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ASYMMETRIC SYNTHESIS OF γ-ALKYL-α-METHYLENE-γ-BUTYROLACTONES VIA 1,6-REMOTE INDUCTION USING 2-[(TRIBUTYLSTANNYL)METHYL]PROPENAMIDES

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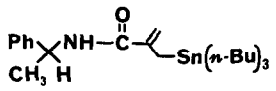
Summary: Reaction of chiral 2-[(tributylstannyl)methyl]propenamides with aldehydes proceeded with 1,6-asymmetric induction to give, after hydrolysis, α-methylene-γ-butyrolactones in enantiomeric excesses as high as 80%.

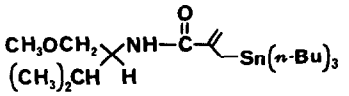
In recent years there has been considerable interest in the development of new methods for the synthesis of α-methylene-γ-butyrolactones (dihydro-3-methylene-2(3H)-furanones), since such compounds possess antitumor, cytotoxic, and growth-inhibitory activity, and fungitoxicity,[1] and also serve as intermediates for the synthesis of furans and insect pheromones.[2]

Although various routes to achiral α-methylene lactones have been developed,[3] little attention has been given to the asymmetric synthesis of this class of compounds.[4]

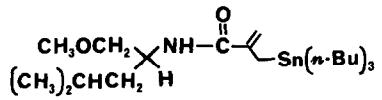
We have previously reported the enantioselective addition of the chiral dianion of N-[(S)-1-methoxymethyl-2-methylpropyl]-2-methylpropenamide to aldehydes.[4] However, the optical yield in this reaction was quite low (12% ee).



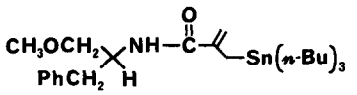
(S)-(−)-1a
(R)-(+)-1a



(S)-(−)-1b
(R)-(+)-1b



(S)-(−)-1c
(R)-(+)-1c



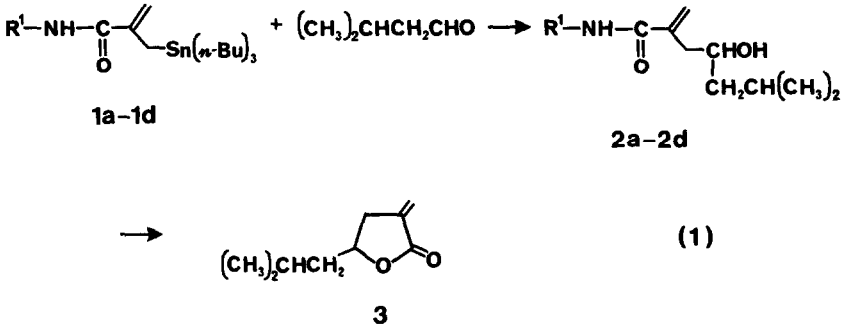
(S)-(−)-1d
(R)-(+)-1d

Scheme 1

We now report the successful asymmetric synthesis of γ-alkylsubstituted α-methylene-γ-butyrolactones via 1,6-remote chirality transfer using new chiral reagents, 2-[(tributylstannyl)methyl]propenamides.

Optically active 2-[(tributylstannyl)methyl]propenamides 1a-1d (Scheme 1) were prepared in 58-93% yields by adding 1.2 equiv of tributyltin chloride to a THF solution of the dianions of the corresponding 2-methylpropenamides.[4,5,6] The amides 1a-1d can be readily isolated as viscous oil by silica gel chromatography and stored in a freezer for several months without decomposition.[5]

Since both the absolute stereochemistry and the optical purity of γ-isobutyl-α-methylene-γ-butyrolactone are known,[2a] we first investigated the reaction of these chiral reagents with isovaleraldehyde as the electrophile (eq 1).



Thus, reaction of N-[(S)-α-methylbenzyl]-2-[(tributylstannyl)methyl]-propenamide ((S)-(-)-1a) with isovaleraldehyde using 4 equiv of BF_3OEt_2[7] proceeded efficiently at low temperature to afford γ-hydroxy-α-methyleneamide 2a in 80% yield, which was readily hydrolyzed by refluxing in dioxane containing 5% hydrochloric acid to give γ-isobutyl-α-methylene-γ-butyrolactone (3) in 81% yield (Table 1).[5]

Although the use of BF_3OEt_2 resulted in negligible asymmetric induction (~3%), an enhancement in selectivity was observed when N-[(S)-1-methoxymethyl-2-methypropyl]-2-[(tributylstannyl)methyl]propenamide ((S)-(-)-1b) derived from (S)-(+)-valine was treated with the aldehyde in the presence of 1 equiv of $TiCl_4$. The use of N-[(S)-1-methoxymethyl-3-methylbutyl]-2-[(tributylstannyl)-methyl]propenamide ((S)-(-)-1c) obtained from (S)-(+)-leucine caused a marked increase in optical purity. The highest enantioselectivity was finally achieved by the use of N-[(S)-α-(methoxymethyl)phenethyl]-2-[(tributylstannyl)-methyl]propenamide ((S)-(-)-1d), prepared from (S)-(-)-phenylalanine, in the the presence of 4 equiv of $TiCl_4$ in dichloromethane, and (S)-(-)-3 being formed in optical yield of 79%. The R antipode 3 with 78% enantiomeric excess is available in 96% chemical yield by using the amide (R)-(+)-1d, derived from (R)-(+)-phenylalanine, and isovaleraldehyde. No reaction took place when

$SnCl_4$, $TiCl(O\text{-}i\text{-}Pr)_3$, or $Ti(O\text{-}i\text{-}Pr)_4$ was employed as a Lewis acid.

