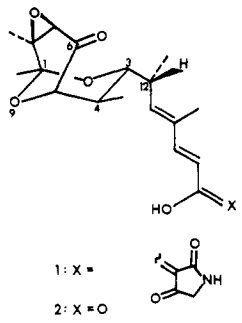
Furans as Intermediates for the Synthesis of Oxygenated Natural Products. A Formal Asymmetric Synthesis of (+)-Tirandamycic Acid

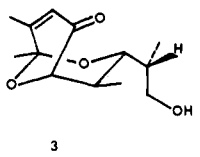
Summary: An efficient, asymmetric synthesis of the 2,9-dioxabicyclo[3.3.1]nonane derivative **4**, which was a key intermediate in Ireland's synthesis of tirandamycic acid (**2**), has been completed in nine steps from 4,5-dimethylfuraldehyde.

Sir: Tirandamycin (**1**)[2] is a representative member of a class of antibiotics that is characterized by the presence of a 3-dienoyltetramic acid moiety linked to a functionalized 2,9-dioxabicyclo[3.3.1]nonane ring system. The biological activities of this family of antibiotics, which also includes streptolydigin[3] and Bu-2313 A and B,[4] differ markedly from those of the simpler 3-acyltetramic acids, a fact which has been attributed to the presence of the functionalized 2,9-dioxabicyclo[3.3.1]nonane ring system. For example, in addition to their antibacterial and antimicrobial activity, tirandamycin inhibits bacterial DNA polymerase and interferes with oxidative phosphorylation,[5] whereas streptolydigin displays selective inhibitory activity against bacterial DNA-directed RNA polymerase and terminal deoxynucleotidyl transferase from leukemic cells.[6] Thus, the unique structures of these antibiotics coupled with their interesting biological properties has stimulated a number of synthetic investigations.[7-13] Indeed, the asymmetric synthesis of tirandamycic acid (**2**), a product



1: X =

2: X = O



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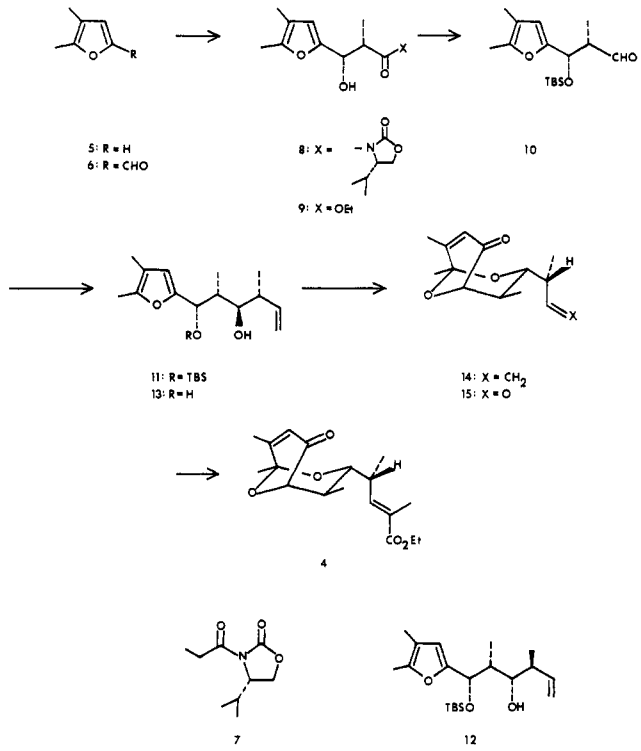
obtained by the degradation of tirandamycin, from D-glucose has been reported by Ireland,[8] and syntheses of the alcohol **3**, which was an important intermediate in Ireland's synthesis of **2**, in both racemic[11] and optically active form[12] have recently been completed.

Scheme I



Some time ago we embarked upon an investigation directed toward the development of a general protocol for the asymmetric synthesis of oxygenated natural products by exploiting substituted furan derivatives as the key intermediates.[13] The central basis for this synthetic strategy lay in the well-established knowledge that furans may be valuable precursors of 1,4-enediones, 1,4-diones, hydro-3-pyranones, and carbohydrates.[14] Since the 2,9-dioxabicyclo[3.3.1]nonanone ring system of tirandamycin (**1**) contains a latent 1,4-dicarbonyl moiety at C(1) and C(6), we and others[9-13] became intrigued by the prospect of executing a synthesis of tirandamycic acid (**2**) from a furan. We now record the successful application of this methodology to a facile, asymmetric synthesis of the unsaturated ester **4**[13] as outlined in Scheme I.

In the event, condensation of 4,5-dimethylfuraldehyde (**6**),[15] which was readily prepared in 96% yield by the Vilsmeier–Haack formylation (1.1 equiv of $POCl_3$/DMF; 0 °C, 15 min; room temperature, 2.5 h) of 2,3-dimethylfuran (**5**)[16] with the boron enolate derived from the chiral oxazolidinone **7** according to the method of Evans,[17] proceeded with a high degree (>98%) of diastereoselectivity to give the erythro-β-hydroxy adduct **8** (90%). Ethanolysis (EtOLi/EtOH/THF; −78 °C → room temperature, 15 min;

