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A NEW PROTECTING GROUP FOR AMINES. SYNTHESIS OF ANTICAPSIN FROM L-TYROSINE[1]

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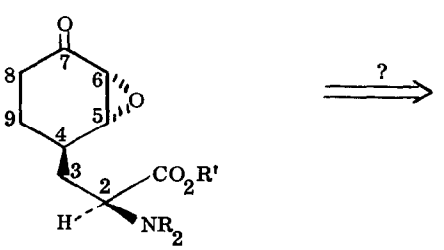
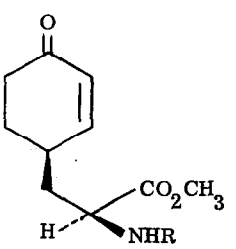
Summary: An acid and base-stable, nucleophile-resistant protecting group for primary amines and α-amino acids is described which has been used in a synthesis of the title compound.

While most amine protecting groups often diminish nitrogen's basicity they do not entirely eliminate its nucleophilic character. This is particularly true for primary amines whose amides can still undergo substitutions, conjugate additions and ring-forming processes. Then it sometimes becomes necessary to block the R-NH_2 function with tertiary substitution. As an alternative to the very stable, commonly-used phthalimide derivative,[3] we have perfected an acid and base-resistant protecting group which is inert to nucleophiles and can readily be removed during a complex synthesis. Here we describe applications of the N,N-diallyl moiety and its utility in the first chiral total synthesis of anticapsin 1.[4-6] This naturally occurring α-aminoacid antibiotic originates by an unknown mechanism from shikimic acid in microorganisms[5,7] and serves to inhibit the formation of hyaluronic acid capsules in Group A streptococci.

Our initial strategy to approach 1 from the Birch reduction product of L-tyrosine-O-methyl ether was thwarted by the ease with which amino or amido-enones like 2 undergo 1,4-addition forming 6-oxo-octahydroindoles.[8]





1 R, R' = H

7 R = $CH_2CH=CH_2$, R'=CH_3

2 R = H, $COCH_3$, $COCF_3$

TABLE

Deallylation of N,N-Diallylamines

Substrate[a,b]	$[\alpha]_D^{23}$	Product (% Yield)
N,N-diA-OMe-L-tyr-OMe (84)	-2.9° (c 1, CH_2Cl_2)	OMe-L-tyr-OMe (85)
N,N-diA-L-tyr	+7.4° (c 2, AcOH)	L-tyr (70)
N,N-diA-L-phe-OMe (75)	-50.8° (c 0.8, CH_2Cl_2)	L-phe-OMe (76)
N,N-diA-L-try-OMe (62)	-5.6° (c 1, CH_2Cl_2)	L-try-OMe (70)
1-adamantyl-diallylamine	———	1-adamantylamine (65)[c]
n-decyldiallylamine	———	n-decylamine (90)[c]

(a) diA = diallyl; (b) Numbers in parentheses refer to distilled or recrystallized yields from the primary aminoester; (c) This lower yield is due to inadvertent sublimation of product during vacuum drying.

EXPERIMENTAL

The following are typical experimental procedures for the protection and deprotection steps described in the Table.

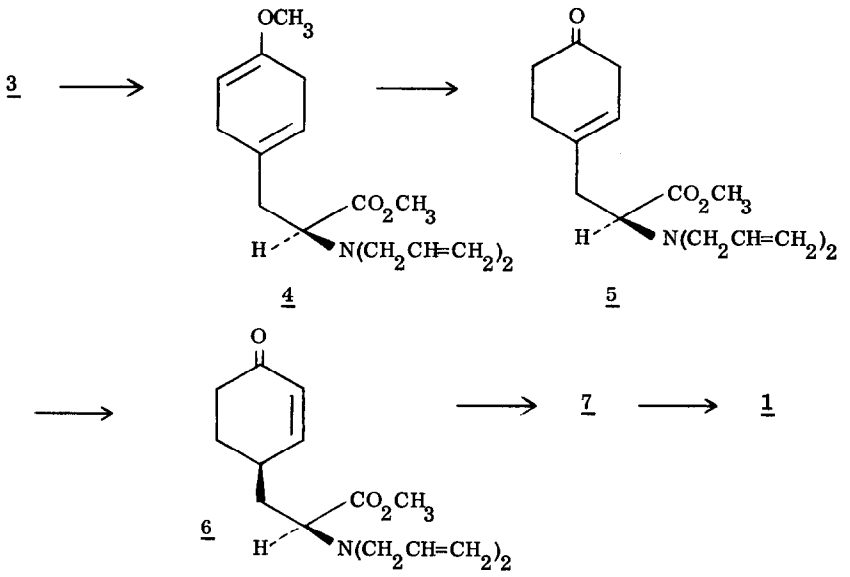
(1) Allylation of O-methyltyrosine methyl ester. - A flame-dried, 250 mL, 3-necked flask containing O-methyltyrosine methyl ester (4.0 g, 19.1 mmol) in toluene (40 mL) was fitted with N_2 inlet, addition funnel and condenser, then cooled to 0°. Diisopropylethylamine (7.42 g, 50.5 mmol) was added to the solution, followed by allyl bromide (20.3 g, 168 mmol) dropwise over 10 minutes. The resulting yellow solution was warmed to rt, then to reflux for 1.5 h by which time a white precipitate had appeared. After cooling, the separated solid was filtered and washed several times with toluene. The combined toluene layers were concentrated in vacuo to a red-brown liquid which, upon column chromatography (Brinkmann Silica Gel 60) and kugelrohr distillation, afforded 4.63 g (84%) of N,N-diallyl-O-methyltyrosine methyl ester as a colorless oil.

