

Towards the Synthesis of the Side Chains of Brassinolides: Diastereodivergent Alkoxyaldehyde–Ene Reaction and Nickel-catalysed Transformation of Vinyl Sulfide

Koichi Mikami* and Shu-ichi Sakuda

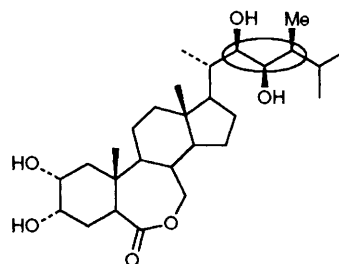
Department of Chemical Technology, Tokyo Institute of Technology, Meguro-ku, Tokyo 152, Japan

Chelation(SnCl_4)-controlled carbonyl–ene reaction of 2-benzyloxypropionaldehyde with vinyl sulfides is shown to provide a stereodivergent route to chelation-*erythro* and -*threo* diastereoisomers of steroid (brassinolide) side chains *via* the nickel-catalysed coupling reaction of the vinyl sulfide products.

In continuation of our research project directed towards the synthesis of the side chain of the plant growth promoting steroidal hormone, brassinolide,^{1,2} we report a stereodivergent route to either chelation-*erythro* or -*threo*-diastereoisomer based on the carbonyl–ene reaction³ of an α -alkoxy aldehyde with vinylic sulfides⁴ as the ene components, and an efficient transformation of the vinyl sulfide products to the side chain unit of brassinolide *via* a nickel-catalysed coupling reaction⁵ (Scheme 1).

Table 1 summarizes representative results of the chelation-controlled⁶ carbonyl–ene reaction of the α -benzyloxy aldehyde **1** with vinylic sulfides **2** (Table 1).[†] The ene reaction of the aldehyde **1** provides exclusively a high level (>99%) of

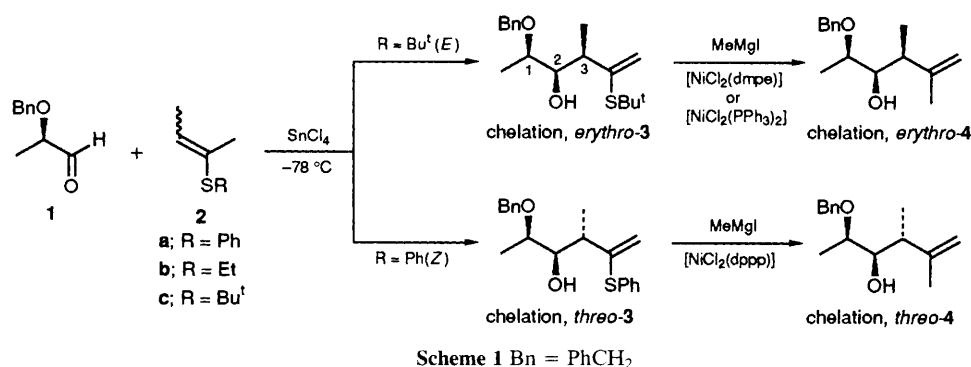
1,2-*syn* (chelation) diastereofacial selectivity on using SnCl_4 [‡] (entries 1–11). Of particular interest is the fact that the degree



Brassinolide

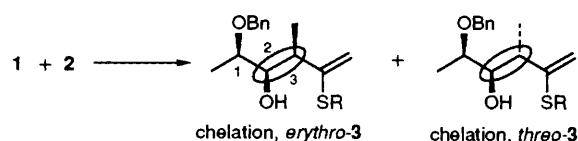
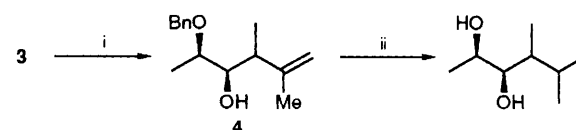
[†] The stereoisomeric ratios of the carbonyl–ene products were determined by capillary GLC analysis (see refs. 2*f*, *g*).

[‡] For the use of this specific Lewis acid for efficient chelation control in the ene reaction and allylmetal reactions with alkoxyaldehydes, see refs. 2*f*, *g*.

