Tetrahedron: Asymmetry Vol. 4, No. 7, pp. 1645-1650, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00

SYNTHESIS OF OPTICALLY PURE ALKYNOLS

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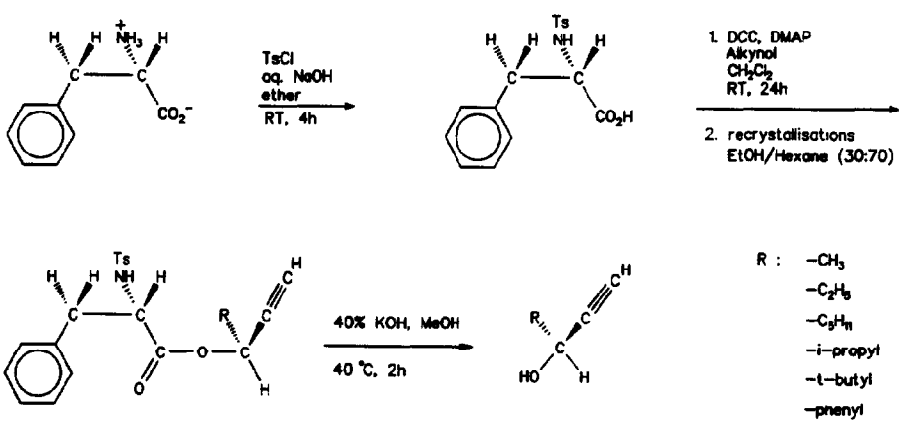
(*Received in UK* 6 *April* 1993; *accepted* 5 *May* 1993)

Abstract: (R,S)-1-alkylprop-2-yn-1-ols have been separated by a 2-step procedure, esterification with N-p-tosyl-(L)-phenylalanine (or valine), recrystallisation of the diastereomeric esters from ethanol/hexane and saponification of the optically pure esters.

To investigate their oligomerisation catalysed by metal complexes, optically pure 1-alkyn-3-ols were required in a larger quantity. In the literature a variety of different paths to enantiomerically pure 1-alkyn-3-ols has been reported [1]. Hashimoto prepared (S)-oct-1-yn-3-ol via its amino acid ester [1k]. We thought that this method might be suitable for larger quantities and therefore began to study its scope for the synthesis of enantiomers of 1-alkyn-3-ols (Scheme I).



Scheme I

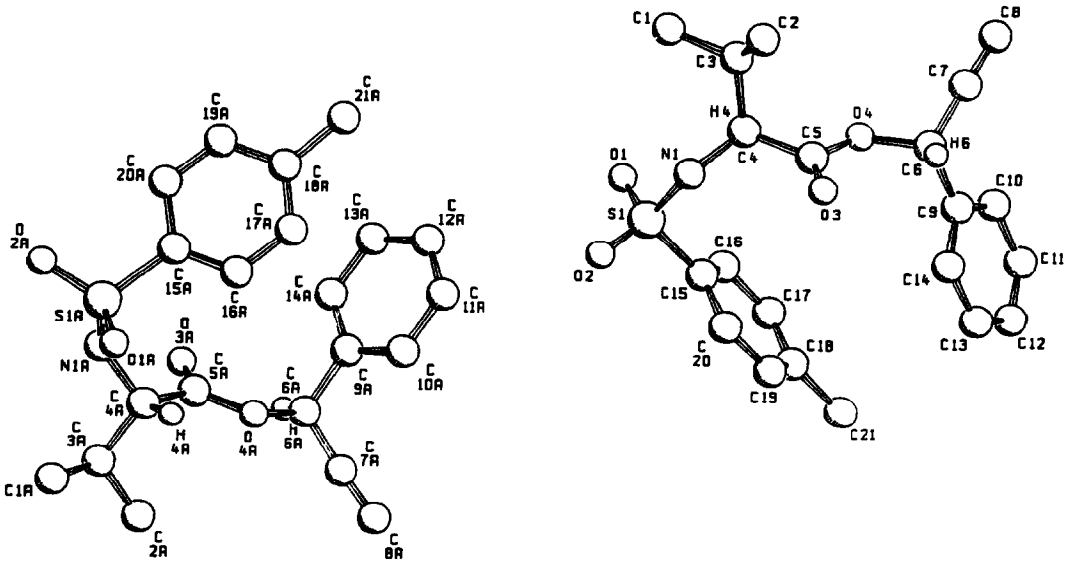
In contrast to Hashimoto the N-p-tosyl-(L)-aminoacid alkynol esters were not prepared using the acid chlorides, but two different N-p-tosyl-(L)-aminoacids [2] were directly esterified with the racemic alkynols at room temperature using N,N`-dicyclohexylcarbodiimide as a coupling reagent and 4-(dimethylamino)pyridine as catalyst [3] (Scheme I, 2nd step).

