

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

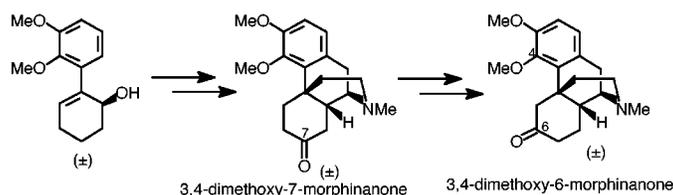
Osamu Yamada and Kunio Ogasawara*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan

konol@mail.cc.tohoku.ac.jp

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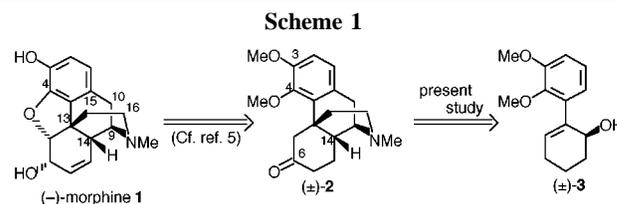
ABSTRACT



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-aryl cyclohexenols.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-dimethoxyphenylcyclohexen-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).



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 acetate⁶ (+)-**4**, $[\alpha]_{\text{D}}^{25} +145.5$ (*c* 1.0, CHCl₃), in 47% yield, leaving the enantio-enriched alcohol (–)-**3**, $[\alpha]_{\text{D}}^{31} -60.2$ (*c* 0.9, CHCl₃), (97% ee),⁶ in 48% recovery yield. On alkaline methanolysis, (+)-**4** afforded (+)-**3**, $[\alpha]_{\text{D}}^{26} +60.6$ (*c* 1.0, CHCl₃). The absolute

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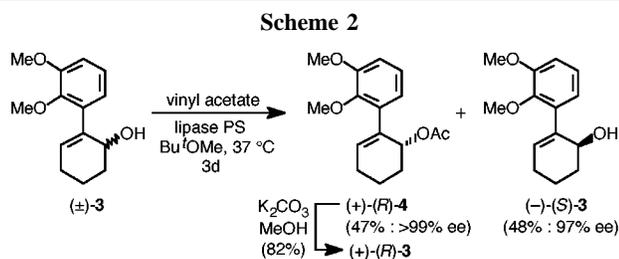
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(6) Enantiomeric excess was determined by HPLC using a column with a chiral stationary phase (CHIRALCEL OD, elution with ³PrOH–hexane 3:97 v/v).

configuration of the resolution products was determined by comparison with an authentic material, prepared from the chiral 2-iodo-2-cyclohexen-1-ol⁷ and 3,4-dimethoxyphenylboric acid by Suzuki coupling conditions.⁸ This comparison revealed (+)-**3** to be *R* and (–)-**3** to be *S* (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

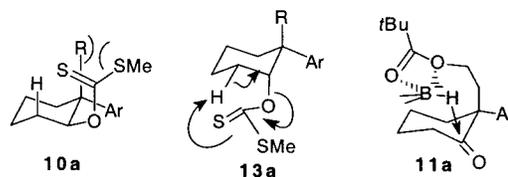
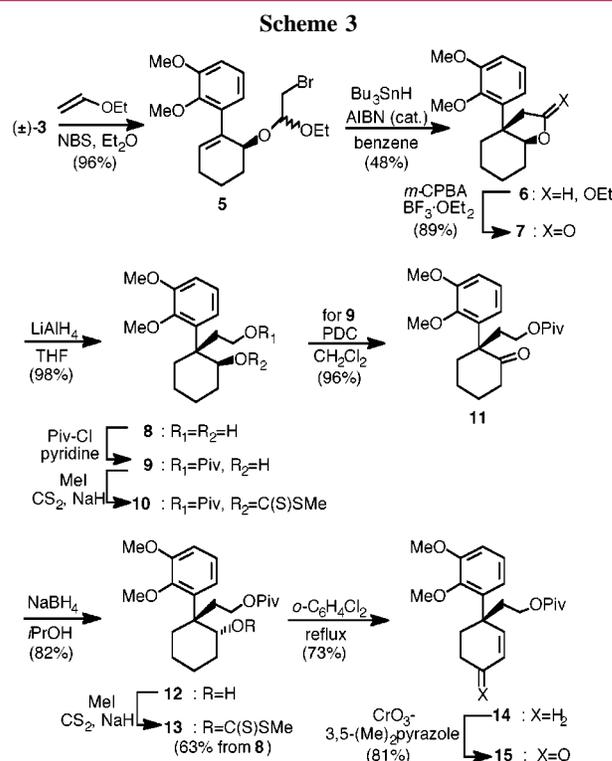


Figure 1.

