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Synthesis of (2S, 3R, 4S)-3,4-Methanoproline and Analogues by Cyclopropylidene Insertion

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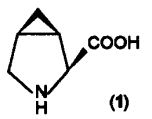
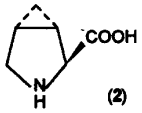
Abstract: Intramolecular insertion of single enantiomers of cyclopropylidenes into 5,6-related C-H bonds adjacent to nitrogen has been used to obtain enantiomerically pure methanoproline and a number of analogues with a high degree of one- or two-fold asymmetric induction. © 1997 Elsevier Science Ltd.

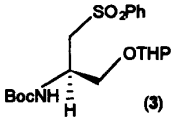
Although methanoproline (**1**) was isolated some years ago from the American horse chesnut, *Aesculus parviflora*,[1] it is still attracting considerable attention.[2,3] It was shown to be a potent inhibitor of proline metabolism;[4] as such it was targeted as a potential chemical control agent in the production of hybrid wheats.[5] In addition, methanoproline inhibits the proline transport system of *Escherichia coli*,[6] while amide derivatives of methanoproline are inhibitors of angiotensin converting enzyme.[7] Although a number of routes to racemic methanoproline have been reported,[8] only one synthesis of enantiomerically pure (**1**)[9] and one synthesis of the N-Boc derivative have appeared.[10] The first involves the cyclopropanation of dehydroproline in a reaction which is not very diastereoselective and from which the major product is the trans-isomer (**2**).



(1)

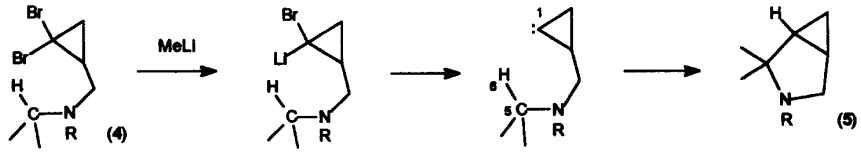


(2)



(3)

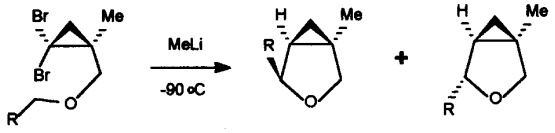
The second involves the coupling of two chiral starting materials, (**3**) and (2R)-glycidyl triflate, followed by cyclisation and functional group interconvertion to give N-Boc protected (**1**) in seven steps with overall yield of less then 25 %. We reported some years ago that 2-dialkylaminomethyl-1,1-dibromocyclopropanes such as (**4**) react with methyllithium to give 3-azabicyclo[3.1.0]hexanes (**5**) by a formal insertion of the derived cyclopropylidene or a related carbenoid into the CH-bond adjacent to nitrogen and 5,6-related to the carbene centre:[11]



(4) (5)

It has also been shown that a similar insertion of cyclopropylidenes derived from the ethers (**6a**) and (**6b**)

by reaction with methyllithium leads to the 3-oxabicyclo[3.1.0]hexanes (**7a**) and (**7b**) with a moderate to high diastereoselectivity for the endo-R isomer.[12]

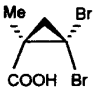


(**6a**-(±), R = Vinyl) (**7a**, R = Vinyl, 73 %, endo/exo = 17:1)

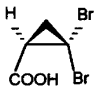
(**6b**-(±), R = t-PhCH=CH) (**7b**, R = t-PhCH=CH, 41 %, endo/exo = 7:1)

We now report the application of the insertion reaction to the synthesis of methanoproline and of a number of related compounds each as a single enantiomer. The method has the advantage that, although involving a number of steps, the starting materials are cheap and readily available on a large scale and the reactions involved are generally extremely high yielding; moreover it may be varied to produce in principle any required stereoisomer and a range of analogues.

Reaction of methyl methacrylate with bromoform and base leads very readily to 2,2-dibromo-1-methylcyclopropane carboxylic acid;[13] this is simply resolved using dehydroabietylamine in methanol to give (**8**, R) and its enantiomer, and the absolute stereochemistry of the amide of (**8**, R) has been established by X-ray crystallography.[14] The corresponding non-methylated acid (**9**, R) and its enantiomer were readily obtained on a multi-gram scale by oxidation of 1,1-dibromo-2-vinylcyclopropane with potassium permanganate to give 2,2-dibromocyclopropane carboxylic acid followed by resolution of this with dehydroabietylamine.[14]



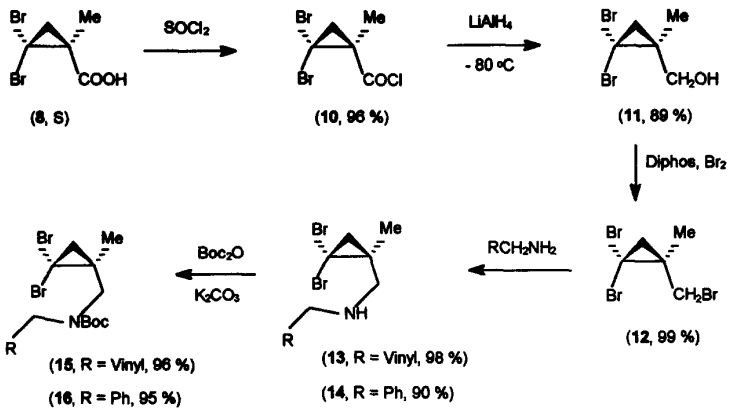
(**8**, R)



