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Asymmetrization of a *Meso* 1,2-Enediol Bis(trimethylsilyl) Ether Using a (*S*)-BINOL Monoisopropyl Ether(BINOL-Pr^i)-Tin Tetrachloride Complex: An Alternative Route to (–)-Ketodicyclopentadiene and (–)-Ketotricyclononene

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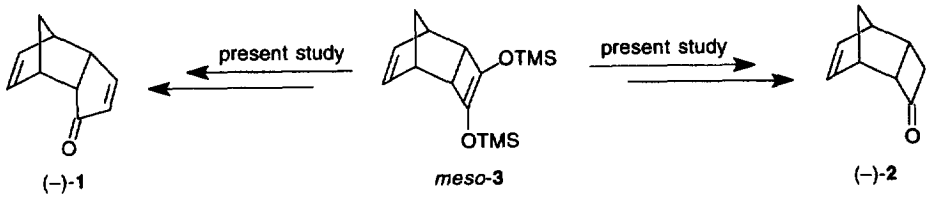
Abstract: A tricyclic *meso* 1,2-enediol bis(trimethylsilyl) ether having an *endo*-tricyclo[4.2.1.0^{2,5}]nonene framework has been asymmetrically desymmetrized by protonation with a complex generated from (*S*)-BINOL monoisopropyl ether (BINOL-Pr^i) and tin tetrachloride to give the optically enriched acyloin in 90% ee. The chiral acyloin thus obtained has been transformed into two versatile chiral building blocks, (–)-ketodicyclopentadiene and (–)-ketotricyclononene, in optically pure forms *via* a sequence involving concurrent enzymatic acetylation and optical purification.

Optically active 3-oxotricyclo[5.2.1.0^{2,6}]deca-4,8-diene (ketodicyclopentadiene)[1] **1** and 3-oxotricyclo[4.2.1.0^{2,5}]non-7-ene (ketotricyclononene)[2] **2** are both useful chiral building blocks for the construction of a variety of optically active molecules. Synthetic efforts are, therefore, currently aimed at the development of efficient construction of these molecules in optically pure forms.[1,2] Herein we report a unified route to these two chiral building blocks starting from the readily accessible *meso* 1,2-enediol bis(trimethylsilyl) ether[3] **3** by enantioselective protonation with a complex of (*S*)-binaphthol (BINOL) monoalkyl ether and tin tetrachloride, originally developed for the asymmetric protonation of prochiral silyl enol ethers and ketene bis-silyl acetals by Yamamoto and co-workers,[4] as the key step (**Scheme 1**).

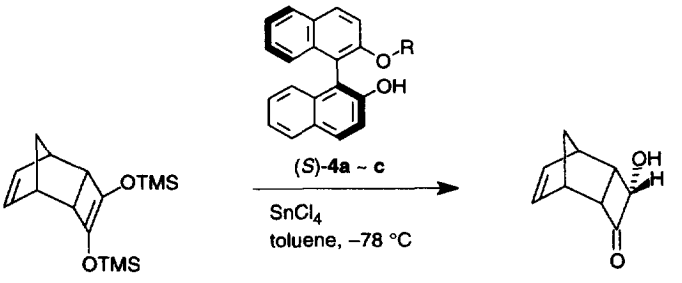


Scheme 1

By following the Yamamoto procedure,[4a] we first treated the bis-silyl ether **3** with a complex generated from (*S*)-BINOL **4a** (1.2 equiv.) and tin tetrachloride (1.2 equiv.) in toluene at –78 °C. The expected reaction took place to give the optically active acyloin (–)-**5** in 88% yield. However, the optical yield of the product was

found to be 9% ee which was determined by hplc using a chiral column (CHIRALCEL OD, 5% Pr^{i}OH-hexane). Since an improved procedure using BINOL monomethyl ether (BINOL-Me) **4b** in place of BINOL **4a** was later disclosed by the same group,[4b] we next examined the reaction using (*S*)-BINOL-Me **4b** (1.2 equiv.) in place of (*S*)-BINOL **4a** which resulted in generation of the optically active acyloin (–)-**5** in 86% yield with much better optical yield of 72% ee (CHIRALCEL OD, 5% Pr^{i}OH-hexane). Application of the catalytic conditions established by the same group[4b] using a catalytic amount (10 mol%) of BINOL-Me **4b** in the presence of tin tetrachloride (0.08 equiv.) and 2,6-dimethylphenol (1.1 equiv.) also transformed the *meso* bis-silyl ether **3** into the acyloin **5**, excellently, but the product had no optical activity.

