

# Cocaine chemistry



PHARMACEUTICALS

## PROPERTIES AND HISTORY

Few chemicals have caused such undesirable political and social consequences as cocaine. Its consumption in some developed countries is reaching epidemic level and the stability of the governments in some producing countries is threatened by the enormous power of those trafficking illegally with this drug.

Cocaine is an alkaloid found in the leaves of the small tree *Erythroxylon coca*, which is native to the tropical mountains of Peru, Bolivia and Colombia. Indians in this area place in the cheek a mixture of coca leaves and basic material like ground seashell or ashes, so that the saliva extracts the free base that is ingested. Consumers of the drug are easily spotted by their hump in the cheek. There is evidence of very ancient consumption of coca leaves. Ceramics depicting human figures with a cheek bulge were found in archaeological sites from Peru, dated from 1900-1750 B.C. Remains of coca leaves were encountered in 2000 years-old mummies from Nazca in Peru.

As the content of cocaine in dry coca leaves is only 0.4-0.8%, it is very doubtful that its traditional ingestion causes any serious threat for the health, producing a damage akin to moderate tobacco smoking (1).

The Incas consumed coca leaves for religious and ceremonial purposes. In 1533, the Incas were conquered by the troops of the Spanish conquistador Pizarro. A few years later in 1551, the Bishop of Cuzco prohibited the cultivation and consumption of coca, and its possession was punished by death. Coca ingestion was viewed as an obstacle for the conversion of the Indians into Christianity, for it was a tie with their past religion. Nevertheless, later it was found that coca increased the stamina of Indian

laborers and in 1569 King Philip II decreed that coca was not devilish.

As the long journey by ship to Spain caused coca leaves to deteriorate, the effects of coca ingestion were not experienced in Europe for a long time.

Following the isolation of pure cocaine from coca leaves in 1862 (2), the pure drug became available in Europe from the Merck Company. At the same time coca extracts began to be added to beverages that were sold as tonics. One of the most popular was the so-called Mariani's Coca Wine, which was advertised as a drink able to lift spirits and alleviate fatigue. The original recipe for the preparation of Coca-Cola, which was invented in 1886 as a "tonic" medicine by John Pemberton, included an extract of coca leaves, and sugar was added to abate the bitterness of cocaine. By 1903 the alkaloid was removed and substituted for caffeine in order to keep the tonic properties of the liquor.

In these early days of candid use of cocaine, this drug was considered a healthful medicine that helped to abate depression; a many distinguished scientists endorsed its use. One notable instance was Sigmund Freud (3), the father of Psychoanalysis. He tried the drug on himself and even wrote a book called "On Cocaine" in which he praises its consumption and gives very detailed accounts over the effect of the drug on himself. Thus, he wrote for example "During this first trial I experienced a short period of toxic effects, which did not recur in subsequent experiments. Breathing became slower and deeper and I felt tired and sleepy; I yawned frequently and felt somewhat dull. After a few minutes the actual cocaine euphoria began, introduced by repeated cooling eructation." He recommended cocaine to one of his patients who were suffering from morphine addiction. His enthusiasm for

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the drug was later completely removed when he observed the increasing doses needed by this patient, and the onset of full-fledged cocaine psychoses including "white snakes creeping over his skin." In fact, this is an example of "formication," a hallucination commonly experienced by cocaine abusers, consisting in feeling ants, insects, spiders, or – as in this case – snakes, crawling over or under the skin.

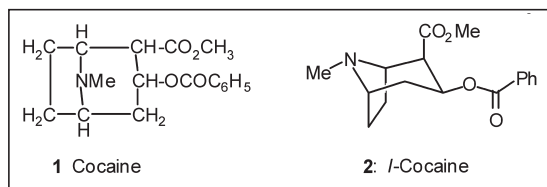
Beginning at 1890, a growing number of scientific evidences showed the highly addictive nature of cocaine consumption and by 1914, the possession or sale of cocaine was prohibited in the United States, with the exception of medical uses.

Cocaine is a white powder with bitter taste that produces stimulation of the central nervous system, due to blockage of reuptake of dopamine (4). This is followed by depression, and as the timing of the depression phase varies depending on

the area of the nervous system, a mixed effect of stimulation and depression can be simultaneously observed (5). Another effect of cocaine is local anaesthesia and it was used in surgery – mainly in the eye – until drugs with less addictive properties became available. Interestingly, most of the cocaine substitutes for surgery have share several structural features with cocaine, and normally consist in amino alcohol benzoates or *p*-aminobenzoates (1).

