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Asymmetric desymmetrization of *meso*-cyclopentitol using a C_2-symmetric bis-sulfoxide: A synthesis of (−)-allosamizoline

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Abstract

A synthesis of (−)-allosamizoline was accomplished via asymmetric desymmetrization of a *meso*-cyclopentitol using the C_2-symmetric bis-sulfoxide **5** as a chiral auxiliary. © 1998 Elsevier Science Ltd. All rights reserved.

Allosamizoline **1** is a naturally occurring *N*-acetyl-β-D-allosamine analogue and is part of the structure of allosamidin **2**, isolated from the mycelia of *Stroptomyces* sp. no. 1713[1] and from the fermentation broth of sp. AJ 9463.[2] Due to its unusual bicyclic structure and strong chitinase inhibiting activity,[3] several synthetic studies have been reported.[4] The asymmetric syntheses previously studied can be categorized into two approaches: (1) a chiral pool approach using sugar;[4d–i] and (2) an enzymatic desymmetrization of *meso*-4-benzyloxymethyl-3,5-dihydroxycyclopentene.[4j–l]

Herein, we describe a novel approach using chemical asymmetric desymmetrization of a *meso*-cyclopentitol derivative **4** as a key step and creating five stereogenic centers in **1** simultaneously. Our synthetic plan is illustrated in Scheme 1. Although allosamizoline has a high density of functional groups and multi-stereogenic centers on its cyclopentane ring, the molecule has inherent symmetry. A suitably protected cyclopentitol derivative **3** is envisioned as a precursor of **1**, which can be converted into **1** via S_N2 displacement of the hydroxy group with an amino group followed by formation of an oxazoline moiety. The cyclopentitol derivative **3** can be derived from a *meso*-cyclopentitol **4** by differentiation of an enantiotopic hydroxy group. In this step, we planned to use the C_2-symmetric bis-sulfoxide **5** which has recently been developed in our laboratory as a novel chiral auxiliary for asymmetric desymmetrization of *meso*-1,2-diols.[5]

meso-Diol **7** was prepared starting from the known *meso*-diol **6**[6] via benzylation followed by dihydroxylation with a catalytic amount of OsO_4 in the presence of *N*-methylmorpholine *N*-oxide (NMO) (Scheme 2). Dihydroxylation proceeded diastereoselectively from the opposite side to the adjacent benzyloxy groups to give the desired *meso*-diol **7** along with a diastereomer (ratio 8:1), which was separable by column chromatography.[7] Acetalization of the mono silyl ether of **7** with the (*R*,*R*)-bis-sulfoxide

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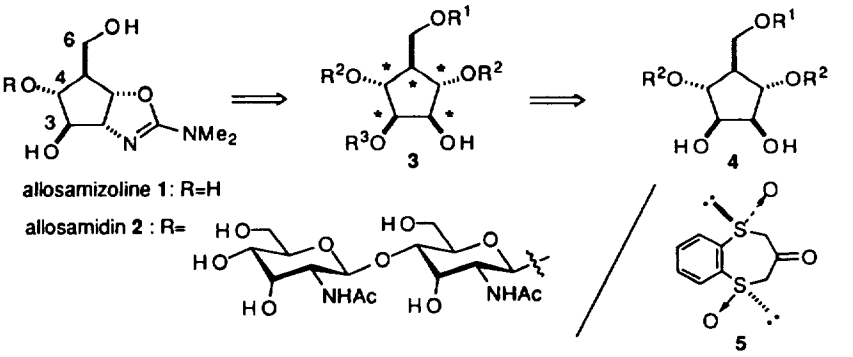

Scheme 1.

