Tetrahedron Letters, Vol.31, No.52, pp 7623-7626, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

CONJUGATE ADDITION TO CHIRAL γ-HETEROSUBSTITUTED δ-LACTONES AS PIVOTAL SYNTHONS FROM L-GLUTAMIC ACID. SYNTHESIS OF AN OPTICALLY ACTIVE LIGNAN LACTONE; (-)-HINOKININ

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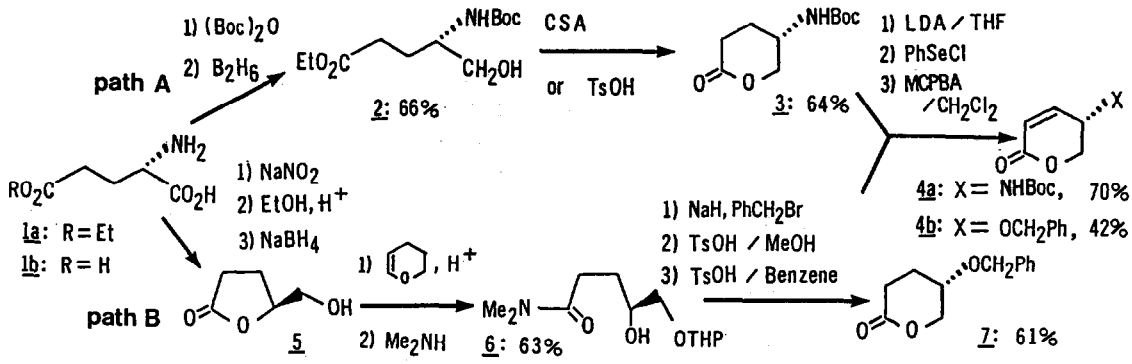
Summary: Asymmetric induction in conjugate addition of new chiral γ-heterosubstituted-α,β-unsaturated δ-lactones from L-glutamic acid was accomplished in high diastereoselectivity with the formation of trans-(R,S)-adducts and was disclosed to serve as a versatile procedure for the asymmetric synthesis of antileukemic lignan lactones.

Stereoselective conjugate addition to α,β-unsaturated carbonyl compounds has been receiving considerable interest[1] in the synthesis of naturally occurring compounds possessing sequences of consecutive and highly functionalized carbon atoms.[2] Thus, a great deal of effort has been expended in the development of methods for new asymmetric induction employing chiral Michael acceptors.[3] Recently, Fleming has revealed that silylcuprate reagents undergo the conjugate addition with γ-substituted-α,β-unsaturated δ-lactones to afford the products bearing trans-relationship at β-position with respect to the γ-substituent.[4] In the preceding paper,[5] we reported that the Gilman reagents added to γ-amino-α,β-unsaturated carbonyl compounds to furnish trans-adducts predominantly. In this communication we describe Michael reactions of S-γ-heterosubstituted-α,β-unsaturated δ-lactones (4) with organometallic reagents and demonstrate the δ-lactone (4a) to be a useful chiral unit for the asymmetric synthesis of lignan lactones.

Chiral γ-aminosubstituted-α,β-unsaturated δ-lactone (4a; $[\alpha]_D^{22}$+112°(c 2.10, $CHCl_3$)), one of the crucial intermediates, was synthesized from γ-ethyl L-glutamate (1a) through the olefination of saturated δ-lactone (3; $[\alpha]_D^{21}$-38.4°(c 2.28, $CHCl_3$))[5,6] as shown in path A in Scheme 1. Preparation of the chiral S-γ-benzyloxy δ-lactone (4b; $[\alpha]_D^{21}$+135.0°(c 1.04, MeOH))[7] was also performed by sequential treatment of the known hydroxy lactone (5)[8] with several reagents followed by the same type of olefination of saturated δ-lactone (7; $[\alpha]_D^{21}$-33.3°(c 1.19, MeOH)) as indicated in path B.



Scheme 1

Reactions of 4 with various organometallic reagents were examined and the results are listed in Table 1. With Grignard reagents 4a afforded the trans-(βR,γS)-adducts with extremely high diastereoselectivity[9] in ether (entry 1) compared with 4b (entry 2), although the ratio was improved by the addition of the excess of TMSCl in the latter case (entry 8). The cuprate reagents were proved to give excellent trans-selectivity for both chiral substrates (entry 3-6).[11] When the reactions of cuprate addition were carried out in the presence of Me_3SiCl,[12,13] the rate of reactions was greatly enhanced (entry 9-11). Analogous results were obtained for the reactions[6a] of 4a with the anions of phenylthioethers prepared with lithium diisopropylamide in THF and the trans-products were produced predominantly after desulfurization reaction (entry 12,13).

