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Total Synthesis of (±)-Thebainone A by Intramolecular Nitrone Cycloaddition

Yuzhou Wang, André Hennig, Thomas Küttler, Christian Hahn, Anne Jäger, and Peter Metz*

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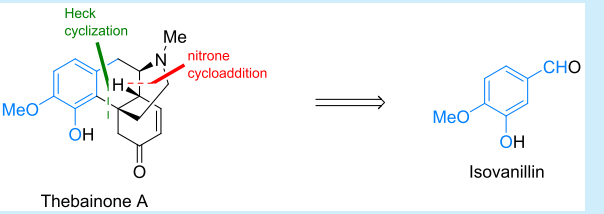
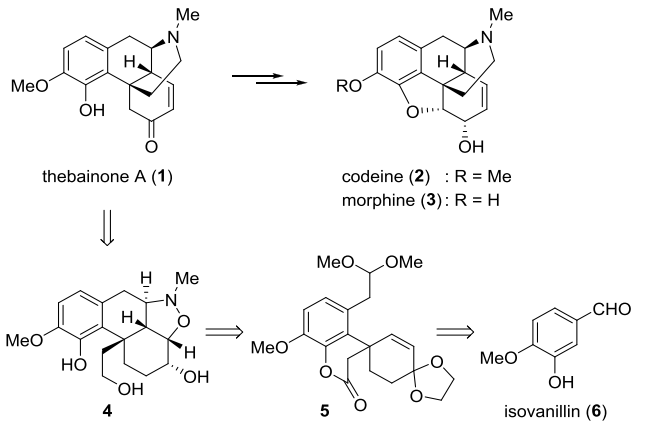
ABSTRACT: Using an intramolecular nitrone cycloaddition and a Heck cyclization as the crucial transformations, a total synthesis of the racemic morphine alkaloid thebainone A was accomplished in 22 steps commencing with isovanillin.



The alkaloids morphine (**3**) and codeine (**2**) present in the opium poppy (*Papaver somniferum*) are among the most important drugs when the treatment of severe pain is necessary (Scheme 1). Gates succeeded in the first total synthesis of morphine (**3**) in 1952.[1] Since then, more than 30 total and formal syntheses have been published.[2−4] Due to our interest in the application of intramolecular nitrone cycloadditions toward the synthesis of morphine alkaloids,[5,6] we recently devised a novel access to thebainone A (**1**), which in turn is a known precursor for **2** and **3**. This was already shown by Gates in his pioneering work.[1] A second total synthesis of **1** was described by Tius in 1992.[7]

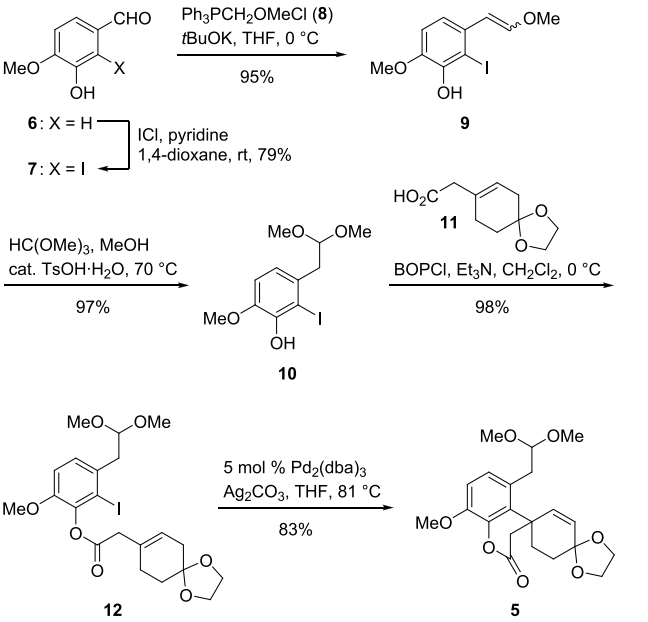
Scheme 1. Retrosynthetic Analysis



As depicted in Scheme 1, we envisioned to trace thebainone A (**1**) back to isoxazolidine **4**. The heterocyclic moiety in **4** might be generated by a nitrone cycloaddition of a substrate derived from bisacetal **5**. Ultimately, readily available isovanillin (**6**) serves as the starting material for the bisacetal **5**, with the demanding construction of the quaternary benzylic center being planned by a Heck reaction.[8]

