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TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of acetomycin

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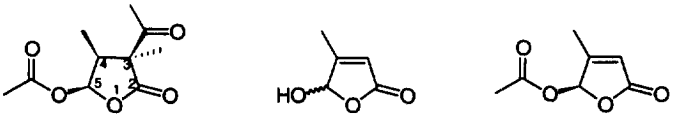
Abstract

The synthesis of (−)-acetomycin **1**, a highly functionalized γ-lactone with antitumor activity, was achieved in five steps with nearly complete enantioselectivity. The key step was realized by a large scale lipase R catalyzed esterification of 5-hydroxy-4-methyl-2(5*H*)-furanone **2** providing (−)-(5*R*)-5-acetoxy-4-methyl-2(5*H*)-furanone **3** with an e.e. of 99%. © 1998 Published by Elsevier Science Ltd. All rights reserved.

1. Introduction

(−)-Acetomycin **1** was first isolated from *Streptomyces ramulosus* sp. (ETH 17653) by Prelog and co-workers in 1958 and showed weak antimicrobial activity towards both Gram-positive and Gram-negative bacteria.[1] The Swiss group elucidated its structure at the same time[2] and the biosynthesis was revealed a few years later.[3] The relative and absolute configuration was established in 1984 by Zeeck and co-workers.[4] In 1987 it became clear that acetomycin exhibits anti-tumor activity (in vitro) against several tumor cells, such as HCT-human colon adenocarcinoma, L1210 murine leukemia and human tumor stem cells.[5] These findings prompted the development of synthetic routes towards acetomycin, to elucidate its structure–pharmacological activity relationship[6] and to open pathways towards several analogues (see Fig. 1).[6,7]



1 **2** **3**

Fig. 1.

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The first total synthesis of (−)-acetomycin and (+)-5-*epi*-acetomycin was completed by Tadano et al.[8] The stereoselective introduction of the acetoxy group at C-5 was found to be a problem, because this group had to be introduced from the sterically hindered α-side by displacement of a lactol mesylate.

Uenishi et al.[9] improved the concept of Tadano in their synthesis of (±)-acetomycin by using a stereocontrolled, crown ether assisted, displacement of a lactol mesylate. This problem was circumvented by Ziegler and Kim in their stereoselective synthesis of (−)-acetomycin, starting from L-threonine.[10] These authors used a selective Baeyer–Villiger oxidation to generate the acetoxy group in the last step. Echavarren et al.[11] have reported the synthesis of (±)-4-*epi*-acetomycin via a stereoselective ester enolate Carroll rearrangement. Recently a short route to (±)-acetomycin was reported by Sprules and Lavallée.[12] A bulky methyl equivalent, 1,3-dithienium tetrafluoroborate, was used to introduce the methyl at C-3 with complete stereoselectivity.

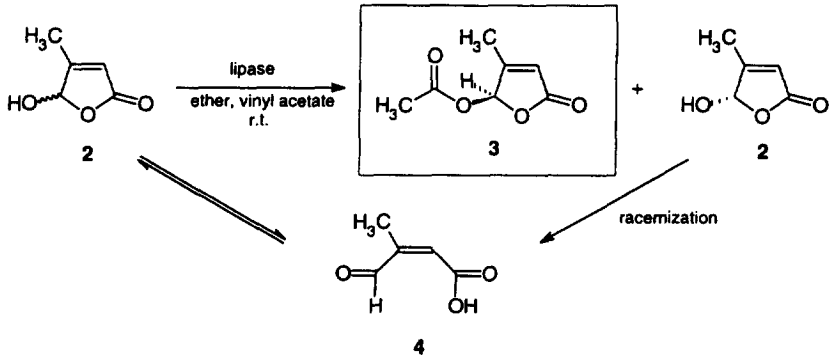
Our goal was to develop a total synthesis of (−)-acetomycin with *high enantioselectivity*, taking advantage of the expertise in our laboratories with the use of γ-alkoxybutenolides as chiral synthons[13] as well as the enzymatic resolution of 5-hydroxy-2(5*H*)-furanones,[14] to obtain key intermediate **3** with high enantiomeric excess.

