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ß-VINYL-γ-BUTYROLACTONES VIA THE PALLADIUM-CATALYSED REACTION OF VINYL TRIFLATES WITH Z-2-BUTEN-1,4-DIOL

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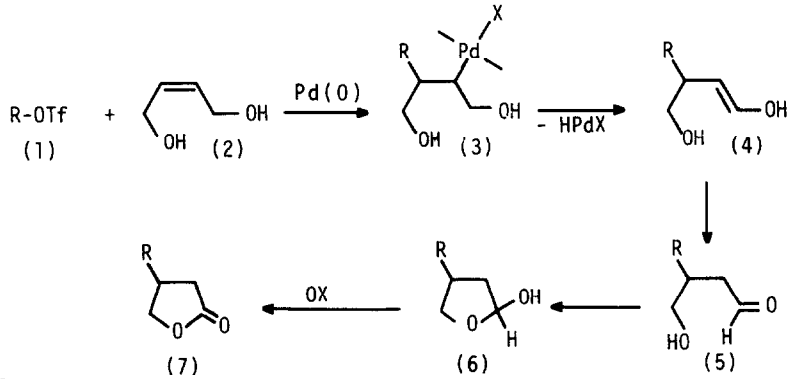
Summary - The palladium-catalysed reaction of vinyl triflates with Z-2-buten-1,4-diol affords ß-vinyl-γ-butyrolactols (4-vinyl-2-hydroxy-tetrahydrofurans) which are converted into the corresponding ß-vinyl-γ-butyrolactones by a smooth oxidation with Ag_2CO_3 on celite. Preparation of ß-substituted-γ-butyrolactones can be performed without the isolation of the intermediate γ-butyrolactols, thus simplifying the procedure and usually with higher overall yields. The outcome of the palladium-catalysed formation of ß-substituted-γ-butyrolactols strongly depends on the nature of the added base. Best results are obtained by using $NaHCO_3$ or K_2CO_3 in the presence of n-Bu_4NCl or TEBA.

A large number of γ-butyrolactones are known as neurologic drugs and show convulsant and anticonvulsant activity depending on the nature of the substituents on the pentaatomic ring.[1] The γ-butyrolactone ring is also part of a number of natural substances[2] and is a useful intermediate in organic synthesis.[2a,3] Because of these reasons a variety of approaches to their synthesis has been published and many of them rely upon palladium chemistry. γ-Butyrolactones have been prepared through palladium-catalysed 1,4-oxy-lactonization of cyclo-2,4-dien-1-yl acetic acids,[4] oxycarbonylation of 4-en-1,3-diols,[5] di-alkoxycarbonylation of 3-en-1-ols,[6] and coupling of vinyl halides or triflates with 3-butenoic acid.[7]

As part of our ongoing interest in the palladium-catalysed synthesis of five-membered oxygen-containing heterocyclic rings[8] and in the palladium chemistry of organic triflates, we decided to investigate the reaction of vinyl triflates (1) with the inexpensive, commercially available Z-2-buten-1,4-diol (2). Based on the successful use of vinyl triflates as vinyl donors in the palladium-catalysed reactions with olefinic systems[9] and on the known behaviour of allylic alcohols in palladium-catalysed reactions with organic halides,[10] we thought the scheme 1 a viable route to ß-alkenyl-γ-butyro-

lactones and attemped to realize it.



R = vinyl

Scheme 1

According to this scheme, the oxygenated four-carbon building block (2) can be considered as a synthetic equivalent of 4-hydroxy-2-butenal and the aldol (5) corresponds to its conjugate addition-type derivative.[11] Subsequent cyclization of (5) to the hemiacetal (6) and oxidation of (6) should give the desired γ-butyrolactone (7).

It is worth noting that ß-substituted-γ-butyrolactols (6) may represent an interesting synthetic target not only on the route to γ-butyrolactones, but also as precursors of substituted tetrahydrofurans. γ-Butyrolactols have been indeed proved to undergo substitution of the hydroxy group by hydride[12] and a variety of carbon nucleophiles.[12d,13] Therefore, in view of the presence of substituted tetrahydrofuran rings as structural units in many natural products,[2a,b] the development of a new entry into this class of compounds may be of wide scope.

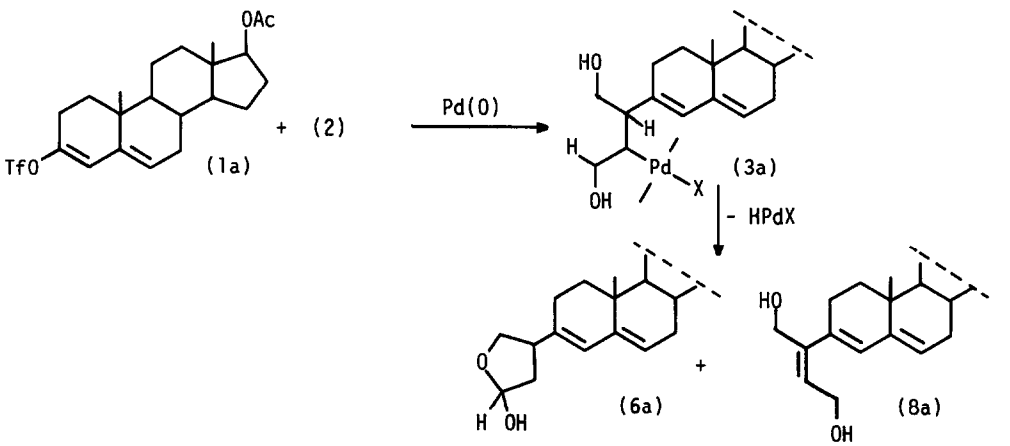
Hereafter we report the results of this study.

