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The First Syntheses of the 1-Oxo-2-oxa-5-azaspiro[3.4]octane Ring System Found in Oxazolomycin

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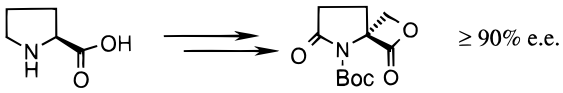
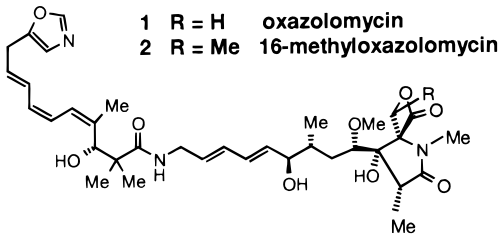
ABSTRACT

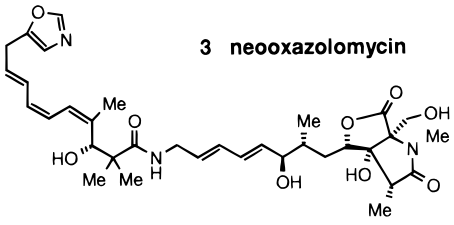


L-Proline was utilized to prepare an optically active 1-oxo-2-oxa-5-azaspiro[3.4]octane for the first time. The synthesis of the racemic system, using a tandem aldol–lactonization reaction, is also described. Ruthenium tetroxide oxidation of these compounds afforded the corresponding spiro β-lactone γ-lactams.

Oxazolomycin (**1**) was isolated in 1985 by Uemura and co-workers from a strain of *Streptomyces* and was the first member of a new class of antibiotics containing a spiro β-lactone γ-lactam ring system to be discovered.[1] It was



found to exhibit activity against P-388 leukaemia cells, Ehrlich ascites tumor, and Gram positive bacteria and also to prevent crown gall formation.[2] It was later found to suppress the replication of vaccinia, herpes simplex type 1, and influenza A viruses during one-step growth cycle experiments in both human and chicken cells.[3] Five analogues of **1** have since been isolated, including 16-methyloxazolomycin (**2**), which was described in 1997.[4] Although no total synthesis of these natural products has been published, in 1990 Kende and co-workers[5] disclosed an enantioselective total synthesis of neooxazolomycin (**3**), the



γ-lactone congener of **1**, whose isolation and structure was reported by Uemura and co-workers.[6] Whiting and Hénaff also recently reported the synthesis of racemic phthoxazolin A, the oxazole-triene "half" of oxazolomycin.[7] In addition, the related compound lactacystin has received considerable attention.[8]

Herein we disclose our preliminary studies toward the spiro lactone moiety of oxazolomycin and the synthesis of the

(1) Mori, T.; Takahashi, K.; Kashiwabara, M.; Uemara D. *Tetrahedron Lett.* **1985**, *26*, 1073−1076.
(2) Kawazu, K.; Kanzaki, H.; Kawabata, G.; Kawai, S.; Kobayashi, A. *Agric. Biol. Chem.* **1989**, *53*, 1127−1133.
(3) Tonew, E.; Tonew, M.; Gräfe, U.; Zöpel, P. *Acta Virol.* **1992**, *36*, 166−172.
(4) (a) Ryu, G.; Hwang, S.; Kim, S. *J. Antibiot.* **1997**, *50*, 1064−1066. (b) Ryu, G.; Kim, S. *J. Antibot.* **1999**, *52*, 193−197.
(5) Kende, A. S.; Kawamura, K.; De Vita, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4070−4072.
(6) Takahashi, K.; Kawabata, M.; Uemara, D. *Tetrahedron Lett.* **1985**, *26*, 1077−1078.
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(8) Corey, E. J.; Li, W.-D. Z.; Nagamitsu, T.; Fenteany, G. *Tetrahedron* **1999**, *55*, 3305−3316 and references therein.