As an application of the reaction described herein, synthesis of (-)-hinokinin (19)[14] known to exhibit antileukemic and cytotoxic activities was achieved as shown in Scheme 2. Thus, treatment of 11a with Bu_3SnH afforded (13; 68%, $[\alpha]_D^{22}$-26.1°(c 2.03, $CHCl_3$)), which was subjected to a ring-opening and deprotection reaction to give unstable aminoalcohol (15) in high yield. Conversion of 15 into (-)-hinokinin (19) was accomplished by the following sequence of reactions: (1) oxidative cleavage of 15 with $NaIO_4$, (2) reduction of the resulting aldehyde 16 to the alcohol 17 ($[\alpha]_D^{19}$-28.0°(c 2.15, $CHCl_3$)), (3) cyclization of 17 to the γ-lactone 18 ($[\alpha]_D^{22}$+5.02°(c 1.07, $CHCl_3$), lit.[14a] $[\alpha]_D^{20}$+5.22°(c 1.13, $CHCl_3$)), and (4) stereoselective introduction of piperonyl group at α-position of the lactone ring. The spectral data of 19 ($[\alpha]_D^{22}$-35.0°(c 1.72, $CHCl_3$)) obtained was identical in all respects with those of reported (-)-hinokinin.[14]

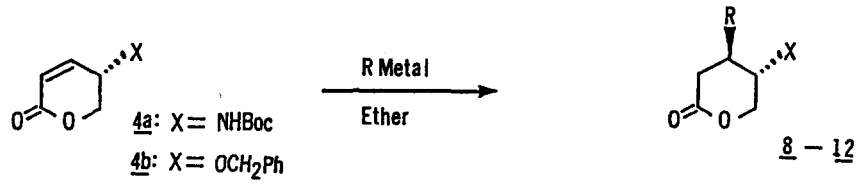
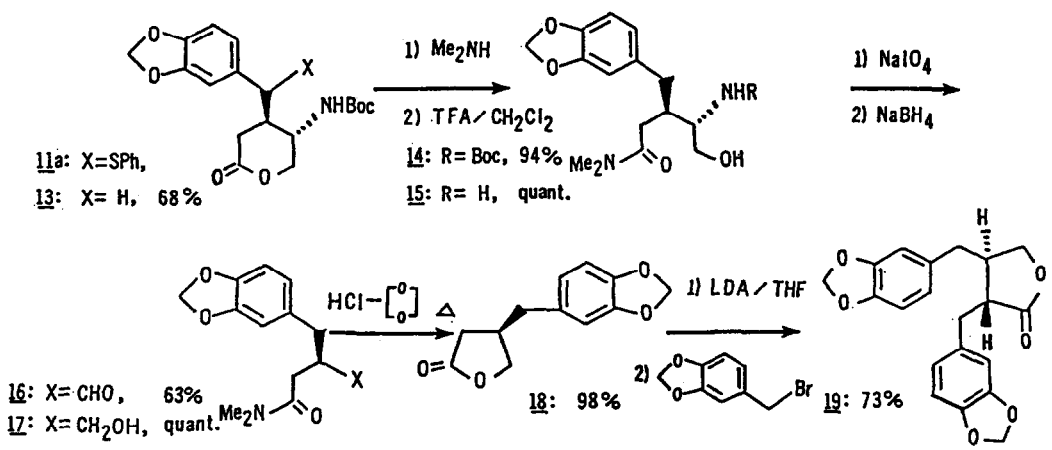


Table 1. Conjugate Addition of Organometallic Reagents to Chiral δ-Lactones (4)

Entry	Substrate	RM[a]	Temp/°C (Time/h)	Yield of (8)-(12)/%[b]	trans:cis ([R,S]:[S,S])[c]	$[\alpha]_D$,deg (Temp(°C),c)
1	4a	PrMgBr(cat.CuI)	-78(3)	41(8a)	>99:1	-69.9(21,2.60)[d]
2	4b	PrMgBr(cat.CuI)	-78(3)	43(8b)	64:36	-41.1(22,2.42)[e]
3	4a	$(CH_3)_2CuLi$[f]	-78(2)	42(9a)	>99:1	-46.8(23,1.56)[e]
4	4b	$(CH_3)_2CuLi$[f]	-78-0(7)	26(9b)	95:5	+58.2(21,0.66)[d]
5	4a	Bu_2CuLi[f]	-78(2)	52(10a)	>99:1	-50.0(20,0.93)[d]
6	4b	Bu_2CuLi[f]	-78(1)	14(10b)	>99:1	-45.6(20,1.20)[e]
7	4a	PrMgBr(cat.CuI)[g]	-78(2)	42(8a)	>99:1	-69.4(21,1.23)[d]
8	4b	PrMgBr(cat.CuI)[g]	-78(6)	44(8b)	71:29	-54.6(21,2.70)[e]
9	4a	$(CH_3)_2CuLi$[f,g]	-78(2)	73(9a)	>99:1	-46.6(22,0.87)[e]
10	4a	Bu_2CuLi[f,g]	-78(2)	75(10a)	>99:1	-51.2(19,1.03)[e]
11	4b	Bu_2CuLi[f,g]	-78(1)	54(10b)	>99:1	-44.3(20,1.43)[e]
12	4a	PhS-CH(OCH3)-C6H3(O2CH2)	-78(1.5)	58(11a)	>99:1	-26.1(22,2.03)[e,h]
13	4a	PhS-CH(OCH3)-C6H3(O2CH2)	-78(1.5)	70(12a)	94:6	-21.7(21,1.46)[e,h]

a) 2-5 equiv. of reagents was used. b) Isolated yield. c) Determined by ^{13}C NMR and HPLC analyses.[10] d) Measured in MeOH. e) Measured in $CHCl_3$. f) Prepared from RLi and CuI. g) In the presence of TMSCl (5 equiv.). h) Measured after desulfurization reaction with Bu_3SnH.



Scheme 2

(-)-hinokinin

Acknowledgment: This work was partly supported by a Grant-in-Aid from the Ministry of Education, Culture and Science (No. 63740282).

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(Received in Japan 15 October 1990)