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Enantiospecific Preparation of *gem*-Dimethylcyclopropane Fused Cycloheptanes *via* Valence Tautomerization of 3,4-Homotropilidene under Thermodynamic and Kinetic Control

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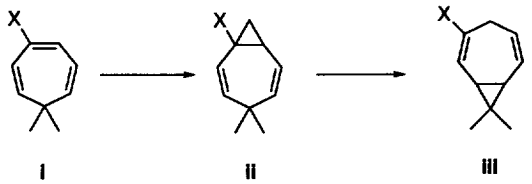
Abstract: 3,4-Homotropilidene derivatives were obtained as a stable compound by regioselective dichlorocarbene addition to 4-alkoxy-8,8-dimethylcycloheptatrienes. Substitution of chlorine atomes to hydrogens in them by reduction with sodium affords rearranged products. By using stereospecificity of the rearrangement, the corresponding optically active products were also prepared.

Valence tautomerization of 3,4-homotropilidene (bicyclo[5.1.0]octa-2,5-diene)[1] consisting of a quick divinylcyclopropane rearrangement[2] was well studied with respect to mechanistic interest, but has not been used in synthetic studies because of lack of a proper formation method and a control method of its equilibrium though reversible rearrangement. Since the cyclopropane fused seven membered ring skeleton widely exists in natural products, quickness of the tautomerism was fascinating us to establish it as a synthetic tool. The notable advantage of this rearrangement in synthesis is that it proceeds through a single transition state of the *boat-cisoid* conformation indicating its stereospecificity.[3] This report deals with the first example of its application for enantiospecific synthesis. The sequence of the present study is outlined in Scheme 1; cyclopropanation to the 3-substituted-7,7-dimethylcycloheptatriene **i** producing **ii** followed by divinylcyclopropane rearrangement affording **iii**. Here, the substituent X is expected to control the cyclopropanation at the 3,4-position of **i** and to make **iii** thermodynamically more stable than **ii**.

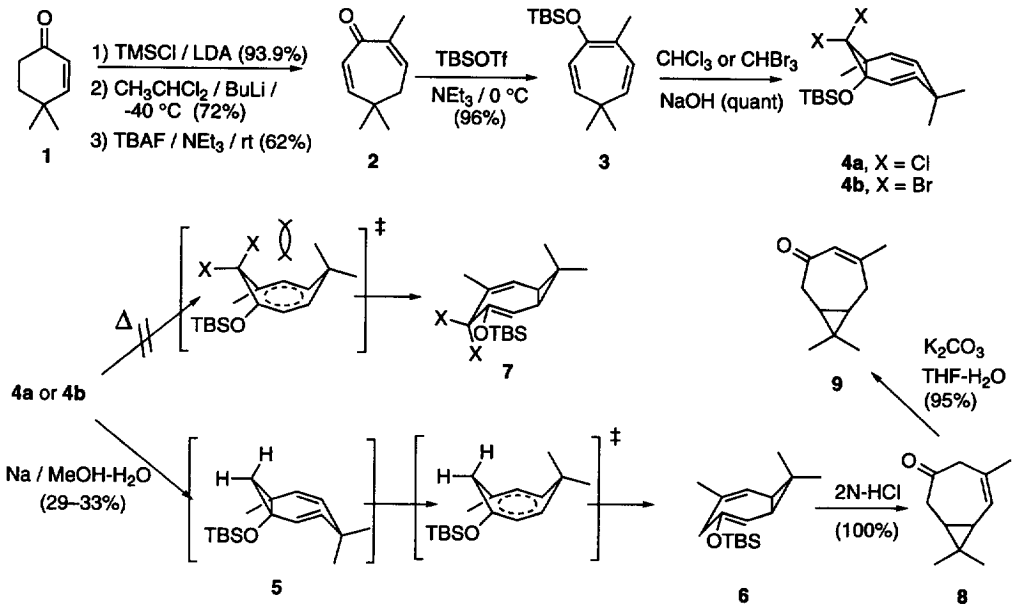


Scheme 1

Achiral substrate **3** was prepared from **1** in three steps as shown in Scheme 2. Cyclopropanation of **3** with various unsubstituted carbenoids (such as zinc, samarium or aluminum carbenoid) afforded a complex mixture consisting of poly-cyclopropanated compounds. In contrast, the addition of dichlorocarbene or dibromocarbene to **3** yielded **4** under complete regiocontrol in a quantitative yield (98.0% yield for **4a** and 97.8% yield for **4b** after purification). The isolated **4a** and **4b** were stable in a solution at 100°C for a few hours,[4,5] because the rearrangement was interrupted in **4** by the steric repulsion between the halogen and the methyl at the *cisoid-boat* transition state.

