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Asymmetric Total Synthesis of (*S*)-(+)-Cocaine and the First Synthesis of Cocaine C-1 Analogs from *N*-Sulfinyl β-Amino Ester Ketals

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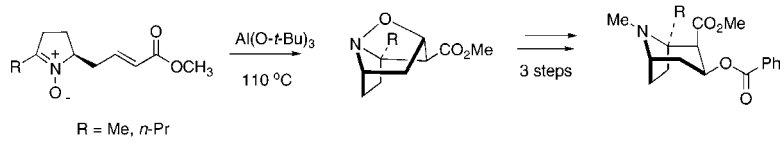
ABSTRACT



Sulfinimine-derived α,β-unsaturated pyrrolidine nitrones, on heating with Al(O-*t*-Bu)$_3$, undergo a highly stereoselective intramolecular [3 + 2] cycloaddition to give tricyclic isoxazolidines, which are transformed in three-steps to give C-1 substituted cocaine analogs.

The synthesis of the tropane alkaloid (*R*)-(−)-cocaine (**1**) and its analogs has been a subject of significant focus for nearly a century (Figure 1).[1] In the past, the reasons for this interest were the intellectual challenge of accessing the tropane skeleton and the difficulty of introducing substituents into the ring stereoselectively. More recently the challenge has been the search for therapeutically useful antagonists and partial agonists for the treatment of cocaine abuse, a major problem in the United States and of worldwide concern.[2] There are eight stereoisomers of cocaine, but only the R-isomer (−)-**1** is addictive.[2,3] The enantiomer, S-isomer (+)-**2**, is 155 less potent than (−)-**1** and is rapidly metabolized.[4]

The major difficulty in the asymmetric synthesis of cocaine and cocaine analogs is the aforementioned problem of introducing substituents into the tropane skeleton. Specifically, this relates to the necessity for a cis relationship between the C-2 and C-3 substituents where the C-2 carbomethoxy group occupies the thermodyamically unfavorable axial position. For this reason, most nonracemic cocaine analogs are prepared from natural cocaine (*R*)-(−)-**1**.[3] While many analogs of cocaine have been prepared using this approach and have provided useful information on the cocaine-binding site, the types of substituents that can be introduced are severely limited, that is, bridgehead or C-1 substituents. To date, no therapeutically useful cocaine derivatives have been reported.[2]

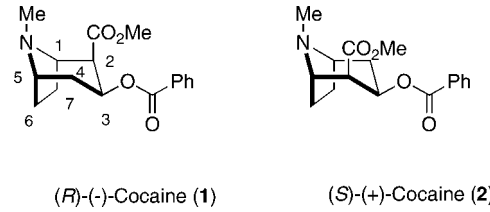


Figure 1. Cocaine and its enantiomer.

There are few asymmetric syntheses of cocaine and only two total asymmetric syntheses[5a,6] that do not rely on resolution to produce enantiomerically pure materials.[5] Mans

(1) For reviews, see: (a) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435. (b) Humphrey, A. J.; O'Hagan, D. *Nat. Prod. Rep.* **2001**, *18*, 494. (c) Hemscheidt, T. *Top. Curr. Chem.* **2000**, *209*, 175.

(2) For a review of these methods, see: Singh, S. *Chem. Rev.* **2000**, *100*, 925.

(3) Carroll, F. I.; Lewin, A. H.; Abraham, P.; Parham, K.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1991**, *34*, 883.

(4) Gatley, S. J.; MacGregor, R. R.; Fowler, J. S.; Wolf, A. P.; Dewey, S. L.; Schlyer, J. J. *J. Neurochem.* **1990**, *54*, 720.

