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AN ASYMMETRIC APPROACH TO THE SYNTHESIS OF TRANS-DIHYDRINDANDIONE

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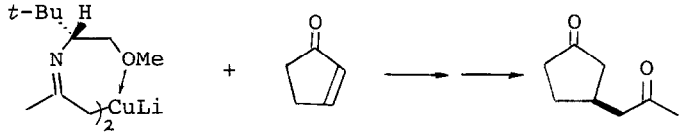
Summary: A three-step asymmetric approach to the synthesis of (3a*S*, 7a*S*)-3a,4-dihydro-7a-methyl-1,5(7a*H*)-indandione in 60% enantiomeric excess is described.

Contrary to virtually complete diastereoface-differentiation in the conjugate addition of certain organocopper reagents to chirally substituted 2-cyclopentenones,[1,2] attempted asymmetric conjugate additions of alkylcuprates containing chiral auxiliary ligands to prochiral cycloalkenones so far gave rise to uniformly low selectivity.[3] On the other hand, conjugate transfer of a chirally functionalized vinyl group from a copper reagent to 2-methyl-2-cyclopentenone followed by enolate trapping (double Michael addition) has met considerable success.[4]

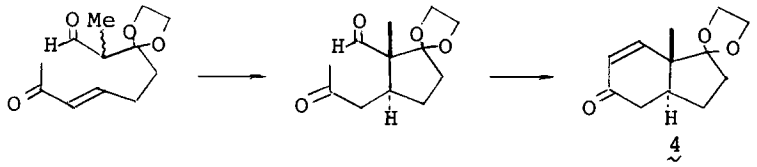
We have also reported an effective enantioface-differentiating conjugate addition of copper azaenolates as synthetic equivalent of enolates to cyclic enones.[5] Thus, metalation of an acetone imine of (*R*)-*tert*-leucinol methyl ether[6] with butyllithium followed by treatment with one-half equivalent of copper(I) iodide-dimethyl sulfide gave a homocuprate (1), presumably with a chelate structure shown. Conjugate addition of 1 to 2-cyclopentenone (2) gave, after facile hydrolysis, (*R*)-3-acetonylcyclopentanone (3) with 75% e. e. and in satisfactory chemical yield (eq. 1).



1 2 3 (1)

Recently, Stork and collaborators have developed a novel method for stereochemical control to construct *trans*-hydrindan system *via* an internal Michael addition and aldol condensation (eq. 2).[7] The potential importance of this route prompted us to disclose our own approach to the synthesis of a molecule like 4 in an enantioselective manner.

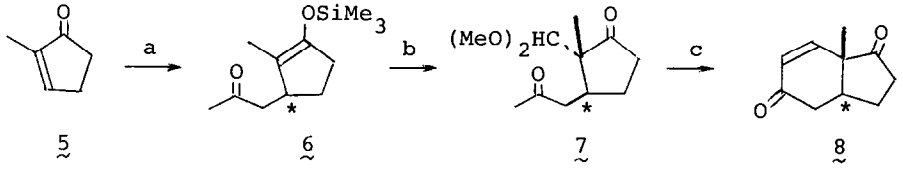
We report here an application of the new and efficient conjugate addition



(2)

4

of an enolate equivalent to a short synthesis of *trans*-dihydrindandione system *via* the resulting enolate trapping as depicted in Scheme 1.



5 6 7 8

a: i) (*S*)- or (*R*)-1, ii) $ClSiMe_3$, iii) aq NH_4OH-NH_4Cl. b: $CH(OMe)_3/SnCl_4$. c: $AcOH/PhCH_2CH_2NH_2$.

