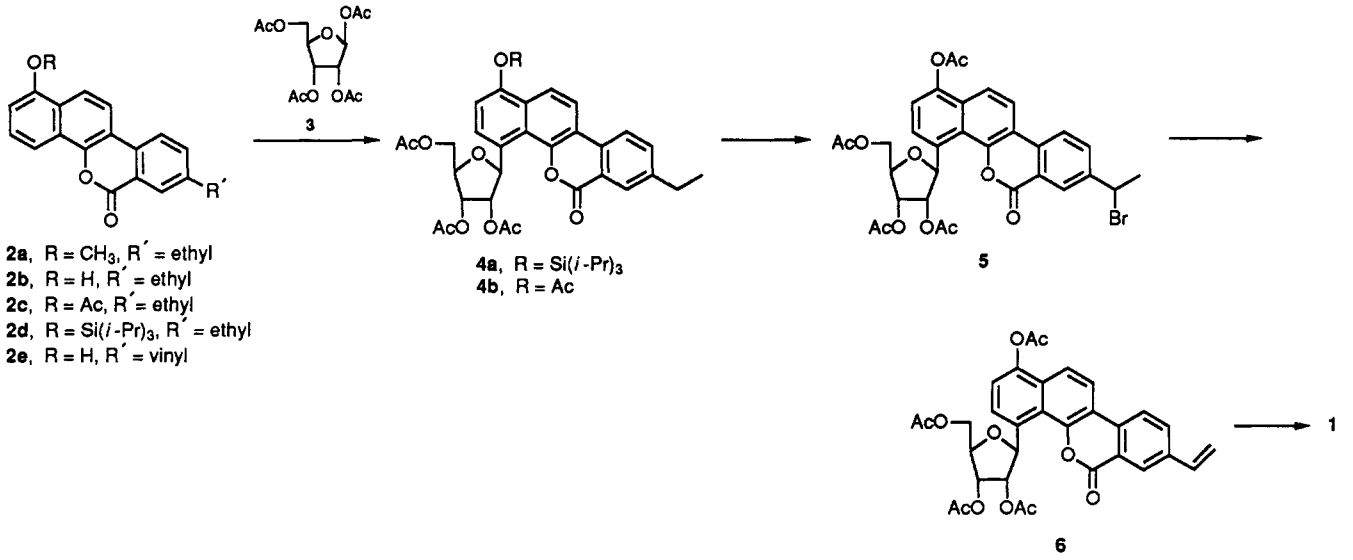
Scheme I



1-Hydroxy-4-(β-D-ribofuranosyl)-8-vinylbenzo[*d*]-naphtho[1,2-*b*]pyran-6-one (**1**) was prepared as shown in Scheme I. Achievement of this synthesis required that a number of tactical problems be solved. Lewis acid catalyzed coupling of the tetracyclic aglycon system with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose[19] (**3**) was first achieved[3] by using the *O*-methyl aglycon **2a**. However, no conditions were found that would permit removal of the *O*-methyl group of the resulting *C*-glycoside without effecting partial anomerization of the glycosidic linkage. Efforts to effect coupling of the carbohydrate with the free phenolic compound **2b** or its acetyl derivative **2c** were unsuccessful. Similarly, attempts to use aglycon derivatives with an 8-vinyl substituent in Lewis acid catalyzed glycosidic coupling reactions failed.

Stannic chloride catalyzed coupling of 8-ethyl-1-[(triisopropylsilyl)oxy]benzo[*d*]naphtho[1,2-*b*]pyran-6-one[20] (**2d**) with carbohydrate **3** yielded a 1:1 mixture of *C*-glycoside **4a**[21] and its α-anomer[3] in 80% combined yield. Following anomer separation by silica gel chromatography, removal of the triisopropylsilyl protective group (CsF) and acetylation (acetic anhydride/pyridine) yielded tetraacetate **4b**[21] (95%). This change in phenolic protective group was necessary because attempted benzylic bromination of **4a** with *N*-bromosuccinimide yielded a complex mixture that included products with apparent substitution within the triisopropylsilyl group.

