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A Novel Synthesis of nor-C-Statine.

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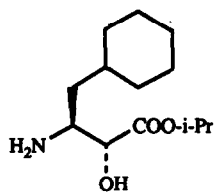
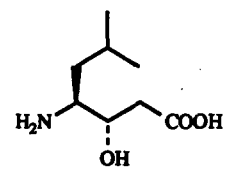
Abstract: A new synthesis of nor-C-statine is described. Benzylation of a malate dianion, differentiation of the two carboxylates and a Hofmann degradation of one of the carboxylates constitute the key steps of the synthesis.

The isopropyl ester of nor-C-statine (1), a mimic of statine (2), has been used by Pfizer and other companies in the synthesis of renin inhibitors.[1]



nor-C-Statine

1

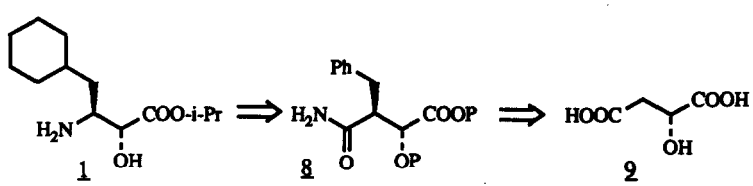


Statine

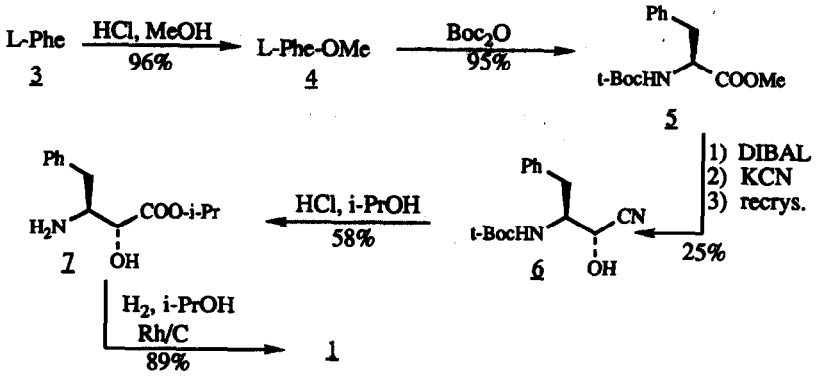
2

Nor-C-Sta was originally prepared as shown in Scheme 1.[2] Although the cyanohydrin reaction produces a mixture of diastereomers, the desired diastereomer can be obtained in pure form by crystallization. We typically obtain a 25% overall yield of the desired cyanohydrin. Although suitable for small scale work this route was not acceptable for the preparation of large quantities of 1. We therefore undertook a new synthesis of 1.

We envisioned amide 8 as a key intermediate. Hofmann rearrangement of 8, known to occur with retention of configuration at the migrating carbon, should introduce the amino group of 1 in the proper configuration. Amide 8 should be easily prepared from (R)-malic acid (9).

