A NEW SYNTHETIC APPROACH TO (+)-GALANTINIC ACID, DEGRADATION PRODUCT FROM THE PEPTIDE ANTIBIOTIC GALANTIN I, VIA 4-AMINO-3-HYDROXYPYRANOSE

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Abstract —— 5-Phenylthiooxazolidin-2-ones, derived from L-serine, were subjected to photo-induced radical allylation to give the correspondg 4-substituted 4,5-trans-5-allyloxazolidin-2-ones. 4-Ethoxyethy derivative (**13c**) was led to N-Boc galantinic acid methyl ester via N-Boc 4-amino-3-hydroxypyranose.

The presence of 2-amino alcohol in biologically active molecules such as amino sugars, antibiotics and peptides has raised the interest in the diastereoselective synthesis of these compounds.[1] Furthermore, 2-amino alcohols have been used as the dipeptide isostere in peptidomimetic chemistry.[2] In the previous paper,[3] we demonstrated a photo-induced radical allylation at the 5-position of oxazolidin-2-ones to get 4-substituted 4,5-trans-5-allyloxazolidin-2-ones, protective form of threo 2-amino alcohols.

The method was extensively applied to a synthesis of (+)-galantinic acid,[4,5] the degradation product of the peptide antibiotic galantin I.[5,6] The results of our studies are described in this paper. At first, 4-substituted 5-phenylthiooxazolidin-2-ones, used for photo-radical allylation reaction, were prepared by starting from L-serine and L-threonine as outlined in the Scheme. The alcohols (**2a,b**), obtained by reduction of **1a,b** ($NaBH_4$, MeOH), were treated with diphenyl disulfide in the presence of tri-n-butylphosphine[7] followed by O-deprotection (EtOH, PPTS) of the resulting sulfides (**3a,b**) to give the corresponding sulfur-containing 2-amino alcohols (**4a**),[8] mp 64-65°C, $[\alpha]_D$ +51.2° (c 0.7, MeOH) and **4b**, mp 83-84°C, $[\alpha]_D$ +22.7° (c 1.0, $CHCl_3$), respectively. Acetylation of **4a,b** gave **5a,b** chlorination of which with N-chlorosuccinimide and subsequent cyclization with $SnCl_4$ (-78°C, 20 min then rt 20 min in CH_2Cl_2) yielded the corresponding 4-substituted 4,5-trans-5-phenylthio-oxazolidin-2-ones (**6a**) in 84 % yield, mp 115-118°C, $[\alpha]_D$ -241.8° (c 1.0, $CHCl_3$) and **6b** in 86 % yield, mp 175-176°C, $[\alpha]_D$ -224.5° (c 1.0, $CHCl_3$), with high diastereoselectivity. Replacement of acetyl group of **6a** with ethoxyethyl group (i. Cs_2CO_3, MeOH ii. CH_2=CHOEt, PPTS) afforded **7** as an oil. The epimer at 4-(α)- position of **6b** was also easily prepared from **4b** as follows. Methane-sulfonylation of **4b**, followed by treatment with CsOAc in DMF afforded **8** which was led to **9** according

