Enantioselective Synthesis of Unnatural (*S*)-(+)-Cocaine

Jae Chol Lee, Kwangho Lee, and Jin Kun Cha*

Department of Chemistry, The University of Alabama, Tuscaloosa, Alabama 35487

cha@jkc.ch.ua.edu

Received March 13, 2000

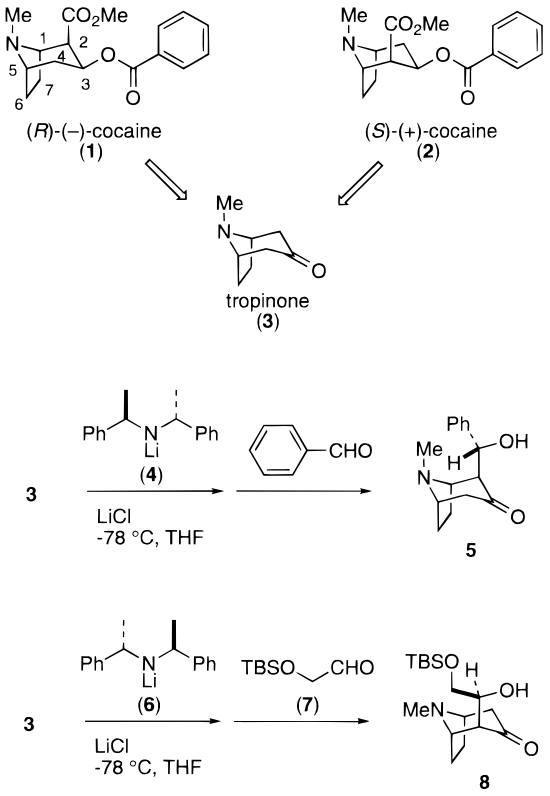
Introduction

Since Willstätter's first synthesis of (*R*)-(−)-cocaine (**1**) in 1923,[1] a substantial amount of research has been devoted to the synthesis and biosynthesis of cocaine, the most prominent member of the tropane alkaloids isolated from different plant sources.[2] As cocaine abuse has emerged as one of the serious societal problems, notoriety is attached to cocaine. Development of antagonists and partial agonists of cocaine, which could find use in the treatment of cocaine abuse, has recently attracted considerable attention.[3] Herein we report a stereoselective synthesis of (*S*)-(+)-cocaine (**2**), the unnatural enantiomer, starting from the known and commercially available tropinone (**3**). The underlying strategy would not only provide access to enantiomerically pure analogues of cocaine and other medicinally significant tropane alkaloids, but also be of general utility in asymmetric synthesis.

Results and Discussion

As part of ongoing applications of the oxyallyl [4 + 3] cycloaddition reactions, we recently required an efficient method for asymmetrization of the meso [4 + 3] cycloadducts.[4] A particularly attractive approach was found in enantioselective deprotonation of cyclic ketones, the full scope and utility of which have been elucidated by Koga, Simpkins, Majewski, and others.[5] For example, treatment of **3** with lithium (*R*,*R*)-bis(1-phenylethyl)amide (**4**) in the presence of lithium chloride, followed by benzaldehyde, was found to proceed in excellent (85−90%) enantiomeric excess to afford the exo-anti adduct **5** as a single diastereomer (Scheme 1).[6] Despite the apparent structural similarity of **5** to (−)-cocaine (**1**), surprisingly, no elaboration has been reported to date. Toward this end, enantioselective deprotonation of **3** by the action of lithium (*S*,*S*)-bis(1-phenylethyl)amide (**6**) in the presence of lithium chloride, followed by in situ trapping with a known aldehyde (**7**),[7] afforded the aldol product **8** (mp 72−73 °C) as a single diastereomer in 72% yield.[8] Its ee was determined to be 90−92% by ^{1}H NMR studies with the chiral shift reagent, (+)-Eu(tfc)$_3$. While inconsequential, the exo-anti configuration for C-1′ is assigned on the basis of the previous work of Majewski[6b] and steric considerations for the transition state involved. At the outset, we decided to eschew direct carbomethoxylation of **3**, since the resulting β-ketoester had been shown to exist as a mixture of keto and enol tautomers.

