Tetrahedron Letters,Vol.25,No.51,pp 5911-5912,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

STEREOSELECTIVE CONJUGATE ADDITION OF ORGANOALUMINUM REAGENTS TO CHIRAL α,β-UNSATURATED KETALS

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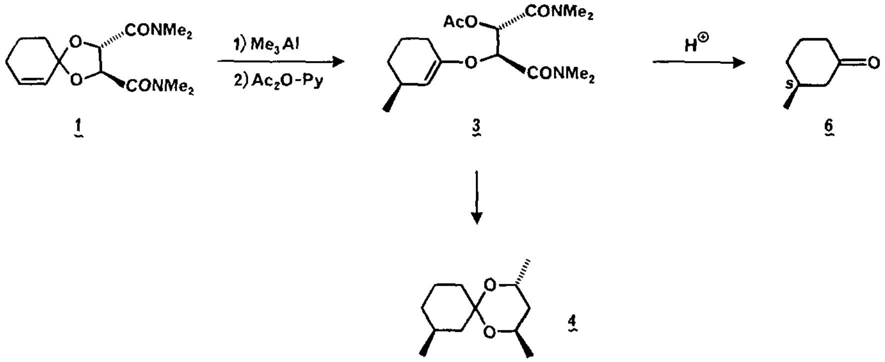
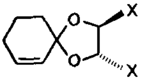
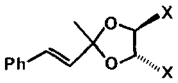
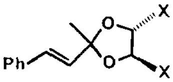
Summary: A new asymmetric synthesis of both enantiomers of β-substituted ketones is described.

Our recent investigation on the chemistry of activating a chiral protecting group by organometallic reagents[1] has prompted us to report a stereoselective conjugate addition of organoaluminum compounds to chiral α,β-unsaturated ketals, which, complementary to hitherto existing methodologies, provides a useful synthetic tool for preparation of optically active β-substituted ketones.[2]



The starting α,β-unsaturated ketal **1** was readily prepared by transacetalization of 2-cyclohexenone dimethyl ketal[3] with (S,S)-(-)-N,N,N',N'-tetramethyltartaric acid diamide (**2**)[4] in 85~90% yield. Treatment of **1** in toluene with trimethylaluminum (5 equiv) at 25°C for 3 h furnished after acetylation the conjugate adduct **3** exclusively in 94% yield. The optical purity of **3** was established to be 77% ee by GC analysis after converting to the acetal **4** of (-)-(2R,4R)-2,4-pentanediol (**5**) (cat. TsOH, toluene reflux, 90% yield). Hydrolysis of **3** (6N HCl-Dioxane) gave rise to (S)-3-methylcyclohexanone (**6**)[5] in 85% yield. The choice of the tartaric acid diamide **2** as a chiral auxiliary is crucial for obtaining the high diastereoselection: Attempted reaction of 2-cyclohexenone ketal derived from (-)-(2R,3R)-2,3-butanediol (**7**) with Me$_3$Al under the comparable conditions resulted in formation of the conjugate adduct (91% yield) with a low level of asymmetric induction (~23% ee).[6]

Table I. Conjugate Addition of Trialkylaluminums to α,β-Unsaturated Ketals

entry	ketal[a]	aluminum reagent	solvent	condition (°C, h)	yield, %[b]	opt. yield, % ee[c] (confign)
1		Me_3Al	toluene	-15, 144	94	65 (R)
2			toluene	5, 24	97	77 (R)
3			toluene	25, 3.5	91	78 (R)
4			CH_2Cl_2	25, 4	94	69 (R)
5		Me_3Al	toluene	-15, 120	79	35 (S)[d]
6			toluene	5, 24	84	72 (S)[d]
7			toluene	25, 19	81	64 (S)[d]
8			CH_2Cl_2	25, 9	83	44 (S)[d]
9			$ClCH_2CH_2Cl$	25, 8	77	33 (S)[d]
10		Et_3Al	toluene	25, 13	74	70 (S)[e]
11		Me_3Al	toluene	5, 24	84	54 (R)[d]

[a] X = $CONMe_2$. [b] Isolated yield. [c] Obtained by GC after converting to the acetal of 5 and 7. [d] Determined by conversion to (S)- or (R)-4-phenylpentan-2-one, see ref 5. [e] Brienne, M.-J.; Ouannes, C.; Jacques, J. Bull. Soc. Chim. Fr. 1967, 613.

As revealed in Table I, acyclic as well as cyclic substrates are equally employable. The ready accessibility of both (R,R)- and (S,S)-tartaric acid diamide in optically pure form[4] allows the facile synthesis of β-substituted ketones in both enantiomeric forms from α,β-unsaturated ketones or their synthetic equivalents in a predictable manner. It should also be pointed out that the optical yield appeared to decrease by lowering the reaction temperature (entries 1~3, 5~7).[7]

REFERENCES AND NOTES

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2) Recent review: Tomioka, K.; Koga, K. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Part A, p 201.

3) Garbisch, Jr., E. W. J. Org. Chem. 1965, 30, 2109.

4) Seebach, D.; Kalinowski, H.-O.; Langer, W.; Crass, G.; Wilka, E.-M. Org. Syn. 1983, 61, 24.

5) Leyendecker, F.; Jesser, F.; Ruhland, B. Tetrahedron Lett. 1981, 22, 3601.

6) A similar result (26% ee) was obtained by using $Me_2CuLi\text{-}BF_3$ system: Ghribi, A.; Alexakis, A.; Normant, J. F. Tetrahedron Lett. 1984, 25, 3083.

7) The totally reverse trend was observed in the case of chiral α,β-unsaturated acetals. See ref 1.

(Received in Japan 31 August 1984)