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Total Synthesis of (+)-Cocaine via Desymmetrization of a *meso*-Dialdehyde

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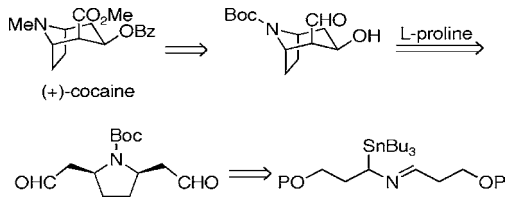
ABSTRACT



The total synthesis of (+)-cocaine is described. An extension of the recently reported proline catalyzed intramolecular enol–*exo*-aldol reaction to a *meso*-dialdehyde provided the tropane ring skeleton directly with good enantiomeric excess. The *meso*-dialdehyde was prepared using a 2-azaallyllithium [3 + 2] cycloaddition to generate a *cis*-2,5-disubstituted pyrrolidine. Overall, the synthesis proceeded in 6.5% yield and 86% ee over 14 linear steps starting from commercially available 3-benzyloxy-1-propanol.

There have been numerous reports of the synthesis of cocaine in the literature. A common approach has been to use rather advanced starting materials such as tropinone and anhydroecgonine (a cocaine degradation product).[1] A few examples of total syntheses have been reported, including the classic biomimetic approach by Wilstätter,[2] Tufariello's consecutive nitrone cycloaddition approach,[3] Rapoport's enantiospecific synthesis from glutamic acid,[4] and Cha's asymmetric synthesis via enantioselective deprotonation of tropinone.[5] In addition, considerable work has been done on the synthesis of cocaine analogues.[6] To this end, most efforts have relied upon derivatization of natural cocaine and/or resolution/separation of racemic or diastereomeric mixtures. Numerous approaches involving cycloadditions to access the tropane ring skeleton have been developed including higher order cycloaddition reactions,[7] [4 + 3] oxyallyl cation cycloadditions,[8] and 1,3-dipolar cycloadditions.[3,9] In addition, intramolecular nucleophilic substitution reactions,[10] intramolecular Michael addition reactions,[1b,11] rhodium carbenoid reactions,[12] intramolecular 6-*endo*-*trig* radical cyclizations,[13]

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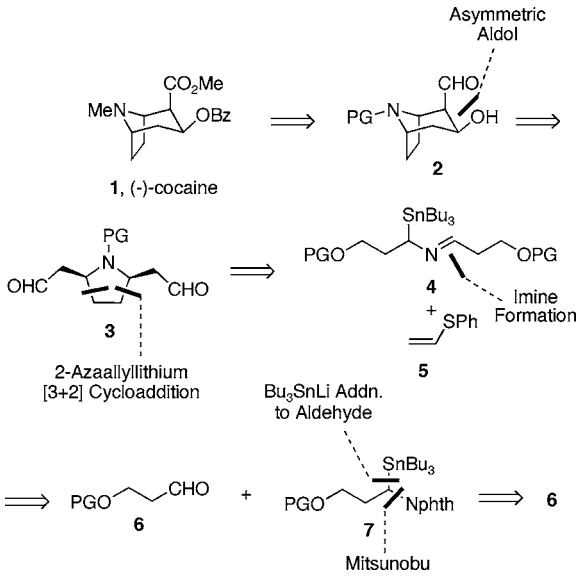
cyclizations onto iminium ions,[14] and Grubb's ring-closing metathesis reactions[15] have also been explored as methods to generate the tropane ring skeleton. However, asymmetric methods are still rare, suffer from lengthy routes, and lack generality.