Scheme 1



Following silylation (96%) of **8**, stereoselective reduction of the keto group was achieved by lithium in liquid ammonia to give alcohol **10** in 97% yield (Scheme 2). Benzoate **11** was then obtained by standard esterification (85%). The thermodynamically unstable axial carboxylate group was then established by RuO_4 oxidation[9] of the diol **12** (not isolated) obtained by desilylation of **11**. This final

(1) Willstätter, R.; Wolfes, O.; Mäder, H. *Ann.* **1923**, *434*, 111.

(2) For recent reviews, see: (a) Lounasmaa, M.; Tamminen, T. *The Alkaloids* **1993**, *44*, 1. (b) Robins, R. J.; Walton, N. J. *The Alkaloids* **1993**, *44*, 115. (c) Lounasmaa, M. *The Alkaloids* **1988**, *33*, 1.

(3) See, inter alia: (a) Kozikowski, A. P.; Araldi, G. L.; Ball, R. G. *J. Org. Chem*. **1997**, *62*, 503. (b) Kozikowski, A. P.; Eddine Saiah, M. K.; Johnson, K. M.; Bergmann, J. S. *J. Med. Chem*. **1995**, *38*, 3086. (c) Carroll, F. I.; Kotian, P.; Dehghani, A.; Gray, J. L.; Kuzemko, M. A.; Parham, K. A.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem*. **1995**, *38*, 379. (d) Giros, B.; Wang, Y.-M.; Suter, S.; McLeskey, S. B.; Pifl, C.; Caron, M. G. *J. Biol. Chem*. **1994**, *269*, 15985. (e) Davies, H. M. L.; Saikali, E.; Huby, N. J. S.; Gilliatt, V. J.; Matasi, J. J.; Sexton, T.; Childers, S. R. *J. Med. Chem*. **1994**, *37*, 1262. (f) Clarke, R. L.; Daum, S. J.; Gambino, A. J.; Aceto, M. D.; Pearl, J.; Levitt, M.; Cumiskey, W. R.; Bogado, E. F. *J. Med. Chem*. **1973**, *16*, 1260.

(4) Cf. Cho, S. Y.; Lee, J. C.; Cha, J. K. *J. Org. Chem*. **1999**, *64*, 3394 and references therein.

(5) For excellent reviews, see: (a) Simpkins, N. S. *Chem. Soc. Rev*. **1990**, 335. (b) Cox, P. J.; Simpkins, N. S. *Tetrahedron*: *Asymmetry* **1991**, *2*, 1. (c) Koga, K.; Shindo, M. *J. Synth. Org. Chem. Jpn*. **1995**, *53*, 1021. (d) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439.

(6) For enantioselective enolization of **3**, see: (a) Momose, T.; Toyooka, N.; Seki, S.; Hirai, Y. *Chem. Pharm. Bull*. **1990**, *38*, 2072. (b) Majewski, M.; Zheng, G.-Z. *Can. J. Chem*. **1992**, *70*, 2618. (c) Bunn, B. J.; Simpkins, N. S.; Spavold, Z.; Crimmin, M. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3113. (d) Bunn, B. J.; Simpkins, N. S. *J. Org. Chem*. **1993**, *58*, 533. (e) Majewski, M.; Lazny, R. *Tetrahedron Lett*. **1994**, *35*, 3653. (f) Newcombe, N. J.; Simpkins, N. S. *J. Chem. Soc., Chem. Commun*. **1995**, 831.

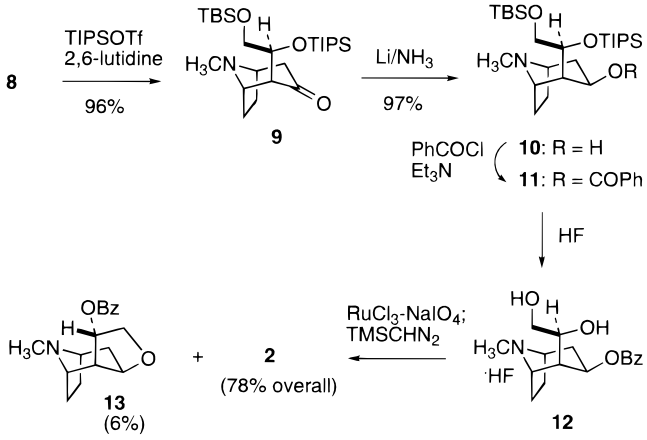
(7) Aszodi, J.; Bonnet, A.; Teusch, A. *Tetrahedron* **1990**, *46*, 1579.