Benzylic bromination[11a] of tetraacetate **4b** (NBS, benzoyl peroxide) was effected, producing **5**[21] (62%). It is noteworthy that no bromination occurred at C-1 of the carbohydrate moiety, which is also benzylic. Dehydrobromination of **5** for introduction of the 8-vinyl substituent of **6**[21] was achieved (73%) by using tetrakis(triphenylphosphine)palladium(0).[22] The synthesis of **1**[21] was completed by removal of the four protecting acetyl groups using sodium carbonate in methanol in 83% yield.

This synthesis foreshadows the preparation of a number of *C*-glycoside analogues of the antibiotics of this class for detailed biological evaluation of the structural parameters associated with antitumor and antiviral activities.

Acknowledgment. We thank the American Cancer Society for generous financial support of this research.

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(20) Prepared by demethylation of **2a**[3,11a] (BBr_3, 97%) followed by silylation (chlorotriisopropylsilane, imidazole, 92%).

(21) All new compounds have been characterized by ^1H and ^{13}C nuclear magnetic resonance and elemental analysis and/or high-resolution mass spectrometry.

(22) We found Pd(0)-catalyzed dehydrobromination to be preferable to procedures using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), LiBr/Li_2CO_3,[11a] or phenyl selenoxide (Findlay, J. A.; Daljeet, A.; Murray, P. J.; Rej, R. N. *Can. J. Chem.* **1986**, *65*, 427-431).

Highly Stereoselective Radical Cyclization: Copper- or Ruthenium-Catalyzed Preparation of *cis*- and *trans*-β,γ-Dialkyl γ-Lactams from Acyclic *N*-Allyltrichloroacetamide Derivatives

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Summary: Efficient 1,2-asymmetric induction was achieved in the copper-catalyzed cyclization of *N*-allyltrichloroacetamides derived from 3-amino-1-butene or 3-amino-1-heptene, in which the stereochemical course was dependent on nitrogen protecting groups.

Sir: Although free-radical cyclization has become an attractive synthetic method for five-membered ring skele-

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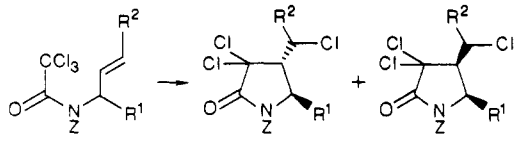
Table I

substrate	catalyst[a] (mol %)	temp, °C	time, h	product	yield,[b] %	trans/cis[c]
1a	Ru (5)	140	3	**2a**	82	100/0
1b	Ru (5)	140	6		86	71/29
	Cu (30)	140	2	**2b**	78	70/30
		80	35		72	86/14
	Cu* (30)	25	2		98	88/12
		−15	43		93	95/5
1c	Ru (5)	80	24	**2c**	74	21/79
	Cu (30)	50	5		90	27/73
	Cu* (5)	25	0.2		99	22/78
		−70	72		90	10/90
1d	Cu (30)	50	60	**2d**	99	25/75
	Cu* (30)	−70	86		83	14/86
1e	Cu (30)	50	8	**2e**	85	28/72
1f	Cu (30)	50	18	**2f**	74	29/71
1g	Ru (5)	140	2	**2g**	79	100/0[d]
1h	Cu* (30)	−15	23	**2h**	98	20/80[d]

[a] Ru = $RuCl_2(PPh_3)_3$ in benzene, Cu = CuCl in acetonitrile, Cu* = CuCl/bipyridine in dichloromethane. [b] Isolated yields. [c] Determined by NMR. [d] A mixture of diastereomers derived from the chlorine-bound chiral center. The cis/trans ratios were determined after the reductive dechlorination with Bu_3SnH.