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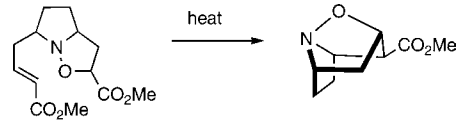
and Pearson synthesized (*S*)-(+)-cocaine (**2**) in 86% ee using a 2-azaallyllithium [3 + 2] cycloaddition reaction to prepare a *meso*-pyrrolidine dialdehyde that was subjected to an asymmetric proline-catalyzed intramolecular enol-*exo*-aldol reaction. This required separation of a 1:1 mixture of epimers at C-2.[5a] Rapoport prepared (−)-**1** from glutamic acid using an intramolecular nucleophilic substitution reaction to form the tropane ring.[6] They controlled the relative stereochemistry at C-2 and C-3 in (−)-**1** by a [3 + 2] cycloaddition of an in situ generated nitrile *N*-oxide to a nonracemic tropene. Cha prepared (+)-cocaine (**2**) by desymmetrization of tropinone, an advanced intermediate, using a chiral lithium base and an aldol reaction to install the axial carbomethoxy group.[7]

In the late 1970s, Tufariello and co-workers introduced perhaps the most innovative method to control the stereochemistry at C-2 and C-3 in their synthesis of (±)-cocaine.[8] On heating, α,*β*-unsaturated isoxazolidine **3** undergoes a [3 + 2] cycloreversion to give an intermediate nitrone that cyclizes to tricyclic isoxazolidine **4**, which was transformed into (±)-cocaine (Scheme 1). It would be very difficult to

Scheme 1. Tufariello Synthesis

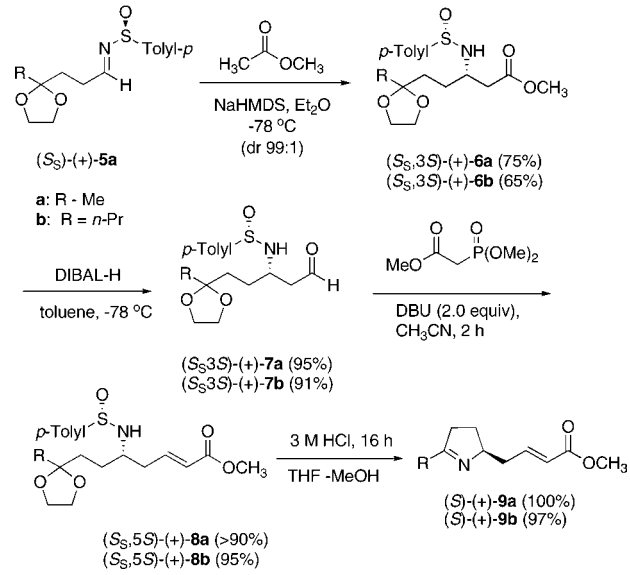


3 **4**

install functionality at other positions in the cocaine skeleton with this synthesis, which is also true of the asymmetric routes to this molecule. Recently, we described a new method for the asymmetric syntheses of substituted tropinones[9] and homotropinones[10] from *N*-sulfinyl *β*-amino ketone ketals via an intramolecular Mannich cyclization reaction.[11] We report here application of *N*-sulfinyl *β*-amino ester ketals for the asymmetric synthesis of (*S*)-(+)-cocaine (**2**) and the first syntheses of cocaine analogs to have a C-1 bridgehead substituent.

Our synthesis of C-1 cocaine analogs begins with masked oxo-sulfinimines (*S*)-(+)-**5**.[12] On treatment with an excess of the sodium enolate of methyl acetate in Et_2O at −78 °C, (+)-**5** afforded the corresponding *N*-sulfinyl *β*-amino ester ketals (S_S,3*S*)-(+)-**6** as single diastereoisomers (Scheme 2). Reduction of (+)-**6** with DIBAL-H in toluene at −78 °C gave aldehydes (+)-(S_S,3*S*)-(+)-**7** in good yield without

