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DARK Classics in Chemical Neuroscience: Cocaine

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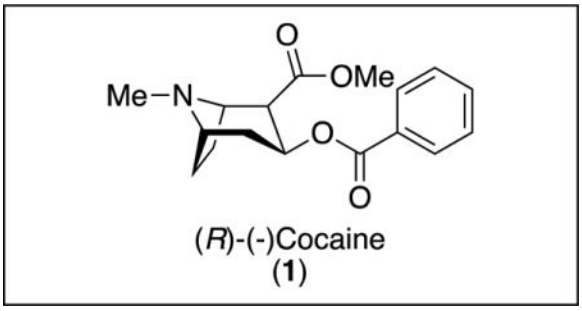
Abstract

In this review, we consider the story of cocaine from its humble origins in South America to its status as one of the most abused substances in 21st century society. The synthesis and biosynthesis of cocaine are discussed, as well as its pharmacokinetics, metabolism, pharmacology, and importance in modern neuroscience and molecular imaging.

Graphical abstract



Keywords

Cocaine; Crack cocaine; Alkaloids; Stimulant; Molecular imaging; Pablo Escobar

CULTURAL AND HISTORIC RELEVANCE

> “For there was never any elixir so instant magic as cocaine.”
>
> –Aleister Crowley, Cocaine (1917)[1]

The story of cocaine is old. Very old. Fascinating and alluring, but equal parts destructive and tragic, this relatively simple alkaloid has a long and complex past. Cocaine’s history

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spans millennia, is peppered with enigmatic characters including actors, rock stars, athletes and gangsters, and is full of paradoxes, unimaginable wealth, scandal, murder, passion and intrigue. Cocaine bridges the old world to the new, the practice of modern medicine to the illicit drug market and the drug cartels, one of the largest illegal businesses with one of the largest legal ones, and the means of survival for one society at the expense of damage and destruction to another.

Cocaine is an alkaloid that is produced biosynthetically by *Erthroxylum coca* (Figure 1), a shrub native to the Andean Highlands and northern parts of the Amazon in South America. Pure cocaine (blow, snow, Charlie, C) is a white powder, and as the hydrochloride salt is water soluble and usually snorted up the nose. “Crack cocaine” (rock, base) is the free base. It is a yellow solid and is usually smoked in a crack pipe (Figure 2). While there are eight possible stereoconformers, only one of them, (*R*)–(-)cocaine (**1**), is addictive.[2]

For thousands of years, indigenous South Americans have consumed coca tea or chewed on dried coca leaves with lime or ash, promoting the release of cocaine in saliva. In addition to the general stimulating and rejuvenating benefits associated with coca, including the alleviation of hunger and thirst, the practice has been used by locals as well as travelers to South America specifically for the relief of altitude sickness.[3] These “magical” effects, associated with the slow release of cocaine from chewing or brewing tea, has given the coca plant mythical status amongst the local population. Considered a gift from heaven, it has been referred to as “the divine plant” of the Incas.[4] When the Spaniards invaded South America and enslaved the indigenous population, they found that allowing the slaves to chew coca leaves while working made them more affable and likely to do more perilous tasks.[5]

Since its introduction to modern society, cocaine has captured the imagination and inspired the creativity of artists and scientists alike. Artistic references to cocaine are abundant in literature (*Sherlock Holmes* by Sir Arthur Conan Doyle,[6] *The Curious Case of Dr. Jekyll and Mr. Hyde* by Robert Louis Stevenson), Hollywood movies (*Blow, Traffic, Scarface, Pulp Fiction*), TV shows (*Narcos, Snowfall*), artwork (at the time of writing Banksy’s *Snorting Copper* is estimated to be worth $1.75 million[7]) and songs (*Cocaine* by JJ Cale and made famous by Eric Clapton, *Cocaine Blues*, different songs with the same title recorded by Johnny Cash and Bob Dylan, *Champagne Supernova* by Oasis, and *Crack City* by David Bowie).

In the scientific community, bringing cocaine back to Europe allowed for the first isolation in 1855 by Niemann and the later development of “coca wine” by Angelo Mariani. *Vin Mariani* (Figure 3) was a Bordeaux wine laced with coca leaves.[10, 11] It contained 10% alcohol and 8.5% alkaloid cocaine from the leaves of *Erythroxylum coca* and, famously, Thomas Edison, Queen Victoria and Pope Leo XIII were reportedly all fans. Subsequently cocaine has proven an addictive target for total synthesis chemists (*vide infra*), while elucidating the biosynthesis, metabolites and mechanisms of pharmacological action have been of similar interest to biochemists and pharmacologists alike. The latter quickly developed a better understanding of the medicinal properties of cocaine, and backed up the lore of the South American natives with biochemistry. However, the popularization of

cocaine at this time can perhaps mostly be attributed to Sigmund Freud, who documented the stimulant and euphoric effects of cocaine in his 1884 publication "A contribution to the knowledge of the effects of cocaine," which was republished more recently in *The Cocaine Papers.*[12] Freud was also able to show dose-dependent relationship effects of cocaine on mood, hand strength, and measure of perception, and was immensely proud of these discoveries.

The chronicles of coca from the Inca,[4] as well as the preliminary scientific investigations from Freud (and others),[12] caused the medicinal properties of cocaine to be seized upon, and prescription of cocaine for toothaches (Figure 4), headaches, dyspepsia, gastrointestinal disorders, neuralgia, and melancholy soon followed around the turn of the 20th century. *Coca Cola* was developed during this period from coca leaves and kola nuts, though the exact recipe remains a secret, and marketed as the "intellectual beverage and temperance drink" during prohibition America.[13] Today, *Coca Cola* obtains coca leaves with a special permit and, although the drink no longer contains cocaine, it remains one of the world's most valuable companies. Cocaine was also used in solutions of 4 to 20% for local anesthesia, chiefly in ophthalmologic surgery, because of cocaine's unique ability to block nerve conduction and cause vasoconstriction in mucous membranes.[14, 15] Notably, today cocaine remains approved by the US Food and Drug Administration (FDA) as a nasal solution (Figure 5), and is indicated for the induction of local anesthesia of the mucous membranes when performing diagnostic procedures and surgeries on or through the nasal cavities in adults.[16]

If our story stopped there, then perhaps cocaine would have earned a place in the recent issue of this journal devoted to *Classics in Chemical Neuroscience*.[17] However, since this paper is part of the issue dedicated to *Dark Classics in Chemical Neuroscience*,[18] it is imperative that we acknowledge the other darker side of cocaine. William S. Burroughs described cocaine as "*the most exhilarating drug I have ever used,*"[19] and Dominic Streatfeild concurred: "*Cocaine is a sensational drug… Nothing will make you feel as good.*"[20] This ability to cause pleasure stems from cocaine's ability to block uptake of neurotransmitters such as dopamine and norepinephrine (see *Pharmacology* section for more details), and is what makes the drug extremely addictive.[21] Perhaps the first description of cocaine addiction was in the popular Sherlock Holmes detective stories, written in the 1880's by former ophthalmologist Arthur Conan Doyle. In *The Adventures of Sherlock Holmes*: *A Scandal in Bohemia*, Dr. Watson describes Holmes as: *"…alternating from week to week between cocaine and ambition."*[6] Notably, Freud claimed that cocaine could cure medical and physiological ailments, and he treated his morphine-addicted friend with cocaine. His effort was entirely successful in treating the opioid addiction — by replacing it with a cocaine addiction![12] This garnered Freud some negative press and, famously, Friedrich Albrecht Ehrlenmeyer, physician and psychiatrist, accused Freud of having "unleashed the third scourge of humanity," after alcohol and opioid addiction.[22]

Despite the early evidence of the addictive properties (or perhaps because of them!), snorting cocaine for recreational use became popular in the early 20th century, and by 1910 the first reports of nasal damage from snorting cocaine appeared in the scientific and medical literature.[26] By 1912, thousands of people were dying on an annual basis from

cocaine abuse, prompting the United States to ban the drug in 1914.[26] The use of cocaine in consumer products was severely lowered in 1914 by the Harrison Narcotics Act, which forbade the use of cocaine in proprietary medicines and required regulation of those involved with the importation, manufacturing, and distribution of cocaine and opium products. Unfortunately, this American law also misidentified cocaine as a "narcotic" which added confusion to any medical usefulness of the natural product.[10] In 1970, the Comprehensive Drug Abuse Prevention and Control Act would define cocaine as "Schedule II:" having medical use and a high abuse potential.[27] To this day cocaine remains a controlled substance, and is classified Schedule II by the US Drug Enforcement Administration (DEA). The increased control of the substance and the development of local anesthetics based on cocaine (see the *Importance in Neuroscience* section), have replaced most of the use of cocaine medically.

Abuse of cocaine increased in the 1970's, with some experts pointing to the demonization of amphetamines as a turning point for cocaine's popularity. Later in this decade the infamous Medellin cartel kingpin Juan Pablo Escobar (Figure 6), would monopolize the import and sale of cocaine in the United States.[28] The incredible story of Escobar's cocaine empire has been dramatized in movies *(Blow*) and television (*Narcos*) and paints a picture of extravagant wealth in Colombia from the coca trade. During his prime, Escobar's cartel supplied ~80% of the cocaine smuggled into the USA (~15 tonnes per day), turning over almost $22 bn a year in personal income. For this reason, Escobar was dubbed the *King of Cocaine*, and he was the wealthiest criminal in history. Not only that, but his estimated net worth of ~$30 bn actually made him one of the wealthiest people in the world, too! He was eventually confined to house arrest, but following his escape he died in a shootout in 1993.

In meta-analysis of music, television, and movies, despite more media referencing drug use now than compared to 1968, there are also more mentions of "negative" consequences and side effects of illegal drug use.[29–31] Indeed, the biggest tragedy of cocaine's story is that many of the creative people described above who drew inspiration from the drug also died prematurely as a result of abusing it.[32] Thus a number of high profile musicians (Ike Turner, Scott Weiland, Whitney Houston) and entertainers (John Belushi, Philip Seymour Hoffman, River Phoenix, Corey Haim, Chris Farley, Carrie Fisher) ended up dying from a cocaine overdose, or indirect causes likely resulting from cocaine use and abuse.