In order to improve the enantioselectivity, we examined the protonation reaction using (*S*)-BINOL monoisopropyl ether[5,6] (BINOL-Pr^i) **4c** having a bulkier alkyl group and obtained an 80% yield from (*S*)-BINOL **4a** and 2-propanol (3.0 equiv.) by the Mitsunobu reaction[7] in the presence of triphenylphosphine (1.0 equiv.) and diethyl azodicarboxylate (1.0 equiv.). Thus, the *meso* bis-silyl ether **3** was added to a stirred solution of (*S*)-BINOL-Pr^i **4c** (1.2 equiv.) and tin tetrachloride (1.2 equiv.) in toluene at –78 °C and, after 3 h at the same temperature, the mixture was quenched by addition of 2% hydrochloric acid to give the optically active acyloin (–)-**5** in 87% yield. The optical yield of the acyloin (–)-**5** was found to be 90% ee which was determined by hplc (CHIRALCEL OD, 5% Pr^{i}OH-hexane). (*S*)-BINOL-Pr^i **4c** used was recovered excellently from the reaction mixture without losing the original integrity (>99% ee: CHIRALCEL OD, 2% Pr^{i}OH-hexane). However, the optically active acyloin **5** was not generated under the catalytic use of (*S*)-BINOL-Pr^i (10 mol%) in the presence of tin tetrachloride (0.08 equiv.) and 2,6-dimethylphenol (1.1 equiv.)[4b] (**Scheme 2**).

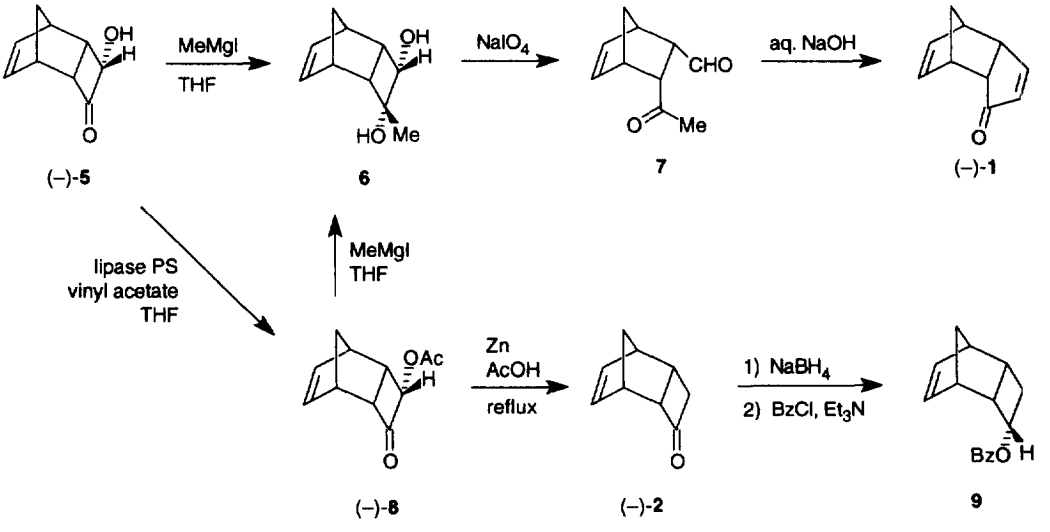


Scheme 2

Having found the good conditions for the transformation of the *meso* 1,2-enediol bis-silyl ether **3** into the optically enriched acyloin (–)-**5** in high enantioselectivity, we next examined its conversion into the known chiral building blocks ketodicyclopentadiene[1] **1** and ketotricyclononene[2] **2** to determine its absolute configuration and to explore its utility. To obtain optically enriched ketodicyclopentadiene **1**, the optically enriched acyloin (–)-**5** (90% ee) was exposed to an excess amount of methylmagnesium iodide in tetrahydrofuran (THF) to give the diol **6** excellently as a single epimer which was oxidatively cleaved with aqueous sodium periodate. The resulting crude keto-aldehyde **7** was immediately treated with 0.5 N aqueous

