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Diastereoselective Synthesis of 3,4-Dimethoxy-7-morphinanone: A Potential Route to Morphine

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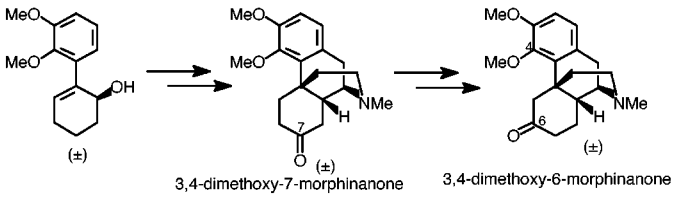
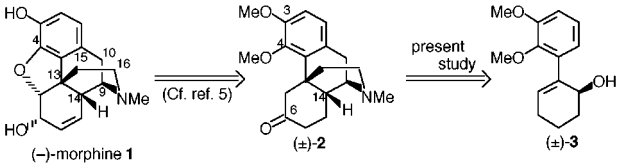
ABSTRACT



Diastereoselective synthesis of racemic 3,4-dimethoxy-7-morphinanone from racemic 2-(2,3-dimethoxyphenyl)cyclohexen-1-ol has been achieved. The relative structure has been determined by transformation of the product into the known 3,4-dimethoxy-6-morphinanone. Resolution of the starting cyclohexenol has also been accomplished for use in a future enantiocontrolled synthesis of morphine.

The synthesis of morphine **1** has engaged the interest of organic chemists both from its characteristic physiological activity and from its unique structure.[1,2] We are interested in the enantiocontrolled synthesis of (−)-morphine **1** from 2-(2,3-dimethoxyphenyl)cyclohexen-1-ol[3,4] **3** since we have recently developed an efficient resolution method for the closely related 2-arylcyclohexenols.[4] In this paper, we report the successful resolution of racemic 2-(2,3-dimethoxyphenyl)cyclohexen-1-ol **3**, diastereoselective conversion of racemate (±)-**3** into 3,4-dimethoxyphenyl)cyclohexen-1-ol **3**, and diastereoselective conversion of racemate (±)-**3** into 3,4-dimethoxy-6-morphinanone **2**, the 4-*O*-methyl derivative of the Gates ketone. The latter is the key intermediate in the first synthesis of morphine **1**.[5] These studies position us to pursue for future work on an enantiocontrolled synthesis of morphine **1**. The present study provides an efficient method for the highly diastereoselective introduction of the C14 stereogenic center and the facile construction of the C9−C10 bridge of the morphinan system (Scheme 1).

Scheme 1



Thus, by following the established procedure,[4] (±)-**3** was stirred with vinyl acetate (1 equiv) in *tert*-butyl methyl ether for 3 days to give the enantiopure acetate[6] (+)-**4**, $[\alpha]^{25}_{D}$ +145.5 (*c* 1.0, $CHCl_3$), in 47% yield, leaving the enantioenriched alcohol (−)-**3**, $[\alpha]^{31}_{D}$ −60.2 (*c* 0.9, $CHCl_3$), (97% ee),[6] in 48% recovery yield. On alkaline methanolysis, (+)-**4** afforded (+)-**3**, $[\alpha]^{26}_{D}$ +60.6 (*c* 1.0, $CHCl_3$). The absolute

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(2) For the synthesis of morphine after ref 1, see: (a) White, J. D.; Hrncier, P. *J. Org. Chem.* **1999**, *64*, 7271. (b) White, J. D.; Hrncier, P.; Stappenbeck, F. *J. Org. Chem.* **1999**, *64*, 7871.

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(6) Enantiomeric excess was determined by HPLC using a column with a chiral stationary phase (CHIRALCEL OD, elution with ^{i}PrOH−hexane 3:97 v/v).

