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LETTERS

Synthesis of enantiomerically pure 9-[(1′*R*,2′*R*,3′*S*)-bis(hydroxymethyl)thietan-1′-yl]adenine, 3′-thio analog of oxetanocin A

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Abstract

The enantiomerically pure synthesis of 9-[(1′*R*,2′*R*,3′*S*)-bis(hydroxymethyl)thietan-1′-yl]adenine **2**, 3′-thio analog of oxetanocin A, was achieved via coupling with sulfoxide **17** and 6-chloropurine in the presence of TMSOTf and Et_3N under the Pummerer reaction conditions.

Keywords: nucleosides; Pummerer reactions; thietanes.

Various nucleoside compounds have been reported as potent and selective inhibitors against the replication of HIV-1, HSV-1, HSV-2, HBV, and HCMV in vitro and in vivo. At present, AZT, ddI, ddC, d4T, and (−)-3TC have been approved as drugs for the clinical treatment of AIDS and AIDS-related complex. In the search for effective, selective, and nontoxic antiviral agents, a variety of strategies have been devised to design nucleoside analogs. These strategies have involved several formal modifications of the naturally occurring nucleosides, especially, alteration of the carbohydrate moiety. Since the naturally occurring purine nucleoside oxetanocin A **1** and its derivatives have been found to be effective as anti-HIV-1 and anti-herpes virus agents,[1] the syntheses of different types of hydroxymethyl-branched nucleosides have been reported.[2] To further evaluate the structure–activity relationship of hydroxymethyl-substituted nucleosides, we became interested in developing a synthesis of 3′-thio analog **2** (thietanocin A as a coined name) of **1**, which has a sulfur atom instead of an oxygen atom in the oxetane ring of **1**. Very recently, pioneering studies on the syntheses of optically active thietanose derivatives and thietanosyl nucleosides were achieved by Uenishi et al. and Matsuda et al., respectively.[3] These findings prompted us to report our results. Herein, we describe the first synthesis of 9-[(1′*R*,2′*R*,3′*S*)-bis(hydroxymethyl)thietan-1′-yl]adenine **2** from (*S*,*S*)-1,4-bis(benzyloxy)-2,3-epoxybutane **3**.

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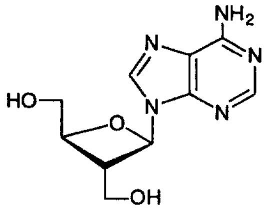
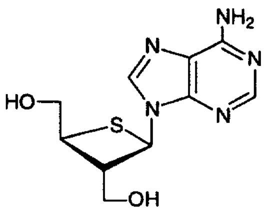
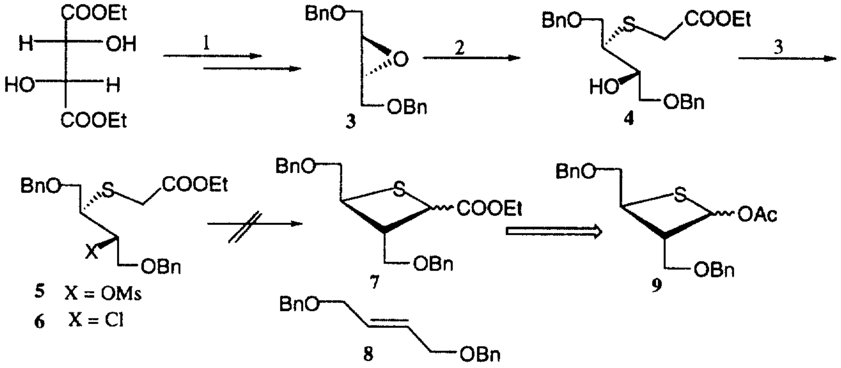


Oxetanocin A **1**



2

Our initial strategy to synthesize 1-*O*-acetylthietanose compound **9** is depicted in Scheme 1. Reaction of epoxide **3**, which was easily obtained from (+)-diethyl L-tartrate in five steps,[4] with ethyl mercapto-acetate in the presence of CuI and EtMgBr afforded alcohol **4**. When **4** was reacted with methanesulfonyl chloride in order to obtain mesylate **5**, chloride **6** was obtained instead of **5** due to SN2′ reaction. Several attempts to obtain the thietane compound **7** from **6** with base failed and just afforded the olefin compound **8**.

