Stereoselective Intramolecular Radical Addition of Polyhaloacetyl Functions to 2-Oxazolones. A Facile Synthesis of Statine and Its 2,2-Dichloro and 2,2-Difluoro Analogues

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Summary: Intramolecular Ru(II)-catalyzed cyclization of 3-[[(1*S*,2*R*)-2-[(polyhaloacetoxy)ethoxy]-1-apocamphanyl]carbonyl]-2-oxazolones results in the exclusive formation of the 12-membered cycloadducts with *complete* diastereoselectivity, thus providing a new synthetic route to enantiomerically pure statine analogues including dichloro and difluoro derivatives.

The unusual amino acid statine[1] (4-amino-3-hydroxy-6-methylheptanoic acid) is a key component of pepstatin, a naturally occurring pentapeptide and a general aspartyl protease inhibitor. Designed as mimics of the transition state associated with peptide bond hydrolysis,[2] numerous pepstatin-based inhibitors of aspartyl proteinases have been prepared containing statine skeletal analogues, including difluoro amino acids.[3] In this paper, we describe a completely stereoselective and facile synthetic approach to statine analogues, including 2,2-dihalo-3-hydroxy-4-amino carboxylic acids.[4] The key step involves the highly efficient intramolecular addition of haloacetyl radicals to 2-oxazolone derivatives, permitting introduction of C_2-units at the 5-position with extremely high diastereoselectivity.

The intermolecular ruthenium(II) [$RuCl_2(PPh_3)_3$]-catalyzed addition of methyl trichloroacetate and trichloroacetonitrile to 3-[[(1*S*)-2-*exo*-(methoxyethoxy)-1-apocamphanyl]carbonyl]-2-oxazolone (**3**)[5] or 3-(1*S*)-ketopinyl-2-oxazolone[5] resulted in nondiastereoselective formation of the 1:1 adducts in only poor yield.[6]

In sharp contrast, the chiral 3-acyl-2-oxazolone **4**, derived from DPPOx (**1**)[5a] and (1*S*)-2-*exo*-[(trichloroacetoxy)-ethoxy]-1-apocamphanecarboxylic acid (**2**: R = $COCCl_3$), underwent unexpectedly favorable intramolecular cyclization to the 12-membered lactone **9**[7] with perfect regio- and diastereoselectivity on heating with a catalytic amount of $RuCl_2(PPh_3)_3$[8] The trichloro macrolide **9** was treated with bonding methanol to give a quantitative yield of the 4-methoxycycloadduct (**11a**), the structure of which was confirmed by X-ray crystallographic analysis[9] (Scheme II). Similarly, the bromodifluoroacetyl derivative **5**, readily prepared from the (bromodifluoroacetoxy)apocamphanecarboxylic acid (**2**) (R = $COCBrF_2$), gave **10**,[10] which was methanolyzed to the 4-methoxy-2-oxazolidinone derivative **11b**, free from the other diastereoisomer, in 87% yield (two steps). The chlorodifluoroacetoxy derivative **6** and bromoacetoxy derivative **7** were unreactive under the Ru(II)-catalyzed radical conditions. The extremely high diastereoselectivity can be rationalized by assuming a favored conformation (**8**) similar to that revealed by the X-ray crystal structure of the *N*-acyl-2-oxazolone **3**[5b] with the anti-coplanar amide carbonyl groups.

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(6) The Ru(II)-catalyzed reaction of **3** with methyl trichloroacetate at 100 °C for 7 d gave the *trans*-4-chloro-5-[(methoxycarbonyl)methyl]-2-oxazolidinone derivative as a 1:1 diastereomeric mixture in 6% yield.

(7) General procedure for intramolecular cyclization is as follows. To a solution of the polyhaloacetoxy derivative **4** or **5** (0.5 mmol) in benzene (28 mL) was added $RuCl_2(PPh_3)_3$ (0.038 mmol), and the whole mixture was refluxed under argon atmosphere for 72 h (high dilution was not necessary). Chromatographic purification on silica gel followed by methanolysis gave the *gem*-dihalogeno-containing cycloadducts **11** and **11b** in 93% and 87% yields (two steps), respectively.

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(10) The combustion analysis and mass spectral data for **10** showed contamination with the 4-chloro derivative (**10**: X = F, X′ = Cl). This was inseparable by recrystallizaton and chromatography.