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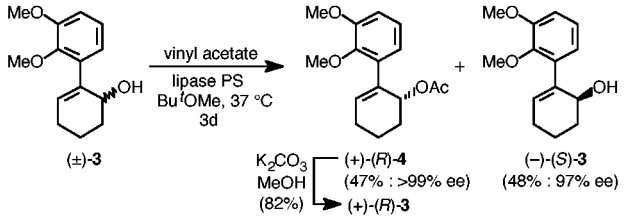
configuration of the resolution products was determined by comparison with an authentic material, prepared from the chiral 2-iodo-2-cyclohexen-1-ol[7] and 3,4-dimethoxyphenylboric acid by Suzuki coupling conditions.[8] This comparison revealed (+)-**3** to be *R* and (−)-**3** to be *S* (Scheme 2).

Scheme 2



On the other hand, transformation of the same racemic alcohol (±)-**3** into morphinanone **2** was examined to prepare for future utilization of (−)-(*S*)-**3** for construction of natural (−)-morphine **1**. To construct the quaternary 13-stereogenic center first, (±)-**3** was treated[4,9] with ethyl vinyl ether in the presence of *N*-bromosuccinimide (NBS) to give bromoacetal **5** as a mixture of two epimers. In contrast to the 3,4-dimethoxyphenyl analogue which gave the cyclization product in excellent yield,[4] **5** furnished the cyclization product **6** in moderate yield under the same radical initiated conditions,[10] probably because of steric hindrance by the 2-substituent on the aromatic ring. Since we could not optimize the conditions to improve the cyclization, we carried out the present examination using product **6** obtained in 48% yield. Thus, **6** was first transformed into lactone **7** on peracid treatment in the presence of a Lewis acid.[11] Product **7** was then transformed into xanthate **10** by a sequential three-step reaction via diol **8** and monopivalate **9**. Upon thermolysis under various conditions, **10** afforded no cyclohexene **14** but instead gave a complex mixture. As this was presumed to be due to steric repulsion between the xanthate moiety and the axially disposed alkyl functionality in a transition state (Figure 1, **10a**), its epimer **13**, with no such steric hindrance, seems to be more appropriate for *syn*-elimination. Although the Mitsunobu reaction of **9** failed to give the inverted alcohol **12**, oxidation of **9** followed by reduction of the generated ketone **11** with sodium borohydride furnished the epimeric alcohol **12**, diastereoselectively. The observed diastereoselective reduction may be due to prior coordination of the pivalate moiety with the borohydride reagent which delivered a hydride exclusively from the β-face of the molecule (Figure 1, **11a**). As expected, on thermolysis in *o*-dichlorobenzene, the epimeric xanthate **13**, obtained from **12**, afforded cyclohexene **14** in satisfactory yield presumably through conformer **13a** (Figure 1). Intermediate **14** was then treated

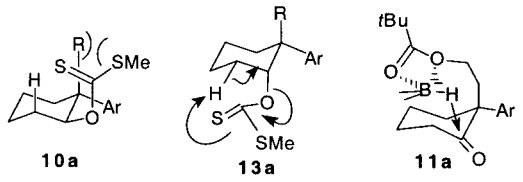
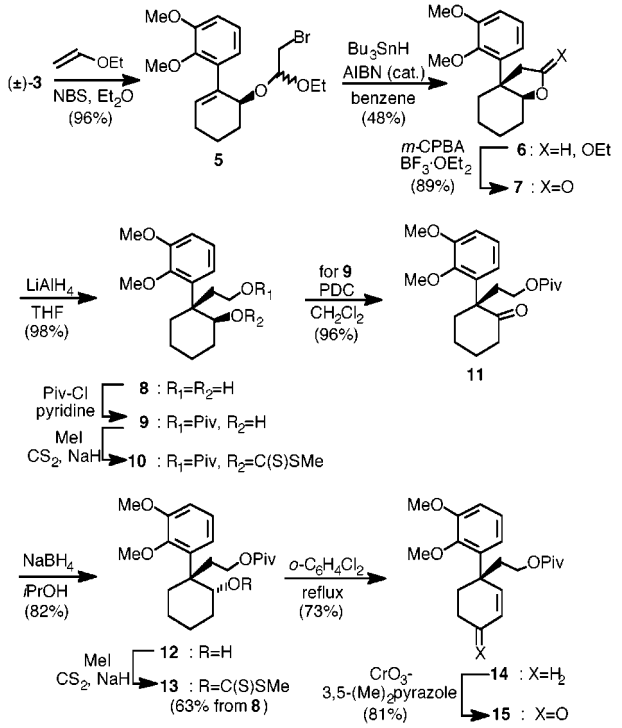


Figure 1.

with chromium trioxide and 3,5-dimethylpyrazole complex[12] in dichlomethane to give rise to cyclohexenone **15** by allylic oxidation (Scheme 3).

