

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

Toru Morita, Hirofumi Matsunaga, Eiji Sugiyama, Tadao Ishizuka and Takehisa Kunieda*

Faculty of Pharmaceutical Sciences, Kumamoto University, Oe-honmachi, Kumamoto 862-0973, Japan

Fax: +81-96-362-7692; email: tkuni@gpo.kumamoto-u.ac.jp

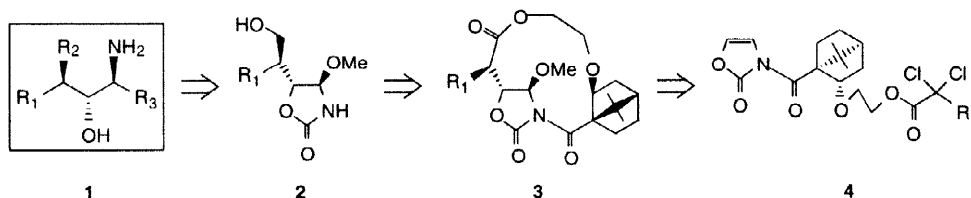
Received 15 June 1998; revised 12 July 1998; accepted 13 July 1998

Abstract: The intramolecular Ru(II)-catalyzed radical addition of the 2,2-dichloroacetyl pendant group to the 2-oxazolone moiety followed by reductive dechlorination with $(\text{TMS})_3\text{SiH}$ 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.

Keywords: Oxazolones; Radicals and radical reactions; Diastereoselection; Amino alcohols

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 cyclosporins⁶ and echinocandins.⁷

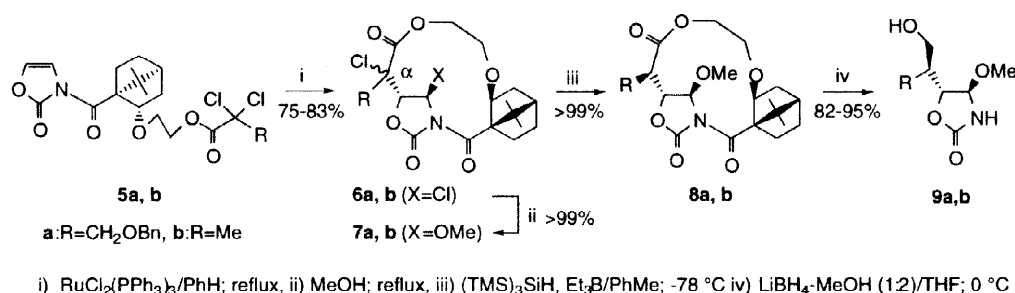


Scheme 1

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-

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

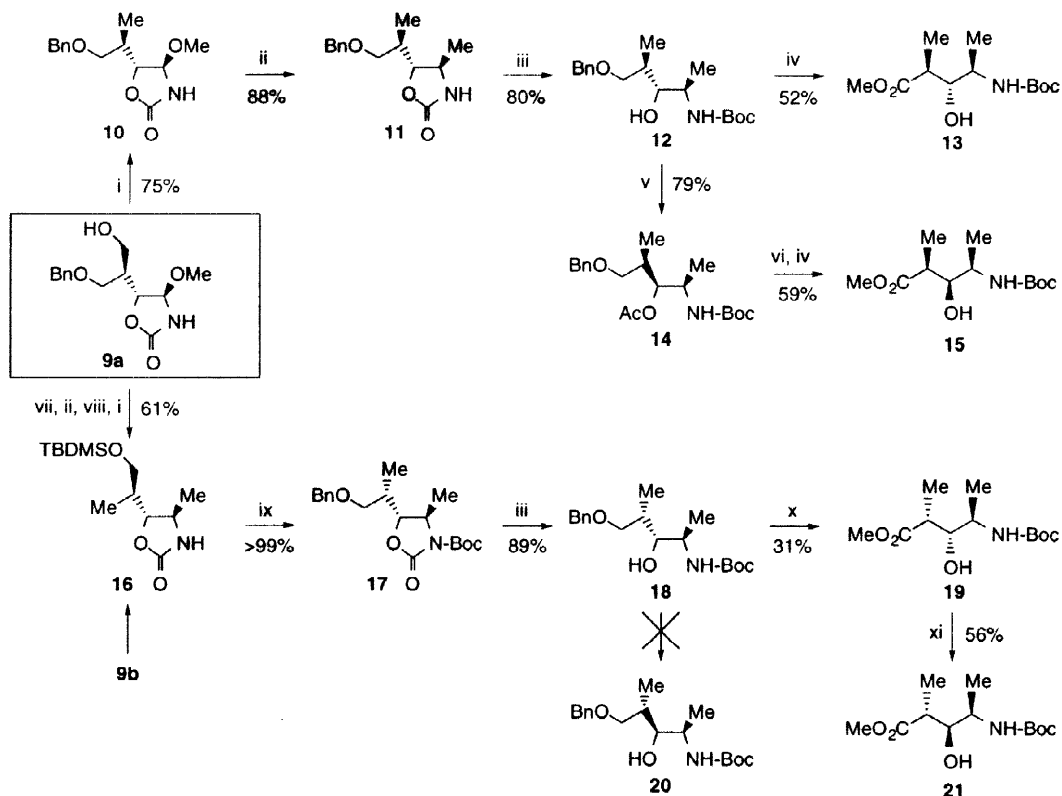
Thus, the 3-apocamphanecarbonyl-2-oxazolones **5a** and **b**⁸, containing 2,2-dichloropropionyl pendant groups were heated with a $\text{RuCl}_2(\text{PPh}_3)_3$ ^{9a} catalyst in benzene resulting in smooth cyclization to the 12-membered lactones **6a** and **b**, respectively,^{9b} each of which was quantitatively methanolized to a diastereomeric mixture of **7** (1:1.4), attributable only to two C α -isomers. Reductive dechlorination of **7a** and **b** thus obtained with $(\text{TMS})_3\text{SiH}$ 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 $\text{LiBH}_4\text{-MeOH}$ (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.



