Remote Chirality Control in 1,2-Asymmetric Induction: a Remarkable Difference between the *meso*- and (±)-Isomers of Dimethylglutaric Hemialdehyde

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The Lewis acid mediated reaction of the *meso*-dimethylglutaric hemialdehyde (**2**) with pent-3-en-2-yltributyltin (**1**) gave the anti-Cram *erythro* isomer (**4**) predominantly, while the reaction of the (±)-isomer (**3**) produced the Cram *erythro* derivative (**5**) preferentially.

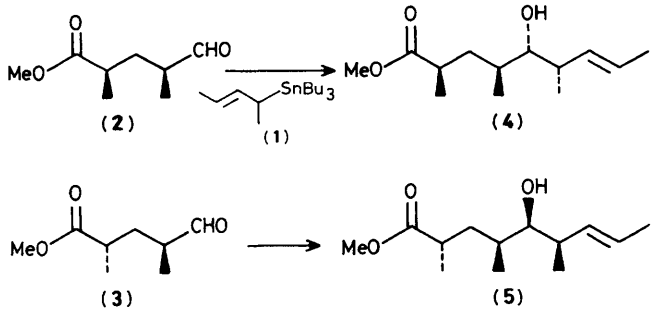
It is generally accepted that asymmetric induction in the reaction of aldehydes bearing multi-chiral centres with nucleophiles is dictated primarily by the geometry of the nearest chiral centre to the carbonyl group.[1] For example, 1,2-asymmetric induction is controlled in this way, and the generalization is given by Cram, Karabatsos, and Felkin models. We report the surprising stereochemical behaviour in the Lewis acid mediated reaction of pent-3-en-2-yltributyltin (**1**) with dimethylglutaric hemialdehydes (**2**) and (**3**); (**2**) (*meso*) produces the anti-Cram *erythro* isomer (**4**) predominantly, while (**3**) (±) gives the Cram *erythro* isomer (**5**) preferentially. The results are summarized in Table 1.

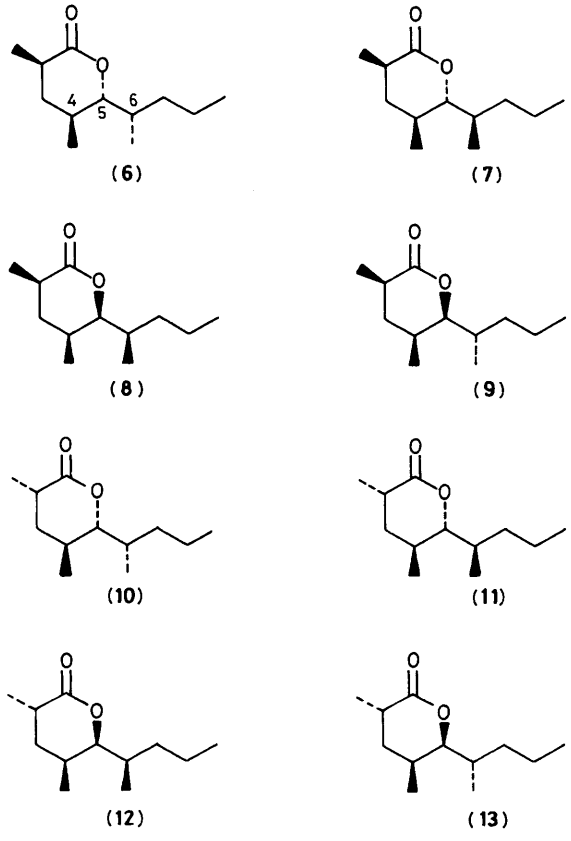
To a dry CH_2Cl_2 solution of (**2**) [or (**3**)] cooled to −78 °C

Table 1. Reactions of (**1**) with (**2**) and (**3**).[a]

Entry	Aldehyde	Lewis acid (equiv.)	Product ratio: anti-Cram *erythro*	anti-Cram *threo*	Cram *erythro*	Cram *threo*	Cram/anti-Cram	*erythro*/*threo*
	(**2**)		(**6**)	(**7**)	(**8**)	(**9**)		
1		$BF_3 \cdot OEt_2$ (1)	83	7	10	—	10/90	93/7
2		$BF_3 \cdot OEt_2$ (2)	58	7	35	—	35/65	93/7
3		$BF_3 \cdot OEt_2$ (3)	41	9	50	—	50/50	91/9
4		$TiCl_4$ (1)	89	11	—	—	—/100	89/11
5		$TiCl_4$[b] (2)	12	88	—	—	—/100	11/88
6		[c]	10	54	6	30	64/36	16/84
	(**3**)		(**10**)	(**11**)	(**12**)	(**13**)		
7		$BF_3 \cdot OEt_2$ (1)	20	—	77	3	80/20	97/3
8		$BF_3 \cdot OEt_2$ (2)	24	—	73	3	76/24	97/3
9		$BF_3 \cdot OEt_2$ (3)	19	2	76	3	79/21	95/5
10		$TiCl_4$(1)	7	—	86	7	93/7	93/7
11		$TiCl_4$[b] (2)	—	53	5	42	47/53	5/95