Scheme 2. Dehydropyrrolidine Synthesis



epimerization at the C−N stereocenter. When aldehyde (+)-**7a** was subjected to the Roush-Masamune modification of the Horner-Wadsworth-Emmons olefination reaction (DBU-LiCl)[13] with trimethylphosphonoacetate, α,*β*-unsaturated *N*-sulfinyl amino ketal (S_S,5*S*)-(+)-**8a** was isolated as an inseparable 9:1 *E*:*Z* mixture of isomers. The 16 Hz coupling constant observed for the olefinic protons in (+)-**8a** is consistent with the major isomer having the desired *E*-geometry.[13] It is noteworthy that when LiCl was omitted from the HWE reaction only the *E*-isomer of (+)-**8a** was obtained in >90% yield (Scheme 2). Similar results were observed in the preparation of (+)-**8b**. Hydrolysis of α,*β*-unsaturated *N*-sulfinyl amino ketals (S_S,5*S*)-(+)-**8** with 3 N HCl gave the corresponding dehydropyrrolidines (*S*)-(+)-**9a** (R = Me) and (*S*)-(+)-**9b** (R = *n*-Pr) in excellent yields.

With the dehydropyrrolidines (+)-**9** in hand the idea was to oxidize them to the corresponding nitrones with the expectation that on heating they would undergo an intramolecular [3 + 2] cycloaddition to give tricyclic isoxazolidines. While most oxidations of imines lead to oxaziridines,[14] Goti and co-workers recently described the catalytic oxidation of imines to nitrones with urea hydrogen peroxide (UHP) catalyzed by methyltrioxorhenium (MTO).[15] Oxidation of (+)-**9** with 3.3 equiv of UHP and cat. MTO in anhydrous MeOH for 15 h gave nitrones **10**, which were used crude in the next step because attempted purification resulted in

(5) For leading references and an excellent summary of methods used in the synthesis and asymmetric synthesis of cocaine, see: (a) Mans, D. M.; Pearson, W. H. *Org. Lett.* **2004**, *6*, 3305. (b) Mans, D. M. *Aza-Bridged Bicyclic Amines From (2-Azaallyl)stannanes and the Total Synthesis of (+)-Cocaine*. Ph.D. Thesis, University of Michigan, Ann Arbor, MI, 2004.

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(8) 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.

(9) Davis, F. A.; Theddu, N.; Gaspari, P. A. *Org. Lett.* **2009**, *11*, 1647.

(10) Davis, F. A.; Edupuganti, R. *Org. Lett.* **2010**, *12*, 848.

(11) For leading references to the chemistry of *N*-sulfinyl imines see: Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993.

(12) For applications of masked oxo sulfinimines in asymmetric synthesis, see: (a) Davis, F. A.; Zhang, H.; Lee, S. H. *Org. Lett.* **2001**, *3*, 759. (b) Davis, F. A.; Lee, S. H.; Xu, H. *J. Org. Chem.* **2004**, *69*, 3774. (c) Davis, F. A.; Gaspari, P. M.; Nolt, B.; Xu, P. *J. Org. Chem.* **2008**, *73*, 9619. (d) Reference 9. (e) Reference 10.

(13) Blanchette, M. A.; Choy, W.; Davis, J. T.; Esssenfield, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

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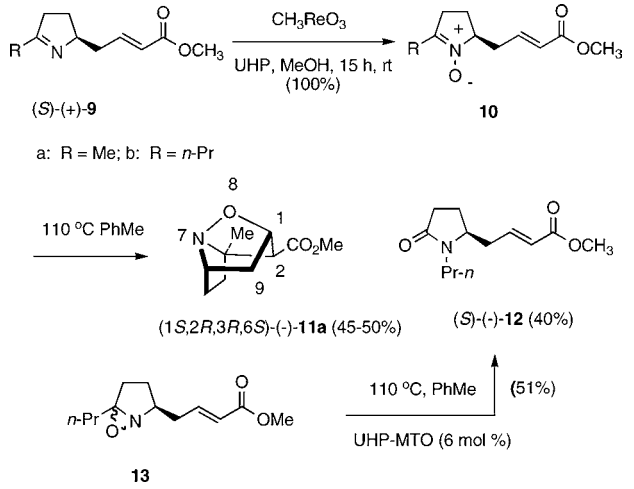
(15) Soldaini, G.; Cardona, F.; Goti, A. *Org. Lett.* **2007**, *9*, 473.

