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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 4- AND 8-METHOXY TRINEMS

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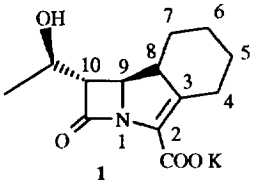
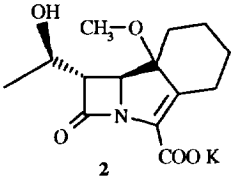
Abstract. The synthesis of all the isomers of 8-methoxy-(9*S*,10*S*,12*R*)-10-(1-hydroxyethyl)-11-oxo-1-azatricyclo-[7.2.0.0^{3,8}]-undec-2-ene-carboxylates **2** and 4-methoxy-(9*R*,10*S*,12*R*)-10-(1-hydroxyethyl)-11-oxo-1-azatricyclo-[7.2.0.0^{3,8}]-undec-2-ene-carboxylates **3** is described. The biological data obtained indicated that the (4*S*,8*S*)-4-methoxy derivative (**3b**) is the best compound in terms of microbiological activity, breadth of spectrum of action and stability to hydrolytic enzymes, namely β-lactamases.

The β-lactams constitute a very important class of antibacterial agents which encompass penicillins, cephalosporins, monobactams, carbacephalosporins, penems and carbapenems. Their potent biological activity and superior safety profile have ensured their dominant position in antibacterial chemotherapy. However, now more than ever, the number of clinically isolated resistant strains is increasing thus producing a need for new antibacterial compounds which are effective against such strains. In our search for a new class of antibacterial agents, tricyclic β-lactams **1** (*Trinems* formerly known as *Tribactams*) were proposed as potential targets for our studies.[1]



1



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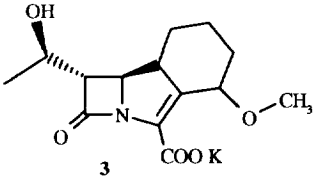
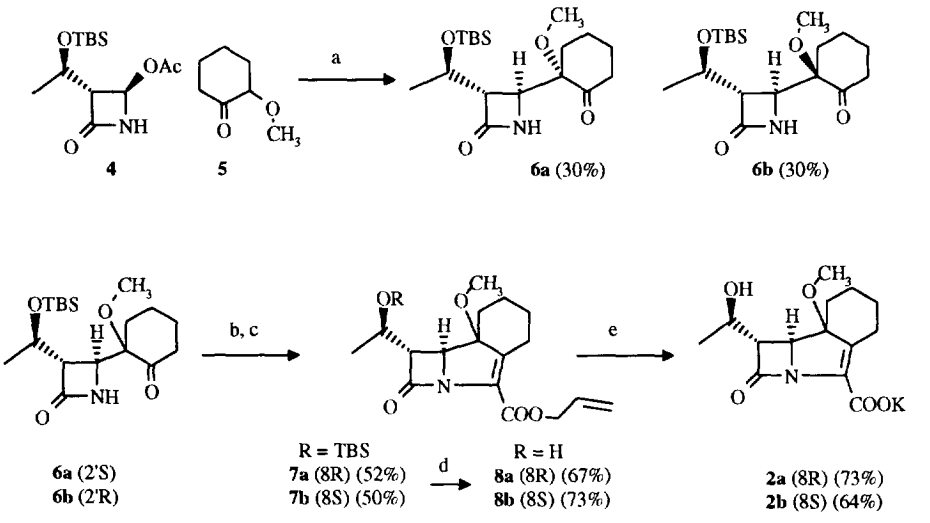


3

The potency and breadth of spectrum of action shown by the first examples synthesized, together with the novelty of the structure, prompted us to undertake further exploration of the class in order to evaluate its full potential. Some derivatives of **1**, with substituents at the allylic positions C-4 or C-8 were designed and, among them, the methoxy derivatives **2** and **3** were considered compounds of interest and the synthesis of all the possible isomers was undertaken.