We felt that application of our 2-azaallyllithium cycloaddition methodology in conjunction with an intramolecular enol−*exo*-aldol desymmetrization reaction would allow a concise synthesis of a tropane skeleton with appropriate functionalization for elaboration into cocaine. Beyond the well-known difficulties in setting and retaining the delicate stereochemistry found in cocaine, a second obstacle that needed to be overcome was the efficient production of *cis*-2,5-disubstituted pyrrolidine **3** (Scheme 1). Unlike the

Scheme 1. Retrosynthesis of Cocaine

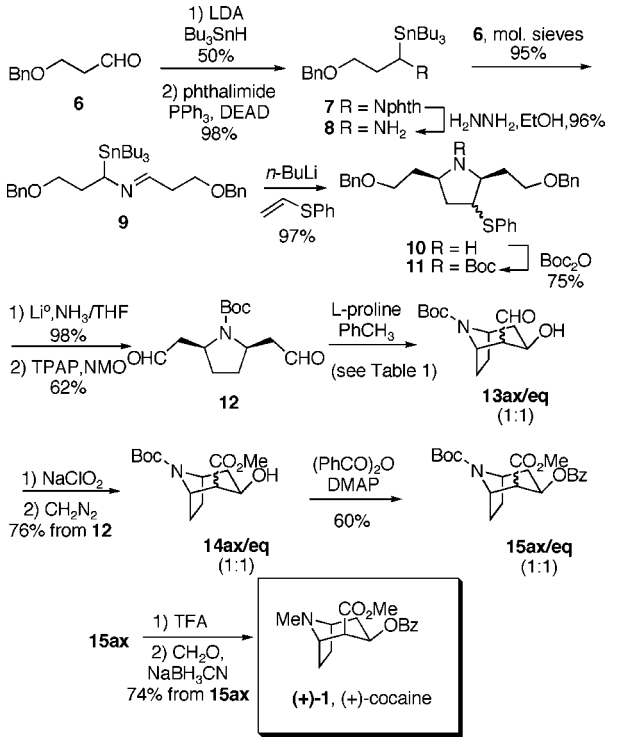


homologous *cis*-2,6-disubstituted piperidines,[16] methods to access *cis*-2,5-disubstituted pyrrolidines are rather limited.[17] Many of these methods involve nucleophilic addition to a cyclic iminium species[18] or reduction of 1-pyrrolines,[19] but with rather poor *cis*/*trans* selectivities. However our [3 + 2] cycloaddition methodology allows access to either the *cis*- or *trans*-2,5-disubstituted pyrrolidines. Previous reports have demonstrated that using (2-azaallyl)stannanes in azomethine ylide [3 + 2] cycloadditions leads predominantly to the *trans*-2,5-disubstituted pyrrolidines, while 2-azaallyllithium [3 + 2] cycloadditions provide the *cis*-2,5-disubstituted pyrrolidines as the sole products.[20] With an efficient and highly selective route to the desired *cis*-2,5-disubstituted pyrrolidine **3**, the synthesis of cocaine was pursued and is reported herein.

Our retrosynthetic plan hinged on the formation of *β*-hydroxy aldehyde **2** and *meso*-dialdehyde **3** (Scheme 1). *β*-Hydroxy aldehyde **2** was envisioned to arise from an intramolecular aldol reaction of the *meso*-dialdehyde **3**. A 2-azaallyllithium [3 + 2] cycloaddition between the (2-azaallyl)stannane **4** and phenyl vinyl sulfide **5** would provide the requisite *cis*-2,5-disubstituted pyrrolidine **3** after deprotection and oxidation. Both "sides" of the (2-azaallyl)-stannane **4** would arise from the same suitably protected aldehyde using methodology previously reported.[21]

Thus, 3-benzyloxypropionaldehyde **6** (Scheme 2),[22] prepared from commercially available 3-benzyloxy-1-propanol,

Scheme 2. Total Synthesis of (+)-Cocaine



was treated with tributylstannyllithium to give an intermediate α-hydroxy stannane in 50% yield. A Mitsunobu reaction

(12) (a) Davies, H. M. L.; Huby, N. J. S. *Tetrahedron Lett.* **1992**, *33*, 6935. (b) Davies, H. M. L.; Matasi, J. J.; Hodges, L. M.; Huby, N. J. S.; Thornley, C.; Kong, N.; Houser, J. H. *J. Org. Chem.* **1997**, *62*, 1095. (c) Davies, H. M. L.; Hodges, L. M. *J. Org. Chem.* **2002**, *67*, 5683.

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(16) See ref 15b and references therein.

(17) For a leading reference, see: Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927.

