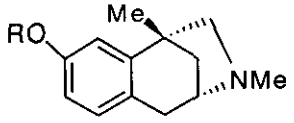
ASYMMETRIC SYNTHESES OF *O*-METHYLAPHANORPHINE†

Albert I. Meyers,* Wolfgang Schmidt,[1] and Braulio Santiago[2]

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, U.S.A.

Abstract-*Two routes leading to the preparation of racemic, (+), and (-) O-methylaphanorphine via the asymmetric alkylation of 2-oxazolines are described.*

Aphanorphine (**1**), isolated from the fresh water blue-green alga *Aphanizomenon Flos-Alquae*,[3] exhibits an interesting structural framework closely related to the natural narcotic morphine. The absolute configuration of **1** was determined through its recent synthesis by Takano.[4] We felt that the chiral quaternary center in **1** could be readily reached via alkylation of chiral oxazolines.[5] Herein we wish to describe two routes to reach racemic, **(+)** and **(-)-1a**.



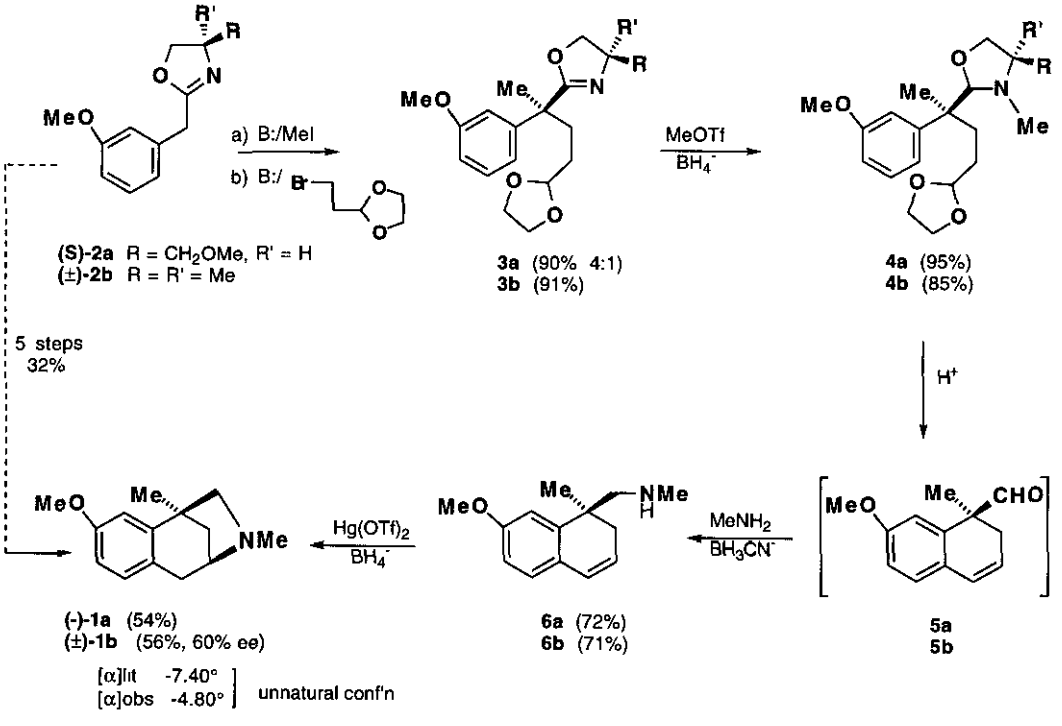
1, R = H
1a, R = Me

(S)-2a and **(±)-2b** were prepared from the commercially available 3-methoxyphenylacetic acid (Aldrich) and (S)-serine methyl ether[6] or 2-amino-2-methyl-1-propanol utilizing previously reported conditions.[7a] Metalation-alkylation of these species occurred smoothly using n-butyllithium or LDA at -78°C in THF followed by alkylation with iodomethane. The second

† Dedicated to Professor Rolf Huisgen on the occasion of his 75th birthday.