5[5] in the presence of TMSOTf proceeded in good yield to give the acetal **8**.[8] On treatment of **8** with KHMDS followed by benzylation, an acetal cleavage reaction proceeded with high diastereoselectivity (>96% *d.e.*) to give the benzyl ether **9**.[9] Then, the chiral auxiliary was readily removed by hydrolysis with dilute hydrochloric acid.[10] The enantiomeric excess of the resulting alcohol **10** was determined as 95% *e.e.* by ^{1}H-NMR spectroscopy after conversion into the Mosher's ester. The absolute configuration was determined as (1*R*,2*S*) by Mosher's method.[11] S_N2 Displacement of the hydroxy group into the amino group was carried out via triflation of **10** with triflic anhydride and pyridine followed by azidation with *n*-Bu_4NN_3 to give the azide **11**, which was transformed into the carbamate **12** by the sequence of chemoselective reduction of the azide moiety in the presence of benzyl groups and methoxycarbonylation of the resulting amine. After deprotection of the four benzyl groups on $Pd(OH)_2$–C,[12] the known triacetate **13**[4d–h] was obtained via cyclization with MeONa in refluxing MeOH in the presence of 4 Å molecular sieves[13] followed by acetylation of the remaining alcohols with acetic anhydride in pyridine. The spectroscopic data of the synthesized **13** {$[\alpha]_D^{30}$ −26.0 (*c*=0.56, $CHCl_3$), lit.[4d] $[\alpha]_D$ −25, lit.[4e] $[\alpha]_D^{20}$ −29.4 (*c*=1.48, $CHCl_3$), lit.[4f,g] $[\alpha]_D^{26}$ −24.1 (*c*=0.46, $CHCl_3$), lit.[4h] $[\alpha]_D$ −25 (*c*=0.41, $CHCl_3$)} was consistent with authentic data.[14] Since **13** leads to **1** in two steps,[4h] we achieved a formal synthesis of (−)-**1**.

In conclusion, highly potent chitinase inhibitor, allosamizoline (**1**), was synthesized using asymmetric desymmetrization of the *meso*-cyclopentitol derivative with the C_2-symmetrical bis-sulfoxide as a key step. Our approach should be effective for the synthesis of other cyclitols having a regioselectively protected polyhydroxy structure, and thus for the synthesis of other naturally occurring sugar mimics and their related analogs, which are of great interest as tools for biological research or as potential therapeutic agents.

Acknowledgements

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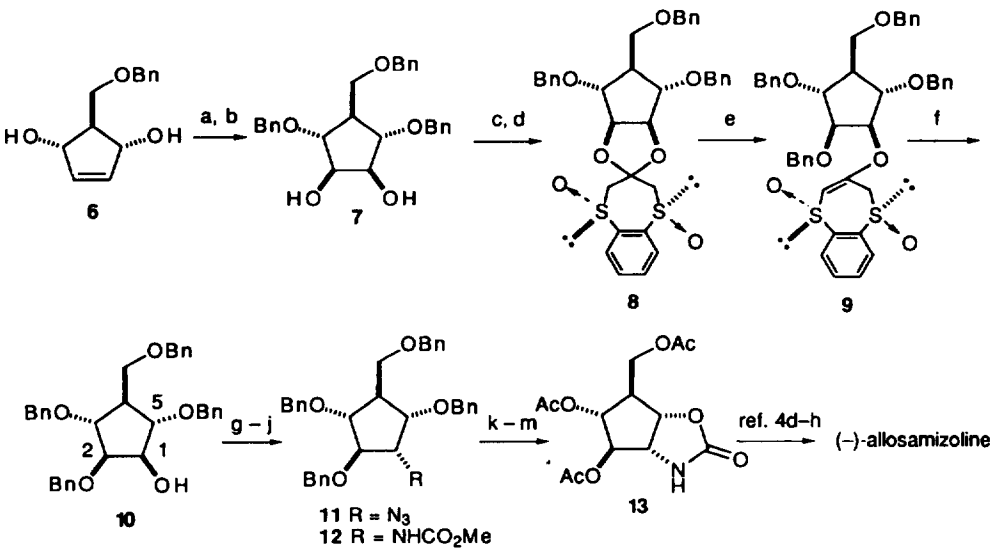

Reagents: a) BnBr, NaH, cat. n-Bu_4NI, THF, 0 °C to room temp. (85%); b) cat. OsO_4, NMO, acetone-H_2O (10:1), room temp. (88%); c) TMSCl, Et_3N, THF, 0 °C [67% (99% based on recovery of 7)]; d) (*R,R*)-**5**, TMSOTf, $CHCl_3$, 4 °C (92%); e) KHMDS, 18-crown-6-ether, THF, –78 °C then BnBr (91%); f) 10% HCl, acetone, room temp. (91%); g) Tf_2O, pyridine, CH_2Cl_2, 0 °C; h) n-Bu_4NN_3, benzene, room temp. (83% from **10**); i) H_2, Pd-C, MeOH, 3 atom; j) MeOCOCl, Na_2CO_3, CH_2Cl_2-H_2O (2:1), 0 °C (94% in 2 steps); k) H_2, $Pd(OH)_2$-C, 3 atom, MeOH, room temp. (76%); l) NaOMe, 4A MS, MeOH, reflux; m) Ac_2O, pyridine, room temp. (88% from **12**).