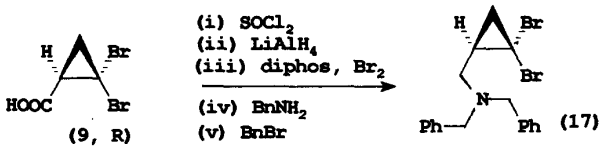
(**9**, R)

The acid (**8**, S) (>99% e.e.) was converted into the corresponding acid chloride by reaction with thionyl chloride, and this was reduced to the alcohol (**11**) by reaction with lithium aluminium hydride. This route was chosen in order to avoid competing reduction of the dibromocyclopropane to the corresponding isomeric monobromides. It was necessary to add a solution of the acid chloride in ether to lithium aluminium hydride in ether at - 80 °C, as addition of the hydride to the acid chloride led to up to 30 % of an ester derived by reaction of the product alcohol with the acid chloride. At higher temperatures monobromides were formed in addition to dibromides. The alcohol (**11**) was converted into the corresponding bromide (**12**) by reaction with 1,2-bis(diphenylphosphino)ethane and bromine, and reaction of this with either allylamine or benzylamine gave the amines (**13**) and (**14**).*

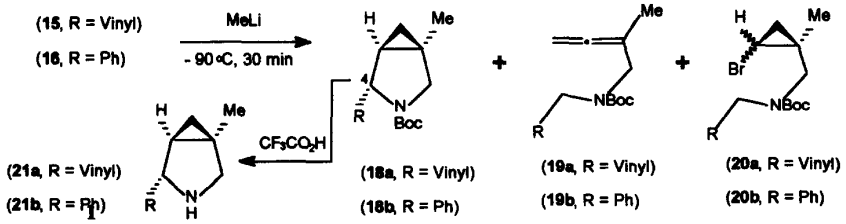
* Attempted direct reduction of amides of acid (**8**, S) to amines with LAH, $NaBH_4$ or $BH_3{\cdot}SMe_2$ led to mixtures of products. Attempts to make the tosylate from the alcohol (**11**) led to only a moderate yield.



By a similar sequence of reactions, the acid (**9**, R) (93 % e.e.) was converted into the dibenzylamine (**17**) in an overall yield of 86 %. Attempts to prepare (**17**) from 1,1-dibromo-2-bromomethylcyclopropane derived from (**9**, R) directly by reaction with dibenzylamine led to only 80 % yield of (**17**) after 4 days at 50 °C.



The amines (**13**) and (**14**) were protected as their Boc derivatives (**15**) and (**16**); reaction of these with methyl lithium led to a mixture of products, the major component of which was the azabicyclo[3.1.0]hexane (**18a**) or (**18b**) respectively. The yields of each of the products were highly dependent on the reaction conditions (Table 1). The stereochemistry of the allyl and phenyl groups in (**18a**) or (**18b**) was assigned on the basis of the fact that the signal for H-4 in the proton NMR spectrum in each case appeared as a singlet rather than the doublet expected for the epimer.[12,15] Moreover, in each case these compounds showed the signals for two rotamers about the amide bond by ^{1}H and ^{13}C NMR; deprotection gave the amines (**21a**) and (**21b**) which showed only the expected number of signals in ^{1}H and ^{13}C NMR.

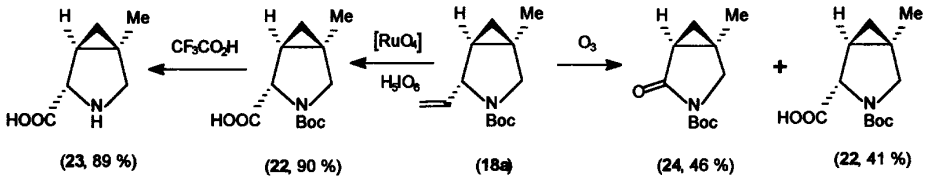


Reactions of (15) and (16) with methyl lithium

Starting material	Temperature during reaction, °C [a]	Compounds determined by NMR in reaction mixture, yields, % [b]				
		(18)	(19)	(20) [c]	unknown substance [e]	starting material
(15)	20	40	45	9	2	-
	-30	50	19	17	7	3
	-60	61	8	16	2	1
	-90	49	8	29	8	1
(16)	20	40 [d]	27	7	1	11
	-90	25 [d]	8	17	3	24

a) Addition time was 5 min; stirring time was 30 min; b) these data were confirmed by glc; c) stereochemistry of monobromides was not determined; d) isolated yield; e) this might be the diastereomer of monobromide c.

