Control of Ring-Junction Stereochemistry *via* Radical Cyclization.
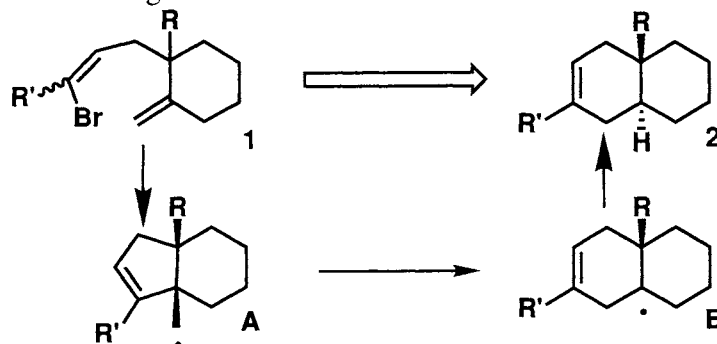## A New Construction of *trans*-Decalins

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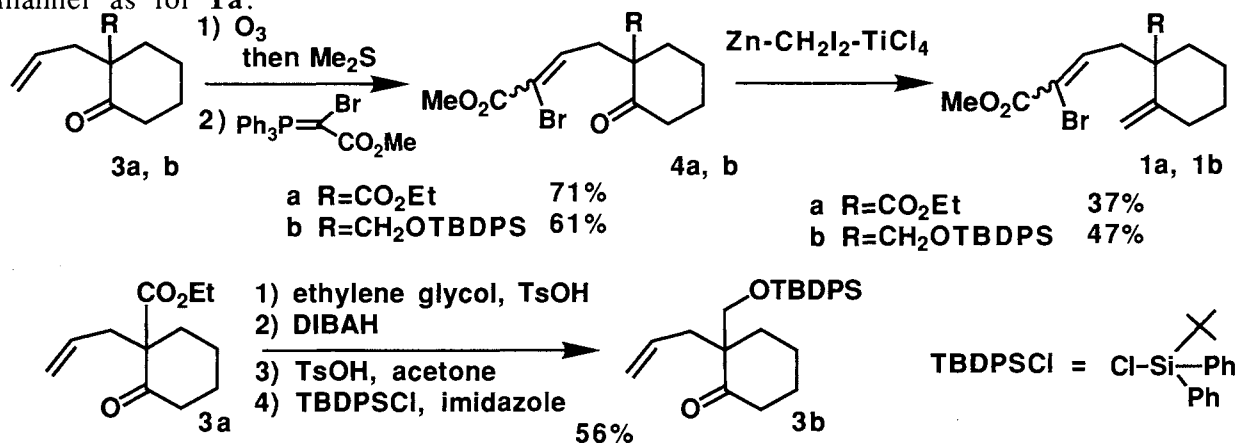Bunkyo-ku, Tokyo 113

A stereoselective synthesis of *trans*-decalins has been developed by use of regiocontrolled 6-*endo-trig*-radical cyclization of alkenyl bromides with an *exo*-methylene group in cyclohexane ring.

trans-Decalin derivatives are found in many biologically active substances such as steroids, azadirachtin and aphidicolin. However, the direct stereocontrolled synthesis of *trans*-decalins by ring closure is in general difficult.[1] Recently we reported a stereoselective synthesis of *trans*-hydrindans *via* 6-*endo-trig*-radical cyclization of alkenyl bromides with an *exo*-methylene group in cyclopentane ring.[2] The reaction was carried out under the low concentration of Bu$_3$SnH, thereby making possible the rearrangement of kinetically preferred 5-*exo*-cyclized radicals to thermodynamically more stable ones. We have further studied on the direct stereoselective synthesis of *trans*-decalins by radical cyclization. The very recent paper[3] prompts us to record our preliminary successes in a stereoselective synthesis of *trans*-decalins **2** starting with alkenyl bromides with an *exo*-methylene group in cyclohexane ring **1**.