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 group¹⁶ *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) $n\text{-Bu}_3\text{SnH}$, Et_3B /THF; -78°C , ii) $\text{CuCN}:\text{MeLi}=1:2$, $\text{BF}_3\cdot\text{OEt}_2$ /THF; -30°C , iii) $\text{Ba}(\text{OH})_2/\text{EtOH}-\text{H}_2\text{O}$; reflux; $(\text{Boc})_2\text{O}$, $\text{NEt}_3/\text{CH}_2\text{Cl}_2$; r.t., iv) 1) $\text{MeC}(\text{OMe})_2\text{Me}$, TsOH/PhH ; reflux, 2) H_2 , $\text{Pd}-\text{C}/\text{CH}_2\text{Cl}_2$; r.t., 3) PDC/DMF ; r.t., CH_2N_2 , 4) HCl/MeOH ; 0°C ; $(\text{Boc})_2\text{O}$, $\text{NEt}_3/\text{CH}_2\text{Cl}_2$; r.t., v) 1) $\text{ClCH}_2\text{SO}_2\text{Cl}$ /pyridine; r.t., 2) CsOAc , 18-crown-6/ PhH ; reflux, vi) $\text{LiOH}/\text{dioxane}-\text{H}_2\text{O}$; r.t., vii) TBDMSCl , imidazole/ DMF ; r.t., viii) H_2 , $\text{Pd}-\text{C}/\text{CH}_2\text{Cl}_2$; r.t., ix) 1) $(\text{Boc})_2\text{O}$, $\text{NEt}_3/\text{CH}_2\text{Cl}_2$; r.t., 2) TBAF/THF ; 0°C , 3) BnBr , NaH/DMF ; r.t., x) 1) H_2 , $\text{Pd}-\text{C}/\text{MeOH}$; r.t., 2) TBDMSCl , imidazole/ DMF ; r.t., 3) $\text{MeC}(\text{OMe})_2\text{Me}$, TsOH/PhH ; reflux, 4) TBAF/THF ; 0°C , 5) PDC/DMF ; r.t., CH_2N_2 , 6) HCl/MeOH ; 0°C ; $(\text{Boc})_2\text{O}$, $\text{NEt}_3/\text{CH}_2\text{Cl}_2$; r.t., xi) $\text{ClCH}_2\text{CO}_2\text{H}$, PPh_3 , DEAD/PhMe ; 60°C

Scheme 3

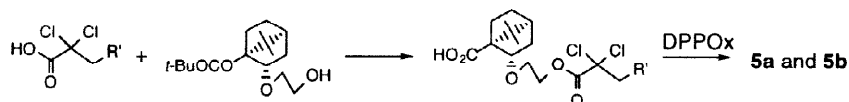
In addition the (2*R*,3*R*,4*R*)- and (2*R*,3*S*,4*R*)-isomers (**19** and **21**)¹⁵ were conventionally prepared by an alternative route *via* the key intermediate **18** diastereomeric with **12**, in which the benzyloxymethyl and hydroxymethyl groups of the synthon **9a** were converted into the methyl 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 reaction¹⁸ 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-dichloroacetyl 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.

REFERENCES AND NOTES

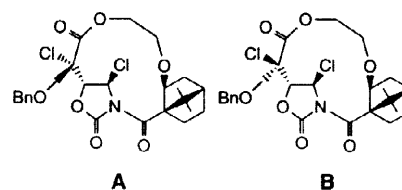
1. a) Kunieda, T.; Ishizuka, T.; Higuchi, T.; Hirobe, M. *J. Org. Chem.* **1988**, *53*, 3381-3383. b) Ishizuka, T.; Ishibuchi, S.; Kunieda, T. *Tetrahedron* **1993**, *49*, 1841-1852. c) Ishibuchi, S.; Ikematsu, Y.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1991**, *32*, 3523-3526. d) Ishibuchi, S.; Nagatani, T.; Ishizuka, T.; Kunieda, T. *Natural Products Lett.* **1992**, *1*, 21-24.

