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ENANTIOSELECTIVE SYNTHESIS OF THE α,α-DIMETHYL-β-HYDROXY ACID SUBUNIT OF THE OXAZOLOMYCIN ANTIBIOTICS

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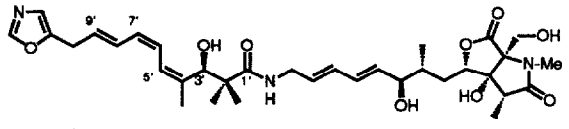
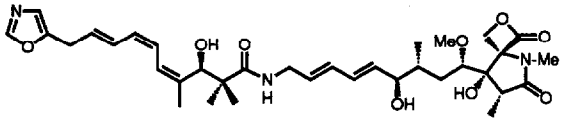
SUMMARY: Reaction of the Sn(II) enolate, generated by the action of $SnCl_2$-$LiAlH_4$ on oxazolidinone **5**, with benzaldehyde or conjugated Z-enal **8** yields respectively oxazinedione **6** or **9** with not less than 97 : 3 diastereoselectivity. Removal of the chiral auxiliary from **9** produces a homochiral model of the C1'-C5' subunit of the oxazolomycin antibiotics.

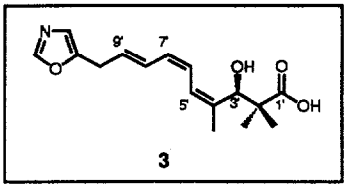
The novel polyene lactam-lactone antibiotics neooxazolomycin (**1**) and oxazolomycin (**2**) are amides of a common oxazole triene carboxylic acid with dienamines possessing fused bicyclic and spirocyclic lactam-lactone end groups, respectively.[1] We have recently described the synthesis of the fused bicyclic lactam-lactone terminus of neooxazolomycin in proper chiral form by condensation of a dianion of a propionylaminomalonic ester with an (S)-(-)-MOM lactate, followed by lactonization.[2]



1 NEOOXAZOLOMYCIN



2 OXAZOLOMYCIN



3

While the full elaboration of the chiral dienamine half of neooxazolomycin is in progress we have focused on the synthetic problem inherent to the construction of the chiral α,α-dimethyl-β-hydroxy-γ,δ-(Z)-unsaturated carboxylic acid subunit, shown to be in the 3'-R configuration, which constitutes carbons 1' through 5' of the oxazole triene acid half of these antibiotics (cf **3**).

To date, the only direct enantioselective synthesis of α,α-dimethyl-β-hydroxy acid derivatives has been by asymmetric aldol reactions which unfortunately give very low enantiomeric excess.[3] We now wish to report that chiral reagent **5** derived from the Evans chiral oxazolidinone[4] and α-bromoisobutyryl bromide[5] can be used in a diastereoselective "Reformatsky type" aldol reaction with α,β-unsaturated aldehydes leading to the desired system in good chemical yield and high enantioselectivity.

Since there appears no literature precedent for the diastereoselective aldol reaction of chiral N-isobutyryloxazolidinone **4**,[5] we initially explored the reaction of its boron enolate ($^nBu_2BOTf$, $^iPr_2EtN$, CH_2Cl_2, -78°C, then rt.) with benzaldehyde. This produced (Table 1) oxazinediones R,S-**6** and S,S-**6** as a 92 : 8 diastereomeric mixture, inseparable in our hands by TLC or HPLC, in a mediocre yield of 23%. When the lithium enolate from oxazolidinone **4** (LDA, THF, -78°C) was reacted with benzaldehyde, the opposite stereoselection (R,S-**6** / S,S-**6** = 13 : 87) was observed, albeit in better yield. Success was ultimately achieved by preparing active Sn

metal and $AlCl_3$ *in situ* from $SnCl_2$ and $LiAlH_4$ according to Mukaiyama's procedure,[6] and allowing this system to generate an Sn(II) enolate by reduction of the α-bromoisobutyryloxazolidinone **5** in THF at room temperature. Reaction of this enolate with benzaldehyde now produced in 69% yield a 97 : 3 ratio of R,S-**6** to S,S-**6**, with the major diastereomer corresponding at the newly formed stereogenic center to the "natural" 3' stereochemistry of the target acid **3**.

