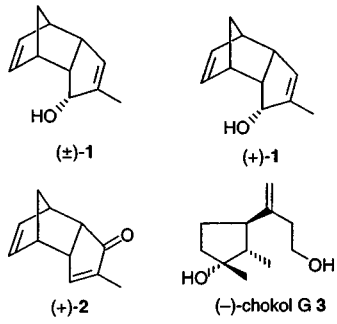
Asymmetric hydrogen transfer protocol for enantiocontrolled synthesis of (−)-chokol G

Regina Mikie Kanada, Takahiko Taniguchi and Kunio Ogasawara*†

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan

An enantiocontrolled route to the (−)-chokol G, a fungitoxic metabolite from stromata of *Epichloe typhia*, has been devised by employing a Ru^{II}-catalyzed asymmetric hydrogen transfer reaction as the key step.

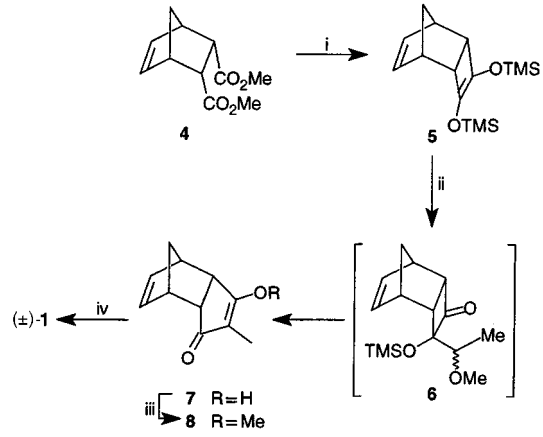
Noyori and co-workers have found that Ru^{II}-complexes of chiral *N*-tosyl-1,2-diphenylethylenediamines are efficient catalysts for the kinetic resolution of racemic aryl and alkenyl alcohols under asymmetric hydrogen transfer conditions in acetone.[1] In general, the reaction proceeds facilely to give highly enantiomerically enriched alcohols with generation of achiral ketones *via* consumption of the enantiomeric alcohols. The reaction, therefore, loses one half of the starting material unless *meso* substrates having a ene-1,4-diol functionality are used. We envisaged that the catalytic asymmetric hydrogen transfer reaction might be carried out without loss of half of the starting material by using substrates having an appropriate structural background. In this regard we chose 2-methylcyclopent-2-enol derivative **1**, having a cyclopentene-3,5-diyl functionality attached to its 4,5-carbons, which does not lose the chirality due to the 4,5-functionality even though its allylic alcohol functionality loses its chirality. We report herein the first example of the asymmetric resolution of racemic allylic alcohol (±)-**1** by asymmetric hydrogen transfer reaction, without formation of an achiral waste product, to give the chiral enone (+)-**2** and the chiral alcohol (+)-**1**, both of which may be converted into (−)-chokol G[2,3] **3**, a fungitoxic metabolite from stromata of *Epichloe typhia*.[2]



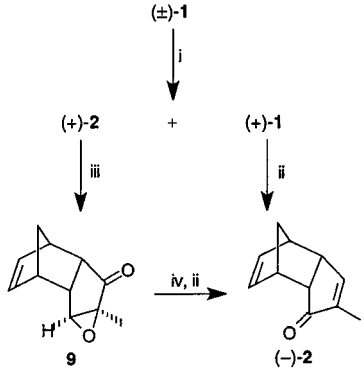
The tricyclic ene-1,2-diol bis-silyl ether[4] **5**, obtained in 90% yield from the diester **4**, was reacted with 1,1-dimethoxyethane in the presence of $BF_3{\cdot}OEt_2$[5,6] to give the aldol product **6**. Without purification, **6** was immediately refluxed in TFA to initiate the ring expansion[5,6] to furnish the β-hydroxy enone **7**,‡ which was treated with Me_2SO_4 in the presence of NaH to give the β-methoxy enone **8** in 56% overall yield from **5**. Treatment of the enone **8** with LAH in refluxing Et_2O afforded in one step the *endo*-allyl alcohol (±)-**1** stereoselectively as a single product in 65% overall yield (Scheme 1).

To carry out the asymmetric hydrogen transfer reaction, the racemic allyl alcohol (±)-**1** was stirred in acetone at room temperature in the presence of a catalytic amount (1 mol%) of the ruthenium catalyst,[1,7] prepared from [{$RuCl_2$(η⁶-mesitylene)}$_2$] and (1*S*,2*S*)-1-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine (TsDPEN). The reaction terminated within 5 h to afford the enantiomerically enriched enone (+)-**2**, in 44% yield, leaving the highly enantiomerically enriched allylic alcohol (+)-**1**, $[\alpha]_D^{31}$ +185.4 (*c* 1.1, $CHCl_3$), in 37% yield.§ The enantiomeric purities of the products were determined to be 87 and 98% ee by HPLC using a chiral column (CHIRALCEL OD, elution with 0.1% Pr^iOH–hexane) after converting **1** into the benzoate. When the catalyst, prepared similarly from [{$RuCl_2$(η⁶-cymene)}$_2$] in place of [{$RuCl_2$(η⁶-mesitylene)}$_2$], was used under the same conditions, virtually the same results were obtained to give the enone (+)-**2** in 49% yield with 73% ee and (+)-**1** in 36% yield with >99% ee, although the reaction proceeded at a much faster rate (2 h). The latter alcohol (+)-**1** afforded the enone (−)-**2**, $[\alpha]_D^{27}$ −85.8 (*c* 1.3, $CHCl_3$) [lit.,[8] −85.4 (*c* 1.4, $CHCl_3$)], in 89% yield upon oxidation with manganese(II) dioxide. On the other hand, the former (+)-enone (+)-**2** may be inverted without loss of the original chiral integrity to the enantiomeric (−)-enone **2** in 50% overall yield *via* the epoxide **9** by sequential Wharton rearrangement and oxidation[8] (Scheme 2).