**Table 1** Carbonyl-ene reaction of **1** with **2**^a (Scheme 2)

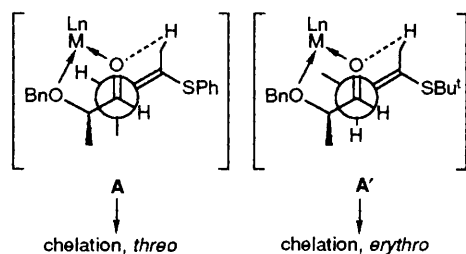
Entry	2 (R)	E/Z	equiv.	3 (% Yield)	erythro:threo
1	Ph	81% E	1.2	89	21:79
2	Ph	57% Z	1.2	79	9:91
3	Ph	>99% Z	1.5	82	4:96
4	Et	>99% Z	1.4	93	9:91
5	Et	>99% E	1.3	79	65:35
6	Et	>99% E	0.8	44	62:38
7	Bu ^t	>99% Z	1.1	55	13:87
8	Bu ^t	>99% E	1.2	87	80:20
9	Bu ^t	>99% E	1.0	61	98:2
10 ^b	Bu ^t	>99% E	1.0	95	93:7
11 ^{b,c}	Bu ^t	>99% E	1.0	97	94:6

^a Unless otherwise noted, **2** was added to a CH₂Cl₂ solution of **1** and SnCl₄ at -78 °C. ^b Toluene was used for reproducibility. ^c In the presence of 4 Å molecular sieves.

**Scheme 2** Reagents and conditions: SnCl₄ (1 equiv.), -78 °C**Scheme 3** Reagents and conditions: i, MeMgI (3 equiv.), catalyst (5 mol. %), benzene; ii, Na-hexamethylphosphoric triamide; Bu^tOH-tetrahydrofuran (quantitative)**Table 2** Nickel-catalysed coupling reaction of **3** with MeMgI^a (Scheme 3)

Entry	3 (R)	Catalyst ^b	4 (% Yield)
1 ^c	Et	[NiCl ₂ (dppp)]	65
2 ^c	Ph	[NiCl ₂ (dppp)]	64
3 ^d	Bu ^t	[NiCl ₂ (dppp)]	Trace
4 ^d	Bu ^t	[NiCl ₂ (dmpe)]	54
5 ^d	Bu ^t	[NiCl ₂ (PPh ₃) ₂]	68

^a In hot benzene. ^b dppp = 1,3-bis(diphenylphosphino)propane; dmpe = 1,2-bis(dimethylphosphino)ethane. ^c *threo*-3. ^d *erythro*-3.



and sense of 2,3-simple diastereoselection (*erythro* vs. *threo*) depend critically not only on the geometry but also the steric bulk of the vinyl sulfides **2**. The 2,3-*threo* diastereoisomer is obtained mainly with (*Z*)-vinyl sulfides (entries 1–4), and a remarkably high level of 2,3-*threo* diastereoselectivity is attained with geometrically pure phenyl sulfide (>99% *Z*) (entry 3). In contrast, the 2,3-*erythro* diastereoisomer is obtained with (*E*)-vinyl sulfide (entries 5, 6, 8–11). An unprecedentedly high level of 2,3-*erythro* selectivity is established with the sterically bulky *tert*-butyl sulfide (>99% *E*) in comparison with the ethyl sulfide (entries 9–11).

This diastereodivergent process is of interest not only from synthetic but also from mechanistic viewpoints. The *anti*-diastereoselection observed for the (*Z*)-vinyl sulfide is evidence of the chelation synclinal transition state for the *trans*-ene [(*Z*)-vinyl sulfide] component (**A**).^{2f,g,7} In contrast, the *syn*-diastereoselection implies a different chelation synclinal transition state for the *cis*-ene [(*E*)-vinyl sulfide] component (**A'**). The former transition state conformation would be sterically more favourable than the latter, because the alkoxyaldehyde-ene reaction with 2-methylbut-2-ene^{2f}

(SnCl₄) afforded the chelation-*threo* diastereoisomer despite the '*cis*-effect'.⁸ These two transition state conformations (**A** and **A'**) are diastereo-complementary and hence are components of a divergent route to give chelation-*threo* and -*erythro* diastereoisomers, respectively.

We then examined the nickel-catalysed transformation of the vinyl sulfide products **3** to the side chain unit of brassinolide (Table 2). The chelation-*threo* and -*erythro* diastereoisomers can be converted to the corresponding methylated product **4**^{2g} by the judicious choice of nickel catalyst (entries 2, 4 and 5). The coupling reaction of the *threo*-phenyl sulfide with methylmagnesium iodide was accomplished by using the commercially available [NiCl₂(dppp)] to give eventually the 24-*epi*-brassinolide^{1a,2f,g,9} side chain unit (entry 2) *via* the reductive cleavage of the benzyl group.¹⁰ A similar coupling reaction of the sterically demanding *erythro-tert*-butyl sulfide was found to proceed in reasonable yield with the sterically less demanding [NiCl₂(PPh₃)₂] or [NiCl₂(dmpe)]^{5g} and hence completes the

synthetic route to the side chain unit of brassinolide (entries 4 and 5).

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