As expected, the 3,4-homotropilidene analogs, **4a** and **4b**, were rearranged just by substituting the halogen with hydrogen. Reduction of **4a** or **4b** with sodium in methanol-water[6] produced **6** as the sole

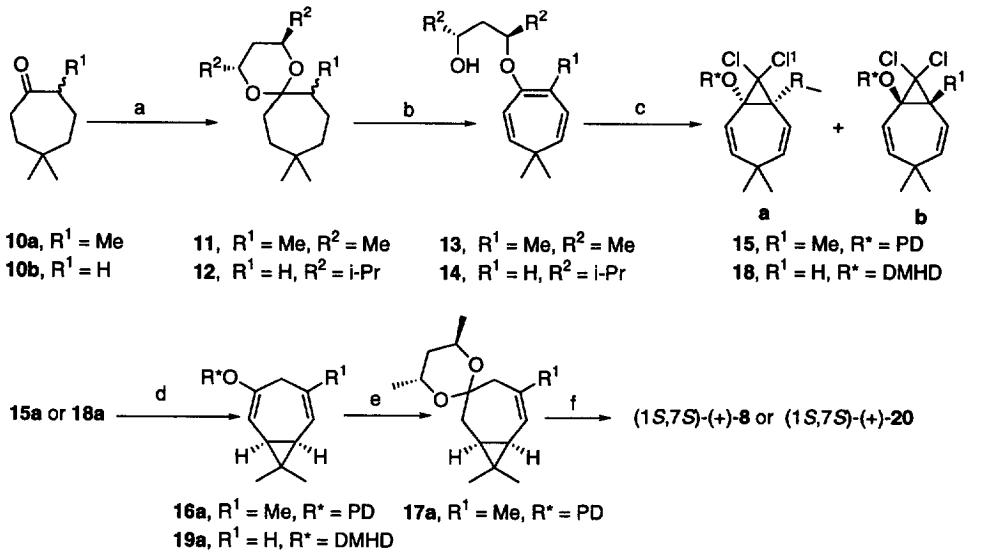
product.[7] Here, **5** was not detected at all in the reaction mixture and the ^{1}H-NMR of the isolated **6** showed a single structure in the temperature range of -95 °C and 100 °C. Thus, the rearrangement of **5** to **6** was quick enough below room temperature and the equilibrium of the rearrangement shifted completely toward **6**.[8] The fact suggested that the cyclopropanation of **3** with the unsubstituted carbenoids afforded **6** through **5** and the produced **6** was further cyclopropanated immediately since the skipped diene in **6** is more reactive than the conjugate triene in **3**. The obtained **6** was converted to **8** and then **9**, whose spectra were identical with those of a reported compound that is a potential key intermediate for ingenol,[9] a tetracyclic diterpene including the 8,8-dimethyl-3,4-homotropilidene skeleton.



Scheme 2

Next, we studied chiral substrates, **13** and **14**, to get optically active **9** and its analog **20**. The substrates were prepared from readily available **10**[10] in 3–4 steps. The addition of dichlorocarbene to **13**, a chiral analog of **1** having a (2*R*,4*R*)-2,4-pentanediol (PD) moiety instead of the TBS group, yielded a mixture of **15a** and **15b** in a ratio of 2.3 to 1 in quantitative yield. The major isomer **15a** isolated by HPLC was reduced by sodium in methanol-water giving the diastereomer-free **16a** (36% yield) and **17a** (36% yield). Acid treatment of **16a** converted it to **17a**, which was further transformed to (+)-**8** and then (+)-(1*S*,7*R*)-**9** in good yield.[11] The minor isomer **15b** was also converted to (-)-**8** and (-)-**9** *via* the diastereomers of **16a** and **17a** in the same way.

