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The Highly Enantiocontrolled Functionalization of a 2-Oxazolone Heterocycle by Intramolecular Radical-based Addition. A Chiral Synthon for 2-Amino Alcohols which Contain Three Contiguous Stereocenters

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Abstract: The intramolecular Ru(II)-catalyzed radical addition of the 2,2-dichloroacyl pendant group to the 2-oxazolone moiety followed by reductive dechlorination with $(TMS)_3SiH$ provides an effective tool for the formation of the chiral 2-amino alcohol synthon in a completely regio- and stereocontrolled manner. The prepared synthon is useful in the preparation of isomers of unusual amino hydroxy acids including the key component of bleomycins. © 1998 Elsevier Science Ltd. All rights reserved.

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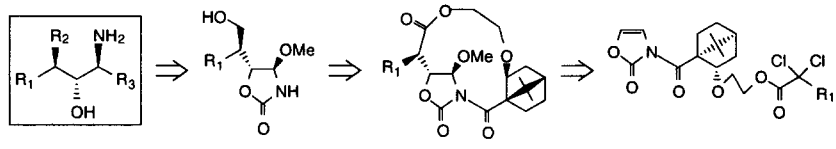
The simple heterocycle, 2-oxazolone, has proven to be a promising building block for the 2-amino alcohol skeleton.[1] The latter is a structural unit found in a substantial number of bioactive compounds including peptidic enzyme inhibitors, aminosugar containing antibiotics and sympathomimetic amines.[2] We previously reported the development of synthetic methods for the preparation of biologically interesting amino hydroxy acids which contain adjacent chiral centers, based on highly diastereoselective functionalization of a 2-oxazolone heterocycle.[3] Among these, the 2,2-dichloro and 2,2-difluorostatines were conveniently prepared by an intramolecular radical-based addition of the trihaloacetyl pendant group to the 2-oxazolone moiety, which proceeded smoothly with excellent facial selectivity.[4]

As retrosynthetically shown in Scheme 1, this procedure can be applied to the general synthesis of chiral 2-amino alcohols (**1**) which contain three contiguous stereogenic centers, since the 4-methoxy group of the intermediate 2-oxazolidinones (**2**), which is formed in thoroughly stereocontrolled manner, is readily convertible into a wide variety of primary to tertiary alkyls, phenyl and alkenyl groups with full retention of configuration.[1c] Such chiral skeletons are commonly found in the amino hydroxy acids which are the key components of bleomycins,[5] cyclosporins[6] and echinocandins.[7]



1 **2** **3** **4**

Scheme 1

In this paper, we describe a stereocontrolled approach to the chiral 2-amino alcohol synthon with three contiguous stereocenters, which involves an intramolecular Ru (II)-catalyzed addition of the 3-benzyloxy-2,2-

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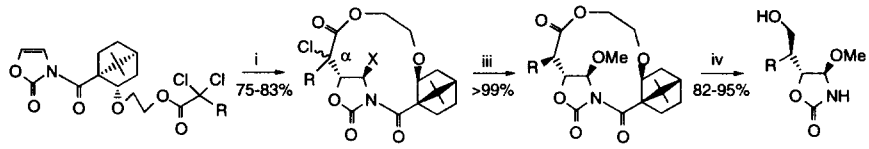
dichloropropionyl pendant group to the 2-oxazolone moiety as the key step. The synthon thus obtained is successfully employed in the distinct synthesis of the isomeric 4-amino-3-hydroxy-2-methylpentanoic acids, which were chosen as polyfunctional model compounds in this study , and which includes an amino acid component of the bleomycins.[5]

Thus, the 3-apocamphanecarbonyl-2-oxazolones **5a** and **b**[8], containing 2,2-dichloropropionyl pendant groups were heated with a $RuCl_2(PPh_3)_3$[9a] catalyst in benzene resulting in smooth cyclization to the 12-membered lactones **6a** and **b**, respectively,[9b] each of which was quantitatively methanolyzed to a diastereomeric mixture of **7** (1:1.4), attributable only to two Cα-isomers. Reductive dechlorination of **7a** and **b** thus obtained with $(TMS)_3SiH$ in the presence of an initiator Et_3B at -78 °C proceeded smoothly with complete diastereoselectivity (>99% de) to give the macrolides **8a** and **b**[10], respectively, in quantitative yield, while treatment with Bu_3SnH in refluxing benzene resulted in a much lower diastereoselectivity of 78% de. The excellent diastereoselectivity observed is rationalized by assuming a completely stereocontrolled intramolecular radical-based addition to the 2-oxazolone moiety, as has been previously pointed out,[4] followed by the less hindered side attack of the bulky reductant to the radicals generated *in situ*. The stereochemistry of **8a**, as evidenced by the NOE analysis,[11] was unequivocally determined by chemical correlation with **8b**,[12] whose enantiomer **ent-8b** was structurally established by X-ray analysis.[13] Reductive removal of the apocamphanecarbonyl auxiliary from **8a** and **b** with $LiBH_4$-MeOH (1:2)[14] gave the 2-oxazolidinone alcohols **9a** and **b**,[10] the former of which represents a versatile intermediate for the possible preparation of isomeric skeletons of type **1** amino alcohols, considering the ease of configurational inversion of the hydroxy groups of this compound.