Scheme 2.

4. For synthesis of racemic allosamizoline, (a) Goering, B. K.; Ganem, B. *Tetrahedron Lett.* **1994**, *35*, 6997–7000; (b) Trost, B. M.; Vranken, D. L. V. *J. Am. Chem. Soc.* **1993**, *115*, 444–458; (c) Trost, B. M.; Vranken, D. L. V. *J. Am. Chem. Soc.* **1990**, *112*, 1261–1263. For synthesis of (−)-allosamizoline from sugar: (d) Blattner, R.; Furneaux, R. H.; Kemmitt, T.; Tyler, P. C.; Ferrier, R. J.; Tiden, A.-K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3411–3421; (e) Kitahara, T.; Suzuki, N.; Koseki, K.; Mori, K. *Biosci. Biotech. Biochem.* **1993**, *57*, 1906–1909; (f) Simpkins, N. S.; Stokes, S.; Whittle, A. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2471–2477; (g) Simpkins, N. S.; Stokes, S.; Whittle, A. J. *Tetrahedron Lett.* **1992**, *33*, 793–796; (h) Nakata, M.; Akazawa S.; Kitamura, S.; Tatsuta, K. *Tetrahedron Lett.* **1991**, *32*, 5363–5366; (i) Takahishi, S.; Terayama, H.; Kuzuhara, H. *Tetrahedron Lett.* **1991**, *38*, 5123–5126. For synthesis of (−)-allosamizoline via enzymatic desymmetrization: (j) Shrader, W. D.; Imperiali, B. *Tetrahedron Lett.* **1996**, *37*, 599–602; (k) Griffith, D. A.; Danishefsky, S. J.; Samuel, J. *J. Am. Chem. Soc.* **1996**, *118*, 9526–8538; (l) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863–5864.
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7. The stereochemistry of the diastereomeric isomers was determined by examining the nuclear Overhauser effect (NOE). By irradiating the α-methine proton of the benzyloxymethyl group, NOE was registered on the α-methine protons of the hydroxy groups in the major product and the hydroxy protons in the minor products, respectively.
8. The reaction should be carried out at 4°C in the shortest possible time. Partial racemization of sulfurs was observed at higher temperature and with longer reaction times.
9. The diastereomeric excess of **9** was determined by ^{1}H-NMR spectroscopy.
10. The chiral auxiliary was recovered without decreasing the enantiomeric excess.
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12. Lin, C.-C.; Weitz-Schmidt, G.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 6826–6840. Debenzylation using 10% Pd–C for 5 days gave the complex mixture.

13. The reaction conditions were the same as those in Ferrier's,[4d] except that molecular sieves were used in order to obtain reproducible results.
14. Data for compound **13**: $[\alpha]_D^{30}$ −26.0 (c=0.56, $CHCl_3$). δ_H (500 MHz, $CDCl_3$) 2.10 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.12 (s, 3H, OAc), 2.60–2.65 (m, 1H, 5-H), 3.95 (dd, 1H, J=9.2, 4.3 Hz, 2-H), 4.22 (d, 2H, J=4.9 Hz, 6-H), 4.76 (dd, 1H, J=7.3, 4.3 Hz, 3-H), 4.87 (dd, 1H, J=9.2, 6.1 Hz, 1-H), 5.24 (dd, 1H, J=9.8, 7.3 Hz, 4-H), 5.70 (br s, 1H, NH). δ_C (67.8 MHz, $CDCl_3$) 20.65, 20.69, 20.72, 47.99, 59.28, 60.68, 72.53, 77.47, 83.49, 157.29, 169.90, 170.57, 171.36. ν_{max} (KBr) 3336, 2924, 2854, 1743, 1371, 1230, 1041 cm^{-1}. HR-FAB-MS m/z: 316.1036 (calcd for $C_{13}H_{17}NO_8+H^+$: 316.1032).