Already after the first four steps of the synthesis, all carbon atoms required for the basic framework of thebainone A (**1**) were assembled (Scheme 2). Iodination of isovanillin (**6**) to

Scheme 2. Conversion of Isovanillin (6) into Lactone 5



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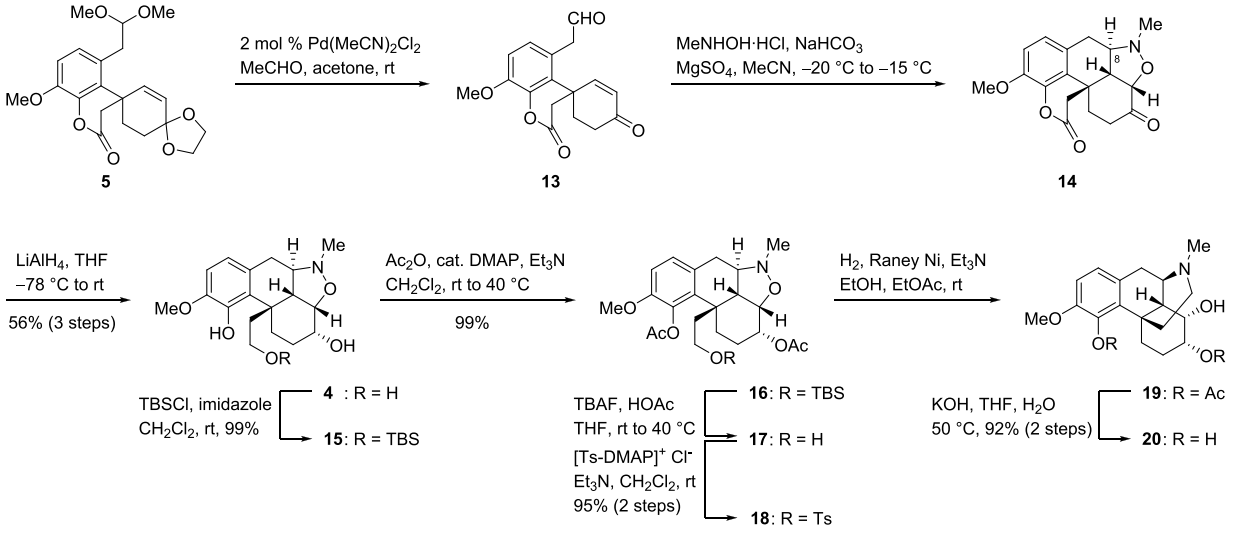
Scheme 3. Synthesis of Morphinan 20 from Lactone 5



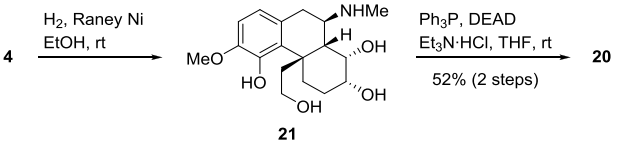
give derivative **7**[9] was followed by a Wittig reaction with the ylide derived from phosphonium salt **8** to provide a diastereomeric mixture of enol ethers **9** and subsequent conversion of **9** into the known acetal **10**[10] in very good yield.

By avoiding the use of protecting groups, the published routes from **6** to **10** could be streamlined to three steps. Esterification of phenol **10** with acid **11**[8,11] through activation with BOPCl[12] led to ester **12** with high efficiency. After intense screening of reaction conditions, the Heck cyclization of **12** to give lactone **5** was best effected without any phosphine ligands[8a] in the presence of silver carbonate.