When the commercially available azetidinone **4**[2] was reacted with the lithium enolate of 2-methoxycyclohexanone **5** (generated from lithium bis(trimethylsilyl) amide in anhydrous THF at 0°C) a 1:1 mixture of azetidinones **6a** and **6b** was obtained in 60% overall yield (Scheme 1). These intermediates could not be easily separated by flash chromatography. However, their conversion to fully protected compounds **7a** and **7b**, as indicated in Scheme 1 (acylation with allyl oxalyl chloride and triethylamine followed by refluxing the resulting oxalimide in anhydrous xylene in the presence of an excess of triethyl phosphite),[3] allowed us to separate them. These compounds were transformed into our target compounds **2a** and **2b**. The silyl protecting group of **7a** and **7b**, was removed by standard methods (TBAF, acetic acid, THF, r.t., several hours) and palladium catalyzed[4] deallylation of the resulting allyl esters, from **8a** and **8b**, afforded then the desired compounds **2a** and **2b**, respectively.

Scheme 1

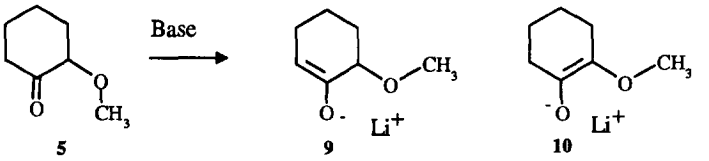


a) LHMDA, THF, O° C: b) COClCOOCH2CH=CH2, TEA, DCM: c) $P(OEt)_3$, xylene: d) TBAF, AcOH, THF: e) $Pd(PPh_3)_4$, potassium-2-ethyl-hexanoate.

While the formation of the enolate **10** (using LHMDA as base at 0°C) and its reaction with **4** has been found a straightforward procedure, unsatisfactory low selectivity was observed during the formation of the kinetic enolate **9** using LHMDA or LDA as base at -78°C (Fig. 1).[5] Therefore, ketone **11**[6] was selected in order to overcome this regioselectivity problem.

Condensation of the lithium enolate formed from ketone **11**, with **4** gave a mixture of azetidinones **12a** and **12b** in about 20% and 46% isolated yields, respectively (Scheme 2).

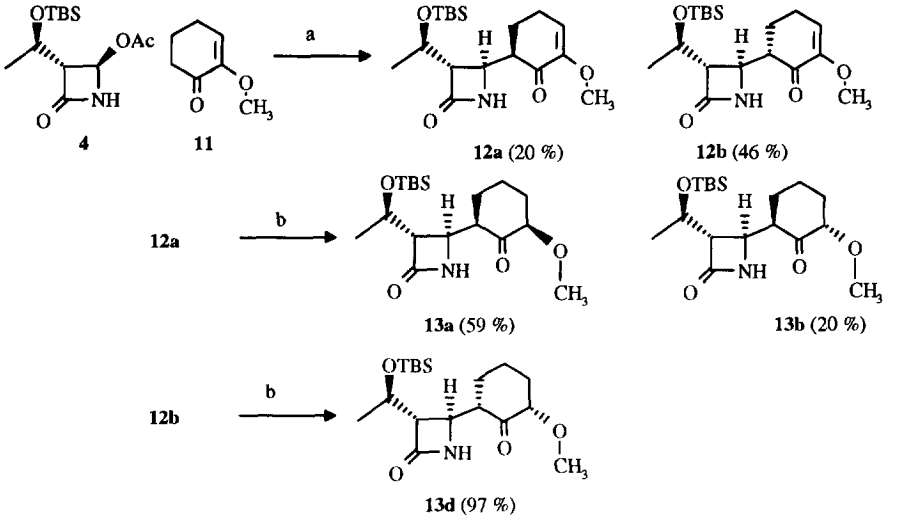
Fig. 1



Base = LHMDA, LDA, LTMP

Palladium catalyzed hydrogenation of **12a** gave isomers **13a** and **13b** in 59 % and 20 % yield respectively after flash chromatography. When isomer **12b** was hydrogenated under the same condition only isomer **13d** was obtained in almost quantitative yield.

