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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NEW TROPONE-SUBSTITUTED PHENYLOXAZOLIDINONE ANTIBACTERIAL AGENTS. 1. IDENTIFICATION OF LEADS AND IMPORTANCE OF THE TROPONE SUBSTITUTION PATTERN.

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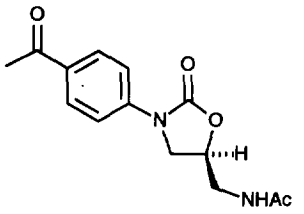
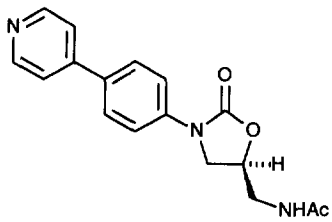
Abstract: Incorporation of a substituted tropone moiety into the *para* position of suitably functionalized 3-phenyl-2-oxazolidinones affords novel and potent antibacterial agents. The effect of the tropone regioisomer and its attendant substituents on antibacterial activity is discussed. Analogues such as **11c** and **13b** display *in vitro* and *in vivo* activity approaching that of the current clinical benchmark, vancomycin.

The incidence of infections caused by gram-positive bacteria broadly resistant to current treatment regimens is increasing at an alarming rate.[1] Especially problematic organisms include vancomycin-resistant enterococci (VRE),[2] methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE),[3] and penicillin-resistant streptococci.[4]

The oxazolidinones, exemplified by DuP 721 (**1**), are a relatively new class of orally active, totally synthetic antibacterial agents discovered by workers at DuPont.[5] Their spectrum of activity encompasses gram-positive aerobic bacteria (including MRSA),[6] gram-negative anaerobes, and *Mycobacterium tuberculosis*.[7] Preliminary inquiries into the mechanism of action of the oxazolidinones have revealed that they are bacterial protein synthesis inhibitors, with inhibition uniquely occurring at an early event in the initiation phase of protein synthesis.[8] DuP 721 was entered into Phase I clinical trials. However, development of this agent was subsequently discontinued.[9] In drug safety studies conducted at The Upjohn Company, it was shown that (±)-DuP 721 exhibited lethal toxicity in rats when dosed orally at 100 mg/kg b.i.d. for 30 days.[10] Further investigations into the structure–activity relationships of the oxazolidinones by workers at DuPont led to the discovery of more potent biaryl analogues such as E3709 (**2**),[11] but apparently there has been no clinical development of these compounds.

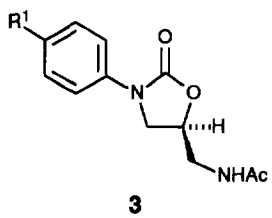


1



2

In contemplating new oxazolidinone targets, we wondered whether hybrid analogues of **1** and **2** might have utility. Conceptually, we were attracted to cyclic vinylogous carbonyl systems, for example the tropone moiety, as potential surrogates for the acetyl appendage of **1** and/or the pyridyl moiety of **2**. Integration of such a substituted tropone into a hypothetical oxazolidinone analogue would give rise to, for example, compounds of generic structure **3**. We further speculated that variation of the tropone R^2 substituent might allow for optimization of the antibacterial activity and physicochemical properties of **3**. In this paper we describe the synthesis and antibacterial activity of a preliminary series of tropone-substituted phenyloxazolidinones **3**.[12]



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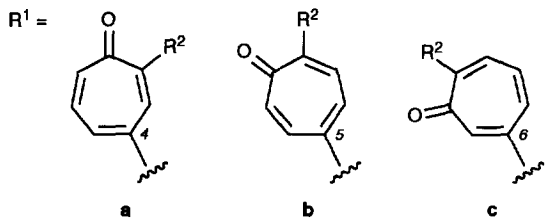


(R² = alkoxy, amino)

