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A STEREOSELECTIVE SYNTHESIS OF (Z)-α,β-DISUBSTITUTED ACRYLATES

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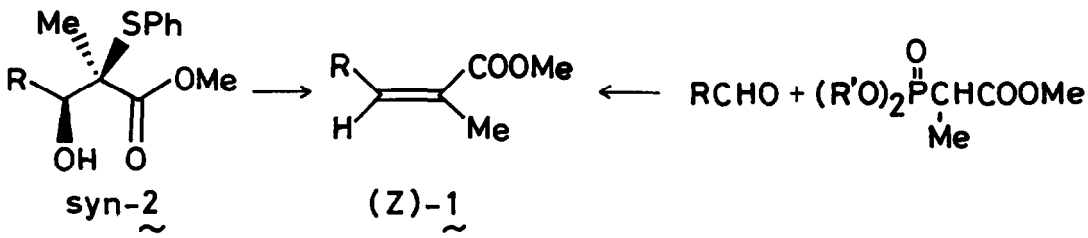
Summary : A new route for (Z)-α,β-disubstituted acrylate is described which is made up of 1) stereoselective reduction of ketones **3** and 2) conversion of the resulting syn-**2** into (Z)-**1**.

Developement of a stereoselective method for the synthesis of (Z)-α,β-disubstituted acrylate **1** has attracted considerable attention, since the Wittig type reaction proceeding through stabilized ylides prefer to afford the more stable (E)-isomer. Recently, it was reported that the long-desired (Z)-isomer could be synthesized effectively by the Horner-Emmons reaction provided phosphonoester reagent was properly designed.[1] However, in view of the importance of these moieties in natural product synthesis, it seemed worthwhile to explore another practical approach. We now report that (Z)-**1** could be synthesized effectively by the sequence 1) stereoselective synthesis of syn-β-hydroxy-α-phenylthio esters and 2) trans elimination of SPh and OH groups from the resultant esters.



2-Fluoropyridinium salt-LiI promoted elimination of β-phenylthio alcohols (R^1-CH(OH)-CH(SPh)-R^2) has been reported by Mukaiyama and Imaoka to proceed stereoselectively to give (Z)- and (E)-olefins from syn- and anti-isomers, respectively.[2] The validity of this unique procedure was proved by Hoye and Kurth in their approach to dl-aplysistatin synthesis.[3] However, there is a problem in the synthesis of the starting syn-**2** in this route. The aldol condensation has been adopted for this purpose, but the syn-selectivity is reported to be unsatisfactory (syn/anti=1/1-100).[3] Therefore, development of a new stereoselective method for the synthesis of syn-isomer **2** is essential for this trans-elimination procedure being a practical method for the synthesis of the desired (Z)-**1**.

On the basis of our previous experience for stereoselective reduction of ketones having functional groups on the α- or β-positions,[4] we intended to synthesize syn-**2** by the metal hydride reduction of the corresponding ketones. Among several metal hydrides tested, $Ca(BH_4)_2$-MeOH/THF (5:1) was found to be a reagent of choice. The results were shown in Table I. syn-Selectivity was excellent in most cases (entry 1-9 except 2) when R are aryl, alkenyl

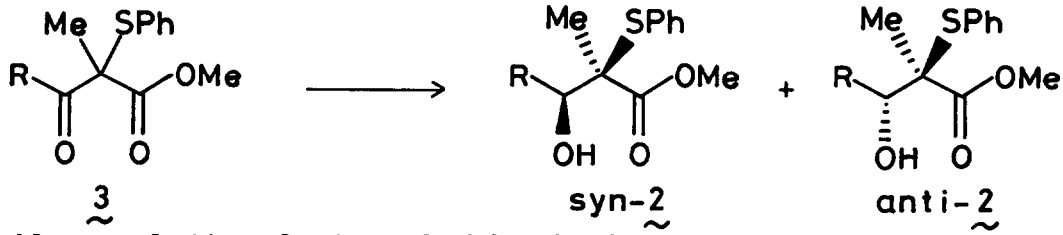


Table I. Reduction of Ketones 3 with $Ca(BH_4)_2$ in MeOH-THF (12:1)

