Pergamon

Tetrahedron Letters 42 (2001) 6319–6322

TETRAHEDRON LETTERS

Stereoselective intramolecular radical addition of polyhaloacyl pendant groups to the 1,3-dihydro-2-imidazolone moiety: the chiral synthesis of *threo*-diaminocarboxylic acids

Tomokazu Katahira, Tadao Ishizuka, Hirofumi Matsunaga and Takehisa Kunieda*

Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862-0973, Japan

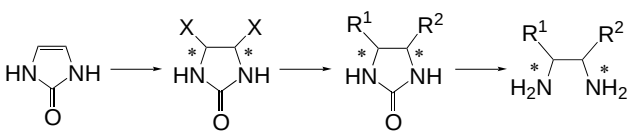
Received 8 June 2001; revised 25 June 2001; accepted 6 July 2001

Abstract—The intramolecular Ru(II)-catalyzed radical addition of trichloroacetyl and 2,2-dichloro-4-hexenoyl pendant groups to a 1,3-dihydro-2-imidazolone moiety provides a perfectly stereocontrolled approach to the preparation of 1,2-diamines which contain contiguous multi-stereocenters. Typical examples for this approach are given by the chiral synthesis of *vicinal*-diaminocarboxylic acids, which are amino analogs of statine and MeBmt. © 2001 Elsevier Science Ltd. All rights reserved.

Diamines are, biologically, medicinally and synthetically, an important class of compounds.[1] The 1,2-diamine skeleton can be a structural unit found in a number of bioactive compounds of medicinal interest such as peptidic antibiotics, vitamin H, antitumor agents and opioid receptor agonists[1] and also functions as a chelating ligand for metal catalysts in asymmetric synthesis.[2] The simple heterocycle, 1,3-dihydro-2-imidazolone,[3] which is susceptible to various modes of addition reactions, represents a potential building block for the synthesis of 1,2-diamines,[4] as outlined in Scheme 1.

In this paper, we describe an alternative stereocontrolled approach to the preparation of chiral 1,2-diamines with contiguous multi stereocenters, which involves an intramolecular Ru(II)-catalyzed addition of polyhaloacyl groups to the 2-imidazolone moiety as the key step.

Thus, the 1-apocamphanecarbonyl-2-imidazolones (**1**),[5] containing a trichloroacetyl pendant group, were



Scheme 1.

heated with $RuCl_2(PPh_3)_3$[6] as the catalyst in benzene, resulting in completely diastereocontrolled cyclization to the 12-membered macrolides (**2**) with or without the use of Lewis acid additives, such as rare metal triflates or zinc chloride.[7] As seen in Table 1, the addition of catalytic amounts of $La(OTf)_3$ and $ZnCl_2$ as the additives was found to dramatically accelerate the rate of intramolecular cyclization to near completion within 1 h, while the reaction was much more sluggish in the absence of these additives. The use of $La(OTf)_3$ in less than equimolar amounts of the $RuCl_2(PPh_3)_3$ catalyst was found to be preferable.[8]

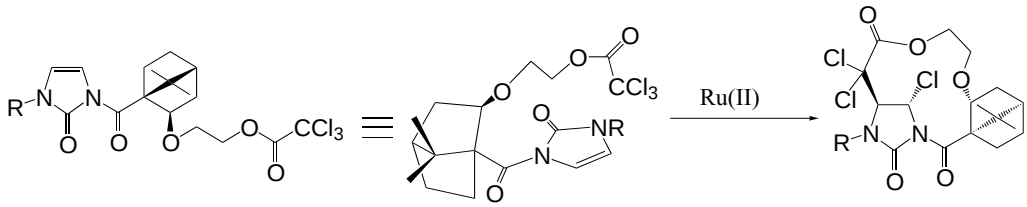
The cyclization product (**2**), which was obtained diastereoselectively (99% de), was treated with boiling methanol followed by *N*-tosylation to give the *N*-tosyl-4-methoxy-cycloadduct (**4**) (Scheme 2). The stereostructure of **3** was unequivocally confirmed by X-ray crystal analysis.[9]