Results and Discussion

17-ß-Acetoxy-androsta-3,5-dien-3-yl triflate (1a) was selected as the model system and the preparation of the corresponding γ-butyrolactol (6a) was initially attempted using Et_3N as the base in the presence of catalytic amounts of $Pd(OAc)_2(PPh_3)_2$ in DMF at 60°C. However, only partial conversion of the starting material was observed after 7 h and (6a) was isolated in only 26% yield (compound (1a) was recovered in 33% yield). Even worse, the reaction showed a very low selectivity in the ß-elimination step and the 2-substituted diol (8a)*, derived from "internal" elimination of hydridopalladium species from the

* The configuration of (8a) was assumed to be Z on the ground of the well established syn-relationship between the ß-hydrogen and the palladium which is normally required for the ß-elimination of hydridopalladium species from σ-alkylpalladium complexes.

addition intermediate (3a), was isolated in 21% yield (Table 1, entry 1). The addition of an equimolar amount of n-Bu_4NCl resulted in the recovering of (1a) in 83% yield (Table 1, entry 2). Changing the electron-donating power of the ligand (Table 1, entries 3,4) or omitting it (Table 1, entry 5) produced only minor modifications of the reactivity and/or selectivity, at least from a synthetic point of view. Compound (6a) was always isolated in low yield and the (6a):(8a) ratio ranges from 1.6:1 to 1.1:1. Using the hindered tri-o-tolylphosphine as the ligand resulted in a higher convertion of (1a) but the main product was the diol (8a), isolated in good yield (Table 1, entry 6).



Scheme 2

Switching to K_2CO_3 or $NaHCO_3$, in the presence of n-Bu_4NCl, and catalytic amounts of $Pd(OAc)_2$ in DMF,[14] produced the desired butyrolactol as a mixture of stereoisomers in high isolated yield (Table 1, entries 10,13). Only traces of the diol (8a) were in this case obtained.

Omitting the ammonium salt, lower yields were obtained (Table 1, entries 7,11) even though in the presence of K_2CO_3 the yield of (6a) was not as low as it might be expected. Using K_2CO_3 as the base resulted in a higher reaction rate while $NaHCO_3$ produced the γ-butyrolactol in higher yield. Good results were also obtained with the less expensive TEBA (Table 1, entry 8). As found in other palladium-catalysed reactions of organic halides and triflates with olefinic systems,[9h-i,15] the use of n-Bu_4NHSO_4 proved to be unsuccessfull (Table 1, entries 9,12).

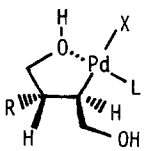
The very high selectivity observed in the syn-β-elimination step in the presence of carbonate and bicarbonate bases, n-Bu_4NCl, and $Pd(OAc)_2$ could be tentatively accounted for by assuming that, in the absence of phosphine ligands and amines, hydroxyl coordination[10f,16] to the palladium occurs in the initial adduct favouring the formation

Table 1 - Base, Catalyst, and Ammonium Salts in the Reaction of 17-ß-Acetoxy-androsta--3,5-dien-3-yl Triflate (1a) with Z-2-Buten-1,4-diol (2).[a]

Entry	Base	Ammonium salt	Catalyst	React. time(h)/ /temperature(°C)	γ-Butyrolactol (6a) % yield[b]	Diol (8a) % yield[b]
1	Et_3N[c]	-	$Pd(OAc)_2(PPh_3)_2$	7/60	26 (33)	21
2	"	n-Bu_4NCl	"	"	6 (83)	traces
3	"	-	$Pd(OAc)_2[P(p\text{-}Tol)3]2$	"	18 (44)	11
4	"	-	$Pd(OAc)_2[P(p\text{-}MeOC_6H_4)_3]_2$	"	10 (64)	9
5	"	-	$Pd(OAc)_2$	"	14 (65)	12
6	"	-	$Pd(OAc)_2[P(o\text{-}Tol)_3]_2$	"	26 (6)	50
7	K_2CO_3[d]	-	$Pd(OAc)_2$	1/70	51 (18)	15
8	"	TEBA[e]	"	1.5/70	74 (2)	5
9	"	n-Bu_4NHSO_4[e]	"	1/70	4 (85)	1
10	"	n-Bu_4NCl[e]	"	"	73 (2)	5
11	$NaHCO_3$[f]	-	"	3.5/70	18 (70)	3
12	"	n-Bu_4NHSO_4[e]	"	"	48 (21)	9
13	"	n-Bu_4NCl[e]	"	"	82 (-)	-

a) All of the reactions were carried out with 0.54 mmol of (1) in DMF (4 ml) at 60/70°C under argon by using the following molar ratios: (1):(2):Pd(II):phosphine ligand (when used) = 1:1.5:0.05:0:1 molar ratio. b) Yields refer to single runs and are for pure, isolated products. In most cases, TLC monitoring showed that the reaction apparently stops in less time than the time allotted. c) (1):Et_3N =1:2. d) (1):K_2CO_3 = 1:2.5. e) (1):ammonium salt = 1:1. f) (1):$NaHCO_3$ = 1:2.5.

of the five membered cyclic intermediate (9), and this directs the elimination of hydridopalladium species to the enol (4).

