Asymmetric Synthesis of *gem*-Dimethylcyclopropane-fused Compounds through Chemo-, Regio-, and Stereoselective Cyclopropanation and Stereospecific Rearrangement

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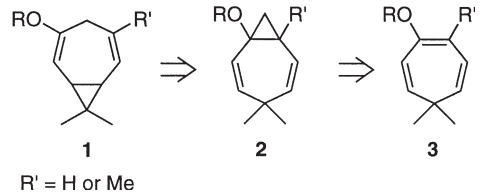
Optically active *gem*-dimethylcyclopropane-fused compound was synthesized by a tandem reaction consisting of chemo-, regio-, and stereoselective cyclopropanation of a 4-substituted 7,7-dimethylcycloheptatriene with an internal diazo ester and following stereospecific rearrangement.

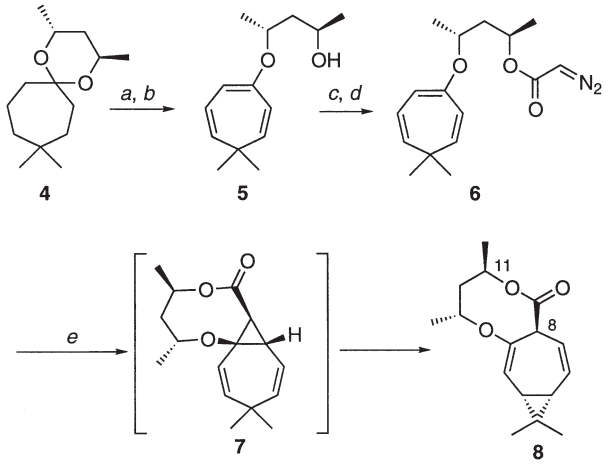
gem-Dimethylcyclopropane is one of key structures of natural terpenes.[1] We have been studying synthesis of *gem*-dimethylcyclopropane-fused compounds **1** from **2** by using tautomerization of 3,4-homotropilidene[2] (bicyclo[5.1.0]octa-2,5-diene).[3,4] The conversion through the tautomerization is practically irreversible, and thus, regioselective cyclopropanation of **3** should present a handy method for synthesis of **1**. However, the product **1** is more reactive toward the carbenoid than **3**, and **1** cannot be obtained even in a low yield. Synthesis of **1** could only be achieved by a stepwise process using dihalocyclopropanation to inhibit the tautomerization during the reaction.[3]

Another tactics to address the overreaction problem is incorporation of a carbenoid into **3** at the R group. With this reaction design, intramolecular addition of **3** becomes favorable over the intermolecular reaction with **1**. This is successfully attained when a diazo ester, a precursor of carbenoids, is tethered to **3** with (2*R*,4*R*)-2,4-pentanediol. The chiral tether also provides a chiral synthon in a high stereoselectivity.[5] The results will be summarized in this communication.



Scheme 1.

Acetal **4** (>99% pure) was converted to cycloheptatriene **5** by the reported method,[4] and the ensuing introduction of diazo acetate to **5** resulted in substrate **6** (Scheme 2). When **6** was treated with a catalytic amount of $Rh_2(OAc)_4$ in dichloromethane (0.1 M of **6**) at room temperature,[6] the desired intramolecular cycloaddition and the succeeding rearrangement proceeded smoothly to give **8** in 70% yield after silica gel column chromatography.[7] Since no isomeric product other than **8** was detected (<1%) before or after the purification, the carbenoid addition of **6** must be sufficiently stereoselective in addition to the stereospecific and practically irreversible rearrangement of **7**. Stereochemistry of **8** was determined to be 8*S* by ^{1}H NMR, where NOE enhancement was observed between the peaks of H8 and H11 (12%). Stereochemistry of the corresponding intermediate **7** shown in

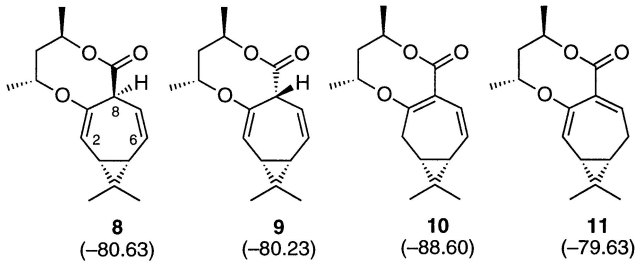


Scheme 2. Reagents and conditions. *a*: pyridinium perbromide, *b*: potassium *tert*-butoxide (6 equiv.)/KI/DMSO (59.0% for two steps), *c*: diketene/triethylamine (85.4%), *d*: tosyl azide/triethylamine and then 1 M NaOH aq./12 h (93.1%), *e*: $Rh_2(OAc)_4$ in dichloromethane (69.7%).

Scheme 2[8] is that expected from the stereodirection of (2*R*,4*R*)-2,4-pentanediol tether.[5]

Three functional groups of **8**, ester, enol ether and olefin, are convenient for conversion of **8** to various *gem*-dimethylcyclopropane compounds, while existence of these groups may reduce stereochemical stability of **8** at the C8 position; e.g. epimerization to give **9**. However, **8** is relatively stable under basic conditions, and isomerization occurred to give a conjugated regioisomer **10**, only when **8** was heated with DBU (50 °C, 86.1% yield). Stereoisomer **9** was accidentally obtained. When **8** was heated to 110 °C in toluene with 5-diazo-2,2-dimethyl-1,3-dioxane-4,6-dione and CuI catalyst aiming at cycloaddition,[9] **9** was produced in a ratio of **9/8** = 1.5–2.5, while formation of **10** was negligible. Conversion of **9** to **10** was easily carried out by treatment with either acid or base.