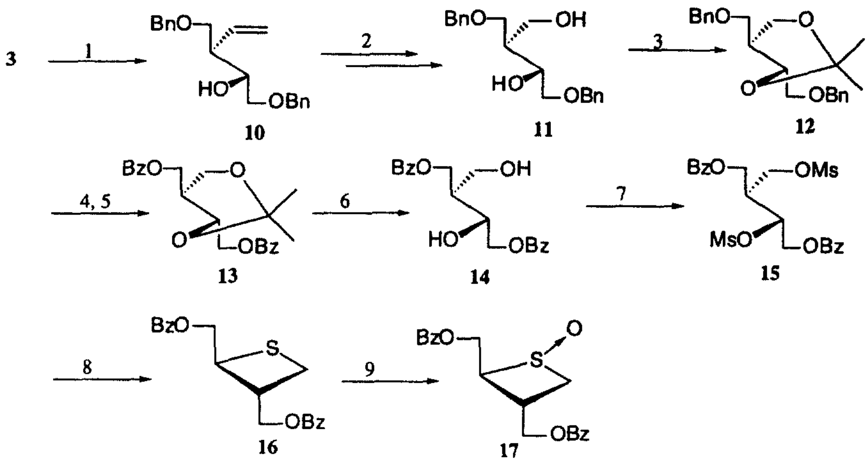


Scheme 1. *Reagents and conditions*: (1) see Nicolaou et al.;[4] (2) $HSCH_2COOEt$, EtMgBr, CuI, THF, 16 h, 45%; (3) MsCl, Et_3N, CH_2Cl_2, 0°C, 16 h, 71%

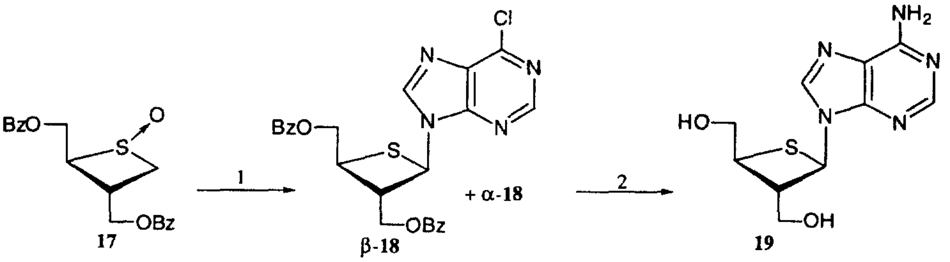
Next, we focused on the preparation of thietane ring from diol **11** which could be facilely prepared from epoxide **3** by a four-step sequence: (1) reaction of **3** with vinyl magnesium bromide in the presence of CuI; (2) dihydroxylation of the olefin with OsO_4; (3) oxidative cleavage of the vicinal diol with $NaIO_4$; and (4) reduction of the intermediate aldehyde with $NaBH_4$.[5] At first, the benzyl protecting groups of **11** were replaced by benzoyl groups for the sake of future reactions (Scheme 2). Protection of two hydroxyl groups of **11** by treatment with 2,2-dimethoxypropane by the aid of *p*-TsOH gave acetonide **12**. Hydrogenolysis of **12** over 10% Pd-carbon, followed by benzoylation of the diol with benzoyl chloride in pyridine afforded dibenzoate **13**. Deprotection of **13** under acidic conditions gave diol **14**, which was mesylated to give dimesylate **15**. When **15** was submitted to a formation of a thietane ring by treatment with $Na_2S \cdot 9H_2O$ in DMF, thietane **16** was obtained in 30% yield. Oxidation of **16** with *m*-CPBA in CH_2Cl_2 gave sulfoxide **17** as a diastereomeric mixture.[6]

With regard to the target compound **19**, sulfoxide **17** was condensed with 6-chloropurine in the presence of TMSOTf and Et_3N in toluene according to the protocol of O'Neil and Hamilton[7b] to give the glycosylated products **18** in 22% yield with an anomeric ratio of $\alpha:\beta=1:3$.[8,9] Finally, the simultaneous deblocking and amination of β-anomer **18** with ethanolic ammonia provided thietanocin A **19** (Scheme 3).[9]

In conclusion, we have developed the first synthesis of 9-[(1′*R*,2′*R*,3′*S*)-bis(hydroxymethyl)thietan-1′-yl]adenine as a novel analog of oxetanocin A. The synthetic strategy outlined in this report seems to be efficient and applicable to the chiral synthesis of a number of potential antiviral purine and pyrimidine



Scheme 2. *Reagents and conditions*: (1) $CH_2{=}CHMgBr$, CuI, THF–Et_2O, –30°C, 4 h, 95%; (2) see Hosono et al.;[5] (3) DMP, acetone, *p*-TsOH·H_2O, rt, 1 h, 99%; (4) H_2, 10% Pd-C, MeOH, rt, 16 h, 85%; (5) PhCOCl, pyridine, rt, 15 h, 96%; (6) MeOH, *p*-TsOH·H_2O, rt, 0.5 h, 91%; (7) MsCl, Et_3N, CH_2Cl_2, 0°C, 0.5 h, 88%; (8) $Na_2S{\cdot}9H_2O$, DMF, 100°C, 15 min, 30%; (9) *m*-CPBA, CH_2Cl_2, 0°C, 10 min, 97%