[a] All reactions were carried out on 1 mmol scale under N_2. The isomer ratio was determined by ^{13}C and ^1H n.m.r. analyses of the crude mixture. [b] Inverse addition, addition of aldehyde to a solution prepared from (**1**) and $TiCl_4$, was employed according to Keck's procedure (ref. 3). [c] Pent-3-en-2-ylbis(cyclopentadienyl)ZrCl reagent was used, which was prepared *in situ* from pent-3-en-2-ylmagnesium chloride and $(\eta^5\text{-}C_5H_5)_2ZrCl_2$; Y. Yamamoto and K. Maruyama, *Tetrahedron Lett.*, 1981, 2895.



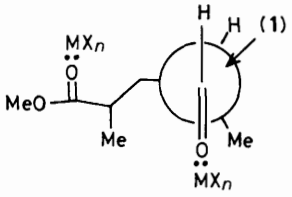


was added the Lewis acid and the mixture was stirred for a few minutes. Subsequently, (**1**) was added and the mixture was stirred for 2 h at this temperature. The reaction was quenched with water at 0 °C, and $BF_3 \cdot OEt_2$ (2 equiv.) was added. The mixture was stirred for 2 h at room temperature. The usual work-up gave the lactone derivatives, which were hydrogenated over Pd–C catalyst. (±)-Invictolide and its epimers (**6**)—(**13**) were isolated in yields of 80 to 90% for entries 1—3 and 7—9, or in yields of 70 to 80% for entries 4—6, 10, and 11.

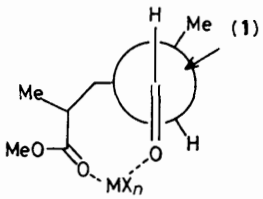
The normal Lewis acid mediated reaction of (**2**) produced (**6**) predominantly (entries 1 and 4), as expected from our previous observations.[2] Here again, increase of $BF_3 \cdot OEt_2$ caused decrease of the stereoselectivity (entries 2 and 3). The inverse addition[3] of $TiCl_4$ gave (**7**) predominantly (entry 5), indicating that the allylic titanium intermediate is involved as suggested by Keck.[3] The reaction of the zirconium derivative resulted in low diastereoselectivity (entry 6). On the other hand, the normal reaction of (**3**) produced (**12**) preferentially (entries 7 and 10). The Cram *erythro* selectivity was not influenced by the increase of $BF_3 \cdot OEt_2$ (entries 7—9). The inverse addition produced high *threo* selectivity, but resulted in low Cram/anti-Cram selectivity (entry 11).

The structures of diastereoisomers were determined as follows. ^1H n.m.r. data of (**6**) and (**10**) were provided by Rocca[4] and compared with our data: (**6**) ($CDCl_3$, 400 MHz) J_{5H-4H} 10.1 and J_{5H-6H} 1.4 Hz; (**10**) ($CDCl_3$, 400 MHz) J_{5H-4H} 10.1 and J_{5H-6H} 1.5 Hz. The structures of (**8**) and (**12**) were determined by 400 MHz ^1H n.m.r. spectra: (**8**) ($CDCl_3$) J_{5H-4H} 2.7 and J_{5H-6H} 9.8 Hz; (**12**) ($CDCl_3$) J_{5H-4H} 2.6 and J_{5H-6H} 9.8 Hz. The *erythro* conformation of these derivatives was assigned by the inherent characteristic of the Sn reagent.[2] The structures of (**7**), (**9**), (**11**), and (**13**) could not be determined unambiguously, but were assigned by an analogy between the present reaction and the Prelog–Djerassi lactone synthesis.[2a,5]

The drastic stereochemical difference exhibited between (**2**) and (**3**) is explained as follows; however it is highly speculative. The fact that the Cram *erythro* selectivity in the reaction



(A)



(B)

of (**3**) does not depend upon the amount of $BF_3{\cdot}OEt_2$ suggests a non-chelation transition state model (A).[6] The anti-Cram *erythro* selectivity *via* (**2**) is a reflection of a chelation eight-membered transition state (B), as proposed previously.[2,5] The reason why chelation can occur in (**2**) but (**3**) can not take such a cyclic structure is not clear. The conformational stability of eight-membered rings might play an important role in this difference.[7] Regardless of the precise mechanism, the present result provides an interesting example of remote chirality control (1,4-position) in the 1,2-asymmetric induction.

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