Scheme 1

In a preliminary experiment, acetone imine of cyclohexylamine (0.695 g, 5.0 mmol) in dry THF (15 mL) was lithiated with BuLi (1.6 M in hexane, 3.15 mL). To the solution at -60 °C strictly under a nitrogen atmosphere was added a solution of CuI (0.475 g, 2.5 mmol) and Me_2S (0.5 mL) in dry THF (4 mL). The resulting copper azaenolate solution was kept at this temperature for 1 h, being treated with 2-methylcyclopentenone (5) (0.243 g, 2.5 mmol) in THF (2 mL) by a slow addition at -60 °C. The whole mixture was allowed to warm to -20 °C, cooled again to -65 °C, and treated with $ClSiMe_3$ (0.405 mL, 1.2 eq) in a cource of 1 h. Hydrolysis and usual work up of the reaction mixture[5] gave a product mixture. Cyclohexylamine was recovered first by careful distillation under reduced pressure. From a residual oil there was obtained 3-acetonyl-2-methyl-1-(trimethylsiloxy)cyclopentene (6)[8] (0.496 g, 86% yield) by distillation (Kugelrohr). Attempted column chromatographic purification (silica gel) resulted in partial decomposition of the enol silyl ether.

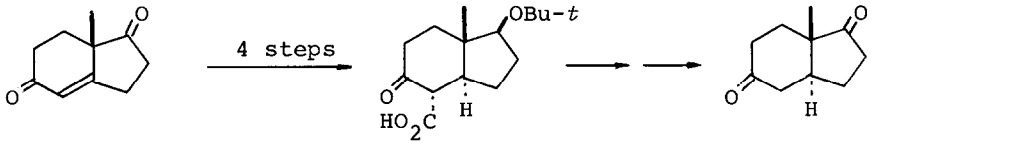
After many trials for the Lewis acid-mediated reaction of 6 with trimethyl orthoformate,[9] tin(IV) chloride was found to be an only choice for introducing the formyl group equivalent to the present enol silyl ether: To a solution of $SnCl_4$ (0.841 g, 3.2 mmol) in dry CH_2Cl_2 (10 mL) was added at -40 °C a mixture of 6 (0.30 g, 1.3 mmol) and $CH(OMe)_3$ (0.276 g, 2.6 mmol) dissolved in CH_2Cl_2 (5 mL) over a period of 0.5 h. The reaction mixture was allowed to stand for 1.5 h at -30 °C. Hydrolytic workup (aq K_2CO_3) and chromatographic separation of the products (silica gel, 10-30% ether-hexane) afforded 3-acetonyl-2-(dimethoxy)-methyl-2-methylcyclopentanone (7)[10] (0.146 g, 49%) and recovered 3-acetonyl-2-methylcyclopentanone (9)[11] from unreacted 6 (0.073 g, 25%).

Then, 7 was subjected to acidic aldol condensation: A mixture of 7 (0.14 g, 0.61 mmol) and $PhCH_2CH_2NH_2$ (47 mg) in acetic acid (3 mL) was heated at 100 °C for 2 h. Chromatographic purification (silica gel, 25% ether-hexane) afforded racemic *trans*-3a,4-dihydro-7a-methyl-1,5(7a*H*)-indandione (8) (0.48 g, 48%)

contaminated with 9, the latter arising from deformylation of 7 and being hardly separated by TLC. Pure sample of 8[12] was obtained by preparative GLC (PEG 20M 3 m, at 190 °C). GLC analysis also revealed that the crude 8 contained 2% of the cis isomer.

Chiral version of the sequence of reactions was carried out exactly in the same manner as above except for the use of 3 mmol of 1 from acetone imine of (*S*)-*tert*-leucinol methyl ether. Partially active 8 thus obtained in 24% overall yield, $[\alpha]_D^{25}$ -59.6° (*c* 0.46, $CHCl_3$),[13] was readily hydrogenated (5% Pd-C) in methanol to give (-)-*trans*-7a-methyl-1,5-indandione (10) in quantitative yield, $[\alpha]_D^{25}$ -105.3° (*c* 0.38, $CHCl_3$).

