Pergamon

Tetrahedron Letters, Vol. 37, No. 23, pp. 4015-4018, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00750-2

First Total Synthesis of New Diglycosides, Neohancoside A, and B from *Cynanchum Hancockianum*

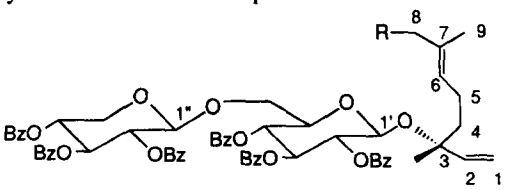
Yaeko Konda,*[a] Tsuneyuki Toida,[a] Eisuke Kaji,[a] Kazuyoshi Takeda,[b] and Yoshihiro Harigaya[a]

[a]School of Pharmaceutical Sciences, Kitasato University, Shirokane, Minato-ku, Tokyo, 108, Japan. [b]Department of Chemistry, School of Science, Kitasato University, Kitasato, Sagamihara-shi, Kanagawa, 228, Japan

Abstract : First total synthesis of monoterpene diglycosides, neohancosides A (**1**) and B (**2**) from *Cynanchum hancockianum* were achieved stereoselectively using fluoride as a glycosyl donor. The absolute configurations of **1** and **2** were determined by enzymatic degradation of synthetic intermediates Copyright © 1996 Elsevier Science Ltd

Cynanchum hancockianum (Maxim) Al. Iljinski (Asclepidaceae), distributed in Inner Mongolia, is known as a Chinese folk medicine possessing antitumor activity. During the continuation of our work to search bioactive compounds, our detailed examination of the constituents of this plant have led to the isolation and structure determination of four novel diglycosides, neohancoside A (**1**), B (**2**), C, D[1,2] together with various other novel compounds.[3] Although various monoterpene glycosides have been recently found from plants, their bioactivities have been scarecely reported so far to our knowledge. Furthermore, we could not determine the absolute configuration of the linalool moiety in **1** and **2** due to their insufficient supply from natural source, which was the background that led our interest to their synthesis. This paper deals with the first total syntheses of these monoterpene diglycosides, **1** and **2**, that opened a supply to investigate their antitumor and other bioactivities and also enabled us to determine the absolute configuration of the linalool moiety of **1** and **2**.

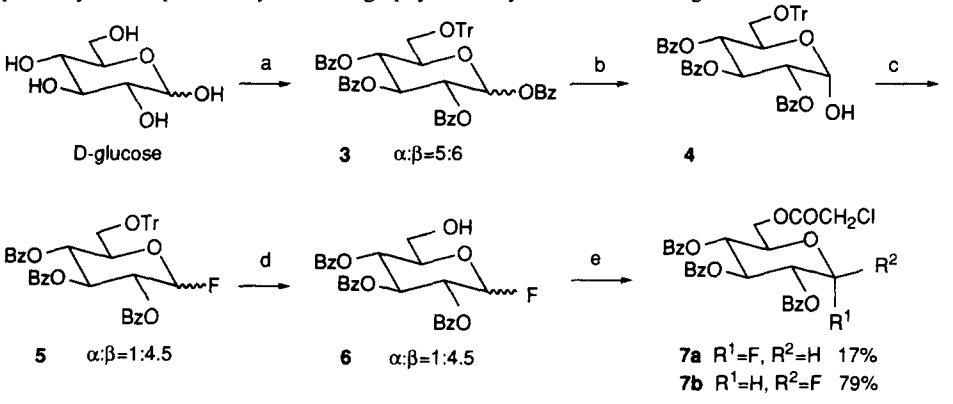
The diglycoside moiety of **1** and **2** is β-D-xylopyranosyl (1→6)-β-D-glucopyranose, which is glycosidated by the teriary hydroxyl group of linalool and 9-hydroxylinalool. As a *tert*-alcohol are much the less reactive toward the glycosylation reaction than primary and secondary alcohol, it is important to select the most suitable reaction conditions in terms of the promoter and the glycosyl donor. We selected glycosyl fluoride which is most effective in the halides for its stability in stores, purification and potent reactivity even in the case of *tert*-alcohols by combination with silver perchlorate and zirconocene dichloride.[4]



1 R=H Neohancoside A
2 R=OH Neohancoside B

Our synthetic strategy toward neohancoside A (**1**) consists of the glycosylation reaction of linalool with a glucosyl fluoride by treatment with silver perchlorate and zirconocene dichloride followed by the selective deprotection of the 6-*O*-protective group in the glucose unit, and glycosylation reaction of the resulting monoglycoside with a xylosyl bromide by treatment of AgOTf and 2,4,6-collidine (Scheme 2). Furthermore, we chos chloroacetyl group for protection of the 6-hydroxyl in the glucosyl fluoride.

