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Rhodium-Catalysed Redox Isomerization of Hydroxy Alkynes to Trans Keto and Hydroxy Vinyl Esters. A Short and Stereoselective Synthesis of Dipeptide Isosters.

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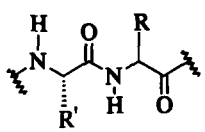
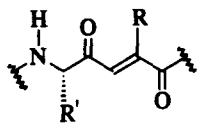
Abstract: Tris(triphenylphosphine)Rhodium(I) Chloride in the presence trialkyl phosphine catalyses the isomerization of hydroxy alkynes to unsaturated trans keto and hydroxy esters depending on the nature of the phosphine. Dipeptide isosters were obtained in a an efficient manner by the application of this methodology.

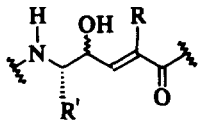
Many efforts are currently being directed towards the design and the synthesis of peptidomimetics in which the amide bond in (1) is replaced by a functionality conferring to the parent peptide improved resistance against proteases degradation and restricted conformation mobility[1]. The keto vinyl ester (2) and the trans hydroxy vinyl ester (3) first reported by Hanson et al.[2] are interesting dipeptide analogs which combine conformational restriction and the ability to undergo conjugate addition to nucleophilic species from the respective receptor or enzyme binding sites. They have been also incorporated in various angiotensin converting enzyme inhibitors[2,3]. Dipeptide (3) moreover is the key intermediate in the synthesis of trans alkene dipeptide isosters (4)[4a,b] which were used in the syntheses of peptidomimetic analogs of enkephalin, substance P and protein kinase inhibitors[4c]. More recently, Martin et al.[5] identified (5) and (6) as novel conformationally restricted isosteric replacements of the natural fragment (1) by incorporating these surrogates in renin[5b] and collagenase inhibitors[5c].



(1)



(2)



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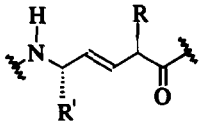

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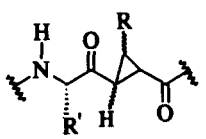
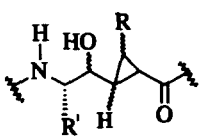


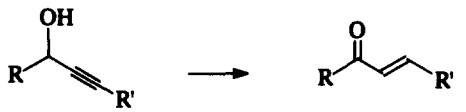
(5)



(6)

R, R', R_1,R_2= H, alkyl, aryl

Having decided to incorporate dipeptide isosters such as (2) and (3) in enzyme inhibitors currently under development in our laboratory, we have explored the possibility to prepare them by a synthetic route simpler than that hitherto reported[2]. We were intrigued in particular by the possibility to prepare these dipeptide isosters by transforming a suitable hydroxy alkyne precursor (A) into the corresponding keto vinyl derivative (B) by transition metal promoted internal redox.



A B

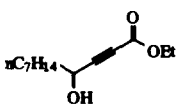
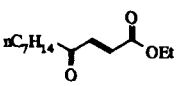
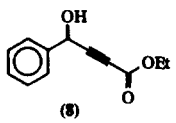
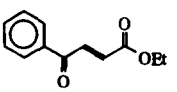
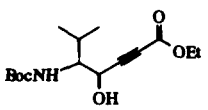
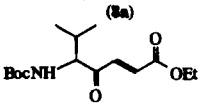
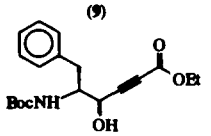
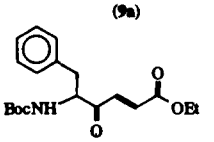
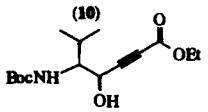
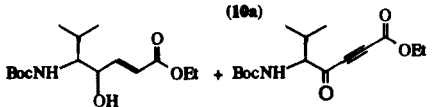
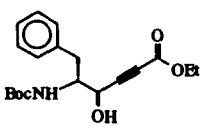
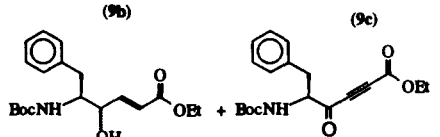
This strategy has been previously used for the isomerization of allylic alcohols to saturated ketones[6–8], primary hydroxy alkynes to trans vinyl aldehydes[9] and secondary hydroxy alkynes to α–β enones[10] and trans dienes[11]. Herein, we report that $[P(Ph)_3]_3Rh(I)Cl$ is able to isomerize efficiently and stereoselectively secondary hydroxy alkynes to trans keto or hydroxy alkenes depending on the nature of the added phosphine. Thus, a series of hydroxy alkyne esters[12] were treated with 3% of $[P(Ph)_3]_3Rh(I)Cl$ and 5% of $n(Bu)_3P$ in toluene. As illustrated in table I (entry 1), clean isomerization of hydroxy alkyne (7) bearing an alkyl chain occurred to give the keto vinyl ester (**7a**) in 82% yield[14]. The reaction does not occur at room temperature (see entry 2) or in the absence of the trialkylphosphine as catalyst (entry 3). ^1H NMR spectra of product (**7a**) indicated the presence of two doublets centred respectively at 7.00 ppm and 6.58 ppm with a coupling constant of 16 Hz and confirm a trans stereochemistry of the double bond. The presence in ^{13}C NMR of a signal at 199.8 ppm confirmed the existence of the ketone. No trace of the cis isomer was detected by NMR or by HPLC. The phenyl hydroxy alkyne ester (**8**) proved to react much slower and proceeded in lower yield comparing to its alkyl counterpart (56% versus 82% for (7)). It is worthy to note that product (**8a**) can be used as a useful precursor for the synthesis of trans keto epoxy amides which have been reported to be active antilipogenic agents[15].

