SYNTHESIS OF THE B/C-RING SYSTEM OF TETRONASIN (ICI-139603)

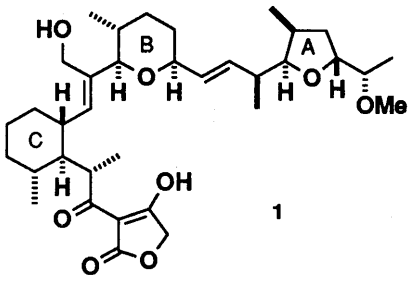
Kozo HORI, Shuho MORI, Keiichi NOMURA, Atsushi INAGAKI, and Eiichi YOSHII*

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan

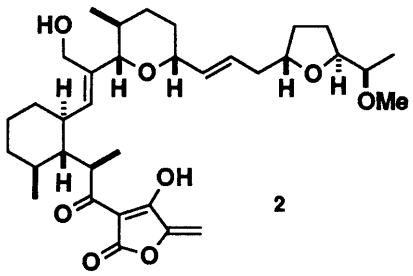
An efficient entry to the tetrahydropyran/cyclohexane moiety of tetronasin has been developed. An aldol reaction between a cyclohexanecarboxaldehyde,**8**, and a (tetrahydropyranyl)acetate ,**9** ,under controlled conditions followed by dehydration of the adduct **10** afforded predominantly (*E*)-ester **11**, which on photoisomerization and subsequent reduction with iso-Bu_2AlH provided the B/C ring system **13**.

KEYWORDS ionophore antibiotic; tetronasin, total synthesis; enzymatic resolution

A reasonable approach to the total syntheses of tetronasin (**1**)[1] and the closely related antibiotic tetronomycin (**2**)[2] would be in the first place to synthesize the three subunits (A-, B-, and C-rings) suitable for coupling reaction, then their assemblage in an appropriate order, and lastly introduction of the acyltetronic acid appendage.[3] To date we and S.V. Ley's group have been able to synthesize all three cyclic fragments[4] and achieved connection of the two heterocycles.[5] The remaining problem in accomplishing the total synthesis is how to join the cyclohexyl and tetrahydropyranyl groups.[6] Here we provide a solution to the problem as realized in a successful synthesis of the B/C ring system of **1**.