We prepared the key compound **7** as shown in Scheme 1. 6-*O*-Trytylation of D-glucose followed by benzoylation afforded an anomeric mixture of **3** in 46% yield.[5] Benzoate **3** was converted to lactol **4** by treatment with hydrazonium acetate in 83% yield, which was treated with DAST to give fluoride **5** as an anomeric mixture in 94% yield. Fluoride **5** was detrytylated by treatment with HBF_4 to an anomeric mixture of **6** in 92% yield. Treatment of **6** with chloroacetyl chloride provided **7a** and **7b** in 17%, 79% yields, respectively after separation by chromatography. Total yield of **7b** from D-glucose was 26%.



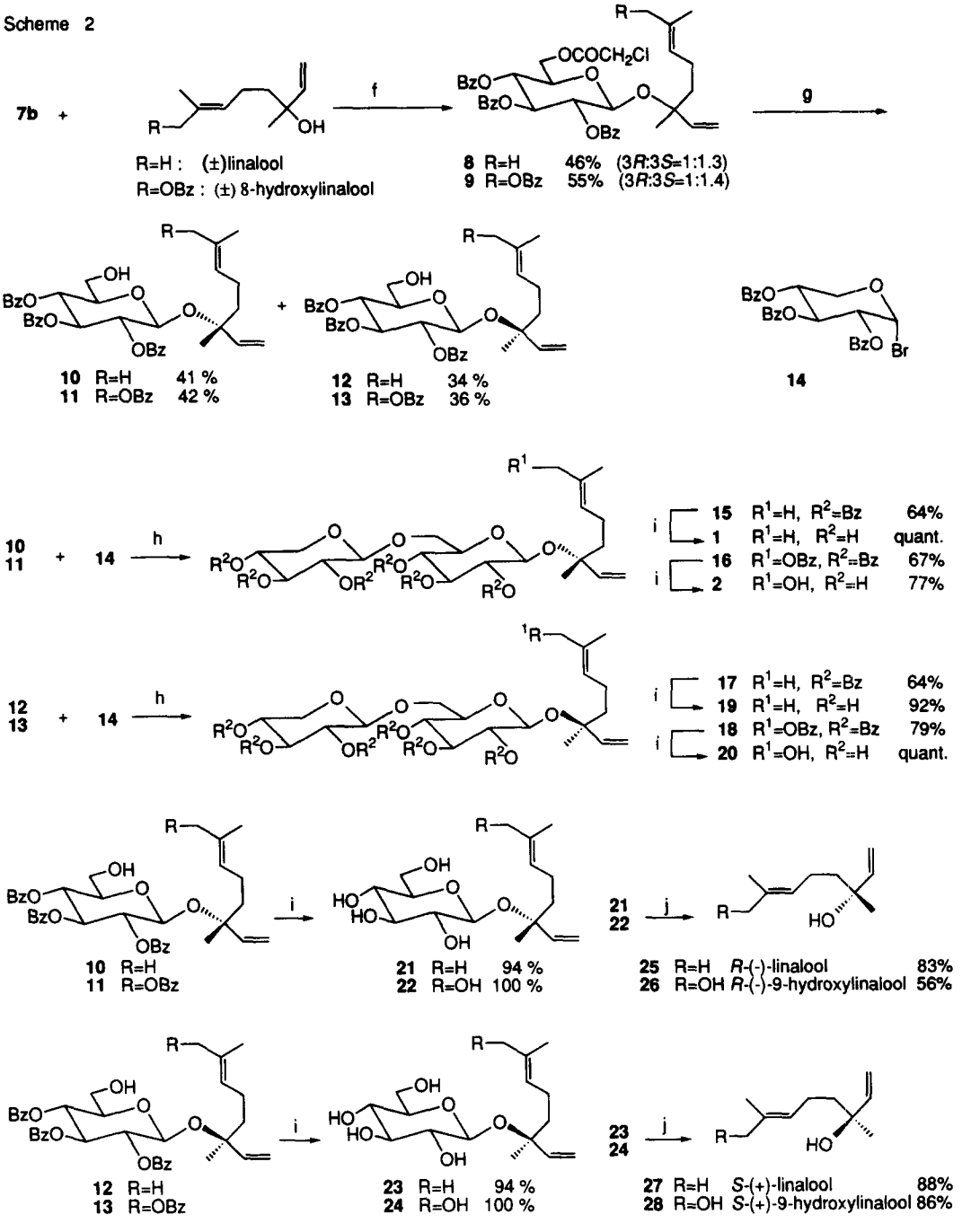
Scheme 1 a) (i) TrCl, pyridine, DMF, rt; (ii) BzCl, -20 °C, 46%; b) NH_2NH_2.AcOH, DMF, 25 °C, 83% c) DAST, CH_2Cl_2, -30 °C, 94%; d) HBF_4, CH_3CN, rt, 92%; e) $ClCH_2COCl$, pyridine