Perception of cocaine abuse in America and portrayal in the media in the 1970's and 80's was decidedly racial; crack cocaine was reported in nightly news segments as always being associated with African American men.[33] This largely informed the mandatory minimum sentencing laws, which would greatly affect African American men instead of their Caucasian counterparts.[34] Despite the stimulant and euphoric effects being the same between cocaine and crack cocaine (see *Pharmacology*), there is a significantly higher sentencing law associated with crack.[27] The Anti-Drug Abuse Act of 1986 originated the mandatory minimum sentences for those convicted with drugs that exceed an amount for trafficking and not use. Under this law, the eligibility for mandatory minimum for crack cocaine was only 0.005 kg and for powder cocaine 0.5 kg.[27] Obviously from the harsher guidelines, significantly more crack cocaine users were sent to jail and this propelled a demonization of crack cocaine over pure cocaine powder. In 2010, the Fair Sentencing Act

responded to the complaint that powder cocaine was given preferential treatment; it changed the minimum amounts of crack cocaine to 0.028g, merely closing the weight ratio from 100:1 to 20:1.[27] This leniency toward cocaine correlates to shorter prison sentences as well.[34] Although changes have been made, it still appears an unjust differentiation between cocaine and crack.

In the last decade, cocaine use has slightly decreased in the United States from 2% of adults aged 18-25 who reported use in 2002, to 1.7% in 2015.[35] Overall, 1.9 million people (0.7% of the US population) identify as cocaine users, with 394,000 (0.1%) of those using crack cocaine.[36] Despite a small number of users in comparison with opioids (heroin: 0.6 million/ prescription opioids: 3.8 million) and cannabis (4 million),[35] cocaine is the most highly intercepted drug globally. In 2015 for example, 864 tons of cocaine were seized from an estimated global manufacturing total of 1,125 tons of pure cocaine, produced in Colombia, Bolivia and Peru.[36] In response to the increased interception, it is estimated that coca plant cultivation has increased 25% from 2013 to 2015.[36] Despite the increase in manufacturing and trafficking risk, the price of cocaine in the United States has hardly changed.[37] Cartels control the entire manufacturing process and only pay $10,000 for a kilo of pure cocaine, despite the final markup of that pure kilo being $150,000 when a dealer divides it into gram quantities. Depending on the location, one gram of cocaine is sold for $100-$150.[37]

The expense, and low purity, associated with cocaine may be attributable to its relatively low popularity compared to other drugs. In the party scene, younger users (aged 13-25) report using 3,4-methylenedioxymethamphetamine (MDMA, molly, ecstasy or E) as a stimulant because it is cheaper in comparison to cocaine for a similar one-time high. For those still using cocaine, most report co-abuse with alcohol and other drugs.[38] Unfortunately, the mixing of cocaine with other drugs of abuse can prove deadly. Of the entertainers mentioned above, Philip Seymour Hoffman, John Belushi, Chris Farley and River Phoenix all died after using Speedball (a mixture of cocaine and morphine/heroin).[39] The most common co-abuse occurs with drinking alcohol while ingesting cocaine; the metabolism profile changes and results in a more toxic metabolite (see *Pharmacokinetics and Drug Metabolism*),[38, 40–42] and the combination of cocaine and alcohol was responsible for death of baseball pitchers José Fernández and Tommy Hanson, novelist Jacques d'Adelswärd-Fersen and musician Jay Reatard.

This is cocaine's story, and it is clearly a complex one. As we stated in our introduction, cocaine intersects and connects many different parts of the modern world. Thus, *Coca Cola* is reliant upon the coca industry and is one of the world's most valuable companies, with an estimated net worth of $188 bn. Contrastingly, the estimated value of the illegal cocaine market is $88 bn per year. Today it is estimated that ~150,000 hectares of land is used to cultivate coca and with these staggering numbers in mind, clearly the coca producing countries of Colombia, Peru and Bolivia depend upon the crop for their livelihood despite the fact that cocaine is responsible for almost 50,000 deaths per year worldwide. Coca's importance to the region was known as long ago as the 16th Century when Juan Matiezo de Peralta once remarked: "*if there were no coca there would be no Peru*,"[20, 43] and for this reason a century of cocaine abuse is unlikely to topple a multi-billion dollar industry based on a crop that has been part of a peoples culture for thousands of years. In this review we

describe the science underpinning the wealth, power and scandal, the methods behind the money, and the pharmacology of cocaine's pleasure. The synthesis and biosynthesis of cocaine are discussed, as well as the alkaloids pharmacokinetics, metabolism, pharmacology and importance to modern neuroscience and molecular imaging.

CHEMICAL PROPERTIES, SYNTHESIS, AND BIOSYNTHESIS

Cocaine is an alkaloid (Table 1), and the first total synthesis of cocaine was achieved by Richard Martin Willstätter in 1901 which also secured the exact structure of the compound.[44] Leading to this discovery, Willstätter prepared the tropane ring system in a lengthy synthesis involving a historic reaction for the time, a double bond dibromination to prime a cyclisation reaction.[45] He carried out degradation studies on the product tropine, cocaine, and ecgonine to elucidate cocaine, and completed the first synthesis of cocaine starting from tropinone (**2**) (Scheme 1).[44] Including the formation of tropinone, this synthesis would take an overall 17 steps. Willstätter earned the Nobel Prize for Chemistry in 1915 for exceptional achievements in organic synthesis; however, it was mostly for his contributions to chlorophyll chemistry rather than tropane syntheses.

In the mid-1900's, other syntheses of (-)cocaine emerged utilizing another natural product, l-ecgonine (**6**), and achieving 95% conversion after esterification and benzoylation (Scheme 2).[50] Most total syntheses of cocaine, regardless of starting material, included 2-carbomethoxytropinone (2-CMT, **4**) and focused effort on optimizing the steps to this intermediate.[51–54] In 1974, generation of tropane alkaloids was facilitated by use of the polybromo ketone-iron carbonyl reaction of 1,3-dibromopropan-2-one (**7**) with methyl 1*H*-pyrrole-1-carboxylate (**8**) to access complex intermediates such as tropinones (**10**) and tropine (**11**) (Scheme 3).[55, 56] Another interesting route involved [4+2] nitroso cycloadditions of 1,3-cycloheptadienes (**12**) and 1-chloro-1-nitrosocyclohexane (**13**) via a Diels-Alder reaction (Scheme 4).[57] However, these attempts were unable to control the stereochemistry of cocaine. The exact structures and physical properties of four of the eight possible diastereomers (cocaine (**1**), pseudococaine (**20**), allococaine (**21**) and pseudoallococaine (**22**)) were described (Figure 7), and the focus shifted toward controlling the stereochemistry in the synthesis.[58] Optimized total syntheses of cocaine quickly followed the advent of nitrone cycloaddition.[59–61] For example, Tufariello started from 3,4-dihydro-2*H*-pyrrole 1-oxide (**23**). A cycloaddition with methyl but-3-enoate (**24**) gave nitrone **25**, which was converted to **26** with mCPBA. This was then converted to isoxazolidine ester **28** which, upon refluxing in xylene, rearranged to give the key cycloadduct **29**; from this intermediate they were able to control the stereochemistry and make (-)-cocaine in three additional steps (Scheme 5).[60]

A recent total synthesis of (-)-cocaine by Cheng *et al.*, was accomplished in nine steps beginning with Betti base derivative **31** (Scheme 6).[62] After five steps, including a Grubbs II catalyzed ring closing metathesis and a 1,3-dipolar cycloaddition, the 3-bromo-2-isoxazoline intermediate **34** was synthesized. After four more steps to open the isoxazoline ring, install the benzoyl substituent in a stereoselective fashion, and deprotect the amine, (-)-cocaine (**1**) was produced in 55% overall yield.[62] Shing & So also developed a 15 step synthesis in 2011 (13% overall yield), starting from the cheap and commercially available D-(-)-ribose **38**,

which allowed for analogue derivation at the C6 and C7 positions through a key endo-selective intramolecular nitrone-alkene cycloaddition reaction (Scheme 7).[63] An alternative synthesis, which focuses on synthetically simple techniques, controls stereoconfiguration and permits access to many active tropane alkaloids.[64] They begin with a one-pot catalytic, enantioselective three-component reaction catalytic aza-Michael/Witting tandem reaction between enal **45**, hydroxylamine **46**, and alkyl 2-triphenylphosporanylidene acetate **47**, to yield ester **48**. The synthesis to active cocaine progressed in 5 total steps and 39% overall yield (Scheme 8).[64]

Elucidating the biosynthesis of cocaine (and related tropane alkaloids) has been a focus of biochemists for over a century. While there are over 200 known species of the coca plant, only three are routinely cultivated for the specific use of cocaine extraction.[10] Sir Robert Robinson won the Nobel Prize for Chemistry in 1947 for his investigations on plant products of biological importance, especially the alkaloids.[65] In 1917, Robinson published a one pot synthesis of tropinone (**2**) by the addition of succinaldehyde (**51**) to an aqueous solution of methylamine (**53**) and acetonedicarboxylic acid **52** at physiological pH (Scheme 9).[66] This observation led to Robinson considering that the biosynthesis may occur via an analogous route involving an amino acid to provide a pyrrolidine ring moiety, and an acetone equivalent to furnish C-2, C-3, and C-4 of the tropane ring.[66]

The plant can use either the fundamental amino acid arginine or the unnatural amino acid ornithine as a precursor for putrescine (1,4-diaminobutane, **54**). Edward Leete first confirmed the involvement of ornithine as a precursor to the amino acid portion of the tropane ring.[67] Leete performed a feeding experiment with [2-^{14}C]ornithine in *Datura stramonium* plants, and observed the label incorporated into C-1 of the tropane ring of hyoscyamine;[68, 69] however, in *Hyoscyamus albus*[70] and *Erthroxylon coca*[71] equal labeling was observed in C-1 and C-5. This accumulation of evidence suggested that the most likely route involved a symmetrical intermediate. Leete proposed a pathway from ornithine to putrescine. Putrescine can then be converted to cocaine in 7 steps (Scheme 10). Putrescine (**55**) is methylated to generate **55**, quickly followed by oxidation of the other amino group to produce 4-methylaminobutanal (**56**).[65] Aldehyde **56** then spontaneously cyclizes to *N*-methyl-Δ^1-pyrrolinium cation **57**. To this intermediate, the equivalent of two acetyl units are added and then condensed to afford the oxobutanoic acid intermediate (**58**).[72] The source of the two acetyl units remains highly protested, with acetate, acetoacetate, or malonate suggested as the possible carbon sources. Another cyclization reaction then leads to 2-CMT (**4**).[73] This is the first tropane intermediate and is reduced by methylecgonone reductase, named specifically, to generate EME (**5**). These two tropane intermediates are critical for synthetic pathways, and also provide opportunities for derivatization. The final step in the biosynthesis is the esterification of EME (**5**) to afford cocaine (**1**) by a BAHD acetyltransferase.[74] Hydrolysis of this ester bond occurs readily in human plasma and, as such, EME is a commonly observed metabolite of cocaine.[65]

