Pergamon

Tetrahedron Letters, Vol. 38, No. 8, pp. 1367-1368, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00033-6

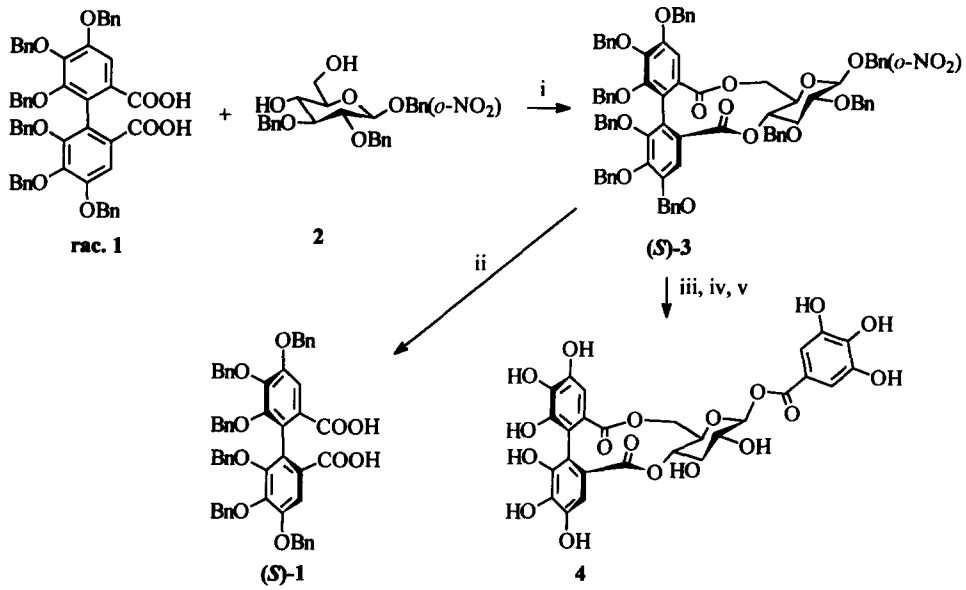
Synthesis of Enantiomerically Pure Strictinin Using a Stereoselective Esterification Reaction

Karamali Khanbabaee*, Christian Schulz, Kerstin Lötzerich

Universität-GH-Paderborn, Fachbereich 13 - Organische Chemie,
Warburger Straße 100, 33098 Paderborn, Germany

Abstract: The total synthesis of strictinin (**4**) has been achieved using a diastereoselective esterification of benzyl protected hexahydroxydiphenic acid **1** with D-glucose derived sugar **2**.

Strictinin (**4**)[1,2] is a member of the broad class of hydrolyzable vegetable extracts known as ellagitannins.[3,4] To date, over 500 structurally characterized ellagitannins have been identified.[5] Plant polyphenols are of commercial use in the leather and wine industries[3] as well as in a variety of traditional herbal medicines.[3] Accordingly, much attention has been focused on the development of general approaches to the compounds of this class.[4,6-9] Up to now there are three general approaches to produce enatiomerically pure ellagitannins (for a review s. lit.[4]). Meyers et al.[10] described the oxazoline-mediated asymmetric Ullmann coupling to produce (*S*)-hexamethoxydiphenic acid, which was used to synthesize the *O*-permethyl derivative of the naturally occurring tellimagrandin I. In that sense Lipshutz et al.[9] also described an asymmetric synthesis of a biaryl system by an intramolecular oxidative coupling reaction of cyanocuprate intermediates. The second approach, based on the intramolecular diastereoselective oxidative coupling reaction of phenolic aromatic systems, was described by Feldman et al.. The diastereoselectivity is caused by a chiral sugar core, which holds two aryl moieties.[5] The third methodology is the kinetic resolution of axially chiral biaryl compounds described by Itoh and co-workers.[6,7] They performed a stereoselective esterification of methyl-4,6-*O*-benzylidene-α-D-glucopyranoside at the free 2,3-*O*-positions with racemic hexamethoxy-1,1′-diphenyl-2,2′-dicarboxyl chloride. Our synthetic strategy towards the synthesis of enantiomerically pure strictinin (**4**) also relied on the concept of kinetic resolution for axially chiral biaryl compounds. However, we anticipated that the esterification of benzyl protected racemic diphenic acid[11] **1** with an appropriately substituted sugar would occur with high diastereoselectivity. Accordingly, we started with the esterification of racemic hexabenzyloxydiphenic acid[11] (**1**) with 1-*O*-(*o*-nitrobenzyl)-2,3-di-*O*-benzyl-β-D-glucopyranoside (**2**)[12,13] to assemble the carbon framework of **4** (Scheme 1). In agreement with our expectation, under the Keck-modified Steglich esterification[14], an excellent diastereoselectivity with respect to the axially chiral biaryl carbon-carbon bond of the hexabenzyloxydiphenoyl system was observed (24% yield). We detected only one of the two possible diastereoisomers. In order to determine the absolute configuration of this stereoisomer, the product was subjected to hydrolysis using anhydrous potassium hydroxide (potassium *tert*-butoxide, H_2O, THF) as proposed by Gassman.[15] An optically pure (*S*)-hexabenzyloxydiphenic acid was obtained from this reaction as shown by comparison of its specific rotation with that reported for (*S*)-**1**.[11] Thus, the absolute configuration of the observed stereoisomer was unambiguously determined to be (*S*)-**3**. Compound (*S*)-**3** was subsequently subjected to irradiation at 320 nm in a photochemical apparatus (PYREX) to give the anomerically deprotected derivative in 86% yield. Further anomeric acylation[16] of this compound with (3,4,5-tri-*O*-benzyl)gallic acid chloride afforded the precursor of the target compound **4** in 82% yield. Finally, the totalsynthesis of strictinin (**4**) was completed by hydrogenolysis to remove the benzyl protecting groups (Scheme 1). Purification of the crude ellagitannin was carried out using reversed-phase thin layer chromatography to give a yellow glass in 69% yield. The physical properties ($[\alpha]_D$, ^{1}H-NMR, IR, MS) unambiguously established the identity of our synthetic and the natural strictinin (**4**), including the absolute (*S*)-configuration.[1,2]



