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Enantioselective Synthesis of (−)-Dihydrocodeine and Formal Synthesis of (−)-Thebaine, (−)-Codeine, and (−)-Morphine from a Deprotonated α-Aminonitrile

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Supporting Information

ABSTRACT: The α-benzylation of a deprotonated bicyclic α-aminonitrile, followed by Noyori's asymmetric transfer hydrogenation combined with the Grewe cyclization onto a symmetrical A-ring precursor, are the key steps of a short and high-yielding enantioselective synthesis of the morphinan (−)-dihydrocodeine. This compound can be converted to (−)-thebaine in high yield by known transformations, while (−)-codeine and (−)-morphine are available from an advanced intermediate.

Morphine (**1**, Figure 1), the major constituent of the opium poppy latex, has been used for medical purposes

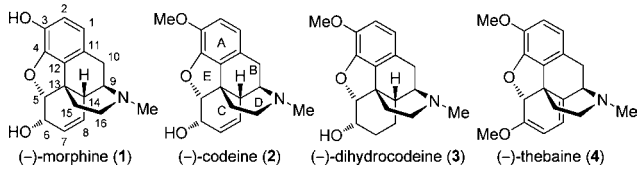


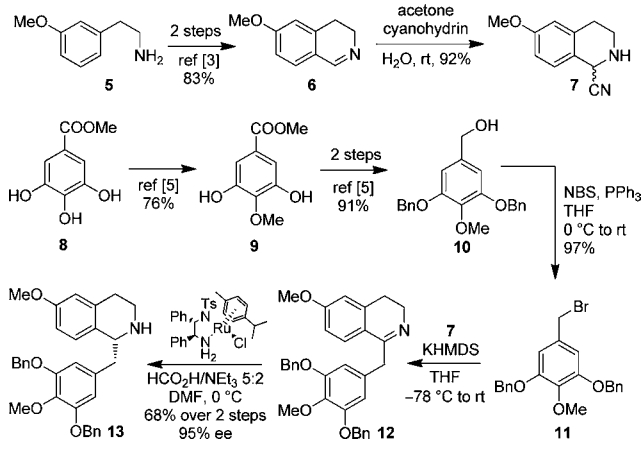
Figure 1. Structures of bioactive opioids.

since as early as 3000 B.C. by the Sumerians in Mesopotamia.[1] Today it is still one of the most common and effective analgesic drugs with a strong influence on mankind, both in a positive and negative sense. For decades, this fascinating molecule has attracted attention not only for its extraordinary pharmacological effects but also because it is a challenging target for total synthesis due to its unique and complex molecular architecture. More than 60 years after the first total synthesis by Gates in 1952, around 30 papers have been published concerning synthetic approaches to morphine (**1**) or its relatives codeine (**2**), dihydrocodeine (**3**), and thebaine (**4**),[2] but until now only 10 of them reported enantioselective syntheses.[2n,r,y−ab,af,ai,ak,am] Among these, the highest yield (6.8%) was achieved by Trost in his synthesis of (−)-codeine in 15 steps.[2aa]

Although highly creative approaches toward the morphinan skeleton have been developed, most routes suffer from a low yield. From a practical viewpoint, the Rice synthesis of dihydrocodeinone in 29% overall yield is the most efficient route known to date but furnishes only the racemate.[2h] The isolation of morphinan alkaloids from the dried plant material of *Papaver somniferum* (poppy straw) is currently the predominant source, but due to uncertain social, political, and climatic conditions in some producing regions, high-yielding methods for the chemical synthesis of opium alkaloids are, however, still attractive. Herein, we report an efficient enantioselective total synthesis of (−)-dihydrocodeine (**3**) from a deprotonated α-aminonitrile, which also represents a formal total synthesis of (−)-morphine (**1**), (−)-codeine (**2**), and (−)-thebaine (**4**).

