Tetrahedron Letters, Vol.32, No.44, pp 6421-6424, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

Stereoselective Synthesis of (±)-4-epi-Acetomycin by the Ester Enolate Carroll Rearrangement

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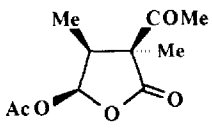
Key Words: (±)-4-epi-Acetomycin; stereoselective synthesis; Carroll rearrangement; Claisen rearrangement; γ-butyrolactone.

Abstract: *The synthesis of (±)-4-epi-acetomycin has been completed by the stereoselective ester enolate Carroll rearrangement of (E)-2-butenyl 2-methylacetoacetate, followed by ozonolysis and acetylation. The synthesis of (±)-acetomycin and its three diastereomers by a related route is also described.*

The densely functionalized antibiotic acetomycin (**1**) was isolated in 1958 from *Streptomyces ramuculosus*.[1,2] Its structure, originally based on degradation reactions and spectroscopic data,[3] was later determined by two independent X-ray crystallographic studies.[4,5] This antibiotic is moderately active against Gram-positive bacteria, fungi, and protozoae,[1,4] and, more interestingly, shows antitumor activity *in vitro*.[6]



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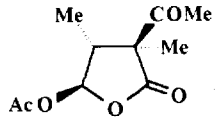

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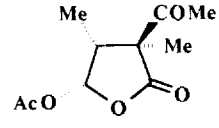

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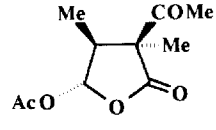

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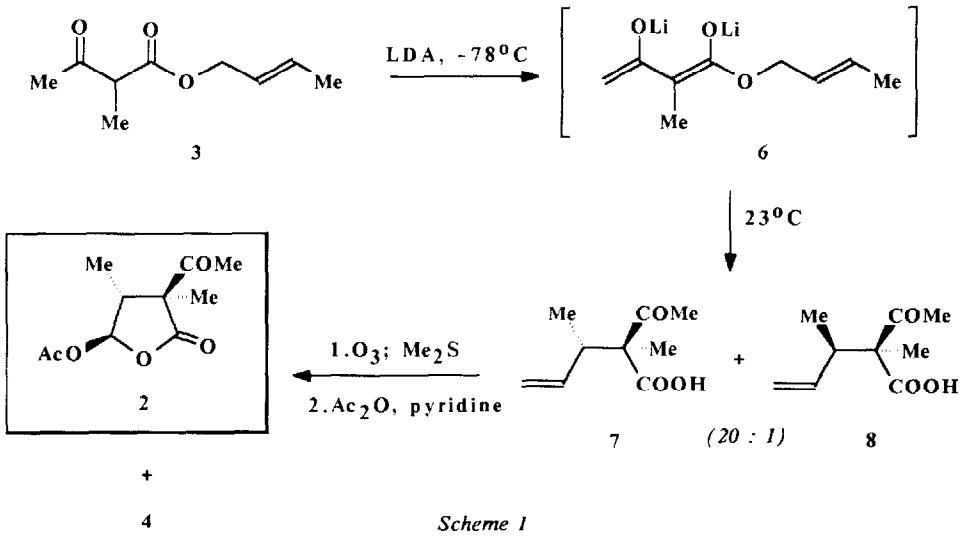
The synthesis of (-)-**1** from a derivative of D-glucose has been described by Tadano,[7,8] and a synthesis of (±)-**1** that addresses the sterocontrolled introduction of the 5-acyloxy group has been reported by Uenishi.[9] Herein we report on a steroselective synthesis of the 4-epimer **2**[10] by using the

Carroll rearrangement of (*E*)-2-butenyl 2-methylacetoacetate (**3**) as the key step.[11] A related synthesis of (±)-**1** and its diastereomers (**2**, **4**, and **5**) by using the ester dienolate Claisen-Ireland rearrangement[12,13] is also reported.

Reaction of **3**[14] with 2 equiv of LDA in THF at -78°C gave dienolate **6**, which smoothly rearranged at 23°C. After 3.5 h at this temperature, careful acidic work up at 0°C gave a 20:1 mixture of ß-ketoacids **7** and **8** (100 % crude yield) (Scheme 1).[15] The stereochemistry of the major isomer **7** is that expected from the rearrangement of the (*E*)-enolate[16] through a chair-like transition state[12,13] The same diastereoselection was obtained when the dienolate was generated by treatment with NaH in THF at 0°C, followed by reaction with *n*-BuLi at -78°C. On the other hand, the corresponding silyl enolates, formed by trapping of the dienolates with either Me_3SiCl or *t*-$BuMe_2SiCl$, led only to recovered starting material **3** under the same reaction conditions (-78 to 23°C; acidic work up).



