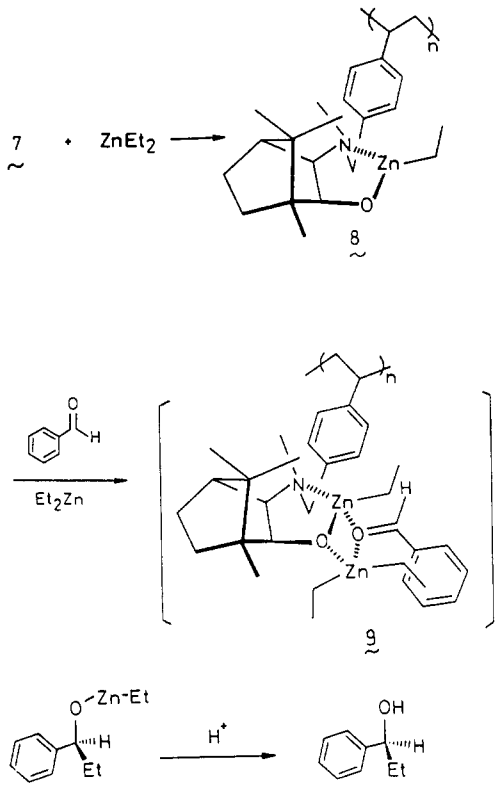
Scheme II



agreement with the reported[9] formation of stable organozinc alkoxides from alcohols and diorganozinc. If the alkoxide group bound to zinc contains another electron-rich ligand, as is the case with **1** which possesses a dialkylamino group, a chelate is formed.[10] While benzaldehyde does not react with diethylzinc alone at 0 °C, the 1:1 chelate of **1** and diethylzinc reduces benzaldehyde slowly to afford a low yield of benzyl alcohol. In contrast, the presence of a *catalytic* amount of **1** was sufficient to afford the addition product in 74% ee even at room temperature. The same result is obtained by using a 1:2 mixture of **1** and diethylzinc. Filtration of the polymer after reaction affords the *soluble* chiral zinc alkoxide which can be hydrolyzed to (*R*)-1-phenylpropanol in good yield and ee. Meanwhile the filtered unhydrolyzed chiral polymeric zinc chelate can be used over and over again in further asymmetric reactions at room temperature without requiring regeneration. These observations show clearly that the chiral alkoxide produced by the reaction is *not* bound covalenty to the initially formed polymeric zinc complex and suggest that transfer of ethyl occurs from the excess free diethylzinc in solution. The polymer-bound zinc serves to activate the carbonyl function of benzaldehyde in a chiral environment but does not participate directly in the ethylation. This was confirmed by a study in which a polymer-bound butylzinc alkoxide complex was formed by reaction of polymer **1** with dibutylzinc (1:1) and then used with excess diethylzinc and benzaldehyde in a process which, at room temperature, affords the desired *ethylated* product in 79% ee (vs. 74% ee for the ethylated catalyst). Similarly, if diisobutylzinc is used to form the initial polymer-bound complex, subsequent reaction with benzaldehyde and free diethylzinc affords the ethylated alcohol in 80% ee.[11]

These observations support the formation of chiral chelate complexes such as **8** in Scheme II. The polymer-bound zinc acts to coordinate the aldehydic oxygen to form a chirally fixed transition state such as **9**. Using polymer **7**, this would afford a final product having the *S* configuration (Table I) as the unbound ethyl of diethylzinc would attack the *si* face of benzaldehyde. The alternate mechanism[7] proposed by Wynberg involving transfer of ethyl from the chiral complex would not account for our observations.

This mechanism does not account for the observed stereochemical outcome of reactions involving polymers **4** or **6** for which the presence of additional labile hydrogens on the amino functionality may cause the reaction to proceed through a different intermediate.

(9) Coates, G. E.; Ridley, D. *J. Chem. Soc.* **1965**, 1870. Boersma, J. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: New York, 1982; Chapter 16.

(10) Boersma, J.; Noltes, J. G. *J. Organomet. Chem.* **1986**, *13*, 291. Coates, G. E.; Ridley, D. *J. Chem. Soc. A* **1966**, 1064.

(11) It should be noted that using excess diisobutylzinc for the reaction results in reduction of benzaldehyde to benzyl alcohol due to the greater activity of the β-hydrogens of diisobutylzinc.

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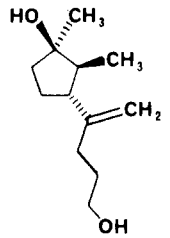
Homochiral Ketals in Organic Synthesis. Enantioselective Synthesis and Absolute Configuration of (-)-Chokol A[1]

Summary: An enantioselective synthesis of (-)-chokol A from 2-methyl-2-cyclopenten-1-one is described.

