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Formal Synthesis of (−)-Codeine by Application of Temporary Thio Derivatization

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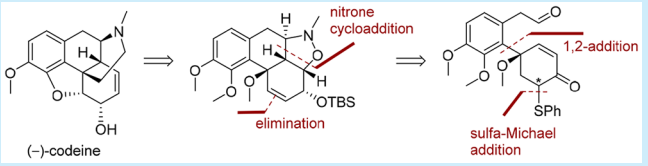
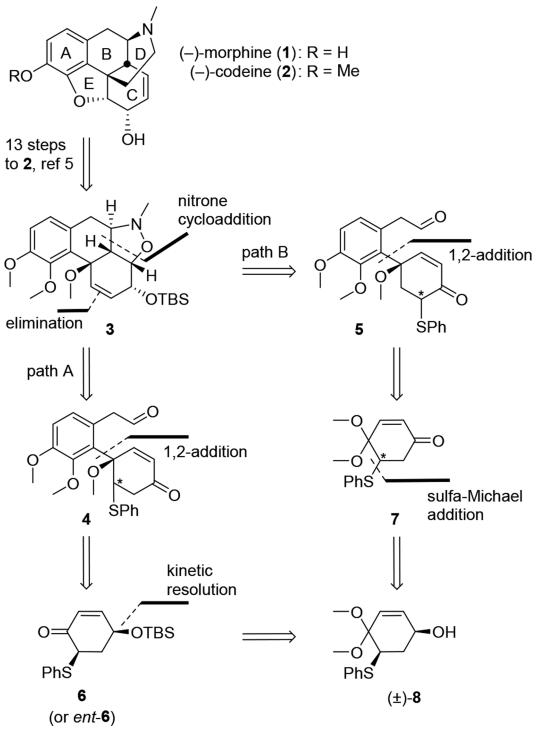
Supporting Information

ABSTRACT: Desymmetrization of a *p*-quinone monoacetal by organocatalytic sulfa-Michael addition provided rapid access to a C-ring building block for a formal synthesis of (−)-codeine. By means of a diastereoselective 1,2-addition for A/C-ring union, an intramolecular nitrone cycloaddition for construction of the phenanthrene core, and a sulfoxide elimination, an enantiopure key intermediate of the authors' previous synthesis of racemic codeine was available in 12 steps from isovanillin.



Despite groundbreaking changes in medicine during the past centuries, (−)-morphine (**1**) and (−)-codeine (**2**) have remained indispensable drugs for the treatment of pain (Scheme 1).[1] Produced from the opium poppy (*Papaver somniferum*) until the present time, these alkaloids have been a challenging synthetic target ever since the structure proposal for morphine by Robinson in 1925.[2] More than 30 total and formal syntheses[3,4] give evidence of the enormous interest of the scientific community. These endeavors contribute to the development of flexible routes toward morphine and ensure a certain independence from poppy cultivation.[3b]

Scheme 1. Retrosynthetic Analysis



In 2011 we disclosed a total synthesis of (±)-codeine (**2**) featuring an intramolecular nitrone cycloaddition to construct the ABC-ring system with simultaneous generation of four contiguous stereogenic centers.[5] We recently turned to the enantioselective preparation of the key isoxazolidine **3**. We planned to carry out the crucial cycloaddition step from a chiral precursor in which an olefin was temporarily masked with a phenylthio group instead of the prochiral *p*-quinol ether used before. This concept of desymmetrization by reversible thiol addition has been applied previously in enantioselective synthesis by the Figueredo, Evans, and Roberts groups.[6−8]

As depicted in Scheme 1, we reasoned that enantiopure **3** could be synthesized from *β*-sulfenyl ketone **4** (path A) or *α*-sulfenyl ketone **5** (path B). Depending on the position of the phenylthio group, reinstallation of the double bond might be achieved by base-promoted elimination (path A) or thermal elimination of the corresponding sulfoxide (path B). Construction of aldehyde **4** could involve 1,2-addition to known chiral enone **6**.[9,10] For path B, an analogous disconnection leads to dimethyl acetal **7** as the C-ring unit, the racemic mixture of which is known.[11] Both enones could be synthesized by enzymatic kinetic resolution of allylic alcohol (±)-**8**, an approach based on the previous preparation of **6**, where the analogous ethylene acetal was used.[12] Alternatively, asymmetric sulfa-Michael addition[13] of thiophenol to the corresponding *p*-quinone monoacetal might enable more rapid access to the desired enones.