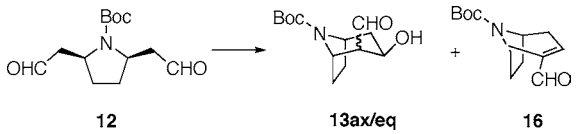
(18) For examples of nucleophilic addition to *N*-acyliminium ions, see: (a) Asada, S.; Kato, M.; Asai, K.; Ineyama, T.; Nishi, S.; Izawa, K.; Shono, T. *J. Chem. Soc., Chem. Commun.* **1989**, 486. (b) Chiesa, M. V.; Mazoni, L.; Scolastico, C. *Synlett* **1996**, 441. (c) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (d) Harris, P. W. R.; Brimble, M. A.; Gluckman, P. D. *Org. Lett.* **2003**, *5*, 1847.

with phthalimide then provided the α-stannyl phthalimide **7** in 98% isolated yield. In general, the tin addition/Mitsunobu reaction can be carried out without purification of the intermediate α-hydroxy stannane. However, in this instance, the overall yield for the two steps was improved by purifying the intermediate α-hydroxy stannane prior to the Mitsunobu reaction.[23]

Phthalimide **7** was then deprotected by hydrazinolysis to give the α-amino stannane **8** in 96% yield (Scheme 2). Condensation of 1 equiv of 3-benzyloxypropionaldehyde **6** with **8** generated (2-azaallyl)stannane **9** in 95% yield after simple filtration. Gratifyingly, treatment of imine **9** with *n*-butyllithium and phenyl vinyl sulfide led to the [3 + 2] cycloaddition and formation of *cis*-pyrrolidine **10** in 97% yield as a 1:1 mixture of C(3)-isomers. Following protection of the secondary amine as the Boc carbamate, dissolving metal reduction removed both benzyl ethers and the phenylthio group in excellent yield to give a *meso*-diol, which was oxidized to dialdehyde **12**. Oxidation to **12** proved to be less straightforward than anticipated. Treatment of the diol with Dess−Martin periodinane led only to decomposition, whereas attempted Swern oxidation returned a complex mixture of products. Oxidation with PCC was rather slow, requiring 12 h at room temperature to reach completion, but provided the dialdehyde **12** in 67% yield after eluting through a short silica plug. In addition, PDC was also examined but proved prohibitively slow, needing 36 h to reach completion with no improvement in yield. Ultimately, oxidation with TPAP/NMO[24] gave **12** with the quickest reaction time (4 h) and modest yields (62%).

With the key *meso*-dialdehyde **12** now in hand, the proline-catalyzed aldol reaction was attempted. Using the conditions reported by List and co-workers,[25] an 87% yield of aldol products **13ax/eq** as a 1:1 mixture of inseparable C(2)-epimers was obtained (Table 1, entry 1). Attempts to separate and/or purify the aldol products **13ax/eq** led only to decomposition. Various other solvents, concentrations, catalyst loadings, and temperatures were evaluated in attempts to improve the diastereoselectivity, but to no avail. More polar solvents such as DMF (entries 5 and 6) led only to the dehydration product. However, it was found that use of toluene as solvent gave the highest yields and cleanest reactions by ^{1}H NMR analysis of the crude mixture (Table 1, entry 8).

Table 1. Diastereoselectivity Studies for the Aldol Reaction



12 **13ax/eq** **16**

entry	solvent	L-proline (mol %)	*T* (°C)	time (h)	yield[a] (%)	ratio (**12**/**13ax**/**13eq**/**16**)[b]
1	CH_2Cl_2	5	25	14	87	0:1:1:0
2	CH_2Cl_2	20	0	18	82	0:1:1:0
3	CH_2Cl_2	20	−10	30	64	0:1:1:0
4	CH_2Cl_2	20	−20	N.R.		
5	DMF	20	−20	N.R.		
6	DMF	20	0	12		1:0:0:1
7	$PhCH_3$	20	−10	N.R.		
8	$PhCH_3$	20	25	24	91	0:1:1:0

[a] Yield reported is of the crude product obatined after aqueous workup. [b] Based on ^{1}H NMR of crude aldol products.