Due to lack of a direct and reliable method for control of trans angularly methylated hydrindanones[14] starting from (+)-(7a*H*)-7,7a-dihydro-7a-methyl-1,5(6*H*)-indandione (11),[15] six-step conversion was required to obtain an authentic sample of 10 (Scheme 2).[16]



11, $[\alpha]_D$ +362°(PhH) 12 10, $[\alpha]_D$ +171°($CHCl_3$)

Scheme 2 (Hajos procedure)

By comparing the optical rotation with that of authentic sample 10, 8 was found to be 62% optically pure. GLC purification does not change the rotation. In the same way, (+)-8, $[\alpha]_D^{25}$ +58.2° (*c* 0.44, $CHCl_3$), with 60% e. e. was obtained starting with 1 derived from (*R*)-*tert*-leucinol methyl ether.

The most unexpected feature of the chiral approach to *trans*-dihydrindandione 8 was inverse enantioface-selection of (*R*)-1 from 2 to 5 as an acceptor in asymmetric conjugate addition step, *i. e.* 75% e. e. R for 2 and 60% e. e. S for 5, respectively.

The results implicate very subtle stereodifferentiation of chiral copper azaenolate 1 between two cyclic enones employed. In addition, existing difficulties in enantioface-differentiating conjugate addition of alkylcuprates which are simply modified by added chiral auxiliary ligands may result from the lack of any face-matching between the reactant and cycloalkenones.

Nevertheless, the present approach to the synthesis of *trans*-dihydrindandione may have its own right because of a simple and short procedure.

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8) Enol silyl ether 6: ^{1}H NMR (90 MHz, $CDCl_3$, TMS) δ0.16(s, SiMe), 1.48(br. s, Me), 1.77(s, MeCO), and 2.03 ppm(d, *J*=8 Hz, CH_2CO). IR (film) 1685 and 1655 cm^{-1}.

9) K. Narasaka, K. Soai, Y. Aikawa, and T. Mukaiyama, Bull. Chem. Soc. Jpn., 49, 779 (1976).

10) Diketone 7: ^{1}H NMR 0.93(s, Me), 2.16(s, MeCO), 3.43 and 3.48(diastereotopic MeO), and 4.28(s, CH). ^{13}C NMR (22.5 MHz, $CDCl_3$, TMS) δ14.4(q), 25.9(t), 30.1(q), 34.8(d), 38.1(t), 46.0(t), 55.4(s), 58.6(q), 58.9(q), 111.0(d), 207.8(s), and 219.9(s).

11) Recovered 9 was found to consist of trans and cis isomers in a ratio of 80 : 20. Diagnostic ^{1}H NMR signals; 1.06(d, *J*=6.6 Hz, Me) for trans and 0.94(d, *J*=7.3 Hz, Me) for cis isomer, respectively.

12) Racemic 8: mp 67-68 °C. Anal. calcd. for $C_{10}H_{12}O_2$ C, 73.15; H, 7.37%. Found C, 72.84; H, 7.36%. ^{1}H NMR 1.11(s, Me), 5.94(d, *J*=10.0 Hz, CH=), and 7.33(d, *J*=10.0 Hz, COCH=). ^{13}C NMR 15.5(q), 23.1(t), 35.5(d), 38.9(t), 42.4(t), 49.3(s), 129.7(d), 151.3(d), 198.7(s), and 213.4(s). IR (film) 1745, 1680, and 1635 cm^{-1}.

13) *cf.* P. A. Grieco, N. Fukamiya, and M. Miyashita, Chem. Commun., 573 (1976).

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16) According to the Hajos procedure[15] 12 was obtained from optically pure 11. The former (crude 1.68 g) was hydrolyzed and then oxidized (PCC in CH_2Cl_2) to give 10, contaminated with cis fused isomer (18% by GLC), in 68% overall yield. Authentic pure 10: mp 73.5-74.0 °C, $[\alpha]_D^{25}$ +171.1° (*c* 0.45, $CHCl_3$). Cis-isomer of 10 (93% purity by GLC), $[\alpha]_D^{25}$ +95.7° (*c* 0.22, $CHCl_3$) (maximum rotation estimated).

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