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THE TOTAL SYNTHESIS OF (-)-MESEMBRANONE

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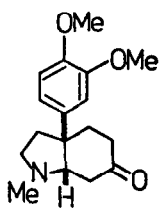
Summary: Elaboration of the novel chiral amide acetal (S)-4, constitutes the first total synthesis of natural (-)-mesembranone.

The total synthesis of mesembrane alkaloids e.g. mesembranone [(±)-1], has received considerable attention in recent years[1]. Several synthetic routes to these alkaloids exist, the most notable involving the annulation of 3-aryl-2-pyrrolines with vinyl ketones[2] or the application of the amide acetal Claisen rearrangement[3] as the key steps. Further elaboration of the latter approach forms the subject matter of this communication.

Applications of the amide acetal Claisen rearrangement have hitherto been limited to acetals of (N,N-dimethyl) tertiary amides resulting in the synthesis of (N,N-dimethyl) tertiary amides only. The N-benzyl amide acetal 2 reacts smoothly with allylic alcohols to produce the corresponding N-benzyl amides (e.g. amide 3 was obtained from allyl alcohol) in high yield[4]. The secondary amides were obtained after debenzylation with lithium in liq. NH_3. Extending this principle, we utilized the new chiral acetal 4 in a facile synthesis of (-)-mesembranone (1). This constitutes the first total synthesis of the natural antipode[5].

Accordingly, (±)-allylic alcohol 5[3(b)] was heated in toluene with 1.5 eq. of amide acetal 4[6] to yield a 1 : 1 diastereoisomeric mixture of thioacetal amides 6 (87 - 92% after silica gel chromatography). The mixture of 6a and 6b could be separated by fractional crystallization : isomer 6a is crystalline whereas 6b (a solid foam) was obtained homogeneous after chromatography of the mother liquor. The stereochemistry of 6a and 6b was only assigned after 6b was transformed to the title compound (vide infra). Dethioacetalization of 6b was accomplished in 72% yield with 1 mole eq. each of $HgCl_2$ and HgO in refluxing aq. methanol. The resulting enone was reduced with $NaBH_4$ in abs. ethanol to afford alcohol 7 (96%). The lithium alcoholate of 7 (n-BuLi/THF) was N-dephenylethylated with 2.6 eq. sodium in liq. NH_3-THF (solid NH_4Cl quench). The crude epimeric secondary amide alcohols 8 (R = H) thus obtained were protected as their THP ethers in 70% yield from 7 after chromatography. Reduction of amide 8 (R = THP) with LAH in THF followed by deprotection with aq. HCl, yielded a mixture of epimeric alcohols 9, which were oxidized with activated MnO_2 in benzene to afford (-)-mesembranone[8] (1), α_D^{17} - 54.0° (MeOH)[9], in 39% overall yield from 8 (R = THP).



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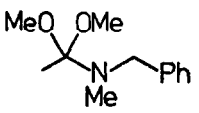

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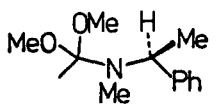

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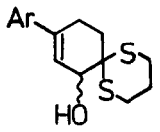

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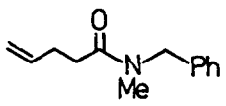

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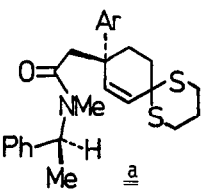
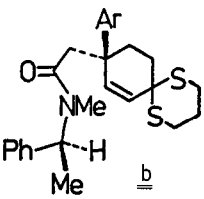


a



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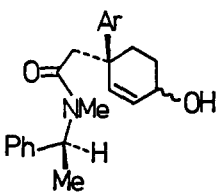

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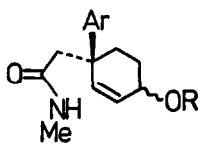

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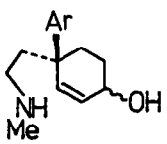

9

Ph = phenyl
Ar = 3,4-dimethoxyphenyl

References and notes.

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4. H.F. Strauss, G.H. van der Klashorst, and A. Wiechers, unpublished results.
5. Yamada et al. reported the synthesis of (+)-mesembranone (optical purity 27%) : G. Otani and S. Yamada, Chem. Pharm. Bull., 1973, 21, 2130.
6. Synthesized from (S)-N-methyl-N-phenylethyl acetamide by modification of the Bredereck procedure[7].
7. H. Bredereck, F. Effenberger, and H.P. Beyerlin, Chem. Ber., 1964, 97, 3081.
8. Spetral (ir, pmr and ms) data and chromatographic properties of synthetic (-)-mesembranone were identical with those of an anthentic specimen.
9. Natural (-)-mesembranone has α_D^{20} - 59° (MeOH)[10]. The optical purity (91.5%) of the synthetic product correlates well with that observed for N-phenylethyl acetamide (the starting material for the synthesis of amide acetal 4[6]) which had α_D - 152,5° (literature value[11] - 168,1°).
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