For the key nitrone cycloaddition, the two protected carbonyl functions of **5** first had to be deblocked. This was cleanly achieved with the mild Lewis acid $Pd(MeCN)_2Cl_2$ in acetone (Scheme 3).[13] It was not necessary to purify the labile keto aldehyde **13** on silica gel. Thus, nitrone formation and subsequent intramolecular cycloaddition were carried out with crude **13** and *N*-methylhydroxylamine. Running this reaction at low temperature effected a high diastereoselectivity in the formation of the desired isoxazolidine **14** (**14**:8-*epi*-**14** ca. 10:1). Since this keto lactone was also rather unstable, it was immediately reduced with a large excess of lithium aluminum hydride to give dihydroxy phenol **4** in good overall yield from **13**. The relative configuration of **4** was confirmed by X-ray diffraction analysis. An efficient transformation of the primary alcohol of **4** into a tosylate without competing phenol ether formation succeeded by chemoselective silylation to give silylether **15** followed by double acetylation and desilylation of the resultant diacetate **16** to provide alcohol **17** and finally tosylation.[14] Tosylate **18** was then subjected to reductive cleavage of the heterocycle with concomitant intramolecular nucleophilic substitution to generate piperidine **19**.[5b] Subsequent saponification of **19** provided dihydroxy phenol **20** that was also characterized by X-ray diffraction analysis.

We also investigated a potentially shorter route from isoxazolidine **4** to morphinan **20** using a Mitsunobu reaction of trihydroxy phenol **21** that was readily obtained from **4** by hydrogenolytic cleavage of the N–O bond (Scheme 4). In order to avoid a competing intramolecular alkylation of the phenol oxygen, triethylamine hydrochloride was added.[15]

Scheme 4. Transformation of Isoxazolidine 4 to Morphinan 20 by Mitsunobu Reaction



While we sometimes observed the formation of morphinan **20** in good yield, this reaction turned out to be rather capricious, and we could not find suitable conditions for the conversion of **21** to **20** in a reproducible fashion. Nevertheless, even though some more steps are required for the sequence leading from **4** to **20** in Scheme 3, its overall yield (75%) is far better than the best result obtained according to Scheme 4.

Completion of the synthesis of thebainone A (**1**) is shown in Scheme 5. In order to activate the C-6 position for introduction of the ketone function, the *cis* diol moiety of **20** was reductively eliminated by formamide acetal pyrolysis[16] with simultaneous esterification of the phenol to give olefin **22**. Prior to allylic oxidation, the tertiary amine was converted to ethyl carbamate **23**.[17] Subsequent reaction of **23** with selenium dioxide[18] and further oxidation of the resultant allylic alcohol to the ketone with the Dess–Martin periodinane (DMP)[3b,8a,18c,d] afforded enone **24** in moderate overall yield. We first opted for a reduction/oxidation sequence in order to convert **24** to **1**. However, treatment of **24** with lithium aluminum hydride to give α-thebainol[19] led to partial overreduction of the enone, and reoxidation of the highly sterically hindered allylic alcohol in α-thebainol featuring a free phenol could not be achieved by Swern oxidation. Thus, ketone **24** was protected as the dioxolane **25** without migration of the double bond[20] under mild reaction conditions.[21] Finally, lithium aluminum hydride reduction of the carbamate[17] and acetate function in **25** gave rise to acetal **26** that was deprotected uneventfully to provide (±)-thebainone A (**1**).

The relatively low yield of the allylic oxidation of **23** at C-6 is probably due to an unfavorable conformation of the C ring cyclohexene (Scheme 6). All of the tetracyclic morphine precursors that have been successfully subjected to selenium