Entries 5–8 report the results obtained in the preparation of dipeptide isosters. Compound (**9**) reacted smoothly in the conditions described above affording the keto vinyl ester (**9a**) in 76% yield. Confirmation of the assigned structure was based on the ^1H NMR and ^{13}C NMR spectra (see the typical procedure). No trace of the cis isomer or of the trans diene was observed. The phenylalanine derivative reacted in a similar manner. Entries 7 and 8 illustrate the role of the added phosphine on the outcome of the reaction. Isomerization of compound (**9**) using triisopropyl phosphine as catalyst afforded unexpectedly the trans γ–hydroxy vinyl ester (**9b**) together with the γ-keto alkyne ester (**9c**). In this case the products apparently arise from intermolecular hydrogen transfer. Compound (**10**) reacted similarly and gave the products (**10b**) and (**10c**) in 87% combined yield.

It is known that the mechanism of the isomerization of unsaturated alcohols can differ depending on the metal catalyst employed[8]. Most probably in our case, the mechanism that accounts for the observed reaction follows the one proposed by Trost for the redox isomerization of allylic alcohols[7]. The hydroxy alkyne is recognised in this case as the bidendate ligand for the rhodium catalyst. The exclusive formation of the trans olefin can be rationalized by the severe steric interaction between the metal ligand and the ethyl ester moiety of the Z isomer.

In conclusion, we have developed a short and stereoselective method for the synthesis of trans keto and hydroxy vinyl ester derivatives. This approach is mild and gives ready access in good yields to trans dipeptide isosters in two steps starting from the corresponding α–amino aldehyde. Application of the present methodology for the synthesis of dipeptide isosters (**5**) and (**6**), starting from (**2**) and (**3**) respectively, is under way and will be reported in due course.

Table I. Rhodium (I) Isomerization of Hydroxy Alkynes[a].

Entry	Substrate	T° (C)	Phosphine[b]	Yield	Product(s)
(1)	 (7)	110°C	$(nBu)_3P$	82%	 (7a)
(2)	(7)	RT	$(nBu)_3P$	0%	starting material
(3)	(7)	110°C	None	0%	starting material
(4)	 (8)	110°C	$(nBu)_3P$	56%	 (8a)
(5)	 (9)	110°C	$(nBu)_3P$	76%	 (9a)
(6)	 (10)	110°C	$(nBu)_3P$	68%	 (10a)
(7)	 (9)	110°C	$(iPr)_3P$	82%[c]	 (9b) 1:1 (9c)
(8)	 (10)	110°C	$(iPr)_3P$	87%[c]	 (10b) 1:1 (10c)

[a] The reactions were performed on 1 mmol scale in toluene, in the presence of 3% of rhodium catalyst.
[b] 5% of trialkyl phosphine was used as catalyst.
[c] Combined yield of the recovered isomerized products.

Typical procedure: A solution of the hydroxy alkyne (9) (299 mg; 1mmol), tristriphenylphosphinerhodium (I) chloride (0.03 mmol, 27.75 mg) and tri-n-butylphosphine (0.05 mmol, 10.12 mg) in 5 ml of anhydrous toluene is heated under argon at reflux for 12 h. The reaction mixture was then cooled to room temperature, concentrated in vacuo and chromatographed on silica gel using petroleum ether-AcOEt (85:15) as eluant to

give 76% of the trans keto vinyl ester (**9a**). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.00 (d, J=15.8 Hz, 1H); 6.75 (d, J=15.8 Hz, 1H); 5.09 (br, 0.7H, NH); 4.48 (m, J= 7.3Hz, 1H); 4.12 (q, J= 7.12 Hz, 2H); 2.08 (m, 1H); 1.45 (s, 9H); 1.38 (t, J =7.12, 3H); 0.6–0.8 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 198.2; 165.2; 156.1; 136.8; 132.1; 63.4; 61.5; 30.1; 28.3; 19.8; 16.8; 14.1. $[\alpha]_D^{22}$ = +14.4 (c = 2, CH_2Cl_2).

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12. Intermediates (**7**) to (**10**) were prepared by the condensation of the lithium acetylide anion of ethylepropiolate on the corresponding aldehyde[13] in 47–69% yield. For the synthesis of the dipeptide isosteres, the α-amino aldehydes were obtained by Swern oxidation of the corresponding α–amino alcohols and were used crude in the condensation step to avoid any possible racemisation.
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