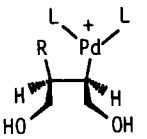


(9)

In the event, the outcome of the reaction is affected by an intriguing combination of coordinating, steric, and electronic effects. Among these, the nature of the counterion occupying a ligand site on palladium in the σ-complex (3) appears to play a non negligible role. A number of experimental observations suggest that the presence of halide salts in palladium-catalysed reactions of vinyl and aryl triflates can produce organopalladium halides through a ligand exchange mechanism.[9b,h,17] Therefore, we believe that in the

presence of n-Bu_4NCl such a ligand exchange may occur and that the regiochemistry of β-elimination is, at least in part, dependent on it. An organopalladium triflate complex contains a more electrophilic palladium than an organopalladium chloride complex. Thus, it may be argued that the higher selectivity in hydroxyl coordination is achieved by the least electrophilic palladium and consequently in the presence of the chloride counterion. Accordingly, worse regiochemistry was observed in the absence of the ammonium salt or substituting n-Bu_4NHSO_4 for n-Bu_4NCl (Table 1, compare entry 7 with entries 9,10 and entry 11 with entries 12,13).

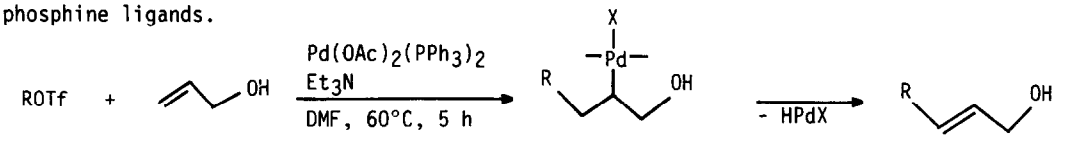
An almost non selective hydroxyl coordination on the highly electrophilic palladium[9g] of the addition intermediate (10) might account for the results obtained in the reactions carried out in the presence of Et_3N with (Table 1, entries 1,3,4) or without (Table 1, entry 5) phosphine ligands.*



(10)

The observation that there have been no significant changes in the balance between "internal" and "external" elimination of hydridopalladium species from (3) by using phosphine ligands with different electron-donating power or omitting them (Table 1, entries 1,3-5), suggest that the result obtained in the presence of tri-o-tolylphosphine (Table 1, entry 6) can be ascribed mainly to steric factors. The addition of n-Bu_4NCl could turn organopalladium triflate intermediates into organopalladium chloride intermediates and conceivably a different regiochemical outcome should be expected. This

* The result obtained in the palladium-catalysed reaction of cholest-2-en-3-yl triflate with allyl alcohol[9a] seems to support the view that hydroxyl coordination to palladium can play a role in controlling the reactivity even in the presence of tertiary amines and phosphine ligands.



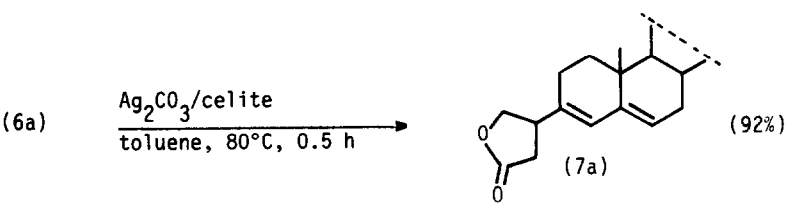
R = cholest-2-en-3-yl

Indeed, most likely because of hydroxyl coordination, the σ-alkylpalladium adduct undergoes the syn-β-elimination of HPdX species producing 3-substituted-allyl alcohol (50%). The corresponding carbonyl derivative (one of the main products with vinyl halides[10f]) derived from the β-elimination leading to the enol was detected only in traces, if any. 2-Substituted allyl alcohol derived from the reverse addition of organopalladium species to the carbon-carbon double bond was isolated in 15% yield.

modification has been indeed observed even though the convertion of (1a) was too low to be of synthetic value (Table 1, entry 2). In any case, it is apparent that the presence of the chloride anion tends to favour the formation of the γ-butyrolactol. This results can be related to that obtained in the reaction of (2) with 4-methoxyphenyl iodide (Table 2, notes e,g) and supports the idea that both reactions may proceed through the decomposition of similar $RPdL_2X$ complexes (X = halide; L = triarylphosphine). Their decomposition occurs mainly through "external" elimination of HPdX species most likely because of steric effects. This point will be commented later.

It is of interest to note that relatively stable π-allylpalladium complexes derived from elimination/readdition of HPdX species are known to be involved in the allyl alcohol reactions with vinyl halides.[10f] The addition of a nucleophile such as piperidine is required to allow a catalytic cycle to occur with, however, the formation of desired products and also amino alcohols. Apparently, problems arising from the formation of such π-allylpalladium complexes are irrelevant to the present reaction. This observation is consistent with the presence of the intermediate (9) along the reaction coordinate when the reaction is carried out in the presence of carbonate or bicarbonate bases and quaternary ammonium chlorides. The directing effect of hydroxyl coordination favours the formation of the enol (4), at which point the elimination of HPdX is virtually irreversible. When the reaction is carried out in the presence of tertiary amines with or without phosphines and in the absence of chloride anions, the ß-elimination step should involve HPd species so that both "external" and "internal" elimination is expected to be irreversible. Indeed, evidences that leaving of HPd species from the carbon framework is an irreversible process have been reported.[9b] The irreversibility of the elimination step clearly prevents the formation of π-allylpalladium complexes.