(8) Inasmuch as natural (−)-cocaine (**1**) is an illicit drug, we decided to prepare the unnatural enantiomer by use of **6**.

(9) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem*. **1981**, *46*, 3936.

10.1021/jo000348c CCC: $19.00
Published on Web 06/23/2000

Scheme 2



conversion was accomplished in a one-pot operation by sequential treatment with HF, followed by $RuCl_3-NaIO_4$[9] and subsequent methylation with $TMSCHN_2$[10] to furnish (*S*)-(+)-cocaine (**2**), $[\alpha]^{25}_D = +15.0$ (*c* 0.48, $CHCl_3$) [lit.[11d] $[\alpha]^{25}_D = -16.0$ (*c* 4.0, $CHCl_3$) for **1**] in 78% overall yield.[12] Thus, the enantiomeric purity of synthetic (+)-**2** was ~90% ee and identical to that of **8**, which can be improved to 100% by a single recrystallization.

In summary, a concise (4−5 steps), stereoselective synthesis of (*S*)-(+)-cocaine (**2**) was achieved from tropinone (**3**). The present work underscores the general utility of enantioselective deprotonation of meso cyclic ketones in asymmetric synthesis.

Experimental Section[13]

(+)-(1*S*,2*R*,5*R*,1′*S*)-2-[(2′-*tert*-Butyldimethylsiloxy-1′-hydroxy)ethyl]-8-methyl-8-azabicyclo[3.2.1]octan-3-one (8). To a solution of (*S,S*)-bis(1-phenylethyl)amine hydrochloride (2.19 g, 8.37 mmol) in THF (25 mL) was added dropwise *n*-BuLi (10.4 mL of a 1.6 M solution in hexane) at 0 °C. The mixture was stirred for 1.5 h at 0 °C and cooled to −78 °C. Tropinone (**3**) (0.78 g, 5.6 mmol) in THF (5 mL) was added dropwise, and the resulting solution was stirred for 3 h at −78 °C, followed by addition of 2-(*tert*-Butyldimethylsiloxy)ethanal (**7**) (1.48 g. 8.49 mmol) in THF (5 mL) at −78 °C. After the reaction mixture was stirred for 3.5 h, saturated aqueous NH_4Cl was then added and the mixture was stirred for an additional 0.5 h at room temperature. The mixture was poured into Et_2O and water. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (EtOAc) afforded the aldol product **8** (1.26 g, 72%) as a white solid: mp 72−73 °C; $[\alpha]^{23}_D = +77.0$ (*c* 0.6, $CHCl_3$); IR (film) 3390, 1713, 1471 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.02 (br s, 1H), 4.05 (ddd, *J* = 6.9, 5.6, 2.2 Hz, 1H), 3.51 (dd, *J* = 10.1, 5.6 Hz, 1H), 3.42 (dd, *J* = 10.1, 6.9 Hz, 1H), 3.46−3.38 (m, 2H), 2.69 (ddd, *J* = 16.1, 4.9, 1.9 Hz, 1H), 2.40 (s. 3H), 2.39 (d, *J* = 2.2 Hz, 1H), 2.30 (d, *J* = 16.1 Hz, 1H), 2.29−2.10 (m, 2H), 1.67−1.55 (m, 2H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 209.5, 75.6, 67.8, 64.7, 61.5, 58.6, 51.5, 40.8, 26.5, 26.4, 26.0, 18.4, −5.4; HRMS ($M^+ - C_4H_9$) calcd for $C_{12}H_{22}NO_3Si$ 256.1369, found 256.1357.

