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Synthesis and Absolute Stereochemistry of the Aminosugar Moiety of Antibiotic C-1027 Chromophore

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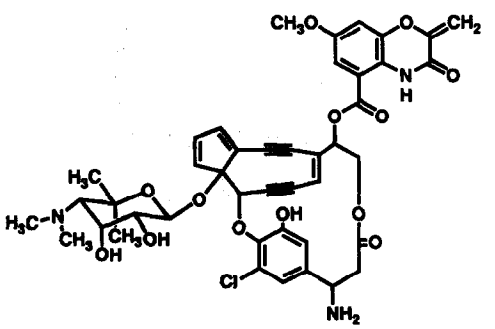
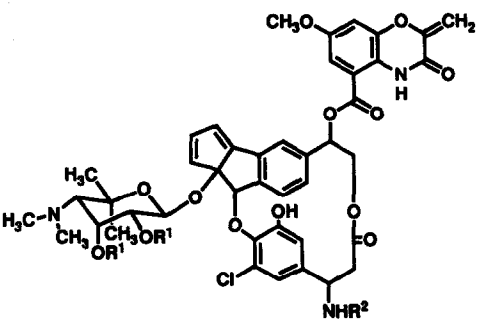
Abstract: Stereocontrolled synthesis and absolute stereochemistry of the aminosugar moiety of C-1027 chromophore have been disclosed.

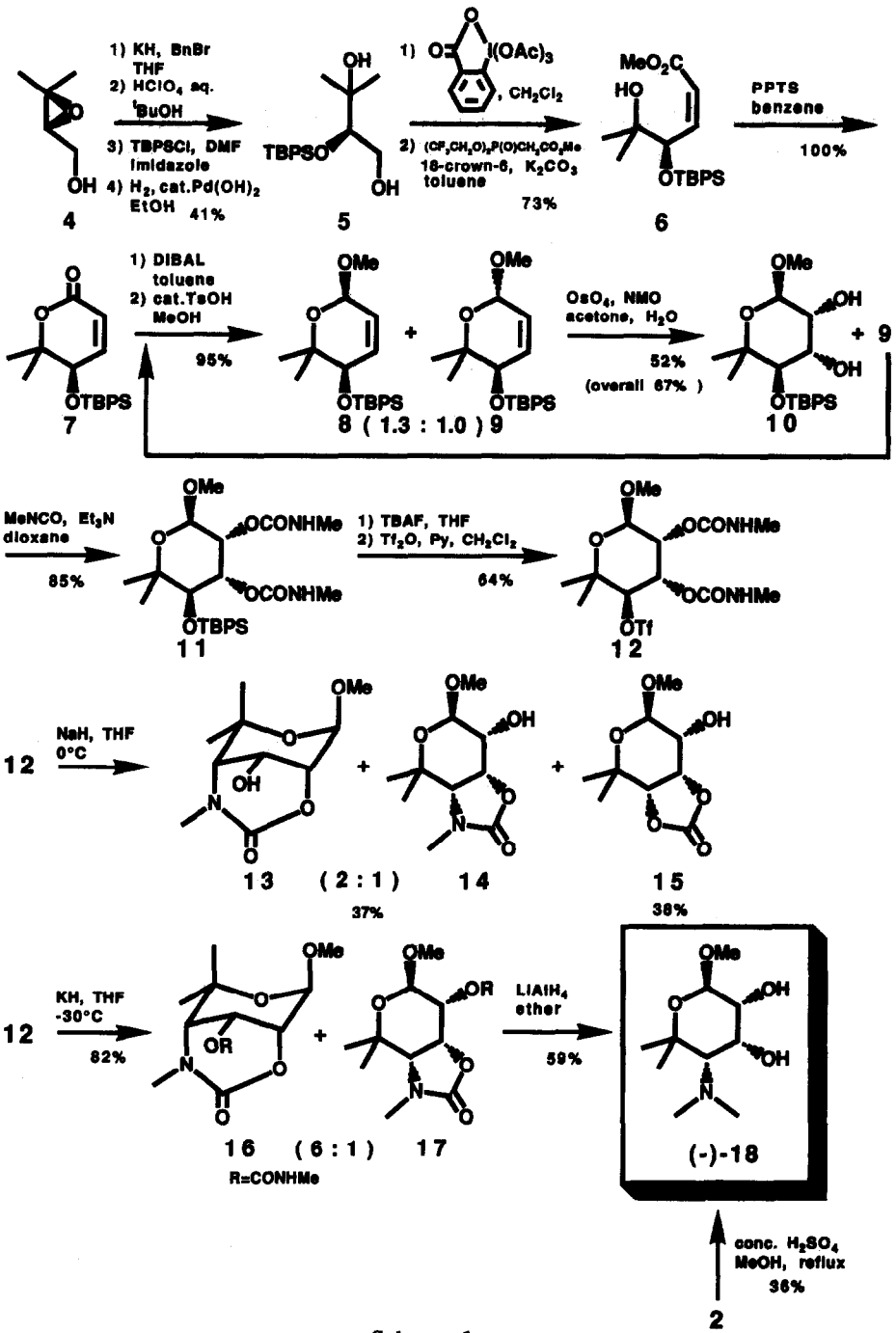
The chromoprotein antibiotics are a rapidly emerging class of highly potent antitumor agents, which comprise an unstable enediyne chromophore and a carrier apoprotein.[1] Antibiotic C-1027 is one of the latest members, isolated from the broth filtrate of *Streptomyces globisporus* C-1027.[2] Very recently, structures of the labile C-1027 choromophore **1** and its cycloaromatized product **2** have been determined by detailed 2D-NMR studies.[3,4] While the novel aminosugar moiety is supposed to play an important role in DNA strand scission, its absolute stereochemistry has not been elucidated.[3] We originally planned to determine it by applying the CD exciton chirality method[5] directly to the bis-p-bromobenzoate **3**. However, **3** showed too complicated CD Cotton effects due to the interactions among the many aromatic segments. In this paper, we report the stereocontrolled synthesis and the absolute configuration of the sugar moiety.