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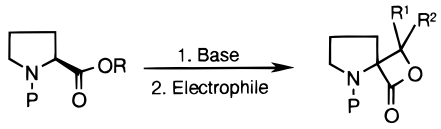
1-oxo-2-oxa-5-azaspiro[3.4]octane system in both racemic and optically active forms.

Racemic Route. Tandem Aldol-Lactonization. Tandem aldol−lactonization reactions have been reported on acyclic enolate precursors,[9] and we envisioned producing the spiro-fused ring systems **11**−**14** by reaction between a suitable *N*-protected activated ester of proline and a carbonyl compound. The initial study was carried out on *N*-carbobenzyloxy and *N*-*tert*-butoxycarbonyl L-proline esters **4**−**10**. The results of this investigation are summarized in Table 1.

Table 1. Tandem Aldol−Lactonization Using *N*-Alkoxycarbonyl Proline Esters[a]



4 : P=Cbz, R=PfP
5 : P=Boc, R=PfP
6 : P=Boc, R=Ph
7 : P=Boc, R=SPy
8 : P=Boc, R=Succ
9 : P=Boc, R=Bu^t
10 : P=Boc, R=Me

11 : P=Cbz, R^1=R^2=Me
12 : P=Cbz, R^1=Ph, R^2=H
13 : P=Boc, R^1=R^2=Me
14 : P=Boc, R^1=Ph, R^2=H

substr	base	conditions[b]	electrophile	product	yield (%)
4	LDA	−90 °C, THF	Me_2CO	**11**	9
4	LDA	−90 °C, THF	PhCHO	**12**	30 (8:7)[c]
4	LDA[d]	−78 °C, THF	PhCHO	**12**	no prod.
4	NaH[e]	−78 °C, DMF	PhCHO	**12**	16 (3:1)[c]
5	LDA	−90 °C, THF	Me_2CO	**13**	9, 19[f]
5	LHMDS	−78 °C, THF	Me_2CO	**13**	11
5	LICA	−90 °C, THF	Me_2CO	**13**	9
5	TMPLi	−78 °C, THF	PhCHO	**14**	20[g]
6	LDA	−78 °C, THF	Me_2CO	**13**	34
7	LDA	−78 °C, THF	Me_2CO	**13**	9
8	LDA	−78 °C, THF	Me_2CO	**13**	traces
9	LDA	−78 °C, THF	Me_2CO	**13**	decomp.
10	LDA	−78 °C, THF	Me_2CO	**13**	no prod.

[a] All reactions were carried out on a 1 mmol scale using 1.1 mmol of base unless otherwise noted. [b] Temperatures for deprotonation and addition of the electrophile. [c] Ratio of isolated diastereomers. [d] 2.2 equiv of LDA was used. [e] 2 equiv of NaH was used. [f] Yield obtained when reaction was carried out on a 4 mmol scale. [g] Only one diastereomer could be detected by ^{1}H NMR spectroscopy. Abbreviations: PfP = pentafluorophenyl, Succ = succinimide.

Deprotonation of the *N*-Cbz pentafluorophenyl ester **4** with lithium diisopropylamide (LDA) at −90 °C followed by trapping with acetone gave the spiro β-lactone **11**, albeit in extremely low yield. This system was characterized by the typical 1824 cm^{-1} carbonyl stretching frequency of β-lactones and a ^{13}C NMR δ_{CO} of 170 ppm. The corresponding reaction using benzaldehyde gave β-lactone **12** in 30% yield as a mixture of diastereomers. The *N*-Boc proline **5** gave the β-lactone **13** on treatment with LDA and acetone; an X-ray crystallographic analysis of a single crystal confirmed the structure of **13** (see Figure 1).[10]

(9) See for example: Wedler, C.; Kunath, A.; Schick, H. *J. Org. Chem.* **1995**, *60*, 758−760.