decomposition (Scheme 3).[16] Refluxing **10a** (R = Me) in toluene for 48 h afforded tricyclic isoxazolidine (1*S*,2*R*,3*R*,6*S*)-**14** in 90−98% yield (Scheme 4). Hydrogenolysis (Pd−C/H_2) cleaved the N−O bond affording (−)-**15** in excellent

Scheme 3. Isoxazolidine Synthesis



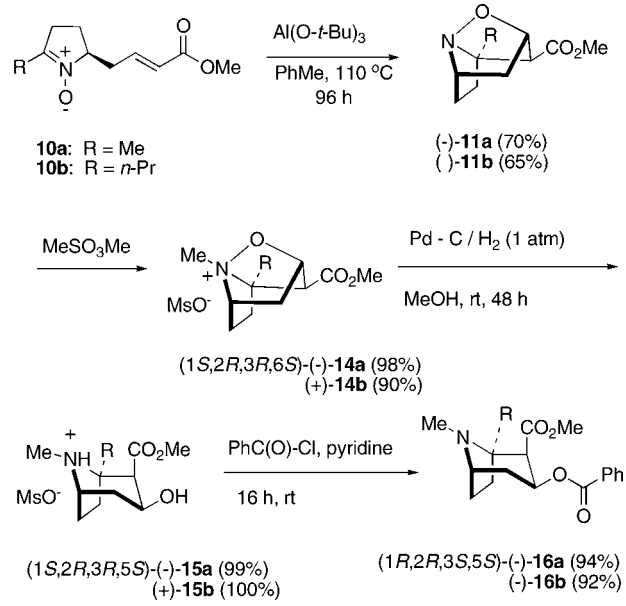
(−)-**11a** in 45−50% yield. The structure of (−)-**11a** is supported by characteristic proton resonances at δ 4.93 ppm for the C-1 (doublet) and at δ 2.44 ppm C-2 (singlet) in the ^{1}H NMR spectra.[8] Nitrone **10b** (R = *n*-Pr) did not give the tricyclic isoxazolidines on heating but amide (*S*)-(+)-**12** in 40% yield as a single isomer (Scheme 3). The olefinic protons in (+)-**12** are present at δ 6.96 and δ 5.90 ppm in the ^{1}H NMR and in the ^{13}C NMR the amide C═O carbon appears at δ 179.5 ppm. On heating, it is known that nitrones rearrange to oxaziridines, and oxaziridines rearrange to amides.[14] However, heating oxaziridine **13** under the reaction conditions resulted in no reaction. When **13** was heated at 110 °C for 96 h in the presence of a catalytic amount of peroxorhenium complex amide (*S*)-(+)-**12** was obtained in 51% yield.[17] Oxaziridine **13** was prepared in 77% yield, as a 2.5:1 mixture of isomers, by *m*-CPBA oxidation of (*S*)-(+)-**9b**. Intramolecular [3 + 2] cycloaddition of the nitrone to form the isoxazolidines apparently competes with rearrangement to the oxaziridine. The *n*-propyl group in **10b** may sterically inhibit the cycloaddition reaction.

Lewis acids catalyze 1,3-dipolar cycloadditions by activation of the α,β-unsaturated carbonyl functionality.[18] Because the Lewis acid can also coordinate to the nitrone, it was thought that a bulky Lewis acid, such as aluminum *t*-butoxide [(Al(O-*t*-Bu)$_3$], might preferentially activate the α,β-unsaturated ester group in **10**. Heating **10a** (R = Me) in toluene with 0.5 equiv of Al(O-*t*-Bu)$_3$ for 96 h improved the yield of (−)-**11a** from 45−50% to >70% yield (Scheme 4). Significantly, under similar conditions, tricyclic isoxazolidines (−)-**11b** (R = *n*-Pr) was obtained in 65% and amide (+)-**12** was not detected.