The diastereomeric N-p-tosyl-(L)-amino acid esters were recrystallized two or three times from ethanol/hexane until one of the esters was optically pure (NMR data Table 2 and 3). The diastereomeric excess of the esters has been checked by ^{1}H-NMR-spectroscopy (200 MHz) adding 0.2 equivalents of Eu(fod)$_3$ [4]. After saponification (Scheme I, 3rd step) the optically pure 1-alkyn-3-ols could be isolated by distillation in good yields.

The absolute configuration has been assigned by comparing the optical rotation of (S)-oct-1-yn-3-ol (α_D^{22} -22,1; c=1.0 in ether) and (R)-1-phenyl-prop-2-yn-1-ol (α_D^{27} -24,0; c=2.1 in ethanol) with reference values from the literature [1k,5] or by an X-ray structure analysis (Scheme II and III).

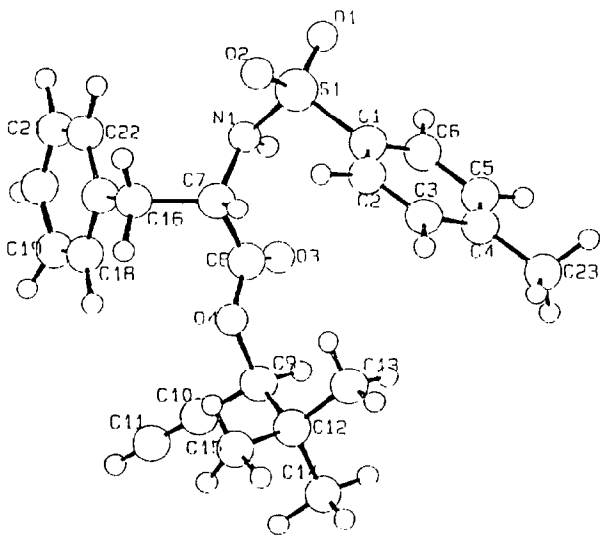
The crystal structure of the N-p-tosyl-(L)-valine-1-phenyl-prop-2-yn-1-yl ester (Scheme II) contains two conformational isomers in one elementary cell. Both isomers possess the absolute configuration R at carbon C6 respectively C6A. The C9-atom of N-p-tosyl-(L)-phenylalanine-4,4-dimethyl-pent-1-yn-3-yl ester has the same absolute configuration (Scheme III).

Our sequence of preparation abbreviates the synthesis by one step and it has the further advantage of a simpler work up and separation of the esters.



Scheme II: The crystal structure of the N-p-tosyl-(L)-valine-1-phenyl-prop-2-yn-1-yl ester. The crystals are monoclinic $P2_1$ with a= 10.526(1) A, b= 18.328(1) A, c= 11.172(9) A, ß= 106.56(1)°.

The attempt failed to resolve alk-1-yn-3-ols, which are disubstituted in the 3-position by this method. Only the acid anhydrides could be isolated.



Scheme III: The crystal structure of the N-p-tosyl-(L)-phenylalanine-4,4'-dimethylpent-1-yn-3-yl ester. The crystals are monoclinic $P2_1$ with a= 10.5055(6) Å, b= 5.6351(3) Å, c= 19.7666(8) Å, ß= 101.991(5)°.

Experiments:

N-p-tosyl-(L)-amino acids

800 ml of a solution containing 0.5 mol (L)-phenylalanine and 0.5 mol NaOH were layered with 300 ml diethylether containing 0.55 mol p-toluenesulfonic acid chloride. The two phases were well mixed by an ultraturax and 100 ml 5 M NaOH were added over a period of 4 hours. Thereupon the mixture was acidified and the upper layer separated. The aqueous phase has been extracted three times with 100 ml ether. From the combined organic solutions the solvent was distilled and the product recrystallized two times from ethanol. N-p-tosyl-(L)-valine has been prepared similarly. Analytical findings were conform with literature data [2].