2. Results and discussion

2.1. Enzymatic resolution

5-Acetoxy-4-methyl-2(5*H*)-furanone **3** was partially resolved by an enzymatic transesterification.[15] The lipase AKG catalyzed transesterification of **3** afforded (+)-(*S*)-5-acetoxy-2(5*H*)-furanone in 46% yield with an e.e. of 68%. However, we have found that with the lipase-catalyzed esterification of **2** much higher selectivities can be obtained. Esterification of **2** was performed in diethylether (lipase R) or in hexane/n-BuOH (3:1) (lipase PS), using vinyl acetate as acyl donor. Of the fifteen lipases that were screened, lipase R and lipase PS, both immobilized on Hyflo Super Cell (R-HSC, PS-HSC), showed to be most promising.[16]

When the lipase-catalyzed esterification was performed on a small scale (0.18 mmol), with reaction times up to 240 h, lipase R-HSC and lipase PS-HSC yielded product **3** with e.e.s of 99% and 89%, respectively (Scheme 1). According to GC analysis, complete conversion was reached with lipase PS, but for lipase R the conversion was 60% after 240 h. Because of the higher e.e., the large scale esterification of **2** was performed with lipase R-HSC.

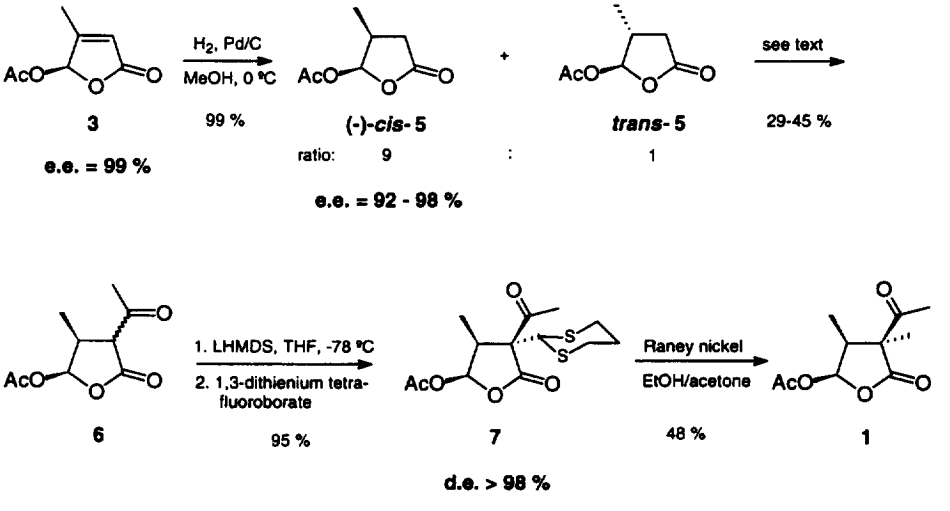


Scheme 1.

Starting material **2**[17] was therefore stirred in diethyl ether at room temperature in the presence of lipase R-HSC (4.3 g lipase R-HSC, immobilized at pH 7, per gram of substrate) and vinyl acetate (Scheme 1). It was necessary to add fresh enzyme during the reaction to get higher conversion. The progress of the reaction (on 25 mmol scale) could be readily followed with ^{1}H-NMR. After 240 h enantiomerically pure **3** (e.e.=99%; determined by chiral GC) was obtained in 52% yield, after filtration of the immobilized enzyme and purification by column chromatography, with an e.e. of 99% as determined by chiral gas chromatography. In this enzyme-catalyzed second-order asymmetric transformation the unreactive enantiomer of **2** racemizes under the reaction conditions via its open form **4**, which is in equilibrium with **2** (in situ racemization). The theoretical yield can therefore reach 100%. It should be noted that although the rate of esterification is rather low at R.T., the use of immobilized lipase R-HSC in ether results in a very simple procedure.

2.2. *Stereoselective hydrogenation*

With enantiomerically pure **3** in hand the synthesis of (−)-acetomycin **1** was completed, analogous to the route developed by Sprules and Lavallée,[12] with some modifications as depicted in Scheme 2.



Scheme 2.

The olefinic bond of **3** was stereoselectively hydrogenated[18] in methanol at 0°C in the presence of palladium on carbon. Compound (−)-*cis*-**5** was obtained in this way together with the *trans*-product in a total yield of 99%. With racemic **3** the diastereoselectivity was always found to be 95%. Much to our surprise, with enantiomerically pure **3** we repeatedly found a drop of selectivity to d.e.=80%. So far we do not have an explanation for this observation. The e.e. of (−)-*cis*-**5** slightly differed from batch to batch. In one case an e.e. of 98% was found, in another case 92% e.e. (determined by chiral GC). It appeared that if the temperature is allowed to get higher than approximately 5°C in methanolic solution, some racemization of **3** takes place in the presence of palladium. It must be noted that the synthesis of (−)-acetomycin was completed with **5** having an e.e. of 92%.

