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

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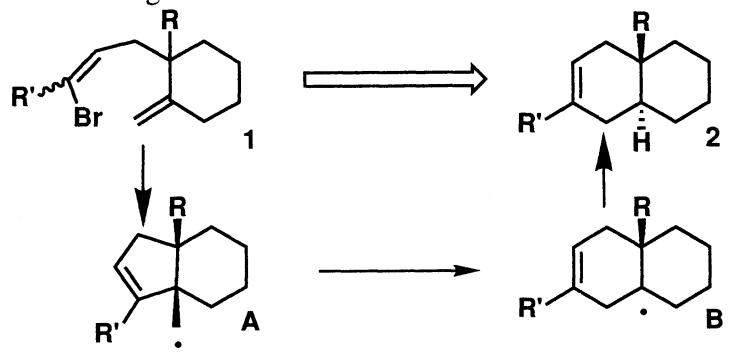
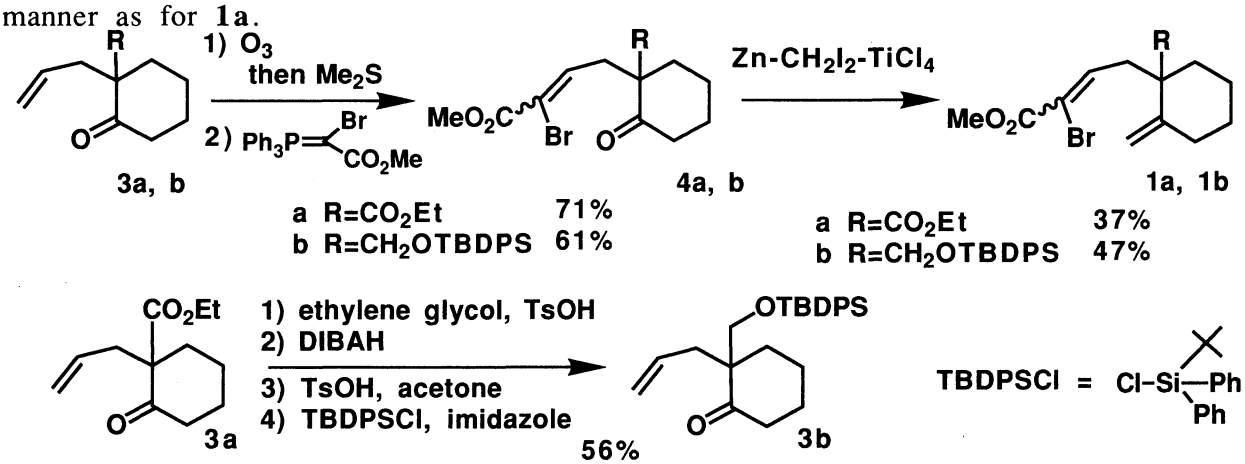
A stereoselective synthesis of *trans*-decalins has been developed by use of regiocontrolled 6-*endo*-*trig*-radical cyclization of alkenyl bromides with an *exo*-methylene group in cyclohexane ring.

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_3SnH, 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**.



When a toluene solution of **1a**, Bu_3SnH (1.2 equiv.), and Et_3B (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_3SnH 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_3SnH 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**.

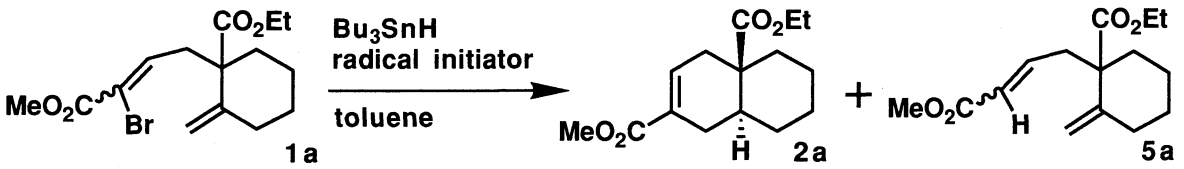
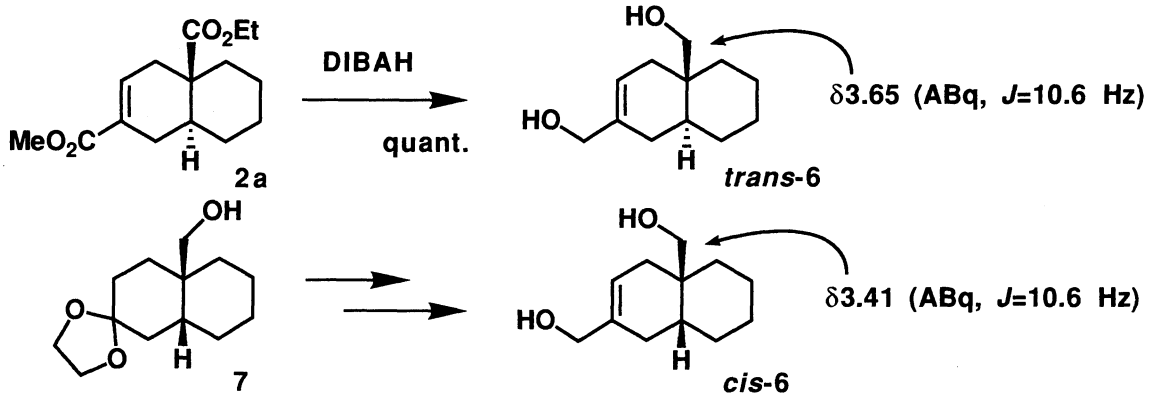