1

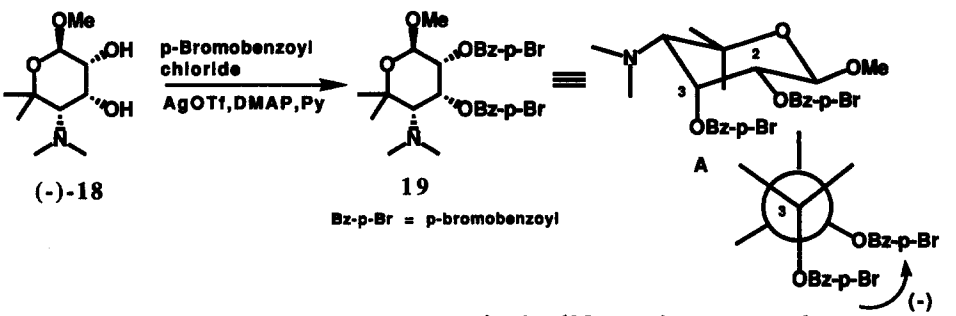


2 R^1=H R^2=H
3 R^1=Bz-p-Br R^2=$COCH_3$


1) KH, BnBr THF
2) HClO4 aq. tBuOH
3) TBPSCl, DMF imidazole
4) H2, cat.Pd(OH)2 EtOH 41%
4
5
1) I(OAc)3, CH2Cl2
2) (CF3CH2O)2P(O)CH2CO2Me 18-crown-6, K2CO3 toluene 73%
6
PPTS benzene 100%
1) DIBAL toluene
2) cat.TsOH MeOH 95%
7
8 (1.3 : 1.0) 9
OsO4, NMO acetone, H2O 52% (overall 67%)
10
MeNCO, Et3N dioxane 85%
11
1) TBAF, THF
2) Tf2O, Py, CH2Cl2 64%
12
NaH, THF 0°C
13 (2 : 1) 14 37%
15 38%
KH, THF -30°C 82%
16 (6 : 1) 17
R=CONHMe
LiAlH4 ether 59%
(-)-18
conc. H2SO4 MeOH, reflux 36%
2