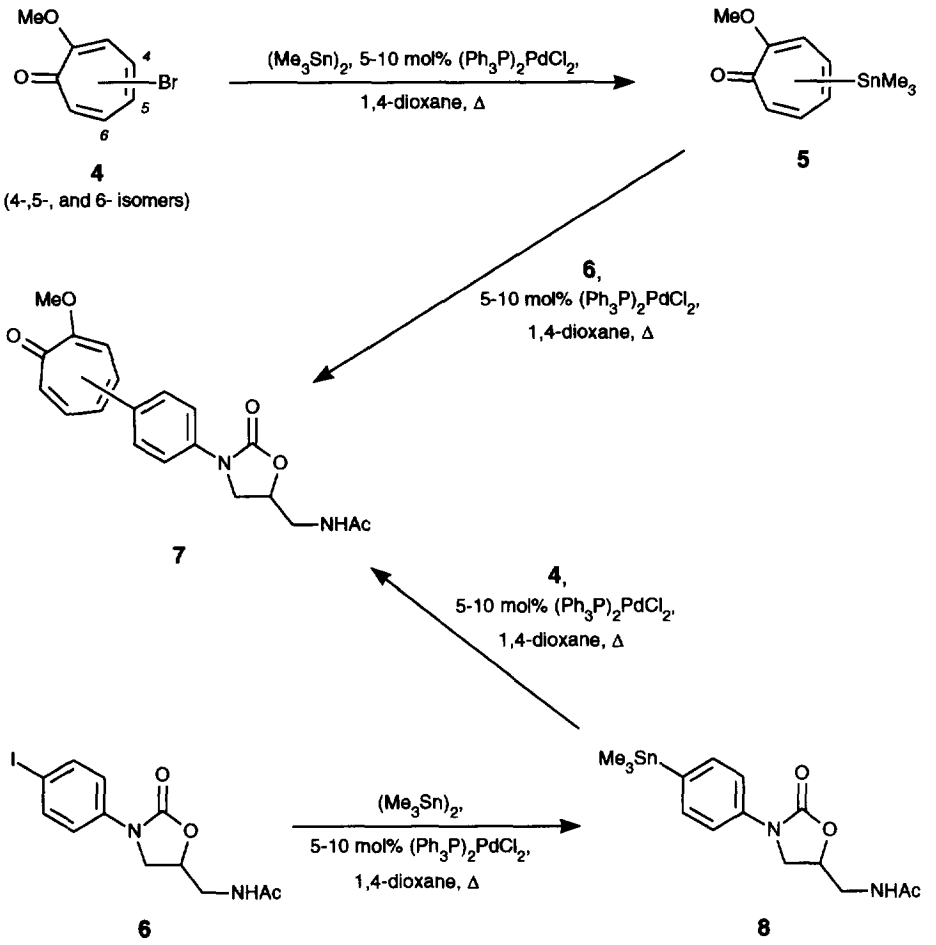
Chemistry

At the outset, we felt that the preparation of racemic examples of **3** would be satisfactory to probe the utility of the conceived compounds. A subsequent synthetic effort was envisioned to address preparation of the antibacterially active (*S*)-enantiomers,[5] provided that the activity of the preliminary series of racemic analogues warranted it. Convergent synthetic routes for the preparation of racemic tropone-substituted phenyloxazolidinones are shown in Scheme 1. The requisite bromomethoxytropones **4**[13] were converted to the previously unknown tin derivatives **5**[14] in 75–86% isolated yields, employing a palladium-catalyzed coupling reaction with hexamethylditin.[15] A Stille coupling[16] of **5** with (±)-3-(4-iodophenyl)-2-oxazolidinone **6**[17] then provided the targeted methoxy-substituted troponylphenyloxazolidinones **7** in excellent yield (84–94%). In an alternative process, the iodophenyloxazolidinone **6** was first elaborated to the trimethyltin compound **8**. Intermediate **8** was then coupled with **4** under palladium-mediated conditions to generate **7** in high yield (80–85%).