The requisite alkenyl bromides with an *exo*-methylene group **1a** and **1b** were prepared as follows. Ozonolysis of ethyl 1-allyl-2-oxocyclohexanecarboxylate **3a** followed by Wittig reaction afforded the compound **4a**. Methylenation of **4a** by

Nozaki-Lombardo method[4] gave the *exo*-methylene **1a**[5] in a modest yield.[6] On the other hand, treatment of **3a** with ethylene glycol in the presence of *p*-TsOH followed by reduction with DIBAH gave the alcohol, which, after deprotection, led to the silyl ether **3b** in 56% overall yield. The silyl ether **3b** was converted to **1b** in a similar manner as for **1a**.

a R=CO$_2$Et   71%
b R=CH$_2$OTBDPS 61%

a R=CO$_2$Et   37%
b R=CH$_2$OTBDPS 47%

1) ethylene glycol, TsOH
2) DIBAH
3) TsOH, acetone
4) TBDPSCl, imidazole
56%

TBDPSCl = Cl–Si(–Ph)(Ph) (t-Bu)

When a toluene solution of **1a**, Bu$_3$SnH (1.2 equiv.), and Et$_3$B (0.8 equiv.) as a radical initiator[7] was stirred at -30 °C for 4 h, the desired cyclized product **2a** was obtained as a single isomer (27% yield) along with the dehalogenated product **5a** (26% yield, Table 1, run 1).[8] Although the lower concentration of Bu$_3$SnH improved the yield of the desired compound **2a**, a fair amount of the dehalogenated product **5a** was stil produced at this temperature (Table 1, run 2). However, the remarkable acceleration of the cyclization was observed when the reaction was carried out at room temperature, giving **2a** in 62% yield. Finally, it was found that a toluene solution of **1a** in the presence of Bu$_3$SnH and AIBN was refluxed for 2 h to afford the desired decalin **2a** in high yield (84%) as a single isomer. The reaction appears to proceed *via* the kinetically preferred radical **A** and thermodynamically more stable radical **B**.
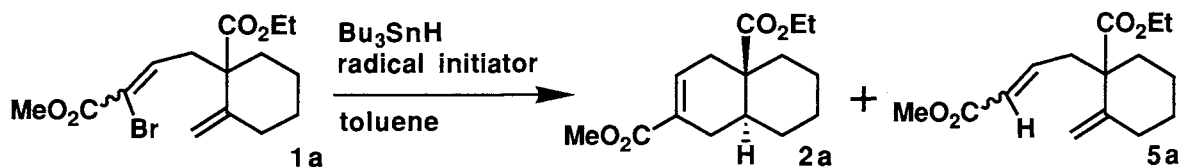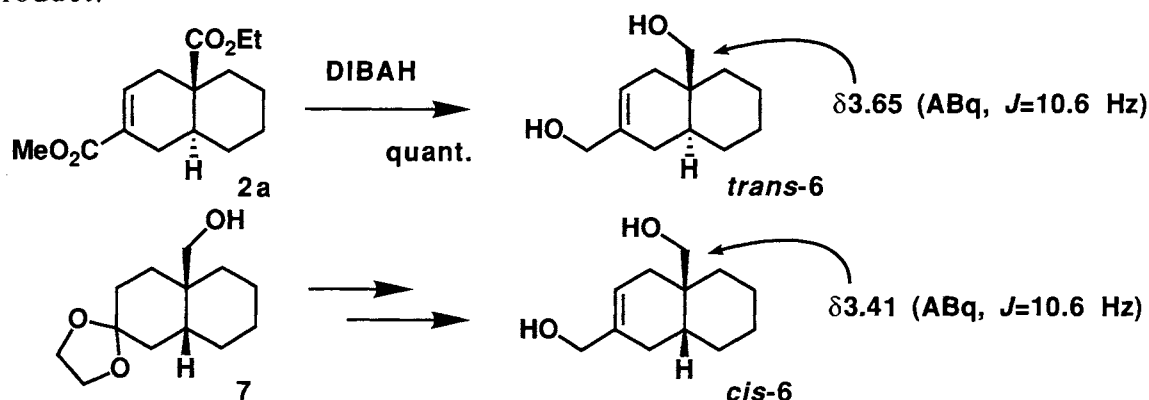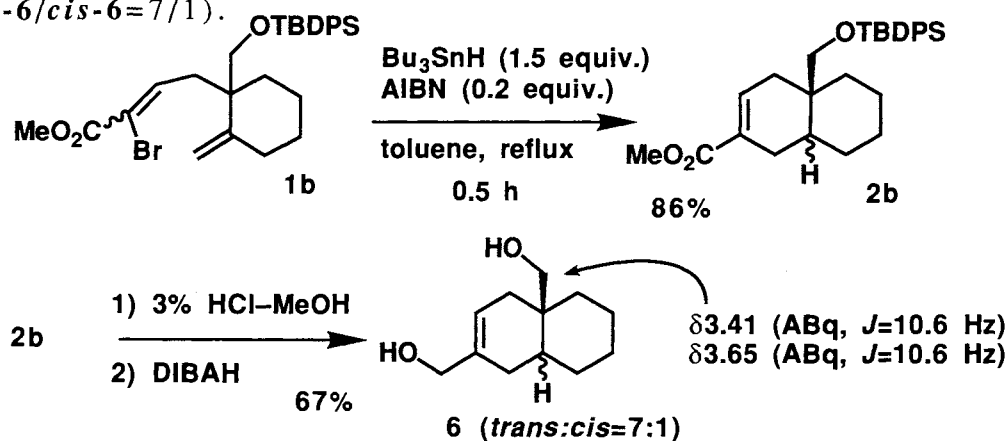

