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Facile and Enantiospecific Syntheses of (6*S*,7*R*)-6-Chloro-7-benzyloxy-, (7*S*)-Halo-, and (7*S*)-Hydroxy-cocaine and Natural (−)-Cocaine from D-(−)-Ribose

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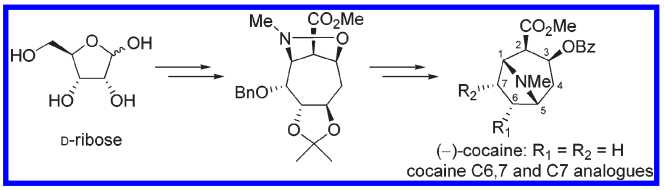
ABSTRACT



First syntheses of C6,7 and C7 enantiopure cocaine analogues were achieved from D-(−)-ribose via a *trans*-acetonide controlled *endo*-selective intramolecular nitrone-alkene cycloaddition (INAC) as the key step. This synthetic scheme allows practical preparation of cocaine analogues for bioevaluation as potential candidates for the treatment of cocaine addiction and as potential conjugates for immunotherapy.

Notorious tropane alkaloid (−)-cocaine (**1**)[1] is a powerful stimulant of the central nervous system, and its neuronal reinforcing properties are attributable to its inhibition of dopamine reuptake.[2] Cocaine abuse has been a pivotal medical problem in the world, and 1.6 million current users by age 12 are estimated in the U.S.[3] Furthermore, cocaine abuse has indirectly enhanced the spread of human immunodeficiency virus infection and drug-resistant tuberculosis.[4] To date, an effective medication to treat patients addicted to cocaine is still elusive and research effort on the synthesis of cocaine analogues for bioevaluation must continue. Tremendous studies have been made on C2 and C3 cocaine analogues, but C6 and C7 analogues are relatively underexplored.[5,6] This is because C2 and C3 analogues were readily derived from (−)-cocaine (**1**) whereas access to C6 and C7 analogues must rely on total synthesis. Existing C6 and C7 analogues were synthesized as racemates by modifying the classical Willstätter synthesis of cocaine.[5a,b] Resolution is required to produce enantiopure analogues which hampers the development of a pharmacotherapy. Recently, Davis et al. described the asymmetric synthesis of cocaine C1-alkyl analogues using essentially an asymmetric variant of the Tufariello

(1) Simoni, D.; Rondanin, R.; Roberti, M. In *Targets in Heterocyclic Systems*; Attanasi, O. A., Spinelli, D., Eds.; Italian Society of Chemistry: Roma, 1999; Vol. 3, pp 147−183.

(2) (a) Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. *Science* **1987**, *237*, 1219–1223. (b) Kuhar, M. J.; Ritz, M. C.; Boja, J. W. *Trends Neurosci*. **1991**, *14*, 299–302. (c) Koob, G. F.; Bloom, F. E. *Science* **1988**, *242*, 715–723.

(3) Substance Abuse and Mental Health Services Administration. (2010). *Results from the 2009 National Survey on Drug Use and Health: Vol. I. Page 1. Summary of National Findings* (Office of Applied Studies, NSDUH Series H-38A, HHS Publication No. SMA 10−4586Findings), Rockville, MD. http://oas.samhsa.gov/NSDUH/2k9NSDUH/2k9ResultsP.pdf.

(4) Herman, B. H.; Elkashef, A.; Vocci, F. *Drug Discovery Today: Therapeutic Strategies* **2005**, *2*, 87–92.

(5) For some reports of synthesis of cocaine analogues, see: (a) racemic 6*β*- and 7*β*-methoxylated cocaine: Simoni, D.; Stoelwinder, J.; Kozikowski, A. P.; Johnson, K. M.; Bergmann, J. S.; Ball, R. G. *J. Med. Chem*. **1993**, *36*, 3975–3977. (b) racemic 6*β*- and 7*β*-hydroxylated cocaine: Kozikowski, A. P.; Simoni, D.; Manfredini, S.; Roberti, M.; Stoelwinder, J. *Tetrahedron Lett*. **1996**, *37*, 5333–5336. (c) enantiopure C1-alkyl cocaine analogues: Davis, F. A.; Theddu, N.; Edupuganti, R. *Org. Lett*. **2010**, *12*, 4118–4121.