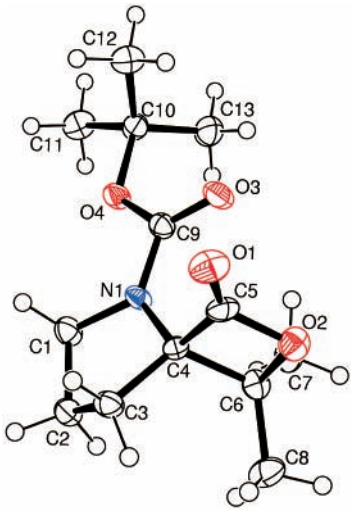
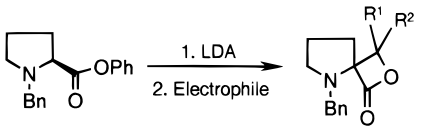


Figure 1. ORTEP drawing of **13** (50% probability thermal ellipsoids).

An extensive study of the conditions of the reaction using the PfP esters **4** and **5** was carried out but offered no significant improvements of yield. Addition of LDA to the ester and generally poor starting material recovery prompted us to investigate the use of less reactive esters and different bases. As shown in Table 1, the phenyl ester **6** in combination with LDA was clearly the best but still afforded no major improvement.

We then turned our attention from alkoxycarbonyl to alkyl *N*-protecting groups. The results using *N*-benzyl proline phenyl ester (**15**) are shown in Table 2.

Table 2. Tandem Aldol−Lactonization Using *N*-Benzyl Phenyl Proline Ester[a]



15

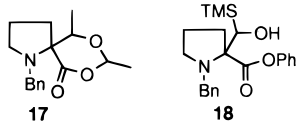
16 : R^1=R^2=Me

	electrophile		reaction	
entry	R^1	R^2	time (h)	yield (%)
1	Me	Me	0.25	62, **16**
2	H	Me	2	33, **17**[b]
3	H	TMS	2	65, **18**
4	TMS	TMS	2	no product

[a] The reactions were performed at −78 °C in THF using 1.1 equiv of LDA. [b] 39% of starting material **15** was recovered.

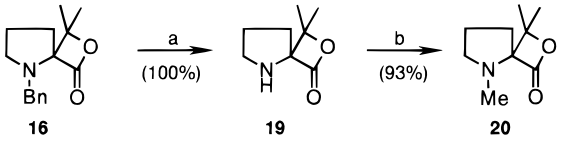
The enolate of *N*-benzyl proline phenyl ester **15** reacted rapidly at −78 °C with acetone to afford the β-lactone **16** in a gratifying 62% yield. In a attempt to prepare a methyl-substituted β-lactone (as found in **2**), we utilized ethanal as the electrophile and only isolated **17** (33% yield). The fact

that the β-lactone formation was observed with acetone but not with ethanal suggested the importance of the Thorpe−Ingold effect.[11] In an attempt to exploit this observation, reaction with trimethylsilylformaldehyde[12] was carried out but gave exclusively the uncyclized product **18** in 65% yield. Bis(trimethylsilyl)ketone[13] was also prepared and utilized in this process, but no adduct was obtained.[14]



Compound **16** could be easily converted into 1,1-dimethyl-3-oxo-2-oxa-5-azaspiro[3.4]octane **19** as a stable white powder using H_2, 10% Pd/C. *N*-Methylation was successfully carried out using methyl iodide and potassium carbonate in dry DMF to give **20** (Scheme 1).

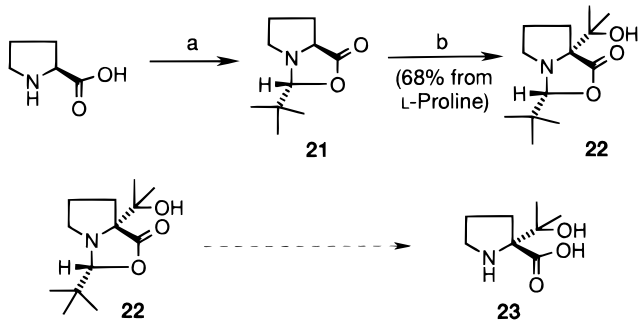
Scheme 1[a]



[a] (a) H_2, Pd/C 10%, EtOAc; (b) MeI, K_2CO_3, DMF.

