model using external fields of 0.000, 0.001, 0.002 and 0.004 au was used to calculate the static dipole polarizabilities for Ba, Au/Au^- and Hg. Table 2 shows the excellent agreement of our CCSD(T) properties with available reference data.

Calculations were performed at Hartree–Fock (HF), MP2, CCSD and CCSD(T) level using the programs Gaussian 98[29] and Aces II.[30] At least 20 single points were calculated to describe the potential curves and corrected for the BSSE using the counterpoise correction by Boys and Bernardi.[31] The corrected potential curves were fitted by an extended Morse potential (Table 3).[32] Spectroscopic parameters were derived from a numerical Numerov–Cooley procedure as implemented in MOLCAS 3.[33]

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A General Approach to L-(+)-Furanomycin and Some Stereoisomers and Analogues Using Furoisoxazoline Intermediates**

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In 1967 Katagiri et al. reported on the isolation of the antibiotic α-amino acid L-(+)-furanomycin (**1**) from the fermentation broth of *Streptomyces threomyceticus* (ATCC 15795).[2] L-(+)-Furanomycin shows considerable activity against different bacteria, for example *E. coli*.[2] Later, **1** was found to be charged to isoleucine tRNA by isoleucyl-tRNA synthetase from *E. coli* and incorporated into protein.[3]

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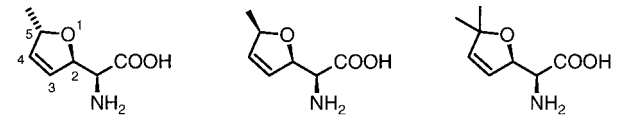
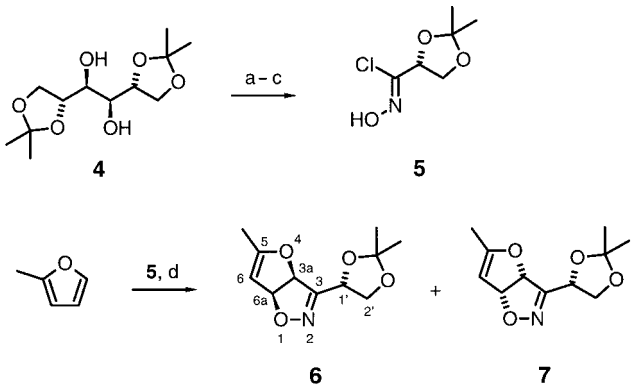


1 **2** **3**

Originally, **1** was assigned the $\alpha S,2R,5R$ configuration (**2**).[2, 4] Later, this was revised in favor of (+)-($\alpha S,2R,5S$)-α-amino-2-(2,5-dihydro-5-methyl)furan-2-acetic acid (**1**), based on an unambiguous synthesis from D-glucose and an X-ray structure analysis of the *N*-acetyl derivative.[5, 6]

Over the last 20 years several strategies for the synthesis of **1** and its stereoisomers were advanced, starting from various carbohydrate precursors,[5, 7] substituted furans,[4, 5a] or dimethyl L-tartrate.[8] The new approach presented here is based on our earlier work, in which the 1,3-dipolar cycloaddition of nitrile oxides to furan was studied in view of synthesizing polyhydroxypiperidines and amino sugars.[9] The new route is illustrated by the preparation of **1**–**3**. The cycloaddition products obtained from 2-methylfuran and nitrile oxide (furo[2,3-*d*]isoxazolines) and the derived epoxide served as key intermediates; twofold deoxygenation led to the C=C bond at a late stage, when the relative configuration of the remaining stereocenters had already been established.

