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3-(Alkylthio)-1,2-Bis(siloxy)-3-Butenes as Efficient Chirality Transferred Building Blocks

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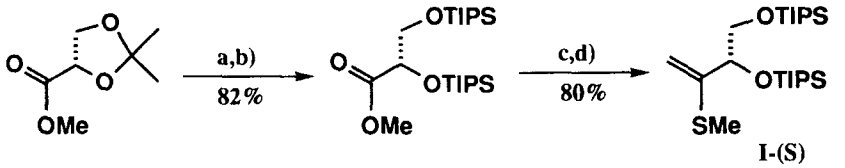
Abstract: In the presence of Me_2AlCl, reactions of the title compounds with a variety of aldehydes proceeded with high efficacy of chirality transfer to give the corresponding optically pure ene adducts, which could be converted to the γ-lactones, e.g., rove beetle pheromone.

In connection with our synthetic studies on vinyl sulfide chemistry,[1] we have reported that the ene reaction of 2-(alkylthio)allyl silyl ethers has constituted a powerful methodology for selective carbon-carbon bond formation.[2] Further, use of chiral substrates induced an enantioselective ene reaction through chirality transfer.[2b] To develop a more useful chiral building block for optically pure anthracycline synthesis[3] we designed 3-(alkylthio)-1,2-bis(siloxy)-3-butene **I**. This paper describes ene reactions of **I** yielding optically pure adducts, which can be converted to synthetically useful γ-butyrolactones or their derivatives through α-hydroxy ketones.

The optically pure ene **I**-(S) was easily prepared in four steps as shown in Eq 1. Thus, methyl (S)-(-)-2,2-dimethyl-1,3-dioxolane-4-carboxylate[4] was deprotected, silylated and then converted to the thiol ester by reaction with $^{i}Bu_2AlSMe$. Treatment of the resulting thiol ester with Tebbe reagent afforded the optically pure (S)-3-(methylthio)-1,2-bis(triisopropylsiloxy)-3-butene **I**.



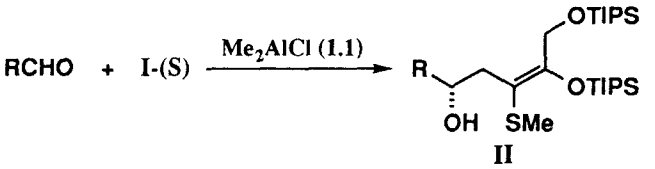
(Eq 1)

a) HCl / MeOH. b) TIPSCl, imidazole. c) $^{i}Bu_2AlSMe$. d) $Cp_2TiCl_2/AlMe_3$.

Under the influence of Me_2AlCl, the reactions of **I**-(S) with various aldehydes readily proceeded to afford the corresponding (Z)-ene adducts **II** in good yields. The enantiomeric excess of the product was determined by conversion of **II** to the (R)-MTPA ester and comparison of the NMR spectrum. The results were summarized in the Table.

From synthetic viewpoints, the following characteristic features of this reaction should be notable: (1) Introduction of 1-siloxy group greatly enhances the optical purity of the ene adduct. For example, on using

Table. Chirality Transfer Ene Reactions with Aldehydes

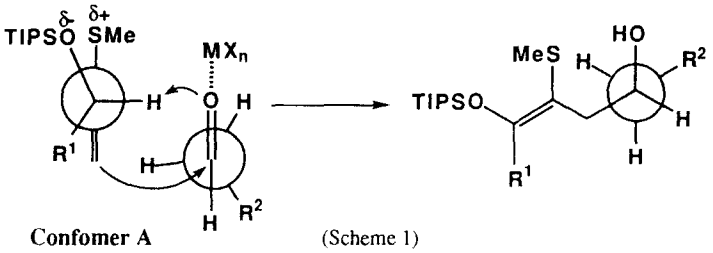


II

entry	R	Solvent	Conditions	Yield (%)	ee(%)
1	C_8H_{17}	CH_2Cl_2	-78 °C, 3h	82	94
2		toluene	-78 °C, 4h	84	97
3		hexane	-78 °C, 17h	90	>98
4	c-C_6H_{11}	CH_2Cl_2	-45 °C, 7h	85	86
5		toluene	-45 °C, 16h	96	91
6		hexane	-45 °C, 16h	99	96
7	C_6H_5	CH_2Cl_2	-78 °C, 2days	79	>99
8		toluene	-45 °C, 3days	90	>99
9	2,5-$(MeO)_2C_6H_3$	CH_2Cl_2	-23 °C, 2days	86	>98
10	$C_8H_{17}C{\equiv}C$	toluene	-78 °C, 5h	82	>99
11		hexane	-78 °C, 5h	66	>99