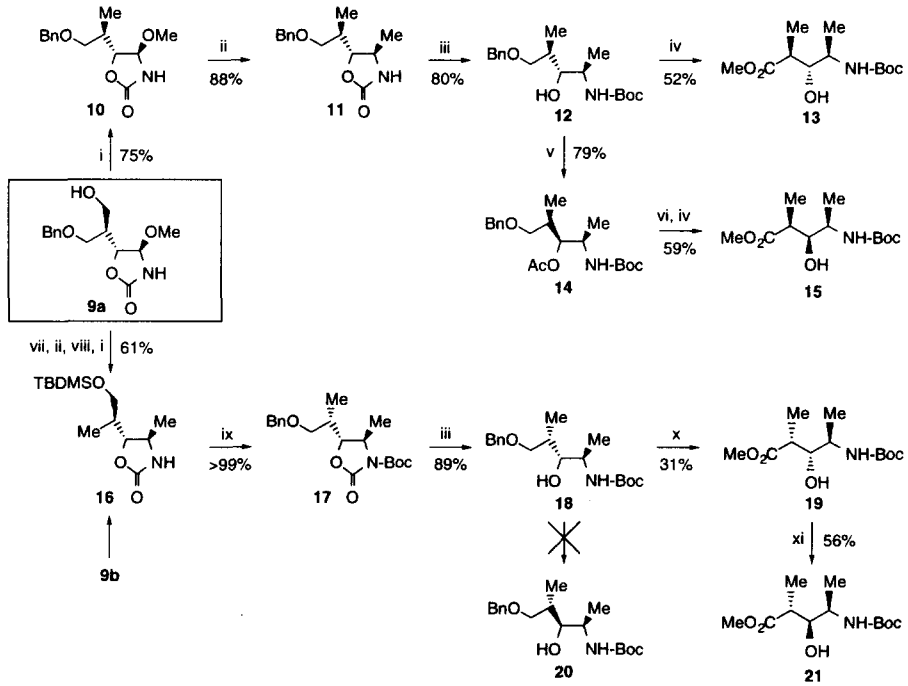


i) $RuCl_2(PPh_3)_3$/PhH; reflux, ii) MeOH; reflux, iii) $(TMS)_3SiH$, Et_3B/PhMe; -78 °C iv) $LiBH_4$-MeOH (1:2)/THF; 0 °C

Scheme 2

The synthetic potential of the chiral synthon **9a** is demonstrated by its conversion to four distinct stereoisomers of polyfunctional pentanoic acids (**13**, **15**, **19** and **21**), each of which contain three contiguous chiral centers, as is outlined in Scheme 3.

Thus, compound **9a** was readily converted to the key intermediate **11** by reductively converting the hydroxymethyl group to a methyl group followed by displacement of the 4-methoxy group for the methyl with full retention of configuration. The protected (2*S*,3*R*,4*R*)-amino hydroxy acid **13**[15] was obtained by successive ring-opening to the amino alcohol **12** followed by oxidation, and the (2*S*,3*S*,4*R*)-isomer **15**,[15] an amino acid component of bleomycins, was obtained from **12** in a protected form by configurational inversion of the hydroxy group[16] *via* the amino alcohol **14**. The smooth conversion to the free amino acid forms is a well established procedure.[5d]



i) 1) MsCl, NEt_3/THF; r.t., 2) NaI/DME; reflux, 3) *n*-Bu_3SnH, Et_3B/THF; -78 °C, ii) CuCN:MeLi=1:2, BF_3·OEt_2/THF; -30 °C, iii) $Ba(OH)_2$/EtOH-H_2O; reflux: $(Boc)_2O$, NEt_3/CH_2Cl_2; r.t., iv) 1) $MeC(OMe)_2Me$, TsOH/PhH; reflux, 2) H_2, Pd-C/CH_2Cl_2; r.t., 3) PDC/DMF; r.t.,: CH_2N_2, 4) HCl/MeOH; 0 °C: $(Boc)_2O$, NEt_3/CH_2Cl_2; r.t., v) 1) $ClCH_2SO_2Cl$/ pyridine; r.t., 2) CsOAc, 18-crown-6/PhH; reflux, vi) LiOH/dioxane-H_2O; r.t., vii) TBDMSCl, imidazole/DMF; r.t., viii) H_2, Pd-C/CH_2Cl_2; r.t., ix) 1) $(Boc)_2O$, NEt_3/CH_2Cl_2; r.t., 2) TBAF/THF; 0 °C, 3) BnBr, NaH/DMF; r.t., x) 1) H_2, Pd-C/MeOH; r.t., 2) TBDMSCl, imidazole/DMF; r.t., 3) $MeC(OMe)_2Me$, TsOH/PhH; reflux, 4) TBAF/THF; 0 °C, 5) PDC/DMF; r.t.,: CH_2N_2, 6) HCl/MeOH; 0 °C: $(Boc)_2O$, NEt_3/CH_2Cl_2; r.t., xi) $ClCH_2CO_2H$, PPh_3, DEAD/PhMe; 60 °C