Due to their instability, the 1:1 mixture of crude aldol products **13ax/eq** were immediately converted to the methyl esters via oxidation to the acid followed by esterification to provide *β*-hydroxy esters **14ax/eq** in 76% overall yield from **12** (Scheme 2). Unfortunately, separation of the diastereomers was not possible at this stage. Gratifyingly, benzoylation with benzoic anhydride and DMAP provided a 60% yield of Boc-protected tropane compounds **15ax/eq**, which were now separable by HPLC. Removal of the Boc carbamate from the desired **15ax** with trifluoroacetic acid followed by reductive amination provided cocaine **1** in 74% yield over two steps with spectral properties matching that reported in the literature.[26,27] However, determination of the enantiomeric excess revealed that instead of (−)-cocaine we had actually synthesized the (+)-isomer.[28] Indeed, separation of the enantiomers by chiral HPLC[4] showed an 86% ee for the (+)-cocaine isomer.[29] This result was puzzling since on the basis of the proposed transition-state model[25] using L-proline, the (−)-isomer was predicted to be the favored aldol product (Figure 1).

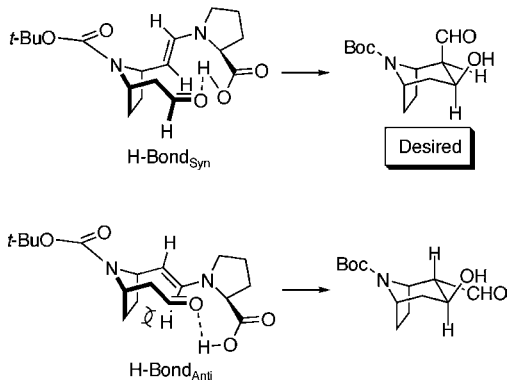


Figure 1. Predicted aldol transition states.

(19) For examples of reductions of 1-pyrrolines, see: (a) Shiosaki, K.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1229. (b) Bacos, D.; Celerier, J. P.; Marx, E.; Saliou, C.; Lhommet, G. *Tetrahedron Lett.* **1989**, *30*, 1081. (c) Li, H.; Sakamoto, T.; Kikugawa, Y. *Tetrahedron Lett.* **1997**, *38*, 6677. (d) ref 14c.

(20) For a leading reference, see: (a) Pearson, W. H.; Stoy, P. *Synlett* **2003**, 903. See also: (b) Pearson, W. H.; Mi, Y. *Tetrahedron Lett.* **1997** *38*, 5441. (c) Pearson, W. H.; Clark, R. B. *Tetrahedon Lett.* **1997**, *38*, 7669.

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(22) Kozikowski, A. P.; Stein, P. D. *J. Org. Chem.* **1984**, *49*(*13*), 2301.

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(25) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785.

On the basis of work done by List and Houk,[25,30,31] enamine formation leads to two possible chairlike conformations in which H-bonding can occur between the acid and free aldehyde (Figure 1) with the *anti*-arrangement being slightly preferred. The *anti* and *syn* terminology refer to the dihedral angle of the acid moiety and the terminal carbon of the olefin.[32] In this instance, the *anti*-arrangement (cf. H-bond$_{anti}$) is predicted to be destabilized by an A^{1,3}-interaction with the pyrrolidine ring, whereas no such interaction is present in the *syn*-arrangement (cf. H-bond$_{syn}$), but may still be disfavored due to the axial placement of the bulky enamine. These transition-state models, though, still predict the (−)-enantiomers to be formed. However, the presence of the Boc carbamate would provide a more Lewis basic site that may dominate in the formation of hydrogen bonding with the carboxylic acid (cf. Boc$_{anti}$ and Boc$_{syn}$, Figure 2) forcing enamine formation to occur on the opposite