1



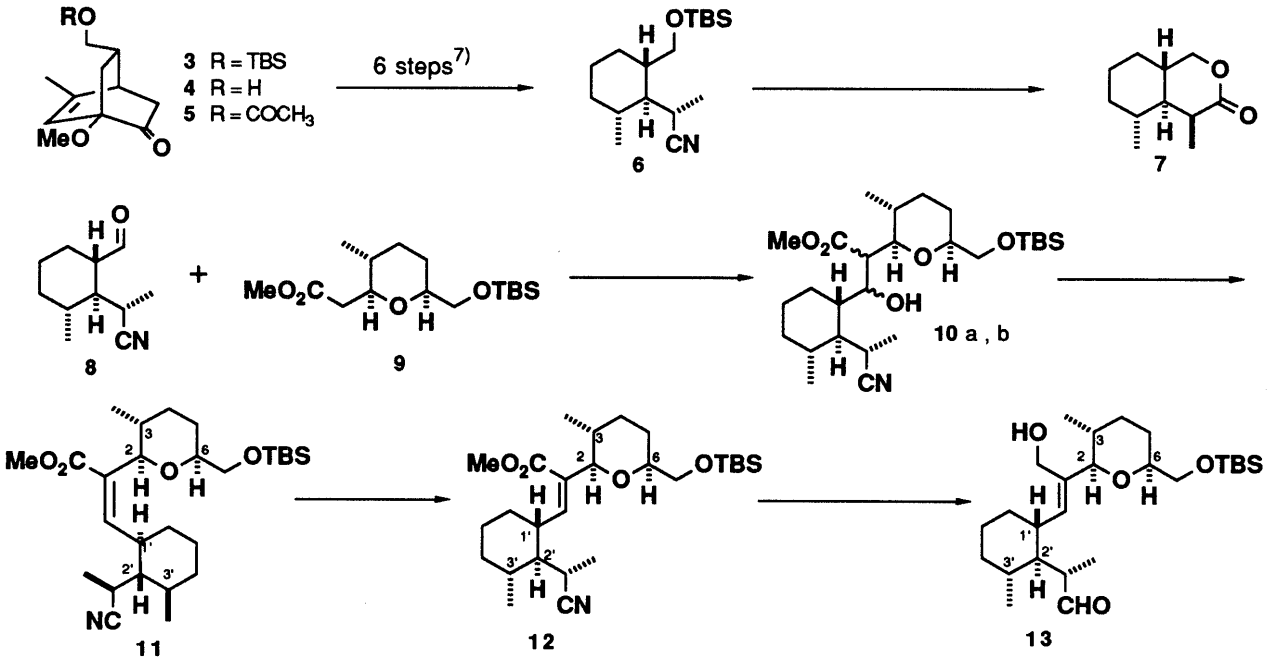
2

In a previous paper[7] we reported the synthesis of a racemate of bicyclic ketone **3** and its transformation into cyclohexane fragment (±)-**6**. To obtain both enantiomers of **6**, which can be used for the total syntheses of tetronasin (**1**) and tetronomycin (**2**), we resolved the racemate *via* ketalization with (2*R*,3*R*)-butanediol to furnish **4** and ***ent*-4**[8] whose absolute stereochemistries were determined at a later stage of the transformations. The resolution was also accomplished by an enzyme-catalyzed enantioselective acetylation.[9] Thus, treatment of (±)-**4** with acetic anhydride (2 eq) in a 9:4 mixture of isooctane and benzene in the presence of Amano lipase CES (*Pseudomonus* sp.) on Celite (23 °C, 9h) afforded **5** (62.5% ee, 52% yield), and ***ent*-4** (65.2% ee, 48% yield).[10,11] The optical purity of (-)-**5** could be enhanced to 90% ee (35% yield) by single recrystallization from hexane-iso-Pr_2O (1:1).

The bicyclic ketone (-)-**4** was transformed into functionallized cyclohexane **6**, $[\alpha]_D^{26}$ +4.83° (*c*=1.69, $CHCl_3$) according to the procedure we reported earlier.[7] The absolute configuration as depicted was assigned by an acid-catalyzed lactonization[7] leading to **7**, $[\alpha]_D^{26}$ -98.2° (*c*=0.5, $CHCl_3$), and by comparison of the $[\alpha]_D$ with that of ***ent*-7**, $[\alpha]_D^{28}$ +89.9° (*c*=0.16, $CHCl_3$) obtained by an exhaustive ozonolysis of

tetronomycin.[12] Compound **6** was then converted to aldehyde **8** by a conventional 2-step reaction: desilylation (HF in aq. MeCN) and Swern oxidation.[13]

Coupling of **8** and pyran segment **9**[14] by an aldol reaction have been accomplished under controlled conditions. Thus treatment of **9** with lithium diisopropylamide in THF at -100 °C for 15 min followed by addition of **8** (0.65 eq),[15] then quenching the reaction after 15 min produced in 79% yield an easily separable mixture of two diastereomeric adducts, **10**a (less polar)/**10**b (more polar) = 1:1.[7] The individual isomer was dehydrated by *O*-mesylation (5 eq $MeSO_2Cl$ and 0.5 eq 4-dimethylaminopyridine in pyridine, room temperature, 24 h) followed by treatment of the crude *O*-mesylate with DBU (neat, room temperature, 20 h). By this procedure the isomer **10**a produced (*E*)-ester **11** exclusively, whereas **10**b afforded a 10:1 mixture of **11** and (*Z*)-ester **12**. The assignments of the olefin geometries were based on the downfield chemical shift of the vinyl proton in **11** (δ 6.65) relative to that observed in **12** (δ 5.79).[16,17]