Although the purified yield of (18a) obtained in this way was only 47 %, it could readily be converted into the methanoproline analogue (23) by oxidation with ruthenium tetroxide, generated *in situ* from $RuCl_3$, followed by deprotection. Attempted ozonolysis also led to (22) but in this case a second product was the lactam (24).



The amine (14) was benzylated by reaction with benzyl bromide to give (25). In contrast to (16), the dibenzylamine (25) reacted with methyllithium to give the endo-phenyl isomer (26) as the major product (Table 2):

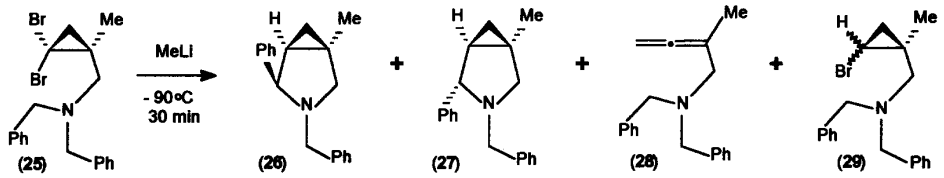


Table 2. Reaction of compound (25) with methyl lithium.

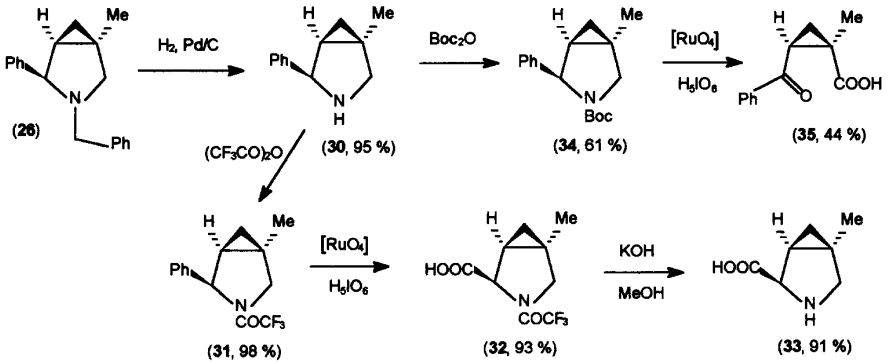
Temperature during reaction, °C [a]	Compounds determined by NMR in reaction mixture, yields, % [b]			
	(26)	(27)	(28)	(29) [c,f]
20	56	5 [d]	33	-
-90	90	1.8 [d]	2	6

a, b, c, d see Table 1; f) strucure assigned on the basis of cyclopropane signals in the ^1H NMR of the mixture of (26), (28) and (29).

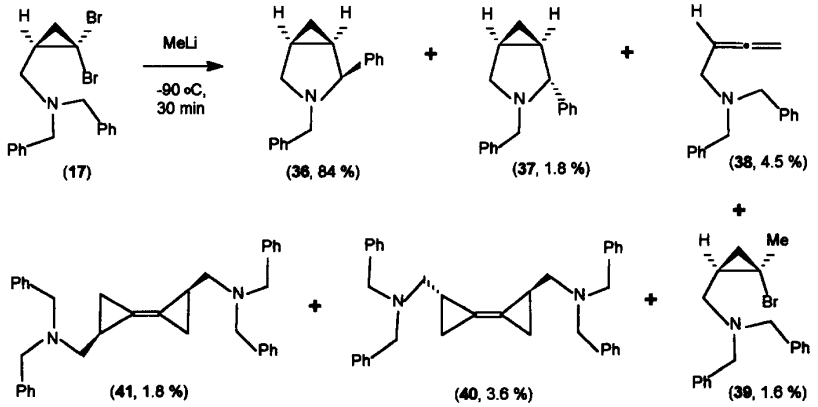
The amine (26) could be separated from its bicyclic isomer (27) by chromatography (96 %, >90 % pure).

It could be obtained pure by removal of the impurities (**28**) and (**29**) by selective debenzylation with hydrogen and a catalyst (5 % Pd/C, 0.01 mol.eq., 1 h) followed by flash chromatography.

The crude amine (**26**) was debenzylated to (**30**) under more vigorous conditions (0.05 mol.eq. of the same catalyst, 15 h). Protection by trifluoroacetylation, then oxidation of the phenyl group by reaction with ruthenium tetroxide at 80 °C for 3 h gave (**32**), and then deprotection gave the aminoacid (**33**), a second methylated analogue of methanoproline. It is interesting to note the remarkable stability of CH and CH_2 groups near nitrogen to oxidation under these conditions. It is well known that ethers RCH_2OMe (R=Ph or Alk) can readily be oxidised to esters with ruthenium tetroxide even at room temperature.[16] Attempts to oxidise (**31**) with ruthenium tetroxide at 20 °C even using more catalyst and for 1 day were unsuccessful. In the case of the Boc - protected amine (**34**), ruthenium tetroxide oxidation at room temperature led to ring opening, to give (**35**).



Reaction of (**17**) with methyl lithium gave one major product (**36**) together with a number of minor products with structures typical of those usually obtained in similar reactions of non-functionalised dihalo-cyclopropanes.[17]



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