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Preliminary communication

Cyclopentanone ring-cleaved pleuromutilin derivatives

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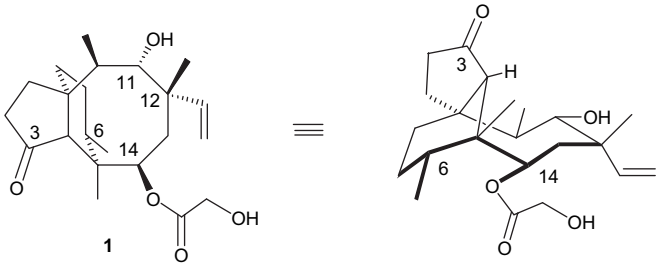
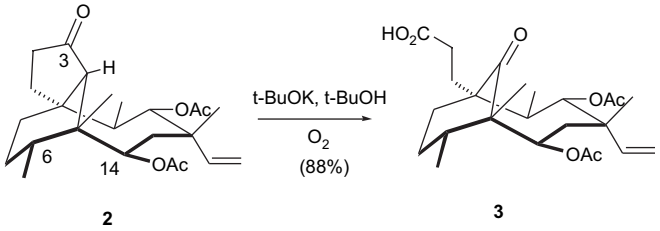
Abstract

Ring-cleaved pleuromutilin derivatives comprised of a [5.3.1] bicyclic core structure have been synthesized and evaluated in vitro as antibacterial agents. Four of the compounds described were found to have MICs ≤ 4 μg/mL against marker strains of *Streptococcus pneumoniae* and *Staphylococcus aureus*.



As part of our program to discover a pleuromutilin (**1**) derivative for use in human antibacterial therapy, we wished to synthesize compounds containing novel core structures [1,2]. One of our approaches took advantage of chemistry developed by Birch during structural studies of the antibiotic [4]. Birch observed that autoxidation of diacetoxymutilin (**2**) using potassium *t*-butoxide in *t*-butanol afforded the ring-cleaved ketoacid **3** in good yield.



We decided to reproduce this ring-cleavage chemistry on a more suitably functionalized C-14 glycolic ester derivative, to more rapidly access biologically active pleuromutilin analogues containing acyl groups at C-14 [5]. Our first attempt utilized the bis-methoxy ethyl (MOM) ether **4** as the starting material. Unfortunately, compound **4** was substantially degraded upon exposure to the autoxidation conditions successfully applied in the conversion of **2** to **3**. We surmised

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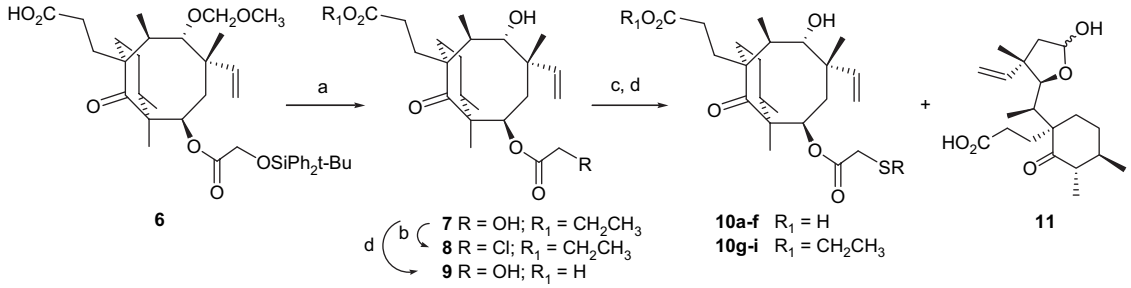
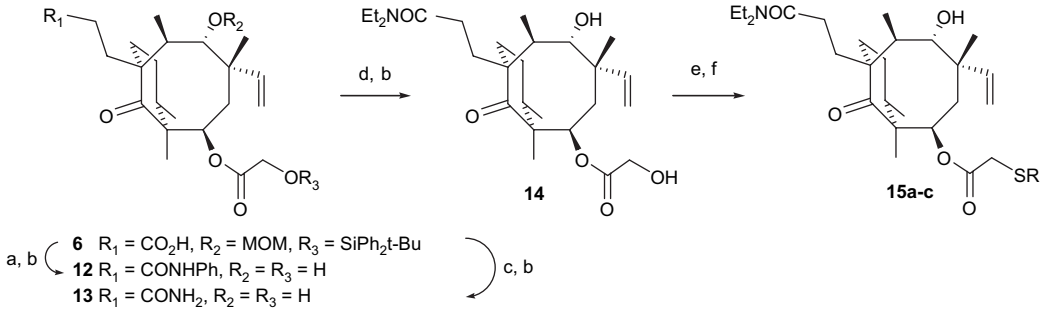
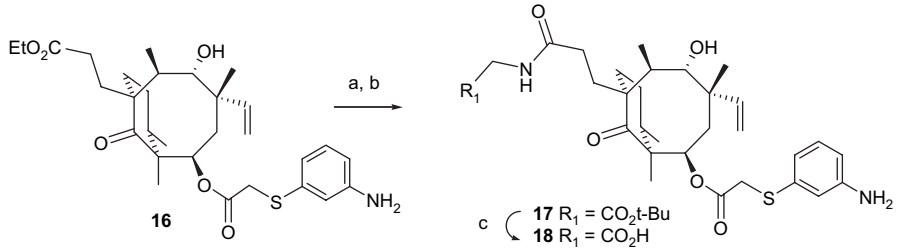