Entry		R	syn-2 : anti-2[a]	(Yield)[b]	Entry		R	syn-2 : anti-2	(Yield)
1	**3a**	Ph	98 : 2	(92 %)	7	**3g**	i-Pr	>99 : 1	(80 %)
2	**b**	PhCH=CH	88 : 12	(87)	8	**h**	$c\text{-}C_6H_{11}$	>99 : 1	(90)
3	**c**	$n\text{-}C_3H_7CH=CH$	93 : 7	(90)	9	**i**	$TrOCH_2$	97 : 3	(84)[c]
4	**d**	$PhCH_2CH_2$	95 : 5	(83)	10	**j**	$BnOCH_2$	50 : 50	(50)[c]
5	**e**	$n\text{-}C_7H_{15}$	96 : 4	(82)	11	**k**	EtO_2C	2 : 98	(43)
6	**f**	$c\text{-}C_6H_{11}CH_2$	>99 : 1	(93)					

a. The ratio was determined by 400 MHz NMR.
b. Combined yield of syn- and anti-**2**. syn- and anti-**2** could be separated by preparative TLC (silica gel) except entry 11.
c. Reductions were carried out in CH_2Cl_2-THF (12:1).

or alkyl groups. Even in the case where R involved an oxygen function, excellent syn-selectivity was obtained, provided its coordinating function was masked with trityl group (entry 9). These results show that a variety of syn-**2** can be synthesized by the $Ca(BH_4)_2$ reduction of ketone **3**. However, no reasonable explanation to account for this high syn-selectivity can be offered at the present time.[5] $Zn(BH_4)_2$ gave only a fair to poor syn-selectivity when the substrates were **3a-k**.[6] It was striking that when R was ethoxycarbonyl group having a strong coordinating ability to the metal cation, anti-**2k** was obtained with high selectivity.[7] anti-Selectivity was also observed in the reduction of benzyloxymethyl ketone **3j**, as well as keto ester **3k**, with Super-Hydride (syn-**3j**/anti-**3j**=5/95; syn-**3k**/anti-**3k**=1/>99).

Then, conversion of syn-**2** into (Z)-acrylate **1** by Mukaiyama's method[2] was carried out. In our cases, the sterically less demanding N-methyl-2-fluoropyridinium salt was more effective than the originally used N-ethyl derivative in promoting the reaction, which may be attributable to the structural feature of the substrates that the hydroxyl group to be activated is sterically conjested. Moreover, in most cases, the use of $LiI\cdot 3H_2O$ in place of anhydrous one gave better yields. Results are shown in Table II.

When R was PhCH=CH group, the thermodynamically more stable (E)-isomer **1** was obtained as a major product, which showed that epimerization took place during the reaction facilitated by

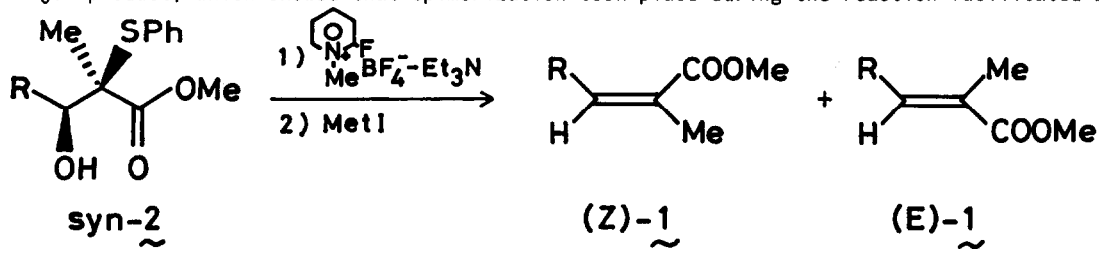


Table II. Conversion of syn-2 into Olefins 1

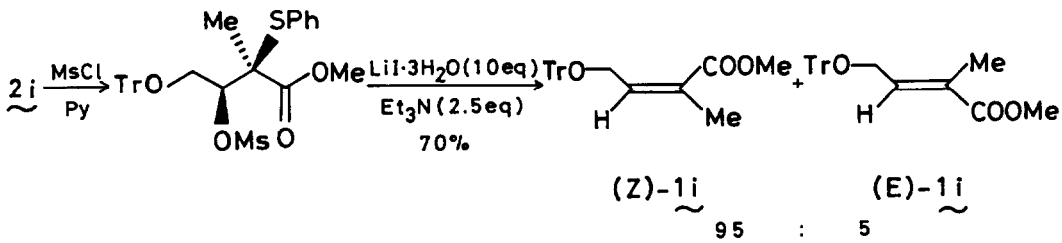
	R	Reagents	Products (Z)-1 : (E)-1[a]	Yield (%)[b]
2a	Ph	$LiI \cdot 3H_2O$	97 : 3	81
b	PhCH=CH	$LiI \cdot 3H_2O$	32 : 68	78
d	$PhCH_2CH_2$	LiI	95 : 5	78
d	$PhCH_2CH_2$	NaI	98 : 2	76
e	$n\text{-}C_7H_{15}$	$LiI \cdot 3H_2O$	98 : 2	56[c]

a. The ratio was determined by 400 MHz NMR.