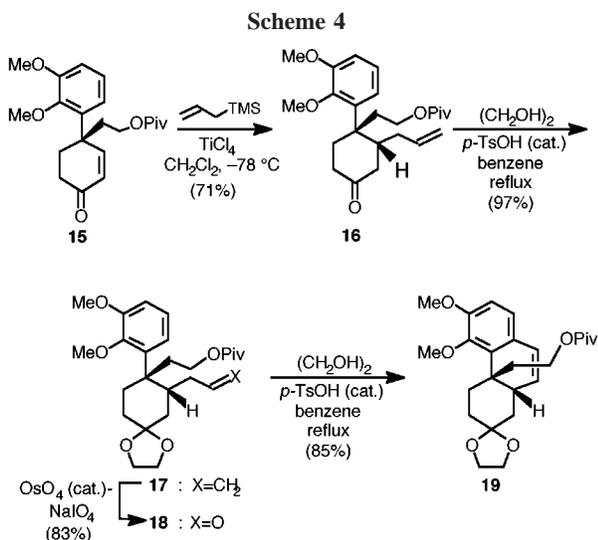
with chromium trioxide and 3,5-dimethylpyrazole complex¹² in dichloromethane to give rise to cyclohexenone **15** by allylic oxidation (Scheme 3).



To construct the C9–C10 bridge, an allyl functionality was introduced at the C14 center of **15** under Sakurai conditions¹³ 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- β H configuration. The diastereoselective reaction observed at this pivotal point which determined the direction of the natural 14- β H and the unnatural 14- α H stereochemistry was noteworthy. This may be elucidated by assuming the structure

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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

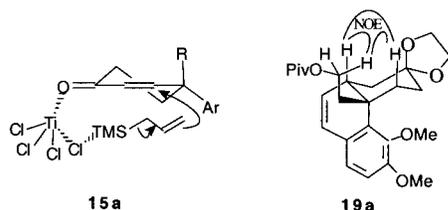
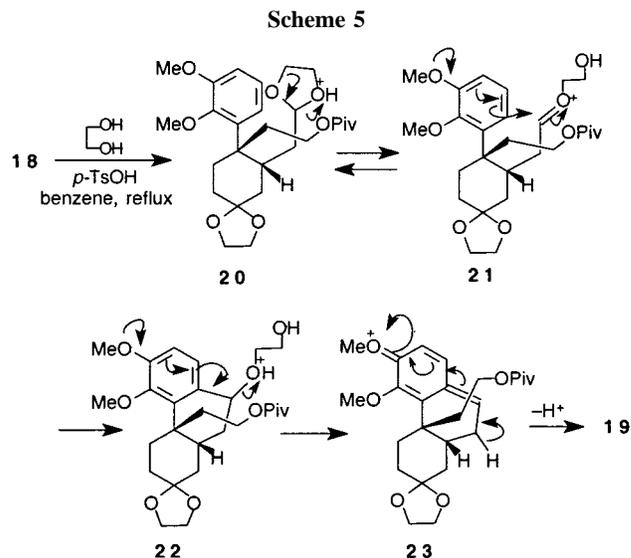


Figure 2.

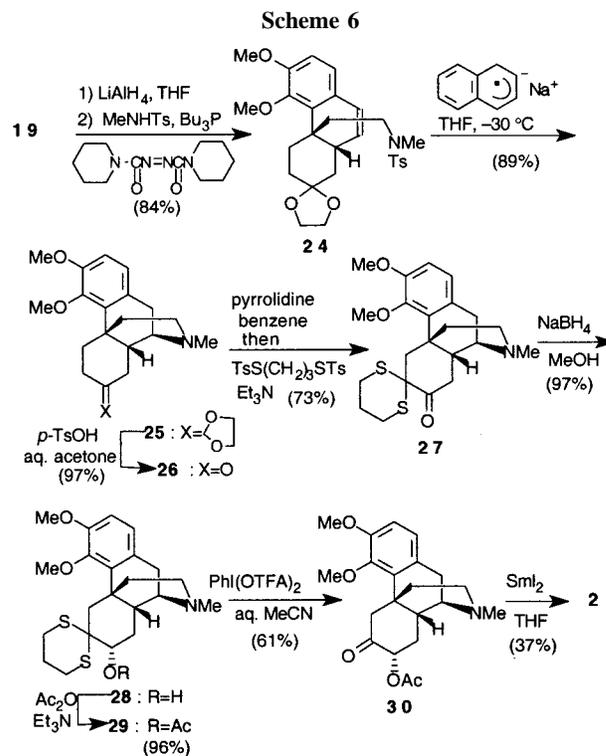
of the C14-functionality, ketone **16** was transformed into ketal **17**, whose olefin functionality was oxidatively cleaved to give aldehyde **18**. On reflux in benzene containing ethylene glycol in the presence of a catalytic amount of *p*-toluenesulfonic acid, this furnished hydrophenanthrene **19** in excellent yield. The stereochemistry of the product was confirmed at this stage by a NOESY experiment (Figure 2, **19a**). Since it was reported¹⁴ that a similar aldehyde did not cyclize under acid-catalyzed conditions, the present cyclization in the presence of ethylene glycol may be particularly

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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).



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*-toluenesulfonylamide under modified Mitsunobu conditions¹⁶ to give the tertiary sulfonamide **24**. Upon treatment with sodium naphthalenide



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 ketone¹⁷ as well as the degradation product of thebaine.¹⁸ Thus, ketone **26** was first converted into α -diketone monothioacetal **27** through pyrrolidine enamine **26** upon reaction with trimethylene dithiotosylate¹⁹ 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 conditions²¹ 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) iodide²³ 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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