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An Asymmetric Synthesis of Benzylic Quaternary Carbon Centers. A Formal Total Synthesis of (-)-Mesembrine

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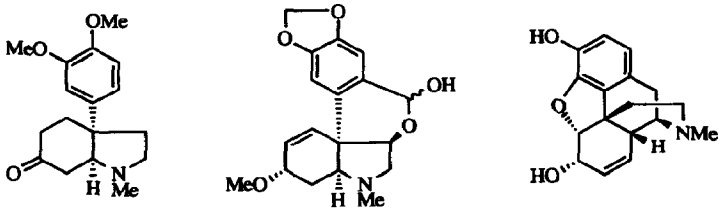
Abstract: The optically pure sulfone **15**, prepared by the tandem asymmetric epoxidation and 1,2-rearrangement of the cyclopropylideneethanol **11** as a key step, was converted into the olefinic cyclobutanone **20** which was then transformed into the ketonic lactone **22** *via* the olefinic lactone **21**. This constitutes the formal total synthesis of (-)-mesembrine (**1**).

Enantiocontrolled creation of quaternary carbon center is one of the most important problems for the enantioselective synthesis of biologically important natural products such as terpenoids, steroids, and alkaloids. A number of methods have been reported recently[1] for the highly enantioselective construction of quaternary carbon centers in various molecular frames, of which the isoquinoline alkaloids possessing benzylic quaternary carbon centers such as mesembrine (**1**),[2] pretazettine (**2**),[3] and morphine (**3**)[4] have remained attractive target molecules for total synthesis (Figure 1).

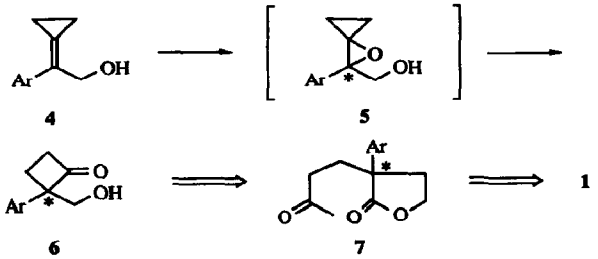
Figure 1



1 **2** **3**

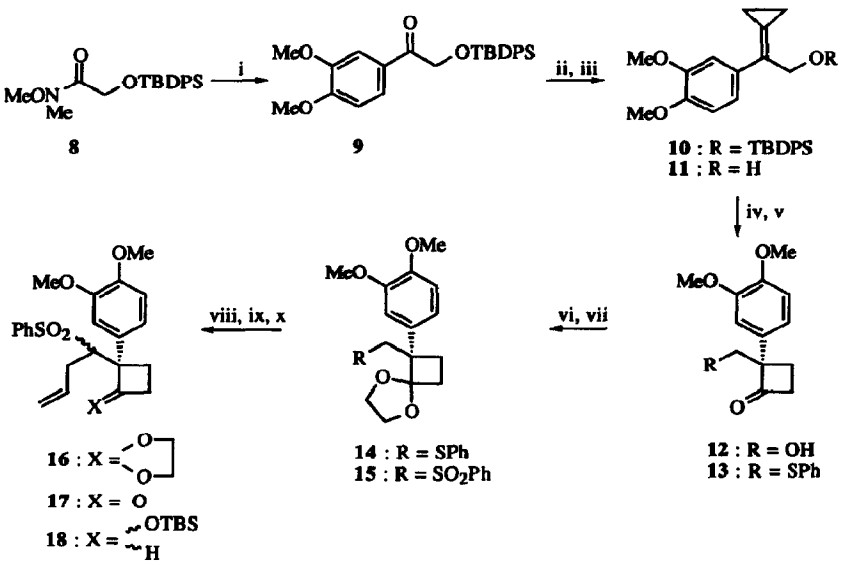
During our study directed toward the enantioselective construction of cyclobutanones and its application to the synthesis of biologically desirable compounds, we developed a new enantiocontrolled approach to (-)-mesembrine (**1**). This synthesis consists of the enantiocontrolled creation of geminally substituted cyclobutanones **6** *via* the tandem Katsuki-Sharpless asymmetric epoxidation of 2-aryl-2-cyclopropylideneethanols **4** and the enantiospecific ring expansion of chiral bicyclooxapentanes **5** followed by the conversion of **6** into the lactone **7** (Scheme 1).