In contrast to the aldol reaction of the related secondary enolates studied by Evans,[4] our system yields 1,3-oxazine-2,6-diones *via* rearrangement of the normal aldol adducts during the reaction conditions, presumably accelerated by the gem-dialkyl effect which destabilizes the acyclic tautomers relative to the cyclic counterparts.[7] The gross structures and diastereomeric ratios of R,S-**6** and S,S-**6** were established by 300MHz ^{1}H-NMR,[8] notably by the benzyl proton signals at δ 5.24 (s) for R,S-**6** and δ 5.27 (s) for S,S-**6**, indicating the presence of an acyloxy group at this position. The absolute configuration at the newly formed chiral center was determined by hydrolysis with LiOH. Thus the oxazinedione mixture **6** obtained *via* the tin(II) enolate was converted by LiOH in 3 : 1 THF-H_2O at room temperature to the acids **7** with $[\alpha]_D^{24}$=-7.1°(c=1.0, MeOH), cf lit.[9] $[\alpha]_D^{24}$=-5.2°(c=0.98, MeOH), indicating predominantly the R configuration. On the other hand, the diastereomeric mixture of oxazinedione **6** from the lithium enolate gave acids **7** with $[\alpha]_D^{24}$=+4.5°(c=0.6, MeOH), indicating mainly the S configuration. The formation of predominantly R product from the tin(II) and boron enolates, vs. mainly S product from the lithium enolate, is fully consistent with the results and transition state models reported by Pridgen et al. for the condensation of α-haloacetyloxazolidinone enolates with aldehydes to yield α,β-epoxyacid derivatives.[10] Based on that model, we picture our boron and tin(II) enolate aldols to proceed mainly by way of the transition state T,[11] with subsequent rearrangement of the resulting major metal alkoxide diastereomer as shown to produce the observed R,S-**6** as the predominant product.

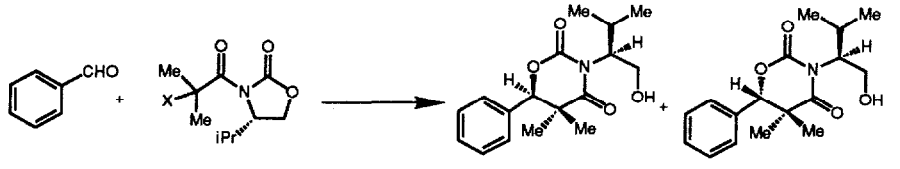
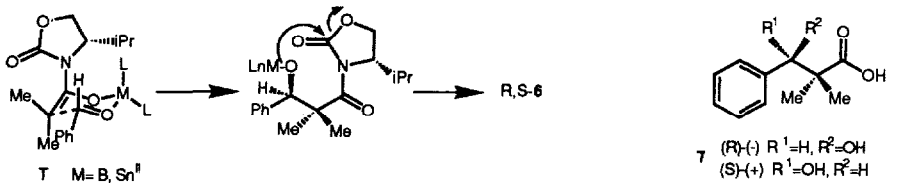


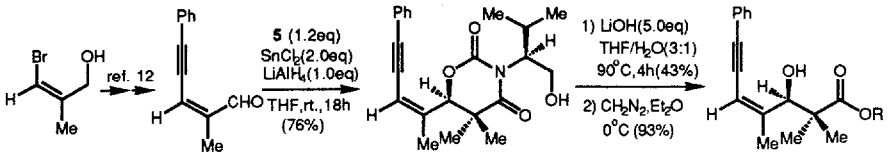
Table 1

Entry	Subst.	Reagent and Condtn.	Yield (%)	Ratio (RS/SS)-6	$[\alpha]_D^{22}$ (CH_2Cl_2)
1	4	^{n}Bu_2BOTf(1.1eq), iPr_2EtN(1.2eq) CH_2Cl_2, -78°C (1h), rt., (1.5h)	23	92 : 8	-34.9° (c = 3.5)
2	4	LDA (1.1eq), THF, -78°C, (1h)	64	13 : 87	+38.2° (c = 2.9)
3	5	$SnCl_2$(2.0eq),$LiAlH_4$(1.0eq) THF, rt., (15h)	69	97 : 3	-47.9° (c = 1.8)