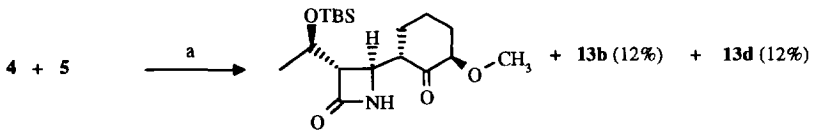
Scheme 2



a) LHMDA, THF, -78°C; b) Pd/C, H_2, EtOAc

In order to synthesize the missing isomer, 4-methoxy trinem **3c**, a more sterically hindered lithium amide than LHMDA, obtained from butyl lithium and 2,2,6,6-tetramethylpiperidine (Fig. 1) to generate the enolate of **5** in THF at -78°C was employed. Reaction of the latter with **4** gave a complex mixture (Scheme 3) containing three major products **13b**, **13c** and **13d**. While the isomer **13d** was isolated after flash chromatography in 12 % yield, isomers **13b** and **13c** formed an inseparable 1:2 mixture, in 35 % yield. The latter mixture was cyclized to give trinems **14b** and **14c** which were separable by flash chromatography and **14c**, after removal of the protective groups, gave the expected isomer **3c** in a satisfactory yield (Scheme 4).

Scheme 3

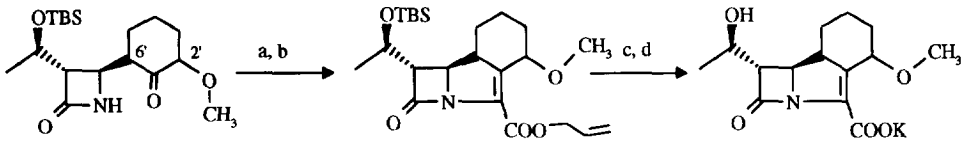


13c (23%)

a) LTMP, THF, -78 °C

Compounds **13a, 13b** and **13d** were then transformed into the corresponding final compounds **3a, 3b** and **3d** according to the procedure used for trinems **2a** and **2b** (Scheme 4).

Scheme 4



13a (2'R,6'R)
13b (2'S,6'R)
13c (2'R,6'S)
13d (2'S,6'S)

14a (4R,8S) (27%)
14b (4S,8S) (22%)
14c (4R,8R) (35%)
14d (4S,8R) (44%)

3a (4R,8S) (31%)
3b (4S,8S) (27%)
3c (4R,8R) (45%)
3d (4S,8R) (40%)

a) COClCOOCH2CH=CH2, TEA, DCM: b) $P(OEt)_3$, xylene: c) TBAF, AcOH, THF: d) $Pd(PPh_3)_4$, potassium-2-ethyl-hexanoate.

Yields of cyclisation for the azetidinones **13a-d** to the corresponding trinems **14a-d**, were in the range of 22-44 %, while yields for their two step conversion into final trinems **3a-d** were in the range of 27-45 %. The absolute configuration of compounds **14a-d** and **12a-b** was established by NOE experiments.[7]

In Table 1 *in vitro* activities towards representative gram positive and gram negative strains (including anaerobes) are reported. The tested compounds showed from moderate to extremely good antibacterial properties and **3b** shows the best profile in terms of potency and spectrum of activity. **3b** is the first member of the trinem series to be extensively evaluated *in vitro*.[8] It is a highly potent agent with a broad antibacterial spectrum that encompasses a wide range of gram-negative, gram-positive, and anaerobic pathogenic bacteria. Moreover, **3b** has been shown to be stable to all clinically relevant β-lactamases.

In conclusion, **3b** appears to be an extremely promising compound and it has been selected for clinical studies.

Table 1. In vitro antibacterial activity* (MIC mg/ml) of 4- and 8-methoxy trinems in comparison with imipenem, as determined by the microtiter broth dilution test.