2.3. *Acylation at C-3*

Acylation at C-3 in *cis*-**5** turned out to be a critical step in the synthesis. The acylation of **5** (mixture of *cis* and *trans*) at C-3 to obtain **6** (Scheme 2) was examined using LDA and LHMDS as bases. Although

Ziegler and Kim[10] reported the use of LDA as base to alkylate at C-3 in a five membered ring lactone, in our case this procedure gave an indistinct mixture of products. The presence of a second acidic position makes the use of the milder base LHMDS necessary. A protocol in which 1.5 equiv. LHMDS is used, with deprotonation for 1 min and subsequent quenching of the enolate with 2.0 equiv. of acetyl chloride for 1 min,[12] did not give satisfactory results either.

Therefore we investigated the acylation procedure in detail in order to find a good reproducible method with satisfactory yields. The results of these acylations are summarized in Table 1.

Table 1
Results on the Acylation of **5**

entry	LHMDS (eq.)	Temp (°C)	time (min)	AcCl (eq.)	time (min)	proton source	purification[a]	Yield **6** (%)
1	1.5	-75	1	2.0	1	HCl	II + I	30
2	1.5	-80	15	2.0	3	NH_4Cl	III	31
3	2.0	-80	15	2.0	3	NH_4Cl	IV + V	50
4	2.0	-80	15	2.0	3	NH_4Cl	V	63
5	2.0	-80	15	2.0	5	NH_4Cl	VI	mixture
6	2.0	-80	15	2.0	5	NH_4Cl	V	mixture
7	2.0	-70	10	1.5	3	NH_4Cl	VII	34
8	2.0	-65	10	1.5	3	NH_4Cl	VII	25
9	2.0	-75	10	2.0	3	NH_4Cl	VII	51
10	1.5	-75	5	1.5	2	NH_4Cl	V	29-45

a) Column chromatography (SiO_2): I= Hex/EtOAc/Et_3N 25:25:1; II = Hex/EtOAc/Et_3N 75:20:5 (flash); III = EtOAc/Pent/Et_2O 15:10:3; IV = EtOAc/Pent/Et_2O 10:10:3 (flash); V = EtOAc/Pent/Et_2O 6:12:3; VI = EtOAc/Pent/Et_2O 9:12:3; VII = CH_2Cl_2/Hex/EtOAc 5:5:2.

Entry 1 shows the results following a reported method[12] and performing the work up with HCl. Under these acidic conditions we found that concomitant lactone ring opening occurred. To avoid racemization at the acetal center in the product we therefore always used NH_4Cl as mild proton donor. The chromatographic isolation also turned out to be critical.

It was found that elongated reaction times up to 15 min for deprotonation together with a quenching period of 3 min with acetyl chloride usually gave improved yields (entries 2–4 and 9). When in these cases 2.0 equiv. of base were used, the yield could be enhanced to more than 50%, but then simultaneous acylation at the acetoxy group was found. In the case of entries 5 and 6 quenching with acetyl chloride was allowed for 5 min, leading to mixtures of all plausible products. When the temperature was allowed to rise too much (entries 7 and 8), less mono-acylated product was found and more di-acylated product was observed. It can be concluded that the best procedure to be followed is deprotonation with LHMDS for 5–10 min, followed by quenching with acetyl chloride for 2–3 min and work up with NH_4Cl. Following this protocol, pure acetyl derivative **6** was isolated in 29–45% yield after column chromatography.

2.4. Methylation at C-3

In order to introduce the methyl group at C-3 we followed the procedure using a dithiane methyl equivalent and subsequent reduction.[12]

The diastereomeric mixture of **6** was therefore treated with LHMDS in THF at −78°C and the corresponding enolate was quenched with an excess of 1,3-dithienium tetrafluoroborate salt[19] (Scheme 2).

After aqueous work up, **7** was obtained in 50–95% yield. Only one diastereomer could be observed in the ^{1}H-NMR spectrum, indicating a d.e.>98%.