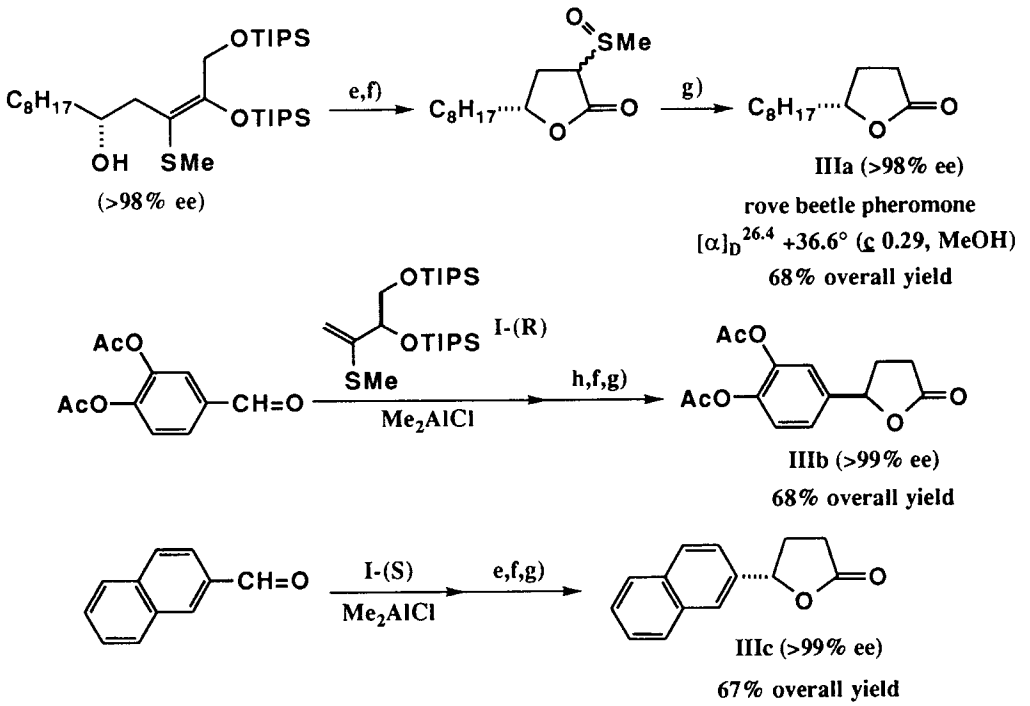
(S)-3-(ᵗbutyldimethylsiloxy)-2-(alkylthio)-1-butene, cyclohexanecarbaldehyde (cf entry 6) and 2,5-dimethoxybenzaldehyde (cf entry 9) gave the corresponding ene adduct with 56 and 90% ee, respectively.[5] (2) Choice of the solvent is crucial in the reaction with aliphatic aldehydes; use of non-polar solvent such as hexane is preferable (cf entries 3 and 6), yet the reaction becomes much sluggish. (3) Synthesis of useful optically active intermediate for adriamycinone has been performed (entry 9).[3]

The observed high selectivity may be rationalized by assuming **A** as the most stable conformer possibly due to an electrostatic interaction between MeS and TIPSO group. The reaction through the conformer **A** results in a preferential formation of (*Z*)-ene adduct. In addition to such characteristic feature, five-membered transition state involved in ene reaction favors a highly controlled enantiofacial approach of an aldehyde to **A** shown in Scheme 1.



Confomer A (Scheme 1)

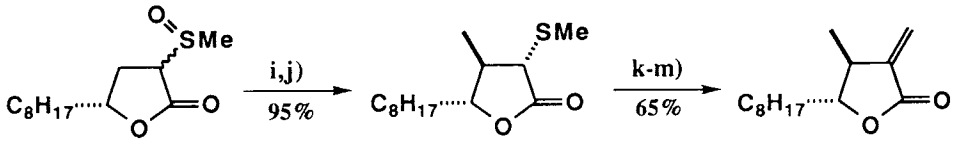
By applying usual synthetic procedures, these ene adducts were readily transformed to γ-butyrolactones:[6] After removal of silyl protecting group with TBAF, cleavage of hydroxy ketone moiety with $NaIO_4$ took place cleanly to give the corresponding α-sulfinyl γ-butyrolactones. Treatment with Raney nickel afforded optically pure lactones. Enantioselective syntheses of rove beetle pheromone **IIIa**, insect sexual pheromone,[7] represents a typical example of the synthetic utility of the present transformation. The important intermediates **IIIb** and **IIIc** for PAF antagonist[8] can also be prepared by using I-(R)[9] as ene substrate.



e) TBAF. f) $NaIO_4$/aq THF-MeOH. g) Raney Ni. h) Et_3NHF.

(Scheme 2)

Further, use of sulfur functional group allowed us to transform the sulfinyl lactones to various types of important α-methylene lactones without any reduction of optical purity. Typical example is shown in eq 2.



i) $(CF_3SO_2)_2O$. j) Me_2CuLi. k) m-CPBA. l) MeI/NaH. m) Δ

(Eq 2)

Thus, Pummerer reaction with trifluoromethanesulfonic anhydride gave the α-sulfenyl α,β-unsaturated lactone, which underwent stereoselective conjugate addition by Me_2CuLi. Oxidation to the sulfoxide followed by methylation and *syn* elimination afforded the corresponding methylene lactone as a single enantimer in an excellent overall yield.

Thus, the present methodology has provided useful and convenient synthetic routes toward important γ-butyrolactone derivatives with high optical purity. We are currently studying on further transformation of these adducts to biologically important substrates.

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3) A. Adachi, K. Masuya, K. Tanino, and I. Kuwajima, *J. Org. Chem.*, **58**, 4189 (1993).

4) The starting material for optically pure **I**-(S) was readily obtained from mannitol.

5) Discussion on analysis of conformers to favor efficient chirality transfer will be done in a full paper.

6) Recent examples on enantioselective synthesis of γ-butyrolactones, see: H. C. Brown, S. K. Kulkarni, and U. S. Racherla, *J. Org. Chem.*, **59**, 365 (1994).

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