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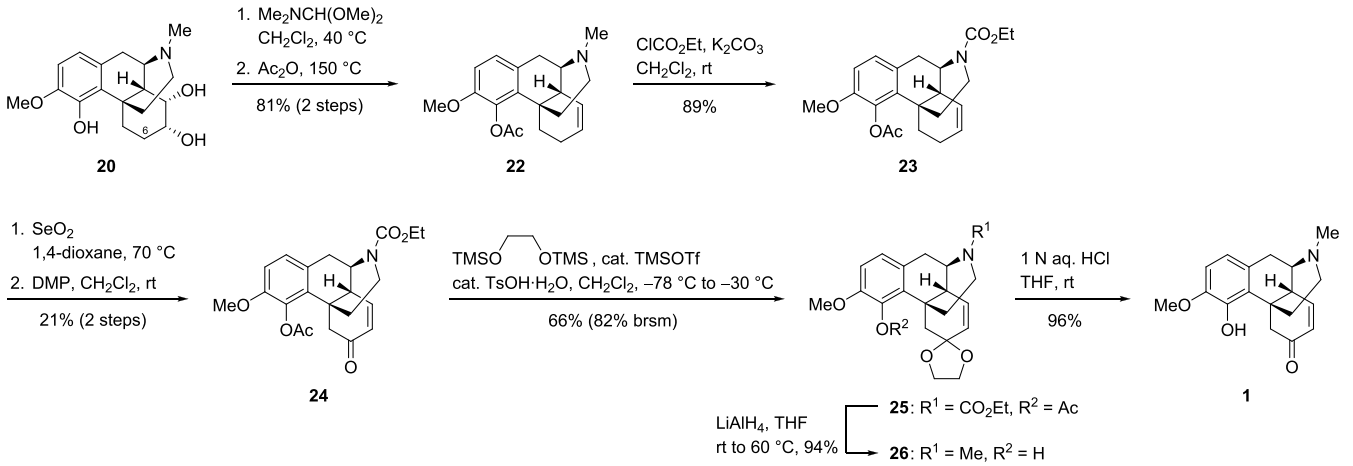
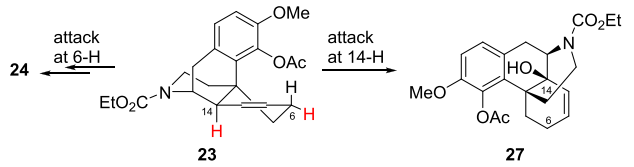
Scheme 5. Completion of the Synthesis of Thebainone A (1)



Scheme 6. Allylic Oxidation of Cyclohexene 23



dioxide oxidation adopt a boat conformation of the C ring with axial orientation of 6β-H.[18] In contrast, **23** lacking the tetrahydrofuran E ring features a half-chair conformation of the C ring. As a consequence, the sterically more accessible 6β-H is oriented equatorially, while 14-H is properly aligned with the adjacent π-system for a hetero ene reaction with selenium dioxide. Indeed, the C-14 hydroxylated morphinan **27** was isolated as another major product of this reaction.[22]

With this shortest total synthesis of thebainone A (**1**) so far, a synthesis of codeine (**2**) and morphine (**3**) is formally completed, too. However, the known route from **1** to **2** and **3** still leaves room for improvement.[1,23] Work along this line as well as further optimization of the allylic oxidation of **23** is currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00905.

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

Accession Codes

CCDC 1968788−1968790 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 emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Peter Metz − *Fakultät Chemie und Lebensmittelchemie, Organische Chemie I, Technische Universität Dresden, 01062 Dresden, Germany;* orcid.org/0000-0002-0592-9850; Email: peter.metz@chemie.tu-dresden.de

Authors

Yuzhou Wang − *Fakultät Chemie und Lebensmittelchemie, Organische Chemie I, Technische Universität Dresden, 01062 Dresden, Germany*

André Hennig − *Fakultät Chemie und Lebensmittelchemie, Organische Chemie I, Technische Universität Dresden, 01062 Dresden, Germany*

Thomas Küttler − *Fakultät Chemie und Lebensmittelchemie, Organische Chemie I, Technische Universität Dresden, 01062 Dresden, Germany*

Christian Hahn − *Fakultät Chemie und Lebensmittelchemie, Organische Chemie I, Technische Universität Dresden, 01062 Dresden, Germany*

Anne Jäger − *Fakultät Chemie und Lebensmittelchemie, Organische Chemie I, Technische Universität Dresden, 01062 Dresden, Germany*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00905

Notes

The authors declare no competing financial interest.

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(22) Allylic alcohol **27** was isolated after SeO_2 oxidation in 21% yield. In addition, an allylically transposed alcohol SI-3 (see the Supporting Information) was formed in ca. 10% yield that was probably derived from **27**. The relative configuration at C-14 of **27** was elucidated by 2D NMR measurements after reduction with lithium aluminum hydride to give the corresponding *N*-methylphenol (see the Supporting Information).
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