Esterification

A solution of 0.05 mol N,N`-dicyclohexylcarbodiimide in 50 ml $CH_2Cl_2$ was added dropwise at 0°C to a solution of 0.05 mol of the N-p-tosyl-(L)-amino acid, 0.055 mol of the 1-alkyn-3-ol and 0.005 mol 4-(N-dimethylamino)pyridine in 200 ml $CH_2Cl_2$. The mixture was stirred for 24 hours. Thereupon the N,N`-dicyclohexyl urea was filtered. The solution was extracted two times with 100 ml 2 M acetic acid and two times with 100 ml H_2O. The organic phase was dried using $MgSO_4$ and then filtered over a 5 cm layer of silica gel. The silica was eluated with 500 ml CH_2Cl_2. The combined filtrates were evaporated under reduced pressure and the ester was recrystallized two to three times from ethanol/hexane (30/70); yields see Table 1. Spectroscopic data of the esters are given in the tables 1-3.

Saponification

About 0,02 mol of the ester was added to a solution of 70 ml ethanol and 40 ml 40% KOH. The mixture was warmed to 40°C for two hours. After distilling the ethanol, the alkynol was extracted with ether. The ether phase was dried with Na_2SO_4 and the alkynol was isolated by a fractional distillation with a yield of about 90%.

Table 1: Mass-spectroscopic data [EI], yield of the esters and absolute configuration of the alkynols.

Fragmentation: I= molecular peak [M], II= [M - $CH_3C_6H_4$], III= [M - $CH_3C_6H_4SO_2NH$], IV= [M - HCCCHRO]

R	fragmentation I	II	III	IV	yield [%]	absolute config.
	N-p-tosyl-(L)-phenylalanine ester					
-methyl	371	280	200	274	28	S
-ethyl	385	294	214	274	28	S
-octyl	427	336	257	274	31	S
-i-propyl	399	308	-	274	29	S
-t-butyl	413	323	-	274	30	R
-phenyl	433	342	-	274	29	R
	N-p-tosyl-(L)-valine ester					
-phenyl	385	294	-	-	25	R

Table 2: ^{13}C-NMR-data [ppm] in $CDCl_3$:

200 Mhz	^{13}C-atom No.						
R	1	2	3	4	5	6	7
	N-p-tosyl-(L)-phenylalanine ester						
-methyl	21.51	39.22	56.48	169.80	61.59	73.87	81.07
-ethyl	21.39	39.04	56.23	169.78	66.24	74.44	78.00
-octyl	21.53	39.28	56.37	169.84	65.43	74.45	80.23
-i-propyl	21.37	39.10	56.17	169.79	70.06	74.97	78.60
-t-butyl	21.56	39.16	56.04	169.84	73.03	75.74	78.74
-phenyl	21.55	39.16	56.41	169.78	61.57	73.89	81.01
	N-p-tosyl-(L)-valine ester						
-phenyl	21.47	31.99	60.69	170.30	66.26	76.12	79.10

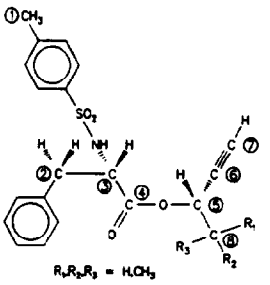
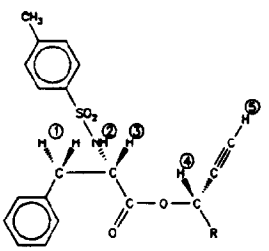


Table 3: ^{1}H-NMR-data [ppm] in $CDCl_3$:

200 Mhz	^{1}H-atom No.				
R	1	2	3	4	5
	N-p-tosyl-(L)-phenylalanine ester				
-methyl	3.04 d J=5.50 Hz	5.05 s -	4.20 m -	5.17 m -	2.45 d J=2.06 Hz
-ethyl	3.07 d J=5.64 Hz	5.05 m -	4.23 m -	5.05 m -	2.46 d J=2.17 Hz
-octyl	3.06 d J=5.65 Hz	5.03 m -	4.22 m -	5.10 m -	2.46 d J=2.16 Hz
-i-propyl	3.08 d J=5.67 Hz -	5.11 d J=9.36 Hz -	4.23 m - -	4.96 dd J=2.14 Hz J=5.66 Hz	2.46 d J=2.25 Hz -
-t-butyl	3.08 d J=5.56 Hz	5.09 d J=9.28 Hz	4.23 m -	4.85 d J=2.03 Hz	2.44 d J=2.05 Hz
-phenyl	3.08 d J=5.69 Hz	5.12 d J=9.32 Hz	4.28 m -	6.19 d J=2.35 Hz	2.67 d J=2.06 Hz
	N-p-tosyl-(L)-valine ester				
-phenyl	3.76 q J=4.92 Hz	5.32 d J=10.05 Hz	2.11 m -	6.11 d J=2.18Hz	2.61 d J=2.25 Hz



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