Our synthesis began with the preparation of bicyclic α-aminonitrile **7** by addition of HCN to commercial dihydroisoquinoline **6**, which can alternatively be prepared from 3-methoxyphenethylamine (**5**) in two steps.[3] In a screening of different cyanide sources, acetone cyanohydrin was found to be superior in terms of yield, purity of the product, and ease of workup and allowed the preparation of **7** in 92% yield (Scheme 1).[4]

Scheme 1. Synthesis of α-Aminonitrile 7, Benzylic Bromide 11, and Asymmetric Transfer Hydrogenation of 12



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The synthesis of the second building block started from commercial ester **9** which itself can be obtained in a single step from methyl gallate (**8**).[5] Benzylation and reduction of **9** followed by treatment with *N*-bromosuccinimide and triphenylphosphine furnished benzylic bromide **11** in 97% yield.[6] While Rice used a bromine atom to block the more reactive position in the A ring fragment, the symmetrical oxygenation pattern used here was first employed by Beyerman to solve the regioselectivity problem in the Grewe cyclization.[2f]

The deprotonation of **7** with KHMDS under controlled conditions furnished a stabilized α-aminocarbanion which was C-alkylated with **11** to yield 1-benzyl-3,4-dihydroisoquinoline **12** upon spontaneous dehydrocyanation. This compound was sensitive to aerial oxidation and was therefore directly carried on to the next step without purification.[7] The alternative synthesis of **12** by Bischler−Napieralski cyclization requires the same number of steps and is less convergent than the present route.[8] Moreover, similar ring closures were found to be less reliable for related substrates.

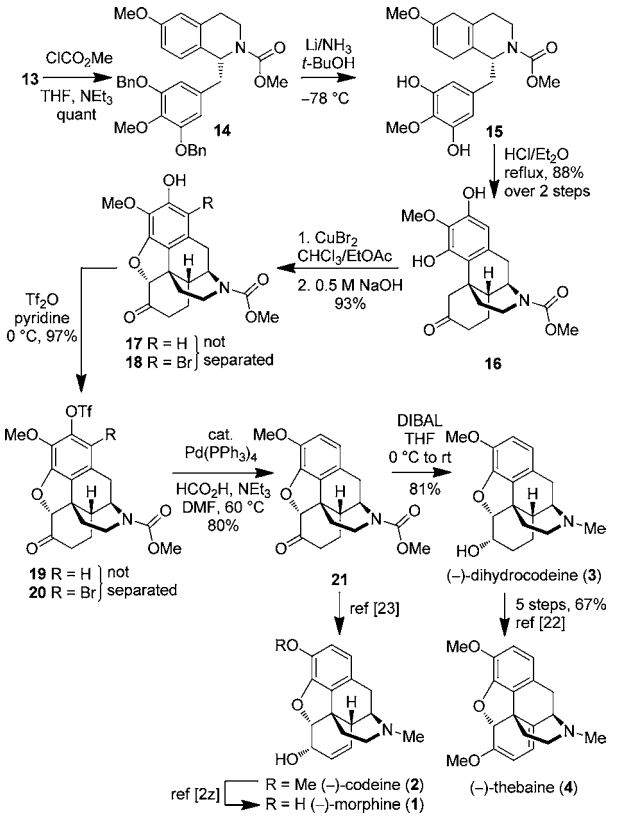
The enantioselective reduction of **12** introduced the first stereocenter at C-1 of the isoquinoline moiety. The use of RuCl[(*S*,*S*)-TsDPEN](*p*-cymene) as the catalyst and the formic acid/triethylamine azeotrope as the hydride source for the reduction of 3,4-dihydroisoquinolines was developed by Noyori[9] and also proved highly useful for the asymmetric synthesis of various alkaloids from deprotonated α-aminonitriles.[7a,10] Meuzelaar et al. achieved the highly enantioselective reduction of the dihydroisoquinoline intermediate of the Rice synthesis but reported poor results (23% yield, 86% ee) for the Beyerman intermediate **12**.[8] No further steps in the direction of morphine were undertaken by these authors.

On the basis of our previous experience with this reaction, attempts for optimization were made, and three variables with influence on the enantiomeric excess were identified: temperature, addition time of reductant, and removal of carbon dioxide from the reaction mixture by argon.[11] These intricacies were not observed for other 1-benzyl-3,4-dihydroisoquinolines, and the electronic properties of the trialkoxybenzyl substituent in **12** are likely to be responsible for the deviant behavior.[7a,8,10]