The methyl substituent at C-4 and the acetyl group at C-3 were found to have the *cis* configuration, as was confirmed by NOE experiments. Important to notice is the fact that the *anti*-diastereomers of **5** and **6**, with respect to C-4 and C-5, are readily eliminated during the purification of **7** by crystallization.

The last step consisted of a reductive desulfurization of **7** in an ethanol–acetone mixture[20] at room temperature with activated Raney nickel (Scheme 2). This afforded pure (−)-acetomycin **1** ($[\alpha]_D^{24}$ −147.5 (*c* 1.27, EtOH) after crystallization from ether:hexane (6:4) as white needles in 48% yield, with an optical purity of 97%. In conclusion, we developed an enantioselective route to acetomycin in five steps (see Fig. 2) and with an overall yield of 10%, starting from readily available 5-hydroxy-4-methyl-2(5*H*)-furanone.

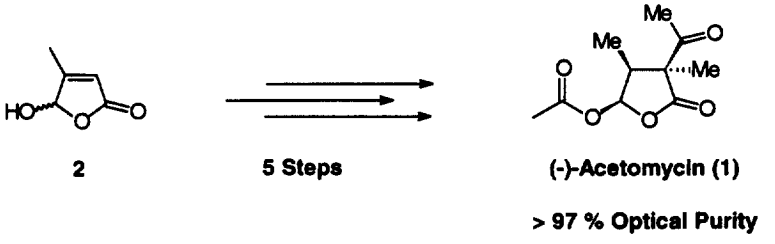


Fig. 2.

Furthermore, it should be noted that by reversing the first step, i.e. using an enzymatic resolution of racemic **3** with the same enzyme,[13,14] instead of asymmetric esterification, the enantiomer of (−)-acetomycin can also be synthesized. With this procedure, a very useful methodology is available to prepare highly functionalized and multi-substituted 2(3*H*)-furanones with high enantioselectivity. This is of prime importance for further studies towards structure–activity relationships of acetomycin and related γ-lactones.

3. Experimental section

All solvents were reagent grade and distilled before use, following standard procedures. Reagents were purchased from Acros Chimica, Aldrich or Fluka and used without purification. 5-Hydroxy-4-methyl-2(5*H*)-furanone[17] and 1,3-dithienium tetrafluoroborate[19] were prepared following literature procedures. Lipases R and PS were obtained from Amano. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Gemini 200 or a Varian VXR-300 spectrometer. The chemical shifts are denoted in δ units (ppm) relative to $CDCl_3$ for protons at δ=7.24 and at δ=76.91 for carbon atoms. Splitting patterns for 1H: s (singlet), d (doublet), t (triplet), dt (double triplet), dq (double quartet) q (quartet), p (quintet), m (multiplet). Melting points (uncorrected) were determined on a Mettler FP-2 melting point apparatus, equipped with a Mettler FP-21 microscope. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. High resolution mass spectra (HRMS) with electronic ionization (EI) or ammonia (NH_3) as a carrier for chemical ionization (CI), were obtained on a AEI MS-902 mass spectrometer. Chiral GC analysis was carried out using either a Hewlett Packard 5890 II GC, with a capillary column coated with CP-cyclodextrin B-2,3,6-M-19, or a Hewlett Packard 6890 GC with a fused silica column FS-lipodex C, 50×0.25 mm. Elemental analyses were performed in the microanalytical department of this laboratory.

3.1. Immobilization of lipases[21]

Lipase (3.0 g) and Hyflo Super Cell (10.0 g) were mixed and enough phosphate buffer solution (pH 7) was added to get a slurry. The slurry was stirred for 15 min and spread out over a Petri dish. The material was dried with a soft stream of air overnight.