Enantioselective Route. Sequential Trapping−Lactonization. Having designed the first synthesis of the 1-oxo-2-oxa-5-azaspiro[3.4]octane system in racemic form, we next investigated an enantioselective route. The method of choice utilized the "self-reproduction of chirality" concept introduced by Seebach et al. for the asymmetric alkylation of proline derivatives (Scheme 2).[15] Our early studies focused

Scheme 2[a]

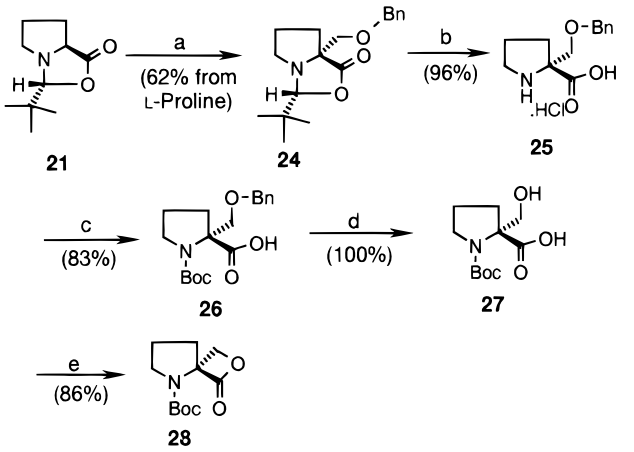


[a] (a) Pivalaldehyde, TFA, pentane, reflux; (b) (i) LDA, THF, −78 °C, (ii) acetone, −78 °C to rt.

on the use of acetone as trapping agent, which would lead to an unprotected tertiary alcohol **22**. We hoped this alcohol would later undergo efficient cyclization owing to the *gem*-dialkyl effect. The trapping was successful, but, disappointingly, all attempts to hydrolyze **22** failed, even under the harshest conditions (48% HBr, reflux).

Assuming that the presence of a quaternary center was responsible for this hydrolytic stability, we turned to benzyloxymethyl chloride (BOMCl) as a highly reactive and easily available alkylating agent. Alkylation of **21** yielded a single diastereomer (as judged by ^{1}H NMR spectroscopy) which underwent smooth hydrolysis (3 M HCl) to give the α-alkylated amino acid **25** in 59% yield from L-proline (Scheme 3). Boc protection using Johnson's conditions[16] and

Scheme 3[a]



[a] (a) (i) LDA, THF, −78 °C, (ii) BOMCl, −78 °C to rt; (b) 3 M HCl, reflux; (c) BOC_2O, $Me_4NOH{\cdot}5H_2O$, CH_3CN; (d) H_2, 10% Pd/C, MeOH; (e) DMAD, PPh_3, THF, −78 °C.

quantitative debenzylation (H_2, Pd/C) afforded the alcohol **27**, ready for lactonization, in 83% yield. Cyclization of the Boc derivative was attempted using Vederas' chemistry.[17] Hydroxyl group activation using modified Mitsunobu conditions [dimethyl azodicarboxylate (DMAD)/PPh_3] afforded the *N*-Boc (4*S*) 1-oxo-2-oxa-5-azaspiro[3.4]octane **28** in a modest 31% yield (54% based on recovered starting material). Use of a larger excess of PPh_3 (1.3 equiv) and DMAD (1.35 equiv) gave total conversion in 10 min at −78 °C and afforded **28** in 86% yield.

(10) Crystallographic data for **13** can be obtained on request from the Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

(11) For an earlier account on the *gem*-substitution effect on β-lactone formation, see: Adam, W.; Encarnación, L. A. A. *Chem Ber.* **1982**, *115*, 2592−2605. See also: Jung, M. E. *Synlett* **1999**, *S1*, 843−846 and references therein.

(12) Linderman, R. J.; Suhr, Y. *J. Org. Chem.* **1988**, *53*, 1569−1572.

(13) Pan, M.; Benneche, T. *Synth. Commun.* **1998**, 1415−1419.