PHARMACOKINETICS AND DRUG METABOLISM

Given its long history of use, formal studies of pharmacokinetics and drug metabolism were already underway by mid-1900 (Figure 8). One of the first studies used a volunteer “regular

user" and administered a controlled, intramuscular injection of cocaine- hydrochloride.[75] Researchers took urine sample and, after liquid extraction into chloroform, identified the main metabolite, benzoylecgonine (BE, **59**), by gas chromatography. They had theorized ecgonine (**6**) would also be a major metabolite, but it was not observed by this method of extraction. A decade later, a different group administered cocaine by intravenous (*i.v.*) injection to three volunteers and followed up with blood and urine analysis; they also observed BE (**59**) as the major metabolite.[76] In 1984, Mastubara *et al.* subcutaneously injected 1.0 mg/kg of pure cocaine-HCl and observed the persistence of the ecgonine methyl ester (EME, **5**) metabolite up to 72 hours in all experimental dogs.[77] It accounted for 6.6-27.1% of a dose of cocaine in dogs and 8.8-31.9% of a dose in rabbits. BE (**59**) and EME (**5**) are the two major metabolites; excretion in feces was less than 1% of administered dose. This study also identified the *in vitro* ester hydrolysis of cocaine (**1**) to form metabolite **60** in plasma from dogs.[77] In 1990, Zhang & Foltz were able to identify 11 cocaine metabolites (4 new), and parent, in a urine specimen.[78] These metabolites: benzoylecgonine (**59**), ecgonine (**6**), ecgonidine (**61**), ecgonidine methyl ester (**62**), ecgonine methyl ester (**5**), norecgonidine methyl ester (**63**), norecgonine methyl ester (**64**), *m*-hydroxycocaine (**65**), *p*-hydroxycocaine (**66**), *m*-norcocaine (**67**), *m*-hydroxybenzoylecgonine (**68**), cinnamoylcocaine (**69**) and cinnamaoylecgonine (**70**), were analyzed and confirmed by GC-MS. However, one potential pitfall of this experiment stems from the lack of control of the subject; it is unknown what dose of cocaine was taken, nor the route of administration.

Most human studies, if they were able to control the route of administration in subjects, focused on intravenous or intramuscular administration, which ignored the intranasal and smoke inhalation routes which are more commonly used. Jeffcoat *et al.*, led one of the first systematic investigations into the differences common routes of administration: intravenous injection (*i.v.*), nasal insufflation (*n.i.*), and smoke inhalation (*s.i.*).[9] The authors estimated the bioavailability of cocaine to be 80% for *n.i.* and 57% for smoking, though the smoking is highly variable and they explain that some individuals were more skilled in smoking a crack pipe than others. The different routes of administration predictably resulted in varied absorption times (*n.i.*: 11.7 min vs *s.i.*: 1.1 min). This also affected the time of observed peak concentration, with smoked cocaine occurring at 6 minutes while insufflation requiring ~45 minutes to reach maximum concentration. The elimination half-lives were calculated from this data set, concluding that plasma cocaine could be fit with a biexponential function and an elimination phase half-life of 78 minutes, renal clearance of 0.12 ml/min/kg, and a total clearance of 23 ml/min/kg. The insufflation studies maintained the same total elimination half-life of 78 minutes; however, the smoking elimination rate constant was slightly faster and resulted in an elimination half-life of 69 minutes, though still comparable.[9] There is an apparent difference in metabolite ratios between the routes of administration. The authors theorize, specifically in the smoke inhalation scenario, that this is due to pyrolysis. Major metabolites observed were EME (**5**), ecgonine (**6**), BE (**59**), and an unidentified species. The *i.v.* route's major metabolite was BE (**59**; 36%) and then EME (**5**; 19%). Major metabolites from *n.i.* and *s.i.* were BE (**59**; 39%)/EME (**5**; 18%) and BE (**59**; 26%)/EME (**5**; 22%), respectively. Importantly, only 64% of the cocaine metabolites were accounted for following *s.i.*, while 68% and 69% were found following *n.i.* and *i.v.*,

respectively. Finally, there is a minor fecal excretion pathway: interestingly, there is more fecal excretion stemming from smoking, compared to *i.v.* and *n.i.* administration.[9]

The pharmacokinetics of cocaine have been of interest because of the frequent coabuse with ethanol and the increased risk of morbidity and mortality.[79] While anecdotally, users report that alcohol consumption can help avoid cocaine-induced headaches, studies in mice have shown potentiation of cocaine-induced psychomotor stimulation.[42] This potentiation could be resultant of vasoconstriction or metabolite activity.[80] Ethylated metabolites of cocaine have been observed in the blood from emergency room patients[40] and from autopsies of individuals succumbing to drug overdose.[81] In mice and rats, administration of ethanol and cocaine increased concentration in the liver by two fold, but did not significantly affect serum or brain concentration.[38] Ethanol treatment also resulted in a three-fold decrease in liver and serum BE levels; the unique cocaethylene (**71**) and norcococaethylene (**72**) metabolites were observed in liver, serum, and the brain.[38] Toxicity studies in mice have found that cocaethylene has a lower LD_{50} (62 mg/kg) than cocaine (95.1 mg/kg) and is likely the mediator of the increased mortality.[41]

PHARMACOLOGY

Cocaine acts as a local anesthetic

Opthamologist, Carl Koller, first demonstrated the ability of cocaine to induce local anesthesia in eyes by experimenting in frogs, guinea pigs, rabbits, dogs, himself, and friends before performing the first painless cataract extraction.[15, 82, 83] Koller, known to be close friends with Sigmund Freud, learned of cocaine from Freud's "Uber Coca" paper in 1884.[12] In the same year, an American opthamologist, Herman Knapp, was also performing surgeries using cocaine and discovered its anesthetizing effects on all mucous membranes, urging its use for more surgical applications.[82, 84] The pharmacodynamic action causing anesthesia is due to the inhibition of voltage-gated sodium channels and stopping neuronal potentiation.[14] However this action also provides cardiotoxicity associated with cardiac sodium channel blockade (see *Toxicity and Coabuse*).

Cocaine acts as a psychomotor stimulant

In the CNS, cocaine inhibits multiple neurotransmitter reuptake transporters, most notably the dopamine reuptake transporter (DAT) and the norepinephrine reuptake transporter (NET).[85] Additional evidence confirmed that cocaine antagonized adrenergic receptors, being that prazosin was able to block cocaine activity in mice.[85] In 1988, Di Chiara and Imperato provided the first microdialysis evidence of the effects of cocaine, and other drugs of abuse, on extracellular dopamine levels in rat brains. Their work provided biochemical evidence for the limbic system's involvement in stimulant action.[86] Inspired by those experiments, Chen and Reith quantified the increase in other extracellular monoamines (norepinephrine and serotonin) after local perfusion of cocaine in the ventral tegmental area (VTA) in rat brains, demonstrating cocaine's global action on monoamine levels.[87] The VTA is the origin of most dopaminergic fibers and is likely the primary region for cocaine's stimulant action and high risk for addiction. Further studies revealed that combined DAT and serotonin transporter (SERT) knockout in mice eliminate cocaine place preference.[88] At low

doses, cocaine produces an alerting response consisting of increases in exploration, locomotion, grooming, and rearing, similar to that of amphetamine.[89, 90] At increased doses, the locomotor activity decreases and the behavioral patterns become stereotyped in rodents.[91, 92]

Toxicity and Coabuse

Cocaine overdoses, which are frequently fatal, are most often due to cardiotoxicity. Myocardial infarction is the best documented complication of chronic cocaine use. Being a vasoconstrictor, cocaine decreases blood flow to the heart. The coronary artery diameter has been shown to decrease between 4 – 29% in humans, due to the stimulation of alpha adrenergic receptors in the heart vasculature. Over time, the prolonged vasoconstriction may lead to endothelial damage because of the increased shear stress on blood vessel walls. Therefore chronic use predisposes all cocaine users to myocardial infarctions and arrhythmias.[93] In extreme cases, cocaine-induced excited delirium can cause sudden death. Also known as “acute exhaustive mania,” individuals exhibit symptoms of hyperthermia, delirium with agitation or aggression, respiratory arrest and then death. These cases are rare and exclusively observed in individuals who are “body-packing” or drug “mules;” it is assumed the acute toxicity ensues from rupture of the packets or disintegration of the packages.[94]

The most common drug combination with cocaine is ethanol, which alters the metabolism profile of cocaine as discussed previously. Other combinations of drug coabuse with cocaine include stimulants, sedatives, cannabis, and opiates. Few studies have systematically investigated the effects of various coadministrations in the context of behavioral outcome in addition to metabolism or toxicity. Hemby *et al.*, studied the relationship between the self-administration of cocaine/heroin (Speedball) and nucleus accumbens dopamine concentrations in rodents. The resultant dopamine concentrations indicated a synergistic effect in dopamine elevation (1000% baseline) as compared to cocaine alone (400% baseline) and heroin alone (not significantly different from baseline).[95] However, the cocaine concentrations in the nucleus accumbens did not change, indicating the synergistic effect could be resultant of increased firing of dopamine neurons by the opiates and then the direct effect of cocaine on blocking dopamine reuptake, and not through a persistence mechanism or change in metabolism.