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79%) of 8 provided 9, which was converted into the labile aldehyde 10 in 80–85% overall yield by sequential protection of the free hydroxyl as the *tert*-butyldimethylsilyl ether[18] and reduction [(a) *t*-$BuMe_2SiCl$/imidazole/DMF, 7 h, room temperature; (b) DIBAL (1.8 equiv, 1.0 N in PhMe)/CH_2Cl_2, −90 °C, 1 h]. For elaboration of the remaining two chiral centers present at C(3) and C(12) in 4, the aldehyde 10 was treated with crotyl bromide in the presence of Cr(II)[19] [$CrCl_2$/$CH_3CH{=}CHCH_2Br$/THF, 0 °C → room temperature, 2 h] which proceeded without a significant degree of stereoselectivity to give the pair of homoallylic alcohols 11 and 12 in an approximately 1:1.5 ratio (70–75%). These diastereomeric alcohols were readily separated by HPLC, and the *tert*-butyldimethylsilyl (TBS) hydroxyl protecting group of 11 was smoothly removed (5.0 equiv, 1 N *n*-Bu_4NF/THF, room temperature, 15 min; 95%) to give the unsaturated diol 13. When the furan ring of 13 was oxidized[14] (1.05 equiv of MCPBA/NaOAc/CH_2Cl_2, −23 °C, 1 h) and the resulting crude mixture of hydropyranones was treated with aqueous acid [2.4 N HI/KI, H_2O–CH_3CN (2.5:1), 0 °C, 50 min], the 2,9-dioxabicyclo[3.3.1]nonane 14 was isolated in 77% yield. Oxidative cleavage of the terminal double bond [1.0 equiv of O_3, CH_3OH/CH_2Cl_2 (1:10), −78 °C, 15 min; Ph_3P, 0 °C, 15 min) afforded the unstable aldehyde 15. Wittig olefination of crude 15 with purified (α-carbethoxyethylidene)triphenylphosphorane (benzene, 80 °C, 15 h) afforded the unsaturated ester 4 in 41% overall yield from 14. The 4 thus obtained gave spectra [NMR and IR and optical rotation ($[\alpha]^{rt}_D$ −185.2° (*c* 1.1, $CHCl_3$), lit.[8] $[\alpha]^{rt}_D$ −186.3° (*c* 1.085, $CHCl_3$)] that were identical with those obtained independently by Ireland for a sample of 4 prepared from D-glucose. Since 4 has been converted in five steps into tirandamycic acid,[8] the sequence described above constitutes a concise (nine steps from 6), formal asymmetric synthesis of this substance.

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Registry No. 2, 34429-71-5; 4, 78686-73-4; 5, 14920-89-9; 6, 52480-43-0; 7 ((*Z*)-dibutylboryl enolate), 87758-64-3; 8, 90432-93-2; 9, 90528-03-3; 9 (TBS ether), 90432-94-3; 10, 90432-95-4; 11, 90432-96-5; 12, 90528-04-4; 13, 90432-97-6; 14, 90432-98-7; 15, 78686-72-3; $CH_3CH{=}CHCH_2Br$, 4784-77-4; (α-carbethoxyethylidene)triphenylphosphorane, 5717-37-3.

Supplementary Material Available: Experimental procedures and data for the intermediates 10–15 in this study (4 pages). Ordering information is given on any current masthead page.

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Stephen F. Martin,*[1] Charles Gluchowski Carlton L. Campbell, Robert C. Chapman

Department of Chemistry The University of Texas Austin, Texas 78712

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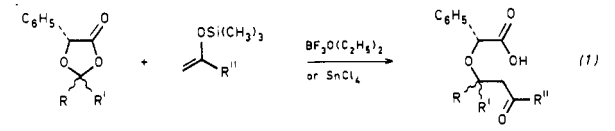
Enantioselective Syntheses of Aldols and Homoallylic Alcohols from 1,3-Dioxolan-4-ones Using Mandelic Acid as Chiral Auxiliary

Summary: The 1,3-dioxolan-4-ones obtained by condensation of (*S*)-(+)- or (*R*)-(−)-mandelic acid with aldehydes and ketones react under electrophilic conditions cleanly and with reasonable diastereoselectivities with enol silyl ethers or allylsilanes. The chiral auxiliary can be removed with $Pb(OAc)_4$ followed by acid hydrolysis to furnish without racemization the aldols or homoallylic alcohols.

Sir: The search continues unabatedly for new enantio- and/or diastereoselective carbon–carbon bond forming reactions.[1] Asymmetric aldol and related condensations form a central part of these efforts.[2] The major approach has been the use of chiral nucleophiles such as enolates wherein the chirality stems from the presence of a chiral auxiliary.[3,4] In contrast examples of the reaction of achiral anion precursors with electrophilic equivalents provided with a chiral auxiliary are few. Notable successes in this approach have been achieved, however, by Johnson and Kishi, who have employed, as electrophilic components, chiral cyclic acetals derived by the condensation of chiral 1,2- and 1,3-diols with the carbonyl acceptors.[5] These are condensed with various achiral carbanion equivalents in the presence of Lewis acids. The diastereoselectivities are good to excellent but the cost of the diols and the removal of the auxiliary form limitations.[5]

In connection with other work,[6] it occurred to us that 1,3-dioxolan-4-ones 1 might fulfill a similar purpose. We expected, and this was borne out in fact, that carboxylate would be the better leaving group in the reaction of 1, illustrated with (*R*)-(−)-mandelic acid, with enol silyl ethers (eq 1).



1 2

The derivatives 1 were obtained as cis,trans mixtures by condensation of commercial (*R*)-(−)- or (*S*)-(+)-mandelic acids with aldehydes and ketones following literature procedures.[7] For **1a–d** the major isomer (cis) was isolated in >99% purity by recrystallization from hexane or hexane/ethanol. Compound **1e** was separated into its cis and trans isomers by chromatography over SiO_2 with hexane–

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