(14) Reaction of *N*-benzyl proline methyl ester with acetone was then carried out to check the importance of the activated ester in this reaction. It gave the alkylated uncyclised product in 70% yield.

(15) Seebach, D.; Boes, M.; Naef, R.; Schweiser, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390−5398.

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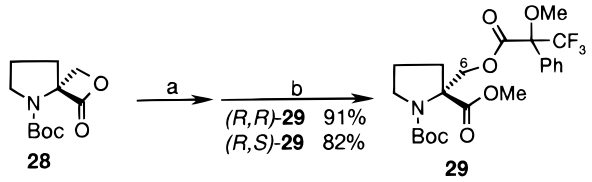
(17) (a) Pansare, S. V.; Huyer, G.; Arnold, L. D.; Vederas, J. C. *Org. Synth.* **1991**, *70*, 1−9. (b) Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105−7109.

The enantiomeric excess of **28** was determined by regioselective ring opening of the β-lactone with sodium methoxide and esterification with (*R*)- and (*S*)-2-methoxy-2-(trifluoromethyl)phenylacetate (MTPA), to give (*R*,*R*)-**29** and *(R,S)*-**29**, respectively (Scheme 4).[18] Determination of

Scheme 4[a]



[a] (a) MeONa, MeOH; (b) (*R*)- or (*S*)-MTPA, DCC, DMAP, DCM.

the diastereomeric excess was accomplished by comparing selected ^{1}H and ^{19}F NMR data of (*R*,*R*)-**29** and (*R*,*S*)-**29**. The method of choice was ^{1}H NMR spectroscopy using the H_6-methylene AB system (δ 4.57 and 4.92 for (*R*,*R*)-**29**, δ 4.60 and 4.87 for (*R*,*S*)-**29**). Both diastereomers could be detected in both spectra in a ratio $\geq$ 95:5 (i.e., ee $\geq$ 90%).

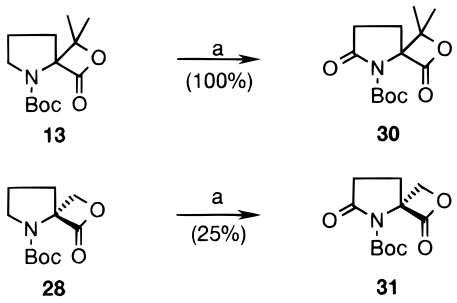
Syntheses of Spiro β-Lactone γ-Lactam. Following the successful preparation of the *N*-protected 1-oxo-2-oxa-5-azaspiro[3.4]octane, attempts were made to functionalize it and complete the first synthesis of a spiro-fused β-lactone γ-lactam. Using Sharpless methodology,[19] oxidation of the dimethyl β-lactone **13** occurred smoothly to afford a quantitative yield of analytically pure **30** (Scheme 5).

Oxidation of **28**, which bears no substituent on the

(18) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549.

(19) Carlsen, P. H. G.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

Scheme 5[a]



[a] (a) $RuCl_3 \cdot xH_2O$, $NaIO_4$, $CH_3CN/CCl_4/H_2O$ 1:1:1.5, rt.

β-carbon of the β-lactone, afforded the γ-lactam **31** in a more modest yield, due to decomposition.

In summary, we have demonstrated that the 1-oxo-2-oxa-5-azaspiro[3.4]octane ring system can be synthesized using either tandem aldol−lactonization methodology or β-hydroxy acid ring closure. Ruthenium tetroxide oxidation afforded, for the first time, spiro β-lactone γ-lactam systems. Investigations are underway to utilize this methodology for the synthesis of oxazolomycin and related compounds.

Acknowledgment. We thank Pharmacia and Upjohn for financial support and Drs. Eric Desarbre and Roger Crossley for their advice and encouragement. Dr. Steve Archibald is gratefully acknowledged for assistance with X-ray crystallography.

Supporting Information Available: Experimental procedures and analytical data for compounds **13**, **16**, **19**, **20**, **28**, **30**, and **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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