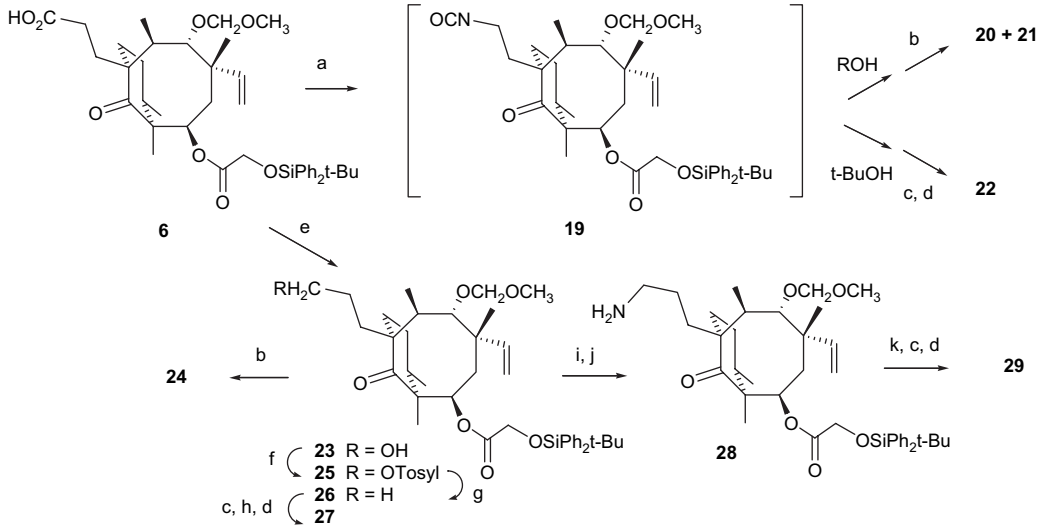
Scheme 1. Reaction conditions: (a) AcCl, EtOH, 20 h rt; (b) MsCl, LiCl, pyr; (c) NaSR, DMF; (d) 1 N NaOH, EtOH, THF rt.



Scheme 2. Reaction conditions: (a) $PhNH_2$, DCC, HOBt, Et_3N, DMF, CH_3CN; (b) AcCl, MeOH, 20 h rt; (c) BOC_2O, NH_4HCO_3, dioxane, pyr; (d) EDC, Et_2NH, CH_2Cl_2; (e) TsCl, pyr; (f) NaSR, DMF (or 2,6-dimethyl-4-mercaptopyridine, MeOH).

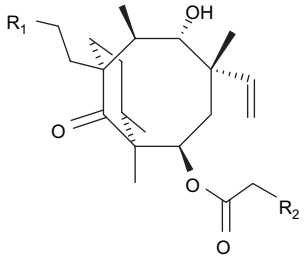


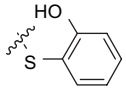
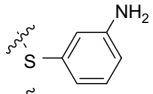
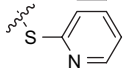
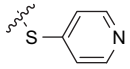
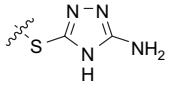
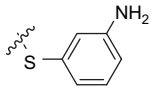
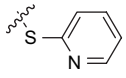
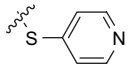
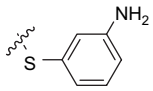
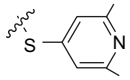
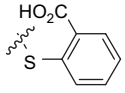
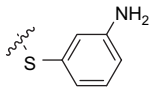
Scheme 3. Reaction conditions: (a) 1 N NaOH, EtOH, THF rt.; (b) *t*-butylglycine hydrochloride, DCC, CH_2Cl_2, Et_3N; (c) TFA, CH_2Cl_2.



