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

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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-Bu₂AlH 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 fragments⁴⁾ 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**.

In a previous paper⁷⁾ we reported the synthesis of a racemate of bicyclic ketone **3** and its transformation into cyclohexane fragment ($\pm$)-**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 ($\pm$)-**4** with acetic anhydride (2 eq) in a 9:4 mixture of isooctane and benzene in the presence of Amano lipase CES (*Pseudomonas* 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-Pr₂O (1:1).

The bicyclic ketone (-)-**4** was transformed into functionalized cyclohexane **6**, [α]_D²⁶ +4.83° (*c*=1.69, CHCl₃) according to the procedure we reported earlier.⁷⁾ The absolute configuration as depicted was assigned by an acid-catalyzed lactonization⁷⁾ leading to **7**, [α]_D²⁶ -98.2° (*c*=0.5, CHCl₃), and by comparison of the [α]_D with that of *ent*-**7**, [α]_D²⁸ +89.9° (*c*=0.16, CHCl₃) 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, **10a** (less polar)/**10b** (more polar) = 1:1.⁷⁾ The individual isomer was dehydrated by *O*-mesylation (5 eq MeSO₂Cl 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 **10a** produced (*E*)-ester **11** exclusively, whereas **10b** 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)}

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⁾ [α]_D²⁵ -15.3° (*c*=0.35, CHCl₃) in 75% yield. Application of the present result to the total syntheses of **1** and **2** is under investigation.

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- 11) Optical purity was determined by the ^1H -NMR spectral method using a chiral shift reagent, $\text{Eu}(\text{hfc})_3$, and also by comparison of the $[\alpha]_D$ with that of the optically pure sample.
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 - 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, ^tBu), 0.96-1.37 (6H, m), 1.06 (3H, d, $J=6.6$ Hz, Me-3'), 1.33 (3H, d, $J=7.6$ Hz, $\text{CH}(\text{Me})\text{CN}$), 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, $\text{CH}(\text{Me})\text{CN}$), 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, ^tBu), 0.93 (3H, d, $J=6.3$ Hz, Me-3'), 1.04-1.75 (12H, m), 1.20 (3H, d, $J=7.3$ Hz, $\text{CH}(\text{Me})\text{CN}$), 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, $\text{CH}(\text{Me})\text{CN}$), 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, CH_2OH), 4.23 (1H, dd, $J=11.9$, 8.4 Hz, CH_2OH), 4.96 (1H, d, $J=10.6$ Hz, olefinic-H), 9.73 (1H, s, CHO).

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