(6) For some reports of synthesis of C2 and C3 tropane analogues, see: (a) Carroll, F. I.; Blough, B. E.; Mascarella, S. W.; Navarro, H. A.; Eaton, J. B.; Lukas, R. J.; Damaj, M. I. *J. Med. Chem*. **2010**, *53*, 8345–8353. (b) Stehouwer, J. S.; Jarkas, N.; Zeng, F.; Voll, R. J.; Williams, L.; Camp, V. M.; Malveaux, E. J.; Votaw, J. R.; Howell, L.; Owens, M. J.; Goodman, M. M. *J. Med. Chem*. **2008**, *51*, 7788–7799. (c) Zhang, S.; Izenwasser, S.; Wade, D.; Xu, L.; Trudell, M. L. *Bioorg. Med. Chem*. **2006**, *14*, 7943–7952. (d) Bois, F.; Baldwin, R. M.; Kula, N. S.; Baldessarini, R. J.; Innis, R. B.; Tamagnan, G. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 2117–2120. (e) Zhao, L.; Johnson, K. M.; Zhang, M.; Flippen-Anderson, J.; Kozikowski, A. P. *J. Med. Chem*. **2000**, *43*, 3283–3294.

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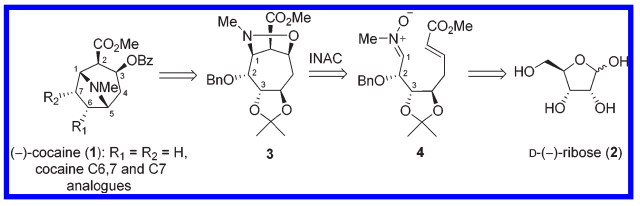
synthesis of cocaine.[5c] Enantiospecific syntheses of C6 and C7 cocaine analogues have not been addressed in the literature, and herein, we report facile and efficient syntheses of (6*S*,7*R*)-6-chloro-7-benzyloxy-, (7*S*)-hydroxy-, (7*S*)-chloro-, (7*S*)-methanesulfonyloxy-, and (7*S*)-iodo-cocaine analogues from inexpensive D-(−)-ribose (**2**) via a *trans*-acetonide controlled *endo*-selective intramolecular nitrone-alkene cycloaddition (INAC) reaction[7] as the key step. The cocaine framework in these analogues was corroborated by conversion into natural (−)-cocaine (**1**).[8]

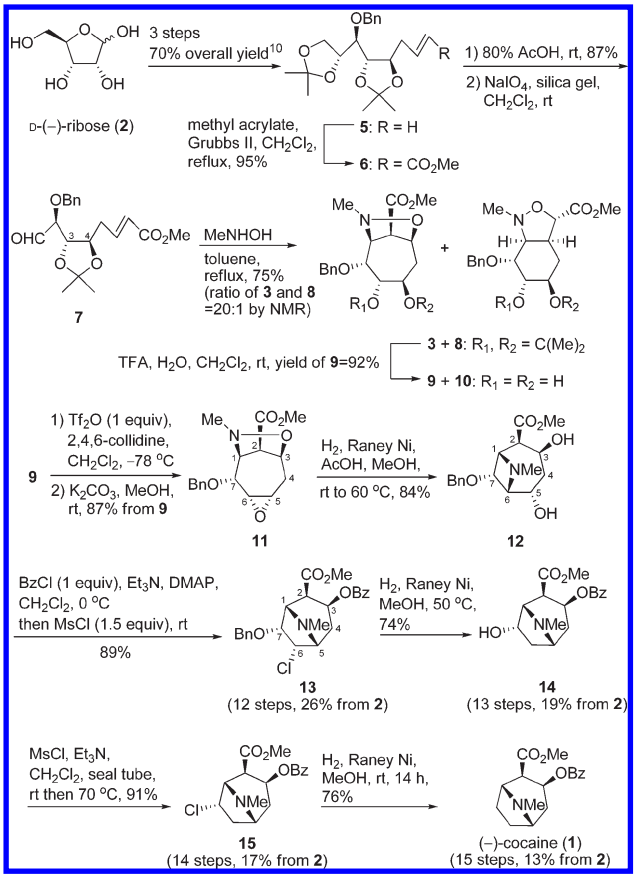
Our retrosynthesis is based on the construction of a seven-membered bridged carbocycle **3** via a key *endo*-selective INAC reaction[7] of nitrone **4**, which is readily prepared from D-(−)-ribose (**2**) (Scheme 1). Our previous work[7] has indicated that hept-6-enoses containing a 3, 4-*trans*-acetonide direct the INAC reactions to give *endo* cycloadducts (cycloheptanes) exclusively. The stereochemistry of the ring junction is also controlled by the *trans*-acetonide whereby the newly formed C−N bond is *anti* to the C3 alkoxy group. Hence, nitrone **4** is expected to give the bridged cycloheptane **3** and the methoxycarbonyl group must be in the β-face as shown, a consequence of the stereospecificity of the pericyclic reaction (*E*-alkene to β-methoxycarbony group). The C1, C2, and C3 stereocenters in the cocaine analogues would therefore be established in one synthetic operation, i.e. the INAC reaction.