The absolute configuration at the benzylic carbon in **4** and **5** depends on both the choice of the starting enantiomers and the stereochemical outcome of the A/C-ring union. In order to

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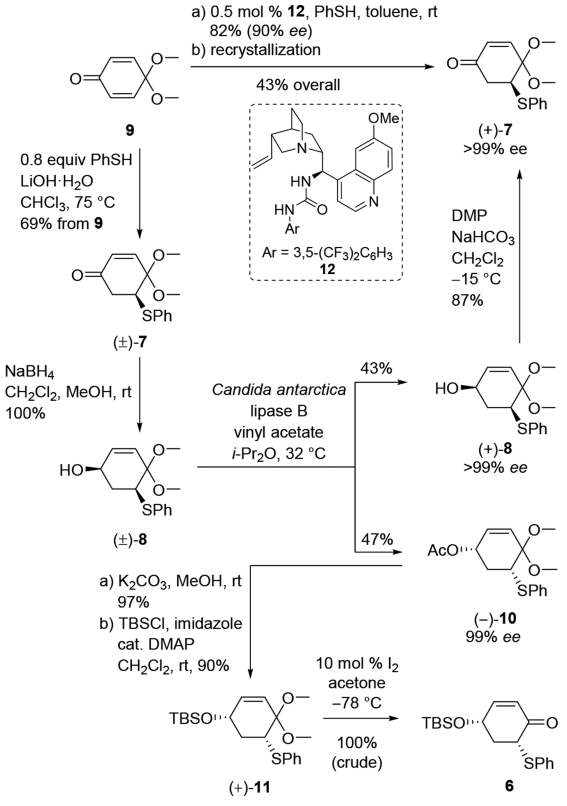
correctly install the *S* stereogenic center required for the synthesis of (−)-codeine (**2**), preliminary examinations were undertaken. They revealed that nucleophilic 1,2-addition of the respective A-ring fragments to ketones **6** and **7** took place exclusively *anti* to the sulfenyl group, leading to (4*S*,6*R*)-**6** and (*S*)-**7** as the required C-ring units.

For the enzymatic route, allylic alcohol (±)-**8** was readily prepared by base-mediated addition of thiophenol[11] to dienone **9** and subsequent diastereoselective 1,2-reduction (Scheme 2).[14]

Scheme 2. Enantioselective Synthesis of Enones 6 and (+)-7

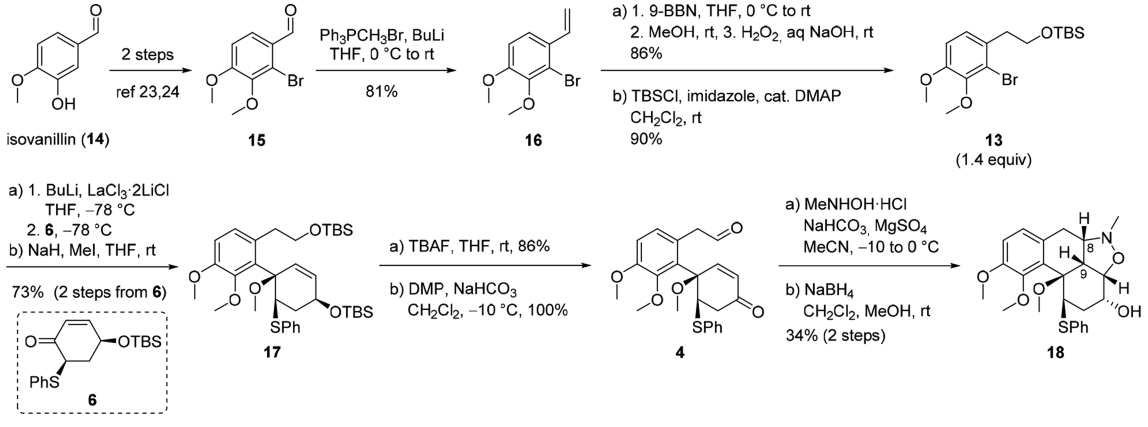


Pleasingly, enantioselective acetylation catalyzed by *Candida antarctica* lipase B yielded alcohol (+)-**8** and acetate (−)-**10** with excellent enantiomeric excesses.[15,16] Oxidation of (+)-**8** using Dess−Martin periodinane (DMP) led to enone (*S*)-(+)-**7**, while methanolysis of (−)-**10**, silylation of the resulting alcohol, and subsequent acetal cleavage[17] in (+)-**11** gave enone (4*S*,6*R*)-**6**. The latter sequence offers an alternative to the previous route toward **6**[9] with improved yield and *ee*.