Our approach to **1** using key compound **7** involves how to introduce the asymmetry at C-3 of linalool. We intended to use racemic linalool in the glycosylation reaction with monosaccharyl fluoride and to separate the resulting diastereomer. Thus, **7b** was successively connected with (±) linalool by treatment with silver perchlorate and zirconocene dichloride[4] in CH_2Cl_2 at -30 °C to give linalyl glycoside **8** as a mixture of diastereomer in 46% yield (3*R*:3*S* ratio=1:1.3).

Selective deprotection of the chloroacetyl group in **8** by using 2-aminoethanethiol and pyridine, triethylamine was successively carried out. The resulting 6'-hydroxyl compounds were successively separated by chromatography to afford diastereomer **10** (3*R*) and **12** (3*S*) in 41%, 34% yields, respectively. Alcohol **10** (3*R*) was glycosylated with bromide **14** under the usual conditions using silver triflate and 2, 4, 6-collidine in CH_2Cl_2 at -20 °C to afford disaccharyl glycoside **15** in 64% yield. Debenzoylation of **15** using sodium methoxide in a mixtured solvent of of THF and methanol gave the completely deprotected compound **1**, quantitatively. Synthetic **1** showed mp of 92-94° (AcOEt)), $[\alpha]_D^{25}$ -26° (c=0.47, MeOH). **1** was identified[6] in all respects (mp, $[\alpha]_D$, HRMS, ^1H NMR, ^{13}C NMR) with natural neohancoside A.[1] The ^1H and ^{13}C NMR spectra were superimposable to those of natural products. Glycosylation reaction of **12** (3*S*) with bromide **14** by a similar procedure as above also afforded diglycoside **17** in 64% yield, which was deprotected in the same way to give **19**, the srereoisomer of neohancoside A (**1**), in 92% yield, which showed mp of 75-77° (AcOEt), $[\alpha]_D$ -20° (c=0.37, MeOH) and ^1H, ^{13}C NMR spectra were clearly distinguishable from **1**. These results show the diastereomer **10** has the same chirality at C-3 of linalool as natural neohancoside A (**1**). Thus, total synthesis of neohancoside A was achieved in 3.1% total yield from D-glucose in 9 steps.

Debenzoylation of **10** and **12** using sodium methoxide in a mixtured solvent of THF-MeOH afforded quantitatively glycosides **21** and **23** in 94% yield, respectively. Glycosylic linkage of **21** and **23** was

Scheme 2



f) $AgClO_4$, zirconocene dichloride, CH_2Cl_2, -30 °C; g) $HSCH_2CH_2NH_2$, pyridine, triethylamine, MeOH, rt; h) AgOTf, collidine, CH_2Cl_2, -20 °C; i) NaOMe, MeOH-THF, rt.; j) β-D-glycosidase, Na_2HPO_4, citric buffer, 37 °C

cleaved by enzymatic hydrolysis using β-D-glycosidase in Na_2HPO_4-citric buffer under incubation at 37 °C for 53 h and 90 h, respectively to give each chiral linalool **25** and **27** in 83 %, 88 %, respectively. Measurements of the optical rotation revealed that **25** is (*R*)-(-)-linalool[7] and **27** is (*S*)-(+)-linalool[8] by comparison with the values in the literature. Thus, the configuration of neohancoside A (**1**) was determined to be 3*R*.