Scheme 4. Reaction conditions: (a) DPPA, Et_3N, toluene; (b) AcCl, EtOH, $CHCl_3$; (c) TBAF, THF; (d) TFA, CH_2Cl_2; (e) BH_3, DMS; (f) TsCl, Et_3N; (g) $NaBH_4$, DMF; (h) i) TsCl, Et_3N; ii) sodium 3-amino-benzenethiolate, DMF; (i) NaN_3, DMF; (j) Ph_3P, THF, H_2O; (k) isoxazole-5-carbonyl chloride, Et_3N.

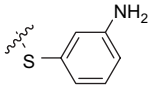
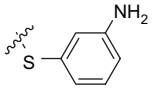
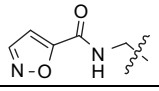
Table 1



Compound	R_1	R_2	MIC (μg/mL)[a]	
			S. pneumoniae	*S. aureus*
1	Pleuromutilin		0.5	0.5
9	CO_2H	OH	8	8
10a	CO_2H	SPh	>64	>128
10b	CO_2H		4	8
10c	CO_2H		0.125	0.25
10d	CO_2H		8	8
10e	CO_2H		64	128
10f	CO_2H		>64	>128
10g	$CO_2CH_2CH_3$		1	1
10h	$CO_2CH_2CH_3$		1	1
10i	$CO_2CH_2CH_3$		8	8
12	CO_2NHPh	OH	>64	>128
13	$CONH_2$	OH	64	128
14	$CON(CH_2CH_3)_2$	OH	>64	>128
15a	$CON(CH_2CH_3)_2$		4	32
15b	$CON(CH_2CH_3)_2$		4	32
15c	$CON(CH_2CH_3)_2$		4	32
17	$CONHCH_2COOt$-Bu		0.5	4

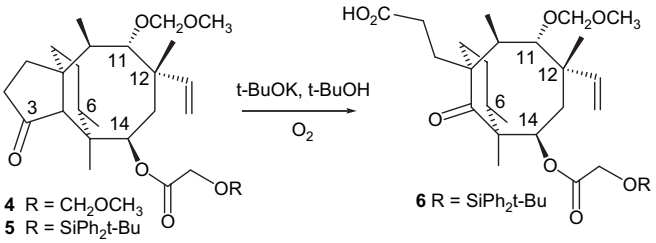
(*continued on next page*)

Table 1 (*continued*)

Compound	R_1	R_2	MIC (μg/mL)[a]	
			S. pneumoniae	*S. aureus*
18	$CONHCH_2CO_2H$		2	8
20	$NHCO_2CH_2Ph$	OH	0.25	16
21	$NHCO_2CH_2CH_3$	OH	0.25	16
22	NH_2	OH	>64	>128
24	CH_2OH	OH	>64	>128
27	CH_3		8	16
29		OH	2	32

[a] MICs were determined according to NCCLS. Strains reported: *Streptococcus pneumoniae* A9585 and *Staphylococcus aureus* A15090, for details, see Ref. [6].

that the decomposition of **4** was related to the presence of the glycolic ester group, since the cleavage performed well with diacetoxymutilin **2** and the corresponding bis-MOM mutilin. We decided to block the C-14 glycol hydroxyl with a bulky protecting group, with the hope to sterically shield this site from undesired reactivity. The *t*-butyldiphenylsilyl group served well in this regard; silyl ether **5** proved to be an excellent substrate for the oxidative cleavage reaction affording acid **6** in 57–70% yield.



With quick access to intermediate **6** we could begin to synthesize derivatives of the glycolate which was previously the C-14 site of the parent ring system. Acid-catalyzed ethanolysis of **6** served to deprotect both the MOM- and silyl-protected alcohols, and simultaneously protects the acid group as an ester (Scheme 1). Ester **7** could be converted to chloroacetate **8**, the precursor to sulfide derivatives **10a–i** via displacement with thiolates, followed by optional hydrolysis of the ethyl ester. The hydrolysis step is capricious in this ring system due to the presence of the keto group in the cyclooctane ring. The use of a slight excess of hydroxide, or longer reaction times, generally favored increased amounts of a by-product assigned structure **11**. Acid **11** is formed by hydrolysis of the thioglycolate, and retro–aldol cleavage of the cyclooctane ring. The nascent aldehyde function is then trapped by the free hydroxyl to render the lactol. Improved yields of the desired targets were obtained when the amount of hydroxide was limited to an equivalent, and the reaction monitored for its completion. The same care had to be exercised in the hydrolysis of ester **7** to yield acid **9**.