3.2. (−)-5-(R)-Acetoxy-2(5H)-furanone 3

To a solution of 5-hydroxy-2(5*H*)-furanone **2** (3.00 g, 26.3 mmol) in ether (450 ml), was added lipase R-HSC (13.0 g) together with vinyl acetate (75 ml) and the mixture was vigorously stirred at room temperature. The progress of the esterification was monitored by ^{1}H-NMR. After 240 h the reaction mixture was decanted. The remaining enzyme slurry was triturated with ether (2×100 ml). The combined ether fractions were concentrated in vacuo and the crude oil was purified by chromatography (SiO_2, EtOAc:hexane:CH_2Cl_2=2:2:1, Rf_3 0.52 or hexane:EtOAc=1:1, Rf_3 0.41), yielding **3** as a slightly yellow coloured oil (2.14 g, 52%). E.e. 99%, $[\alpha]_D^{24}$ −82.9 (*c* 1.40, $CHCl_3$), −91.7 (*c* 1.51, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.76 (s, 1H), 5.94 (s, 1H), 2.15 (s, 3H), 2.06 (s, 3H); ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ 169.87 (s), 169.12 (s), 162.71 (s), 119.40 (d), 20.60 (q), 13.14 (q). MS (CI, NH_3) 174 $[M+NH_4]^+$. Anal. calcd for $C_7H_8O_4$.1/15 H_2O: C, 53.44; H, 5.21, found: C, 53.48; H, 5.37.

3.3. (−)-(4S)(5R)-5-Acetoxy-4-methyl-dihydro-2(3H)-furanone 5

To a solution of **3** (9.06 g, 58 mmol) in dry methanol (80 ml) was added 1.0 g of 10% Pd/C. The mixture was cooled to 0°C and stirred for 7.5 h while exposed to H_2 pressure (balloon). The progress of the reaction can be monitored using TLC (SiO_2, pentane:EtOAc=2:1). The resulting solution was filtered over Celite and concentrated in vacuo to give **5** as a colourless oil in 98% yield. E.e. 92%. $[\alpha]_D^{24}$ −114.3 (*c* 1.29, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.52 (d, *J*=5.1 Hz, 1H), 2.8–2.6 (m, 1H), 2.59–2.51 (dd, *J*=8.4, 17.2 Hz, 1H), 2.34–2.24 (dd, *J*=11.7, 17.2 Hz, 1H), 2.10 (s, 3H), 1.11 (d, *J*=6.9 Hz, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ 175.2, 169.1, 95.8, 33.9, 33.0, 20.5, 12.4. MS (CI, NH_3) 176 $(M+NH_4)^+$. Anal. calcd for $C_7H_{10}O_4$: C, 53.15; H, 6.38, found: C, 52.81; H, 6.38.

3.4. A typical procedure for the synthesis of rac-5-acetoxy-3-acetyl-4-methyl-dihydro-2(3H)-furanone rac-6

To n-BuLi (5.95 ml of a 1.6 M solution in hexanes, 9.48 mmol, 1.5 equiv.) in THF (15 ml) at 0°C under N_2 was added HMDS (2.0 ml, 9.48 mmol, 1.5 equiv.) followed by stirring at room temperature for 10 min The fresh solution of LHMDS was then quickly added to a solution of *rac*-**5** (1.00 g, 6.32 mmol) in THF (100 ml) at −78°C. After stirring for 10 min at −78°C, AcCl (0.7 ml, 9.48 mmol, 1.5 equiv.) was added at once, followed by stirring for another 3 min. The reaction was then quenched by adding a saturated solution of aqueous NH_4Cl (20 ml) and the mixture was allowed to warm to 0°C. Diethyl ether (100 ml) was added and the water layer was extracted with ether (2×40 ml). The combined organic layers were washed with brine (30 ml), dried over $MgSO_4$ and concentrated in vacuo yielding a yellowish oil. Column chromatography (SiO_2, EtOAc:pentane:Et_2O=6:12:3 Rf_6 0.55) yielded *rac*-**6** as a colourless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.53 (d, *J*=5.38 Hz, 1H), 3.47 (d, *J*=11.24 Hz, 1H), 3.18 (m, 1H), 2.45 (s, 3H), 2.11 (s, 3H), 1.08 (d, *J*=6.38 Hz, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ 199.1, 170.7, 168.8, 94.2, 56.7, 35.3, 29.9, 20.4, 11.8. HRMS calcd 200.0685, found 200.0685. Anal. calcd for $C_9H_{12}O_5$: C, 53.98; H, 6.04, found: C, 53.49; H, 6.05.

