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Highly Stereoselective Synthesis of Tetrasubstituted Alkenes via [2,3]-Wittig Rearrangement

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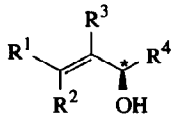
Abstract: A highly stereoselective synthesis of tetrasubstituted alkenes via the sequence Horner-Wadsworth-Emmons-, Grignard- and [2,3]-Wittig reaction is described, eight examples are given.

Despite the wealth of alkene syntheses there is so far no general stereoselective procedure for preparing *tetrasubstituted* olefins[1], especially in form of the synthetic valuable allylic alcohols **1**[2].



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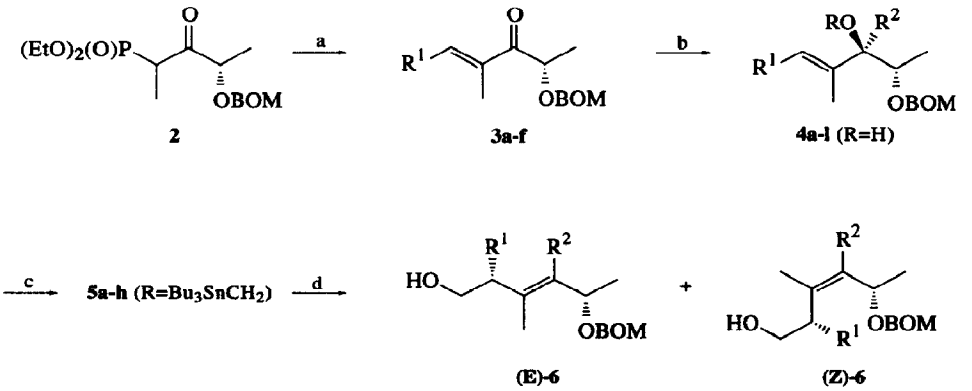
We describe here a highly (E)-stereoselective route[3] which is based on a [2,3]-Wittig-Still rearrangement[4-5] of chiral tertiary allyl stannylmethyl ethers **5**. These were prepared in a *connective* manner from β-keto phosphonate **2**[6] and aldehydes R^1CHO via Horner-Wadsworth-Emmons reaction to the enones **3**, followed by a chelation-controlled Grignard addition giving the tertiary allylic alcohols **4** which were alkylated with iodomethyltributyl tin[7]. The stannylmethyl ethers **5** were transmetallated with n-BuLi at low temperatures to form the olefins **6** (*Scheme 1*). All stereodifferentiating reactions in *Scheme 1* typically proceed with stereoselectivities *>95%*.

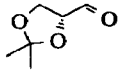


a) R^1CHO, base; b) R^2M, THF, -78°C; c) KH, Bu_3SnCH_2I, THF/DMPU, RT; d) n-BuLi

Scheme 1

The yields of the Horner-Wadsworth-Emmons reactions (**2** → **3**) (*Table 1*) range from fair to very good, the E/Z selectivities are generally high.

Table 1: Horner-Wadsworth-Emmons reactions with β-ketophosphonate **2**

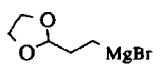
Enone	R^1CHO	Base, Sol., Temp.	Yield (E/Z)[a]
3a	MeCHO	$LiOH{\cdot}H_2O$[8], THF, RT	65% (97:3)
3b	EtCHO	$LiOH{\cdot}H_2O$, THF, RT	72% (97:3)
3c	PhCHO	$LiOH{\cdot}H_2O$, THF, RT	86% (>99:1)
3d	$BnOCH_2CH_2CHO$	KH, THF, 0°C	52% (>99:1)
3e	$BnOCH_2CH_2CH_2CHO$	$Ba(OH)_2{\cdot}8H_2O$[9], THF/H_2O, RT	88% (>99:1)[b]
3f		$LiOH{\cdot}H_2O$, THF, RT	80% (95:5)

a) via ^{1}H-NMR of the isolated isomers; b) the enantiomeric phosphonate ent-**2** was used in this case.

In our hands the new variants of the Horner-Wadsworth-Emmons reaction with lithium[8]- or barium hydroxide[9] turned out to be ideal, whereas other methods (e.g. LDA, NaH, LiCl/DBU) gave unsatisfactory results.

The results of the Grignard reactions (**3** → **4**) are shown in *Table 2*:

Table 2: Grignard additions to enones **3** (THF, -78°C)

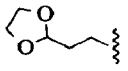
Alcohol	R^1	R^2M	Yield, (de)[a]
4a	Me	MeMgCl	87% (>98%)
4b	Me	VinylMgCl	81% (>98%)
4c	Me	AllylMgCl	90% (23%)
4d	Et	$PhC{\equiv}CMgCl$	90% (>98%)
4e	Et	PhMgCl	95% (>98%)
4f	Ph	MeMgCl	88% (>98%)
4g	$BnOCH_2CH_2$	EtMgBr	91% (>98%)[b]
4h	$BnOCH_2CH_2CH_2$[c]	MeLi	64% (35%)
4h	$BnOCH_2CH_2CH_2$[c]	$MeCeCl_2$[10]	45% [d](60%)
4h	$BnOCH_2CH_2CH_2$[c]	MeMgCl	92% (>98%)
4i	$BnOCH_2CH_2CH_2$[c]	EtMgBr	92% (>98%)
4j	$BnOCH_2CH_2CH_2$[c]	LAH (Et_2O, -10°C)	94% (>98%)
4k		EtMgBr	62%[e] (>98%)
4l			92% (>98%)

[a] via ^{1}H-NMR; [b] de = 80% at -5°C; [c] the (*R*)-enone was used; [d] + 40% recovered starting material; [e] + 20% 1,4-product[11]

All Grignard reactions except the one leading to **4c** proceed with *>98%* asymmetric induction to give the *anti* tertiary allylic alcohols in very good yields. This high selectivity which can be explained in terms of the "chelate-Cram model"[12] is well known[13] for BOM and MOM protected α-hydroxyketones and -aldehydes.