IMPORTANCE IN NEUROSCIENCE

Cocaine has advanced knowledge in the fields of medicine, chemistry, and pharmacology. As described above, the physical study of this tropane alkaloid inspired new synthetic methods as well as investigations into the biochemistry of the natural product synthesis. Concurrent with those efforts, the curious dual effects of anesthesia and euphoria inspired extensive investigation into the mechanisms of action by pharmacologists, neuroscientists and other related disciplines. For example, as an inhibitor of monoamine reuptake transporters and ion channels, cocaine has been an important tool in the biochemical investigation of the dopamine reward pathway over the last century.[96] For the sake of brevity, a detailed discussion of the neuroscience of cocaine is beyond the scope of this

perspective. Rather, we have chosen to highlight two important areas, anesthesia and molecular imaging, and point readers to the recent volume edited by Victor Preedy for a comprehensive treatise on the neuroscience of cocaine.[97]

Anesthesia

As described in the *Pharmacology* section, Carl Koller first demonstrated local anesthesia using cocaine.[15, 82, 83] Cocaine's action as a local anesthetic effect is due to a direct membrane effect. Specifically, cocaine blocks the initiation and conduction of electrical impulses within the nerves by preventing the rapid increase in cell-membrane permeability to Na^+ during depolarization. The first anesthetic applications of cocaine allowed for more advanced, invasive surgeries. However, the addictive nature of the drug meant that cocaine also inspired the synthesis of other longer lasting, less addictive and/or toxic alkaloid anesthetics in order to increase the safety for both local use and surgical applications.

Amylocaine (**73**) was the first synthetic local anesthetic, patented under the name Stovaine by Ernest Fourneau at the Pasteur Institute in 1903.[98] Amylocaine was used as a spinal anesthetic and was seen to be more powerful than cocaine and significantly less toxic; however, cardiac failure was observed during long surgeries.[99] This phenomenon led to the development of cocaine analogues with a longer duration of anesthetic action for surgery, most notably novocaine (procaine), the first synthetic analog of cocaine.[100] Procaine was first synthesized in 1905 by German chemist Alfred Einhorn and the first medical use by Heinrich Braun. Unlike cocaine, amylocaine (**73**), procaine (**74**) and other local anesthetics such as lidocaine (**75**) are not tropane alkaloids, but this began the trend of using the ending "-caine" to classify alkaloids used as anesthetics (Figure 9).[101]

Molecular Imaging

Our laboratory is involved in developing new radiotracers for positron emission tomography (PET) imaging. PET is a powerful and noninvasive medical imaging technique that provides kinetic physiochemical information. Patients are injected with a PET radiotracer (a bioactive molecule tagged with a positron-emitting radionuclide such as ^{18}F or ^{11}C) and, upon completion of a PET scan, emission data are analyzed to produce PET images: multi-dimensional images representing the distribution of the radiotracer throughout the body. Reflecting the value of the functional information PET provides, it has found widespread application in oncology and brain imaging since its introduction.[102]

In the brain imaging space, there has been considerable effort devoted to developing radiotracers for use as presynaptic neuronal markers by targeting neuronal membrane and vesicular neurotransmitter transporters. A detailed discussion of such work is beyond the scope of this article, but the subject has been recently reviewed.[103] Pertinent to this review, however, is the pioneering work with [^{11}C]cocaine from Fowler and co-workers at the Brookhaven National Laboratory, initially to understand the pharmacokinetics and distribution of cocaine and, subsequently, using it as a PET radiotracer for imaging the dopamine transporter.[104]

[^{11}C]Cocaine has been prepared by labeling the methyl ester ([*O*-methyl-^{11}C]cocaine) or the *N*-methyl group of the tropane ring ([*N*-methyl-^{11}C]cocaine, **[^{11}C]1**).[104] The latter appears to be more commonly used, and can be synthesized by treating norcocaine (**67**) with [^{11}C]CH_3I, and purifying the reaction mixture using semi-preparative HPLC (Scheme 11).[105]

Studies with [^{11}C]cocaine mapped the binding sites of cocaine in rodent,[105] primate[106, 107] and human[106] brains, confirming *in vitro* tissue studies. Follow up studies in monkeys and humans have improved our understanding of the metabolism,[108] pharmacokinetics[109] and distribution of cocaine.[104, 110] For example, Fowler *et al.* demonstrated rapid uptake of cocaine in the corpus striatum, and also grouped non-striatal brain regions into high (putamen > accumbens > caudate), moderate (thalamus > precuneus > posterior cingulate gyrus > amygdata, hippocampus and temporal pole) and low (orbital cortex, precentral gyrus and cerebellum) areas of cocaine binding (Figure 10). After these preliminary studies aimed at understanding the properties and distribution of cocaine, it was shown that blocking of striatal uptake was possible with nomifensine (a norepinephrine-dopamine reuptake inhibitor) but not desipramine (norepinephrine inhibitor),[106] making it apparent that [^{11}C]cocaine could also be used as a PET radiotracer for imaging the dopamine transporter in DAT-rich brain regions like striatum. Thus, the Brookhaven group reported methods for estimating DAT occupancy using [^{11}C]cocaine,[111, 112] and predicted that a euphorigenic dose of cocaine (~ 40 mg) occupies 80-90% of the transporters, while a perceptible dose (~5 mg) occupies ~40% of the transporters.[111] Further PET imaging in detoxified cocaine abusers revealed a significant decrease in [^{11}C]cocaine uptake compared to controls, which could inform the observed tolerance of cocaine abusers.[113]

An alternative form of molecular imaging is functional magnetic resonance imaging (fMRI). This modality measures and maps brain activity by detecting changes in blood flow, and then using those measurements to predict neuronal activation. Breiter and colleagues have employed fMRI to investigate the brain circuitry responsible for mediating cocaine's effects (Figure 11).[114–116] In extensive studies they have explored the effects of cocaine on human brain activity and emotion, as well as the brain circuitry responsible for the rush and euphoria associated with cocaine use, and the craving for cocaine amongst users. When compared to saline controls, they found that cocaine activated a number of different brain areas (nucleus accumbens/subcallosal cortex (NAc/SCC), caudate, putamen, basal forebrain (BF), thalamus, insula, hippocampus, parahippocampal gyrus (parahip), cingulate, lateral prefrontal (LPFC) and temporal cortices, parietal cortex, striate/extrastriate cortices, ventral tegmentum (VT), and pons). Contrastingly, signal decreases were noted in amygdala, temporal pole, and medial frontal cortex compared to saline controls. Analysis of the imaging data revealed that brain regions with early activation for a short duration were associated with cocaine's euphoria, while regions with sustained activation were more correlated with drug cravings.[115]

SUMMARY

A century or so after cocaine was brought back to the old world and captured the interest of scientists and artists alike, it remains a staple to the local indigenous communities who

continue to chew coca leaves and drink coca tea. At the same time, in the western world millions of users still consume hundreds of tonnes of cocaine per year, and tens of thousands die on an annual basis as a result. Unsurprisingly then, in first world countries like the United States cocaine is a controlled substance that many still consider it *the third scourge of humanity*, and hundreds of billions of dollars are spent in the war on drugs each year. This is the cocaine paradox, only a recent chapter in the colorful history of our alkaloid which has spanned thousands of years and will, inevitably, span thousands more. It is a paradox without an obvious answer, but ponder *the divine plant of the Inca's* next time you drink an ice cold, cocaine-free *Coca Cola*.

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Abbreviations

AC	anterior commissure
BE	benzoylecgonine
BF	basal forebrain
2-CMT	2-carbomethoxytropinone
CNS	central nervous system
DAT	dopamine transporter
DEA	drug enforcement administration
EME	ecgonine methyl ester
FDA	food and drug administration
fMRI	functional magnetic resonance imaging
GP	globus pallidus
i.v.	intravenous injection LPFC, lateral prefrontal cortex
NAc	nucleus accumbens
NET	norephinephrine transporter
n.i.	nasal insufflation
parahip	parahippocampal gyrus
PET	positron emission tomography
SCC	subcallosal cortex

SERT	serotonin transporter
s.i.	smoke inhalation
SN	substantia nigra
VT	ventral tegmentum
VTA	ventral tegmental area

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Figure 1.
Erthroxylon coca (left, reprinted with permission from reference[3]. Copyright 2015, Elsevier) and cocaine (right, personal photograph by the authors).

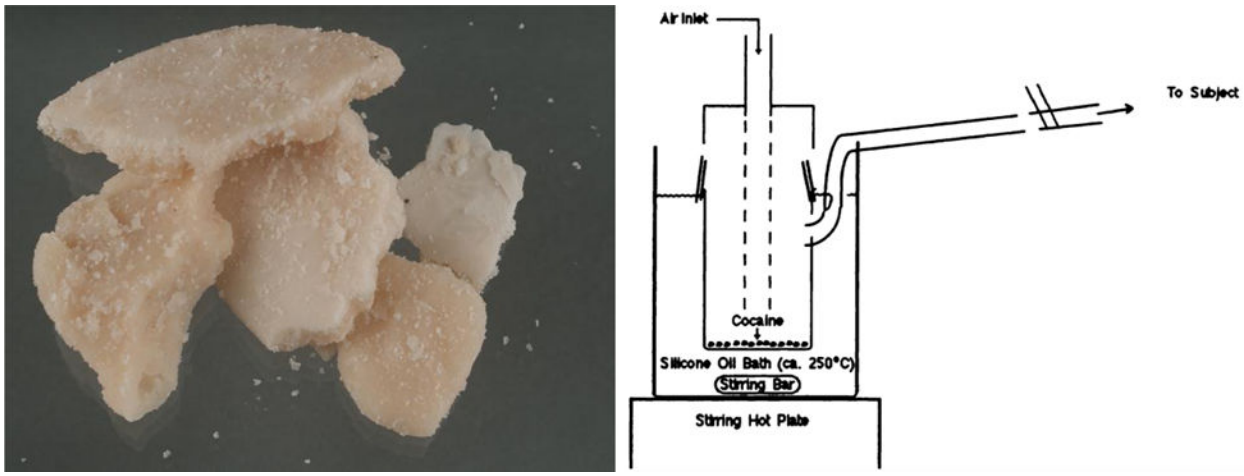


Figure 2.

Crack cocaine (left, cropped from an image that is a work of a Drug Enforcement Administration employee, taken or made as part of that person's official duties. As a work of the U.S. federal government, the image is in the public domain in the United States[8]), and a laboratory crack pipe (right, reprinted with permission from reference[9]. Copyright 1989, American Society of Pharmaceutics and Experimental Therapeutics).

Figure 3.

Mariani Wine (Image reprinted from reference[23] and courtesy of the Smithsonian Libraries. No copyright in the United States).

Figure 4.

Cocaine Toothache Drops (Reprinted from the U.S. National Library of Medicine.[24] Image is in the public domain).