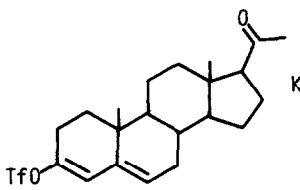
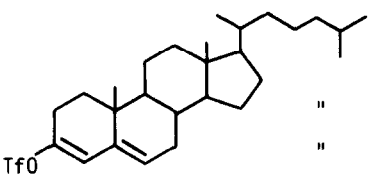
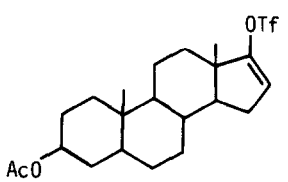
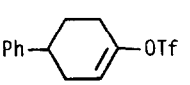
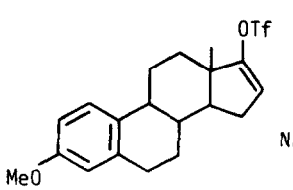
The target ß-substituted-γ-butyrolactone (7a) was obtained in excellent isolated yield (as a mixture of diastereoisomers) through a clean oxidation of (6a) with Ag_2CO_3 on celite.



Scheme 3

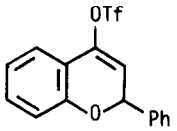
A variety of vinyl triflates were then successfully converted into the corresponding γ-lactone derivatives according to this procedure (Table 2).

Table 2 - Palladium-Catalysed Convertion of Vinyl Triflates (1) into β-Vinyl-γ-butyrolactols (6) and their Oxidation to β-Vinyl-γ-butyrolactones (7).[a,b]

Entry	Vinyl triflates (1)	Base	Ammonium salt	Reaction time (h)[c]	β-Vinyl-γ-butyrolactols (6) % yield[d,e,f]	β-Vinyl-γ-butyrolactone (7) % yield[d,f]
1	 (1b)	K_2CO_3	TEBA	1	65	
2		"	$n\text{-}Bu_4NHSO_4$	"	9 (72)	83
3		"	$n\text{-}Bu_4NCl$	"	70	
4	 (1c)	"	TEBA	2	63	89
5		"	$n\text{-}Bu_4NCl$	1	71	
6	 (1d)	"	TEBA	3	71	88
7		"	$n\text{-}Bu_4NHSO_4$	"	20 (65)	
8		"	$n\text{-}Bu_4NCl$	"	80	
9		"	-	"	49 (22)	
10	 (1e)	"	TEBA	"	64	75
11	 (1f)	$NaHCO_3$	$n\text{-}Bu_4NCl$	"	94	88

(continued)

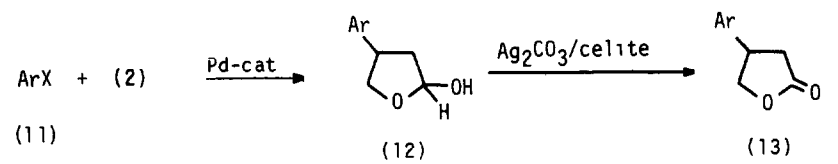
Table 2 - (continued)

Entry	Vinyl triflates (1)	Base	Ammonium salt	Reaction time (h)[c]	ß-Vinyl-γ-butyrolactols (6) % yield[d,e,f]	ß-Vinyl-γ-butyrolactone (7) % yield[d,f]
12	 (1g)	K_2CO_3	n-Bu_4NCl	1	-[g]	

a) Preparation of ß-vinyl-γ-butyrolactols (6) was performed in DMF at 70°C by using the following molar ratios: (1):(2):base:ammonium salt:$Pd(OAc)_2$ = 1:1.5:2.5:1:0.03. b) Oxidation of (6) with Ag_2CO_3 was carried out in toluene at 80°C by using the following molar ratio: (6):Ag_2CO_3 = 1:2. c) Reaction times refer the the preparation of hemiacetals. Their oxidation goes to completion usually in a 10-30 min time. d) Yields refer to single runs and are for pure, isolated products. e) Figures in parentheses refer to the recovered starting triflate. f) Compounds (6) and (7) were isolated as a mixture of stereoisomers. g) Flavanone was isolated in 21 % yield. Control experiments, carried out in the absence of the palladium catalyst, revealed that (1g) decomposes quickly in the presence of n-Bu_4NCl, (2), and K_2CO_3. The same result was obtained by substituting AcOK for K_2CO_3.

We attempted the extension of this approach to ß-substituted-γ-butyrolactones to aryl triflates. Their conversion to the intermediate ß-aryl-γ-butyrolactols, however, appears to be prevented by the competing decomposition to phenols. Reacting the model naphthyl triflate as usual produced ß-naphthol in 64 % yield (60°C, 2 h). Control experiments revealed that the decomposition of ß-naphthyl triflate to ß-naphtol is not palladium catalysed. Treatment of ß-naphthyl triflate with Z-2-buten-1,4-diol, TEBA, and K_2CO_3 in DMF at 60°C (2h) omitting the palladium catalyst afforded ß-naphthol in 68% yield.

On the contrary, as observed by Tsuji and Co.,* aryl halides** were converted into ß-aryl-γ-butyrolactones (12) in good to high overall yield (Table 3).



(11) (12) (13) Scheme 4

* While this work was in progress, a similar two-step approach to ß-substituted-γ-butyrolactones starting from aryl and vinyl halides has been reported.[18]

** The reaction of phenyl iodide and bromide with 2-buten-1,4-diol was previously examined by Chalk and Magennis[10b] who reported the isolation (upon distillation) of 3-phenyl-2,3-dihydrofuran, most likely derived from dehydration of the corresponding hemiacetal.

