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STEREOSELECTIVE SYNTHESIS OF THE (±)-IRELAND ALCOHOL

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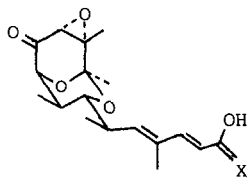
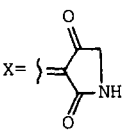
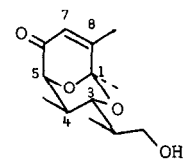
Summary: The Ireland alcohol, a key intermediate for the synthesis of tirandamycin A, was prepared in a stereoselective manner, where titanium-mediated [2,3]Wittig rearrangement and iodolactonization were used as key steps for the construction of four consecutive asymmetric centers.

Tirandamycin A (**1**) isolated from Streptomyces tirandis sp. n.[1] is an antibiotic having an inhibitory activity toward RNA polymerase and is structurally characterized by 3-dienoyltetramic acid and stereochemically interesting bicyclic acetal moieties. Although tirandamycin has been synthesized in several ways,[2] our recent interest in construction of consecutive asymmetric centers[3] was the reason for our noting this unique structure. In 1981, Ireland et al. reported the synthesis of tirandamycic acid, a degradation product of **1**, wherein multistep transformation of D-glucose into an intermediary alcohol (**2**, the Ireland alcohol) containing a bicyclic structure with four consecutive asymmetric centers was involved.[2a] In this communication, we describe the straightforward stereoselective synthesis of the alcohol **2**.