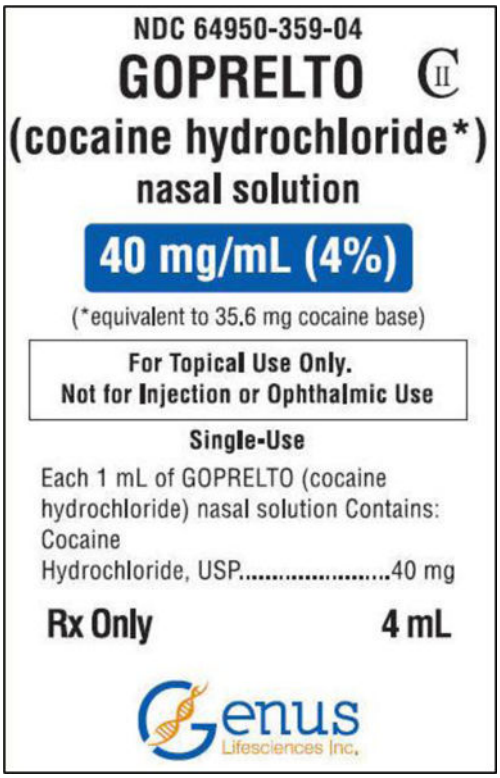


Figure 5.
FDA-approved Cocaine hydrochloride marketed by Genus Lifesciences, Inc. (Reprinted from the U.S. National Library of Medicine.[16] Image is in the public domain[25]).

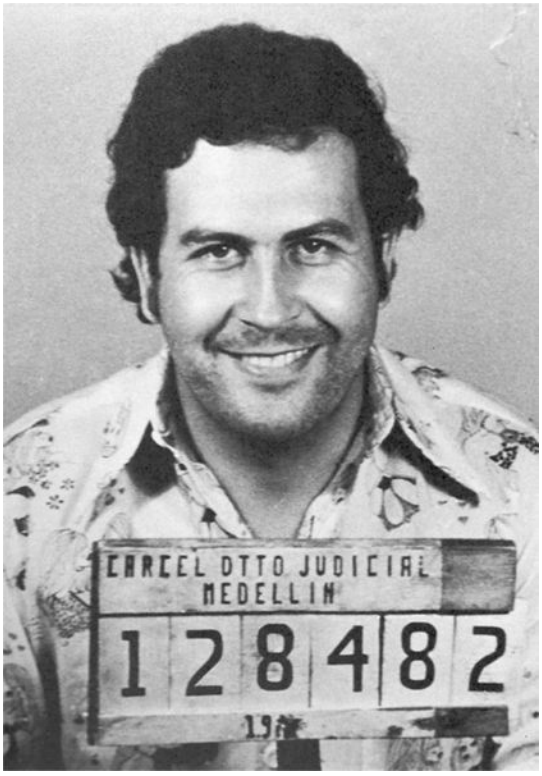


Figure 6.
Juan Pablo Escobar (mugshot taken by the regional Colombia control agency in Medellin in 1977. Image is in the public domain).

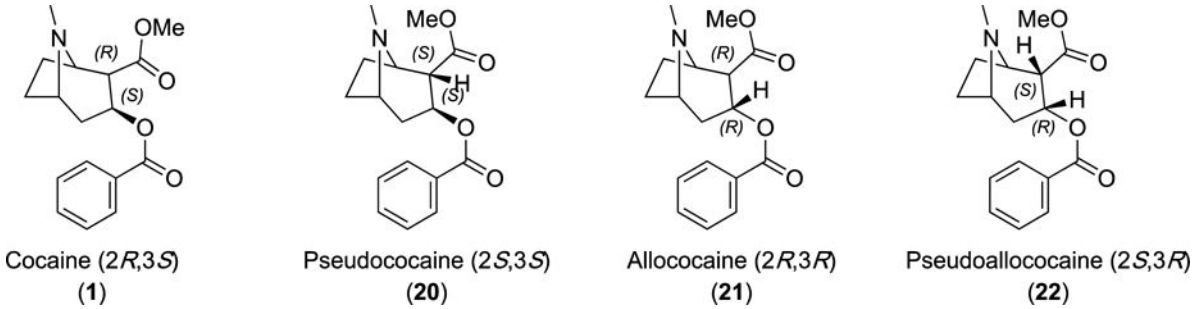


Figure 7.
Stereoisomers of Cocaine

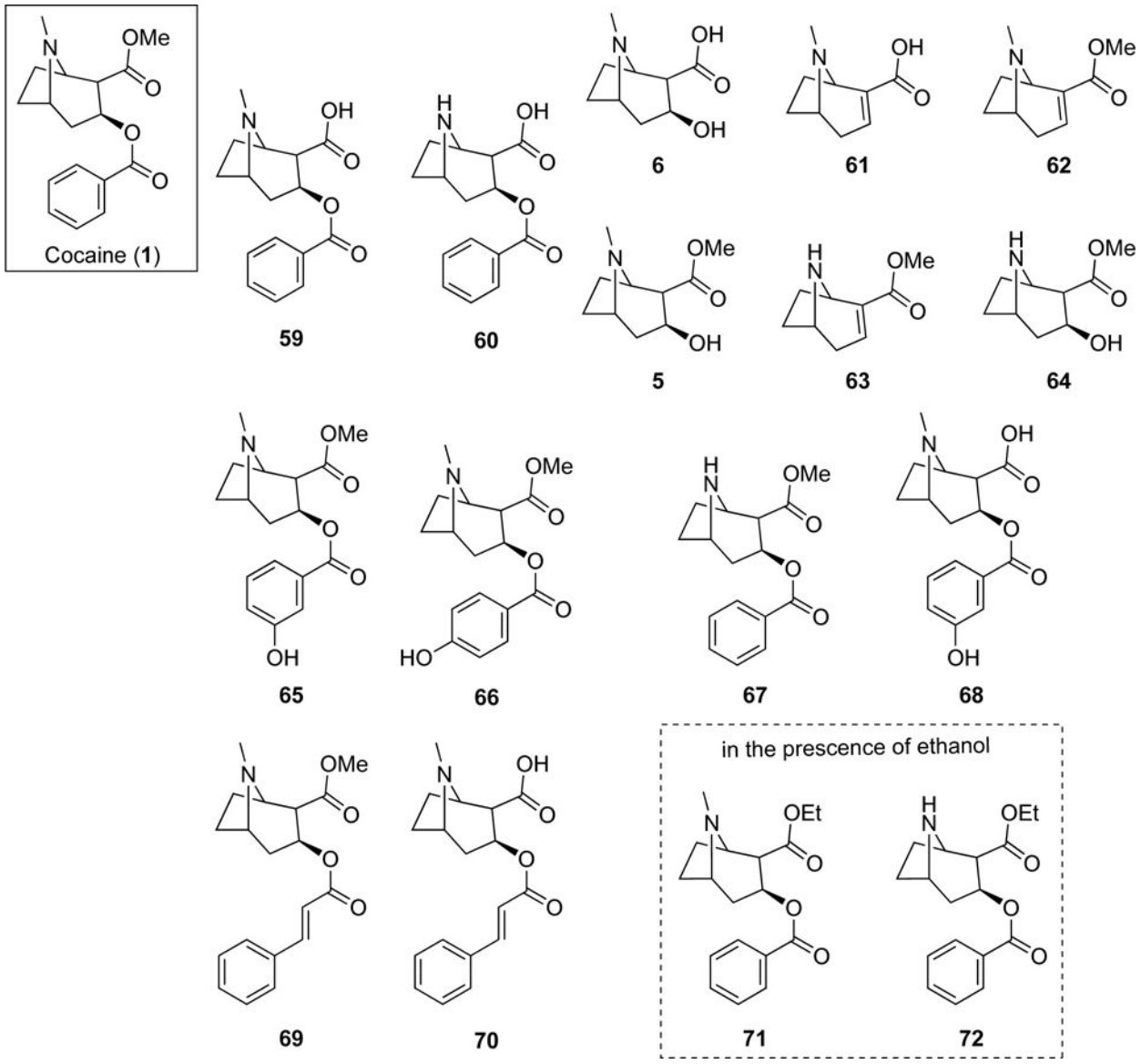
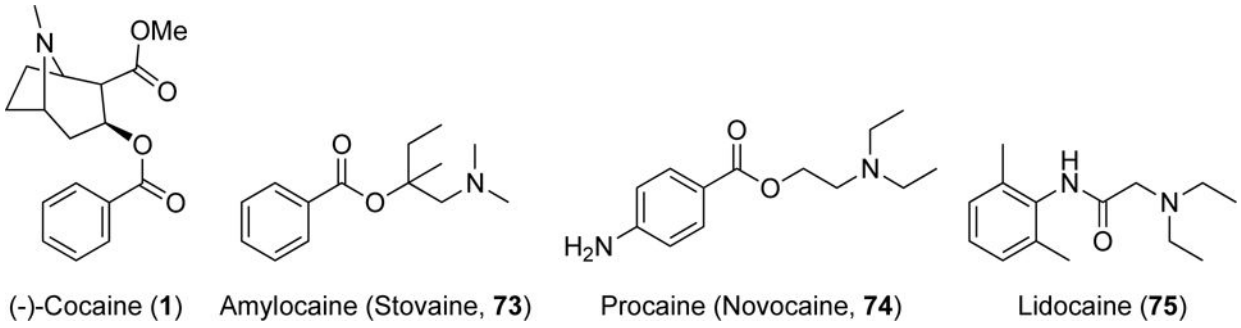


Figure 8.

Metabolites of Cocaine: benzoylecgonine (**59**); benzoylnorecgonine (**60**); ecgonine (**6**); ecgonidine (**61**); ecgonidine methyl ester (**62**); ecgonine methyl ester (**5**); norecgonidine methyl ester (**63**); norecgonine methyl ester (**64**); *m*-hydroxycocaine (**65**); *p*-hydroxycocaine (**66**); norcocaine (**67**); *m*-hydroxybenzoylecgonine (**68**); cinnamoylcocaine (**69**); cinnamoylecgonine (**70**). Ethanol induced metabolites: cocaethylene (**71**); norcocaethylene (**72**).