In the case of **14** having no methyl group at the 5-position, when PD was used as a chiral source, the separation of two dichlorocarbene adducts was not possible, but use of (3*S*,5*S*)-2,6-dimethyl-3,5-heptanediol (DMHD)[12] instead of PD made it possible to separate adducts **18a** and **18b** by MPLC on silica gel (**18a**:**18b** = 1:1.7). Again, the reduction of both diastereomers afforded dehalogenated and rearranged products, **19a** (53 % yield) and **19b** (63 % yield), which were converted to enantiomerically pure 8,8-dimethylbicyclo[5.1.0]oct-5-en-3-one (**20**) having the stereochemistry of 1*S*,7*S* and 1*R*,7*R*, respectively, by acid treatment.[13]



(a) From **10a** to **11**, (2*R*,4*R*)-pentanediol/ pyridinium *p*-toluenesulfonate/ benzene/ reflux (78%). From **10b** to **12**, (3*S*,5*S*)-2,6-dimethyl-3,5-heptanediol/ pyridinium *p*-toluenesulfonate/ benzene/ reflux (97%); (b) From **11** to **13**, pyridinium bromide perbromide (3 eq., 87%), potassium *t*-butoxide / DMSO (24%), trimethylsilyl triflate, and then NaOH (100% for two steps). From **12** to **14**, pyridinium bromide perbromide (3 eq., 90%), and then potassium *t*-butoxide/ DMSO (53%); (c) $CHCl_3$/ aq. NaOH/ benzyltriethylammonium chloride (100%); (d) sodium/ MeOH-H_2O; (e) pyridinium *p*-toluenesulfonate (100%); (f) pyridinium *p*-toluenesulfonate/ H_2O (80–90%)

Scheme 3

In this report, we present a highly regio-differentiating and partially diastereo-differentiating preparation method of functionalized bicyclo[5.1.0]octanes using the sequence through the 3,4-homotropilidene, kinetically stable isomers (**4**, **15**, and **18**) and thermodynamically stable isomers (**6**, **16**, and **19**). The obtained optically pure *gem*-dimethylcyclopropane fused compounds are considered to be promising intermediates for various natural products.

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4. Thermolysis of **4b** in benzene at 130 °C yielded 5-*t*-butoxydimethylsilyloxy-6-bromo-2-(2-methyl-1-propenyl)toluene in a quantitative yield ($t_{1/2}$ = 3.25 hours).
5. The 8-Mono-bromo compound **21** (X = H, Br in **4**) was also prepared. That is, the reaction of **1** with Et_2Zn and $CHBr_3$ gave **21** as a single diastereomer (26.4% yield). Treatment of **4b** with butyl lithium followed by quenching with water also afforded **21** (ca. 40% yield). The diastereomer at the 8-position was not detected at all in both cases.
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7. The isolated yield of **6** by MPLC on silica gel decreased to 29–33% because of its instability. The product **6** was also obtained by the reduction of **4a** or **4b** with Li/NH_3 at -78 °C in 25–30% yield. Sec-butyl lithium treatment of **21** at -72 °C followed by quenching with water also afforded **6** as a sole product (ca. 70%).
8. The results of the MO-calculation study agreed with the present study. The heat of formation of **5**, **4b**, and the corresponding rearranged products, **6** and **7b**, were calculated in the *transoid* and *cisoid* conformers using the AM-1 method. The TBS group in the compounds was replaced by a *t*-butyl group to simplify the calculation. Since an energy minimum was not obtained in the case of *cisoid*-**4b**, the energy shown in parentheses was calculated using the structure of *cisoid*-**5**. Heat of formation (kcal/mol), **5**: transoid -2.30, cisoid 0.78. **6**: cisoid -12.37, transoid -16.92. **4b**: transoid 14.72, cisoid (39.39). **7b**: cisoid 18.18, transoid 12.37.
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11. Since the optical rotation of (1*S*,7*R*)-**9** was reported only as positive, the obtained (+)-**9** was hydrogenated. The product from (+)-**9** was fully identical with the reported (1*S*,5*R*,7*R*)-trimethylbicyclo[5.1.0]octan-3-one ($[\alpha]_D$ = 195, lit.[9] $[\alpha]_D$ = 215).
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13. Since **20** was not isomerized to 8,8-dimethylbicyclo[5.1.0]octane-4-ene-3-one (**22**) in good yield, **20** was hydrogenated to determine its absolute structure. $[\alpha]_D$ = 205 for 8,8-dimethylbicyclo[5.1.0]octane-3-one (**23**) from **19a**. $[\alpha]_D$ = -197 for **23** from **19b**. $[\alpha]_D$ = 223 for (1*S*,7*R*)-**23** from the hydrogenation of (1*S*,7*R*)-**22** prepared by the reported method.[9]

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