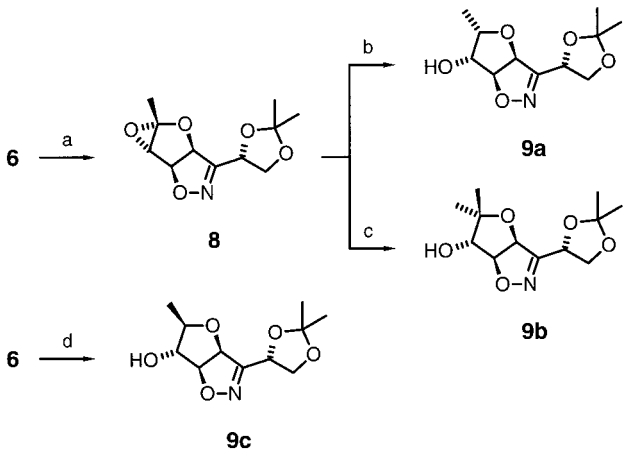
The known hydroxamic acid chloride **5** was prepared in three steps from diisopropylidene mannitol (**4**).[10, 11] On treatment of the nitrile oxide precursor **5** with triethylamine, 1,3-dipolar cycloaddition to 2-methylfuran was effected to give a mixture of the diastereomeric furoisoxazolines **6** and **7** (d.r. 60:40), which were separated by MPLC and isolated on a multigram scale in 40 and 27% yield, respectively (Scheme 1).[12]



4 **5** **6** **7**

Scheme 1. a) $NaIO_4$; b) $HONH_2 \cdot HCl$;[10b] c) *N*-chlorosuccinimide,[11a] 78% from **4**; d) NEt_3 (1.2 equiv), 2-methylfuran, room temperature (RT), 5 d; d.r. 60:40 (crude product); MPLC separation, **6** 40%, **7** 27%.

The major diastereomer **6** served as an entry to the L-amino acids **1**–**3** (with **7**, the D-enantiomers are obtained). First, epoxidation of the dihydrofuran **6** with dimethyldioxirane (DMDO)[13] led to the (unexpectedly) stable, isolable enol ether epoxide **8**, a derivative of a 1,2-anhydrofuranose, in quantitative yield with high selectivity (d.r. > 95:5; Scheme 2).[14] Reductive opening[15] of the epoxide ring in **8** resulted in a highly regio- and *endo*-stereoselective hydride

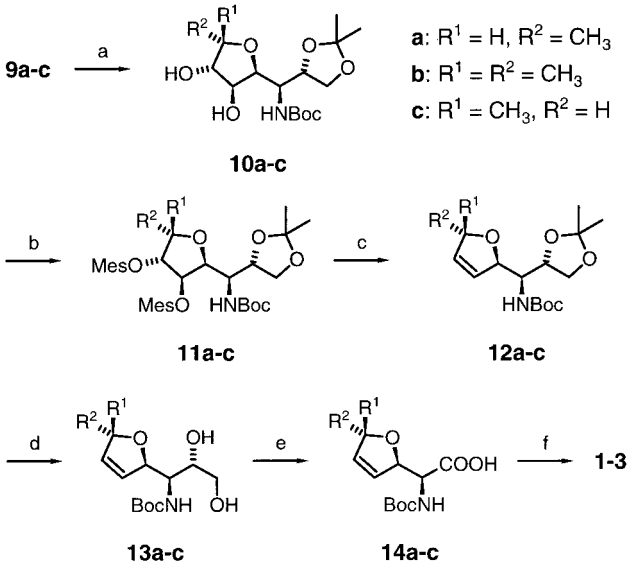


8 **9a** **9b** **9c**

Scheme 2. a) DMDO (2.0 equiv, 0.1M in acetone),[13] CH_2Cl_2, 0 °C, 3 h, quant.; b) $NaBH_3CN$ (2.0 equiv), H_2O (1.0 equiv), THF, 16 h, **9a** 74%; c) MeMgBr (1.5 equiv, 3.0M), THF, CH_2Cl_2, 15 min, **9b** 83%; d) 1. $BH_3 \cdot$ THF (2.0 equiv, 1.0M), THF, 0 °C, 10 h; 2. $Me_3NO \cdot 2H_2O$ (7.0 equiv), diglyme, 0 → 150 °C, 20 h, **9c** 73%. DMDO = dimethyldioxirane.

transfer to give the alcohol **9a** with the required 2,5-*trans* configuration at the tetrahydrofuran ring. After screening of several metal and borohydride reagents, the best results were obtained with sodium cyanoborohydride in THF in the presence of one equivalent of water. On the other hand, the dimethyl compound **9b** was derived from regioselective opening of the epoxide ring of **8** with methylmagnesium bromide.[16] As an alternative method to introduce the hydroxy group onto the 6-position of the heterobicycle, regioselective hydroboration was considered first:[17] Reaction of **6** with $BH_3 \cdot$ THF and subsequent oxidation by trimethylamine *N*-oxide dihydrate[18] led to the alcohol **9c**, the 5-epimer of **9a**, with high *exo* selectivity (> 90:10; Scheme 2).