Yields and stereoselectivities of the [2,3]-rearrangement are generally high except for **6c** (*Table 3*). The lacking stereoselectivity in this case may be due to the different electronic and/or steric properties of the phenyl substituent.

Table 3: Alkylation to- and [2,3]-Wittig rearrangement of tributylstannyl methyl ether **5**

Compounds	R^1	R^2	Yield of **5**	Yield of **6**	Conditions	(E)-**6** : (Z)-**6**[a]
5a, 6a[17]	Me	Me	85%	94%	THF, -78°C	>99:1
5b, 6b	Ph	Me	78%	98%	THF, -78°C	95:5
5c, 6c	Et	Ph	90%	96%	THF, -100°C	~50:50
5d, 6d	$BnOCH_2CH_2$	Et	81%	95%	hexane, -90°	>99:1
5e, 6e	$BnOCH_2CH_2CH_2$[b]	Me	93%	92%	THF, -78°C	>99:1
5f, 6f	$BnOCH_2CH_2CH_2$[b]	Et	77%	87%	hexane, -90°	>99:1[c]
5g, 6g[17]		Et	82%	91%	THF/hexane (1:5), -80°C	97:3
5h, 6h			87%	99%	THF/hexane (1:5), -80°C	97:3

a) via ^{1}H-NOE-difference studies on the isolated pure products; b) the enantiomer was used in this case; c) 75:25 at -78°C in THF.[14]

Allylic alcohol **4b** gave a 4.4 : 1 mixture of dienes (E)-**7** and (Z)-**7** as the only regioisomers:

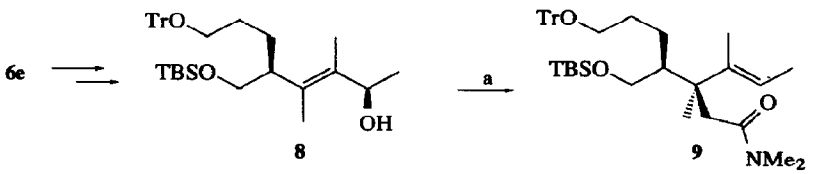
4b **7** (E/Z= 4.4:1)

a) KH, THF/DMPU, Bu_3SnCH_2I; b) n-BuLi, THF/hexane (5:1), -100°C, 86%.

Scheme 2

To our knowledge this reaction represents the first example of a [2,3]-Wittig-Still rearrangement of a diallyl carbinol to a 1,3-diene.

The preparative utility of allylic alcohol derivatives such as **6** lies in the possibility of creating a quaternary stereogenic centre vicinal to a tertiary one, both in stereochemically pure form. Thus allylic alcohol **8**, prepared from **6e**, undergoes a clean and *stereospecific* Eschenmoser-Claisen rearrangement[15] to the corresponding dimethylamide **9** in nearly quantitative yield (*Scheme 3*).

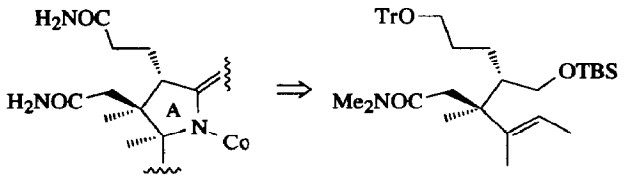


8 **9**

a) Dimethylacetamide dimethylacetal (6eq), toluene, 100°C, 97%.

Scheme 3

Compound **9** is an A-ring precursor in a planned[16] novel synthesis of corbyric acid:



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11. Interestingly this is the only case where the 1,4-product could be detected.

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17. **6a**: $[\alpha]_D^{20}$ = -72.3°, c= 0.70 ($CHCl_3$); **MS** (EI, 80eV, 90°C): m/z= 278 ($M^{+\cdot}$, 1.2%); **^{1}H-NMR** (250MHz, $CDCl_3$, selection): δ = 0.96 (d, *J* = 7.3Hz, 3H); 1.23 (d, *J* = 7.1Hz, 3H); 1.60 (s, 3H); 1.66 (s, 3H); 3.00 (m, 1H); 3.48 (d, *J* = 7.6Hz, 2H); 4.84ppm (q, *J* = 7.1Hz, 1H).

6g: $[\alpha]_D^{20}$ = -133.0°, c= 0.32 ($CHCl_3$); **MS** (EI, 80eV, 150°C): m/z= 378 ($M^{+\cdot}$, 0.1%); **^{1}H-NMR** (250MHz, $CDCl_3$, selection): δ= 1.05 (t, *J* = 7.8Hz, 3H); 1.28 (d, *J* = 7.0Hz, 3H); 2.14 (q, *J* = 7.8Hz, 2H); 3.02 (q, *J* = 7.3Hz, 1H); 3.61 (d, *J* = 7.3Hz,2H); 3.69 (t, *J* = 7.5Hz, 1H); 4.02-4.20 (m, 2H); 4.83ppm (q, *J* = 7.0Hz, 1H).

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