It was our expectation that the 2-methoxytropone moiety of compounds **7** would be readily amenable to nucleophilic substitution reactions. We were gratified to observe that a wide range of alternative alkoxy and

amino substituents could be incorporated into the 2-position of the tropone appendage (see Scheme 2). Yields for the alkoxy exchange reactions were in the 82–96% range and for the amine displacements yields of 84–100% were realized.

Scheme 1

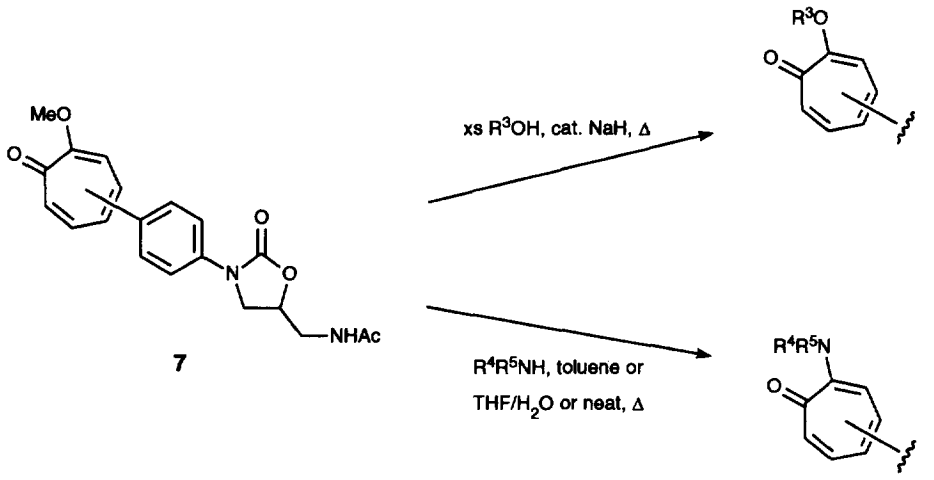


Biological Evaluation and Discussion

The regioisomeric tropone-substituted oxazolidinones were submitted for a preliminary evaluation of their antibacterial activity. The *in vitro* activity of oxazolidinone analogues was assessed by determination of minimum inhibitory concentration (MIC) values, utilizing standard agar dilution methods, and *via* a cell-free prokaryotic transcription coupled translation (T/T) assay, employing S-30 *Escherichia coli* extracts. In the latter test system, expression of plasmid encoded *lacZ* yields the functional reporter enzyme (β-galactosidase). *In vivo*

efficacy was evaluated by effective dose$_{50}$ (ED_{50}) determinations, using a standard lethal-systemic *S. aureus* infection model in mice.

Scheme 2



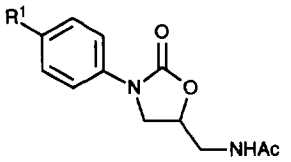
As shown in Table 1, selected examples demonstrated potent *in vitro* activity against gram-positive aerobic bacteria, including the enterococci, streptococci, methicillin-susceptible and resistant staphylococci, and *M. tuberculosis*. The level of *in vitro* antibacterial activity seen for the more active racemic troponylphenyloxazolidinones compares favorably with that of (±)-DuP 721 and vancomycin. A comparison of compounds **7a–c** reveals that the tropone regioisomer has a profound effect on the activity of these oxazolidinone analogues. Compounds **7b** and **7c** displayed approximately equivalent activity. However, regioisomer **7a** was 16–32 times less active than its regioisomeric congeners. The relative equivalency of regioisomers **b** and **c** was also apparent for the allylamine adducts **9**. In general, the intrinsic activity of the oxazolidinones described herein, as measured by the cell-free T/T assay, roughly correlated (*cf.* **7a–c**) with the MICs observed in whole-cell systems.