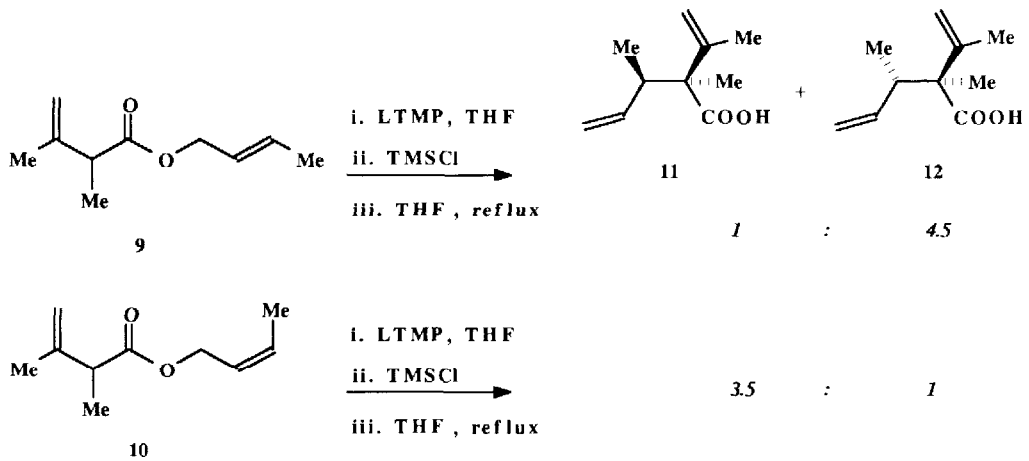
Scheme 1

The synthesis was completed by ozonolysis of the mixture of **7** and **8** at -78°C (O_3, CH_2Cl_2; Me_2S) and *in situ* acetylation with Ac_2O-pyridine (-78 to 23°C, 2 h) to give a 12:1 mixture of **2**[17] and its C-5 epimer **4** ("(±)-3-*epi*-acetomycin")[18] in 55 % yield (two steps).

The synthesis of (±)-**1** was similarly attempted from (*Z*)-2-butenyl 2-methylacetoacetate. However, the rearrangement of the dilithium or the sodium-lithium dienolate failed to yield the corresponding ß-ketoacids, leading to recovered starting materials or decompositions products. On the other hand, when the bis(trimethylsilyl) enolate was heated under reflux in THF, a 1:1 mixture of **7** and **8** was obtained in low yield. Ozonolysis of this mixture and acetylation as before gave a 1.5:1 mixture of **2** and (±)-5-*epi*-acetomycin (**5**).[19a] Although a small amount of **4** was also present in the crude reaction

mixture, none of **1** could be detected.

Treatment of (*E*)- and (*Z*)-2-butenyl 2,3-dimethyl-3-butenoate (**9** and **10**, respectively)[20] with lithium 2,2,6,6-tetramethylpiperidide (LTMP) at -30°C, followed by TMSCl trapping, and rearrangement (reflux THF, 2-3 h) gave acids **11** and **12** (Scheme 2).[21] Selective oxidation of the less hindered olefin was achieved with OsO_4-$NaIO_4$ in aqueous dioxane at 23°C to yield a mixture of aldehydes and hemiacetals which, without purification, was treated with Ac_2O-H_2SO_4 (cat.) at 23°C. Finally, oxidation with $RuCl_3$-$NaIO_4$ in CCl_4-MeCN-H_2O[22] gave a mixture of **1** and **5** (from **11**), and **2** and **4** (from **12**). When this three steps sequence was performed on a 3:1 mixture of **11** and **12**, a 18:44:18:20 mixture of **1**,[19b] **5**, **2**, and **4** was obtained in 38 % overall yield.



Scheme 2

The reported synthesis provides a ready access to (±)-4-*epi*-acetomycin (**2**) by a stereoselective Carroll rearrangement. Further work on the selective synthesis of **1** is in progress.

Acknowledgment: We wish to thank Profs. J. Elguero (Instituto de Química Médica, CSIC) and L. Carrasco (Dep. Biología Molecular, Universidad Autónoma de Madrid) for their interest and encouragement and Prof. R. Schmidt (Universität Konstanz) for a helpful discussion.

References and Notes

1. Ettlinger, L.; Gaumann, E.; Hutter, R.; Keller-Schierlein, W.; Kradolfer, F.; Neipp, L.; Prelog, V.; Zahner, H. *Helv. Chim. Acta* **1958**, *41*, 216.
2. Biosynthesis: Bachmann, E.; Gerlach, H.; Prelog, V.; Zahner, H. *Helv. Chim. Acta* **1963**, *46*, 605.