Following the prohibition of non-medical consumption of cocaine at the beginning of the twentieth century, the number of addicts was drastically reduced, as the black market for the drug was quite small. By the end of the 1960s, the illegal extraction of pure cocaine from *Erythroxylon coca* leaves began to be extensive in South American countries where this plant is native. This marked the beginning of massive illegal trafficking of cocaine to the United States and Europe, causing a second and more intense period of cocaine abuse reaching epidemic levels after half a century of very small consumption. One wonders why the illegal extraction of cocaine from natural sources became prevalent as late as one

Figure 1



century after pure cocaine was first isolated. Nowadays, there are about 2.1 million cocaine consumers in the United States, from whom about 600,000 are severely addicted (6).

## ISOLATION AND STRUCTURAL ELUCIDATION

Pure *l*-cocaine was isolated from coca leaves for the first time by Wöhler in 1862 (2). It was characterized as an alkaloid with the formula  $C_{17}H_{21}O_4N$ . The total synthesis of cocaine by Willstätter in 1923 (7) closed a long chapter of degradative and structural

in 1955 (9). They showed that hydrolysis of the esters in *l*-cocaine, followed by chromic acid oxidation yields the same acid 3, that could be obtained from *L* (+)-glutamic acid (Figure 2).

## SYNTHESIS

**1923: Willstätter's Preparation. Regardless of unknown absolute and relative stereochemistry, the first total synthesis of cocaine is an enantioselective one.**

Cocaine was first prepared in 1923 by Willstätter et al (7). This synthesis is very remarkable because, although at this time both the relative and the absolute stereochemistry of cocaine were unknown, they were able to prepare this alkaloid in optically active form.

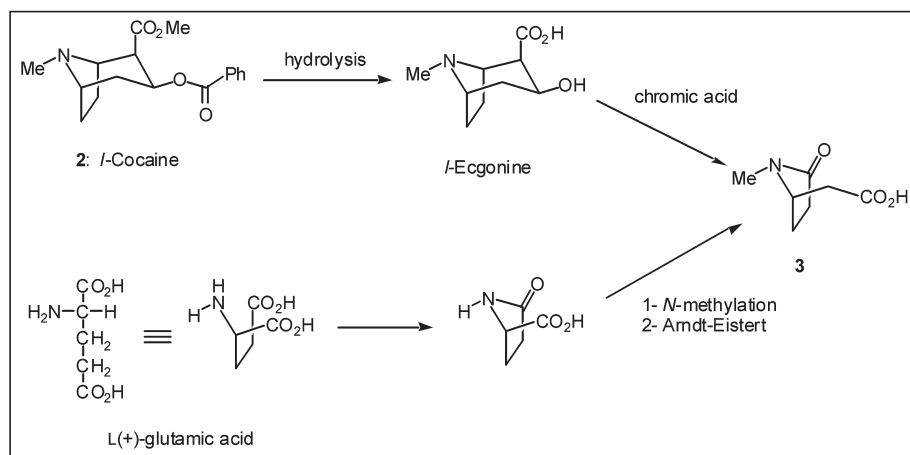
Condensation of butanedial [4] with methylamine and monomethyl acetonedicarboxylate 5 yielded methyl tropinone-2-carboxylate [6]. Reduction of tropinone 6 with sodium amalgam produced a mixture of ecgonine methyl ester [7] and pseudoecgonine methyl ester [8].

The mixture of esters 7 and 8 was benzoylated with benzoyl anhydride, resulting in a mixture of cocaine [2] and pseudococaine [9], which was separated by fractional crystallization. The more soluble benzoate was *dl*-cocaine. Finally, *dl*-cocaine was resolved via the corresponding tartrate. Thus, crystallization with *l*-tartaric acid yielded the *d*-cocaine *l*-bitartrate, whose free base is natural *d*-cocaine (Figure 3).

**1958: Preobrazhenskii's Preparation. Some improvements on Willstätter's synthesis are made.**

This Russian group retook Willstätter's synthesis and introduced some

Figure 2



research and allowed the determination of the right atom connectivity of the alkaloid, which was depicted with formula 1.

