A NOVEL APPROACH TO QUATERNARY SUBSTITUTED CHIRAL CYCLOBUTANES. A FORMAL ENANTIOSELECTIVE TOTAL SYNTHESIS OF 1,3-DIOXOLE PHEROMONE, (-)-FRONTALIN

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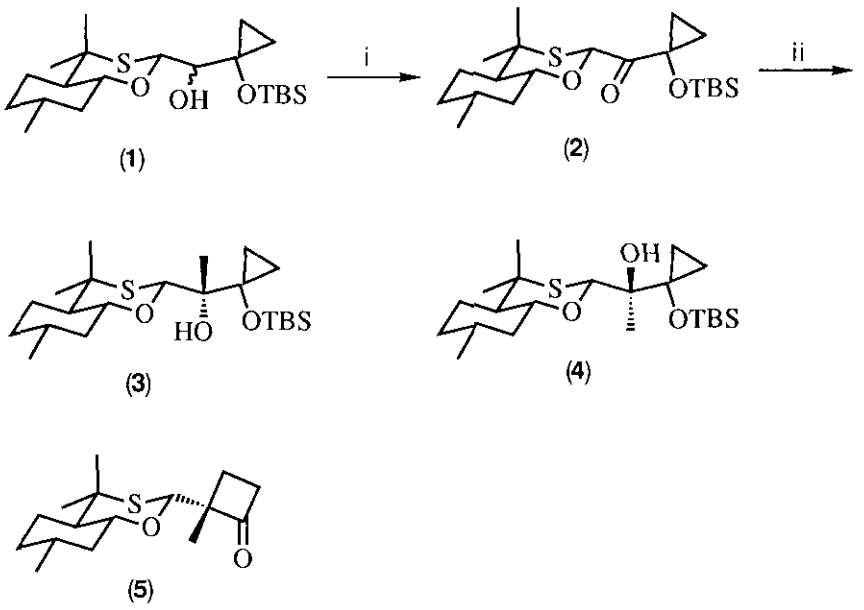
Abstract--A novel synthesis of the quaternary substituted chiral cyclobutanone (**9**) was achieved by the concerted ring expansion of the chiral cyclopropyl epoxide (**8**) which lead to a formal total synthesis of (-)-frontalin (**14**).

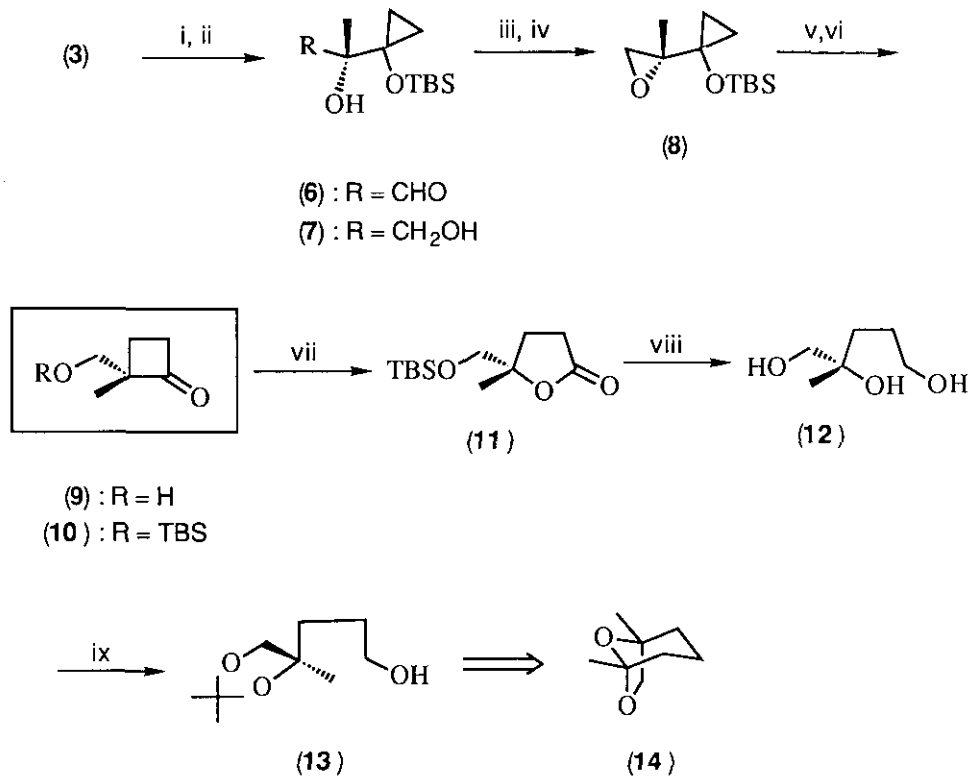
Recently there have been growing interests in the chemistry[1] of cyclobutanes and the flexibility[2] of this type of compound for the synthesis of a wide variety of derivatives stimulated us to develop an efficient methodology for the synthesis of chiral cylobutanes.[3] Herein, we wish to report a novel 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, Et_2O, -78 °C, 30 min] with the ketone (**2**) ($[\alpha]_D^{26}$ -47.97°), which was derived quantitatively by the Swern oxidation [DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 30 min; Et_3N, -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, $(COCl)_2$, CH_2Cl_2, -78 °C, 30 min; Et_3N, -78 °C ⟶ 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**) ($[\alpha]_D^{23}$ -12.81°) [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 cylobutanone alcohol (**9**) ($[\alpha]_D^{22}$ -18.50°) [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**) ($[\alpha]_D^{22}$ -34.60°) (74%), which was then subjected to Baeyer-Villiger oxidation (*t*-BuOOH, 10% NaOH) to give the lactone (**11**) ($[\alpha]_D^{21}$ -1.34°) (85%). Reduction ($LiAlH_4$) of (**11**) followed by acetonization (2,2-dimethoxypropane, *p*-TsOH) of the triol (**12**) furnished the triol acetonide (**13**) ($[\alpha]_D^{21}$ -0.80°; lit.,[6] $[\alpha]_D^{23}$ -0.5°) [67% overall from (**11**)].



Scheme 2. *Reagents and conditions*: i, NCS, $AgNO_3$, MeCN, 0 °C, 10 min; ii, $NaBH_4$, MeOH, room temperature, 10 min; iii, MsCl, Et_3N, CH_2Cl_2, 0 °C, 20 min; iv, NaH, THF, 0 °C, 10 min; v, silica gel, 6 h; vi, TBSCl, Et_3N, DMAP, CH_2Cl_2, room temperature, 10 h ; vii, mCPBA, sat. aq. $NaHCO_3$, CH_2Cl_2, 0 °C, 2 h; viii, $LiAlH_4$, THF, 0 °C, 20 min; ix, $Me_2C(OMe)_2$, *p*-TsOH, CH_2Cl_2, room temperature, 10 min

Since the triol acetonide (**13**) thus obtained has been converted[6] into (-)-frontalin (**14**), this work constitutes a formal total synthesis of (-)-frontalin (**14**).

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4. All new substances exhibited spectroscopic data [IR, ^{1}H 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 ^{1}H 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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