The apocamphanecarbonyl auxiliary was reductively removed by treatment with $LiBH_4$–MeOH (1:2)[10] to give the 4-methoxy-2-imidazolidinone (**5**), in which the methoxy group could be substituted for a variety of alkyl, alkenyl and aryl groups with full retention of configuration, as has been previously pointed out.[11] Thus, compound (**5**) would be expected to serve as a versatile chiral synthon for the preparation of a wide variety of 2,3-diamines. This versatility was demonstrated by a facile conversion to the amino analog of (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid (statine), a key structural component of amastatine.[12]

* Corresponding author. Tel.: +81-96-371-4680; fax: +81-96-362-7692; e-mail: tkuni@gpo.kumamoto-u.ac.jp

PII: S0040-4039(01)01242-4

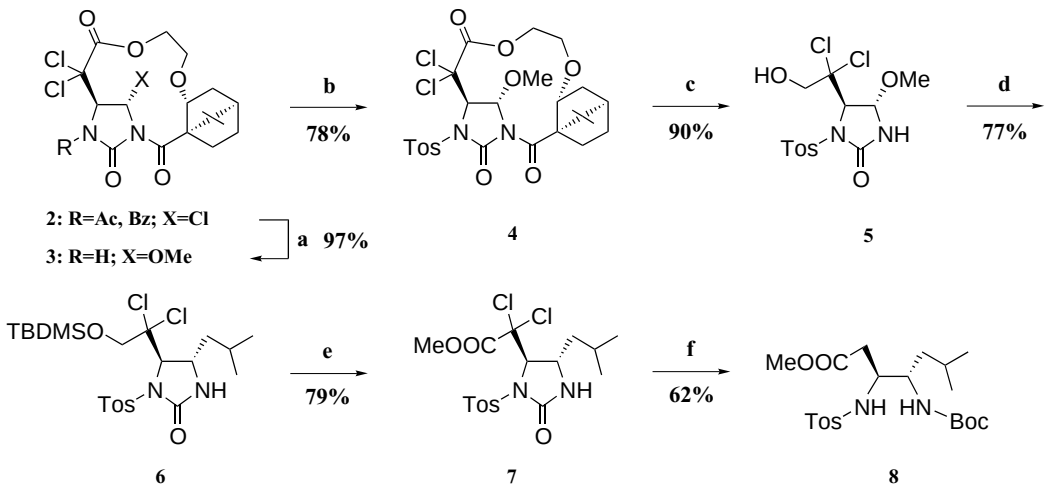
Table 1. Diastereoselective Ru(II)-catalyzed intramolecular additions of the trichloroacetyl pendant group[a]



1 **2**

Entry	R	$RuCl_2(PPh_3)_3$ (equiv.)	Additive (equiv.)	Time (h)	Yield (%)[b]
1	Ac	0.1	–	93	48
2	Ac	0.1	$La(OTf)_3$ (0.05)	1	76
3	Ac	0.05	$La(OTf)_3$ (0.025)	7	72
4	Ac	0.1	$La(OTf)_3$ (0.1)	1	57
5	Ac	0.1	$ZnCl_2$ (0.05)	1	82
6	Ac	0.1	$ZnCl_2$ (0.1)	1	85
7	PhCO	0.1	$La(OTf)_3$ (0.05)	1	92

[a] The reaction was performed in refluxing benzene under an argon atmosphere.
[b] Isolated yield.

