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Studies into the Diels–Alder reactions of 5-trimethylsilylthebaine

Weibin Chen,[a] Gary D. Strahan,[a] Damon A. Parrish,[b] Jeffrey R. Deschamps[b] and Andrew Coop[a,*]

[a]*Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, 20 Penn Street, Room 637, Baltimore, MD 21201, USA*
[b]*Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, DC 20375, USA*

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Abstract—The introduction of a 5-trimethylsilyl group on the least hindered face of the diene thebaine was anticipated to favor attack by dienophiles from the alternate face, but only gave rise to a rearrangement product when treated with 3-butene-2-one at 110 °C. Reaction with the more reactive benzoquinone at lower temperature gave rise to a very slow reaction from the same face as the silyl group, indicating that a trimethylsilyl group does not sufficiently hinder this face to achieve reaction at the other face.
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1. Introduction

The opium alkaloid thebaine (**1**) readily undergoes Diels–Alder reactions with various dienophiles to give the adducts such as thevinone (**2**).[1,2] Further manipulation of these adducts leads to an extremely potent class of opioid analgesics termed the orvinols, which continue to receive extensive attention.[3–5] The diene system of thebaine could potentially be attacked from both faces, yet reactions with dienophiles always occur from the same face as the nitrogen bridge (upper face) due to the nitrogen bridge causing the lower face to be hindered through concealment inside a concave system.[3] Attempts to entice Diels–Alder reactions to occur at the lower face have concentrated on introducing substituents into the 5-position of thebaine, thereby providing additional steric hindrance on the upper face. Maat showed that the introduction of a 5β-methyl substituent[6,7] caused some attack from the lower face, and that the corresponding orvinols possessed lower opioid activity than the traditional orvinols.[3] Although these studies provide compelling evidence that the orvinols derived from adducts at the lower face possess little activity, the influence of the 5-methyl group cannot be ignored as 5-methyl groups are known to significantly affect the pharmacology of opioids.[3] Our recent studies into

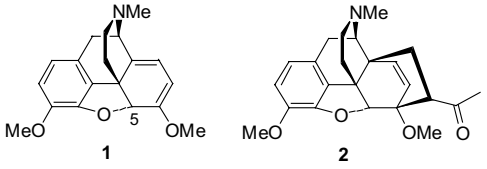

Figure 1. Structures of thebaine (**1**) and thevinone (**2**).

Diels–Alder reactions of 5β-butyl thebaine gave exclusive attack from the upper face, contrasting with the results of Maat.[8] We considered that the introduction of a sterically demanding removable substituent into the 5β-position would be more likely to direct Diels–Alder reactions to occur from the lower face. The 5β group could be subsequently removed to give the desired 5-unsubstituted adducts, and allow a thorough investigation of the effect of the stereochemistry of the bridge on the pharmacology of this important class of narcotic analgesics Figure 1.

2. Results and discussion

We recently reported the preparation and Lewis acid-catalyzed rearrangement reactions of 5-trimethylsilylthebaine (**3**),[9] and considered that **3** possesses the potential to act as an analog of thebaine with severe steric hindrance to the upper face of the diene. Treatment of **3** with 3-butene-2-one in refluxing toluene gave rise to a single product in 63% yield, which possessed the

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* Corresponding author. Tel.: +1 4107062029; fax: +1 4107065017; e-mail: acoop@rx.umaryland.edu

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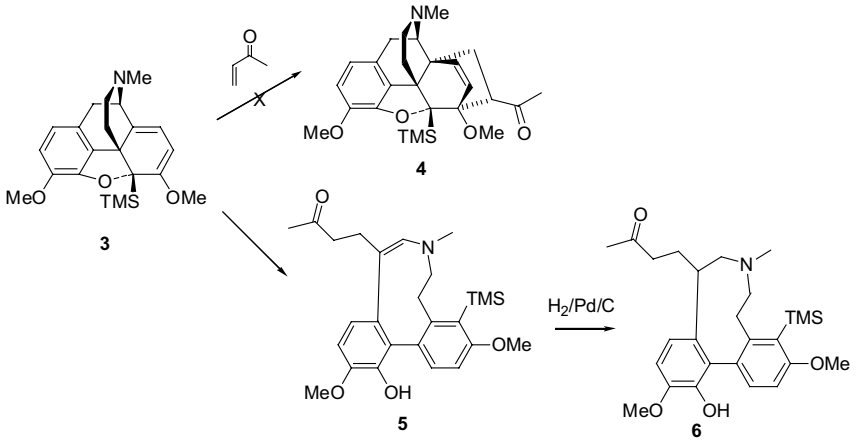


Scheme 1.

anticipated mass spectrum, but possessed four aromatic protons and one vinylic proton as a singlet in the ^{1}H NMR, indicating that the product was not the desired Diels–Alder adduct **4** (Scheme 1). The product could not be crystallized as it proved prone to decomposition when exposed to the atmosphere, and therefore the structure was assigned to be the *Z*-enamine **5** through NMR analysis as detailed in the supplementary data section.