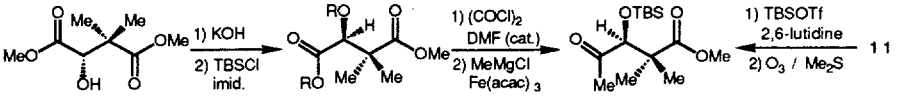
At this point, the Z-enal **8**, a closer model of **1**, was examined to investigate the retention of the Z geometry of the anticipated oxazinedione R,S-**9** under reaction conditions containing the strong Lewis acid $AlCl_3$.[6] Treatment of aldehyde **8**[12] with the tin(II)

enolate, prepared as before from oxazolidinone **5**, in THF at room temperature for 18h furnished exclusively oxazinedione R,S-**9**[13] (mp 110-111°C, $[\alpha]_D^{22}$=+39°(c=0.7, CH_2Cl_2), >99%de by ^{1}H-NMR, 76% chemical yield). Product R,S-**9** exhibited complete retention of Z geometry, and was obtained along with 22% of unreacted aldehyde **8** (as a 4 : 1 E / Z mixture) and ca. 18% of oxazolidinone **4**. Once again, the lithium enolate from oxazolidinone **4** reacted with aldehyde **8** (LDA, THF, -78°C, 70% yield) to produce the R,S and S,S diastereomers of oxazinedione **9** in a 3 : 7 ratio. In this case, two different ^{1}H-NMR signals for the allylic methine proton of oxazinedione **9** (δ 5.53 (s) for R,S and δ 5.55 (s) for S,S isomer) were observed.



8 R,S-**9** (>99%de) **10** R=H, **11** R=Me

Evidence for stability of the Z olefin and for the absolute configuration of oxazinedione R,S-**9** was obtained as follows. Hydrolysis of oxazinedione R,S-**9** with LiOH in aqueous THF at 90°C gave 43% of β-hydroxy acid **10**, accompanied by ca. 50% of the undesired related diol amide formed by hydroxide attack at the urethan carbonyl. Acid **10** was reacted with CH_2N_2 to give methyl ester **11**,[14] $[\alpha]_D^{24}$=-39.5°(c=0.4, CH_2Cl_2), in good yield. Stereochemical integrity of the Z double bond in ester **11** was established by independent synthesis of the racemic E-ester,[15] which had profoundly different ^{1}H-NMR signals. The enantiomeric purity of Z-ester **11** cited above was determined to be >99% by chiral shift reagent comparison ($Eu(hfc)_3$ in $CDCl_3$) employing racemic Z-ester **11**[16] as standard. Finally, the absolute configuration of our chiral Z-ester **11** was shown to be R by its conversion to optically active ketoester **15**, prepared by us from the Seebach diester **12**[17] according to the sequence shown. Thus diester **12** was hydrolyzed (KOH (2.1 eq.), MeOH / H_2O (12 : 1), rt., 5 days, 97%) to afford mono acid **13** which was subjected to silylation (TBSCl (2.4 eq.), imid. (4.4 eq.), DMF, rt., 18h, 88%)[18] to furnish disilyl ester **14**. Optically active ketoester **15**[19] ($[\alpha]_D^{25}$=-23°(c=0.7, CH_2Cl_2)) was obtained on direct formation of acid chloride from silyl ester **14** ($(COCl)_2$ (1.2 eq.), cat. DMF, CH_2Cl_2, rt., 80%)[18] followed by methylation (MeMgCl (1.5 eq.), cat. $Fe(acac)_3$, THF, 0°C to rt., 90%).[20] Conversion of optically active ester **11** into ketoester **15** was achieved by silylation of the secondary alcohol (TBSOTf (1.7 eq.), 2,6-lutidine (1.7 eq.), CH_2Cl_2, rt., 100%) and sequential ozonolysis with reductive workup (O_3, CH_2Cl_2, -78°C then Me_2S(excess), -78° to 0°C, 50%). The ketoester **15** ($[\alpha]_D^{24}$=-21.1°(c=0.8, CH_2Cl_2)) obtained from ester **11** had essentially the same rotation as ketoester **15** obtained from diester **12**.