The molecule contains four asymmetric carbons and thus eight diastereomeric isomers are possible, from which four can be discarded because of geometric constraints. Stephen Findlay and Gábor Fodor established the relative stereochemistry in the 1950's (8), by a close examination of the degradative cocaine chemistry and taking advantage of incisive mechanistic considerations. It was then established that cocaine consists in 2β-carbomethoxy-3β-benzoyloxytropane [2].

Finally, the absolute stereochemistry of natural *l*-cocaine was proved to be as portrayed in Figure 1 by Hardegger and Ott

Figure 3

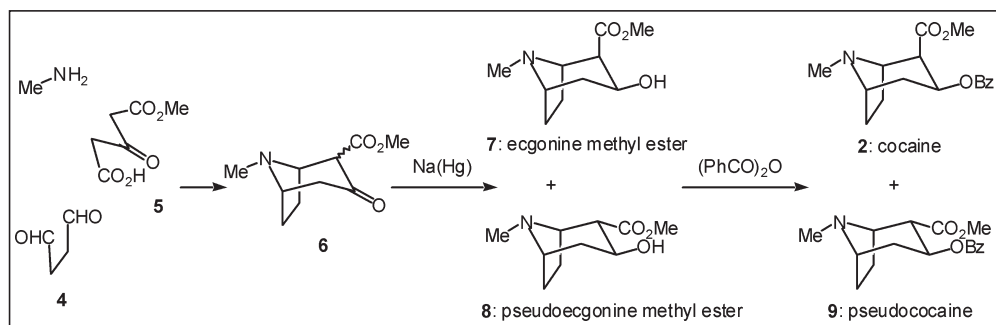
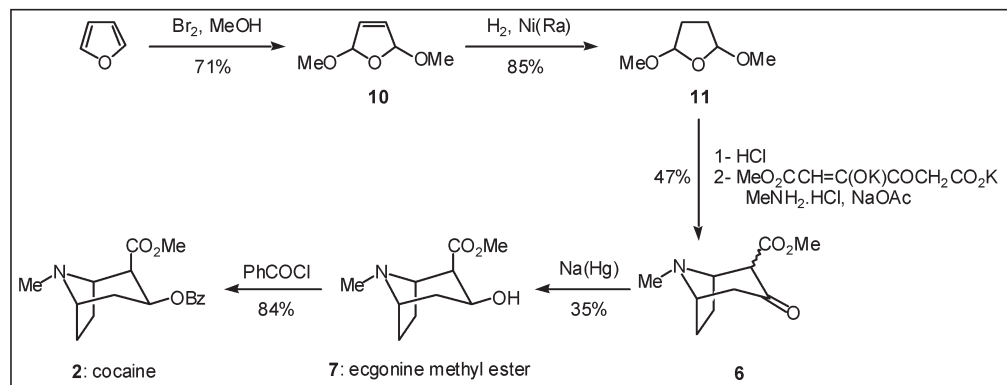


Figure 4



improvements, like the *in situ* generation of the unstable butandiol by acidic hydrolysis of dimethoxytetrahydrofuran **11**. Thus, treatment of furane with bromine in methanol leads to dimethoxydihydrofuran **10** that is hydrogenated to intermediate **11**. Dimethoxytetrahydrofuran **11** is treated with HCl, and the resulting butandiol is condensed with the dipotassium salt of acetonedicarboxylic acid monomethyl ester and methylamine, resulting in 47% yield of methyl tropanonecarboxylate **6**. This is converted to *dl*-cocaine, following Willstätter's procedure, by reduction to ecgonine methyl ester **7** with sodium amalgam, followed by benzoylation with benzoyl chloride (Figure 4) (**10**).

**1978: Tufariello's Preparation. An intramolecular nitronc cycloaddition as the key step for the first stereoselective synthesis of cocaine.**

