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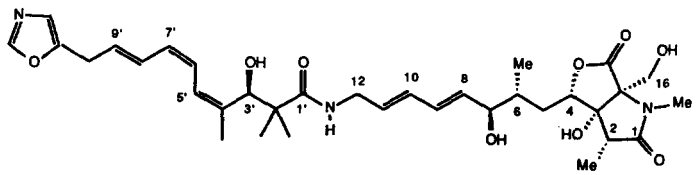
SYNTHESIS OF THE FUSED BICYCLIC LACTAM-LACTONE TERMINUS OF NEOOXAZOLOMYCIN BY A NOVEL DIANION CYCLOCONDENSATION

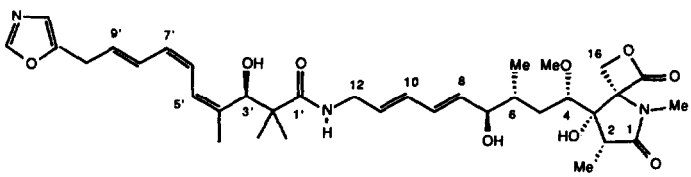
Andrew S. Kende* and Robert J. DeVita
Department of Chemistry
University of Rochester
Rochester, New York 14627

SUMMARY: Reaction of the dianion (5) derived from an acylaminomalonic ester with S-(-)-MOM lactate (6) yields β-hydroxylactams 7 and 8 in a 2:1 ratio. Deprotection and lactonization of 7, followed by saponification and 2 step carboxyl reduction efficiently produces the fused bicyclic lactam-lactone 12, a chiral model of the antitumor antibiotic neooxazolomycin 1.

In 1985, Japanese investigators reported spectroscopic, degradative and X-ray studies leading to the structure elucidation of the two novel polyene lactam-lactone antibiotics neooxazolomycin (1) and its β-lactone congener, oxazolomycin (2).[1] These compounds showed activity against Ehrlich ascites tumor in vivo and oxazolomycin (2) showed activity against P388 leukemia.



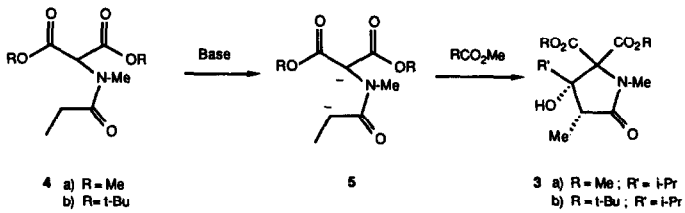
NEOOXAZOLOMYCIN 1



OXAZOLOMYCIN 2

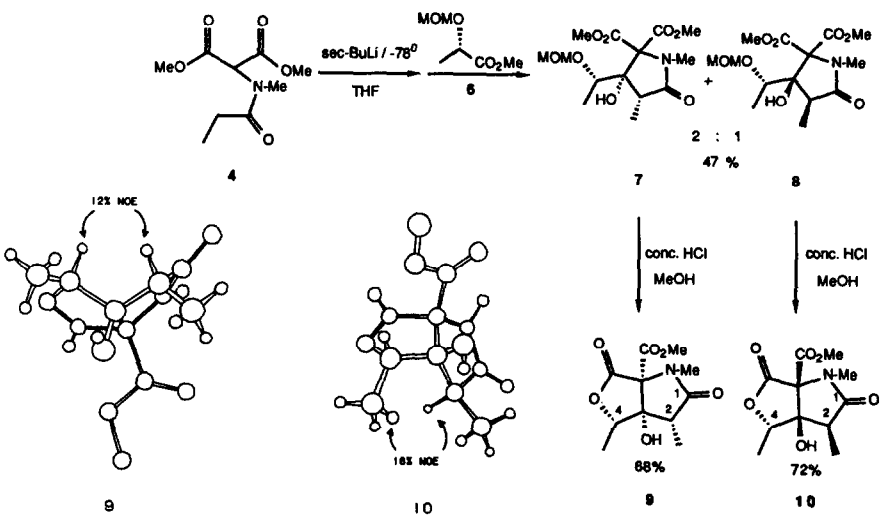
These unusual structures, which represent the absolute configurations, pose an intriguing synthetic challenge. There appears to be no literature precedent for the fused lactam-lactone moiety of 1 nor the spirocyclic lactam β-lactone unit of 2. We now wish to report the first synthesis of the chiral bicyclic lactam-lactone subunit of neooxazolomycin by an efficient new cyclocondensation.