Next, elaboration of the amino group in the side chain and of the C=C bond in the dihydrofuran ring had to be accomplished. As expected from earlier work,[9] reduction of the isoxazolines **9a**–**c** with lithium aluminium hydride in THF/diethyl ether led to the corresponding 1,3-amino alcohols with high *syn-(erythro)* selectivity (> 95:5 from NMR analyses). From these, the *N*-Boc-protected amino diols **10a**–**c** were obtained (Scheme 3). Introduction of the double bond was then effected by twofold mesylation and subsequent twofold mesylate removal.[19] The diols **10a**–**c** were first converted into the corresponding dimesylates **11a**–**c**,[20] which were then treated with sodium naphthalenide in THF[19b] to smoothly afford the 2,5-dihydrofurans **12a**–**c**. Hydrolysis of the acetonide group with dilute trifluoroacetic acid proceeded without cleavage of the carbamate to yield the diols **13a**–**c**. From these, oxidative cleavage with sodium periodate provided the corresponding *N*-Boc-amino aldehydes, which were immediately treated with buffered sodium chlorite[21] to furnish the optically pure, *N*-protected amino acids **14a**–**c** in excellent yield. Finally, deprotection of **14a**–**c** with 6N hydrochloric acid, followed by ion-exchange chromatography and further purification by crystallization from water/acetone, provided the free α-amino acids **1**–**3**. All analytical and spectroscopic data of L-(+)-furanomycin (**1**) thus obtained, and of the known 5-epimer **2**,



Scheme 3. a) 1. $LiAlH_4$ (4.0 equiv), THF, diethyl ether, 0 °C→RT, d.r. > 95:5, 2. Boc_2O (1.5–2.0 equiv), dioxane/H_2O, 0 °C→RT, 16 h, **10a** 71%, **10b** 65%, **10c** 70%; b) CH_3SO_2Cl (3.0 equiv), pyridine, 0 °C→RT, 16 h, **11a** 95%, **11b** 92%, **11c** 97%; c) Na/naphthaline, THF, 0 °C→RT, 15 min, **12a** 85%, **12b** 81%, **12c** 75%; d) CF_3COOH/MeOH/H_2O, 0 °C→RT, 16–30 h, **13a** 88%, **13b** 86%, **13c** 93%; e) 1. $NaIO_4$ (1.2 equiv), MeOH/H_2O 1:1, 0 °C, 15–20 min, 2. $NaClO_2$ (1.5–2.0 equiv), NaH_2PO_4 (1.5–2.0 equiv), *t*BuOH, 2-methyl-2-butene, RT, 2–3 h, **14a** 89%, **14b** 93%, **14c** 93%; f) 1. 6N HCl, 0 °C or RT, 2–16 h, 2. Dowex 50 WX-8 (H^+), 1N NH_3, 3. crystallization from H_2O/acetone, **1** 61%, **2** 60%, **3** 56%. Boc = *tert*-butoxycarbonyl, Mes = methanesulfonyl (Mesyl).

were in complete agreement with those previously reported.[22]

The results shown here present a new, practical, and stereoselective approach to L-(+)-furanomycin (**1**) in 14 steps with an overall yield of 6.3%. Noteworthy features are the use of glyceronitrile oxide as a chiral glycine equivalent,[11a] and the establishment of the relative configuration of the three stereocenters by means of intermediate tetrahydrofuran-3,4-diols. Compared with known syntheses, the scheme outlined here offers the advantage of a short and concise access to four of the eight stereoisomers of **1**. Further, for each case, various structural analogues of **1** can be prepared from the key epoxide **8** (a promising intermediate for other ventures too) by simple variation of the nucleophile (Grignard reagent). The biological evaluation of this group of compounds is pending and will be reported in due course.

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