

A NOVEL APPROACH TO QUATERNARY SUBSTITUTED CHIRAL CYCLOBUTANES.

A FORMAL ENANTIOSELECTIVE TOTAL SYNTHESIS OF 1,3-DIOXOLE PHEROMONE,
(-)-FRONTALIN

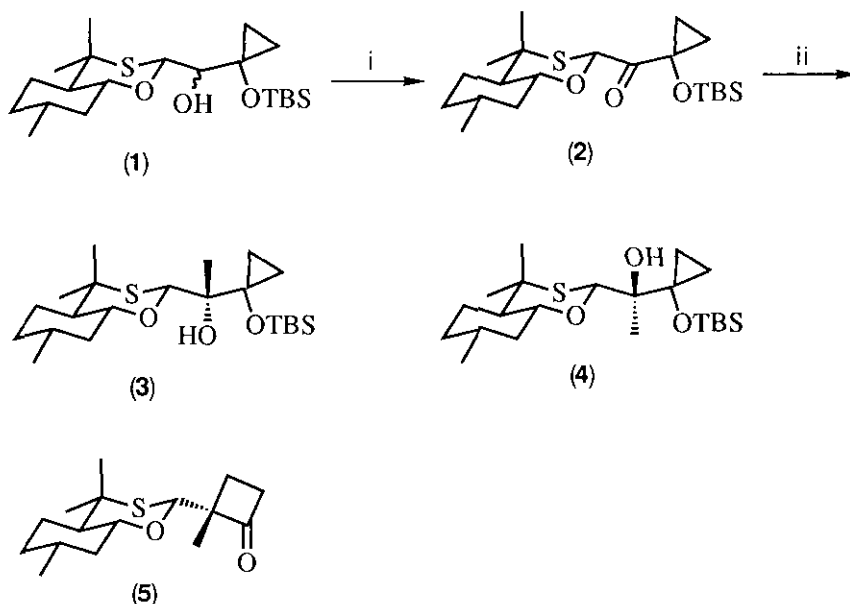
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Abstract--A novel synthesis of the quaternary substituted chiral cyclobutanone (9) was achieved by the concerted ring expansion of the chiral cyclopropyl epoxide (8) which lead to a formal total synthesis of (-)-frontalin (14).

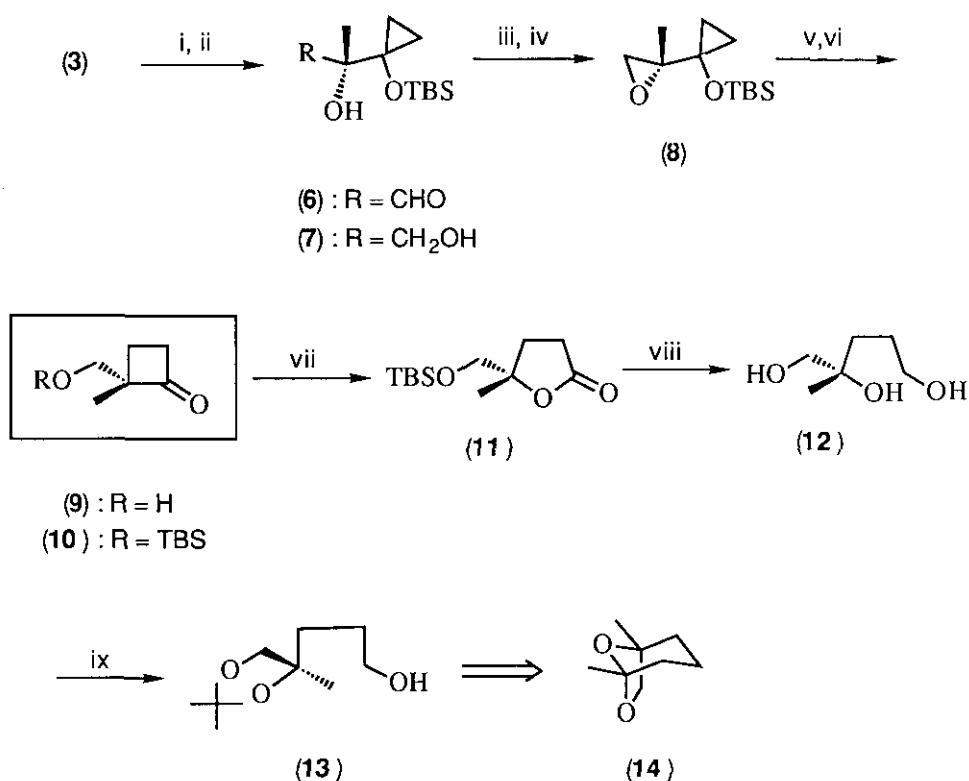
Recently there have been growing interests in the chemistry¹ of cyclobutanes and the flexibility² of this type of compound for the synthesis of a wide variety of derivatives stimulated us to develop an efficient methodology for the synthesis of chiral cyclobutanes.³ Herein, we wish to report a novel strategy for the synthesis of quaternary substituted chiral cyclobutanones and 1,3-dioxole framework.⁴