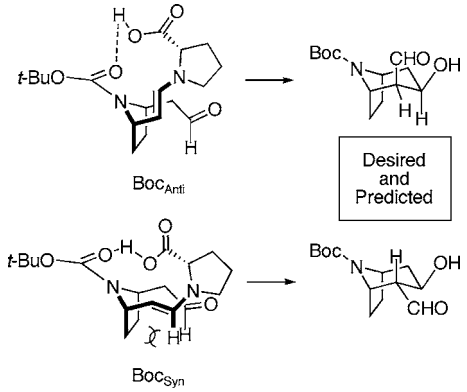

Figure 2. Aldol transition states with H-bonding to the carbamate.[35]

aldehyde.[33] Both transition-state models would now lead to the formation of the (+)-enantiomers. The Boc$_{syn}$ arrangement would suffer from the same type of steric interactions as H-bond$_{anti}$, whereas the Boc$_{anti}$ arrangement might also be disfavored sterically due to the placement of the bulky enamine in an axial position leading to a 1:1 distribution of C(2)-epimers. However, a word of caution is needed, since the rationale just explored has only considered the most likely transition states. To fully explain the reversal in predicted enantioselectivity and moderate diastereoselectivity, calculation of the relative energies of all reasonable transition states would be required.[34]

In conclusion, an efficient and rapid total synthesis of (+)-cocaine has been described using a highly stereoselective 2-azaallyllithium [3 + 2] cycloaddition to generate the desired *meso*-dialdehyde **12** followed by an intramolecular enol−*exo*-proline-catalyzed aldolization reaction to establish the tropane skeleton with good enantioselectivity and moderate diastereoselectivity. The aldol reaction represents the first use of the intramolecular proline-catalyzed aldol reaction to generate aza-bridged bicyclic structures. The versatility in the synthesis of cycloaddition precursors (i.e., **9**),[20] variety of dipolarophiles that can be used in the cycloaddition, and the easily modifiable functionality of the cycloadducts and aldol products combined with the relatively short synthetic route should allow for rapid and varied synthesis of enantioenriched cocaine analogues.

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Supporting Information Available: Experimental procedures as well as ^{1}H NMR spectra for (+)-**1** and **6**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) Carroll, F. I.; Coleman, M. L.; Lewin, A. H. *J. Org. Chem.* **1982**, *47*, 13.

(27) A similar sequence with **15eq** would lead to the synthesis of pseudococaine.

(28) $[\alpha]^{23}_D$ = +14.5 (*c* 0.72, $CHCl_3$) [Lit.[1a] $[\alpha]^{23}_D$ = +15.5 (*c* 1.0, $CHCl_3$)].

(29) It should be noted that although the ee's for **15ax** and **15eq** were not determined, optical rotations for both were determined: **15ax**, $[\alpha]^{23}_D$ = +4.5 (*c* 2.1, $CHCl_3$), **15eq**, $[\alpha]^{23}_D$ = +1.5 (*c* 2.1, $CHCl_3$). Although by no means definitive, these results seem to indicate that **15eq** (arising from aldol **13eq**) would lead to the (+)-isomer of pseudococaine with an ee similar to that obtained for (+)-cocaine.

(30) For a review of proline catalyzed reactions, see: List, B. *Tetrahedron* **2002**, *58*, 5573.

(31) For experimental and theoretical work on the proline-catalyzed aldol transition states, see: (a) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 9922. (b) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273. (c) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475. (d) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16.

(32) A dihedral angle of 180° is termed anti, while an angle of 0° refers to the *syn* arrangement.

(33) Preliminary investigations to test the rationale with other *N*-protecting groups (i.e. *N*-H, *N*-Me, and *N*-CHO) were thwarted as attempted oxidation to the *meso*-dialdehyde led only to the recovery of starting material or decomposition products. Another possibility not investigated by us would be to use a proline derivative incapable of forming such H-bonds such as the methyl ester of L-proline to see if any asymmetric induction occurs at all.

(34) One must consider the issues of the *E*/*Z* enamine geometry, boat/chair conformations, *syn*/*anti* relationship of the carboxylic acid to the olefin, equatorial versus axial placement of substituents, and the issue of H-bond acceptor (Boc carbonyl versus aldehyde) quickly causes the number of reasonable transition states possible to become extremely large. See ref 31 for more detailed discussions.

(35) Based on these rationale, one would expect to obtain (−)-cocaine if D-proline was used instead.