Heating (−)-**11** with 10 equiv of methylmethanesulfonate ($MeSO_3Me$) in benzene afforded methanesulfonate salts (−)-

(16) The nitrone is assumed to be formed quantitatively based on TLC and ^{13}C NMR.

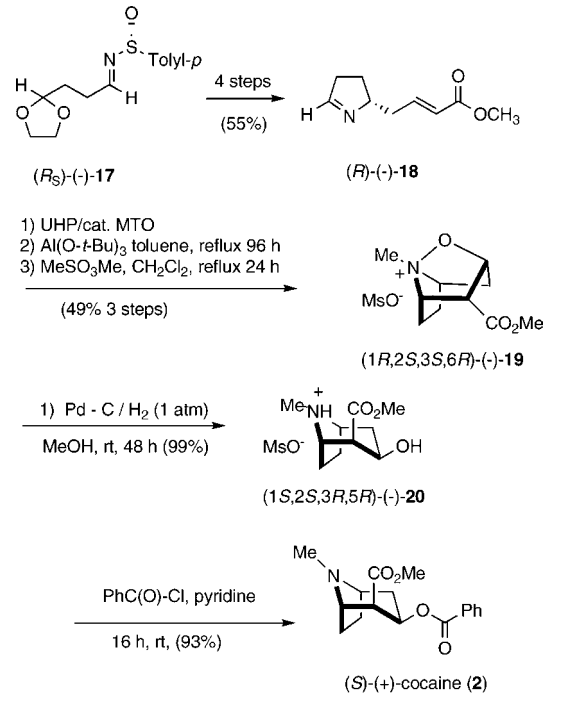
Scheme 4. Cocaine C-1 Substituted Analog Synthesis



yield, which was transformed into the C-1 cocaine analogs (−)-**16a** (R = Me) and (−)-**16b** (R = *n*-Pr) with benzoyl chloride and pyridine in 94 and 92% yields, respectively (Scheme 4).[19]

(*S*)-(+)-Cocaine (**2**) was prepared from masked oxo sulfinimine (R_S)-(−)-**17** (Scheme 5). Sulfinimine (R_S)-(−)-

Scheme 5. Synthesis of (*S*)-(+)-Cocaine (**2**)



17 was transformed, as before (Scheme 2), to dehydropyrrolidine imine (−)-**18** in 55% yield for the four steps. Oxidation and heating afforded the tricyclic isoxazolidine intermediate, which, because of its volatility, was transformed into the methanesulfonate salt (−)-**19** with $MeSO_3Me$. Hydrogenolyses (Pd-C/H_2) gave (−)-**20** which was treated in crude form with benzoyl chloride to give (*S*)-(+)-cocaine (**2**) in 9 steps (8 operations) in 25% overall yield from sulfinimine (−)-**17**. This represents the most efficient enantioselective route to cocaine from acyclic starting materials.

In conclusion, the first enantiopure C-1 analogs of cocaine, (+)-**16a** (R = Me) and (+)-**16b** (R = *n*-Pr), and (*S*)-(+)-cocaine (**2**) were prepared in 9 steps from masked oxo sulfinimines. The key step in this reaction is the highly stereoselective intramolecular [3 + 2] cycloaddition of a nitrone to α,β-unsaturated esters to give tricyclic isoxazolidines which establishes the cis arrangement of substituents at the C-2 and C-3 positions in the tropane skeleton.

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Supporting Information Available: Experimental procedures, characterization and spectroscopic data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) For a review and leading references to the use of Lewis acid in nitrone 1,3-dipolar cycloadditions see: Gothelf, K. V.; Jorgensen, K. A. *Chem. Commun.* **2000**, 1449.

(19) Lewin, A. H.; Naseree, T.; Carroll, F. I. *J. Heterocyclic Chem.* **1987**, *24*, 19.