Scheme 3



To construct the C9−C10 bridge, an allyl functionality was introduced at the C14 center of **15** under Sakurai conditions[13] which proceeded in a highly diastereoselective manner. Thus, treatment of **15** with allyltrimethylsilane in the presence of titanium(IV) chloride gave a readily separable mixture of two products in yields of 71 and 5% (Scheme 4). Although the stereochemistry of the products could not be determined at this stage, the major product was determined at a later stage as the stereoisomer **16** containing the 14-βH configuration. The diastereoselective reaction observed at this pivotal point which determined the direction of the natural 14-βH and the unnatural 14-αH stereochemistry was noteworthy. This may be elucidated by assuming the structure

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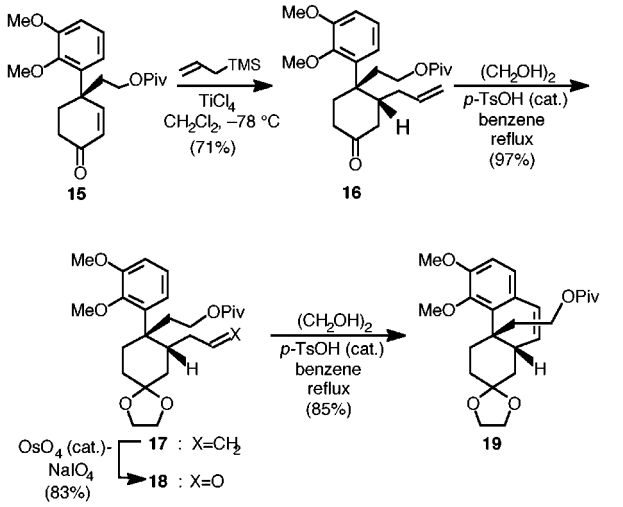
Scheme 4



in transition state **15a** in which the allyl functionality was introduced from the stereoelectronically more favorable face which is the side of the aryl group residing in a *quasi*-equatorial conformation (Figure 2). Following introduction

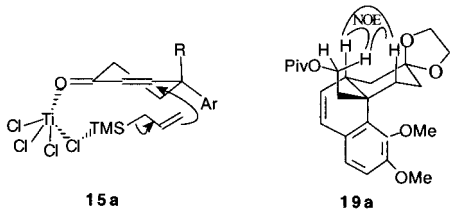
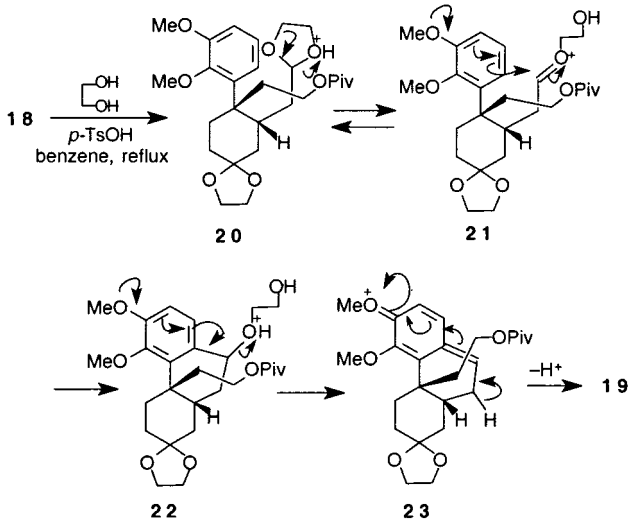


Figure 2.