TBS = *tert*-butyldimethylsilyl

Predominant formation of the (*E*)-ester **11** prompted us to investigate a photochemical *E*/*Z* isomerization. Irradiation of an acetone solution of **11** (*ca.* 8 mM) with 254-nm light using an immersion-type low-pressure Hg lamp at -10 °C for 2.5 h produced a 1:2 mixture of **11** and **12**, from which the desired (*Z*)-isomer **12** was isolated in 50% yield by silica gel chromatography. Finally, the ester and nitrile groups of **12** were reduced by treatment with diisobutylaluminum hydride (3 eq) in toluene at -80°C to provide the B/C ring system **13**,[17] $[\alpha]_D^{25}$ -15.3° (*c*=0.35, $CHCl_3$) in 75% yield. Application of the present result to the total syntheses of **1** and **2** is under investigation.

ACKNOWLEDGEMENT Support of this work by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan is acknowledged. We are also grateful to Amano Pharmaceutical Co. for providing us with samples of several lipases.

REFERENCES AND NOTES

1) D.H. Davies, E.W. Snape, P.J. Suster, T.J. King, and C.P. Falshaw, *J. Chem. Soc., Chem. Commun.*, **1981**, 1073.
2) C. Keller-Julsén, H.D. King, M. Kuhn, H-R. Loosli, W. Pache, T.J. Petcher, H.P. Weber, and A. von Wartburg, *J. Antibiot.*, **35**, 142(1982).