Sir: Chokol A (**1**) is a fungitoxic modified sesquiterpene recently isolated from stroma of the timothy *Phleum pratense* infected by the fungus *Epichloe typhina*.[2] The



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gross structure and relative stereochemistry initially assigned from spectroscopic measurements[2] were recently confirmed by synthesis of racemic chokol A.[3] Left in doubt was the absolute stereochemistry of the natural product, which we have now established by means of the enantioselective synthesis described below.[4]

Ketalization of 2-methyl-2-cyclopenten-1-one[5a] using 1,4-di-*O*-benzyl-L-threitol[5b] (PPTS, C_6H_6, reflux, 340 h)

(1) Presented in part at the 192nd National Meeting of the American Chemical Society, Anaheim, CA, September 1986; ORGN 33.

(2) Yoshihara, T.; Togiya, S.; Koshino, H.; Sakamura, S.; Shimanuki, T.; Sato, T.; Tajimi, A. *Tetrahedron Lett.* **1985**, *26*, 5551–5554.

(3) Oppolzer, W.; Cunningham, A. F. *Tetrahedron Lett.* **1986**, *27*, 5467–5470. This synthesis gave racemic chokol A in 3% overall yield over 13 steps.

(4) All yields refer to isolated and purified compounds. Satisfactory IR, ^1H NMR, ^{13}C NMR, and HRMS data were obtained for all compounds.

(5) (a) Gassman, P. G.; Pascone, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 7801–7813. (b) Ando, N.; Yamamoto, Y.; Oda, J.; Inouye, Y. *Synthesis* **1978**, 688–690.

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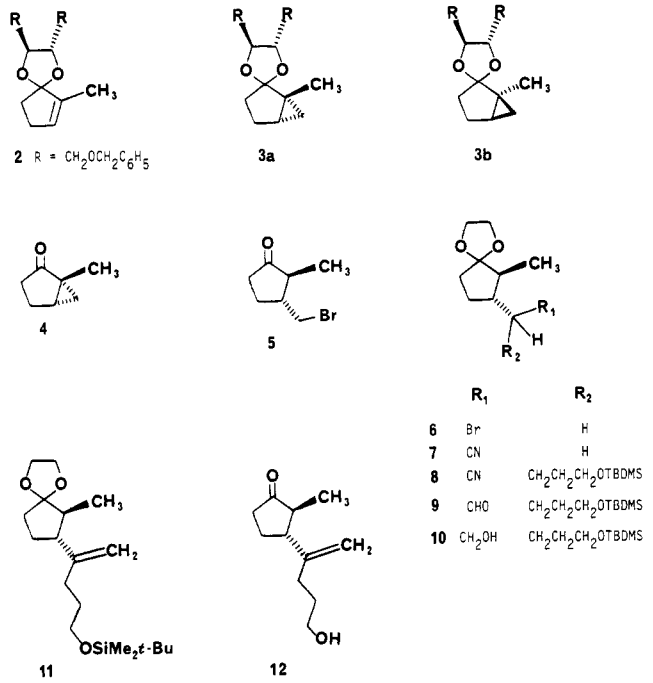
gave ketal **2** in 89% yield. Treatment of **2** with an excess of the Simmons-Smith reagent[6] in refluxing diethyl ether



gave, after 20 h and in 92% chemical yield, an inseparable 9:1 mixture of cyclopropane ketals **3a** and **3b** as determined by 62.9-MHz ^{13}C NMR spectroscopy.[7,8] Hydrolysis of the mixture of **3a** and **3b** (aqueous HCl, CH_3OH, room temperature, 1.5 h) gave enantiomerically enriched cyclopropyl ketone **4**, bp_{26} 84-85 °C, $[\alpha]^{27}_D$ +33.4° (*c* 1.97, $CHCl_3$), in 73% yield. The chiral auxiliary, 1,4-di-*O*-benzyl-L-threitol, was recovered in 93% yield following chromatographic repurification.

Assignment of the 1*R*,5*S* absolute stereochemistry to **4** was based upon application of the "reversed octant rule"[9] in interpreting the CD spectrum of **4**.[10] This assignment was also in accord with all previously examined cyclopropyl ketones.[9,11]