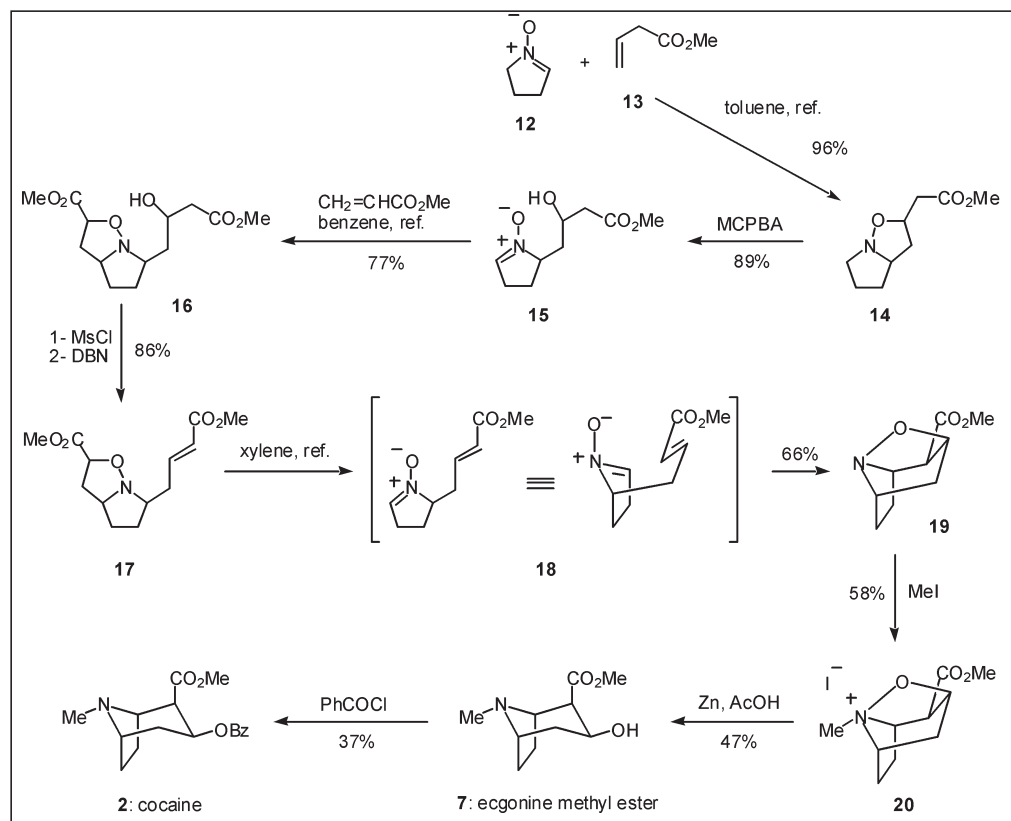
The previous syntheses, which are based on the intermediacy of methyl tropanone carboxylate **6**, have serious stereochemical problems. The ester group in compound **6** so easily epimerised that, for practical matters, it is not relevant which epimer is used for the next carbonyl reduction, as there would be a very quick equilibration before formation of the alcohol **7**. On the other hand, it is very difficult to perform a stereoselective reduction of the ketone in **6**, leading to the desired equatorial alcohol **7**. Not surprisingly, the reduction of tropanone **6** to ecgonine methyl ester [**7**], which contains an unstable axial ester, gives a mixture of diastereomers, from which compound **7** is isolated in low yield.

Tufariello's elegant preparation of cocaine (**11**) addresses the stereochemical problem by means of a highly stereoselective intramolecular cycloaddition of a nitronc on a *trans*-olefin. The

preparation begins with the pyrroline oxide **12** that is reacted with methyl 3-butenate **13**, leading to adduct **14**. Oxidation of compound **14** with *m*-chloroperbenzoic acid produces alcohol **15**. As attempted dehydration of alcohol **15** gave low yields due to interference of the nitronc moiety, it was necessary to protect the nitronc as an adduct by heating with methyl acrylate. The resulting adduct **16** could be efficiently dehydrated by treatment with mesyl chloride, followed by base. In the key reaction, heating of adduct in refluxing xylene led to a retro-addition of methyl acrylate, resulting in the formation of the nitronc intermediate **18** that cyclizes *in situ* to compound **19**. The *trans* stereochemistry in the olefin in intermediate **18** dictates the desired configuration on the ester in compound **19**.

The rest of the synthesis follows a more ordinary chemistry, beginning with *N*-methylation to the salt **20** that is reduced to ecgonine methyl ester **7** with zinc in acetic acid. Finally, compound **7** is

Figure 5



transformed in *dl*-cocaine following a known procedure (Figure 5).