3) For recent advances in α-acylation of β-tetronic acid, see; K. Nomura, K. Hori, M. Arai, and E. Yoshii, *Chem. Pharm. Bull.*, **34**, 5188(1986); S.V. Ley and D.J. Wadsworth, *Tetrahedron Lett.*, **30**, 1001(1989); and reference 7).
4) A.M. Doherty and S.V. Ley, *Tetrahedron Lett.*, **27**, 105(1986); S.V. Ley, *Pure Appl. Chem.*, **61**, 401(1989); K. Hori, K. Nomura, N. Hikage, and E. Yoshii, *Chem. Pharm. Bull.*, this issue.
5) Synthesis of the A/B ring system of **1** by S.V. Ley: delivered in his lecture at the 16th International Symposium on the Chemistry of Natural Products (Kyoto, 1988). Synthesis of the A/B ring system of **2**: K. Hori, K. Nomura, N. Hikage, and E. Yoshii, *Chem. Pharm. Bull.*, this issue.
6) A model study dealing with this subject was reported recently: M.F. Semmelhack, C.R. Kim, W. Dobler, and M. Meier, *Tetrahedron Lett.*, **30**, 4925(1989).
7) K. Hori, K. Nomura, S. Mori, and E. Yoshii, *J. Chem. Soc., Chem. Commun.*, **1989**, 712.
8) **4**: mp 110-112 °C, $[\alpha]_D^{27}$ -419.5° (*c*=1.38, $CHCl_3$); ***ent*-4**: mp 109-111 °C, $[\alpha]_D^{27}$ +426.1° (*c*=0.72, $CHCl_3$).
9) D. Bianchi, P. Cesti, and E. Battistel, *J. Org. Chem.*, **53**, 5531(1989).
10) Lower enantioselectivities and/or longer reaction times were observed with other Amano lipases: A (from *Aspergillus niger*); AK (from a *Pseudomonus* species); AY (from *Candida rugosa*); and P (from a *Pseudomonus* species).
11) Optical purity was determined by the ^{1}H-NMR spectral method using a chiral shift reagent, Eu(hfc)$_3$, and also by comparison of the $[\alpha]_D$ with that of the optically pure sample.
12) Unpublished result in this laboratory.
13) K. Omura and D. Swern, *Tetrahedron*, **34**, 1651(1978); A. J. Mancuso and D. Swern, *Synthesis*, **1981**, 165.
14) K. Hori, K. Nomura, and E. Yoshii, *Heterocycles*, **29**, 663(1989).
15) A side reaction, which is associated with the ring opening of **9** through a β-elimination of the enolate, becomes significant at higher temperatures and by extending the reaction time. D. Seebach, M. Pohmakotr, C. Schregenberger, B. Weidmann, R.S. Mali, and S. Pohmaktor, *Helv. Chem. Acta*, **65**, 419(1982).
16) J.A. Katzenellenbogen and T. Utawanit, *J. Am. Chem. Soc.*, **96**, 6153(1974); G.L. Larson, C.F. de Kaifer, R. Seda, L.E. Torres, J.R. Ramirez, *J. Org. Chem.*, **49**, 3385(1984).
17) ^{1}H-NMR spectral data (270 MHz, $CDCl_3$).
11: δ 0.04 (6H, s, $SiMe_2$), 0.76 (3H, d, *J*=6.6 Hz, Me-3), 0.88 (9H, s, ^{t}Bu), 0.93-1.46 (7H, m), 1.07 (3H, d, *J*=6.3 Hz, Me-3'), 1.32 (3H, d, *J*=7.6 Hz, CH(Me)CN), 1.56-1.82 (5H, m), 1.83-1.91 (1H, m, H-2'), 2.83 (1H, qd, *J*=10.5, 3.4 Hz, H-1'), 2.90 (1H, qd, *J*=7.6, 0.3 Hz, CH(Me)CN), 3.36-3.47 (1H, m, H-6), 3.55 (1H, dd, *J*=10.0, 7.6 Hz, CHHOTBS), 3.74 (3H, s, COOMe), 3.76 (1H, dd, *J*=10.0,4.9 Hz, CHHOTBS), 4.16 (1H, d, *J*=10.3 Hz, H-2), 6.65 (1H, d, *J*=10.5 Hz, olefinic-H).
12: δ 0.036 and 0.043 (each 3H, s, $SiMe_2$), 0.76 (3H, d, *J*=6.6 Hz, Me-3), 0.88 (9H, s, ^{t}Bu), 0.96-1.37 (6H, m), 1.06 (3H, d, *J*=6.6 Hz, Me-3'), 1.33 (3H, d, *J*=7.6 Hz, CH(Me)CN), 1.58-1.86 (7H, m), 2.71 (1H, qd, *J*=11.0, 3.4 Hz, H-1'), 3.09 (1H, q, *J*=7.6 Hz, CH(Me)CN), 3.36-3.45 (1H, m, H-6), 3.51 (1H, dd, *J*=10.6, 4.5 Hz, CHHOTBS), 3.63 (1H, dd, *J*=10.6, 6.1 Hz, CHHOTBS), 3.70 (1H, d, *J*=9.8 Hz, H-2), 3.79 (3H, s, COOMe), 5.79 (1H, d, *J*=11.0 Hz, olefinic-H).
13: δ 0.04 (6H, s, $SiMe_2$), 0.65 (3H, d, *J*=6.6 Hz, Me-3), 0.88 (9H, s, ^{t}Bu), 0.93 (3H, d, *J*=6.3 Hz, Me-3'), 1.04-1.75 (12H, m), 1.20 (3H, d, *J*=7.3 Hz, CH(Me)CN), 1.83-1.91 (1H, m, H-2'), 2.38 (1H, qd, *J*=10.6, 3.7 Hz, H-1'), 2.50 (1H, qd, *J*=7.3, 2.0 Hz, CH(Me)CN), 3.26 (1H, d, *J*=8.4 Hz, OH), 3.37-3.46 (1H, m, H-6), 3.44 (1H, d, *J*=9.8 Hz, H-2), 3.51 (1H, dd, *J*=10.3, 4.9 Hz, CHHOTBS), 3.60 (1H, dd, *J*=10.3, 5.4 Hz, CHHOTBS), 4.09 (1H, d, *J*=11.9 Hz, CHHOH), 4.23 (1H, dd, *J*=11.9, 8.4 Hz, CHHOH), 4.96 (1H, d, *J*=10.6 Hz, olefinic-H), 9.73 (1H, s, CHO).

(Received April 12, 1990)