PM3 calculations show that **9** and another regioisomer **11** have similar thermochemical stability to **8**, while **10** is more stable by ca. 8 kcal mol^{-1} (Figure 1). Stereochemical instability of **8** is governed by its kinetic acidity, and the acidity is due to conjugation of a developing carbanion with the C=O and C=C double bonds on deprotonation. In turn, the dihedral angles between a C8–H bond and the unsaturated bonds of **8** indicate degree of the instability; the most unstable at 90° and stable at 0 or 180°.[10] Such angles in a stable conformation calculated for **8** and **9** are given in Figure 1, suggesting that effects of the carbonyl substituent on the acidity are similar between **8** and **9**, while those by the vinyl groups are larger in **9** than in **8**. Thus, kinetic acidity of **8** is expected to lower than **9**. In reverse, protonation of a common enolate (or enol) of **8** and **9** should give **9** preferentially

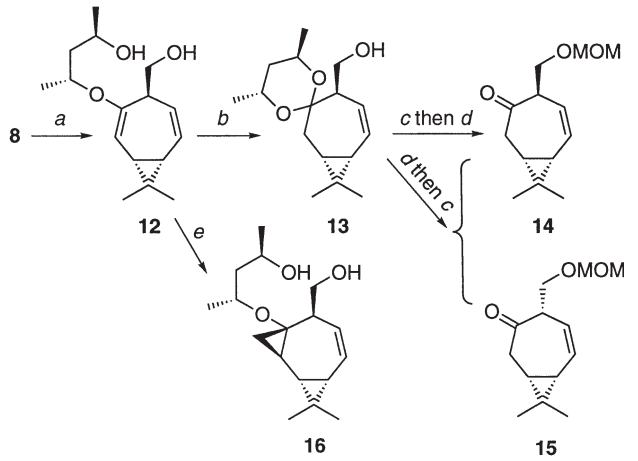


	8	9
H—C8—C9 = O	132.2	128.7
H—C8—C1 = C2	168.9	57.2
H—C8—C7 = C6	169.4	53.7

Figure 1. Heats of formation of **8** and its isomers by PM3 calculation are shown in parentheses (kcal mol^{-1}). Dihedral angles of **8** and **9** are also shown (degree).

under kinetically controlled conditions.[11]

A base-insensitive analogue of **8** can be prepared by reduction of **8** with lithium aluminum hydride to give stereochemically pure **12** (Scheme 3). Acid treatment of **12** produced a more stable analogue **13**. Hydrolysis after a protection of the hydroxy group afforded stereochemically pure ketone **14**. It should be noted that ketone **14** is stereochemically fragile and



Scheme 3. Reagents and conditions. *a*: lithium alminium hydride (98.1% yield), *b*: pyridinium *p*-tosylate in dichloromethane/rt (100%), *c*: methoxymethyl chloride/ethyldiisopropylamine/THF (83.2% from **13**, or 36.1% of **14** and 40.0% of **15** after deacetallization of **13**), *d*: 2 M HCl in acetone (91–98%), *e*: diethylzinc (5 equiv.)/diiodomethane (10 equiv.) in ether (38.0%).

reversal of the two last steps resulted in epimerization to give a mixture of **14** and **15**. Stability of **12** was found to be enough for cyclopropanation reaction with zinc carbenoid to give **16** as a single isomer.

In conclusion, asymmetric synthesis of *gem*-dimethylcyclopropane-fused compounds as sufficiently stable chiral synthons was established utilizing an intramolecular cyclopropanation and tautomerization of 3,4-homotropilidene. Synthetic studies starting with **12** are now in progress.

References and Notes

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7 Data for **8**: $[\alpha]_D^{20} = -77.5^\circ$ (*c* 1.0, CH_2Cl_2); IR (KBr) 1732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (dd, $J = 11.2$, 4.4 Hz, 1H), 5.59 (d, $J = 4.9$ Hz, 1H), 5.38 (ddd, $J = 11.2$, 6.8, 1.0 Hz, 1H), 5.04 (ddd, $J = 18.6$, 12.7, 6.3 Hz, 1H), 4.25 (d, $J = 6.8$ Hz, 1H), 3.87 (ddd, $J = 14.6$, 12.7, 6.3 Hz, 1H), 1.84–1.80 (m, 2H), 1.56 (m, 1H), 1.37 (d, $J = 6.3$ Hz, 3H), 1.29 (d, $J = 6.3$ Hz, 3H), 1.23 (dd, $J = 7.8$, 4.4 Hz, 1H), 1.18 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.0, 153.3, 131.6, 121.3, 115.8, 80.4, 73.1, 49.5, 44.7, 30.5, 27.6, 25.4, 25.2, 22.5, 21.5, 15.7. HRMS (M^+) m/z calcd for $C_{16}H_{22}O_3$, 262.1569; found, 262.1539.
8 Ring fusion of the lactone ring of the intermediate is determined to be *cis*. By PM3 calculations, the *trans*-fused compound is 6.8 kcal mol^{-1} less stable than *cis*-fused **7**.
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