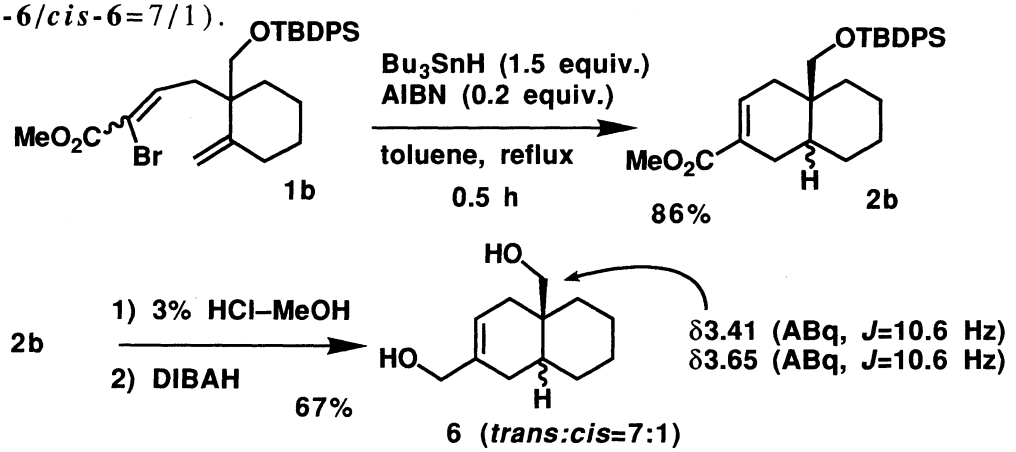
Table 1. Reaction of 1a with Bu_3SnH in the presence of a radical initiator

Run	Bu_3SnH (equiv.)	Radical initiator (equiv.)	Concn. mM	Temp/°C	Time/h	Products yield/% 2a	5a	Recovery of SM/%
1	1.2	Et_3B 0.8	8	-30	4	27	26	20
2	1.5	Et_3B 3.0	2	-30	6	41	23	36
3	1.5	Et_3B 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).

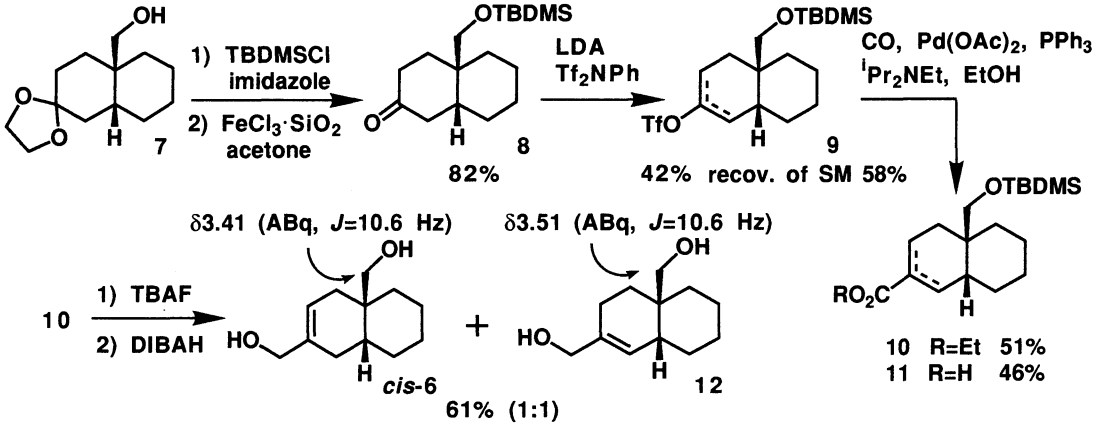
5) Since the *E*- and *Z*-vinyl radicals generated from the compounds **1a** and **1b** are in a state of an equilibrium even at -70 °C, the separation of *E*- and *Z*-isomers was not required.

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 δ3.41 (ABq, J=10.6 Hz) and δ3.51 (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).

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