Neohancoside B (**2**) is a monoterpene diglycoside containing the same disaccharide as **1** having 8-hydroxylinalool[9] as the aglycone in place of linalool in **1**. Neohancoside (**2**) was totally synthesized using racemic 8-hydroxylinalool by the same procedure as in the case of **1** as described in Scheme 2, which showed mp 46-48 °C (AcOEt) and $[\alpha]_D^{28}$ -27° (c=0.59, MeOH), and was identifical[10] in all respects ($[\alpha]_D$, HRMS, ^1H and ^{13}C NMR) with natural neohancoside B.[2] The ^1H and ^{13}C NMR spectra of **2** were superimposable to those of the natural product. Another diastereomer **20** showed mp of 33~35 °C and $[\alpha]_D^{21}$ of -28° (c=1.27, MeOH). The ^1H, ^{13}C NMR of **20** were clearly distinguishable from those of natural neohancoside B. Thus, total synthesis of **2** was achieved in 4.0% total yield from D-glucose. The absolute configuration of **2** was determined by the same procedure as **1** as described in Scheme 2. Glycosides **22** and **24** afforded *R*-(-)-8-hydroxylinalool (**26**)[11] and *S*-(+)-8-hydroxylinalool (**28**)[7] and the aglycone moiety in **2** was also determined to have the 3*R* configuration.

In conclusion, total synthesis of two monoterpene diglycosides (**1**) and (**2**) from *cynanchum hancockianum*, were first achieved stereoselectively and their absolute stereostructure were determined.

Acknowledgement: The author thanks Prof. M. Onda, Prof. X. Li, and Dr. H. Lou for supply of neohancoside A and B.

References and Notes

1. Konda, Y.; Toda, Y.; Harigaya,Y.; Lou, H.; Li, X.; Onda, M. *J. Nat. Prod.* **1992**, *55*, 1447-1453.
2. Lou, H.; Li, X.; Onda, M.; Konda, Y.; Machida, T.; Toda, Y.; Harigaya, Y. *J. Nat. Prod.* **1993**, *56*, 1437-1443.
3. Lou, H.; LI, X.; Onda, M.; Konda, Y.; Urano, M.; Harigaya, Y.; Takayanagi, H.; Ogura, H. *Chem. Pharm. Bull.* **1991**, *39*, 2271-2276.
4. Suzuki, K.; Meata, H.; Matsumoto, T. *Tetrahedron Lett.* **1989**, *30*, 4853-4856. Mastumoto,T.; Maeta.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1988**, *29*, 3567-3570.
5. Kovac, P.; Glaudemans, P. J. *J. Carbohydr. Chem.* **1988**, *7*, 317-335.
6. Neohancoside A (natural product) shows[1] mp 84-86° and $[\alpha]_D^{23}$ -27.7° (MeOH).
7. Barner, R.; Hubscher, J.; *Helv. Chem. Acta* **1983**, *66*, 880-890.
8. Uchiyama, T.; Miyase, T.; Ueno, A.; Usmanghani, K. *Phytochemistry* **1989**, *28*, 3369-3372.
9. Hase, T.; Twagawa, T.; Munesada, K. *Phytochemistry* **1982**, *21*, 1435-1437.
10. Neohancoside B (natural product) shows[2] $[\alpha]_D^{21}$ -25.7° (MeOH).
11. Matsubara, Y.; Sawabe,A.; Iba, H.; Iizuk, Y. *Agri. Biol. Chem.* **1990**, *54*, 555-556.

(*Received in Japan* 23 *January* 1996; *revised* 8 *April* 1996; *accepted* 17 *April* 1996)