Scheme 1

The synthesis of methyl glycoside **18** was started with (*R*)-2,3-epoxy-3-methyl-1-butanol (**4**) (80% ee), readily obtained by Sharpless asymmetric epoxydation using (-)-DIPT (Scheme 1).[6] The epoxide **4** was converted to triol monosilyl ether **5** in 4 steps (41% overall yield). Hydrolytic opening of the epoxide proved to proceed regioselectively, because the optical purity of **5** was identical with that of **4**.[7] Oxidation of **5** with Dess-Matin periodinane[8] followed immediately by coupling with Still's phosphonate reagent[9] gave (*Z*)-α,β-unsaturated ester **6** selectively in 73% yield (2 steps), which was then lactonized with PPTS to lactone **7** quantitatively. DIBAL reduction of **7** and ketalization with acidic methanol afforded an anomeric mixture of **8** and **9** (95%). Osmium catalyzed dihydroxylation of the mixture proceeded selectively only in the 1,4-cis-disubstituted **8**. The exclusive anti-addition of OsO_4 giving rise to **10** (52% yield) was confirmed by NOE experiments. Recovered **9** was equilibrated with acidic methanol, and the resulting mixture was resubjected to the OsO_4 oxidation. Thus the overall conversion to **10** was 67%. Biscarbamate **11** was obtained by refluxing **10** with excess methyl isocyanate in dioxane in the presence of triethylamine (85% yield). Removal of the silyl group and triflation gave **12** in 64% yield. Treatment of the triflate **12** with sodium hydride caused an intramolecular carbamate cyclization.[10] However, the O-cyclization leading to carbonate **15** competed with the N-cyclization. Cyclized carbamates **13** and **14** with free hydroxyl group were produced in low yield (37%). Upon treatment with potassium hydride at low temperature, however, the clean N-cyclization occurred to give a 6 : 1 mixture of **16** and **17** in 82% yield. Thus, the nucleophilic displacement of the triflate at the sterically hindered position was achieved in a good yield and with complete stereochemical inversion. Lithium aluminium hydride reduction of the mixture afforded the methyl glycoside (-)-**18** [colorless needles, mp 120-121°C (hexane/ether), $[\alpha]_D^{18}$ -48.8° (c 1.00, $CHCl_3$)],[11] whose spectral data (^{1}H-NMR, IR, MS) including the molecular rotation were identical with those of the degradation product ($[\alpha]_D^{20}$ -38.2°(c 0.051, $CHCl_3$)) derived from **2**. Furthermore, the absolute stereochemistry of the synthetic and the naturally derived compounds **18** was confirmed by the CD exciton chirality method.[5] The ^{1}H-NMR spectra[12] of the corresponding bis-p-bromobenzoates **19** indicated clearly their conformation (**A**) and their negative splitting CD Cotton effect showed unequivocally their absolute stereochemistry (2*R*,3*R*,4*S*). Thus, the aminosugar moiety of **1** proved to be 4-deoxy-4-dimethylamino-5,5-dimethyl-(*D*)-ribopyranose.



(-)-**18** **19**

Bz-p-Br = p-bromobenzoyl

	synthetic (80% ee)	natural
UV (1.0x10^{-5} M)	λ_{max} 244nm (ε 33000)	λ_{max} 245nm (ε 36000)
CD (1.0x10^{-4} M)	Δεmax 0.68 (237nm)	Δεmax 0.83 (240nm)
	Δεmin -2.88 (254nm)	Δεmin -3.08 (256nm)