3.5. (3S)(4S)(5R)- and (3R)(4S)(5R)-5-Acetoxy-3-acetyl-4-methyl-dihydro-2(3H)-furanone 6

The same procedure as given for *rac*-**6**. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.54 (d, *J*=5.5 Hz, 1H), 3.45 (d, *J*=11.4 Hz, 1H), 3.18 (m, 1H), 2.44 (s, 3H), 2.11 (s, 3H), 1.08 (d, *J*=6.9 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 199.1, 170.7, 168.8, 94.2, 56.8, 35.5, 30.0, 20.5, 11.9. MS (CI, NH_3) 218 $(M+NH_4)^+$. Anal. calcd for $C_9H_{12}O_5$: C, 53.98; H, 6.04, found: C, 53.78; H, 5.99.

3.6. (3R)(4S)(5R)-5-Acetoxy-3-acetyl-3-(1,3-dithianyl)-4-methyl-dihydro-2(3H)-furanone 7

To a solution of n-BuLi (0.21 ml of a 2.5 M solution in hexanes, 0.53 mmol, 1.0 equiv.) in THF (3 ml) at 0°C was added HMDS (0.11 ml, 0.53 mmol, 1.0 equiv.) and the solution was stirred for 5 min at room temperature. This fresh solution of LHMDS was then quickly added to a solution of **6** (0.107 g, 0.53 mmol) in THF (7 ml) at −78°C, followed by stirring for 10 min. Next, 1,3-dithienium tetrafluoroborate (0.120 g, 0.58 mmol, 1.1 equiv.) was added. After stirring for another 20 min the reaction mixture was quenched by adding a saturated solution of aqueous NH_4Cl (5 ml). CH_2Cl_2 (50 ml) and H_2O (25 ml) were added and the water layer was extracted with CH_2Cl_2 (2×40 ml). The combined organic layers were washed with brine (20 ml), dried over Na_2SO_4 and concentrated in vacuo yielding a yellowish solid. The crude product was triturated with ice cold ether to give **7** as a white solid (0.143 g, 85%). $[\alpha]_D^{21}$ −132.4 (*c* 1.00, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.57 (d, *J*=5.5 Hz, 1H), 4.41 (s, 1H), 3.35 (m, 1H), 3.15 (m, 1H), 2.92 (m, 1H), 2.80 (m, 2H), 2.38 (s, 3H), 2.08 (s, 3H), 2.01 (m, 2H), 1.11 (d, *J*=6.9 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 200.2, 173.2, 168.5, 94.2, 65.4, 48.4, 40.6, 30.1, 29.8, 29.5, 24.8, 20.5, 9.7. HRMS calcd for $C_{13}H_{18}O_5S_2$ 318.0595, found 318.0592. Anal. calcd for $C_{13}H_{18}O_5S_2$: C, 49.05; H, 5.70; S, 20.10, found: C, 49.19; H, 5.82; S, 20.07.

3.7. (−)-(3S)(4S)(5R)-5-Acetoxy-3-acetyl-3,4-dimethyl-dihydro-2(3H)-furanone; (−)-acetomycin 1

To a solution of **7** (0.095 g, 0.30 mmol) in dry acetone (4 ml) and abs. EtOH (4 ml) was added approximately 3 g of active Raney nickel (freshly washed with abs. EtOH). The black suspension was vigorously stirred for 7.5 h. The progress of the reaction can be monitored by TLC[22] (SiO_2, CH_2Cl_2:Hex:EtOAc=5:5:1, Rf 0.47). It may be necessary to add more Raney nickel during the reaction. The suspension was filtered over Hyflo Super Cell and concentrated in vacuo. The crude product was purified by crystallization from hexane:Et_2O (3:2), to give (−)-acetomycin **1** as white needles (0.031 g, 48%). Mp 111–112°C (Lit.[6] mp 115–116°C). $[\alpha]_D^{24}$ −147.5 (*c* 1.27, EtOH) (lit.[7] $[\alpha]_D^{20}$ −157 (*c* 1.25, EtOH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.56 (d, *J*=5.5 Hz, 1H), 2.54 (dq, *J*=5.5, 7.3 Hz, 1H), 2.29 (s, 3H), 2.10 (s, 3H), 1.42 (s, 3H), 1.04 (d, *J*=7.3 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 203.2, 176.9, 168.5, 93.9, 56.7, 45.5, 28.9, 21.0, 20.5, 9.3. MS (CI, NH_3) 232 $(M+NH_4)^+$. Anal. calcd for $C_{10}H_{14}O_5$: C, 56.05; H, 6.59, found: C, 55.94; H, 6.61. The e.e. of **1** is higher than that of **5**, presumably due to some enrichment in the final crystallization.

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