We continued with the direct organocatalytic preparation of (+)-**7** from *p*-quinone monoacetal **9**. Our studies of the sulfa-Michael addition to **9** delivered very satisfying results comparable to those reported for enones by Singh and co-workers.[18] Best *ee* values of 90% were obtained with only a 0.5 mol % loading of quinidine-based catalyst **12**[19] in toluene at room temperature. Interestingly, both higher and lower catalyst loadings and lower reaction temperature led to decreased enantioselectivity. Recrystallization of the product raised the *ee* to >99% and provided crystals suitable for X-ray diffraction analysis, which confirmed the absolute configuration of (+)-**7** as *S*. This efficient route to (+)-**7** can additionally be utilized for a rapid synthesis of **6** using the pseudoenantiomeric quinine-based catalyst.[20]

Having gained access to the C-ring building blocks, investigation of the A/C-ring union for path A was undertaken (Scheme 3). The required aromatic A-ring fragment **13** was synthesized from isovanillin (**14**) under optimization of our previous route:[21] Wittig reaction of aldehyde **15**[22,23] to give **16**[24] followed by hydroboration/oxidation and silyl protection furnished **13**. Halogen−lithium exchange with **13** and subsequent reaction with **6** in the presence of the $LaCl_3$·2LiCl complex[25] resulted in the formation of the tertiary alcohol as a single diastereomer, which was methylated to give **17**. The configuration at the benzylic stereogenic center was assigned on the basis of NOE experiments. Desilylation and oxidation then provided cycloaddition precursor **4** in very good yield. It was subjected to nitrone generation/cycloaddition using our previously established conditions[5] with additional dilution (0.01 M). We isolated a highly unstable product matching the expected ^{1}H NMR and MS data. It was quickly reduced with $NaBH_4$ in order to confirm the structure. Unfortunately, the resulting alcohol **18** exhibited the undesired H8,H9 *cis* relationship.[26] No other isoxazolidine was isolable after variation of the solvent (dichloromethane) and reaction temperature (−40 °C). The cycloaddition product thus results from a different transition state geometry (*exo*) than that operating in the racemic route (*endo*).[27] These findings could be attributed to the higher steric constraints due to the additional sulfenyl group. The *exo*/*endo* selectivity of nitrone cycloadditions is in fact not clearly predictable,[28] and different outcomes have been described for cycloadditions similar to the one reported herein.[26,29]

Scheme 3. Synthesis of Cycloaddition Precursor 4 (Path A) and Its Conversion into *cis*-Isoxazolidine 18



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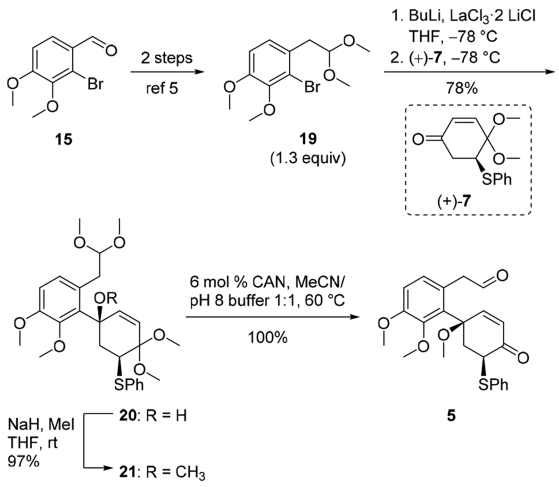
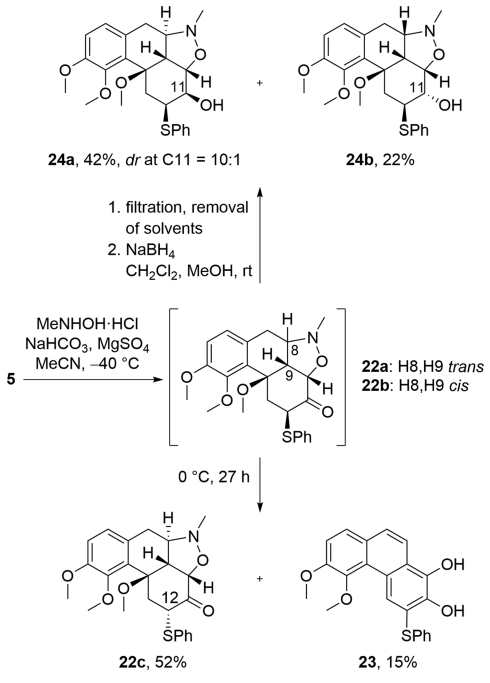
As the nitrone derived from aldehyde **4** failed to undergo cycloaddition with the desired diastereoselectivity, we focused on the synthesis of aldehyde **5** (path B). A/C-ring union was conducted analogously to path A with the known aryl bromide **19**[5] and enone (+)-**7** to give tertiary alcohol **20** in good yield as a single diastereomer (Scheme 4). Its relative configuration was confirmed by X-ray diffraction analysis. Methylation of the alcohol afforded ether **21**, which smoothly underwent double acetal cleavage with a catalytic amount of ceric ammonium nitrate[30] to afford aldehyde **5** in excellent yield.