Scheme 1

Reagents and conditions: (i) DMAP, DMAP · HCl, DCC, CH_2Cl_2, reflux 24 h; (ii) KO *t*-Bu, THF, H_2O, 12 h; (iii) hv; (iv) (3,4,5-tri-*O*-benzyl)gallic acid chloride; (v) Pd/C -H_2

Acknowledgments: Financial support from the Deutsche Forschungsgemeinschaft (5109/99-Totalsynthese) and the donation of a doctoral fellowship to K.L. from the Universität-GH-Paderborn is gratefully acknowledged. We also thank Prof. Krohn for useful discussions and continuing support.

References:

1. G.-I. Nonaka, R. Sakai and I. Nishioka, *Phytochemistry* **1984**, 23, 1753.
2. T. Okuda, T. Yoshida, M. Ashida and K. Yazaki, *J. Chem. Soc., Perkin Trans. 1* **1983**, 1765.
3. E. Haslam, *Plant Polyphenols-Vegetable Tannins Revisited* (Edited by Cambridge University Press) Cambridge New York New Rochelle Melbourne Sydney, **1989**.
4. S. Quideau and K. S. Feldman, *Chem. Rev.* **1996**, 96, 475.
5. K. S. Feldman and R. S. Smith, *J. Org. Chem.* **1996**, 61, 2606.
6. T. Itoh and J.-i. Chika, *J. Org. Chem.* **1995**, 60, 4968.
7. T. Itoh, J.-i. Chika, S. Shirakami, H. Ito, T. Yoshida, Y. Kubo and J.-i. Uenishi, *J. Org. Chem.* **1996**, 61, 3700.
8. J.-H. Lin, G.-I. Nonaka and I. Nishioka, *Chem. Pharm. Bull.* **1990**, 38, 1218.
9. B. H. Lipshutz, Z.-P. Liu and F. Kayser, *Tetrahedron Lett.* **1994**, 35, 5567.
10. T. D. Nelson and A. I. Meyers, *J. Org. Chem.* **1994**, 59, 2577.
11. O. Th. Schmidt and K. Demmler, *Liebigs Ann. Chem.* **1952**, 576, 179.
12. U. Zehavi, B. Amit and A. Patchornik, *J. Org. Chem.* **1972**, 37, 2281.
13. U. Zehavi and A. Patchornik, *J. Org. Chem.* **1972**, 37, 2285.
14. G. E. Keck and E. P. Boden, *J. Org. Chem.* **1985**, 50, 2394.
15. P. G. Gassman and W. N. Schenk, *J. Org. Chem.* **1977**, 42, 918.
16. K. Jansson, S. Ahlfors, T. Frejd, J. Kihlberg, G. Magnusson, J. Dahmen, G. Noori and K. Stenvall, *J. Org. Chem.* **1988**, 53, 5629.

(*Received in Germany* 20 *December* 1996; *accepted* 7 *January* 1997)