Scheme 1. Retrosynthesis of Cocaine Analogues



The syntheses of cocaine analogues and (−)-cocaine (**1**) are shown in Scheme 2. D-(−)-Ribose (**2**) was transformed into alkene **5** in three steps involving aqueous indium allylation,[9] acetonation, and benzylation as reported previously.[10] Cross metathesis of **5** with methyl acrylate catalyzed by a second generation Grubbs catalyst[11] afforded α,β-unsaturated ester **6** in an excellent yield. The large coupling constant (J = 15.7 Hz) of the two alkene signals observed in the ^{1}H NMR spectrum of **6** confirmed its *E*-geometry. Regioselective acid hydrolysis of the terminal acetonide in **6** followed by glycol cleavage oxidation[12] gave aldehyde **7**, which condensated with MeNHOH to generate nitrone **4**. INAC reaction produced a mixture of inseparable seven-membered *endo*-cycloadduct **3** and six-membered *exo*-cycloadduct **8** in a ratio of 20:1, respectively (^{1}H NMR spectral analysis). It is noteworthy that an α,β-unsaturated ester as the dipolarophile did not induce the formation of an *endo*-cycloadduct anticipated from an electronic effect,[13] thereby confirming the steric control of the *endo*-mode of cycloaddition is attributable to the *trans*-acetonide group. This mixture of inseparable cycloadducts **3** and **8** was then subjected to TFA hydrolysis to yield a mixture of diols **9** and **10**, respectively, separable on column chromatography. The structures of **9** and **10** were confirmed by X-ray crystallography.[14]

Scheme 2. Syntheses of Cocaine Analogues **13**, **14**, **15**, and (−)-Cocaine (**1**)



With the diol **9** in hand, it was regioselectively esterified with Tf_2O and the monotriflate ester formed was then treated with basic MeOH to give epoxide **11**. Raney-Nickel

(7) (a) Shing, T. K. M.; Wong, W. F.; Ikeno, T.; Yamada, T. *Chem.—Eur. J.* **2009**, *15*, 2693–2707. (b) Shing, T. K. M.; Wong, A. W. F.; Ikeno, T.; Yamada, T. *J. Org. Chem.* **2006**, *71*, 3253–3263.

(8) For previous asymmetric syntheses of cocaine, see: (a) Lin, R.; Castells, J.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 4069–4078. (b) Lee, J. C.; Lee, K.; Cha, J. K. *J. Org. Chem.* **2000**, *65*, 4773–4775. (c) Mans, D. M.; Pearson, W. H. *Org. Lett.* **2004**, *6*, 3305–3308. (d) Davis, F. A.; Theddu, N.; Edupuganti, R. *Org. Lett.* **2010**, *12*, 4118–4121. (e) Cheng, G.; Wang, X.; Zhu, R.; Shao, C.; Xu, J.; Hu, Y. *J. Org. Chem.* **2011**, *76*, 2694–2700.

(9) Prenner, R. H.; Schmid, B. W. *Liebigs Ann. Chem.* **1994**, 73–78.

(10) Shing, T. K. M.; Wong, W. F.; Ikeno, T.; Yamada, T. *Org. Lett.* **2007**, *9*, 207–209.