3. Keller-Schierlein, W.; Mihailovic, M. L.; Prelog, V. *Helv. Chim. Acta* **1958**, *41*, 220.
4. Uhr, H.; Zeeck, A.; Clegg, W.; Egert, E.; Fuhrer, H.; Peter, H. H. *J. Antibiot.* **1985**, *38*, 1684.
5. Cano, F. H.; Foces-Foces, C.; Elguero, J. *Acta Cryst.* **1988**, *C44*, 919.
6. Mamber, S. W.; Mitulski, J. D.; Hamelehle, K. L.; French, J. C.; Hokanson, G. C.; Shillis, J. L.; Leopold, W. R.; Von Hoff, D. D.; Tunac, J. B. *J Antibiot.* **1987**, *40*, 73. Mamber, S. W.; Mitulski, J. D.; Borondy, P. E.; Tunac, J. B. *J. Antibiot.* **1987**, *40*, 77.
7. Tadano, K.; Ishihara, J.; Ogawa, S. *Tetrahedron Lett.* **1990**, *31*, 2609.
8. For the synthesis of the D-glucose derived starting material by Claisen rearrangement, see: (a) Tadano, K.; Ishihara, J.; Yamada, H.; Ogawa, S. *J. Org. Chem.* **1989**, *54*, 1223. (b) Tadano, K.; Idogaki, Y.; Yamada, H.; Suami. T. *J. Org. Chem.* **1987**, *52*, 1201.
9. Uenishi, J.; Okadai, T.; Wakabayashi, S. *Tetrahedron Lett.* **1991**, *32*, 3381.
10. All new compounds reported in this paper are racemic but for convenience only one stereoisomer is shown.
11. (a) Wilson, S. R.; Price, M. F. *J. Org. Chem.* **1984**, *49*, 722. (b) Snider, B. B.; Beal, R. B. *J. Org. Chem.* **1988**, *53*, 4508. (c) Gilbert, J. C.; Kelly, T. A. *Tetrahedron* **1988**, *44*, 7587.
12. Ireland, R. E.; Muller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.
13. (a) Wilson, S. R.; Myers, R. S. *J. Org. Chem.* **1975**, *40*, 3309. (b) Ziegler, F. E.; Bennett, G. B. *J. Am. Chem. Soc.* **1973**, *95*, 7458. (c) Fráter, G. *Helv. Chim. Acta* **1975**, *58*, 442. (d) Fráter, G. *Helv. Chim. Acta* **1978**, *61*, 2709.
14. Ester **3** was prepared in two steps: *i.* acylation of (*E*)-2-buten-1-ol with diketene and pyridine (cat.).[11a] (61 %); *ii.* NaH, THF, CH_3I (large excess) (80 %).
15. The ß-ketoacids readily undergo decarboxylation at 23°C to give a 1.5:1 mixture of diastereomeric methylketones. The diastereoselection was also determined by esterification of the crude reaction mixture at 0°C with CH_2N_2 in Et_2O to yield a 20:1 mixture of ß-ketoesters: mayor isomer C-3 Me at δ 0.99 (d, J = 6.9 Hz), minor isomer C-3 Me at δ 1.04 (d, J = 6.8 Hz).
16. For the stereochemistry of the dienolates derived from ß-ketoesters, see: Bell, S. H.; Cameron, D. W.; Feutrill, G. I.; Skelton, B. K.; White, A. H. *Tetrahedron Lett.* **1985**, *26*, 6519.
17. **2**: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.11 (d, J = 3.0 Hz, 1 H, H-5), 3.01 (qd, J = 7.4, 3.0 Hz, 1 H, H-4), 2.31 (s, 3 H), 2.05 (s, 3 H), 1.33 (s, 3 H), 1.07 (d, J = 7.4 Hz, 3 H). ^1H NOEDIFF: irradiation at δ 1.07 (C-4 Me) gave rise to enhancements at δ 6.11 (7 %) and 3.01 (9 %). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 202.81, 174.88, 168.84, 98.23, 59.33, 40.78, 25.87, 20.61, 16.11, 11.86.
18. **4**: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.55 (d, J = 5.9 Hz, 1 H, H-5), 3.22 (qd, J = 7.3, 5.9 Hz, 1 H, H-4), 2.36 (s, 3 H), 2.14 (s, 3 H), 1.52 (s, 3 H), 0.98 (d, J = 7.3 Hz, 3H).
19. (a) Identical with the compound reported by Tadano *et al.*[7] (b) Identical with an authentic sample (TLC, ^1H and ^{13}C NMR) supplied by Prof. W. Keller-Schierlein (*via* Prof. L. Carrasco).
20. (a) These esters were prepared by esterification of 2,3-dimethyl-3-butenoyl chloride[20b] with (*E*)- (58 % yield) or (*Z*)-2-buten-1-ol (50 % yield). (b) Karpf, M. *Helv. Chim. Acta* **1984**, *67*, 73.
21. The stereochemistry was tentatively assigned by comparison with that of **7** and **8**.
22. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(Received in UK 24 July 1991)