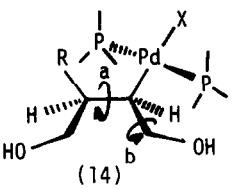
Table 3 - Palladium-Catalysed Convertion of Aryl Halides (11) into β-Aryl-γ-butyrolactols (12) and their Oxidation to β-Aryl-γ-butyrolactones (13).[a,b]

Entry	Aryl Halide (11)	Reaction Time (h)[c]/ /Temperature (°C)	β-Aryl-γ--butyrolactol (12) % yield[d]	β-Aryl-γ--butyrolactone (13) % yield[d]
a	4-MeO-C_6H_4-I	1 /60	80 (36[e,f],67[e,g])	82
b	4-MeCONH-C_6H_4-I	0.5 / "	80	61
c	3-MeCONH-C_6H_4-I	0.75/ "	82	85
d	4-HO-C_6H_4-I	2.5 / "	72	60
e	Ph-I	4 / "	70	93
f	4-MeCO-C_6H_4-Br	1 /80	55	88
g	4-HOC-C_6H_4-Br	4 / "	67	87

a) Preparation of β-aryl-γ-butyrolactols (12) was performed in DMF at 60/80°C by using the following molar ratios: (11):(2):K_2CO_3:n-Bu_4NCl:Pd(II) = 1:1.5:2.5:1:0.03. b) Oxidation of (12) was performed in toluene at 80°C by using the following molar ratio: (12):Ag_2CO_3 = 1:2. c) Reaction times refer to the preparation of (12). Their oxidation goes to completion usually in a 10-30 min time. d) Yields refer to single runs and are for pure, isolated products. e) (11):(2):n-Bu_3N:Pd(II) = 1:2.5:2:0.03. f) 4 h; $Pd(OAc)_2(PPh_3)_2$. g) 4 h; $Pd(OAc)_2[P(o\text{-}Tol)_3]_2$.

Interestingly, 4-methoxyphenyl iodide was found to give the corresponding hemiacetal derivative (12) in high yield in the presence of both $Pd(OAc)_2/K_2CO_3$/n-Bu_4NCl and $Pd(OAc)_2[P(o\text{-}Tol)_3]_2$ (Table 3, entry a), suggesting that with the intermediates (14), whose reactivity is supposed to be less dependent on hydroxyl coordination,[10f] steric hinderance may play a dominant role making it difficult to achieve the conformation required for the internal elimination of HPdX (from rotation a) and the external elimination (from rotation b) may result the preferred decomposition pathway.

X = I or Cl



(14)

Intermediates of this kind may be involved in the formation of γ-lactols from vinyl triflates in the presence of tertiary amines, phosphines, and n-Bu_4NCl (Table 1, entry 2).

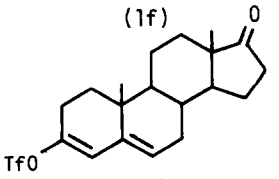
A further comment on this reaction can be drawn. The reaction of allyl alcohols with

aryl halides is known to produce isomeric derivatives through the elimination/readdition/ /elimination of HPdX species from σ-alkyl-palladium adducts.[10a] In our reaction such a mechanism should produce isomeric α-aryl-γ-butyrolactols. However, no evidence was obtained of their formation in the reaction of (2) with aryl halides. Consequently, it is conceivable to infer that this mechanism is not operating here or, if it should, its presence does not affect significantly the reaction course.

Finally, we can report that the oxidation step can be conveniently carried out on the crude mixture obtained from the palladium-catalysed reaction, after extraction, without the isolation of γ-butyrolactols. This modification simplifies the procedure and usually leads to an increase of the overall yield (Table 4).

In conclusion, it seems that the here reported procedure is an attractive route to ß-substituted-γ-butyrolactones from vinyl triflates. The method merits attention due to the usually high overall yield, the simplicity of the experimental conditions, and the use of the inexpensive Z-2-buten-1,4-diol as a four carbon building block. The reaction is also of value as a new and convenient route to ß-substituted-γ-butyrolactols, useful intermediates for the preparation of substituted tetrahydrofurans. As such, the reaction may be a useful alternative to known procedures based on the reduction of γ-butyrolactones[19] or the palladium catalysed oxidation of 3-en-1-ols.[20]

Table 4 - Preparation of ß-Alkenyl-γ-butyrolactones (7) from Vinyl Triflates (1) and ß-Aryl-γ-butyrolactones (12) from Aryl Halides (11) without Isolation of γ-Butyrolactols.[a]

Vinyl triflate (1)	ß-Alkenyl-γ--butyrolactone (7) % yield[b]	Vinyl triflate (1)	ß-Alkenyl-γ--butyrolactone (6) % yield[b]	Aryl halide (11)	ß-Aryl-γ--butyrolactone (13) % yield[b]
(1a)	67	(1f)  (1h)	88	4-MeO-C_6H_4-I	68
(1b)	66			4-MeCONH-C_6H_4-I	69
(1c)	66		64	3-MeCONH-C_6H_4-I	75
(1e)	58				

a) The oxidation was carried out on the crude reaction mixtures, obtained from the palladium-catalysed reactions, by using a two-fold excess (calculated on the starting triflate or halide) of Ag_2CO_3 on celite. Reaction times of the oxidation step were in this case found to range from 15 to 120 min. b) Yields refer to single runs and are for pure isolated products.