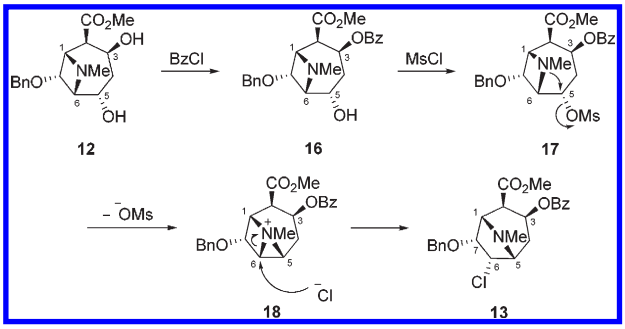
(11) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784.

(12) Zhong, Y. L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622–2624.

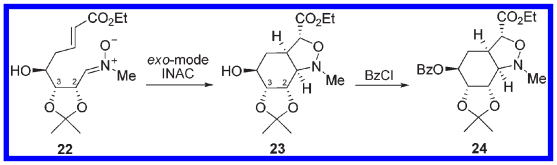
(13) Our studies showed that the INAC of nitrone **22**, bearing an α,β-unsaturated ester and a *cis*-acetonide, gave *exo*-cycloadduct **23** exclusively. The regio- and stereochemistry was confirmed by X-ray crystallographic analysis of its benzoate **24** (CCDC 681970).

mediated hydrogenolysis of **11** yielded azetidine-diol **12**. The N−O bond of **11** was first cleaved to give the corresponding amine, which opened the epoxy ring at C6 to afford bicyclo[4.1.1] diol **12**.[15] The formation of a bicyclo-[4.1.1] skeleton instead of the tropane structure (by attacking C5) might be rationalized by Baldwin's rule,[16] in which the 4-*Exo*-*Tet* cyclization (leading to a bicyclo[4.1.1] skeleton) is more favored than the 5-*Endo*-*Tet* cyclization (leading to a tropane skeleton). This azetidine-diol **12** was then transformed into (6*S*,7*R*)-6-chloro-7-benzyloxy cocaine (**13**) by a one-pot reaction of benzoylation and mesylation in excellent overall yield. The C3-OH of **12** was first benzoylated, and the remaining free C5-OH in **16** was then mesylated (Scheme 3). As the aza-bridge is *anti* to the C5-OMs group, neighboring-group participation would assist the mesylate ion in **17** to dissociate easily, giving ammonium ion **18**.[17] Then the nucleophilic chloride ion attacked the C6α position of **18** to furnish (6*S*)-chloride **13**. The release of ring strain from the bicyclo-[4.1.1] skeleton to the tropane ring is probably the driving force for the attack at C6 instead of C5.

Scheme 3. Proposed Mechanism from **12** to **13**



The presence of a chlorine atom in **13** was confirmed by mass spectrometry. The tropane skeleton in **13** was assigned by ^{1}H−^{1}H connectivities from the 2D COSY NMR spectrum and the strong NOE correlation between H6 and H7 supported the *S*-stereochemistry of the chloride at C6.



(14) Please refer to Supporting Information for X-ray structures of **9** (CCDC 737152) and **10** (CCDC 752110) .

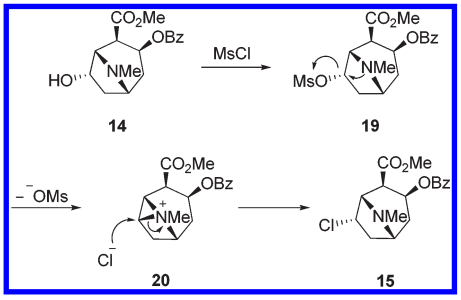
(15) The structure of azetidine-diol **12** was confirmed by X-ray crystallographic analysis of its tribenzoate derivative (CCDC 798275). Its preparation is described in the Supporting Information.

(16) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.

(17) The existence of such ammonium ion **18** was supported by the racemization of acetate product upon acetylation of L-2α-tropanol as reported by Archer et al.; see: Archer, S.; Lewis, T. R.; Bell, M. R.; Schulenberg, J. W. *J. Am. Chem. Soc.* **1961**, *83*, 2386–2387.