Our first goal in this context was a highly diastereoselective Grignard reaction [MeMgI, Et₂O, -78 °C, 30 min] with the ketone (2) ($[\alpha]_D^{26}$ -47.97°), which was derived quantitatively by the Swern oxidation [DMSO, (COCl)₂, CH₂Cl₂, -78 °C, 30 min; Et₃N, -78 °C, room temperature] of the isomeric mixture of the alcohol (1),³ to give the alcohol (3) (mp 96~97 °C; $[\alpha]_D^{22}$ -29.24°) (91%) with no detectable amount of the isomeric alcohol (4), suggesting the important chelation control of Grignard reagent. Next, the direct enantiospecific transformation of the tertiary alcohol (3) into the cyclobutanone (5) was examined and was found not to proceed in this case unlike the secondary alcohols.³



Scheme 1. Reagents and conditions, i) DMSO, $(\text{COCl})_2$, CH_2Cl_2 , -78°C , 30 min; Et_3N , $-78^\circ\text{C} \rightarrow$ room temperature; ii) MeMgI , Et_2O , -78°C , 30 min

The oxathiane (3) was subjected to the oxidative solvolysis [N -chlorosuccinimide (NCS), AgNO_3] to give the aldehyde (6) which was directly reduced (NaBH_4) to yield the diol (7) ($[\alpha]_{\text{D}}^{23} -12.81^\circ$) [92% overall from (3)]. Selective mesylation [mesyl chloride (MsCl), Et_3N] of the diol (7) followed by base treatment (NaH) afforded the epoxide (8) which on treatment with silica gel furnished the cyclobutanone alcohol (9) ($[\alpha]_{\text{D}}^{22} -18.50^\circ$) [99% overall from (7)] in high enantiomeric excess (93% e.e.).⁵ The absolute configuration of (9) was determined by the transformation into the triol acetonide (13). Thus, protection [t -butyldimethylsilyl chloride (TBSCl)] of the alcohol (9) afforded the silyl ether (10) ($[\alpha]_{\text{D}}^{22} -34.60^\circ$) (74%), which was then subjected to Baeyer-Villiger oxidation (t -BuOOH, 10% NaOH) to give the lactone (11) ($[\alpha]_{\text{D}}^{21} -1.34^\circ$) (85%). Reduction (LiAlH_4) of (11) followed by acetonization (2,2-dimethoxypropane, p -TsOH) of the triol (12) furnished the triol acetonide (13) ($[\alpha]_{\text{D}}^{21} -0.80^\circ$; lit.,⁶ $[\alpha]_{\text{D}}^{23} -0.5^\circ$) [67% overall from (11)].



Scheme 2. Reagents and conditions: i, NCS, AgNO₃, MeCN, 0 °C, 10 min; ii, NaBH₄, MeOH, room temperature, 10 min; iii, MsCl, Et₃N, CH₂Cl₂, 0 °C, 20 min; iv, NaH, THF, 0 °C, 10 min; v, silica gel, 6 h; vi, TBSCl, Et₃N, DMAP, CH₂Cl₂, room temperature, 10 h; vii, mCPBA, sat. aq. NaHCO₃, CH₂Cl₂, 0 °C, 2 h; viii, LiAlH₄, THF, 0 °C, 20 min; ix, Me₂C(OMe)₂, *p*-TsOH, CH₂Cl₂, room temperature, 10 min

Since the triol acetone (13) thus obtained has been converted⁶ into (-)-frontalin (14), this work constitutes a formal total synthesis of (-)-frontalin (14).

REFERENCES AND NOTES

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4. All new substances exhibited spectroscopic data [IR, ^1H NMR (500 MHz), and mass] in accord with the assigned structure and provided acceptable combustion or high resolution mass spectral data.
5. The enantiomeric excess of the cyclobutanone alcohol (**9**) was determined by the ^1H NMR (90 MHz) of the corresponding MTPA ester [methoxytrifluoromethylphenylacetic acid (MTPA acid), diethyl azodicarboxylate (DEAD), triphenylphosphine (Ph_3P), benzene, room temperature, 30 min].
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