2. For recent papers, see: a) Hanessian, S.; Ninkovic, S. *J. Org. Chem.* **1996**, *61*, 5418-5424. b) Yuasa, Y.; Ando, J.; Shibuya, S. *J. Chem. Soc. Perkin Trans. 1* **1996**, 793-802.
3. For a review, see: Kunieda, T.; Ishizuka, T. *J. Synth. Org. Chem., Jpn.* **1997**, *55*, 1018-1027.
4. Yamamoto, T.; Ishibuchi, S.; Ishizuka, T.; Haratake, M.; Kunieda, T. *J. Org. Chem.* **1993**, *58*, 1997-1998.
5. a) Yoshioka, T.; Hara, T.; Takita, T.; Umezawa, H. *J. Antibiot.* **1974**, *27*, 356-357. b) Ohgi, T.; Hecht, S. M. *J. Org. Chem.* **1981**, *46*, 1232-1234. c) Narita, M.; Otsuka, M.; Kobayashi, S.; Ohno, M.; Umezawa, Y.; Morishima, H.; Saito, S.; Takita, T.; Umezawa, H. *Tetrahedron Lett.* **1982**, *23*, 525-528. d) DiPardo, R. M.; Bock, M.G. *ibid.* **1983**, *24*, 4805-4808.
6. a) Savignac, M.; Durand, J. O.; Genet, J. P. *Tetrahedron: Asymmetry*, **1994**, *5*, 717-722. b) Tuch, A.; Saniere, M.; Merrer, Y. L.; Depezy, J. C. *ibid.* **1997**, *8*, 1649-6059.
7. a) Kurosawa, N.; Ohfuné, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6041-6043. b) Kurosawa, N.; Ohfuné, Y. *ibid.* **1986**, *108*, 6043-6045.
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 ester⁴, 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.; Nikaïdo, T.; Nagai, Y. *J. Org. Chem.* **1976**, *41*, 396-398.

b) Typical procedure: A solution of **5a** (3.0 mmol) and $\text{RuCl}_2(\text{PPh}_3)_3$ (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*.

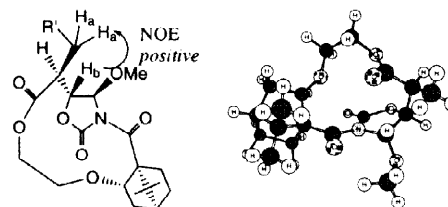


10. **8a**: mp 92-93 °C; $[\alpha]_D -8.9^\circ$ (c 1.01, CHCl_3). **8b**: mp 160-161 °C; $[\alpha]_D +24.0^\circ$ (c 1.02, CHCl_3).
9a: mp 83 °C; $[\alpha]_D +77.5^\circ$ (c 1.00, CHCl_3). **9b**: mp 103 °C; $[\alpha]_D +156.9^\circ$ (c 0.99, CHCl_3).

11. A differential NOE effect between **Ha** and **Hb** protons was observed.

12. The conversion of **8a** to **8b** was conventionally performed by hydrogenolysis ($\text{H}_2/\text{Pd-C}$) followed by tosylation and reduction ($\text{NaI}/\text{Bu}_3\text{SnH}$).

13. Crystal data for **ent-8b** (mp 160-161 °C; $[\alpha]_D -24.4^\circ$): orthorhombic, $P2_1$, $a=14.574(2)$ Å, $b=16.982(2)$ Å, $c=7.880(1)$ Å, $V=1946.6$ Å³, $Z=4$. 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.



8a ($\text{R}'=\text{BnO}$), **8b** ($\text{R}'=\text{H}$)

ent-8b

14. a) Matunaga, H.; Kimura, K.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1991**, *32*, 7751-7754. b) Matunaga, H.; Ishizuka, T.; Marubayashi, N.; Kunieda, T. *Chem. Pharm. Bull.* **1992**, *40*, 1077-1079.
15. **13**: $[\alpha]_D +38.4^\circ$ (c 1.00, CHCl_3). **15**: mp 74 °C; $[\alpha]_D +5.6^\circ$ (c 1.00, CHCl_3).
19: $[\alpha]_D +10.2^\circ$ (c 1.01, CHCl_3). **21**: $[\alpha]_D +3.6^\circ$ (c 0.50, CHCl_3).
16. Shimizu, T.; Hiranuma, S.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6145-6148.
17. a) Mitsunobu, O. *Synthesis*, **1981**, 1-28. b) Hughes, D. L. *Org. React.* **1992**, *42*, 335-656.
18. Lipshutz, B. H.; Miller, T. A. *Tetrahedron Lett.* **1990**, *31*, 5253-5256.