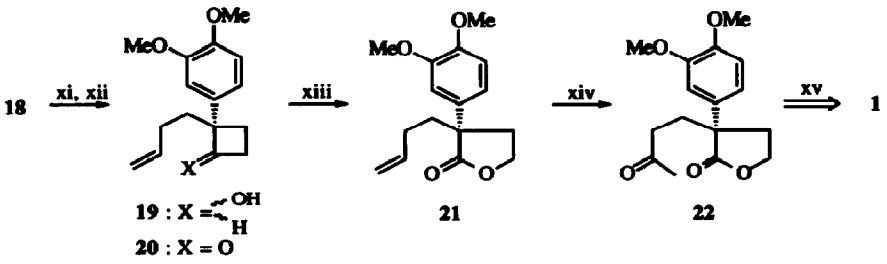
Scheme 1



Thus, the ketone **9**, prepared by Grignard reaction (100%) of the hydroxamate **8**[5k] with 3,4-dimethoxyphenylmagnesium bromide, was converted into the cyclopropylidene ether **10** in 85% yield by Wittig reaction with cyclopropylidenetriphenylphosphorane and then into the alcohol **11** by desilylation of **10** with Bu^n_4NF in 97% yield. The tandem asymmetric epoxidation and 1,2-rearrangement of the cyclopropylidene alcohol **11** was carried out with *tert*-butyl hydroperoxide in the presence of diisopropyl L-(+)-tartrate [(+)-DIPT], titanium tetraisopropoxide [$Ti(OPr^i)_4$], and 4Å molecular sieves to give the cyclobutanone **12** (82%).[6] The sulfide **13**, prepared by following Hata's procedure[7] (93%), was then converted into the ketal **14** (100%) and then into the sulfone **15** by the oxidation [*m*-chloroperbenzoic acid (MCPBA)] (88%) of **14**. The sulfone **15** thus obtained was found to be easily crystallized from ethanol to give the optically pure sample.[8] Then, the optically pure sulfone **15** {$[\alpha]^{23}_D$ +24.4 ° ($CHCl_3$)} was alkylated with allyl bromide to give the olefin **16** as diastereoisomeric mixture which was deprotected to afford the ketone **17** (98%). Reduction ($NaBH_4$) of **17** followed by silylation [*tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), Et_3N] of the resulted alcohol gave the silyl ether **18** (100% overall yield from **17**). Reductive elimination (Na-Hg, Na_2HPO_4) followed by deprotection (Bu^n_4NF) of the silyl ether **18** afforded the alcohol **19** (94% overall yield from **18**) which was then oxidized under Swern conditions to give the ketone **20** {$[\alpha]^{23}_D$ -14.5 ° ($CHCl_3$)} (82%). Successive treatment of **20** with triethylsilyl trifluoromethanesulfonate (TESOTf) in the presence of 2,6-lutidine, ozone followed by $NaBH_4$, and 10% HCl gave the olefinic lactone **21** {$[\alpha]^{23}_D$ -67.3 ° ($CHCl_3$)} (30% overall yield from **20**) which was then subjected to Wacker oxidation to furnish the ketone **22** (100%) {$[\alpha]^{23}_D$ -43.6 ° (MeOH); lit.[2a] $[\alpha]^{23}_D$ -42.6 ° (MeOH)}. Since this ketone **22** thus synthesized was already transformed into (-)-mesembrine (**1**)[2a] in three steps, this work constitutes a formal total synthesis of (-)-mesembrine (**1**).

Scheme 2





Reagents and Conditions; i 3,4-dimethoxyphenylmagnesium bromide, THF, 0 °C, 1.5 h; ii cyclopropyltriphenylphosphonium bromide, NaH, THF, 65 °C, 3 h; iii Bu^n_4NF, THF, room temp., 3 h; iv L-(+)-DIPT, Bu^tOOH, $Ti(OPr^i)_4$, 4Å molecular sieves, CH_2Cl_2, -40 °C, 48 h; v PhSSPh, Bu^n_3P, THF, 65 °C, 1 h; vi $HOCH_2CH_2OH$, *p*-TsOH, benzene, reflux, 4.5 h; vii MCPBA, $NaHCO_3$, CH_2Cl_2-H_2O, room temp., 1.5 h; viii Bu^nLi, allyl bromide, THF, room temp., 5.5 h; ix *p*-TsOH, acetone-H_2O, 62 °C, 72 h; x $NaBH_4$, MeOH, room temp., 1 h then TBSOTf, Et_3N, CH_2Cl_2, room temp., 5 min.; xi Na-Hg, Na_2HPO_4, MeOH, room temp., 12 h then iii; xii DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 1 h then Et_3N, 0 °C, 15 min.; xiii TESOTf, 2,6-lutidine, CH_2Cl_2, room temp., 10 min.; O_3, CH_2Cl_2, -78 °C, 5 h then $NaBH_4$; 10% HCl, room temp., 10 min.; xiv O_2, $PdCl_2$, CuCl, DMF-H_2O, room temp., 48 h; xv ref. 2a.

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6. The enantiomeric excess (e.e.) of **12** was estimated to be 63% by ^{1}H NMR analysis (500 MHz) of the corresponding α–methoxy-α-(trifluoromethyl)phenylacetate (MTPA).
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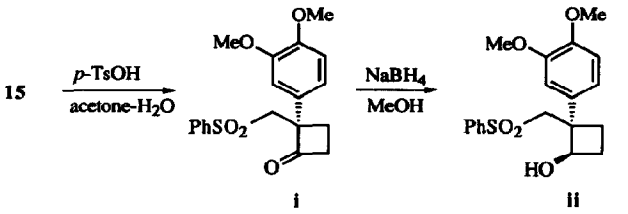
8. The optical purity of **15** was determined by ^{1}H NMR analysis (500 MHz) of MTPA ester of the alcohol **ii** which was prepared by the deprotection of **15** followed by reduction ($NaBH_4$) of the resulted ketone **i**.



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