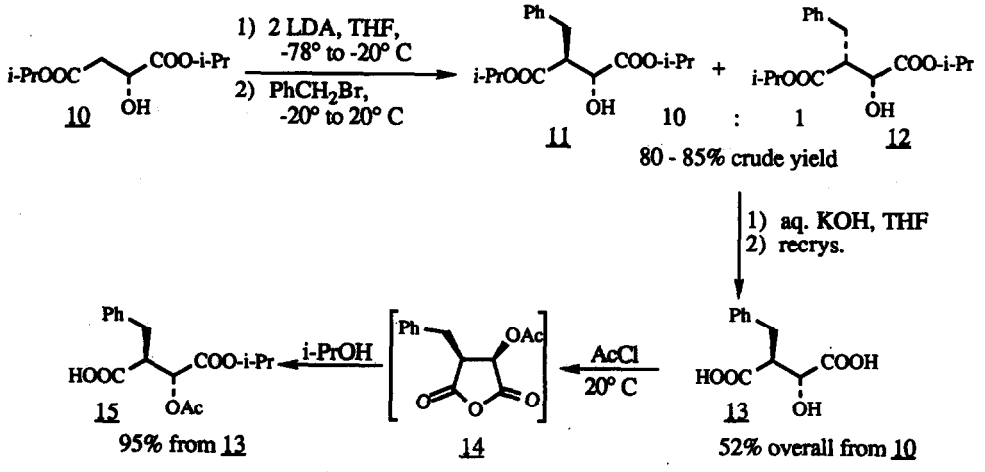


Scheme 1



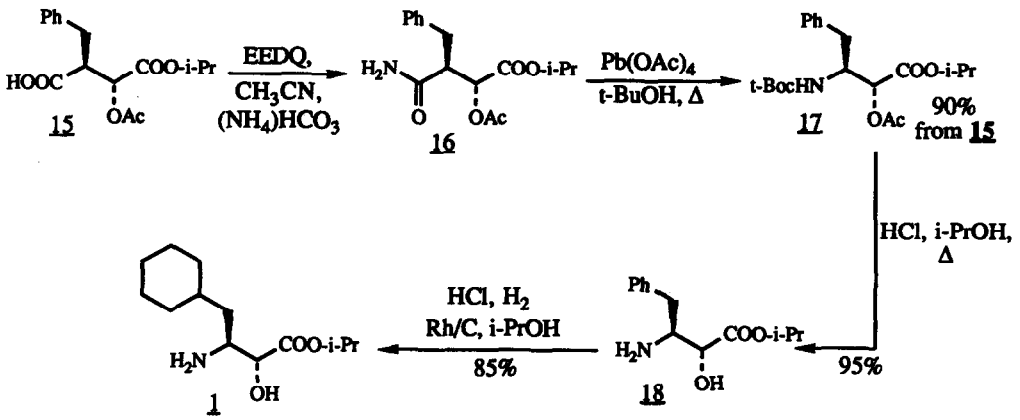
Alkylation of malic acid esters has already been reported.[3] We found that diisopropyl malate gave higher yields than either diethyl or dimethyl malate, presumably due to reduced ester-enolate condensations. The added steric hindrance necessitated raising the temperature of enolate formation to -20° C in order to ensure complete deprotonation. In our hands, alkylation of (R)-10 provides an 80-85% crude yield of a 10:1 mixture of diastereomers (Scheme 2). Purification and separation was accomplished by hydrolysis of the crude mixture followed by recrystallization of diacid 13 from either $CHCl_3$ or EtOAc/hexane. This procedure provided 13, diastereomerically pure, in 52% overall yield from diisopropyl malate. Treatment of diacid 13 with acetyl chloride (5 eq.) either neat or in CH_2Cl_2 followed by removal of the excess acetyl chloride and reaction with isopropanol produced monoester 15, regiochemically pure, in 95% yield.

Scheme 2



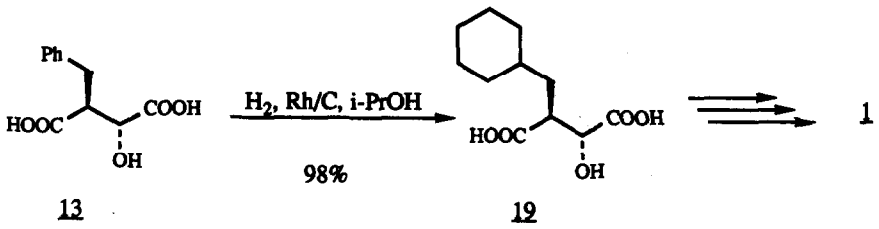
Acid 15 was converted to amide 16 with EEDQ[4] and $(NH_4)HCO_3$ (Scheme 3). The same transformation can be accomplished with ethyl chloroformate and Et_3N followed by NH_3 but in lower yield. The operational ease and mildness of the EEDQ reaction makes it ideal for this transformation. The crucial Hofmann degradation was accomplished by reaction of 16 with $Pb(OAc)_4$ in refluxing t-BuOH[5], the intermediate isocyanate being trapped by t-BuOH yielding the t-Boc protected amine 17 in 90% overall yield from monoacid 15. The use of other methods for the Hofmann degradation [Br_2, NaOH or $PhI(OOCCF_3)_2$] generally gave lower yields and a product of lower purity. Removal of the protecting groups was accomplished by treatment with HCl in refluxing i-PrOH (95% yield). Hydrogenation of 18 with Rh/C provided 1 in 85% yield. This process produces 1 in 38% overall yield from diisopropyl malate.

Scheme 3



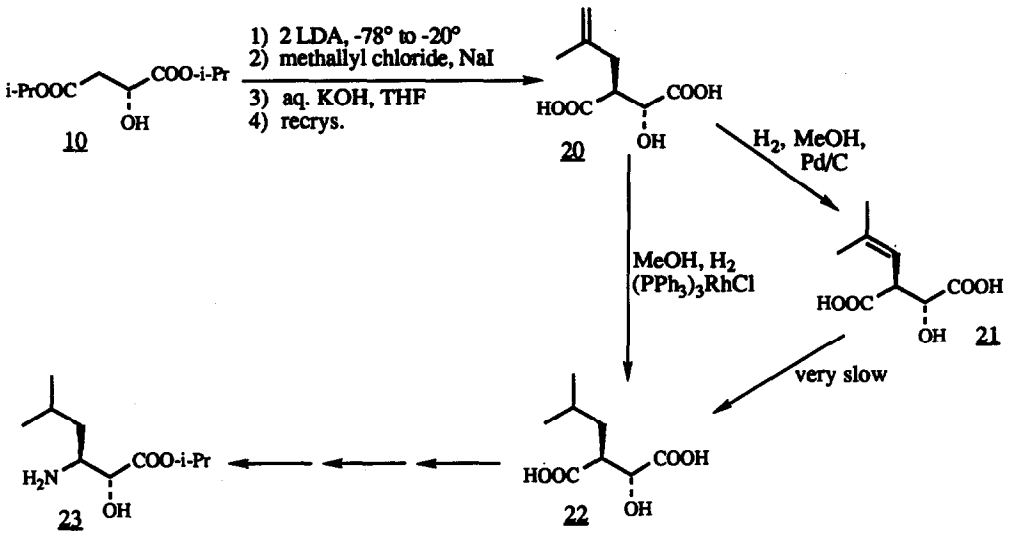
Alternatively, one can hydrogenate diacid 13 to cyclohexyldiacid 19 (Scheme 4, 98% yield). Hydrogenation at this stage requires less catalyst and facilitates isolation. Carrying 19 through the same sequence of reactions as before furnishes 1 in 43% overall yield from diisopropyl malate, however the lack of a UV chromophore makes analysis of the process intermediates somewhat more difficult.

Scheme 4



The same process has been used to prepare nor-statine (23) in similar overall yield (Scheme 4). Interestingly, the attempted hydrogenation of 20 with H_2 and Pd/C rapidly isomerized 20 to the trisubstituted olefin 21, which was very slow to reduce to 22. The use of Wilkinson's catalyst prevented the isomerization and cleanly provided 22. Diacid 22 was carried on to nor-statine (23) by the same sequence used for the preparation of 1.

Scheme 5



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