Acid **6** could be converted to amides such as **12** and **14** using standard coupling agents followed by acidic methanolysis of the hydroxyl protecting groups (Scheme 2). Amide **13** was obtained via mixed anhydride chemistry and deprotection. Thioglycolate derivatives **15a–c** were synthesized from amide **14** via tosylation and thiolate displacement. Ester **16** (made from thiolate displacement of chloroacetate **8**) was hydrolyzed to the corresponding acid and then converted to glycinamide **17** (Scheme 3). Trifluoroacetic acid cleaved the *t*-butyl group of **17** to afford the free acid derivative **18**.

Acid **6** served as the precursor to carbamates **20** and **21** via intermediate isocyanate **19** (Scheme 4). Amine **22** was obtained by trapping **19** with *t*-butanol, followed by desilylation and removal of the BOC and MOM groups with TFA. The carboxyl group of **6** could be reduced to afford alcohol **23** which was deprotected to yield triol **24**. Alcohol **23** was also converted to derivative **27** by reduction of the tosylate **25** followed by desilylation, thiolate displacement, and final MOM cleavage. Tosylate **25** was converted via azide displacement and subsequent reduction to amine **28**. The amine was readily acylated, and the intermediates deprotected to produce derivatives such as **29**.

We observed that structure–activity relationships in the native pleuromutilin series did not always track with the SAR of the ring-cleaved series of compounds presented in Table 1. For example, the thioaryl derivatives **10a–e** have widely ranging activity. However, these thioaryl groups, when used as replacements for the hydroxyl group of pleuromutilin in the natural core system, produced very potent compounds of similar activity. While the activity of any specific compound was difficult to predict using knowledge of pleuromutilin SAR, certain trends within this new class of derivatives could be gleaned from the data in Table 1. Carbamates such as **20** and **21** were more active than amides such as **14**. Esters (represented by **10g–i**) were generally more active than amides, but less potent than the carbamates.

While these compounds were less potent than derivatives of the natural ring system, some compounds possessed surprising activity. Derivatives such as **10c**, **10g–h**, **17**, **20**, and **21** may serve as interesting leads in continuing efforts to develop an antibacterial agent from the pleuromutilin class. Recent advances in understanding the nature of the pleuromutilin

ribosomal binding site [7] may one day be used to rationalize the activity of the compounds reported here [8].

Acknowledgements

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References

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[2] D.M. Springer, M. Sorenson, S. Huang, T.P. Connolly, J.J. Bronson, J.A. Matson, R.L. Hanson, D.B. Brozozowski, T.L. LaPorte, R.N. Patel, Bioorg. Med. Chem. Lett. 13 (2003) 1751.
[4] A.J. Birch, C.W. Holzapfel, R.W. Rickards, Tetrahedron(Suppl. 8, Part II) (1966) 359–387.
[5] Pleuromutilin structure–activity relationships clearly indicate that C-14 acyl derivatives are very active antibacterial agents. The compound (mutilin) derived from basic hydrolysis of pleuromutilin, containing free alcohols at C-14 and C-11, is inactive as an antibacterial agent.
[6] Antibacterial MICs were determined by the microbroth dilution method according to the standard conditions recommended by the National Committee for Clinical Laboratory Standards (NCCLS). MIC assays utilized Mueller–Hinton broth for *S. aureus* and 50% Mueller–Hinton medium plus 50% Todd Hewitt medium for *S. pneumoniae*, a bacterial inoculum of $\sim 5 \times 10^5$ CFU/mL, and were incubated at 35 °C for 24 h. The MIC was defined as the lowest drug concentration that inhibited all visible bacterial growth.
[7] (a) F. Schlunzen, E. Pyetan, P. Fucini, A. Yonath, J.M. Harms, Mol. Microbiol. 54 (2004) 1287–1294;
(b) M. Pringle, J. Poehlsgaard, B. Vester, K.S. Long, Mol. Microbiol. 54 (2004) 1295–1306.
[8] Note added in proof: Reviewers of this manuscript have suggested that it would be useful to assay these compounds in a protein synthesis inhibition assay. Data from such experiments would be of interest in determining the mechanism of antibacterial action of these derivatives. However, these data were not collected on the pleuromutilin derivatives reported here, and it is not possible for us to obtain them in the near future since the antibacterial efforts at Bristol–Myers Squibb have been suspended.