(+)-(1*S*,2*R*,5*R*,1′*S*)-2-[(2′-*tert*-Butyldimethylsiloxy-1′-triisopropylsiloxy)ethyl]-8-methyl-8-azabicyclo[3.2.1]octan-3-one (9). To a solution of **8** (0.50 g, 1.60 mmol) and 2,6-lutidine (0.86 g, 8.0 mmol) in CH_2Cl_2 (4 mL) was added dropwise at 0 °C triisopropyl trifluoromethanesulfonate (0.54 g, 1.76 mmol). The mixture was stirred for 7 h at room temperature and quenched with water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography (4:1 hexanes−EtOAc) afforded **9** (0.72 g, 96%) as a colorless oil: $[\alpha]^{23}_D = +23.0$ (*c* 0.8, $CHCl_3$); IR (film) 1709, 1464 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.26 (ddd, *J* = 6.0, 5.6, 5.3 Hz, 1H), 3.82 (dd, *J* = 10.2, 6.0 Hz, 1H), 3.64 (dd, *J* = 10.2, 5.3 Hz, 1H), 3.43 (br d, *J* = 6.6 Hz, 1H), 3.28 (m, 1H), 2.75 (dd, *J* = 16.4, 4.7 Hz, 1H), 2.34 (d, *J* = 5.6 Hz, 1H), 2.28 (s. 3H), 2.22−2.03 (m, 2H), 2.13 (d, *J* = 16.4 Hz, 1H), 1.60−1.40 (m, 2H), 1.03 (s, 21H), 0.85 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 210.4, 74.7, 66.0, 63.7, 61.6, 61.3, 50.3, 41.3, 27.3, 26.6, 25.9, 18.1, 17.7, 12.7, 12.3, 4.9, 4.8; HRMS ($M^+ - C_3H_7$) calcd for $C_{22}H_{44}NO_3Si_2$ 426.2680, found 426.2867.

(−)-(1*S*,2*R*,5*R*,1′*S*)-2-[(2′-*tert*-Butyldimethylsiloxy-1′-triisopropylsiloxy)ethyl]-3-hydroxy-8-methyl-8-azabicyclo-[3.2.1]octane (10). Lithium (0.4 g) was added to 30 mL of anhydrous ammonia at −78 °C. To the resulting blue solution was added a solution of **9** (0.8 g, 1.7 mmol) in THF (10 mL). After the mixture was stirred for 30 min at −78 °C, methanol (2.5 mL) was added dropwise. Additional 0.12 g of lithium wire was added at −78 °C. The reaction mixture was stirred for an additional 30 min and quenched by cautious addition of solid NH_4Cl. Ammonia was allowed to evaporate slowly, and the residue was extracted with ether. The extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (10:1 CH_2Cl_2−MeOH) afforded **10** (0.78 g, 97%) as a colorless oil: $[\alpha]^{23}_D = -3.0$ (*c* 0.5, $CHCl_3$); IR (film) 3464, 1464 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.36 (ddd, *J* = 6.1, 5.7, 3.4 Hz, 1H), 4.12 (dd, *J* = 10.1, 5.7 Hz, 1H), 3.94 (ddd, *J* = 12.1, 6.2, 5.4 Hz, 1H), 3.70 (dd, *J* = 10.1, 3.4 Hz, 1H), 3.19 (br d, *J* = 5.6 Hz, 1H), 3.08 (br s, 1H), 2.28−1.84 (m, 4H), 2.12 (s, 3H), 1.73 (ddd, *J* = 12.1, 5.7, 3.0 Hz, 1H), 1.54−1.40 (m, 2H), 1.10 (s, 21H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 75.1, 66.1, 65.9, 63.1, 61.4, 48.8, 41.2, 41.0, 29.7, 26.2, 25.9, 25.5, 18.2, 13.1, 5.0, 4.7; HRMS ($M^+ - C_3H_7$) calcd for $C_{22}H_{46}NO_3Si_2$ 428.3016, found 428.2990.

(+)-(1*S*,2*R*,5*R*,1′*S*)-2-[(2′-*tert*-Butyldimethylsiloxy-1′-triisopropylsiloxy)ethyl]-3-benzoyloxy-8-methyl-8-azabicyclo-[3.2.1]octane (11). Benzoyl chloride (0.3 g, 2.2 mmol) was added dropwise at 0 °C to a solution of **10** (0.73 g, 1.55 mmol), 4-(dimethylamino)pyridine (30 mg, 0.25 mmol), and triethylamine (1.3 mL) in CH_2Cl_2 (1.5 mL). The resulting mixture was stirred for 3 h at room temperature and quenched at 0 °C by addition of 5% aqueous NaOH solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (6:1 hexanes−EtOAc) afforded **11** (0.76 g, 85%) as a colorless oil: $[\alpha]^{23}_D = +18.0$ (*c* 0.83, $CHCl_3$); IR (film) 1723, 1471 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.4, 1.4 Hz, 2H), 7.54 (m, 1H), 7.40 (dd, *J* = 7.8, 7.4 Hz, 2H), 5.41 (ddd, *J* = 15.9, 11.1, 7.9 Hz, 1H), 4.17 (ddd, *J* = 8.1, 4.4, 1.9 Hz, 1H), 4.10 (dd, *J* = 11.1, 1.9 Hz, 1H), 3.88 (dd, *J* = 11.1, 8.1 Hz, 1H), 3.57 (br d, *J* = 7.2 Hz, 1H), 3.15 (m, 1H), 2.27 (ddd, *J* = 7.9, 4.4, 2.1 Hz, 1H), 2.22−1.85 (m, 4H), 2.16 (s, 3H), 1.71−1.62 (m, 1H), 1.59−1.50 (m, 1H), 1.04−0.98 (br s, 21H), 0.92 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 165.9, 132.8, 130.4, 129.6, 128.2, 74.5, 68.5, 68.2, 61.0, 60.6, 50.3, 40.7, 37.7, 26.3, 26.1, 25.2, 18.6, 18.2, 12.6, 4.7, 4.6; HRMS ($M^+ - C_3H_7$) calcd for $C_{29}H_{50}NO_4Si_2$ 532.3278, found 532.3282.