12 **13** R=H, **14** R=TBS **15** **11**

We have thus demonstrated the first efficient enantioselective synthesis of the 3'-R enantiomers of model α,α-dimethyl-β-hydroxy acids related to the C-1' to C-5' subunit of the oxazolomycin antibiotics. Our method involves the reductive generation of the tin(II) enolate of oxazolidinone **4** from precursor **5**, and proceeds by way of a rearrangement to chiral oxazinedione (cf **6** and **9**) and subsequent hydrolysis with good chemical yield and enantioselectivity. We are currently employing this method for the construction of oxazole triene acid **3**.

ACKNOWLEDGMENTS. Partial support of this research by grant CA 18846, awarded by the National Cancer Institute, NIH-USPHS, is gratefully acknowledged.

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5. The chiral N-acyloxazolidinones **4** and **5** were prepared from (4S)-(-)-4-isopropyl-2-oxazolidinone and isobutyryl chloride or α-bromoisobutyryl bromide using ^{n}BuLi as a base in THF at -78°C in 87-96% yield.[4] Compound (**4**): $[\alpha]_D^{24}$+94.2°(c=1.1, CH_2Cl_2); IR(CH_2Cl_2)cm^{-1} 1780, 1710; ^{1}H-NMR($CDCl_3$)δ 4.43(m,1H), 4.26(t,1H,J=8Hz), 4.19(dd,1H,J=8Hz,3Hz), 3.77(m,1H), 2.32(m,1H), 1.21(d,3H,J=7Hz), 1.14(d,3H,J=7Hz), 0.90(d,3H,J=7Hz), 0.86(d,3H,J=7Hz); MS m/z 199(M^+). *Anal.* Calcd for $C_{10}H_{17}NO_3$: C, 60.23; H, 8.60. Found: C, 60.16; H, 8.49. Compound (**5**): mp 56.5-57.5°C; $[\alpha]_D^{24}$+56.6°(c=1.0, CH_2Cl_2); IR(CH_2Cl_2)cm^{-1} 1795, 1690; ^{1}H-NMR($CDCl_3$)δ 4.53(m,1H), 4.35(t,1H, J=8.5Hz), 4.24(dd,1H,J=9Hz,3Hz), 2.35(m,1H), 2.13 (s,3H), 2.09(s,3H), 0.94(d,6H,J=7Hz). HRMS Calcd for $C_{10}H_{16}BrNO_3$ (M^+): 277.0314. Found: 277.0345.
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8. Compound (R,S-**6**): mp 93-94°C; IR(CH_2Cl_2)cm^{-1} 3620, 3510, 1765, 1700; ^{1}H-NMR($CDCl_3$)δ 7.41-7.34(m,5H), 5.24(s,1H), 4.45(m,1H), 4.11(m,1H), 3.87(dd,1H,J=12Hz,3Hz), 2.90(br s,1H), 2.48(m,1H), 1.16(s,3H), 1.14(s,3H), 1.07(d,3H,J=6.5Hz), 0.90(d,3H,J=6.5); MS m/z 306(M^++1). Compound (S,S-**6**): mp 114.5-116.5°C; IR(CH_2Cl_2)cm^{-1} 3620, 3510, 1765, 1710; ^{1}H-NMR($CDCl_3$)δ 7.41-7.34(m,5H), 5.27(s,1H), 4.45(m,1H), 4.10(m,1H), 3.90(dd,1H,J=12Hz,3Hz), 2.52(m,1H), 2.41(br s, 1H), 1.18(s,3H), 1.15(s,3H), 1.05(d,3H,J=6.5Hz), 0.89(d,3H,J=6.5Hz). HRMS Calcd for $C_{17}H_{23}NO_4$ (M^+): 305.1627. Found: 305.1661.