Experimental

M.ps. were determined with a BÜchi 510 apparatus and are uncorrected. All starting materials, catalysts, and solvents are commercially available and were used without further purification. Organic triflates were prepared from corresponding commercially available ketones and phenols and trifluoromethanesulfonic anhydride in the presence of 2,6-di-tert-butyl-4-methylpyridine.[21] 3- And 4-acetylaminophenyl iodide were prepared from commercially available 3- and 4-aminophenyl iodide according to standard methods. Silver carbonate on celite was prepared according to literature.[22]

Reactions were carried out on a 0.43-1.08 mmol scale. The products were purified by preparative HPLC (Chromatospac Prep 10, from Jobin-Yvon, equipped with a prep LC/System 500A-Solvent delivery system and refractive index detector from Waters Associates) on axially compressed columns packed with silica gel 20-45 μ (Amicon Co.) eluting with n-hexane/AcOEt mixtures. γ-Butyrolactols (6) and (12) were isolated and reacted as mixtures of isomers. γ-Butyrolactones (7) were obtained and characterized as mixtures of isomers.

^{1}H NMR spectra ($CDCl_3$; TMS as internal standard) were recorded with Varian EM390 (compounds (6), (12), and (13)) and XL-300 (compounds (7) and (8a)) spectrometers. ^{13}C NMR spectra ($CDCl_3$, unless otherwise indicated; TMS as internal standard) were recorded with a Varian XL-300 spectrometer. IR spectra (KBr, unless otherwise indicated) were recorded with a Nicolet 5DX FT/IR spectrometer. MS spectra (compounds (12) and (13)) were recorded with a Hewlett Packard HP 5980A spectrometer equipped with a Data System 5934A.

All of the new products (6), (7), (12), and (13) gave satisfactory microanalyses.

General Procedure of Reaction of Vinyl Triflates (1) with (2) in the Presence of K_2CO_3 or $NaHCO_3$

This is exemplified by the reaction of (1d) with (2) (Table 2, entry 8). A solution of $Pd(OAc)_2$ (5.8 mg, 0.026 mmol) in DMF (1 ml) was added to a stirred mixture of (1d) (0.400 g, 0.86 mmol), (2) (0.114 g, 1.29 mmol), K_2CO_3 (0.297 g, 2.15 mmol), and n-Bu_4NCl (0.239 g, 0.86 mmol) in DMF (2 ml). The reaction mixture was purged with nitrogen and stirred at 70°C under a nitrogen atmosphere for 3 h. Then AcOEt and water were added, the organic layer was separated, washed with water, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was purified by preparative HPLC eluting with a 70/30 n-hexane/AcOEt mixture to give (6d) (0.279 g, 80% yield).

General Procedure of Reaction of Vinyl Triflates (1) with (2) in the Presence of Et_3N

This is exemplified by the reaction of (1a) with (2) (Table 1, entry 6). A solution of

(1a) (0.250 g, 0.54 mmol), (2) (0.71 g, 0.81 mmol), Et_3N (0.109 g, 1.08 mmol), in DMF (1.5 ml) was added with stirring to a solution of $Pd(OAc)_2$ (6.1 mg, 0.027 mmol) and $P(o\text{-}Tol)_3$ (0.017 g, 0.055 mmol) in DMF (1 ml). The mixture was purged with nitrogen and stirred at 60°C under a nitrogen atmosphere for 7 h; work-up as before afforded a residue which was purified by preparative HPLC eluting with a 60/40 n-hexane/AcOEt mixture to give (6a) (0.056 g, 26% yield), (8a) (0.109 g, 50% yield) [IR 3283, 1721 cm^{-1}; ^1H NMR δ 5.74 (bs, 1H), 5.67 (bt, 1H), 5.44 (m, 1H), 4.61 (m, 1H), 4.21 (d, J = 6.3 Hz, 2H), 4.16 (s, 2H), 2.05 (s, 3H), 0.97 (s, 3H), 0.84 (s, 3H)], and the starting vinyl triflate (0.016 g, 6% yield).

General Procedure of Reaction of Aryl Halides (11) with (2) in the Presence of K_2CO_3

This is exemplified by the reaction of 4-methoxyphenyl iodide with (2) (Table 3, entry a). A solution of $Pd(OAc)_2$ (5.8 mg, 0.026 mmol) in DMF (1 ml) was added to a stirred mixture of 4-methoxyphenyl iodide (0.201 g, 0.87 mmol), (2) (0.115 g, 1.3 mmol), K_2CO_3 (0.30 g, 2.17 mmol), and n-Bu_4NCl (0.242 g, 0.87 mmol) in DMF (2 ml). The mixture was purged with nitrogen and stirred at 50°C under a nitrogen atmosphere for 2 h. Then AcOEt and water were added, the organic layer was separated, washed with water, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was purified by preparative HPLC eluting with a 50/50 n-hexane/AcOEt mixture to give compound (12a) (0.135 g, 80% yield).

General Procedure of Oxidation of Isolated ß-Vinyl-γ-butyrolactols

This is exemplified by the oxidation of (6c) (Table 2, entry 4). A solution of (6c) (0.164 g, 0.36 mmol) in toluene (6 ml) was added to Ag_2CO_3 on celite (0.410 g, 0.72 mmol). The mixture was stirred at 80°C for 0.25 h, cooled, filtered, and evaporated at reduced pressure. The residue was purified by preparative HPLC eluting with an 85/15 n-hexane/AcOEt mixture to give compound (7c) (0.145 g, 89% yield).

General Procedure for the Preparation of ß-Vinyl-γ-butyrolactones (7) without Isolation of ß-Vinyl-γ-butyrolactols.