Thus, (6*S*,7*R*)-6-chloro-7-benzyloxy cocaine was obtained for the first time in 12 steps with 26% overall yield from D-(−)-ribose (**2**). Hydrogenolysis of **13** in the presence of Raney-Nickel provided the first synthesis of another cocaine analogue, (7*S*)-hydroxy cocaine (**14**) (13 steps, 19% from **2**). This alcohol **14** is the 7-epimer of the known (7*R*)-hydroxy cocaine.[5b,18] The ^{1}H NMR spectrum of (7*R*)-hydroxy cocaine (obtained from Prof. K. D. Janda) was found to be very similar to that of **14**, except for their H7 splitting pattern (dd in (7*R*)-hydroxy-cocaine and ddd in our **14**), which is in good agreement with the observations on its structurally related compounds in the literature.[5a] The third (−)-cocaine analogue, (7*S*)-chloro-cocaine (**15**) (14 steps, 17% from **2**), was synthesized by reacting **14** with MsCl at 70 °C in a sealed tube. The mesylate **19** formed was displaced readily by a chloride ion at an elevated temperature to give **15** (Scheme 4). The presence of a chlorine atom in **15** was again confirmed by mass spectrometry. From the ^{1}H NMR spectrum of **15**, the *S*-stereochemistry of Cl7 was assigned by comparing its coupling constant ($J_{1,7}$ = 6.4 Hz) with that in structurally related compounds.[5a,b] The retention of configuration upon the displacement reaction of (7*S*)-mesylate **19** by a chloride ion might be rationalized by the proposed mechanism shown in Scheme 4. The neighboring-group participation of the aza-bridge encouraged the dissociation of the mesylate in **19** to form ammonium ion **20** and the chloride ion then attacked from the C7α-face of **20**, furnishing (7*S*)-chloro-cocaine (**15**).

Scheme 4. Proposed Mechanism from **14** to **15**



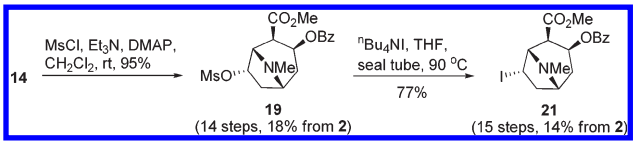
The cocaine framework in these analogues was corroborated by the transformation of chloride **15** into natural (−)-cocaine (**1**) via Raney-Nickel mediated hydrogenolysis. The physical and spectral data of synthetic (−)-cocaine (**1**) were in full accordance with those reported in the literature.[8a] Thus natural (−)-cocaine (**1**) was also synthesized in 15 steps from D-(−)-ribose (**2**) with 13% overall yield. The overall yield of this synthetic scheme was found to be higher than the recently reported (+)-cocaine synthesis (9% overall yield from methyl 4-nitrobutanoate) by Davis et al.[5c,19] The lower cost of our starting material

(18) The (7*R*)-hydroxy cocaine had been used to synthesize haptens for immunopharmacotherapy in cocaine abuse; see: Ino, A.; Dickerson, T. J.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4280–4283.

(19) (a) Simoneau, B.; Brassard, P. *Tetrahedron* **1988**, *44*, 1015–1022. (b) Davis, F. A.; Zhang, H.; Lee, S. H. *Org. Lett.* **2001**, *3*, 759–762.

ensures that our avenue is more economical and our synthetic route has great potential for synthesis of other (−)-cocaine analogues.

Scheme 5. Synthesis of (−)-Cocaine Analogues **19** and **21**



For example, when alcohol **14** was mesylated at room temperature, (7*S*)-methanesulfonyloxy cocaine (**19**) instead of chloride **15** was isolated (Scheme 5). This mesylate **19** readily undergoes displacement reactions with nucleophiles. When **19** reacted with the iodide anion, (7*S*)-iodo-cocaine (**21**) was formed. The retention of configuration of the iodide in **21** was also rationalized by neighboring-group participation as described previously. This iodide **21** is believed to be reactive toward radical reactions hence forming even more (−)-cocaine analogues.

To conclude, we have provided a facile, practical, and high yielding access to five (−)-cocaine analogues, (6*S*,7*R*)-6-chloro-7-benzyloxy-, (7*S*)-hydroxy-, (7*S*)-chloro-, (7*S*)-methanesulfonyloxy-, and (7*S*)-iodo-cocaine, in 12−15 steps with 14−26% overall yields from inexpensive D-ribose. Halo-analogues **13**, **15**, and **21** are also valuable synthetic intermediates which can be elaborated via ionic or radical reactions into a wide variety of cocaine analogues. Research in this direction is in progress.

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Supporting Information Available. Experimental procedures and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.