deprotonation was performed in analogous fashion, followed by alkylation with 2-(2-bromoethyl)-1,3-dioxolane. The reaction afforded achiral **3b** in 91% yield and chiral **3a** in 90% yield as a 4:1 mixture of diastereoisomers. Reversing the alkylation sequence gave epimeric **3a** with lower degree of diastereoselection (1:2). Various attempts to separate the mixture in **3a** proved to be difficult and thus it was taken forward as such. The alkylated oxazolines (**3a**) and (**3b**) were converted[7a] to the *N*-methyloxazolidines (**4a**) (95%) and (**4b**) (85%) by treatment of the oxazoline with 4 equiv of methyl trifloromethanesulfonate followed by reduction with sodium borohydride which also resisted separation into pure diastereomers. Hydrolysis of **4a** and **4b** with 2 M HCl in THF at room temperature resulted in the concurrent removal of the dioxolane and the oxazolidine to the corresponding dialdehyde and simultaneous cyclization to the aromatic ring to furnish the relatively sensitive tetralin systems (**5a**, **5b**). The latter were found to deformylate rather rapidly, thus they were converted, without purification, to the *N*-methylamines (**6a**) and (**6b**) in 72% and 71% respectively. This was accomplished via reductive amination with 15 equiv of methylamine

Scheme I

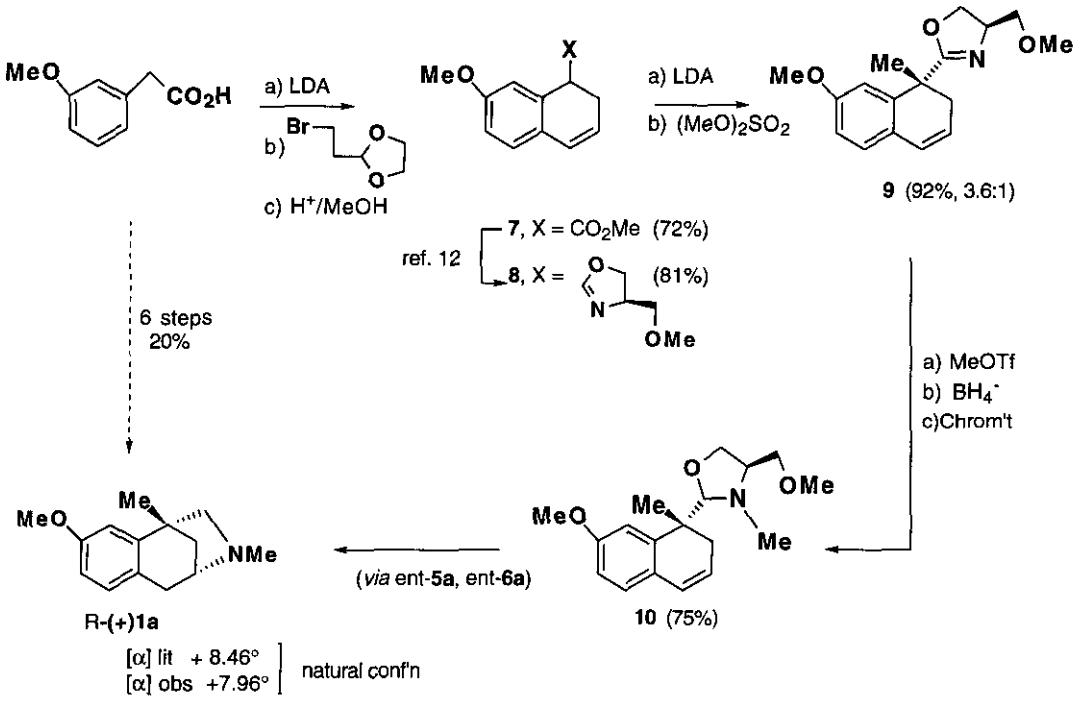


hydrochloride followed by reduction with sodium cyanoborohydride.[8] Cyclization to **1** was performed utilizing the amino-mercuration sequence with mercuric triflate followed by reduction with sodium borohydride.[9] This led to **(±)-1a** in 54% yield and **(-)-1a** in 56% yield[10] and 60% ee.[11]

Due to the less than satisfactory enantiomeric excess for **1a**, we decided to investigate the alkylation of the cyclic oxazoline (**8**). It was felt that the cyclic, more rigid system in **8** would create the desired chiral quaternary center with higher diastereoselectivity. The second approach undertaken is shown in Scheme II.