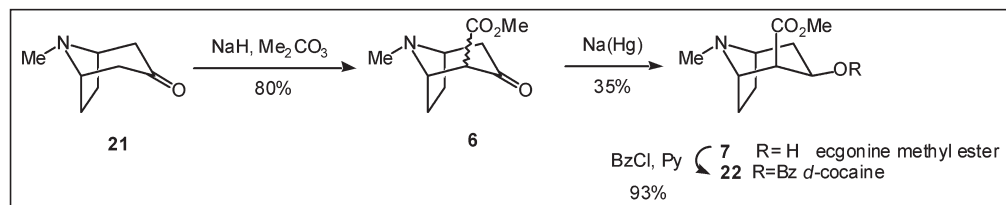
**1987: Carroll's Preparation. A re-examination of the previous syntheses leads to an improved version of the original Willstätter's preparation as the proposed method of choice.**

These researchers predetermined the goal of studying the best practical preparation of optically

active cocaine, regardless of scientific novelty. After judging Tufariello's preparation as too long, they concentrated in improving the original Willstätter's synthesis. In fact, the commercial availability of 3-tropanone **21** allowed an easy entry into methyl tropanonecarboxylate **6** that could be converted by known means into cocaine (**12**). Regardless of ineffective stereocontrol, this route permits the preparation of cocaine from a readily available commercial compound in only four steps (Figure 6).

Treatment of 3-tropanone **21** with dimethyl carbonate and sodium hydride yields methyl tropanonecarboxylate **6** that can be resolved in 34% yield via the corresponding bitartrate. Thereafter, optically active compound **6** was transformed into *d*-cocaine by standard reduction with sodium amalgam, followed by benzoylation. Interestingly, although other more modern reducing agents were tried for the transformation of methyl tropanonecarboxylate **6** into ecgonine

Figure 6



methyl ester **7**, none was as effective as the sodium amalgam originally used for Willstätter in 1923.

Although Carroll et al prepared unnatural *d*-cocaine; the procedure is equally suitable for the preparation of natural *l*-cocaine.

**1998: Rapoport's Preparation.**  
**N-Benzyl D-glutamic acid is used as a chiral starting compound for an enantioselective synthesis of natural l-cocaine.**

In this preparation, Rapoport applies his expertise in amino acid chemistry to derive the stereochemistry of all chiral carbons in *l*-cocaine from a single stereocenter in *N*-benzyl D-glutamic acid [**23**] (Figure 7) (13). Some notable features include the formation of the olefin in compound **32** by a sulfur extrusion reaction, and the installation of the proper stereochemistry on the methyl ester and benzoate moieties in cocaine by a dipolar cycloaddition of a nitrile oxide on tropene **38**.

Thus, cyclization of *N*-benzyl D-glutamic acid **23** in hot water leads to pyrrolidinone **24**, that is protected as a *tert*-butyl ester with oxalyl chloride, followed by *tert*-butanol, resulting in pyrrolidinone **25**. This compound is converted in thiolactam **26** by treatment with  $P_4S_{10}$ . In a separate series of events, malic acid [**27**] is transformed in triflate **29** via dibenzoate **28** by benzylation with acidic benzyl alcohol, followed by triflic anhydride.

Triflate **29** is not isolated, but it is reacted *in situ* with thiolactam **26**, resulting in the formation of thioiminium cation **30**, that is treated *in situ* with *N*-methylpiperidine and triphenylphosphine. This results in the formation of a zwitterion that collapses to episulfide **31**, which is desulfurized to olefin **32** by the action of triphenylphosphine. The conversion of triflate **29** into olefin **32** is achieved in a respectable 76% yield.

Hydrogen-transfer hydrogenation of compound **32** with ammonium formate in the presence of palladium on carbon effects concurrent debenzylation of the acid and the amine moieties, stereoselective hydrogenation of the olefin and monodecarboxylation, yielding *trans*-pyrrolidine **33**. Transesterification with acidic methanol, followed by *N*-protection with Boc anhydride, yields diester **35**, which is subject to a regioselective Dickmann cyclization with KHMDS, resulting in the tropane compound **36**, in which a ketone exists mainly in its keto form. Demethoxycarbonylation of tropane **36**

Demethoxycarbonylation of tropane **36**

**41**. Ethoxycarbonylnitrile **39** approaches the olefin in tropene **38** from the less-hindered *exo*-face, resulting in the emplacement of the desired *cis*-stereochemistry of the prospective ester and benzoate appendices on cocaine.

Mild basic hydrolysis of the ester function in tricycle **41**, followed by heating at 105–110°C, produces the formation of hydroxycyanide **43** after decarboxylation and ring opening of the oxazolidine moiety.