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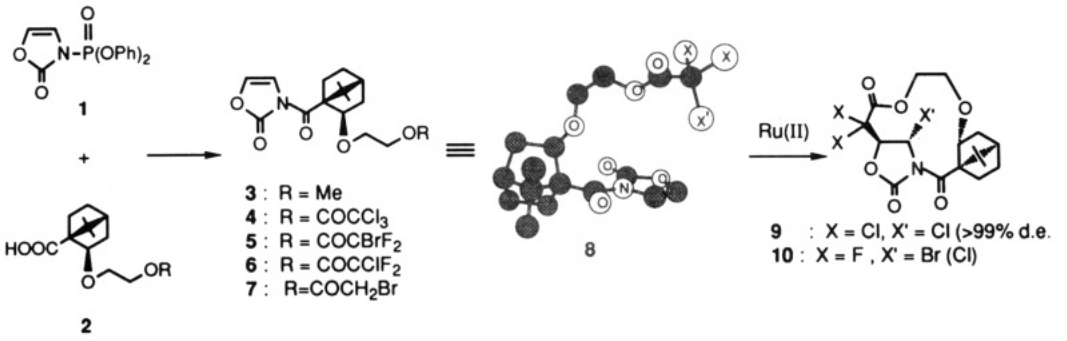
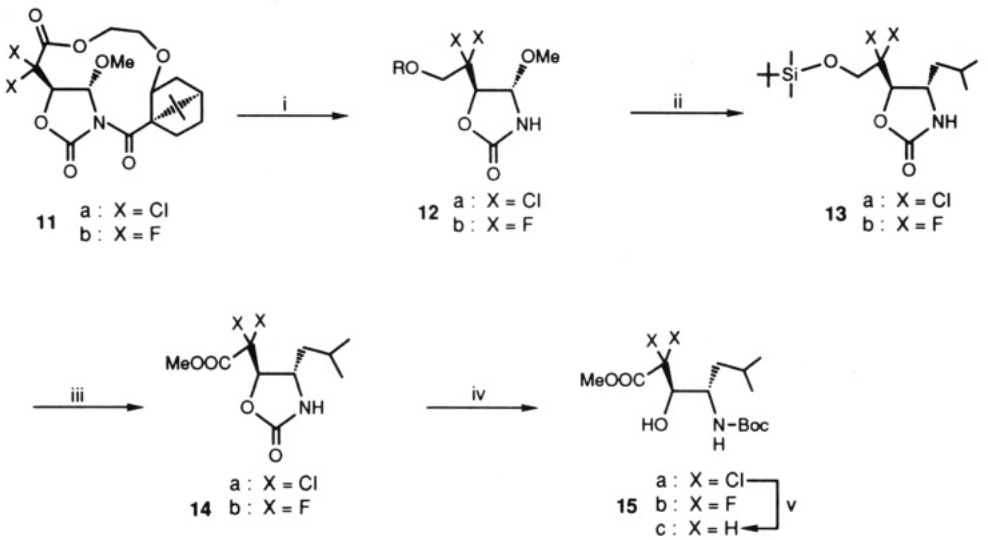
Scheme I



Scheme II



The enantiomerically pure 2-oxazolidinones **11a** and **11b**, thus obtained, were then successfully used for the synthesis of optically active statine and dihalogenostatine analogues as outlined in Scheme II. It is generally difficult to remove sterically congested acyl groups such as apocamphanecarbonyl from oxazolidinones, and conventional reagents for cleavage such as $PhCH_2SLi$[11a] and H_2O_2/LiOH[11b] were unsatisfactory. Instead, reductive cleavage with $LiBH_4$/MeOH[12] proceeded smoothly to give good yields of the 5-(hydroxyethyl)-4-methoxy-2-oxazolidinones **12a** and **12b** (R = H) in addition to 2-*exo*-(hydroxyethyl)-1-apocamphanemethanol. The compounds **12a** and **12b** have potential as versatile chiral building blocks for a wide variety of 3-hydroxy-4-amino carboxylic acids of medicinal interest including difluorostatine, since reliable methods are available for the direct substitution of the 4-methoxy group by a variety of alkyls, alkenyls, and aryls.[13] For example, treatment of **12a,b** (R = TBDMS) with *i*-BuCu(CN)MgBr in the presence of $BF_3{\cdot}OEt_2$ gave the corresponding 4-isobutyl derivatives **13a,b** with complete retention of configuration.[14]

According to the conventional procedures shown in Scheme II, compounds **13a,b** were readily converted to the enantiomerically pure *N*-*t*-Boc-dihalostatine methyl esters **15a,b** by Jones oxidation to the esters **14a,b**, followed by ring cleavage. Reductive dechlorination of (3*R*,4*S*)-dichlorostatine (**15a**) with dibutyltin hydride in the presence of of AIBN at 80 °C smoothly gave a quantitative yield of (3*S*,4*S*)-statine derivative **15c**.[1,13] This allows convenient preparation of deuterated or tritiated amino acids.

In conclusion, a highly diastereoselective and versatile synthetic route to a variety of statine analogues, including difluoro amino acids, has been developed involving functionalization of a simple heterocycle, 2-oxazolone, with the aid of the chiral auxiliary, 2-(hydroxyethoxy)-1-apocamphanecarboxylic acid.

Supplementary Material Available: Details of preparation and characterization data for compounds **4–6** and **9–15a,b** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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