Our initial efforts were directed toward the synthesis of simple β-hydroxylactams such as 3.[2] It was anticipated that double deprotonation of an amidomalonate (4) with a strong base, followed by condensation of the resulting dianion (5) with an acylating agent would result in acylation α- to the amide carbon followed by intramolecular cyclization of the ketoamide to yield a β-hydroxylactam (3).



Reaction of the malonates **4**[3] with 2 equivalents of LDA at 0° and subsequent addition of the resulting solution to methyl isobutyrate (1.2 equiv., 0°, 1 hr) gave on workup the cyclized β-hydroxylactams **3**[4] in 50-55% yield. Use of sec-BuLi with malonate **4a** or t-BuLi/TMEDA with malonate **4b**, at -78° in THF, raised the yields of **3** to 70%.[5] Destruction of the malonates by alkyllithium bases was not observed as a significant side reaction.

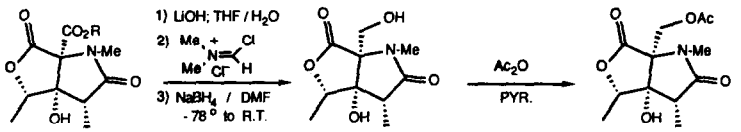
The new dianion methodology was applied to the MOM ether of (S)-(-)-methyl lactate (**6**).[6] Inverse addition of the dianion derived from **4a** (2.1 equiv. sec-BuLi) to 1.2 equiv. of lactate **6** for 1 hr at -78° in THF gave, upon quenching with saturated NH_4Cl and workup, the cyclized products **7** and **8** as a 2:1 mixture of diastereomers (47% yield, 59% based on recovered **4a**). These compounds were separated by column chromatography (EtOAc/hexane; 65/35) and individually refluxed in methanol containing a drop of conc. HCl for 15 minutes. This produced on neutral workup and crystallization the bicyclic lactam-lactone esters **9**[7] (mp 168-171°) and **10**[8] (mp 179-182°) in yields of 68 and 72% respectively.



The minor and less polar diastereomer was assigned structure **10** as a result of an observed 18% NOE of H-2 upon irradiation of the methyl at C-4 (neooxazolomycin numbering). The major and more polar isomer was assigned structure **9** as a result of an observed 12% NOE of H-2 upon irradiation of the C-4 methine

proton of the lactone ring. Further confirmation of the stereochemistries was provided by NMR chemical shift correlation with the natural product after subsequent transformations (vide infra).

With our initially equivalent malonate carbonyls differentiated by lactonization, we explored the selective reduction of the methyl ester. Saponification of ester **9** with LiOH in THF/H_2O (5:1) and acetic acid workup gave acid **11**[9] (100%, mp 189-191°) as a stable crystalline solid. Reduction of acid **11** to the hydroxymethyl functionality proved to be difficult. Treatment with BH_3, or formation of various mixed anhydrides (with ethyl chloroformate[10] or diphenyl phosphorochloridate[11]), then treatment with $NaBH_4$ resulted in destruction of the starting acid. Good yields, however, were obtained by treatment of acid **11** with the Vilsmeier salt of dimethylformamide (DMF, oxalyl chloride) in CH_3CN/THF at 0°, then reduction at -78° (2.0 M $NaBH_4$ in DMF) and warming to 20° overnight.[12] In this manner, the hydroxymethyl lactam-lactone **12**[13,14] (mp 171-173°) was obtained in 60% yield. Acetylation of alcohol **12** yielded acetate **13** (mp 150-152°). Use of the β-isomer **10** in the same sequence of reactions yielded acetate **14**.



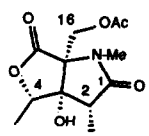
9 R = Me
11 R = H

12

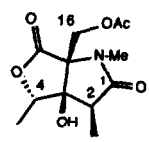
13

NMR chemical shifts of these acetates (Table I, $CDCl_3$ solvent) were compared to those of 3',7,16-tri-O-acetyl-neooxazolomycin **15**.[1] Good correspondence is observed for the chemical shifts of the N-methyl, 2-H, 2-Me, OAc and both protons at C-16 (neooxazolomycin numbering) for acetate **13** and the tri-acetate **15**, derived from the natural product, whereas the N-Me, 2-Me and C-16 signals of acetate **14** did not correspond to those of **15**.