Alkylation of 3-methoxyphenylacetic acid (2 equiv LDA/2-(2-bromoethyl)-1,3-dioxolane) followed by hydrolysis with 10 mol% *p*-TsOH in MeOH afforded **7** in 72% yield. This racemate was converted to the chiral oxazoline (**8**) in 81% yield *via* the hydroxyamide.[12] Deprotonation of the diastereomeric mixture(**8**) with LDA followed by alkylation with dimethyl sulfate[13] gave **9** in 92% yield as a 3.6 : 1 mixture of diastereoisomers. Neither **8** or **9** were separable, but when **9** was reduced to the *N*-methyloxazolidine *via* its treatment with methyl triflate/sodium borohydride,[7a] we were able to isolate **10** in 75% yield as the sole diastereoisomer. Earlier attempts to hydrolyze the acyclic systems (**3a**) or (**4a**) to reach ent-**9** or ent-**10** were unsuccessful, giving either starting materials or complete decomposition. Hydrolysis of **10** in HCl/THF at room temperature afforded ent-**5a** which was quickly converted to ent-**6a** *via* the above mentioned reductive amination sequence in 70% yield. Amino-mercuration or reaction with I_2[14] followed by reduction with $LiAlH_4$[15] gave **(-)-1a** in 61% or 72% yields respectively. The enantiomeric purity of **1a** *via* this route was essentially complete (>99% ee), as determined by chiral hplc analysis.[11] It is also of interest that the natural (+)-enantiomer was obtained *via* Scheme II while the unnatural (-)-enantiomer (60% ee) was reached *via* Scheme I. That the enantiomer containing the natural absolute configuration was reached *via* Scheme II is consistent with the mechanism proposed earlier for facial alkylation. Thus, the electrophile enters the chiral azaenolate *syn* to the chelated lithium-methoxyl moiety. At present, we have no knowledge of the ratio of the two possible azaenolates derived from **8** thus no conclusions can be drawn regarding the observed ratio of products except that the major diastereomer(**9**) is the expected one.[16]

Scheme II



In conclusion, we have demonstrated that the alkylation of chiral oxazolines is a viable method for the preparation of chiral non-racemic quaternary centers in a simple and direct way. This led to two approaches which furnished **(+)** and **(-)1a** in an enantioselective fashion which is in agreement with the absolute configuration previously proposed.[17]

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10. The configuration of **1a**, based upon **3a**, is in complete agreement with that previously reported; A. I. Meyers, E. S. Snyder, and J. J. A. Ackerman, *J. Am. Chem. Soc.*, **1978**, *100*, 8186; also, see ref. 16 below.

11. Determined by chiral hplc; Diacel, Chiralcel OD column, eluted with hexane-isoPrOH, 97:3.

12. Formation of the hydroxyl amide: J. H. Dodd, J. Guan, and C. F. Schwender, *Syn. Comm.*, **1993**, *23*, 1003. For previous reports on the cyclization to the oxazoline, see ref. 6 and 7b above.

13. Alkylation with MeI gave a 2:1 mixture of diastereoisomers.

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16. For a discussion of the mechanistic aspects of oxazoline alkylations, see K. Lutomski and A. I. Meyers, "Chiral Oxazolines" In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, 1982; Vol. 3. Actually, the observed 3.6:1 ratio in **9** is quite close to *statistical deprotonation*. Thus, *one diastereomer* gives only a single azaenolate, the other gives ~1:1 of each.

17. The absolute configuration of natural aphanorphine has been assigned 1R, 4R by Takano (4a above) based on a synthesis starting from (R)-*O*-benzylglycidol. The present synthesis concurs with this conclusion.

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