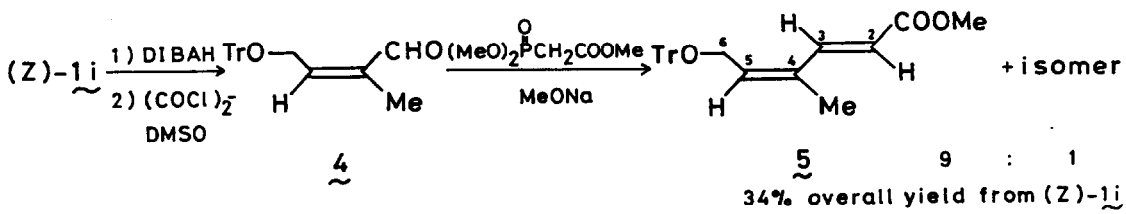
b. Combined yield of (Z)- and (E)-**1**.

c. Yield of the corresponding alcohols ($LiAlH_4$/ether).

the presence of the double bond. It should be noted that when R was a trityloxymethyl group, both of the selectivity and the yield decreased appreciably (syn/anti=86/14, 31% yield). However, this difficulty could be overcome by the revision of reagents and conditions: namely, when activation of the hydroxyl group in syn-**2i** was achieved by simple mesylation and the successive trans-elimination was conducted in the presence of a large excess of $LiI \cdot 3H_2O$ (10 eq)-Et_3N (2.5 eq) in acetone, (Z)-**1i** was obtained preferentially (Z/E=95/5, 70% yield). It should be emphasized that by the above modification the scope of the present method could be extended to the synthesis of the functionalized (Z)-acrylates which may serve as a useful synthon for natural product synthesis but are difficult to be accessible by other means.



Finally, 6-trityloxy-(2E,4Z)-2,4-hexadienoic ester **5** which corresponds to a central part of methyl trisporate B[8] was synthesized starting from (Z)-**1i** by the sequence shown below. The stereostructure of **5** was rigorously determined by carrying out NOE experiment extensively.[9] The above synthesis demonstrates the high utility of (Z)-**1i** or its analogous as a functionalized synthon for natural product synthesis.



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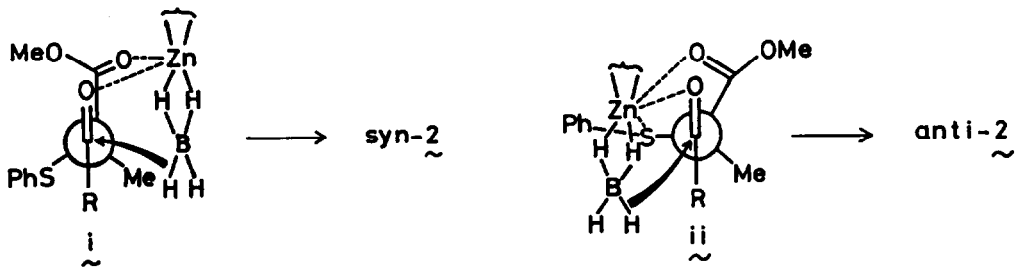
5. Mechanism of ketone reduction by metal borohydrides is known to be heavily influenced by the composition of the reagents and the solvents used. The composition of $Zn(BH_4)_2$ in diethyl ether have been suggested to be a contact ion pairs or its aggregates. On the other hand, the composition of $NaBH_4$ in MeOH is complicated and the linear transiton state where Na^+ is not participating is suggested. However, as far as we know, the composition of $Ca(BH_4)_2$ has not been discussed so far. In particular, the reduction proceeded with excellent syn-selectivity even when methanol was used as a solvent, which makes the mechanism of the present reduction much more difficult than other cases.
6. In the $Zn(BH_4)_2$ reduction, the reduction is supposed to proceed through the zinc-mediated cyclic transition state **i** where the reagent is mainly on the less hindered methyl side. However, participation of a SPh group to the reagent cannot be ignored[4a] in the present case (see **ii**).[cf. 5] From **ii**, undesirable anti-products will be produced causing the decrease of syn-selectivity.



i ii

7. Participation of the third carbonyl oxygen may serve to stabilize the transition state. However, by the reasons noted in reference 5, further discussions should be awaited until direct evidence for the composition of $Ca(BH_4)_2$ is offered.
8. W. Oppolzer and V. Prelog, Helv. Chim. Acta, **56**, 2287 (1973); M. Brufani, W. Fedeli, G. Giocomello, and A. Vaciago, Experiencia, **20**, 339 (1964).
9. (2E,4Z)-**5**; $J_{2,3}$=15Hz. Irradiation at C_4-Me; 16% (H-2) and 14% (H-5) enhancement. Irradiation at C_6-CH_2; 23% (H-3) and 11% (H-5) enhancement.

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