Table 1.   Reaction of 1a with Bu$_3$SnH in the presence of a radical initiator

Run	Bu$_3$SnH (equiv.)	Radical initiator (equiv.)		Concn. mM	Temp/°C	Time/h	Products yield/% 2a	5a	Recovery of SM/%
1	1.2	Et$_3$B	0.8	8	-30	4	27	26	20
2	1.5	Et$_3$B	3.0	2	-30	6	41	23	36
3	1.5	Et$_3$B	2.5	2	rt	2.5	62	6	6
4	1.5	AIBN	0.2	4	reflux	2	84	trace	—

The stereochemistry of the decalin **2a** was determined as follows. The compound **2a** was converted to *trans*-**6** by DIBAH reduction. The nmr spectrum of *trans*-**6** was compared with that of *cis*-**6**[9] prepared from the compound **7**, whose ring-junction is known to be cis.[10]   The methylene protons of the hydroxymethyl group in *trans*-**6** obtained by the radical cyclization had a chemical shift value of δ3.65 (ABq, *J*=10.6 Hz) on the nmr spectrum, while those of *cis*-**6** possessed a chemical shift value of δ3.41 (ABq, *J*=10.6 Hz).   These results clearly indicated that the radical cyclization of the compound **1a** afforded the *trans*-decalin **2a** as a single product.
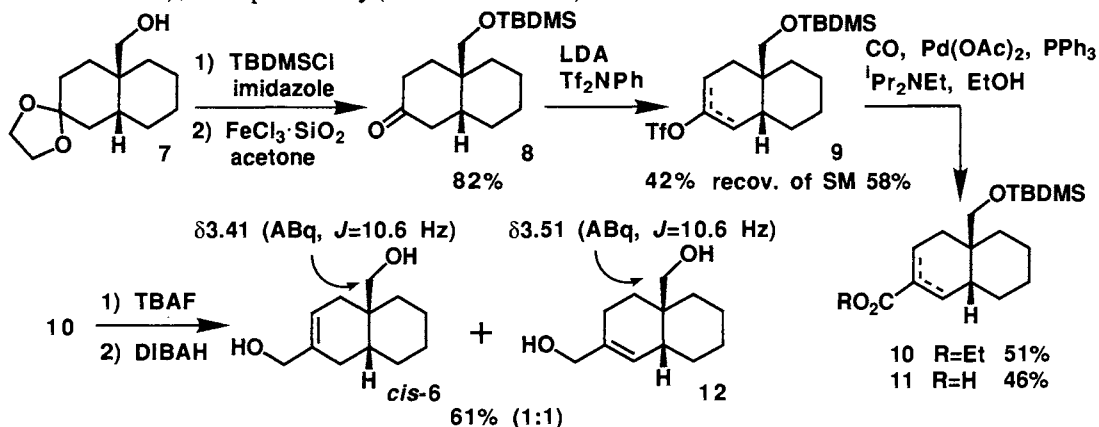