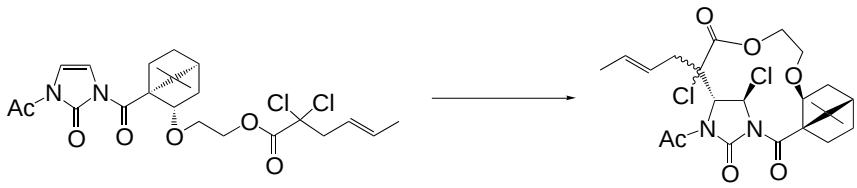


Scheme 2. (a) MeOH; reflux, 1 h; (b) Tos-Cl, Et_3N, DMAP/CH_2Cl_2; rt; (c) (1) $LiBH_4$ (6 equiv.), MeOH (12 equiv.)/THF; rt; (d) (1) imidazol, TBDMS-Cl/DMF; rt, (2) *iso*-BuCuCNMgBr, LiCl, $BF_3{\cdot}OEt_2$; –78°C, 4 h; (e) (1) TBAF/CH_2Cl_2; rt, (2) PCC, NaOAc/CH_2Cl_2; rt, (3) CH_2N_2; (f) (1) Bu_3SnH, AIBN/benzene; reflux, 1 h, (2) $Ba(OH){\cdot}8H_2O$/EtOH–H_2O; reflux, 24 h, (3) $(Boc)_2O$, Et_3N/CH_2Cl_2; rt, (4) CH_2N_2.

Thus, the protection of hydroxy group as the *tert*-butyldimetylsilyl ether followed by treatment with isobutylcuprates in the presence of $BF_3{\cdot}OEt_2$ gave the *trans*-4-isobutyl derivative (**6**) with complete retention of configuration. The removal of the silyl group followed by oxidation with pyridinium chlorochromate (PCC) and subsequent esterification gave **7** in moderate yield. Reductive dechlorination with tributyltin hydride followed by ring-opening smoothly gave the reasonable yield of the optically pure 3,4-diamino carboxylic acid derivative (**8**),[13] an amino analog of statine, in which each of the amino groups was derivatized by a different protecting group.

This methodology was applied to the chiral synthesis of the diaminocarboxylic acid with three contiguous stereogenic centers, which is the amino analog of (2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoic acid (Me–Bmt), an unusual and key amino acid component of cyclosporin.[14] When compound **9** was subjected to the intramolecular Ru(II)-catalyzed reaction, the addition of the 2,2-dichloro-(4*E*)-hexenoyl pendant group to the 2-imidazolone moiety proceeded much more sluggishly than that for the trichloroacetyl function described above and the effect of additives, $La(OTf)_3$ and $ZnCl_2$, on accelerating the cyclization was quite limited and not as effective, as seen in Table 2. The cyclization

Table 2. Ru(II)-catalyzed intramolecular additions of the 2,2-dichloro-(4*E*)-hexenoyl pendant group[a]



9 **10**

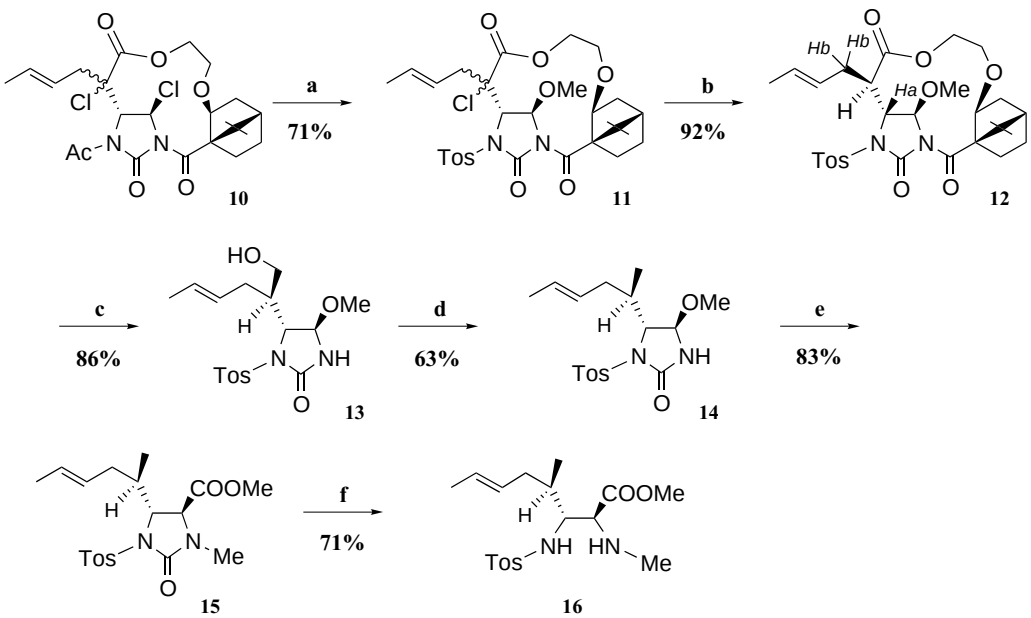
Entry	$RuCl_2(PPh_3)_3$ (equiv.)	$La(OTf)_3$ (equiv.)	Solvent	Time (h)	Yield[b] (%)
1	0.1	0.05	Benzene	48	16 (61)
2	0.3	0.05	Benzene	188	55 (0)
3	0.3	0.05	Toluene	24	34 (36)
4	0.3	–	Toluene	24	29 (44)
5	0.3	0.05	Toluene	48	64 (0)