(2) Deallylation of 1-adamantyldiallylamine. - A mixture of adamantyldiallylamine (.250 g, 1.08 mmol) and $(Ph_3P)_3RhCl$ (.053 g) in 25 mL of 84 : 16 $CH_3CN : H_2O$ was prepared in a magnetically stirred 50 mL round-bottom flask. A Claisen adapter fitted with reflux condenser and addition funnel on one arm and with short path distillation head on the other was then attached to the reaction vessel. The addition funnel was charged with excess 84 : 16 $CH_3CN : H_2O$, the system flushed with N_2 and brought to vigorous boiling. Fresh solvent was added to replace the volume of liquid swept out the distillation head and into a cooled (-70°) receiver by a slow stream of N_2. After 2h the reaction was judged complete by TLC and the solvents removed in vacuo to leave .25 g of a brownish solid. Flash chromatography eluting successively with 1 : 1 $CH_3OH : CHCl_3$ then with 95 : 5 $CH_3OH : NH_4OH$ furnished 1-adamantylamine (.106 g, 65%) after concentration and vacuum drying.

Since allyl systems can be converted to their propenyl isomers by various transition metal complexes,[9,10] N-allylation might permit substituted relatives of 2 to exist in stable form. We have found that N,N-diallyl derivatives of primary amines and α-aminoacids or esters are easily made (see Table) and can be smoothly reconverted to their parent substances using Wilkinson's catalyst. Evolution of propionaldehyde confirms the allyl-to-propenyl isomerization followed by in situ enamine hydrolysis. Results summarized in the Table indicate the high yields for this process and the method's generality.

Since decarbonylation of endogenous propionaldehyde converted the catalyst to much less active $(Ph_3P)_2RhCOCl$,[11] it was essential to remove aldehyde as it formed. In CH_3CN-H_2O at reflux, isomerization proceeded at a convenient rate so that with slow continuous distillation of solvent, both allyl residues were cleaved within 2-4h. No racemization of α-aminoesters was observed. Entry 6 in the Table suggests the utility of diallylamine alkylations as a practical alternative to the classical Gabriel reaction.

The synthesis of (+)-anticapsin proceeded as follows. Reduction of N,N-diallyl-O-methyl-L-tyrosine 3 [mp 101-103.5°C, $[\alpha]_D^{25}$ + 7.4° (c, 2.00, CH_3CO_2H)] with lithium (8 equiv) in NH_3-EtOH followed by esterification of the crude salt (CH_3I-HMPA-H_2O) furnished diene ester 4 $[\alpha]_D$ -9.9° (c, 1.00, CH_2Cl_2) in 83% yield from 3 [NMR δ ($CDCl_3$) 6.01-5.00 (m, 7H), 4.62 (broad s, 1H); IR λ_{max} (film) 5.75 mμ]. Hydrolysis of 4 in 1% HCl afforded β,γ-enone 5 [100%, $[\alpha]_D$ -7.4° (c, 1.00, CH_2Cl_2)].[12] Of the two diastereomeric conjugated ketones arising from acid-catalyzed isomerization of 5 (.3N HCl-DMSO), 2S, 4R-enone 6 was obtained pure by HPLC on μ-Porasil™ [30-35%; $[\alpha]_D$ -16.2° (c, 1.00, CH_2Cl_2)][12] and converted to a mixture of cis and trans epoxides (5:2 ratio) with 30% H_2O_2 ($NaOCH_3$, CH_3OH, O°, 1h). Exposure of chromatographically homogeneous N,N-diallylanticapsin methyl ester 7 [23% after HPLC, $[\alpha]_D$ -29.9° (c, 1.00, CH_2Cl_2)] to $(Ph_3P)_3RhCl$ (0.2 equiv, CH_3CN-H_2O, reflux, 4h) furnished a mixture of 1 and its methyl ester.[13] Saponification (1 equiv NaOH, 0°, 15 min) and cellulose chromatography gave (+) anticapsin, $[\alpha]_D^{25}$ +4° (c, 0.2, H_2O). Since natural anticapsin obtained from Eli Lilly and Co. showed $[\alpha]_D^{25}$ +21° (c, 0.2, H_2O),[14] some epimerization may have occurred in base.[15] Synthetic and natural 1 were otherwise indistinguishable by NMR and in numerous chromatographic systems.[16]



REFERENCES AND FOOTNOTES

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12. Satisfactory IR, PNMR, MS and elemental analysis data were obtained for a chromatographically pure sample of this substance.
13. This substance could be obtained pure by cellulose chromatography. Unlike anticapsin, whose mass spectrum cannot be obtained, the methyl ester of 1 exhibited m/e (CI) 214 (M+1).
14. Lit. $[\alpha]_D^{25}$ +125° (c, 1, H_2O) [Ref. 4b]. We were unable to reproduce this value at lower concentrations.
15. The three remaining cis,trans diastereomers of 6 were also deallylated and saponified. None other corresponded both in rotation and NMR spectrum with anticapsin. Since the rotation of the C2 epimer of 1 is unknown, one referee has argued that our observed rotation of +4° does not per se guarantee the presence of (+)anticapsin. This could in principle be true.
16. We are indebted to the National Institutes of Health for grant support (GM24054) and for a predoctoral traineeship to BCL (GM97273).

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