This is exemplified by the preparation of (7f). A solution of (1f) (0.300 g, 0.72 mmol), (2) (0.095 g, 1.08 mmol), $NaHCO_3$ (0.151 g, 1.80 mmol), n-Bu_4NCl (0.200 g, 0.72 mmol) in DMF (3 ml) was added with stirring to a solution of $Pd(OAc)_2$ (4.9 mg, 0.022 mmol) in DMF (1 ml). The mixture was purged with nitrogen and stirred at 70°C under a nitrogen atmosphere for 3 h. Then AcOEt and water were added, the organic layer was separated, washed with water, dried (Na_2SO_4), and evaporated at reduced pressure. Toluene (11 ml) and Ag_2CO_3/celite (2.529 g, 1.44 mmol) were added to the residue. The mixture was stirred at 80°C for 0.25 h, cooled, filtered, and evaporated at reduced pressure. The residue was purified by preparative HPLC eluting with an 80/20 n-hexane/AcOEt mixture to give (7f)

(0.225 g, 88% yield).

(6a): IR 3378, 1737 cm^{-1}; ^1H NMR δ 5.78 (m, 1H), 5.57 (m, 1H), 5.38 (m, 1H), 4.61 (m, 1H), 1.99 (s, 3H), 0.88 (s, 3H), 0.78 (s, 3H).

(6b): IR 3419, 1704 cm^{-1}; ^1H NMR δ 5.96 (m, 1H), 5.60 (m, 1H), 5.39 (m, 1H), 2.12 (s, 3H), 0.88 (s, 3H), 0.62 (s, 3H).

(6c): IR 3394 cm^{-1}; ^1H NMR δ 5.82 (m, 1H), 5.68-5.32 (m, 2H), 0.82 (s, 3H), 0.71 (s, 3H).

(6d): IR 3419, 1729 cm^{-1}; ^1H NMR δ 5.68-5.33 (m, 2H), 4.92-4.45 (m, 1H) 1.98 (s, 3H), 0.83 (s, 3H), 0.73 (s, 3H).

(6e): IR 3378, 761, 703 cm^{-1}; ^1H NMR δ 7.28 (m, 5H), 5.62 (m, 2H).

(6f): IR 3394 cm^{-1}; ^1H NMR δ 7.33-6.63 (m, 3H), 5.49 (m, 2H), 3.78 (s, 3H), 0.77 (s, 3H).

(7a): IR 1786, 1737 cm^{-1} ; ^1H NMR δ 5.80 (bs, 1H), 5.43 (m, 1H), 4.64-4.58 (m, 1H), 4.48-4.41 (m, 1H), 4.17-4.06 (m, 1H), 3.21 (m, 1H), 2.69-2.59 (m, 1H), 2.55-2.43 (m, 1H), 2.05 (s, 3H), 0.92 (s, 3H), 0.83 (s, 3H); ^{13}C NMR δ 176.8, 171.1.

(7b): IR 1770, 1704 cm^{-1} ; ^1H NMR δ 5.80 (bs, 1H), 5.43 (m, 1H), 4.48-4.42 (m, 1H), 4.17-4.07 (m, 1H), 3.22 (m, 1H), 2.69-2.44 (m, 2H), 2.13 (s, 3H), 0.91 (s, 3H), 0.66 (s, 3H); ^{13}C NMR δ 209.5, 176.8.

(7c): IR 1789 cm^{-1}; ^1H NMR δ 5.79 (bs, 1H), 5.43 (m, 1H), 4.47-4.41 (m, 1H), 4.17-4.06 (m, 1H), 3.20 (m, 1H), 2.68-2.59 (m, 1H), 2.55-2.43 (m, 1H); ^{13}C NMR δ 176.8, 140.7.

(7d): IR 1786, 1729 cm^{-1} ; ^1H NMR δ 5.48 (m, 1H), 4.69 (m, 1H), 4.43 (m, 1H), 4.16 (m, 1H), 3.14 (m, 1H), 2.68 (dd, J = 8.17 Hz, J = 17.1 Hz, 0.8H), 2.56 (m, 0.2H), 2.37 (dd, J = 10.3 Hz, J = 17.1 Hz, 0.8H), 2.02 (s, 3H), 0.86 (s, 3H), 0.77 (s, 3H); ^{13}C NMR δ 176.7, 170.7, 153.0.

(7e): IR 1778 cm^{-1} ; ^1H NMR δ 7.32-7.19 (m, 5H), 5.63 (m, 1H), 4.45-4.40 (m, 1H), 4.16-4.06 (m, 1H), 3.16 (m, 1H), 2.75 (m, 1H), 2.67-2.57 (m, 1H), 2.53-2.42 (m, 1H); ^{13}C NMR δ 176.9.

(7f): IR 1762 cm^{-1}; ^1H NMR δ 7.25-6.63 (m, 3H), 5.53 (m, 1H), 4.53 (m, 0.2H), 4.46 (m, 0.8H), 4.19 (m, 0.8H), 4.00 (m, 0.2H), 3.77 (s, 3H), 3.18 (m, 1H), 2.71 (dd, J = 8.2 Hz, J = 17.1 Hz, 0.8H), 2.64 (dd, J = 8.2 Hz, J = 17.1 Hz, 0.2H), 2.55 (dd, J = 10.5 Hz, J = 17.1 Hz, 0.2H), 2.40 (dd, J = 10.2 Hz, J = 17.1 Hz, 0.8H); ^{13}C NMR δ 176.6.

(7h): IR 1786, 1729 cm^{-1}; ^1H NMR δ 5.82 (bs, 1H), 5.46 (m, 1H), 4.49-4.23 (m, 1H), 4.18-4.07 (m, 1H), 3.22 (m, 1H), 2.70-2.61 (m, 1H), 2.54-2.43 (m, 1H), 0.94 (s, 3H), 0.92 (s, 3H); ^{13}C NMR δ 176.7.