(*S*)-(+)-Cocaine (2). A solution of **11** (0.29 g, 0.5 mmol) in acetonitrile (6 mL) was treated with 50% aqueous HF solution (3 mL) at room temperature. The mixture was stirred for 1 h and concentrated under reduced pressure. After the residue was dissolved in 7 mL of 2:2:3 $CCl_4-CH_3CN-H_2O$, $NaIO_4$ (0.46 g, 2.15 mmol) and $RuCl_3 \cdot 3H_2O$ (12 mg, 0.05 mmol) were then

(10) Shioiri, T.; Aoyama, T. *J. Synth. Org. Chem., Jpn*. **1996**, *54*, 918.

(11) For previous syntheses of cocaine, see: (a) ref 1. (b) Bainova, M. S.; Bazilevskaya, G. I.; Preobrazhenskii, N. A. *Zh. Obshch. Khim*. **1960**, *30*, 3258. (c) Tufariello, J. J.; Mullen, G. B.; Tegeler, J. J.; Trybulski, E. J.; Wong, S. C.; Ali, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2435. (d) Lewin, A. H.; Naseree, T.; Caroll, F. I. *J. Heterocycl. Chem*. **1987**, *24*, 19. (e) Lin, R.; Castells, J.; Rapoport, H. *J. Org. Chem*. **1998**, *63*, 4069.

(12) Also isolated was a small (6%) amount of a byproduct, whose structure was tentatively assigned to be as shown in **13**.

(13) (a) For general procedures, see: Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc*. **1999**, *121*, 10012. (b) Unless noted otherwise, the OH proton resonances are not reported in the ^1H NMR spectral listings.

added. The resulting mixture was stirred vigorously at room temperature for 3 h. The mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was dissolved in 15 mL of 2:1 benzene-MeOH and treated with $TMSCHN_2$ (3.0 mL of a 2.0 M solution in *n*-hexane). The reaction mixture was stirred for 3 h at room temperature and concentrated in vacuo. After the residue was diluted with CH_2Cl_2, 5% aqueous NaOH solution was added, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (10:1 CH_2Cl_2−MeOH) afforded (*S*)−(+)-cocaine (**2**) (0.12 g, 78%) as a white solid: mp 96−98 °C (lit.[11d] mp 98 °C); $[\alpha]^{23}_D = +15.0$ (*c* 0.48, $CHCl_3$); IR (film) 1750, 1718, 1452 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.02 (dd, J = 7.3, 1.2 Hz, 2H), 7.53 (m, 1H), 7.41 (dd, J = 7.8, 7.3 Hz, 2H), 5.25 (quintet, J = 5.9 Hz, 1H), 3.71 (s, 3H), 3.58 (m, 1H), 3.32 (m, 1H), 3.03 (dd, J = 5.9, 3.4 Hz, 1H), 2.44 (dt, J = 11.9, 3.4 Hz, 1H), 2.25 (s, 3H), 2.22−2.06 (m, 2H), 1.90−1.85 (m, 1H), 1.78−1.68 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.7, 166.2, 132.9, 130.3, 129.7, 128.3, 66.8, 64.8, 61.6, 51.4, 50.1, 41.1, 35.5, 25.4, 25.2; HRMS (M^+) calcd for $C_{17}H_{21}NO_4$ 303.1471, found 303.1470.

Acknowledgment. We thank the National Institutes of Health (GM35956) for generous financial support.

Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **2** and **8**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000348C