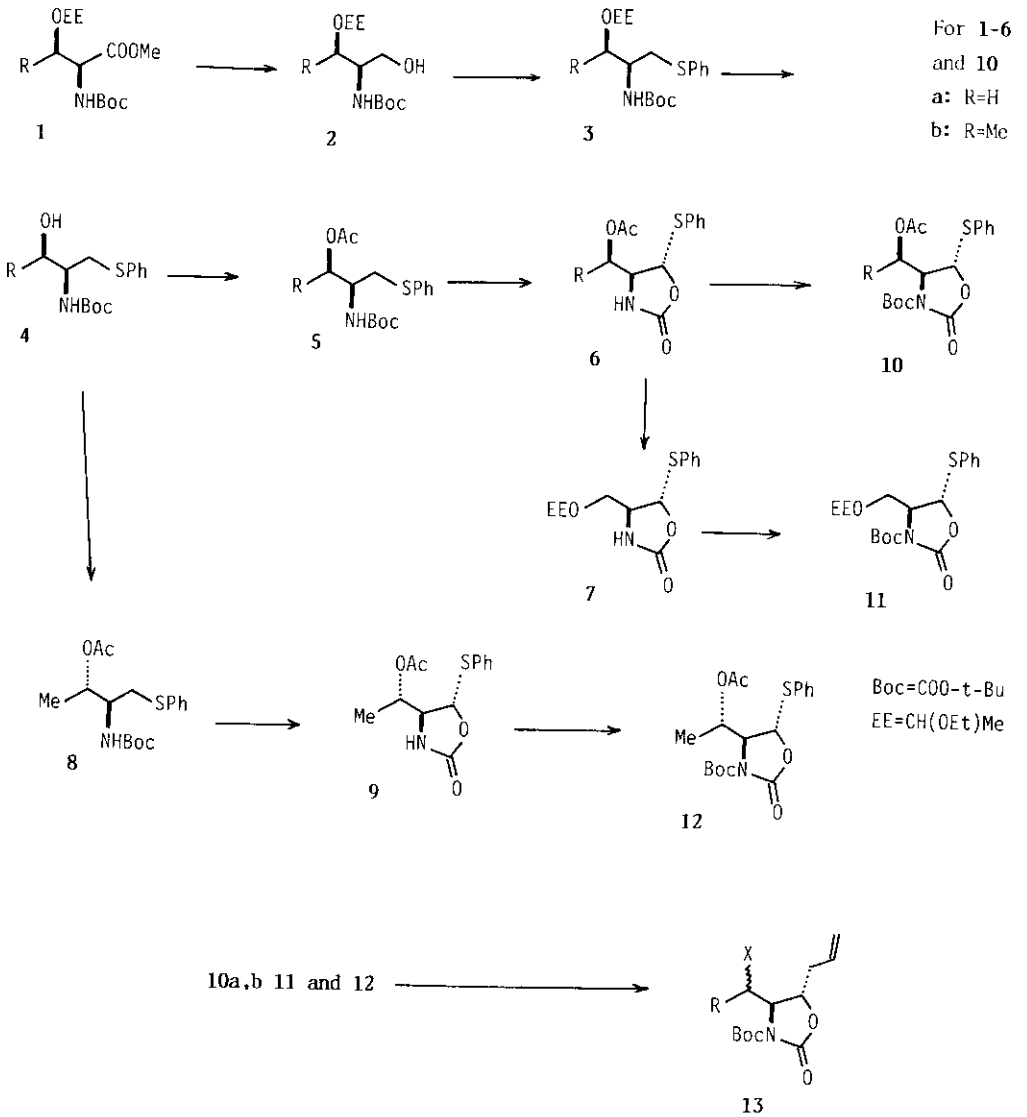
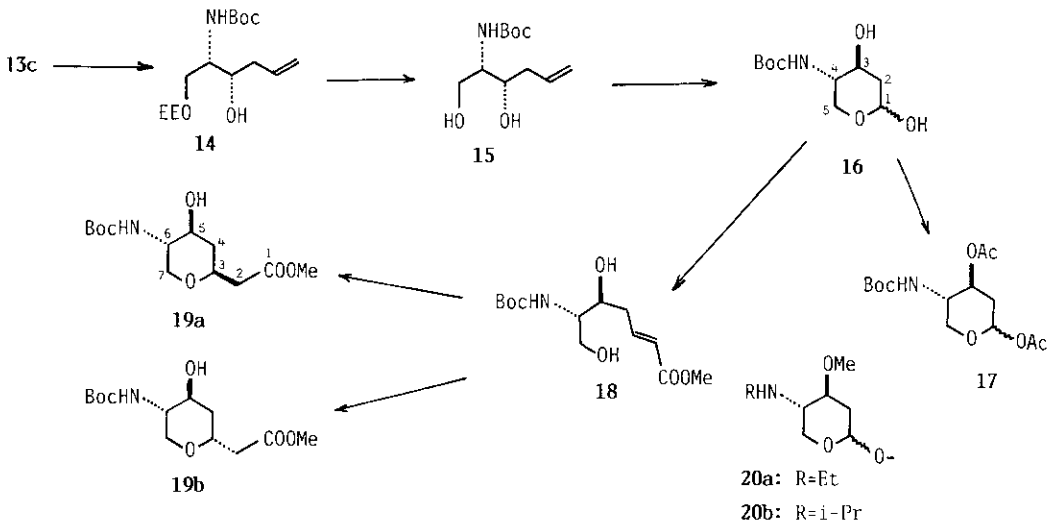