Under the optimized conditions, (*R*)-**13** was obtained in 68% yield over two steps with an ee of 95% (chiral HPLC). After alkoxycarbonylation of **13** with methyl chloroformate, the resulting carbamate **14** was subjected to Birch reduction immediately followed by Grewe cyclization to establish the morphinan skeleton of **16** carrying two new stereogenic centers with defined geometry in 88% yield over two steps (Scheme 2).[2d,f,12] *N*-Methoxycarbonyl was found to be the substituent of choice, while an *N*-methyl group caused problems in the isolation of the product of the Grewe cyclization due to the amphoteric nature of the resulting basic phenol. Noyori reported the catalytic asymmetric pressure hydrogenation of the (*Z*)-*N*-formylenamide derived from **12** and obtained the *N*-formyl derivative of **13** in 70% and 97% ee over three steps including a photochemical *E*/*Z*-isomerization.[13] We found formyl protection to be cumbersome since the formamides displayed an unusually high rotational barrier and the corresponding separable rotamers[14] hampered the purification by chromatographic methods. Moreover, the formyl group is partially cleaved and reduced under Birch conditions.

In the course of the Birch reduction, the benzyl groups were removed as well so that no additional deprotection was required and the future A ring was protected from reductive dearomatization by its increased electron density. Various

Scheme 2. Synthesis of (−)-Dihydrocodeine (3)



attempts were undertaken for the introduction of a suitable leaving group into the α-position of the ketone at C-5 (morphine numbering) to enable the closure of ring E. Neither phenyltrimethylammonium tribromide,[15] tetra-*n*-butylammonium iodide/H_2O_2,[16] Kosers reagent,[17] or copper oxide/iodine[18] gave satisfying results, while the method of Razdan[19] employing copper(II)bromide as a brominating agent successfully closed the ether bridge. A 1:1 mixture of chloroform and ethyl acetate was found to be the solvent of choice and gave fewer side products than chloroform alone. Although copper(II)bromide is known to selectively brominate enolizable ketones in the presence of arenes,[20] the electron density of ring A in **16** is very high so that partial bromination (ca. 50%) at C-1 could not be avoided. Since **17** and **18** were difficult to separate and the additional bromine could be removed simultaneously with the triflate on a later stage, the sequence was continued with the obtained compound mixture.

After triflylation of the remaining phenolic OH group (97% yield), the mixture of **19** and **20** was subjected to a Pd-catalyzed detriflylation/dehalogenation furnishing **21** as single product in 80% yield.[5] Formic acid served as a nontoxic and inexpensive hydride source in this step, which might also be performed with a heterogeneous catalyst to meet the requirements of industrial application. Reduction of the carbonyl group in **21** with DIBAL afforded (−)-dihydrocodeine (**3**) in 81% yield, $[\alpha]^{28}_{D} = -124$ (c = 1, 96% EtOH) [lit.[21] $[\alpha]^{20}_{D} = -130$ (c = 1, 96% EtOH)]. The use of this reducing agent turned out to be crucial for a high diastereoselectivity and reduction with $LiAlH_4$ led to the formation of about 20% of the undesired C-6 epimer. (−)-Dihydrocodeine (**3**) can be converted to (−)-thebaine (**4**) in five steps (67% overall yield) by known procedures.[22] As ketone **21** is a suitable precursor for the introduction of the

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$\Delta^{7,8}$-double bond, the route also represents a formal total synthesis of (−)-morphine (**1**) and (−)-codeine (**2**).[2z,23]

In summary, an enantioselective total synthesis of (−)-dihydrocodeine (**3**) in 31% overall yield over 12 linear steps from commercial starting materials was developed. It is based on the α-alkylation of a deprotonated α-aminonitrile and follows the Beyerman strategy to alleviate the regioselectivity problem in the Grewe cyclization generating the morphinan skeleton. Ketone **21**, which can serve as a starting point for the formal total syntheses of (−)-morphine (**1**) and (−)-codeine (**2**), was obtained in 11 linear steps with an overall yield of 38%. To the best of our knowledge, the present route is by far the most efficient asymmetric approach to morphinan alkaloids reported to date (a comparison of enantioselective approaches to morphinans can be found in the Supporting Information). A first attempt of a linear scale-up to a multigram scale produced ketone **21** in 15% overall yield and 95% ee (unoptimized), still clearly superior to all published small-scale procedures (see the Supporting Information).

The possibility to convert compound **3** into (−)-thebaine in high yield is particularly attractive in view of the present shortage in the supply of this rare opium alkaloid, which serves as a starting point for the preparation of potent and "safer" opioid receptor agonists such as buprenorphine as well as of antagonists such as naloxone and naltrexone.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and ^{1}H, ^{13}C, and 2D NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Johann Mulzer on the occasion of his 70th birthday.

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