sodium hydroxide to initiate intramolecular aldolization[8] to furnish optically enriched ketodicyclopentadiene (–)-**1** in 60% overall yield from (–)-**5**. The absolute configuration of the product as well as that of the starting acyloin (–)-**5** was determined at this stage as shown as the absolute structure of (–)-**1** has been established.[1] However, the optical purity of the product, which was determined by hplc using a chiral column (CHIRALCEL OB, 10% Pr^iOH-hexane), was found to be less than 60% ee indicating that considerable racemization took place during the reaction sequence, presumably in the Grignard addition. We, therefore, blocked the free hydroxy functionality of the acyloin (–)-**5** by acetylation prior to the Grignard reaction so as to prevent metal alkoxide formation as well as to carry out the reductive elimination[3] for the preparation of chiral ketotricyclononene building block **2**. Because the basic conditions required for acetylation induced some racemization,[9] an enzymatic transesterification procedure[10,11] was applied to the optically enriched acyloin (–)-**5** in an organic solvent under neutral conditions. Thus, when (–)-**5** having 90% ee was stirred with vinyl acetate (1.2 equiv.) in THF in the presence of lipase PS (*Pseudomonas* sp., Amano) at room temperature for 14 h, a neat reaction occurred to give the *endo*-acetate (–)-**8** stereoselectively in 90% yield with >99% ee (CHIRALCEL OD, 5% Pr^iOH-hexane) leaving a negligible amount of the unreacted acyloin **5**. Fortunately, the enzymatic reaction allowed not only mild acetylation, but also optical purification by enantioselective discrimination which left (+)-**5** unchanged.[12] Grignard reaction of the optically pure acetate (–)-**8** thus obtained afforded the diol **6** which, on sequential cleavage and intramolecular aldolization as above, furnished the ketodicyclopentadiene (–)-**1** in 60% overall yield with >99% ee (CHIRALCEL OB, 10% Pr^iOH-hexane) without racemization.[1c]

On the other hand, the optically pure acetate (–)-**8** was refluxed with zinc dust in acetic acid[3] to initiate reductive elimination of the acetoxy functionality which afforded the optically pure ketotricyclononene[2] (–)-**2**, in 51% yield, whose absolute configuration has been determined.[2] Optical purity of (–)-**2** was determined to be >99% ee by hplc (CHIRALCEL OD, 2% Pr^iOH-hexane) after transformation into the *endo*-benzoate **9** *via* sequential reduction and benzoylation[2] (**Scheme 3**).



Scheme 3

In summary, the tricyclic *meso* 1,2-enediol bis(trimethylsilyl) ether having an *endo*-tricyclo[4.2.1.$0^{2,5}$]nonane framework has been asymmetrically desymmetrized by enantioselective protonation at best with a complex generated from (*S*)-BINOL monoisopropyl ether (BINOL-Pr^i) and tin tetrachloride to give the optically enriched tricyclic acyloin in good yield with 90% ee. The optically enriched product thus obtained was then transformed into two useful chiral buildings, (–)-ketodicyclopentadiene and (–)-ketotricyclononene, in optically pure forms *via* a sequence of reactions involving concurrent enzymatic acetylation and optical purification.

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7. Mitsunobu, O. *Synthesis* **1981**, 1. Hughes, D. L. *Org. Reactions* **1992**, *42*, 335.
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10. A pertinent monograph, see: Wong, C. H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994.
11. Yamane, T.; Takahashi, M.; Ogasawara, K. *Synthesis* **1995**, 444.
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