Scheme 3

In addition the (2*R*,3*R*,4*R*)- and (2*R*,3*S*,4*R*)-isomers (**19** and **21**)[15] were conventionally prepared by an alternative route *via* the key intermediate **18** diastereomeric with **12**, in which the benzyloxymethyl and hydroxymethyl groups of the synthon **9a** were converted into the methyl and benzyloxymethyl groups, respectively. Compound **16** could be conveniently obtained from **9b**. Contrary to our expectations, attempts to isomerize **18** into **20** were unsuccessful under a wide variety of Mitsunobu conditions,[17] while the secondary hydroxy group of compound **19** was configurationally inverted smoothly under typical conditions of Mitsunobu reaction[18] to give the (2*R*,3*S*,4*R*)-isomer **21**.

In conclusion, the completely stereocontrolled chiral functionalization of a simple heterocycle, 2-oxazolone, by an intramolecular radical-based addition of the 2,2-dichloroacyl pendant groups serves as an excellent and effective tool for the versatile synthesis of the 2-amino alcohols which contain three contiguous stereogenic centers as has been demonstrated in typical examples.

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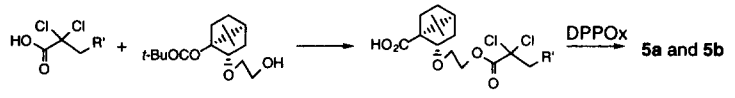
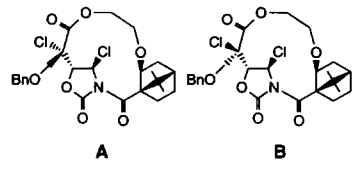
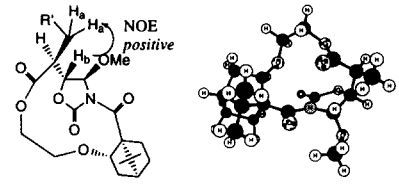
8. Compounds **5a** and **b** were obtained in 70-80% overall yields by esterification of 3-benzyloxy-2,2-dichloropropionic acid (Villieras, J.; Disnar, J.R.; Perriot, P.; Normant, J.F. *Synthesis* **1975**, 524-525) and 2,2-dichloropropionic acid with 2-(2-hydroxyethoxy)-1-apocamphanecarboxylic ester[4], respectively, followed by treatment with DPPOx (Kunieda, T.; Abe,Y.; Higuchi, T.; Hirobe, M. *Tetrahedron Lett.* **1981**, *22*, 1257-1260) as shown below.



9. a) Matumoto, H.; Nikaido, T.; Nagai, Y. *J. Org. Chem.* **1976**, *41*, 396-398. b) Typical procedure: A solution of **5a** (3.0 mmol) and $RuCl_2(PPh_3)_3$ (0.3 mmol) in benzene (60 mL) was refluxed under argon atmosphere for 120h. The usual work-up gave the diastereomeric cycloadducts (**A** and **B**) in a ratio of 1:1.4 in 75% yield. Any other isomers could be detected, indicative of complete regio and diastereofacial selectivity, as previously pointed out.[4] Perfect regioselectivity might be rationalized primarily by the higher stability of the oxazolidin-4-yl radicals than the 5-yl radicals generated *in situ*.



10. **8a**: mp 92-93 °C; $[\alpha]_D$ -8.9° (*c* 1.01, $CHCl_3$). **8b**: mp 160-161 °C; $[\alpha]_D$ +24.0° (*c* 1.02, $CHCl_3$). **9a**: mp 83 °C; $[\alpha]_D$ +77.5° (*c* 1.00, $CHCl_3$). **9b**: mp 103 °C; $[\alpha]_D$ +156.9° (*c* 0.99, $CHCl_3$).
11. A differential NOE effect between **Ha** and **Hb** protons was observed.
12. The conversion of **8a** to **8b** was conventionally performed by hydrogenolysis (H_2/Pd-C) followed by tosylation and reduction (NaI/Bu_3SnH).
13. Crystal data for **ent-8b** (mp 160-161 °C; $[\alpha]_D$ -24.4°): orthorhombic, $P2_1$, a=14.574(2) Å, b=16.982(2) Å, c=7.880(1) Å, V=1946.6 Å^3, Z=4. The structure was refined to the R-value of 3.87%. Atomic coordinates for this structure have been deposited with Cambridge Crystallographic Data Centre. We are much indebted to the Yoshitomi Research Laboratories, Yoshitomi Pharmaceutical Ind. Ltd. (Fukuoka, Japan) for this X-ray crystallographic analysis.



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15. **13**: $[\alpha]_D$ +38.4° (*c* 1.00, $CHCl_3$). **15**: mp 74 °C; $[\alpha]_D$ +5.6° (*c* 1.00, $CHCl_3$). **19**: $[\alpha]_D$ +10.2° (*c* 1.01, $CHCl_3$). **21**: $[\alpha]_D$ +3.6° (*c* 0.50, $CHCl_3$).
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