tirandamycin A (**1**) X= 

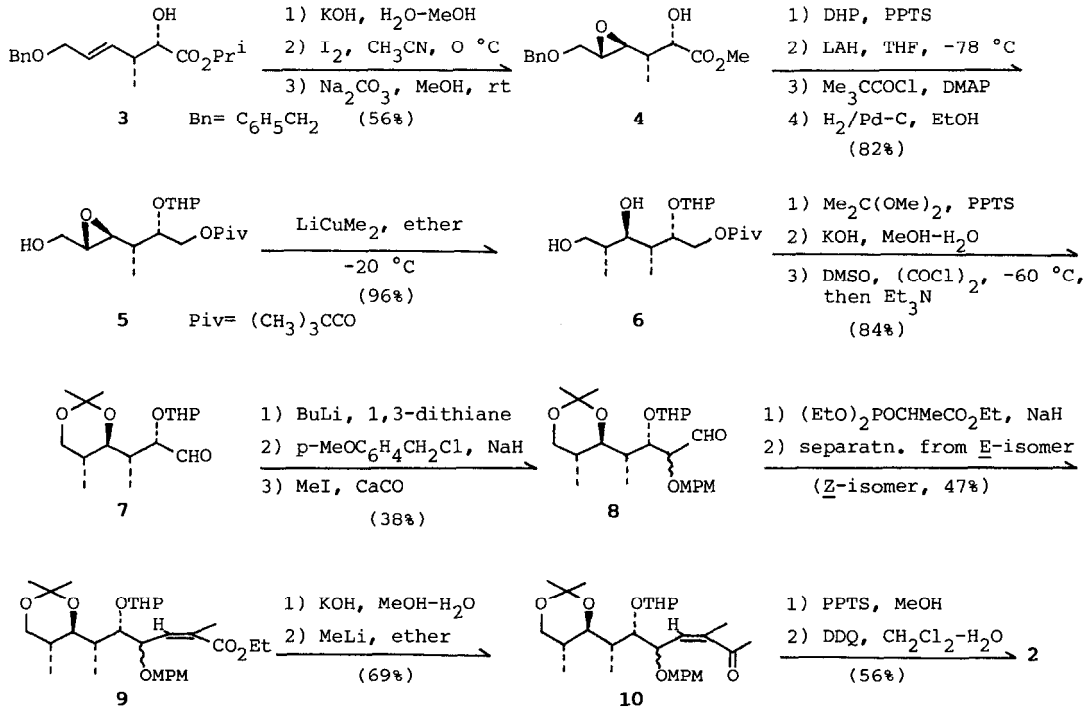
tirandamycic acid X= O



2

The synthesis started with (2,3-syn,4E)-6-benzyloxy-2-hydroxy-3-methyl-4-hexenoic acid ester **3** which was readily prepared by newly developed syn,E-selective [2,3]Wittig rearrangement,[4] and which carried two chiral centers to be C4 and C5 asymmetric carbons of the target molecule **2**. The introduction of other two contiguous chiral centers was achieved using iodolactonization and regioselective alkylative epoxide-ring opening as key reactions. Compound **3** was first converted to (2,3-syn,3,4-anti)-epoxy ester **4** according to the reported procedure.[5] Compound **4** was then transformed into the epoxy alcohol **5** by the sequence: i) Hydroxyl protection as a THP ether[6], ii) LAH reduction, iii) protection of the resulting alcohol with pivaloyl group, and iv) debenzylation. The treatment of **5** with lithium dimethylcuprate gave the desired 1,3-diol **6** where no contamination of the regioisomeric 1,2-diol was detected. The requisite four consecutive asymmetric centers being thus constructed, the remaining introduction of the enone unit was carried out as follows. The 1,3-diol **6** was converted to the aldehyde **7** by the sequence: i) Protection of 1,3-diol as an acetonide, ii) alkaline hydrolysis, and iii) Swern oxidation.[7] Compound **7** was treated with lithiated 1,3-dithiane to give diastereomeric products (1:1)[8] which, after protection of the newly formed hydroxyl group as a p-methoxybenzyl (MPM) ether,[9] were converted to an aldehyde **8**. The Wittig-Horner olefination of **8** with triethyl 2-phosphonopropionate gave a 1:1 mixture of Z- and E-unsaturated esters

which could be readily separated by silica gel chromatography. The alkaline hydrolysis of the Z-isomer **9** followed by the treatment with methyllithium afforded the (Z)-enone **10**, setting the stage for the construction of the bicyclic acetal structure. The desired acetal formation occurred when compound **10** was treated with pyridinium p-toluenesulfonate[6], and deprotection of the MPM ether and oxidation of the resulting allylic alcohol were effected by DDQ treatment[9] affording the Ireland alcohol **2**.[10] The identity of **2** was established by ^{1}H NMR comparisons.[11] All chemical shifts were within 0.01 ppm of the reported signals of **2**.[2b,12]



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References and Notes

1) a) C. E. Meyer, J. Antibiot., **24**, 558 (1971). b) F. A. MacKellar, M. F. Grostic, E. C. Olson, R. J. Wnuk, A. R. Branfman, and K. L. Rinehart, Jr., J. Am. Chem. Soc., **93**, 4943 (1971). 2) a) R. E. Ireland, P. G. M. Wuts, and B. Ernst, J. Am. Chem. Soc., **103**, 3205 (1981); b) F. E. Ziegler and R. T. Wester, Tetrahedron Lett., **25**, 617 (1984); c) S. F. Martin, C. Gluchouski, C. L. Campbell, and R. C. Chapman, J. Org. Chem., **49**, 2512 (1984); d) R. H. Schlessinger, G. R. Bebernitz, and P. Lin, J. Am. Chem. Soc., **107**, 1777 (1985); e) P. DeShong, S. Ramesh, V. Elango, and J. J. Perez, ibid., **107**, 5219 (1985); f) R. K. Boekman, Jr., J. E. Starrett, Jr., D. G. Nickell, and P.-E. Sum, ibid., **108**, 5549 (1986); g) C. Neukom, D. P. Richardson, J. H. Myerson, and P. A. Bartlett., ibid., **108**, 5559 (1986). 3) T. Hanamoto, T. Katsuki, and M. Yamaguchi, Tetrahedron Lett., **28**, 6191, 6195 (1987). 4) S. Kuroda, S. Sakaguchi, S. Ikegami, T. Hanamoto, T. Katsuki, and M. Yamaguchi, Tetrahedron Lett., in press. 5) P. A. Bartlett and J. Myerson, J. Am. Chem. Soc., **100**, 3950 (1978). 6) M. Miyashita, A. Yoshikoshi, and P. A. Grieco, J. Org. Chem., **42**, 3772 (1977). 7) K. Omura and D. Swern, Tetrahedron, **33**, 1651 (1977); A. J. Mancuso, S.-L. Hung, and D. Swern, J. Org. Chem., **43**, 2480 (1978). 8) This diastereomeric mixture was used without separation in the following reactions. 9) Y. Oikawa, T. Yoshioka, and O. Yonemitsu, Tetrahedron Lett., **23**, 885 (1982). 10) As compound **2** has been converted to tirandamycin A (ref. 2a and 2g), the formal total synthesis of tirandamycin A was accomplished. 11) **2**: ^{1}H NMR δ 0.78 (d, J= 6.8 Hz, 3H), 1.09 (d, J= 6.8 Hz, 3H), 1.55 (s, 3H), 1.89 (m, 1H), 1.93 (d, J= 1.5 Hz, 3H), 2.34 (m, 1H, OH), 2.41 (m, 1H), 3.52 (dd, J= 11.5, 2.2 Hz, 1H), 3.62 (m, 1H), 3.94 (dd, J= 11.5, 3.2 Hz, 1H), 4.10 (d, J= 6.3 Hz, 1H), 6.15 (s, 1H). 12) All new compounds gave content ^{1}H NMR data as well as satisfactory elementary analyses.

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