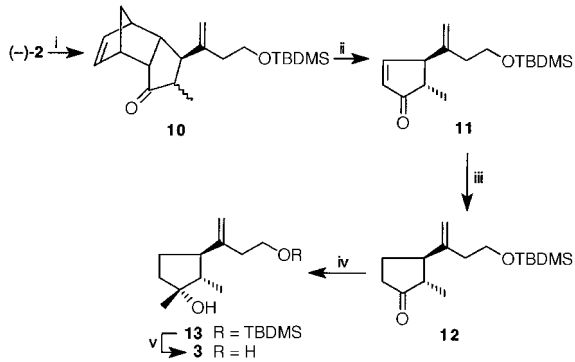
Having established a methodology for the resolution of a particular racemate without losing one enantiomer by employing the asymmetric hydrogen transfer reaction, we next carried out conversion of the resulting enantiomerically pure enone (−)-**2** into (−)-chokol G[3] **3** so as to demonstrate its synthetic potential. The synthesis was commenced by the 1,4-addition reaction of (−)-**2** with 4-*tert*-butyldimethylsiloxybut-2-enyllithium, generated *in situ* by treating 2-bromo-4-*tert*-butyldimethylsiloxybut-2-ene with Bu^tLi,[9] in the presence of lithium 2-thienyl(cyano)cuprate.[9] The reaction furnished the *exo*-addition product **10** in 94% yield as a mixture of the two epimers at the α-methyl center. On thermolysis in refluxing Ph_2O, the mixture afforded the single enone **11**, $[\alpha]_D^{27}$ −97.5 (*c* 1.2, $CHCl_3$), in 87% yield by retro-Diels–Alder reaction and spontaneous α-epimerization to the thermodynamically more stable isomer having *trans*-α,β-configuration. Treatment of **11**



Scheme 1 *Reagents and conditions*: i, Na, TMSCl, toluene, reflux (90%); ii, $MeCH(OMe)_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, then TFA, reflux; iii, Me_2SO_4, NaH, DMF–THF (1:1) (56% from **5**); iv, LAH, Et_2O, reflux (65%)



Scheme 2 *Reagents and conditions*: i, [Ru^{II}(η^6-mesitylene)], (1*S*,2*S*)-TsDPEN (1 mol%), acetone, room temp., 4.6 h, [44% and 87% ee for (+)-**2** and 37% and 98% ee for (+)-**1**]; ii, MnO_2, CH_2Cl_2 (89%); iii, 30% H_2O_2, 0.5 M NaOH, MeOH; iv, $NH_2NH_2{\cdot}H_2O$, AcOH (cat.), MeOH, then MnO_2, CH_2Cl_2 [50% from (+)-**2**]



Scheme 3 *Reagents and conditions*: i, CH_2=C(Br)CH_2CH_2OTBDMS, Bu^tLi, 2-thienyl(CN)CuLi, Et_2O, −25 °C (94%); ii, Ph_2O, reflux (87%); iii, DIBAL-H, CuI, HMPA–THF (1:4), −78 °C (92%); iv, MeLi, $CeCl_3$, THF, −78%; v, Bu_4NF, THF [69% from **12** after separation of the epimer (6%)]

with DIBAL-H in the presence of CuI and HMPA[10] in THF allowed 1,4-reduction to give the cyclopentenone **12**, $[\alpha]_D^{29}$ +45.2 (*c* 1.3, $CHCl_3$), in 92% yield. Reaction of **12** with excess MeLi in the presence of $CeCl_3$[3b,11] afforded a mixture consisted of two epimers which, without separation, was exposed to TBAF to give (−)-chokol G[2] **3**, $[\alpha]_D^{29}$ −58.1 (*c* 0.4, MeOH) [natural[2] −43.3 (*c* 0.24, MeOH)], in 69% overall yield as the major product accompanied with the minor epimeric alcohol, $[\alpha]_D^{29}$ −34.2 (*c* 0.3, MeOH), in 6% overall yield. Since the conversion of chokol G **3** into the other congeners, chokols A, B, C, F and K, chokolic acid B, and chokolal A, in the racemic series has been established,[12] the present synthesis formally constitutes the chiral preparation of these natural products.

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Notes and References

† E-mail konol@mail.cc.tohoku.ac.jp

‡ All new compounds had spectroscopic [IR, ^{1}H NMR, mass] and analytical (high resolution) data consistent with their assigned structure.

§ When the reaction was terminated after 2 h, the highly enantiomerically enriched enone (+)-**2** was obtained in 30% yield with 98% ee, leaving the enantiomerically enriched alcohol (+)-**1** in 47% yield with 59% ee.

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