[a] The reaction was carried out in refluxing benzene or toluene under an argon atmosphere.
[b] Recovery yield in parentheses.

proceeded with excellent diastereoselectivity in excess of 99% de, although a higher temperature and prolonged reaction time were required to give moderate yields.

Methanolysis of the cycloadduct (**10**), followed by *N*-tosylation and diastereoselective dechlorination with $(Me_3Si)_3SiH$ in the presence of an initiator, Et_3B, resulted in the smooth formation of the macrolide (**12**) in excess of 99% de[15] (Scheme 3).

The excellent chiral functionalization observed can be rationalized by assuming a stereocontrolled intramolecular radical-based addition to the 2-imidazolone moiety, followed by attack of the bulky reductant to the less hindered side of the radicals generated in situ. Reductive removal of the chiral auxiliary with $LiBH_4$–MeOH (1:2)[8] gave the 2-imidazolidinone derivative (**13**), of which the hydroxymethyl group was converted to a methyl group by conventional procedures. *N*-Methylation of **14,** followed by 4-cyanation gave a mixture of *trans* and *cis*-cyanides, which, after treatment of the isomeric mixture with K_2CO_3 in MeOH, gave the *trans*-methyl ester (**15**) in good yield. Hydrolytic ring-opening with $Ba(OH)_2$ furnished the 2,3-diamino carboxylic acid with completely controlled (2*R*,3*R*,4*R*)-stereocenters (**16**),[16] the amino analog of MeBmt.



Scheme 3. (a) (1) MeOH, (2) Tos-Cl, *n*-BuLi/THF; (b) Et_3B, $(TMS)_3SiH$/toluene; −78°C; (c) $LiBH_4$ (6 equiv.), MeOH (12 equiv.)/THF; (d) (1) MsCl, Et_3N/CH_2Cl_2, (2) NaI/DME; reflux, (3) Bu_3SnH, Et_3B/THF; −78°C; (e) (1) MeI, NaH/THF; rt, (2) TMSCN, $BF_3{\cdot}OEt_2/CH_2Cl_2$; 0°C, (3) K_2CO_3/MeOH; rt, (4) 2N HCl; rt; (f) (1) $Ba(OH)_2{\cdot}8H_2O$/EtOH–H_2O, reflux, 24 h, (2) CH_2N_2.

In conclusion, a highly enantioselective synthetic route to 1,2-diamines with two and three contiguous stereogenic centers such as the amino-analogs of statine and MeBmt, has been developed via the perfect chiral functionalization of a simple 1,3-dihydro-2-imidazolone skeleton with the aid of intramolecular Ru(II)-catalyzed radical cyclization.