TABLE I



13



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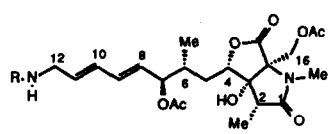

15

Proton($CDCl_3$)	δ	δ	δ
2-H	2.48 (q)	2.71 (q)	2.43 (q)
2-Me	1.28 (d)	1.26 (d)	1.27 (d)
4-H	4.40 (q)	4.57 (q)	4.31 (dd)
N-Me	2.89 (s)	3.05 (s)	2.85 (s)
H-16	4.29 (d, J=13 Hz)	4.53 (d, J=12 Hz)	4.23 (d, J=12 Hz)
H-16	4.74 (d, J=13 Hz)	4.56 (d, J=12 Hz)	4.69 (d, J=12 Hz)
OAc	2.12 (s)	2.10 (s)	2.08 (s)

Thus, a novel dianion cyclocondensation of an amidomalonate dianion with simple esters produces β-hydroxylactams in good yields. When the ester bears α-oxygen, appropriate lactonization, ester hydrolysis and reduction to the hydroxymethyl functionality cleanly yields the complete bicyclic lactam-lactone nucleus of the antitumor antibiotic neooxazolomycin in optically pure form. Application of this methodology toward substrates necessary for elaboration into the natural product are in progress.

ACKNOWLEDGMENTS. Partial support of this research by grant CA 18846, awarded by the National Cancer Institute, NIH-USPHS, is gratefully acknowledged. RJD thanks the University of Rochester for financial support in the form of a Sherman Clarke Fellowship.

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2. The only previous report of such structures is from Simig, G.; Doleschall, G.; Hornyak, G.; Fetter, J.; Lempert, K.; Nyitral, J.; Huszthy, P.; Gizur, T. Tetrahedron **1985**, 41, 479, in which the condensation of aminophenyl malonates and diketene is described to yield an N-phenyl counterpart of **3**.

3. Malonate **4a** was prepared from known dimethyl aminomethyl malonate (Uhle, F.C.; Harris, L.S. J. Am. Chem. Soc. **1956**, 78, 381) by acylation with propionyl chloride in pyridine/CH_2Cl_2. **4b** was prepared in an analogous manner from di-t-butyl bromomalonate (Hollowood, J.; Jansen, A.B.A.; Southgate, P.J. J. Med. Chem. **1967**, 10, 864).

4. The stereochemistry of **3** is assumed to be trans (for the alkyl groups) since this would be the thermodynamically more stable product resulting from a presumably facile retroaldol-aldol process. We have confirmed this by NOE studies.

5. Apparently deprotonation with LDA is slow or does not go to completion even at 0°. This has been observed for other remote dianion systems, e.g., Thomson, C.M., Tetrahedron Lett., **1987**, 28, 4243.

6. Compound **6** was prepared by the same procedure as described for (S)-(-)-ethyl lactate MOM ether by Banfi, L.; Bernardi, A.; Colombo, L.; Gennari, C.; Scolastico, C. J. Org. Chem. **1984**, 49, 3784.

7. Compound **9**: ^{1}H-NMR ($CDCl_3$): δ 4.46 (1H, q), 3.92 (3H, s), 3.49 (1H, s), 2.97 (3H, s), 2.54 (1H, q), 1.48 (3H, d), 1.21 (3H, d) ppm. Found: C, 51.59; H, 5.70.

8. Compound **10**: ^{1}H-NMR ($CDCl_3$): δ 4.75 (1H, q), 3.93 (3H, s), 3.77 (1H, s), 3.09 (3H, s), 2.71 (1H, q), 1.47 (3H, d), 1.27 (3H, d) ppm. Found: C, 50.99; H, 5.98.

9. Compound **11**: ^{1}H-NMR (CD_3CN): δ 4.47 (1H, q), 4.1 (1H, br. s), 2.82 (3H, s), 2.53 (1H, q), 1.37 (3H, d), 1.11 (3H, d) ppm. Found: C, 48.56; H, 5.61. Acid **11** could also be prepared via the t-butyl malonate **4b** by the following sequence: 1) Dianion condensation with methyl TBSO-lactate (68%, 1:1 mixture of diastereomers); 2) Bu_4NF/THF gave t-butyl lactones (82%); 3) chromatography to separate diastereomers; 4) PTSA/benzene, reflux (quant.) to give crystalline **11**.

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12. Fujisawa, T.; Mori, T.; Sato, T. Chem. Lett. **1983**, 835.

13. Compound **12**: ^{1}H-NMR (acetone-d_6): δ 4.75 (1H, s), 4.52 (1H, m), 4.40 (1H, q), 3.96 (1H, dd, J =12, 4Hz), 3.86 (1H, dd, J=12, 4Hz), 2.76 (3H, s), 2.44 (1H, q), 1.36 (3H, d), 1.22 (3H, d) ppm. Found: C, 52.01; H, 6.57.

14. The R-(+)-Mosher ester of **15** was prepared. Both ^{1}H and ^{13}C-NMR showed only one compound, insuring that the chiral center of starting lactate **6** was not racemized.

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