Table 1. Photo-radical Allylation Products (13a-d)

Compound	R	X	Yield (%)	mp (°C)	$[\alpha]_D$ ° ($CHCl_3$)
13a	H	—OAc	80.5	oil	+5.4 (c 1.0)
13b	Me	—OAc	75.0	oil	-9.8 (c 1.0)
13c	H	—OEE	75.8	oil	+3.7 (c 0.7)
13d	Me	····OAc	81.0	68-71	+8.4 (c 1.0)



to the same conditions as in a synthesis of **6a,b**. t-Butoxycarbonylation of **6a,b**, **7** and **9** gave **10a,b**, **11** as an oil and **12**, mp 91-92°C, respectively. These compounds were subjected to photo-induced radical allylation [$(n\text{-}Bu_3Sn)_2$ (1 equiv.), $n\text{-}Bu_3SnCH_2CH{=}CH_2$ (4 equiv.) in toluene-MeCN (7:3, 0.5 M solution), hν 500W Hg lamp, 6 h] to give the corresponding 5-allyloxazolidin-2-ones (**13a-d**). The results were summarized in the Table 1. In their ^{1}H-nmr spectra, 4-H resonated at around δ 3.9-4.1 and 5-H at around δ 4.5 ppm.

Next, ring cleavage of **13a** and **13c** was examined to get N-Boc 2-amino-1,3-dihydroxy-5-hexene (**15**) which would be the key intermediate for preparation of 4-amino-3-hydroxypyranose. Upon ring cleavage of **13a** (Cs_2CO_3, MeOH), the yield for **15** was quite low. However, ring cleavage of **13c** gave **14** in 84 % yield. Subsequent O-deprotection (EtOH, PPTS) of **14** afforded **15**. The desired 4-amino-3-hydroxy-pyranose (**16**) from **15** was successfully achieved by ozonolysis procedure (O_3, MeOH, -78°C then Me_2S) in 76 % yield, mp 168-171°C (decomp.), $[\alpha]_D$ +7.14° (c 0.3, MeOH). The ratio for anomers was determined as 1:4 by conversion to diacetate (**17**), an oil, $[\alpha]_D$ +14.4° (c 0.7, MeOH), ^{1}H-nmr ($CDCl_3$ 400 MHz) δ 6.14 (0.2H, br t, J=3 Hz), 5.87 (0.8H, dd, J=3.59, 5.1 Hz). Wittig reaction of **16** with methyl (triphenylphosphoranylidene)acetate (MeCN, reflux) yielded **18**, cyclization of which (0.1 equiv. K_2CO_3, MeOH) yielded N-Boc galantinic acid methyl ester[5] (**19a**, 43.4 % yield from **16**), mp 104-106°C, $[\alpha]_D$ -4.69° (c 0.9, $CHCl_3$) [lit.,[4] mp 104.5-106°C, $[\alpha]_D$ -4.4° (c 1.2, $CHCl_3$)] and its C_3-epimer (**19b**, 34.2 % yield from **16**), an oil, $[\alpha]_D$ +20.5° (c 0.9, MeOH) [lit.,[4] $[\alpha]_D$ +20.8° (c 1.5, MeOH)]. These were easily separated by column chromatography on silica gel. The spectral data of **19a,b** were identical with those in the literature.[4] The method for a preparation of 4-amino-3-hydroxypyranose described here would be potentially useful for a synthesis of this type of amino sugars such as **20a** in calicheamicin[9] and **20b** in esperamicin.[10]

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