tons,[1,2] little has been explored on the stereoselective preparation of these ring compounds from acyclic precursors via 1,2-asymmetric induction. A partly successful example was given by Stork and Ueno in their β-alkoxy radical cyclization, which realized the trans-selective preparation of β,γ-dialkyl-γ-butyrolactones.[3] Nevertheless, the preparative route to the corresponding cis isomer has not been established. In this paper, we report that judicious choice of nitrogen substituents differentiated the course of the stereoselectivity in the copper- or ruthenium-catalyzed cyclization of *N*-allyltrichloroacetamides prepared from secondary allylic amines. Furthermore, the process can be accomplished with a newly developed catalyst consisting of CuCl and bidentate amines at low temperatures, providing highly stereoselective preparation of either *cis*- or *trans*-β,γ-dialkyl γ-lactams. As described



1 **2**

	R¹	R²	Z		R¹	R²	Z
a:	Me	H	H	**e**:	Me	H	Ms
b:	Me	H	CH_2Ph	**f**:	Me	H	^{t}Boc
c:	Me	H	Ts	**g**:	Me	^{n}Pr	H
d:	Me	H	Cbz	**h**:	Me	^{n}Pr	Cbz

in our previous papers,[4,5] *N*-allyltrichloroacetamides and their *N*-alkyl analogues were cyclized to the corresponding trichlorinated γ-lactams at 80–140 °C by the catalysis of copper salts or a ruthenium complex. Application of this process to the cyclization of 1-buten-3-yl trichloroacetamide (**1a**) gave rise to selective preparation of *trans*-β,γ-dialkyl γ-lactam (**2a**) as a single product.[6] Its *N*-benzyl analogue (**1b**) also gave the corresponding trans lactam predominantly (trans/cis = 7:3 at 80–140 °C). In sharp contrast, trichloroacetamides bearing electron-withdrawing substituents on the nitrogen, such as Ts, Ms, Cbz, and ^{t}Boc, generally provided the corresponding cis isomer as the major products (trans/cis = 1:3–1:4 at 50–80 °C). Thus, the cyclization of trichloroacetamides without nitrogen protection or its *N*-benzyl analogue is a route to prepare *trans*-β,γ-dialkyl γ-lactam derivatives, whereas that of the trichloroacetamides protected by electron-withdrawing auxiliary substituents is to be a candidate for effective stereoselective synthetic method for the correspondng cis isomer. Since benzyl, tosyl, and Cbz groups can be removed after cyclization, the procedure provides a unique method for the preparation of γ-lactams. From the synthetic point of view, we should overcome a problem of unsatisfactory stereoselectivities, except **1a**, under such drastic conditions.

Substantial break-through to attain high selectivity in the cyclization of **1b–d** was obtained by a new catalyst system consisting of CuCl and bidentate amines such as TMEDA and bipyridine (bpy). Although this system did not catalyze the cyclization of **1a**, N-protected trichloroacetamides **1b–d** cyclized smoothly to the corresponding lactams even below 0 °C.[6] The cis/trans ratios in the cyclization of **1b–d** were affected by reaction temperatures. At lower temperatures, the higher trans selectivity was attained in the reaction of **1b**, whereas the higher cis selectivity in that of **1c** and **1d**. The new process makes the reaction proceed even at −70 °C. At these low temperatures, the cyclization provided the products over 9:1 diastereomer ratios as shown in Table I.

In summary, highly stereoselective preparation of either *trans*- or *cis*-β,γ-dialkyl γ-lactam derivatives was accomplished in the cyclization of 1-buten-3-yltrichloroacetamides (**1a–d**), in which choice of nitrogen protecting

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(6) Stereochemistry of the obtained lactams was determined after all of the chlorine atoms were reductively removed. Authentic samples of the corresponding trans isomers were prepared by conjugate addition of dialkyl lithium cuprates to N-tosylated α,β-unsaturated lactams[5] and subsequent modification. Details are given in the supplementary material.

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groups directed the course of the stereoselection. Compound **1a** gave the trans isomer as a single product. Cyclization of **1b** at −15 °C is an alternative method for the trans lactam. For the preparation of cis isomers, introduction of Cbz or Ts to the trichloroacetamides and subsequent cyclization at −70 °C are effective.

