 66.9, 69.5, 85.8, 128.4, 129.8, 130.2, 133.1, 166.2, 170.2. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.79; H, 7.15; N, 4.25.

(−)-8b: oil, $[\alpha]^{25}_D = -14.0$ (*c* 1), ee 99%, 63% yield; IR, ^1H NMR, and ^{13}C NMR spectra are the same as reported for (+)-**8b**.

(−)-9b: oil, $[\alpha]^{25}_D = -30.3$ (*c* 1), ee 95%, yield 89%; IR (neat) 2955, 1737, 1720, 1599, 1452, 1284, 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (m, 1H), 1.93 (m, 1H), 2.06 (m, 1H), 2.28 (dd, 1H, $J_1 = 7.2$ Hz, $J_2 = 14.2$ Hz), 2.60 (s, 3H), 3.12 (dd, 1H, $J_1 = 2.8$ Hz, $J_2 = 10.7$ Hz), 3.31 (m, 1H), 3.31 (s, 3H), 3.65−3.58 (m, 1H), 3.65 (s, 3H), 3.87 (dd, 1H, $J_1 = 2.8$ Hz, $J_2 = 7.2$ Hz), 5.32 (m, 1H), 7.41 (m, 2H), 7.54 (m, 1H), 7.97 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 28.3, 34.1, 35.5, 44.6, 51.7, 56.4, 61.7, 63.4, 67.8, 83.9, 128.1, 129.4, 129.9, 132.7, 165.3, 172.1. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.82; H, 6.88; N, 4.03.

(+)-9b: oil, $[\alpha]^{25}_D = +29.6$ (*c* 1), ee 93%, 85% yield; IR, ^1H NMR, and ^{13}C NMR spectra are the same as reported for (−)-**9b**.

(+)-10b: mp 82−83 °C (diethyl ether−hexane), $[\alpha]^{25}_D = +39.3$ (*c* 2), ee 99%, yield 77%; IR (KBr) 2951, 1737, 1716, 1604, 1456, 1440, 1280 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.78 (m, 1H), 2.0 (m, 2H), 2.19 (dd, 1H, $J_1 = 7.3$ Hz, $J_2 = 13.7$ Hz), 2.19 (s, 3H), 3.15 (dd, 1H, $J_1 = 3.1$ Hz, $J_2 = 10.9$ Hz), 3.26 (s, 3H), 3.40 (m, 1H), 3.54 (d, 1H, $J = 3.1$ Hz), 3.68 (s, 3H), 3.93 (dd, 1H, $J_1 = 3.1$ Hz, $J_2 = 7.3$ Hz), 5.36 (m, 1H), 7.41 (m, 2H), 7.54 (m, 1H), 7.97 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 30.1, 35.8, 37.2, 44.2, 51.9, 56.6, 58.6, 66.1, 67.7, 81.6, 128.2, 129.5, 130.1, 132.8, 165.4, 172.1. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.66; H, 7.22; N, 4.18.

(−)-10b: mp 82−83 °C (diethyl ether−hexane), $[\alpha]^{25}_D = -39.0$ (*c* 1.5), ee 98%, 85% yield; IR, ^1H NMR, and ^{13}C NMR spectra are the same as reported for (+)-**10b**.

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(13) Structures of the carbomethoxy tropinone derivatives (−)-**3**, (+)-**3**, (−)-**4**, and (+)-**4** were confirmed at ^1H NMR where the presence of double singlets (due to enolization) at about 2.4 ppm (NCH_3), 3.3 ppm (OCH_3), and 3.7 ppm ($COOCH_3$) is evident.