Hydroxycyanide **43** contains the natural *l*-cocaine skeleton with a proper stereochemistry in all chiral centers and only several functional group exchanges

Figure 7

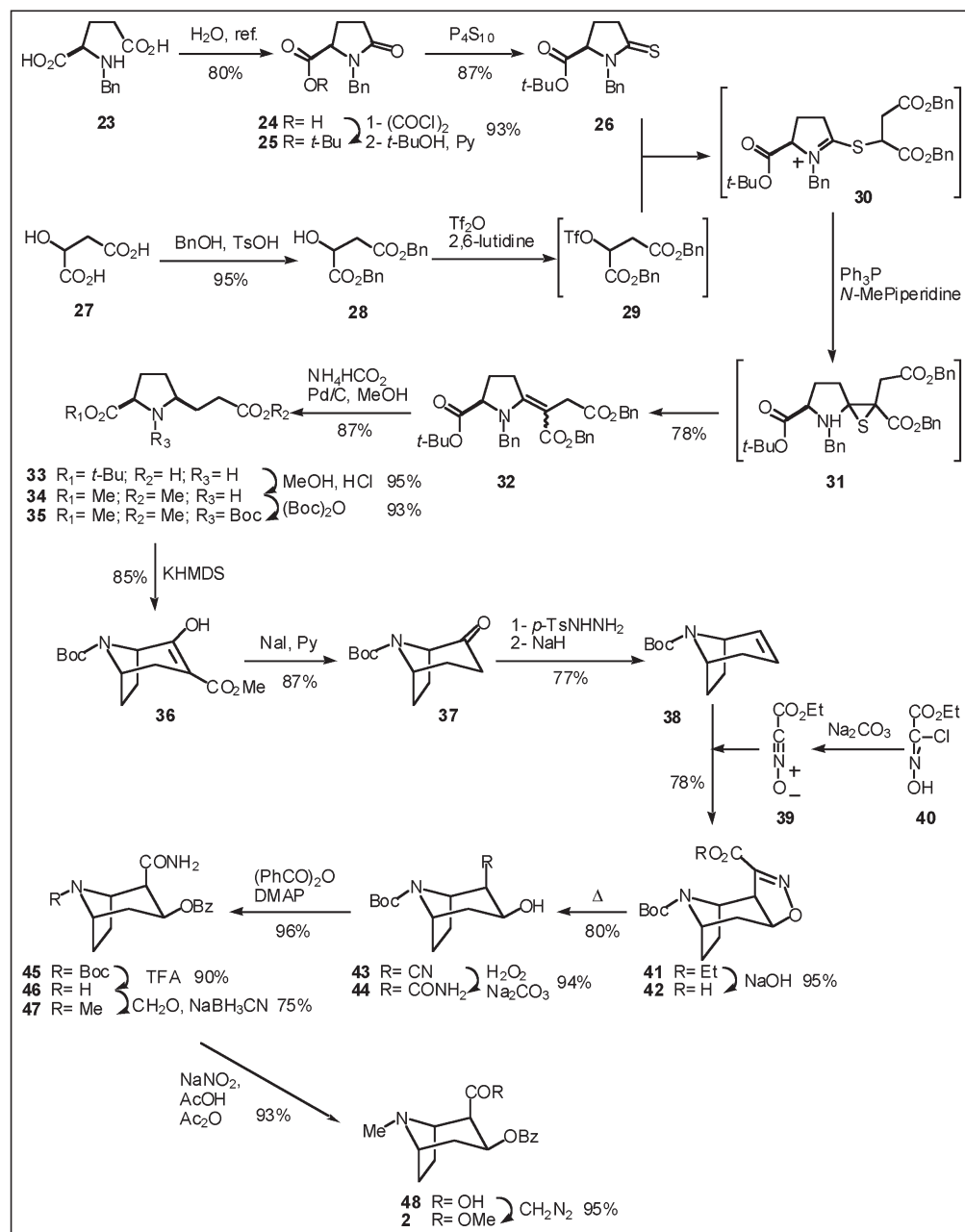
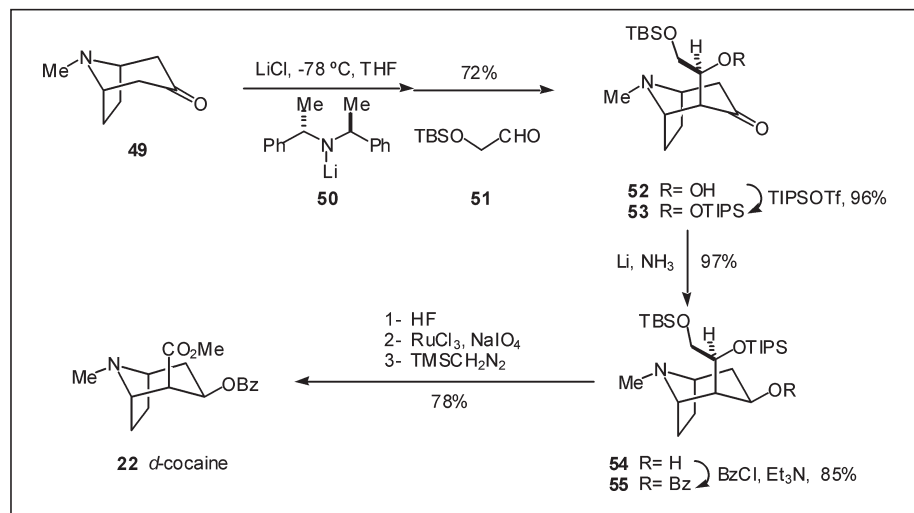