Confirmation of the rearranged skeleton was also achieved through hydrogenation of the double bond of **5** in 90% yield. Crystallographic analysis on crystals obtained through evaporative crystallization from EtOAc/hexane showed the structure to be the substituted bractazonine analog **6** (Fig. 2). The mechanism of this reaction must occur through thermal rearrangement to the iminium ion **7** followed by proton transfer to the enamine **8** (Scheme 2), then reaction with 3-butene-2-one. Thermal rearrangement to enamine **8** was confirmed by heating **3** in toluene at reflux (Scheme 2). The resulting product proved unstable and purification was not possible, but a *trans* double bond ($J = 14$ Hz) of an enamine was clearly observed in the crude reaction product. Hydrogenation to the known compound **9**[9] confirmed the course of reaction. We recently proposed that the rearrangement of **3** on treatment with mild Lewis acids was due to the generation of a β-silyl-stabilized cation after phenyl migration.[9] The fact that the rearrangement also occurs through simple refluxing in toluene without any acidic catalysts, may suggest that the phenolate produced on ring opening is stabilized through a pentacoordinate silicon species.[10,11]

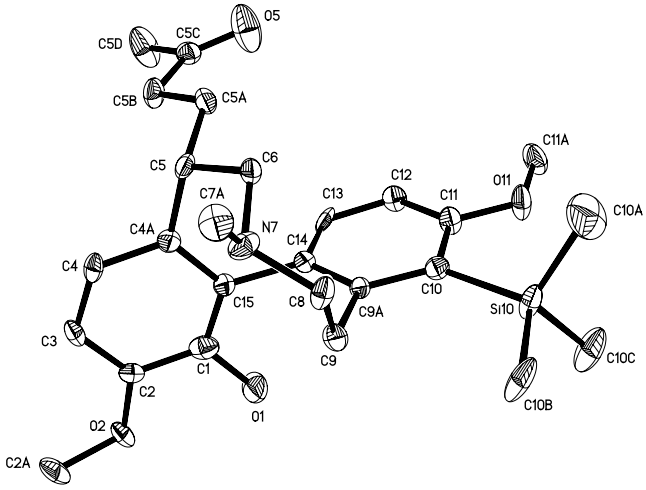
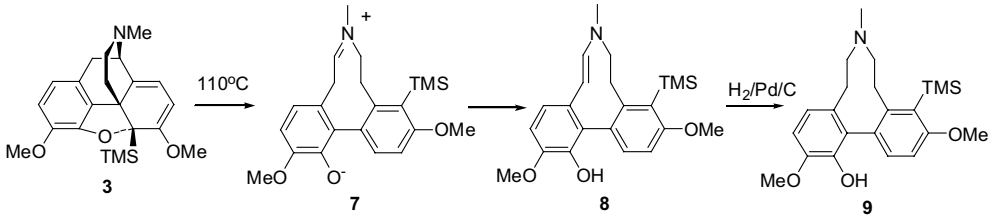
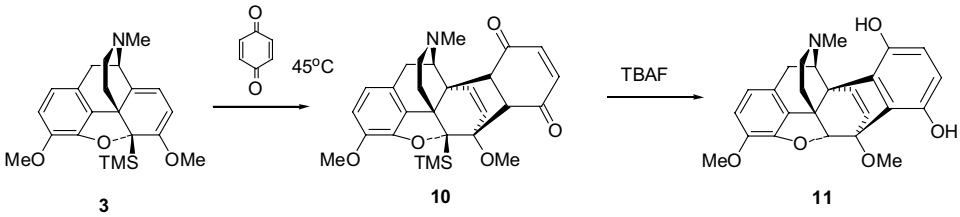


Figure 2. View of **6** as determined by X-ray diffraction analysis. Only one of the two independent molecules in the asymmetric unit is shown, hydrogen atoms have been omitted for clarity and thermal ellipsoids are shown at the 50% level.

In order to continue investigations into Diels–Alder reactions with **3**, a study of the temperature dependence of the rearrangement was initiated. It was found that the maximum temperature where **3** was stable over several days in toluene was 45 °C, but treatment of **3** with 3-butene-2-one at 45 °C for 7 days gave unreacted **3** indicating that both sides of the diene are now very hindered. However, treatment with the more reactive benzoquinone gave rise to a Diels–Alder adduct (**10**), which was isolated in 10% yield after 7 days at 45 °C. Removal of



Scheme 2.



Scheme 3.

the silyl substituent with TBAF also tautomerized the system to give the quinol (**11**) (Scheme 3). Comparison to an authentic sample of the traditional quinol (**11**)[12] confirmed the stereochemistry to be that which resulted from attack of the diene from the undesired upper face (Scheme 3).

3. Conclusion

These results suggest that placing a large group into the 5β-position of thebaine hinders attack from the upper face, but does not necessarily give rise to attack from the lower face, and is consistent with our previous findings with 5-butylthebaine.[8] Further studies into why 5β-methylthebaine, with a small 5-substituent, gives rise to an adduct derived from attack at the lower face are currently underway.

Acknowledgements

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Supplementary data

A supplementary data section is provided, which includes a detailed description of the assignment of structure **5** by NMR, and full experimental details for all reactions. The supplementary data is available online with the paper in ScienceDirect. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 232200. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. [fax: +44-(0)-1223-336033 or e-mail: deposit@ccdc.cam.co.uk]. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.11.010.

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