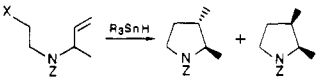
In typical examples, a benzene solution of **1a** was heated in a sealed tube at 140 °C for 1 h in the presence of $RuCl_2(PPh_3)_3$ (5 mol %) to give *trans*-**2a** in 82% yield. Alternatively, a carefully deaerated dichloromethane solution of **1c** was stirred below −70 °C in the presence of CuCl/bpy (1:1, 5 mol %) to give **2c** in 90% yield, in which a cis/trans ratio was 90:10.[8] We found another set of the selective cyclization to form either cis or trans isomers in the reactions of trichloroacetamides from 4-amino-2-heptene as shown in Table I. We are currently investigating the scope and mechanistic aspects to determine the stereochemical course.[9]

(8) This new process can be applied to the cyclization of a wide variety of trichloroacetamides bearing *N*-alkyl or *N*-Ts and *N*-Cbz groups. The reactions were generally completed within 1 h at room temperature to give the corresponding lactams in almost quantitative yields.

Acknowledgment. We are grateful to the Ministry of Education, Science, and Culture for Grant-in-Aid for Scientific Research (63470073) and Saneyoshi Foundation for financial support.

Supplementary Material Available: Experimental details for cyclization of **1a–d**, spectral data of the products **2a–d**, and procedures to determine the stereochemistry (4 pages). Ordering information is given on any current masthead page.

(9) In a typical example, a mixture of CuCl (0.005 mmol) and bipyridine (0.005 mmol) was placed in a Pyrex tube. Compound **1b** (0.1 mmol) dissolved in carefully deaerated dichloromethane (1.4 mL) was added, and the tube was sealed under vacuum. After stirring at −70 °C for 48 h, **2b** was obtained by chromatographic purification. We also found that stereochemical course was dependent on the nitrogen substituents in the β-amino radical cyclization described below. The stereoselectivities are similar to those observed in the copper- or ruthenium-catalyzed system. This result excludes the direct participation of any metallic species in the determining step of the stereochemistry.



X = Cl, Z = CH_2Ph, R = Ph; 110 °C, 5 h, 72% trans/cis = 79:21
X = Br, Z = Ts, R = Bu; 110 °C, 1h, 89% trans/cis = 35:65

Articles

Nonempirical Confirmations of the Absolute Configuration of (+)-α-Methoxy-α-(trifluoromethyl)phenylacetic Acid

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The absolute configuration of the widely used chiral derivatizing agent α-methoxy-α-(trifluoromethyl)phenylacetic (MTPA) acid has been unambiguously determined through the use of two independent, nonempirical methods as *R* and *S* for the (+)- and (−)-enantiomers, respectively. The first approach utilizes the exciton chirality CD method to nonempirically determine the absolute stereochemistry of the *p*-chlorobenzoate derivative of (+)-*trans*-1-hydroxy-2-bromo-1,2,3,4-tetrahydroanthracene. Since the relative stereochemistry of the (−)-MTPA ester of the same alcohol had been elucidated by X-ray crystallographic analysis, the absolute configuration of the (−)-MTPA acid has thus been determined. Alternatively, the single-crystal X-ray analysis of the (+)-MTPA ester derivative of (+)-*trans*-1-hydroxy-2-bromo-1,2,3,4-tetrahydronaphthalene has elucidated its relative stereochemistry. This ester has subsequently been correlated chemically with (+)-naphthalene 1,2-oxide whose absolute stereochemistry had previously been established, thus setting the absolute configuration of (+)-MTPA acid. These configuration proofs, taken together with the three previous empirical correlations and the X-ray structure determination and chemical correlation of Boyd and co-workers, leave no reasonable doubt concerning the absolute configuration of this important reagent.

Optically active α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA acid), the Mosher reagent, was originally developed in 1969[1] for use in determination of the enantiomeric purity of chiral alcohols and amines by NMR spectroscopy. The use of this reagent was subsequently expanded to chromatographic resolution of chiral alcohols[2] and assigning the absolute configuration of its chiral esters based on empirical correlation between their NMR chemical shift and absolute stereochemistry of the alcohol.[3] Despite its general use in organic chemistry,[4,5] the un-

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