Scheme 4. Rapid Access to Cycloaddition Precursor 5 (Path B)



Gratifyingly, subsequent nitrone cycloaddition using aldehyde **5** proceeded with formation of the desired H8,H9 *trans* product, but sulfenyl ketone **22c** epimerized at C12 was isolated along with phenanthrene **23** after column chromatography (Scheme 5). Initially, however, isoxazolidines **22a** and **22b** were formed, as was shown by reduction of the crude mixture to give alcohols **24a** and **24b** in 42% and 22% yield, respectively.[31] Furthermore, **22a** could be isolated by crystallization. It epimerized to **22c** upon standing without formation of **23**. We therefore concluded that **23** originated exclusively from *cis*-isoxazolidine **22b**.

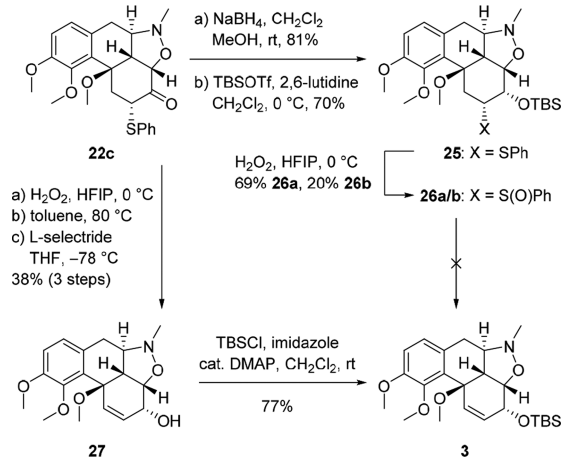
Scheme 5. Assembly of the Phenanthrene Core from 5 by Intramolecular Nitrone Cycloaddition



In principle, the required reinstallation of the alkene by sulfoxide elimination might be realized at the stage of the alcohol or ketone. From the relevant H8,H9 *trans* products, alcohol **24a** exhibited the undesired β-OH configuration at C11, so we focused on the synthesis of **22c**. Eventually we found that the cycloaddition/epimerization sequence was best carried out as a one-pot process with spontaneous epimerization at 0 °C, giving **22c** in 52% yield from **5**.

We then examined the reduction of **22c**, which proceeded with complete diastereoselectivity in high yield (Scheme 6). After protection of the alcohol, silyl ether **25** was oxidized with H_2O_2 in hexafluoroisopropanol (HFIP)[32] to give a separable mixture of diastereomeric sulfoxides **26a** and **26b**. Unfortunately, neither sulfoxide underwent elimination to afford olefin **3** at temperatures up to 160 °C. Presumably, the required conformation for *syn* elimination could not be adopted because of restricted rotation around the C−S bond. An alternative elimination of a phenyl sulfilimine generated in situ by reaction of **25** with *O*-mesitylenesulfonylhydroxylamine[33] proved unsuccessful, too. Subsequently, we investigated an oxidation/elimination/reduction sequence starting from **22c**. Although the derived sulfoxides turned out to be prone to phenanthrene formation analogous to the generation of **23**, we were able to gain access to allylic alcohol **27** in a good overall yield of 38% over three steps. Silylation of **27** finally led to the target compound **3**.

Scheme 6. Completion of the Formal Synthesis of (−)-Codeine (2) by Preparation of 3



In conclusion, we have accomplished a formal synthesis of (−)-codeine (**2**) by straightforward construction of the enantiopure key intermediate **3** in 12 steps from isovanillin. Central to our approach was the temporary installation of a phenylthio group for desymmetrization. We examined two pathways differing in the position of the sulfenyl group and found that only the α-sulfenyl ketone could be used to generate the desired diastereomer in the key intramolecular nitrone cycloaddition step. The latter thio derivative **5** was readily available through a highly enantioselective sulfa-Michael addition to *p*-quinone monoacetal **9**, a reaction that should prove useful beyond the application reported herein.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03972.

Experimental procedures, spectroscopic data, ^{1}H and ^{13}C NMR spectra, and HPLC traces (PDF)

Accession Codes

CCDC 1578109 and 1578110 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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