Treatment of **4** with excess trimethylsilyl bromide (3 equiv, CH_2Cl_2, -25 °C to 0 °C, 9 h) produced (2*S*,3*S*)-2-methyl-3-(bromomethyl)cyclopentanone (**5**), along with lesser amounts of 2-methyl-4-bromocyclohexanone.[12] Ketalization of **5** (ethylene glycol, *p*-TsOH, C_6H_6, reflux, 20 h) provided ketal **6**. Exchange of cyanide for bromide (KCN, NaI, DMSO, room temperature, 72 h) gave nitrile **7**, $[\alpha]^{25}_D$ -31.1° (*c* 6.09, $CDCl_3$), in 59% yield from **4**. Alkylation of nitrile **7** (2 equiv of $LiN(SiMe_3)_2$, THF, -78 °C; $ICH_2CH_2CH_2OSiMe_2$-*t*-Bu, THF, -78 °C to -20 °C) provided in 83% yield nitrile **8** as an inseparable mixture of diastereoisomers. Treatment of **8** with DIBAL (1.1 equiv, CH_2Cl_2, -78 °C, 30 min; mild acid workup) gave aldehyde **9** which, when reduced ($NaBH_4$, EtOH, room temperature, 15 min), gave in 53% yield alcohol **10** as an inseparable mixture of diastereoisomers. Tosylation of **10** (TsCl, pyr, 0 °C, 48 h), displacement of the tosylate with sodium *o*-nitrophenyl selenide[14] (2.2 equiv, EtOH, room temperature, 72 h), and treatment with 30% hydrogen peroxide (7.5 equiv, 2:1 EtOH:THF, room temperature, 48 h) gave olefin **11**, $[\alpha]^{25}_D$ -25.9° (*c* 2.68, $CHCl_3$), in 77% yield. Hydrolysis (aqueous HCl, CH_3OH, room temperature, 8 h) gave keto alcohol **12**, $[\alpha]^{23}_D$ +45.1° (*c* 2.1, $CHCl_3$), in 96% yield. Treatment of **12** with an excess of methyl cerium dichloride[15] (5 equiv, THF, -78 °C, 2 h) provided in 80% yield chokol A (**1**), $[\alpha]^{23}_D$ -46.3° (*c* 1.07, EtOH), lit.[2] $[\alpha]^{22}_D$ -26.6° (*c* 1.0, EtOH), identified by comparison of the IR, ^1H NMR, and ^{13}C NMR spectra of the synthetic material with spectra of the natural material.[16] The yield of (-)-chokol A of approximately 80% ee from 2-methyl-2-cyclopenten-1-one was 9% over 13 steps.[17]

This synthesis demonstrates the utility of the diastereoselective cyclopropanation process for establishing appendages enantioselectively at both α and β carbons of cycloalkanones.[7,11] Since a number of important natural products possess such substructural elements, this methodology should prove to be a useful cornerstone in natural product synthesis in future years.[18]

Supplementary Material Available: Complete experimental details and spectral data for compounds **1-4**, **7**, **8**, **10**, **11**, and **12** (11 pages). Ordering information is given on any current masthead page.

(6) Shank, R. S.; Shechter, H. *J. Org. Chem.* **1959**, *24*, 1825-1826.
(7) For previous examples of the use of this diastereoselective Simmons-Smith cyclopropanation in synthesis, see: (a) Mash, E. A.; Fryling, J. A. *J. Org. Chem.* **1987**, *52*, 3000-3003. (b) Nelson, K. A.; Mash, E. A. *J. Org. Chem.* **1986**, *51*, 2721-2724. (c) Mash, E. A.; Nelson, K. A. *Tetrahedron Lett.* **1986**, *27*, 1441-1444. (d) Mash, E. A.; Nelson, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 8256-8258. Also see: Arai, I.; Mori, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 8254-8256.
(8) An authentic diastereomeric mixture of cyclopropane ketals was prepared for spectral comparison by reketalization of **4** with 1,4-di-*O*-benzyl-DL-threitol. For previous examples of the use of ^{13}C NMR in the measurement of diastereomer ratios, see: Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183-2186.
(9) Lightner, D. A.; Jackman, D. E. *Tetrahedron Lett.* **1975**, 3051-3054, and references cited therein.
(10) From the CD spectrum of **4**: $[\theta]_{305}$ +2750°, $[\theta]_{295}$ +4400°, $[\theta]_{286}$ +4125° (*c* 0.08, pentane).
(11) Mash, E. A.; Nelson, K. A. *Tetrahedron* **1987**, *43*, 679-692.
(12) For a related process involving trimethylsilyl iodide, see: Miller, R. D.; McKean, D. R. *J. Org. Chem.* **1981**, *46*, 2412-2414.
(13) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React.* (*N.Y.*) **1984**, *31*, 1-364.
(14) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947-949.
(15) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233-4236.
(16) We thank Professor T. Yoshihara, Faculty of Agriculture, Hokkaido University, Sapporo, Japan for copies of spectra of natural (-)-chokol A.
(17) This synthesis should provide (-)-chokol A of approximately 80% ee. The actual optical rotation for natural (-)-chokol A should therefore be approximately -58°. The 500-MHz proton NMR spectrum of natural chokol A supplied by Professor Yoshihara provides evidence that the sample of chokol A used for that spectrum was not homogeneous. This may help explain the discrepancy between the rotation of the synthetic material and the value reported for the natural product.
(18) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. Partial support of this research by the American Heart Association, Arizona Affiliate, is gratefully acknowledged.

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New Steroids by Simmons-Smith Methylenation and Subsequent Rearrangement[1]

Summary: Product distribution and stereochemical outcome in the rearrangement of some new steroidal cyclopropyl carbinols were examined. Molecular conformation and nucleophilic assistance were shown to be key parameters for chemoselective formation of products.

(1) Dedicated to Prof. Dr. Erich Gerhards on the occasion of his 60th birthday.

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