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12. Required aldehyde **8** was synthesized from Z-3-bromo-2-methyl-2-propen-1-ol[a] in 83% overall yield by following reaction sequence: (i) protection of alcohol (TBSCl, imidazole, DMF, 0°C), (ii) coupling reaction of vinyl bromide with phenylacetylene ($Pd(PPh_3)_4$ 5mol%, CuI 15mol%, $^{n}BuNH_2$, benzene, rt.),[b] (iii) deprotection of silyl ether ($^{n}Bu_4NF$, THF, rt.), and (iv) oxidation of alcohol to aldehyde (basic MnO_2, hexane-CH_2Cl_2 (4 : 1), rt.).[a]
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13. Compound (R,S-**9**): IR(CH_2Cl_2)cm^{-1} 3700, 3610, 3500, 1760, 1705, 1615; ^{1}H-NMR($CDCl_3$)δ 7.31(s,5H), 5.86(s,1H), 5.53 (s,1H), 4.44(t,1H, J=9Hz), 4.08(m,1H), 3.82(d,1H,J=12Hz), 2.81(d,1H,J=9Hz), 2.46(m,1H), 1.98(s,3H), 1.37(s,3H), 1.27 (s,3H), 1.04(d,3H,J=6Hz), 0.86(d,3H,J=6Hz); N.O.E. (27%) was observed between vinylic and allylic methyl protons.; MS m/z 369(M^+). *Anal.* Calcd for $C_{24}H_{27}NO_4$: C, 71.52; H, 7.37. Found: C, 71.28; H, 7.57. Chemical shifts of methylene and adjacent methine protons on chiral auxiliary were shifted downfield by acetylation of oxazinedione R,S-**9**.
14. Compound (**11**): IR(CH_2Cl_2)cm^{-1} 3480, 1720, 1600; ^{1}H-NMR($CDCl_3$)δ 7.39(m,2H), 7.30(m,3H), 5.69(s,1H), 4.98(d,1H,J= 9Hz), 3.73(s,3H), 3.54(d,1H,J=9Hz), 1.79(s,3H), 1.37(s,3H), 1.23(s,3H); N.O.E. (16.4%) was observed between vinylic and allylic methyl protons; MS m/z 272(M^+). *Anal.* Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.60; H, 7.24.
15. E isomer of aldehyde **8** was prepared from E-3-bromo-2-methyl-2-propen-1-ol[12a] by similar reaction sequence for aldehyde **8**[12] in good overall yield, and the resulting E-aldehyde **8** was subjected to aldol reaction with methyl isobutyrate (LDA, THF, -78°C) to afford E isomer of ester **11** in quantitative yield: IR(CH_2Cl_2)cm^{-1} 3610, 3480, 1735, 1600; ^{1}H-NMR($CDCl_3$)δ 7.43 (m,2H), 7.30(m,3H), 5.72(s,1H), 4.24(d,1H,J=6Hz), 3.71(s,3H), 3.25(d,1H,J=6Hz), 1.93(s,3H), 1.23(s,3H), 1.18(s,3H). HRMS Calcd for $C_{17}H_{20}O_3$ (M^+): 272.1412. Found: 272.1417.
16. The racemic Z-ester **11** was prepared by aldol reaction of aldehyde **8** with methyl isobutyrate (LDA, THF, -78°C, 100%); spectroscopic data were fully identical with those of chiral ester **11**.
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19. Compound (**15**) : IR(CH_2Cl_2)cm^{-1} 1735, 1715; ^{1}H-NMR($CDCl_3$)δ 4.20(s,1H), 3.70(s,3H), 2.17(s,3H), 1.22(s,3H), 1.14(s,3H), 0.95(s,9H), 0.08(s,3H), 0.04(s,3H). *Anal.* Calcd for $C_{14}H_{28}O_4Si$: C, 58.29; H, 9.78. Found: C, 58.60; H, 9.68.
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