Figure 8



remain to be done. Thus, hydration of cyanide **43** into formamide **44** could be done, without epimerization at the cyanide, or dehydration of the alcohol, with basic hydrogen peroxide. *N*-Boc deprotection with trifluoroacetic acid, followed by *N*-methylation with formaldehyde and sodium cyanoborohydride yields compound **47**. Transformation of the formamide in **47** into acid **48** could be done under very mild conditions via *N*-nitrosation, with sodium nitrite in acetic acid and acetic anhydride. Finally, methylation of acid **48** with diazomethane yielded natural *l*-cocaine [2].

### 2000: Cha's Preparation.

#### The enantioselective deprotonation of a meso ketone leads to a highly effective stereoselective synthesis of cocaine.

Cha's synthesis is an outcome of the current alertness paid to the development of new enantioselective synthetic procedures (Figure 8) (14). The starting material is the symmetric tropanone **49**, which is readily accessible and commercially available. Enantioselective deprotonation of tropanone **49** with chiral lithium (*R,R*)-bis (1-phenylethyl) amide [50] gives a chiral enolate that is reacted with aldehyde **51**. This results in a highly stereoselective reaction with an approach from the less-hindered exo-face of tropanone **49**, leading to compound **52** in 90-92% ee.

Silylation of alcohol **52** with TIPSOTf yields ketone **53** that is reduced under

Birch conditions to the thermodynamic cyclohexanol **54**. After benzylation of compound **54** to compound **55** with benzoyl chloride, desilylation with hydrofluoric acid, followed with glycol cleavage with RuCl<sub>3</sub> and NaIO<sub>4</sub>, and methylation of the resulting carboxylic acid with trimethylsilyldiazomethane yielded unnatural *d*-cocaine [22]. Obviously, natural *l*-cocaine [2] could have been obtained, should the enantiomer of base **50** been used. According to the authors "Inasmuch as natural (-)-cocaine is an illicit drug, we decided to prepare the unnatural enantiomer."

### FINAL REMARKS

Cocaine is an exceedingly important molecule of modest complexity. Unlike other flagship natural substances of very complex structure like chlorophyll or vitamin B<sub>12</sub>, the development of new preparations of cocaine is doable by unpretentious research teams. It is therefore quite rare that the number of published synthesis of cocaine is rather limited.

Some of the difficulties encountered in the preparation of cocaine highlight the limitations still present at the beginning of the XXIst century in the art of Organic Synthesis for some key transformations. Regarding the reduction of ketones to alcohols, we have many hydride-transfer reagents based in aluminium and boron at our disposal. These reagents are unable to approach ketones from severely hindered faces, even when this results in alcohols with far greater thermodynamic stability. For

this purpose, reducing agents like sodium amalgam or alkali metals in liquid ammonia that operate by delivering electrons, fare much better. Regrettably, we have a very limited number of such reducing agents at our disposal, especially when commodious reaction conditions, involving preferably room temperature and cheap and safe conditions, are looked for.

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