(-)-Cocaine (**1**) Amylocaine (Stovaine, **73**) Procaine (Novocaine, **74**) Lidocaine (**75**)

Figure 9.
Cocaine and related local anesthetics

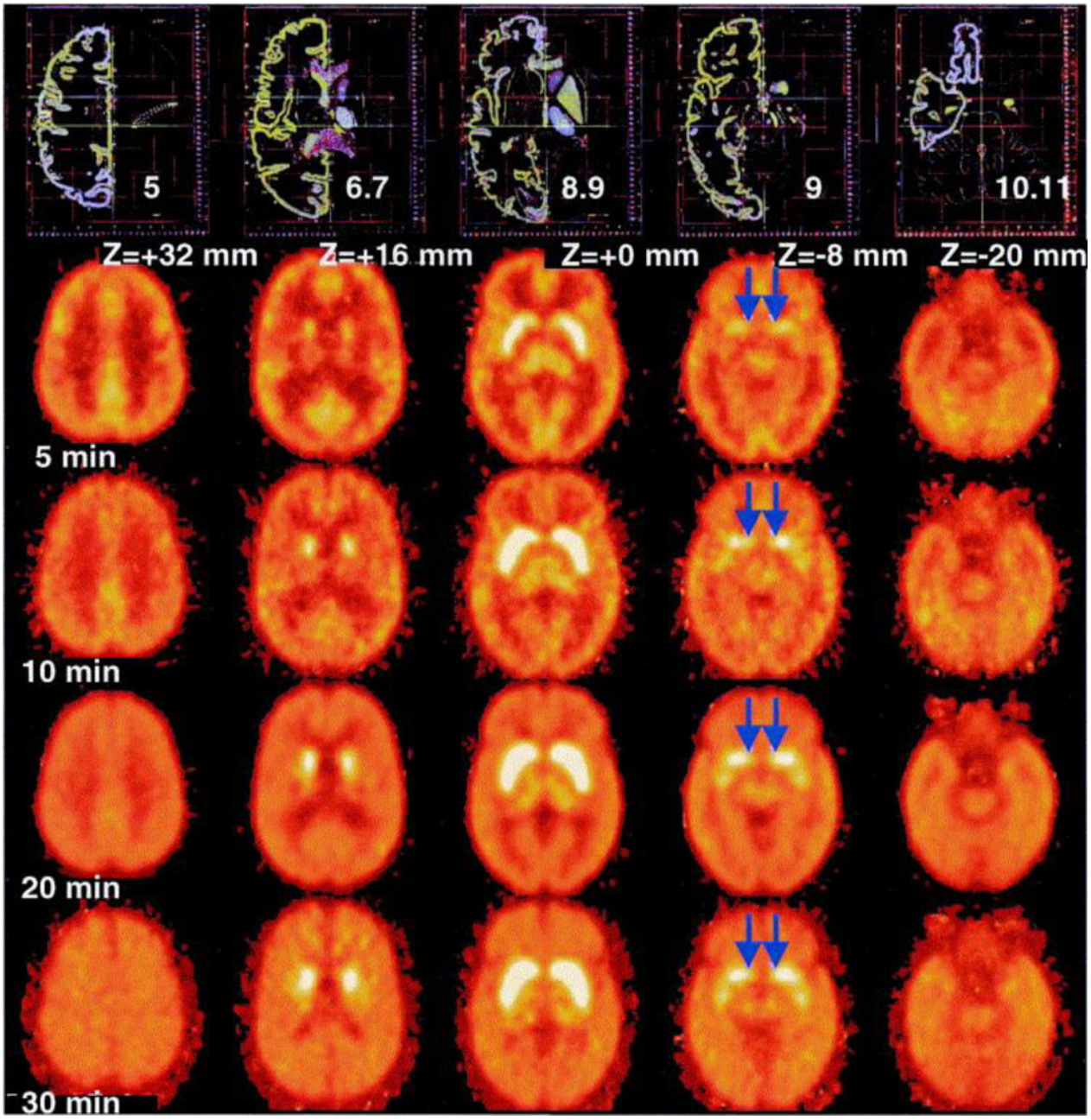


Figure 10.

An average of 17 brain PET images with [^{11}C]cocaine (**[^{11}C]1**)at 4 different time frames after injection (5, 10, 20 and 30 minutes). Images have been normalized to the highest activity in a given time frame. The top row illustrated the Tailarach-Tournoux section. Arrows indicate the nucleus accumbens. (Reprinted with permission from reference[104]. Copyright 2001, Elsevier).

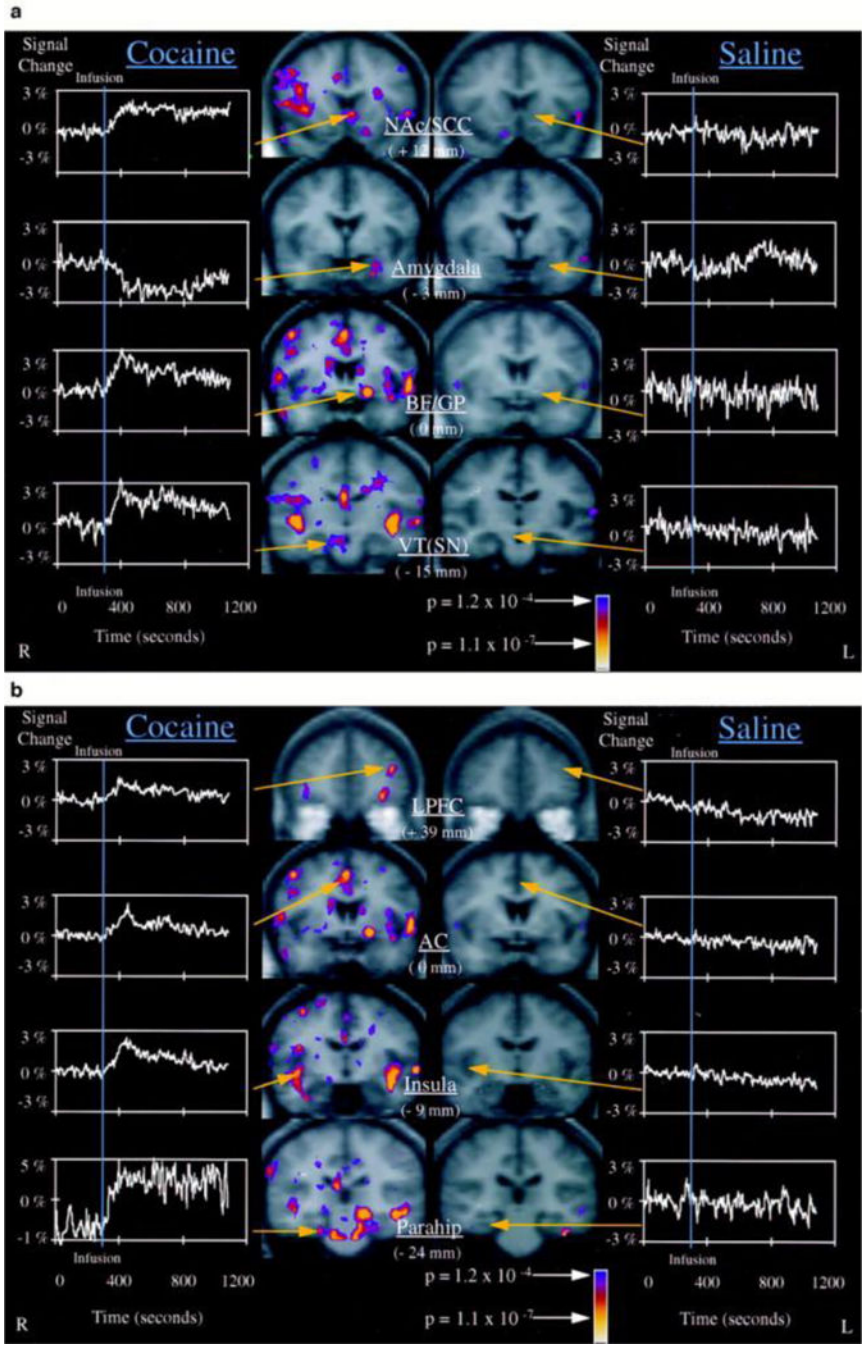
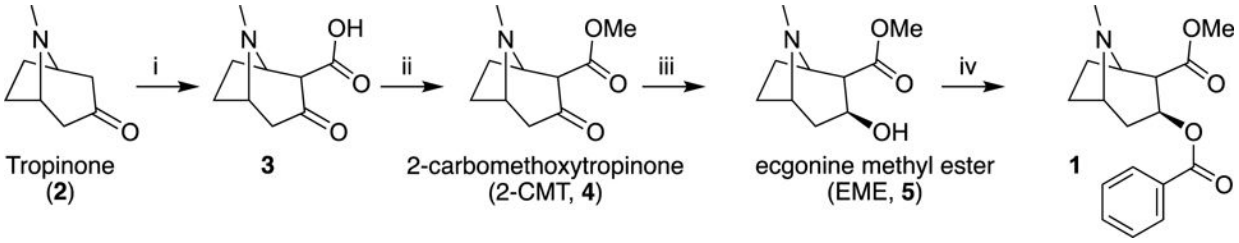


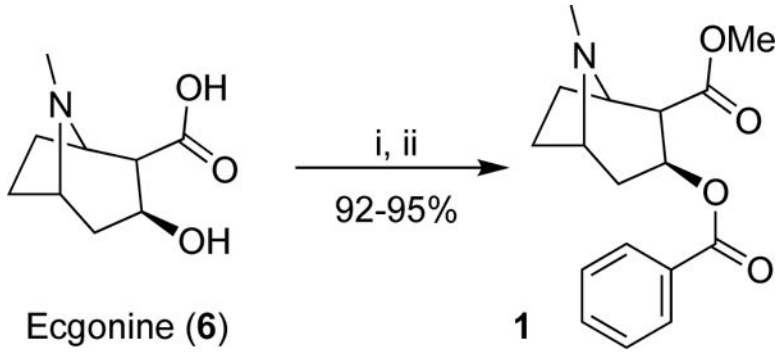
Figure 11.

Regional brain activity as measured by fMRI following administration of cocaine (**1**) and saline control. (Reprinted with Permission from reference[115]. Copyright 1997, Elsevier).



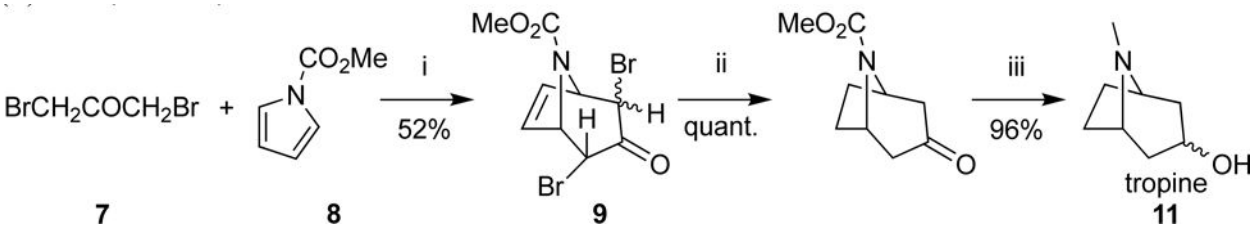
Scheme 1.