Reference and Notes

1. (a) Neocarzinoatatin: Ishida, N.; Miyazaki, K.; Kumagai, K.; Rikimaru, M. *J. Antibiot.*, **1965**, *18*, 68; Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.*, **1985**, *26*, 331; Myers, A.G.; Proteau, P.J.; Handel, T.M. *J. Am. Chem. Soc.*, **1988**, *110*, 7212. (b) Auromomycin: Chimura, H.; Ishizuka, M.; Hamada, M.; Hori, S.; Kimura, K.; Iwanaga, J.; Takeuchi, T.; Umezawa, H. *J. Antibiot.*, **1968**, *21*, 44; Samy, T.S.A.; Hahm, K.-S.; Modest, E.J.; Lampman, G.W.; Keutmann, H.T.; Umezawa, H.; Herlihy, W.C.; Gibson, B.W.; Carr, S.A.; Biemann, K. *J. Biol. Chem.*, **1983**, *258*, 183. (c) Actinoxantin: Khokhlov, A.S.; Cherches, B.Z.; Reshetov, P.D.; Smirnova, G.M.; Sorokina, I.B.; Prokoptzeva, T.A.; Koloditskaya, T.A.; Smirnov, V.V. *J. Antibiot.*, **1969**, *22*, 541; Khokhlov, A.S.; Reshetov, P.D.; Chupova, L.A.; Cherches, B.Z.; Zhigis, L.S.; Stoyachenko, I.A. *J. Antibiot.*, **1976**, *29*, 1026. (d) Kedarcidin: Lam, K.S.; Hesler, G.A.; Gustavson, D.R.; Crosswell, A.R.; Veich, J.M.; Forenza, S.; Tomita, K. *J. Antibiot.*, **1991**, *44*, 472; Hofstead, S.J.; Matson, J.A.; Malacko, A.R.; Marquardt, H. *J. Antibiot.*, **1992**, *45*, 1250; Leet, J.E.; Schroeder, D.R.; Hofstead, S.J.; Golik, J.; Colson, K.L.; Huang, S.; Klohr, T.W.; Doyle, T.W.; Matson, J.A. *J. Am. Chem. Soc.*, **1992**, *114*, 7946; Leet, J.E.; Golik, J.; Hofstead, S.J.; Matson, J.A.; Lee, A.Y.; Clardy, J. *Tetrahedron Lett.*, **1992**, *33*, 6107.
2. (a) Hu, J.; Xue, Y.C. ; Xie, M.Y.; Zhang, R.; Otani, T.; Minami, Y.; Yamada, Y.; Marunaka, T. *J. Antibiot.*, **1988**, *41*, 1575. (b) Otani, T.; Minami, Y.; Marunaka, T.; Zhang, R.; Xie, M.Y. *J. Antibiot.*, **1988**, *41*, 1580.
3. Yoshida, K.; Minami, Y.; Azuma, R.; Saeki, M.; Otani, T. *Tetrahedron Lett.*, in press.
4. Minami, Y.; Yoshida, K.; Azuma, R.; Saeki, M.; Otani, T. *Tetrahedron Lett.*, in press.
5. Harada, N.; Nakanishi, K. "Circular Dichroic Spectroscopy -Exciton Coupling in Organic Stereochemistry-", University Science Books, Carifornia, U.S.A. (1983).
6. Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.*, **1987**, *109*, 5765.
7. Enantiomeric excess of **4** and **5** was determined by HPLC (chiral column DICEL CHIRALPAK AS) analysis of the corresponding benzylether.
8. Dess, D.B.; Martin, J.C. *J. Am. Chem. Soc.*, **1991**, *113*, 7277.
9. Still, W.C.; Gennari, C. *Tetrahedron Lett.*, **1983**, *24*, 4005.
10. Knapp, S.; Kukkola, P.J.; Sharma, S.; Muradi Dhar, T.G.; Naughton, A.B. *J. Org. Chem. Soc.*, **1990**, *55*, 5700.
11. **18**: ^{1}H-NMR(400 MHz, $CDCl_3$): δ 1.34(3H, s, 5-CH_3), 1.52(3H, s, 5-CH_3), 2.26(1H, d, J=2.8Hz, 4-H), 2.50(6H, s, 4-$N(CH_3)_2$), 3.35(1H, dd, J=3.1, 7.8Hz, 2-H), 3.52(3H, s, 1-OCH_3), 4.42(1H, dd, J=2.8, 3.1Hz, 3-H), 4.65(1H, d, J=7.8 Hz, 1-H); FTIR(film): 3448, 2934, 1216, 1093, 756 cm^{-1}; EIMS(70eV): m/z 86(100%), 187(33%), 219(34%, M^+); Anal. Calcd. for $C_{10}H_{21}O_4N$, C: 54.77, H: 9.65, N: 6.39%; Found C: 54.53, H: 9.60, N: 6.27%.
12. **19**: ^{1}H-NMR(200 MHz, $CDCl_3$): δ 1.42(3H, s, 5-CH_3), 1.70(3H, s, 5-CH_3), 2.39(6H, s, 4-$N(CH_3)_2$), 2.74(1H, d, J=2.5Hz, 4-H), 3.48(3H, s, 1-OCH_3), 4.96(1H, d, J=8.0Hz, 1-H), 5.02(1H, dd, J=3.0, 8.0Hz, 2-H), 6.19(1H, dd, J=2.5, 3.0Hz, 3-H), 7.4-7.8(8H, m, phenyl).

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