On the other hand, the radical cyclization of **1b** in refluxing toluene under the same conditions as for **1a** (see: Table 1, run 4) afforded the decalin **2b** in 86% yield. Desilation of the compound **2b** followed by DIBAH reduction provided the compound **6**, whose methylene protons of the hydroxymethyl groups had chemical shift values of δ3.41 (ABq, *J*=10.6 Hz) and δ3.65 (ABq, *J*=10.6 Hz), respectively: the former peak for the methylene protons of *cis*-**6** and the latter for *trans*-**6**. Further, the nmr spectrum indicated that the main product of the radical cyclization was *trans*-**6** (*trans*-**6**/*cis*-**6**=7/1).

In conclusion, we have found that 6-*endo*-*trig*-radical cyclization is also quite useful for the stereoselective construction of *trans*-decalins.   It is noteworthy that *trans*-decalins can be synthesized directly through ring closure.   Application to syntheses of bioactive molecules is under investigation.

References
1) For direct stereocontrolled synthesis of trans-decalins, see: W. R. Bartlett, W. S. Johnson, M. S. Plummer, and V. R. Small, Jr, J. Org. Chem., 55, 2215 (1990). References are cited therein.

2) S. Satoh, M. Sodeoka, H. Sasai, and M. Shibasaki, J. Org. Chem., 56, 2278 (1991). References of radical cyclization are cited therein.

3) S. Pal, M. Mukherjee, D. Podder, A. K. Mukherjee, and U. R. Ghatak, J. Chem. Soc., Chem. Commun., 1991, 1591.

4) J. Hibino, T. Okazoe, K. Takai, and H. Nozaki, Tetrahedron Lett., 26, 5579 (1985); L. Lombardo, Tetrahedron Lett., 23, 4293 (1982).

5) Since the E- and Z-vinyl radicals generated from the compounds 1a and 1b are in a state of an equilibrium even at -70 °C, the separation of E- and Z-isomers was not required.

6) The yield has not been optimized.

7) K. Nozaki, K. Oshima, and K. Utimoto, J. Am. Chem. Soc., 109, 2547 (1987).

8) MM2 calculation suggested that trans-decalin 2a would be produced under the thermodynamically controlled conditions [trans-2a is slightly (0.69 kcal/mol) stable than cis-2a].

9) The cis-decalin 6 was synthesized as follows. The cis-alcohol 7 prepared by the procedure reported[10] was treated with TBDMSCl (t-butyldimethylsilyl chloride) in the presence of imidazole followed by treatment with $FeCl_3$-SiO_2 to give the compound 8, which was treated with LDA and Tf_2NPh to give the enol triflate 9 as an inseparable mixture of the olefinic isomers. The compound 9 was treated with $Pd(OAc)_2$ and PPh_3 in the presence of EtOH under carbon monoxide at 50 °C to give the ester 10 and the acid 11. Deprotection of a TBDMS group of the ester 10 followed by DIBAH reduction gave the desired diol cis-6, which was an inseparable mixture of the olefinic isomers. The chemical shifts of methylene protons of the hydroxymethyl groups are $\delta 3.41$ (ABq, $J=10.6$ Hz) and $\delta 3.51$ (ABq, $J=10.6$ Hz), respectively (cis-6/12=1/1).

10) M. Idelson and E. I. Becker, J. Am. Chem. Soc., 80, 908 (1958).