	S. a. 663	S.a. 853	E.faecalis 850	E. coli 1850	E. coli 1919	C. p. 615
Imipenem	0.12	0.1	2	0.5	0.5	0.03
2a	4	8	32	32	8	2
2b	4	4	16	8	4	2
3a	0.5	0.5	8	1	4	0.12
3b	0.25	0.25	1	0.5	0.5	0.03
3c	2	2	32	16	16	1
3d	2	1	32	32	16	4

* Minimum Inhibitory Concentrations (MIC) determined in Mueller Hinton broth: Anaerobes Schadler broth Inoculum = 5x105 CFU/ml. **S. a. 663**= Staphylococcus aureus 663E ; **S. a. 853**= Staphylococcus aureus 853E β-Lactamases producing strains, **E. faecalis 850** = Enterobacter faecalis 850 ; **E. coli 1850** = Escherichia coli 1850E; **E. coli 1919** = Escherichia coli 1919E β-Lactamases producing strains; **C. p. 615** = Clostridium perfringens 615E.

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To whom correspondence should be addressed.

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7. H^1-NMR assignment of trinems **3a-d**.

3a, H^1-NMR (D_2O, 400MHz): 4.1-4.0 (2H, m), 3.88 (1H, dd, J1= 3.0 Hz, J2= 9.3 Hz), 3.27 (1H, dd, J1= 3.0 Hz, J2= 6.0 Hz), 3.20 (3H, s), 2.70 (1H, m), 1.95 (1H, m), 1.79 (1H, m), 1.62 (1H, m), 1.34 (1H, m), 1.30-1.00 (2H, m), 1.11 (3H, d, J= 6.7 Hz).

3b, H^1-NMR (D_2O, 400MHz): 4.79 (1H, t, J= 3.0 Hz), 4.13 (1H, m), 4.09 (1H, dd, J1= 2.8 Hz, J2= 10.3 Hz), 3.33 (1H, dd, J1= 2.8 Hz, J2= 6.1 Hz), 3.14 (3H, s), 3.05 (1H, m), 1.91 (1H, m), 1.77 (1H, m), 1.64-1.40 (3H, m), 1.25 (1H,m), 1.16 (3H, d, J= 6.1 Hz).

3c, H^1-NMR (D_2O, 400MHz): 4.76 (1H, t, J= 3.2 Hz), 4.07 (1H, m), 3.60 (1H, dd, J1= 3.0 Hz, J2= 7.3 Hz), 3.26 (1H, dd, J1= 3.0 Hz, J2= 5.8 Hz), 3.14 (3H, s), 2.99 (1H, m), 2.00-1.80 (2H, m), 1.50-1.00 (4H, m), 1.13 (3H, d, J= 6.3 Hz).

3d, H^1-NMR (D_2O, 400MHz): 4.05 (1H,m), 4.07 (1H, m), 3.81 (1H, m), 3.64 (1H, dd, J1= 2.8 Hz, J2= 7.3 Hz), 3.27 (3H, dd, J1= 2.8 Hz , J2= 5.8 Hz), 3.23 (3H, s), 2.87 (1H, m), 2.02 (1H, m), 1.90 (1H, m), 1.71 (1H, m), 1.22 (1H, m), 1.20-1.00 (2H,m), 1.12 (3H, d, J= 6.4 Hz).

For **3c**, $[\alpha]_D$ = +122.2° , (c= 1.05, H_2O). Moreover, all the compounds herein described were characterized by routine analysis, and their absolute stereochemistry has been established by NOE measurements. A more detailed description of the NMR studies and assignments of absolute configuration will be reported elsewhere. Mass Spectra data were consistent with the proposed structures.

8. A complete *in vitro* antibacterial evaluation for isomer **3b** is reported in: E. Di Modugno, I. Erbetti, L. Ferrari, G. Galassi, S. M. Hammond, L. Xerri *Antimicrobial Agents and Chemotherapy* 2362, (1994).

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