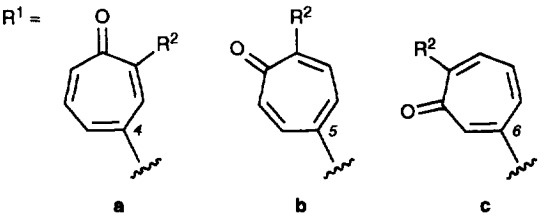
The *in vivo* activity of selected troponylphenyloxazolidinones is depicted in Table 2. The *in vivo* efficacy results for the regioisomeric series **a–c** parallelled the *in vitro* activity trends (*cf.* ED_{50}s of **7a–b** and **9b–c**). That is, regioisomers **b** and **c** were equally efficacious and significantly more active than regioisomer **a**. Analogues such as **10b**, **11c**, and **13b** all demonstrate *in vivo* activity greater than that of (±)-DuP 721 (**1**, ED_{50} = 9.4 mg/kg). Compounds **11c** and **13b** display *in vivo* efficacy approaching that of the clinical benchmark, vancomycin. Consideration of the racemic nature of the tropone-substituted oxazolidinones described herein, and the fact that only the (*S*)-enantiomer possesses antibacterial activity,[5] suggests that the preparation of enantiomerically enriched versions of these oxazolidinones would be of interest.

On the basis of their potent *in vitro* and *in vivo* activity, tropone-substituted phenyloxazolidinones have

potential as therapeutic antibacterial agents. Further studies probing the structure–activity relationships of these compounds and the development of general procedures for their enantioselective synthesis will be presented in due course.

Table 1. *In Vitro* Activity of Selected Racemic Tropone-Substituted Phenyloxazolidinones





Compound	R^2	MIC (μg/mL)[1]						T/T (%)[2]
		S.a.-1	*S.a.*-2	*S.e.*	*E.f.*	*S.p.*	*M.tb.*	
7a	MeO	64	16	8	32	4	(≤16)	39
7b	MeO	2	1	0.5	1	0.25	(≤1)	89
7c	MeO	4	2	0.5	2	0.5	(≤1)	90
9b	allylamino	2	1	0.5	1	0.5	--	81
9c	allylamino	2	1	0.5	1	0.5	--	80
10b	allyloxy	4	1	0.5	2	0.25	--	74
11c	propargylamino	2	1	1	1	0.5	(≤1)	76
12b	4-morpholinyl	2	2	0.5	1	0.5	(≤1)	81
13b	MeNH	2	1	0.25	1	0.25	--	--
(±)-DuP 721	--	8	4	2	8	2	(≤16)	45
vancomycin	--	1	1	2	4	0.5	--	--

[1]Minimum inhibitory concentration: lowest concentration of drug (μg/mL) that inhibits visible growth of the organism. [2]Transcription/translation assay; results reported as % inhibition, compound concentration of 2 μg/mL. *S.a.*-1, *Staphylococcus aureus* UC®9213 (methicillin-susceptible); *S.a.*-2, *S. aureus* UC®6685 (methicillin-resistant); *S.e.*, *Staphylococcus epidermidis* UC®12084 (methicillin-resistant); *E.f.*, *Enterococcus faecalis* UC®9217; *S.p.*, *Streptococcus pneumoniae* UC®9912; *M.tb.*, *Mycobacterium tuberculosis* H37Rv.

Table 2. *In Vivo* Activity of Selected Racemic Tropone-Substituted Phenyloxazolidinones

ED_{50} (mg/kg),[1] *Staphylococcus aureus* UC®9213						
7a	**7b**	**9b**	**9c**	**10b**	**11c**	**13b**
>20 (3.1)	12.2 (1.8)	12.7 (2.3)	12.5 (0.6)	7.9 (2.2)	3.4 (2.5)	4.6 (2.2)

[1]Effective $dose_{50}$: amount of drug required (mg/kg body weight/dose) to cure 50% of infected mice subjected to a lethal systemic infection; oxazolidinones administered orally; vancomycin ED_{50} (subcutaneous administration) in parentheses.

Acknowledgment

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