References

1. For a review, see: Denis, L.; Thierry Le, G.; Charles, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580–2627.
2. For examples, see: (a) Kobayashi, S.; Uchino, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247–4252; (b) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381–1392 and references cited therein.
3. Wang, P. C. *Heterocycles* **1985**, *23*, 3041–3042.
4. Seo, R.; Ishizuka, T.; Abdel-Aziz, A. A.-M.; Kunieda, T. *Tetrahedron Lett.* **2001**, *42*, 6353–6355.
5. Compounds **1** and **9** were obtained in 70–80% overall yields by condensation of *N*-monoacetyl-2-imidazolone with the corresponding 2-(2-acyloxyethoxy)-1-apocamphanecarboxylic acid.
6. Matsumoto, H.; Nikaido, T.; Nagai, Y. *J. Org. Chem.* **1976**, *41*, 396–398; (cf.) Yamamoto, T.; Ishibuchi, S.; Ishizuka, T.; Haratake, M.; Kunieda, T. *J. Org. Chem.* **1993**, *58*, 1997–1998.
7. Exclusive cyclization to the 12-membered macrolide(**2**) may be rationalized by assuming that the pendant chain length would be adjusted to form the less strained ring-structure based on an intramolecular steric and electrostatic interaction, although the details are not clear.
8. It seems likely that coordination of the Lewis acids to carbonyl groups would be responsible for the enormous acceleration observed, but we have no direct evidence for this at present.
9. Crystal date for **3** (mp 227°C): orthorhombic, $P2_12_12_1$, $a=15.314(2)$ Å, $b=20.569(1)$ Å, $c=12.623(1)$ Å, $V=3976.1(6)$ Å^3, $Z=4$. The structure was refined to the R-value of 0.181%. We are much indebted to the Fukuoka Research Laboratories, Welfide Corporation for the X-ray crystallographic analysis.
10. (a) Matsunaga, H.; Kimura, K.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1991**, *32*, 7751–7754; (b) Matsunaga, H.; Ishizuka, T.; Marubayashi, N.; Kunieda, T. *Chem. Pham. Bull.* **1992**, *40*, 1077–1079.
11. Ishizuka, T.; Ishibuchi, S.; Kunieda, T. *Tetrahedron* **1993**, *49*, 1841–1852.
12. (a) Umezawa, H.; Aoyagi, T.; Morishima, H.; Matsuzaki, M.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1970**, *23*, 259–262; (b) Workman, R. J.; Burkitt, D. S. *Arch. Biochem. Biophys.* **1977**, *194*, 157–165.
13. Compound **8**: mp 44–45°C. $[\alpha]_D$ −45.5° (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.65 (d, 3H, $J=6.1$ Hz), 0.68 (d, 3H, $J=6.1$ Hz), 0.81 (m, 1H), 1.41 (s, 9H), (m, 2H), 1.32–1.44 (m, 2H), 1.70 (s, 3H), 2.49 (m, 1H), 2.71 (m, 1H), 3.47 (m, 1H), 3.69 (s, 3H), 4.06 (m, 1H), 4.85 (br s, 1H), 4.91 (br s, 1H), 7.30 (d, 2H, $J=7.9$ Hz), 7.73 (d, 2H, $J=7.9$ Hz).
14. (a) Dreyfuss, M.; Harri, E.; Hofmann, H.; Kobel, H.; Pache, W.; Tscherter, H. *Eur. J. Appl. Microbiol.* **1976**, *3*, 125–132; (b) Wengar, R. M. In *Cyclosporin A*; White, D. J. G., Ed.; Elsevier, Biomedical: Amsterdam, 1982; pp. 19–34.
15. The configurational assignment was made on the basis of a positive NOE effect between *Ha* and *Hb*. Use of Bu_3SnH in the place of $(Me_3Si)_3SiH$ resulted in lower selectivity of 80% de.
16. Compound **16**: $[\alpha]_D$ +30.4° (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (d, 3H, $J=6.7$ Hz), 1.54 (d, 3H, $J=6.1$ Hz), 2.01 (m, 2H), 2.11 (m, 1H), 2.51 (s, 3H), 2.97 (s, 3H), 3.78 (m, 1H), 3.85 (s, 3H), 4.22 (m, 1H), 4.80 (br s, 1H), 4.95 (br s, 1H), 5.41 (m, 2H), 7.29 (d, 2H, $J=7.9$ Hz), 7.75 (d, 2H, $J=7.9$ Hz).