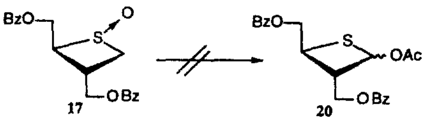


Scheme 3. *Reagents and conditions*: (1) 6-chloropurine, TMSOTf, Et_3N, toluene, 0°C to rt, 2 h, 22%; (2) NH_3, EtOH, sealed tube, 70°C, 17 h, 16%

derivatives of this new class. Further studies on the synthesis of related compounds as well as the investigation of the biological activities are on-going and will be detailed elsewhere.

References

1. Masuda, A.; Kitagawa, M.; Tanaka, A.; Saito, S.; Shimada, N.; Ikeda, R.; Hoshino, H.; Daikoku, T.; Nishiyama, Y. *J. Antibiot.* **1993**, *46*, 1034–1037.
2. (a) Brånalt, J.; Kvarnström, I.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1996**, *61*, 3599–3603. (b) Ichikawa, E.; Yamamura, S.; Kato, K. *Bioorg. and Med. Chem. Lett.* **1999**, *9*, 1113–1114.
3. (a) Nishizono, N.; Koike, N.; Yamagata, Y.; Fujii, S.; Matsuda, A. *Tetrahedron Lett.* **1996**, *37*, 7569–7572. (b) Uenishi, J.; Motoyama, M.; Kimura, Y.; Yonemitsu, O. *Heterocycles* **1998**, *47*, 439–451.
4. Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Magolda, R. L.; Dolle, R. E. *J. Org. Chem.* **1985**, *50*, 1440–1456.
5. (a) Hosono, F.; Nishiyama, S.; Yamamura, S.; Izawa, T.; Kato, K.; Terada, Y. *Tetrahedron* **1994**, *50*, 13335–13345. (b) Kikuchi, Y.; Kurata, H.; Nishiyama, S.; Yamamura, S.; Kato, K. *Tetrahedron Lett.* **1997**, *38*, 4795–4798.
6. Attempts to get 1-*O*-acetylthietanose derivative **20** from **17** by heating in acetic anhydride were unsuccessful.



7. (a) Kita, Y.; Tamura, O.; Yasuda, H.; Itoh, F.; Tamura, Y. *Chem. Pharm. Bull.* **1985**, *33*, 4235–4241. (b) O'Neil, I. A.; Hamilton, K. M. *Synlett* **1992**, 791–792. (c) Yoshimura, Y.; Kitano, K.; Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T.; Matsuda, A. *J. Org. Chem.* **1996**, *61*, 822–823.
8. The stereochemistry of the anomeric carbon was determined by an NOE analysis of α-**18** and β-**18**, respectively. α-**18** showed 12% NOE at the H-1′ proton when irradiated at H-2′.
9. Selected spectroscopic data: β-**18**: $[\alpha]_D^{19}$ +64.6 (*c* 1.05, $CHCl_3$); ^{1}NMR (400 MHz, $CDCl_3$) δ 3.85 (1H, m), 4.05 (1H, m), 4.50 (1H, dd, *J*=4.6, 12.0 Hz), 4.60 (2H, complex), 4.80 (1H, dd, *J*=5.6, 12.0 Hz), 6.71 (1H, d, *J*=6.8 Hz), 7.38 (2H, t, *J*=7.8 Hz), 7.50 (2H, t, *J*=7.8 Hz), 7.56 (1H, m), 7.64 (1H, m), 7.82 (2H, dd, *J*=1.5, 7.8 Hz), 8.08 (2H, dd, *J*=1.5, 7.8 Hz), 8.85 (1H, s), 9.10 (1H, s). α-**18**: $[\alpha]_D^{19}$ −35.8 (*c* 1.01, $CHCl_3$); ^{1}NMR (400 MHz, $CDCl_3$) δ 3.84 (1H, m), 4.11 (1H, m), 4.38 (2H, complex), 4.71 (1H, dd, *J*=5.4, 11.7 Hz), 4.85 (1H, dd, *J*=5.9, 11.7 Hz), 6.84 (1H, d, *J*=7.8 Hz), 7.30 (2H, complex), 7.50 (5H, complex), 7.63 (1H, m), 8.10 (2H, complex), 8.73 (1H, s), 9.13 (1H, s). **19**: ^{1}NMR (400 MHz, CD_3OD) δ 3.50–3.85 (6H, complex), 6.18 (1H, d, *J*=6.8 Hz), 8.25 (1H, s), 8.86 (1H, s); FABMS (positive) *m/z* 268 $(M+H)^+$.