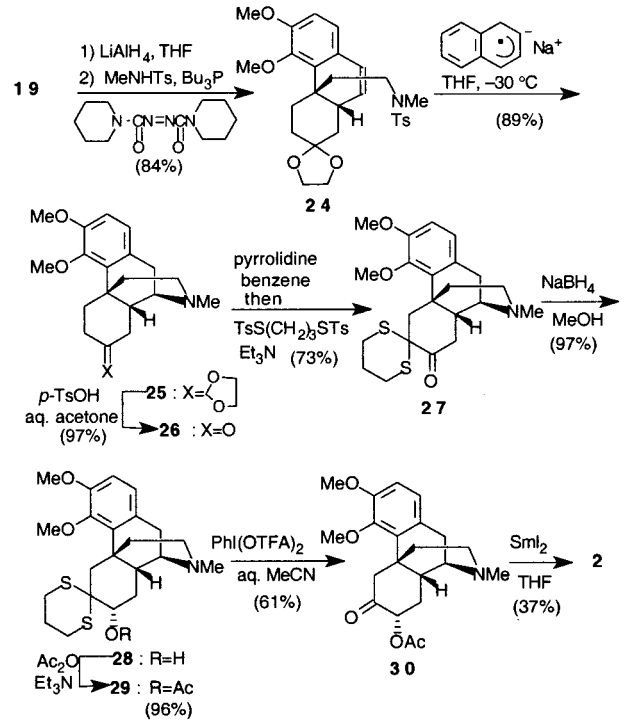
of the C14-functionality, ketone **16** was transformed into ketal **17**, whose olefin functionality was oxidatively cleaved to give aldehyde **18**. On reflux in benzene containing ethylene glycol in the presence of a catalytic amount of *p*-toluenesulfonic acid, this furnished hydrophenanthrene **19** in excellent yield. The stereochemistry of the product was confirmed at this stage by a NOESY experiment (Figure 2, **19a**). Since it was reported[14] that a similar aldehyde did not cyclize under acid-catalyzed conditions, the present cyclization in the presence of ethylene glycol may be particularly interesting. We believe that **18** generates first the acetal **20** which is in equilibrium with the reactive oxonium intermediate **21** to initiate cyclization, giving rise to **19** via **22** and **23** (Scheme 5).

Scheme 5



Construction of the ring D piperidine was best carried out under Parker conditions.[15] Thus, the primary alcohol, generated from **19** by reductive removal of the pivaloyl functionality, was coupled with *N*-methyl-*p*-toulenesulfonylamide under modified Mitsunobu conditions[16] to give the tertiary sulfonamide **24**. Upon treatment with sodium naphthalenide

Scheme 6



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generated in situ in THF, **24** furnished morphinan **25** cleanly in 89% yield by concurrent de-*N*-sulfonylation and regioselective cyclization.[15] Acid-catalyzed hydrolysis of **25** afforded the as yet unknown 3,4-dimethoxyphenyl-7-morphinanone **26** which was correlated to 3,4-dimethoxy-6-morphinanone **2**, which is the *O*-methylated Gates ketone[17] as well as the degradation product of thebaine.[18] Thus, ketone **26** was first converted into α-diketone monothioketal **27** through pyrrolidine enamine **26** upon reaction with trimethylene dithiotosylate[19] in the presence of triethylamine.[20] Reduction of **27** with sodium borohydride occurred diastereoselectively to give the single alcohol **28** which was transformed into the acetate **29**. The dithiane functionality of **29** was then hydrolyzed under oxidative conditions[21] to give the α-acetoxyketone **30**. Reductive elimination of the α-acetoxy functionality was found to be unexpectedly difficult,[22] and it was accomplished to give **2** in 37% yield when **30** was treated with samarium(II) iodide[23] in THF containing methanol (Scheme 6).

In summary, although the present approach does not constitute a formal synthesis of morphine **1** and, moreover, necessitates improvement in the construction of the quaternary C13-stereogenic center, it may be potentially useful for an enantio- and diastereocontrolled synthesis of morphine **1** as no other serious obstacles seem to exist. We are presently pursuing a new enantiocontrolled construction of morphine **1** via 3,4-dimethoxyphenyl-7-morphinanone **26** using the enantiopure starting material **3**.

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