Wilstatter's Total Synthesis of Cocaine. Conditions: (i) a. Na/EtOH, CO_2; (ii) MeOH, H_3O^+; (iii) a. Na/Hg; (iv) Bz_2O, D-tartaric acid chiral resolution.



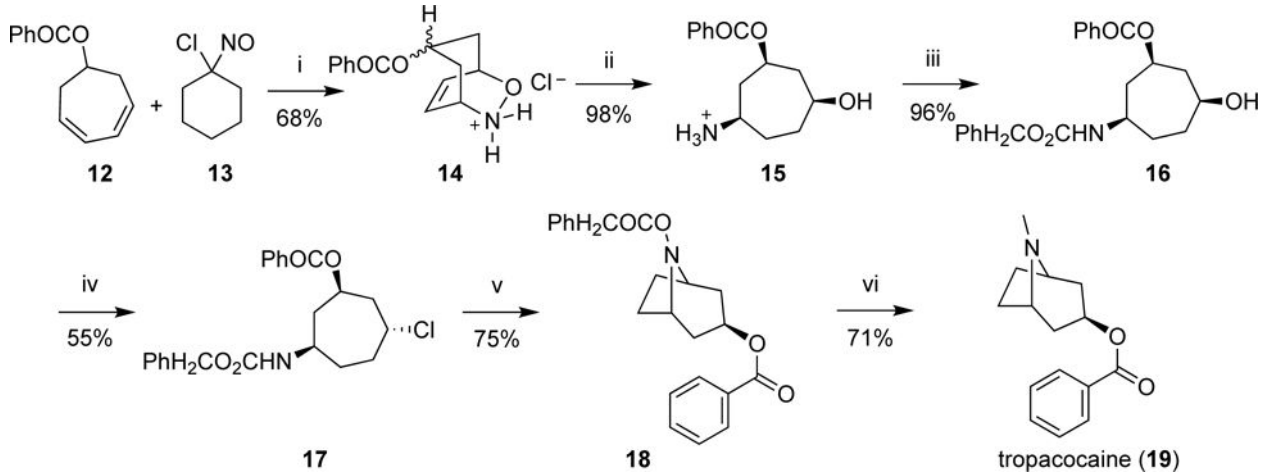
Scheme 2.

De Jong's Conversion of Ecgonine (**6**) to Cocaine (**1**). Conditions: (i) MeOH, Benzene; (ii) BzCl, MeOH, Na_2CO_3.



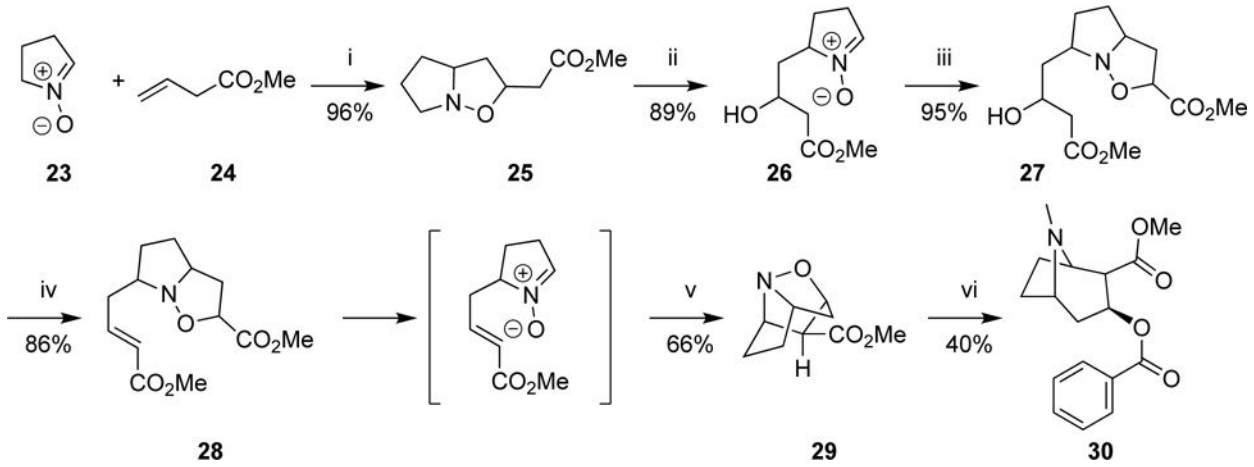
Scheme 3.

Noyori's General Synthesis of Tropane Alkaloids via the Polybromo Ketone-Iron Carbonyl Reaction. Conditions: i) a) $Fe_2(CO)_9$, benzene, 50°C, 72 h; ii) H_2 10% Pd/C, ethanol; iii) DIBAH, THF, −78°C, 10 h.



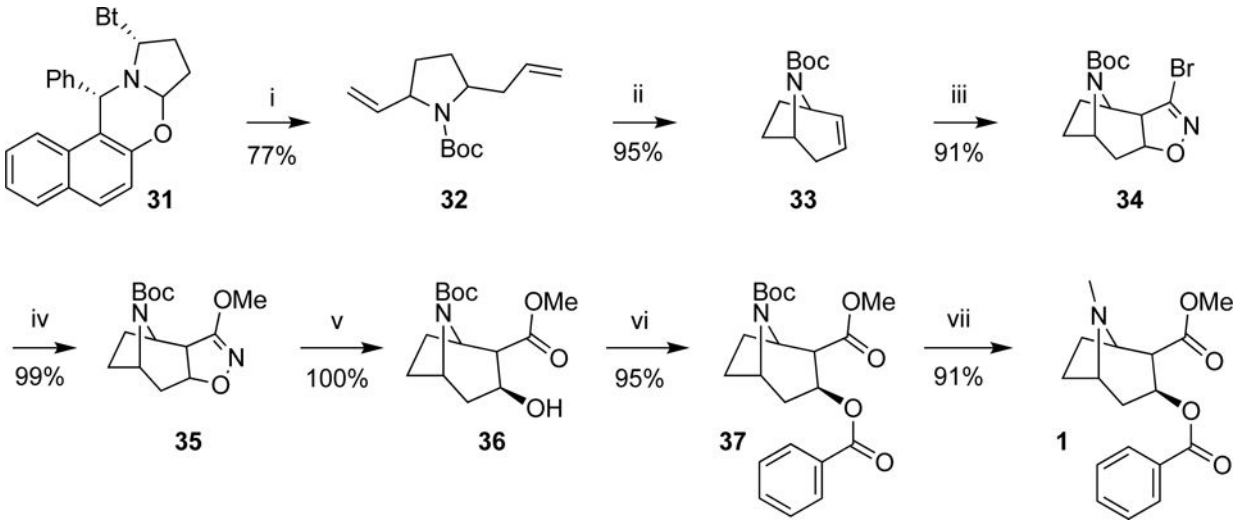
Scheme 4.

[4+2] Nitroso Cyloaddition route to Tropane Alkaloids. Conditions: (i) EtOH: CCl_4, −20°C, 5 h, then −20°C, 14 d; (ii) H_2 Pd/C, MeOH, 7h; (iii) Na_2CO_3, Benzyl chloroformate; (iv) Thionyl chloride, Pyridine, $CDCl_3$, 0°C, 1h; (v) K^tBuO; (vi) a) H_2, Pd/C, MeOH, b) 90% aq. Formic acid, 37% aq. formaldehyde, reflux, 5 h; c) conc. HCl, recrystallized from ethanol:water.



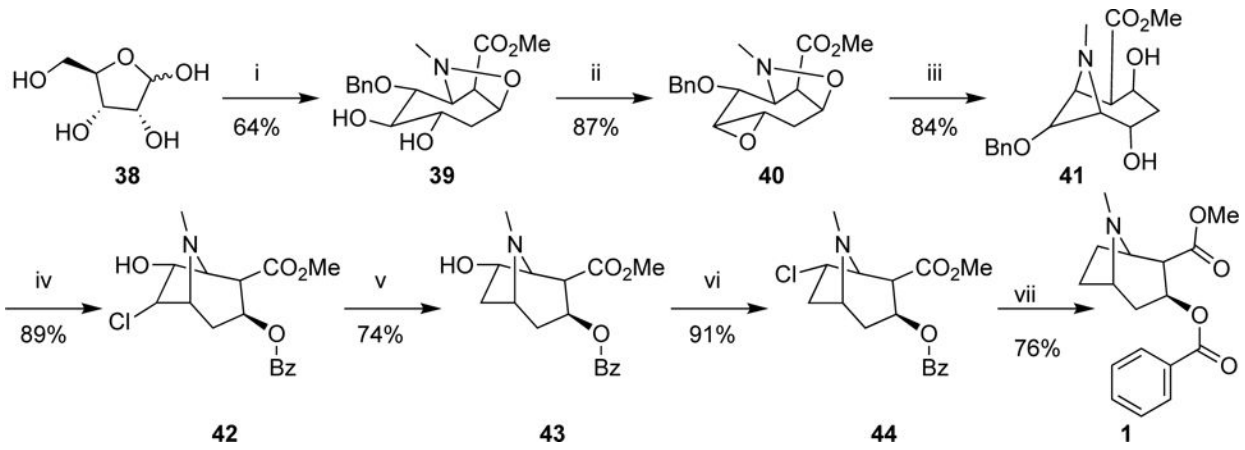
Scheme 5.

Tufariello's Stereospecific Synthesis of (-)-Cocaine. Conditions: (i) toluene, reflux; (ii) mCPBA, CH_2Cl_2; (iii) methyl acrylate, benzene, reflux; (iv) a) MsCl, pyridine; b) 1,5 diaza-bicylco[4.3.0]non-5-ene, benzene; (v) xylene, reflux; (vi) a) MeI, CH_2Cl_2; b) Zn, AcOH; c) benzoyl chloride, MeOH, Na_2CO_3.