(12a): IR 3344, 826 cm^{-1}; ^1H NMR δ 7.04 (AA'BB' system, 4H), 5.72 (m, 1H), 3.77 (s, 3H); MS m/z 194 (M^+).

(12b): IR 3287, 826 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.92 (bs, 1H), 7.37 (AA'BB' system, 4H), 6.13 (m, 1H), 5.49 (m, 1H), 2.02 (s, 3H); MS m/z 221 (M^+).

(12c): IR 3360, 3280, 1665, 780, 685 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.0 (bs, 1H), 7.67-6.94 (m, 4H), 5.53 (m, 1H), 2.01 (s, 3H); MS m/z 221 (M^+).

(12d): IR 3353, 835 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.92 (AA'BB' system, 4H), 5.48 (m, 1H); MS m/z 180 (M^+).

(12e): IR (liquid film) 3360, 740, 680 cm^{-1}; ^1H NMR δ 7.56-7.10 (m, 5H), 5.74 (m, 1H); MS m/z 164 (M^+).

(12f): IR 3320, 1680, 834 cm^{-1}; ^1H NMR δ 7.67 (AA'BB' system, 4H), 5.74 (m, 1H), 2.57 (s, 3H); MS m/z 206 (M^+).

(12g): IR 3320, 1688, 826 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.06 (s, 1H), 8.03-7.35 (m, 4H), 5.77 (m, 1H); MS m/z 192 (M^+).

(13a): mp = 68-70°C; IR 1778, 1614, 835 cm^{-1}; ^1H NMR δ 7.06 (AA'BB' system, 4H), 4.65 (dd, J = 8.2 Hz, J = 9.0 Hz, 1H), 4.23 (dd, J = 8.2 Hz, J = 9.0 Hz, 1H), 3.97-3.53 (m, 1H), 3.80 (s, 3H), 2.92 (dd, J = 8.2 Hz, J = 17.5 Hz, 1H), 2.58 (dd, J = 9.3 Hz, J = 17.5 Hz, 1H); MS m/z 192 (M^+).

(13b): mp = 97-98°C; IR 3328, 1778, 1671, 1598, 835 cm^{-1}; ^1H NMR δ 8.19 (bs, 1H), 7.40 (AA'BB' system, 4H), 4.69 (dd, J = 7.8 Hz, J = 9.0 Hz, 1H), 4.28 (dd, J = 7.5 Hz, J = 9.0 Hz, 1H), 3.98-3.54 (m, 1H), 2.95 (dd, J = 8.4 Hz, J = 17.5 Hz, 1H), 2.68 (dd, J = 9.1 Hz, J = 17.5 Hz, 1H), 2.11 (s, 3H); MS m/z 219 (M^+).

(13c): mp = 125-127°C; IR 3270, 1740, 1660, 780, 675 cm^{-1}; ^1H NMR δ 10.02 (bs, 1H), 7.69-6.97 (m, 4H), 4.66 (m, 1H), 4.20 (m, 1H), 4.02-3.59 (m, 1H), 2.87 (dd, J = 8.2 Hz, J = 17.6 Hz, 1H), 2.60 (dd, J = 9.3 Hz, J = 17.6 Hz, 1H) 2.03 (s, 3H); MS m/z 219 (M^+).

(13d): mp = 120-123°C; IR 3296, 1737, 1614, 835 cm^{-1}; ^1H NMR δ 9.41 (s, 1H), 6.98 (AA'BB' system, 4H), 4.57 (m, 1H), 4.12 (m, 1H), 3.93-3.46 (m, 1H), 2.81 (dd, J = 8.2 Hz, J = 17.1 Hz, 1H), 2.63 (dd, J = 9.6 Hz, J = 17.1 Hz, 1H); MS m/z 178 (M^+).

(13e): mp = 45-47°C; IR 1778, 761, 703 cm^{-1}; ^1H NMR δ 7.36 (m, 5H), 4.70 (dd, J = 7.8 Hz, J = 8.7 Hz, 1H), 4.30 (dd, J = 7.8 Hz, J = 8.7 Hz, 1H), 4.05-3.58 (m, 1H), 2.92 (dd, J = 8.6 Hz, J = 17.2 Hz, 1H), 2.67 (dd, J = 9.1 Hz, J = 17.2 Hz, 1H); MS m/z 162 (M^+).

(13f): mp = 91-93°C; IR 1770, 1680, 1605, 835 cm^{-1}; ^1H NMR δ 7.73 (AA'BB' system, 4H), 4.72 (dd, J = 7.5 Hz, J = 9.2 Hz, 1H), 4.36 (dd, J = 7.5 Hz, J = 9.2 Hz, 1H),

4.13-3.67 (m, 1H), 2.98 (dd, J = 8.5 Hz, J = 17.2 Hz, 1H), 2.68 (dd, J = 8.6 Hz, J = 17.2 Hz, 1H), 2.59 (s, 3H); MS m/z 204 (M^+).

(13g): mp = 79-81°C; IR 1770, 1688, 1606, 843 cm^{-1}; ^1H NMR δ 10.12 (s, 1H), 7.74 (AA'BB' system, 4H), 4.76 (m, 1H), 4.36 (m, 1H), 4.18-3.70 (m, 1H), 2.99 (dd, J = 9.0 Hz, J = 18.0 Hz, 1H), 2.71 (dd, J = 8.25 Hz, J = 18.0 Hz, 1H); MS m/z 190 (M^+).

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