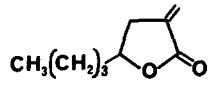
Table 1. Asymmetric Synthsis of α-Methylene-γ-Butyrolactones from Isovaleraldehyde

Entry	Amide	Lewis acid (equiv)[a]	Yield of 2 (%)	Yield of 3 (%)	$[\alpha]_D$, deg (temp(°C), c in EtOH)	Optical Yield of 3(%)[b]	configuration
1	(S)-(-)-1a	BF_3OEt_2 (4)	80	81	-2.3(23, 1.43)	3.4	(S)
2	(S)-(-)-1a	$TiCl_4$ (1)	85	95	+10.8(18, 1.79)	16	(R)
3	(R)-(+)-1a	$TiCl_4$ (4)	80	85	-10.9(24, 1.11)	16	(S)
4	(S)-(-)-1b	BF_3OEt_2 (4)	85	95	-2.2(24, 1.46)	3.3	(S)
5	(S)-(-)-1b	$TiCl_4$ (1)	85	69	-28.0(21, 1.76)	42	(S)
6	(S)-(-)-1b	$TiCl_4$ (4)	81	88	-43.6(22, 1.55)	65	(S)
7	(R)-(+)-1b	$TiCl_4$ (1)	84	99	+31.4(25, 1.51)	47	(R)
8	(S)-(-)-1c	BF_3OEt_2 (4)	88	81	-2.8(24, 1.59)	4.2	(S)
9	(S)-(-)-1c	$TiCl_4$ (4)	77	93	-48.5(24, 1.78)	72	(S)
10	(R)-(+)-1c	$TiCl_4$ (1)	86	98	+40.9(25, 1.55)	61	(R)
11	(S)-(-)-1d	$TiCl_4$ (4)	75	65	-52.9(25, 1.86)	79	(S)
12	(R)-(+)-1d	$TiCl_4$ (4)	99	97	+52.4(25, 1.66)	78	(R)

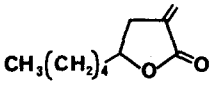
a) The reaction was carried out at -78°C to 0°C for 4 h.

b) Optical pure (S)-(-)-3 is reported to have $[\alpha]_D^{25}$ -66.6°(c 1.83, EtOH) and optical pure (R)-(+)-3 to have $[\alpha]_D^{25}$ +67.0°(c 1.44, EtOH). See ref. 2a.

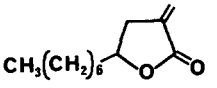
Similarly, pentanal, hexanal, and octanal readily reacted with the chiral amide (S)-(-)-1d or (R)-(+)-1d in the presence of 4 equiv of $TiCl_4$ to furnish, after acid hydrolysis, the corresponding α-methylene-γ-butyrolactones in good chemical yields with high enantiomeric purities.[5,8]



(S)-(-)-4: 82% ee
(R)-(+)-4: 78% ee



(S)-(-)-5: 82% ee
(R)-(+)-5: 80% ee



(S)-(-)-6: 78% ee
(R)-(+)-6: 78% ee

The mothod is apparently quite general, operationally simple, and provides access to both enantiomers by selecting the proper amides as the starting chiral auxiliaries.

We are continuing to explore the mechanism of the present 1,6-remote

asymmetric induction and applications of these chiral reagents to the synthesis of natural products.

References and Notes

1. (a) J.-P. Corbet and C. Benezra, *J. Org. Chem.*, 46, 1141 (1981); (b) B. H. H. Bergman, J. C. M. Beijersbergen, J. C. Overeem, and A. K. Sijpestein, *Recl. Trav. Chim. Pays-Bas*, 86, 709 (1967); (c) P. Barbier and C. Benezra, *J. Med. Chem.*, 25, 943 (1982); (d) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *ibid.*, 14, 1147 (1971).
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3. For reviews, see: (a) R. B. Gammill, C. A. Wilson, and T. A. Bryson, *Synthetic Commun.*, 5, 245 (1975); (b) P. A. Grieco, *Synthesis*, 1975, 67; (c) S. S. Newaz, *Aldrichimica Acta*, 10, 64 (1977); (d) T. Shono and Y. Matsuyama, *J. Synth. Org. Chem., Japan*, 39, 358 (1981).
4. K. Tanaka, Y. Nozaki, N. Tamura, R. Tanikaga, and A. Kaji, *Chem. Lett.*, 1980, 1567.
5. All new compounds gave satisfactory spectral and analytical data.
6. Optically active amines were prepared by the reported procedures. See: (a) H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, and S. Yamada, *Chem. Pharm. Bull.*, 13, 995 (1965); (b) A. I. Meyers, G. S. Poindexter, and Z. Brich, *J. Org. Chem.*, 43, 892 (1978); (c) A. I. Meyers, D. R. Williams, G. W. Erickson, S. White, and M. Druelinger, *J. Am. Chem. Soc.*, 103, 3081 (1981).
7. For a review on Lewis acid mediated reaction of allyltin with carbonyl compounds, see: M. Pereyre and J.-P. Quintard, *Pure Appl. Chem.*, 53, 2401, (1981).
8. The chiral γ-butyl-, γ-pentyl-, and γ-heptyl-α-methylene-γ-butyrolactones are unknown. The enantiomeric excesses were determined by HPLC analyses and ^{19}F NMR spectra of the Mosher's esters prepared from the γ-hydroxy-α-methyleneamides. We found that the enantiomeric purity could be determined by conversion of the γ-hydroxy-α-methyleneamides to a diastereomeric mixture of 3-methylene-2-pyrrolidinones, which were separable by silica gel chromatography. The synthesis of optically active 3-methylene-2-pyrrolidinones will be reported in a separated paper.

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