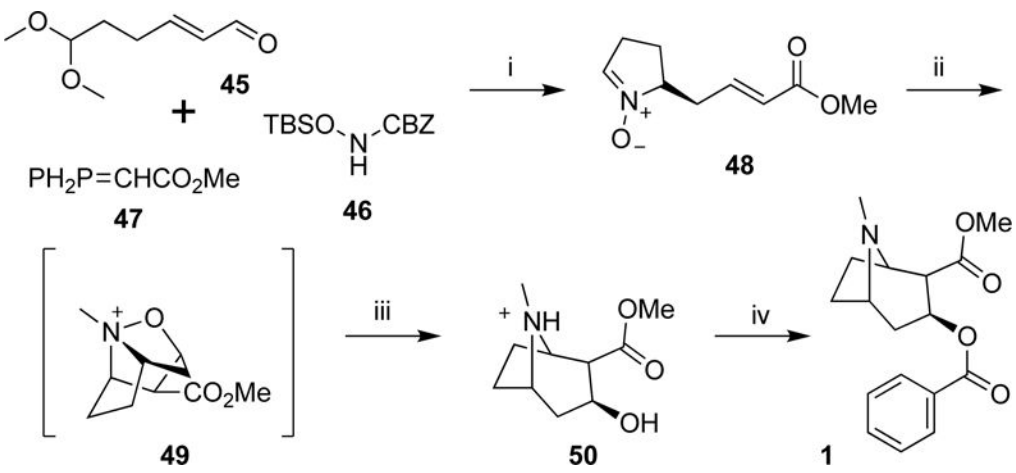
Scheme 6.

Cheng's Total Synthesis of (-)-Cocaine. Conditions: (i) a) HC≡CMgCl added dropwise at −40 °C, THF, then 0 °C for 1 h; b) 5% Lindler catalyst, H_2, THF, ~10 min; c) $H_2C{=}CHCH_2MgBr$, Et_2O, −40 °C, 1 h; d) aq NaOH, MeOH, THF 60 °C, 1 h; e) Boc_2O, K_2CO_3, CH_2Cl_2, rt,1 h; (ii) Grubbs II (0.025 eq) CH_2Cl_2, reflux, 12h; (iii) dibromoformaldoxime, Na_2CO_3, EtOAc, 10°C, 40 h; (iv) NaOMe, MeOH, reflux, 8 h; (v) Raney-Ni, H_2, H_3BO_3, aq MeOH, rt, 3 h; (vi) BzCl, DMAP, Et_3N, CH_2Cl_2, rt, 12 h; (vii) a) TFA, CH_2Cl_2, rt, 1 h b) 37% aq CH_2O, $NaBH_3CN$, rt, 1 h.



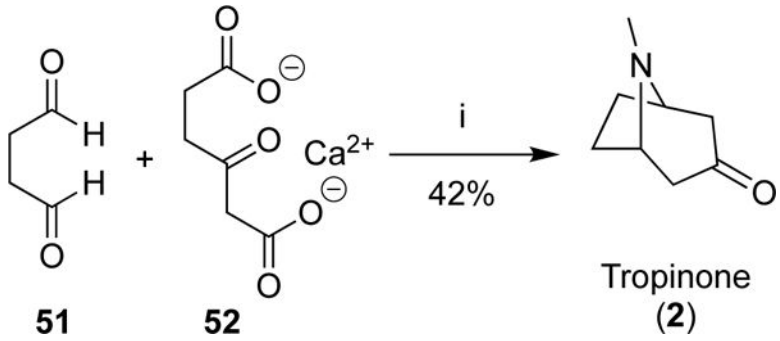
Scheme 7.

Shing & So Synthesis of (-)-Cocaine from D-(-)-Ribose. Conditions: (i) a) aq In, allyl bromide, H_2O: EtOH; b) acetone, aq. AcOH, BzCl; c) methyl acrylate, Grubbs II, CH_2Cl_2, reflux; d) 80% AcOH reflux; e) NaIO4, silica gel, CH_2Cl_2, rt; f) MeNHOH, tol, reflux; (ii) Tf_2O, 2,4,6-collidine, CH_2Cl_2, −78°C; b) K_2CO_3, MeOH, rt; (iii) H_2, Raney Ni, AcOH, MeOH, rt to 60 °C; (iv) BzCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, then MsCl, rt; (v) H_2, Raney Ni, MeOH, 50 °C; (vi) MsCl Et_3N, CH_2Cl_2, rt to 70 °C, (vii) H_2, Raney Ni, MeOH, rt, 14 h.



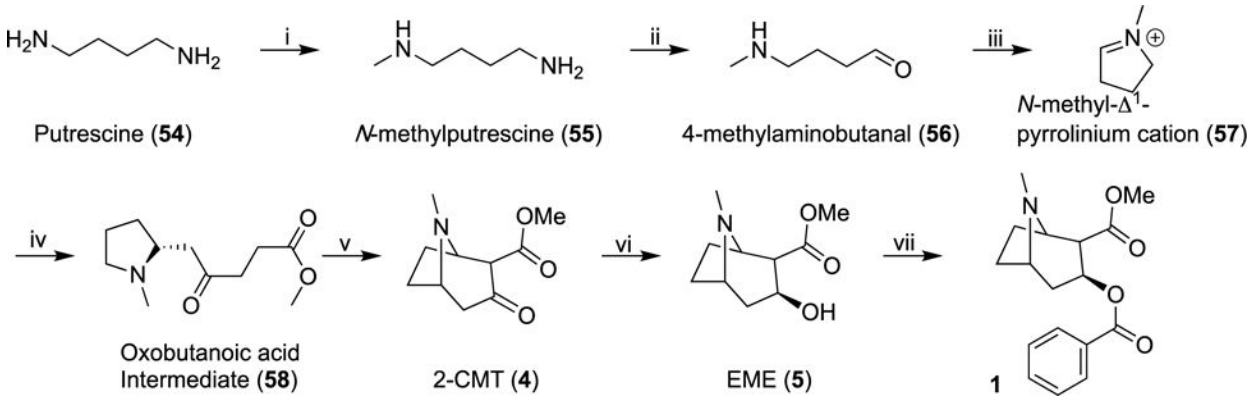
Scheme 8.

Concise Catalytic, Asymmetric Total Synthesis of Tropane Alkaloids. Conditions: (i) a) $CHCl_3$, 4 °C, 17 h; b) cat $PdCl_2$ (10 mol%), Et_3N, Et_3SiH, CH_2Cl_2, reflux 6 h; c) 3M HCl:THF, rt, 2h; (ii) a) $Al(O^tBu)_3$ (50 mol%) toluene, rt, 4 h, + 64 h at 150°C; b) MsOMe, CH_2Cl_2, reflux, 24 h. (iii) cat Pd/C, H_2, MeOH, rt, 48 h; (iv) PhCOCl, Et_3N, cat DMAP, CH_2Cl_2, rt, 17 h.



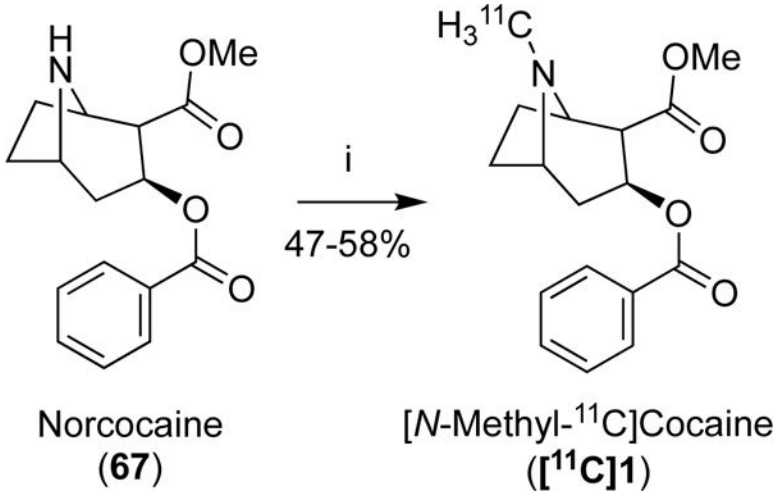
Scheme 9.

Robinson's One-pot synthesis of Tropinone (**2**). Conditions: (i) H_2NMe (**53**), H_2O.



Scheme 10.

Biosynthesis of (-)-Cocaine. Conditions: (i) N-methyltransferase, (ii) oxidation, enzyme unknown, (iii) spontaneous cyclization, (iv) two acetyl groups are incorporated, enzyme unknown (v) Tropinone reductase, (vi) methylecgonone reductase, (vii) cocaine synthase, a BAHD acetyltransferase.

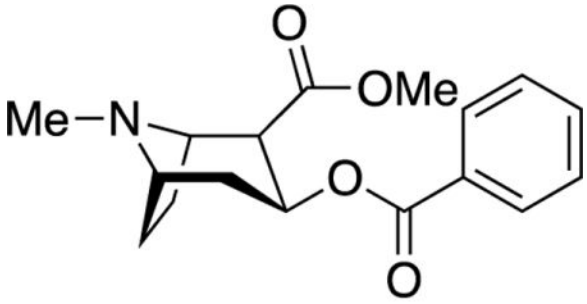


Scheme 11.

Radiosynthesis of [*N*-Methyl-^{11}C]Cocaine (**[^{11}C]1**). Condition: (i) [^{11}C]CH_3I, 50 °C, 5 min.

Table 1

Chemical and Biological Properties of Cocaine



(*R*)-(-)Cocaine
(**1**)

CAS #	**50-36-2 (freebase); 53-21-4 (HCl salt)**
Molecular Formula	$C_{17}H_{21}NO_4$
Molecular Weight	303.358 g/mol
Monoisotopic Exact Mass	303.147 g/mol
IUPAC	8-Azabicyclo[3.2.1]octane-2-carboxylic acid, 3-(benzoyloxy)-8-methyl-, methyl ester, (1*R*, 2*R*, 3*S*, 5*S*)-
Rotation	(-)
Chemical Class	Tropane Alkaloid
Physical Description	Solid as white crystals or white powder
Melting Point	93.5 – 98 °C[46]
Hydrogen Bond Donor Count	0
Hydrogen Bond Acceptor Count	5
Water Solubility	1.8 g/L[47]
Log P	2.3[48]
pKa	8.61
Drug indications	Induction of local anesthesia of the mucous membranes when performing diagnostic procedures and surgeries on or through the nasal cavities in adults[16]
Biological Half-life	1 hour
LD_{50}	95.1 mg/kg[49]