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TRICYCLIC β-LACTAMS: TOTAL SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 5α- AND 5β-METHOXY-TRIBACTAMS

Stephen Hanessian,* Michael J. Rozema, G.Bhaskar Reddy and John F. Braganza

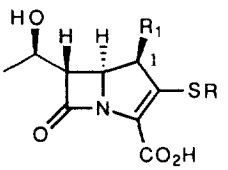
Department of Chemistry, Université de Montréal
P.O. Box 6128, Succ. Centre-ville, Montréal, P.Q., CANADA, H3C 3J7

Abstract: The total synthesis of the tricyclic β-lactams, "5α- and 5β-methoxy tribactams", positional isomers of the Glaxo 4α-methoxy-tribactam is described and preliminary biological evaluation is reported.

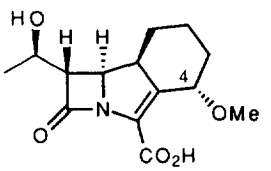
The discovery of thienamycin **1** (Figure 1),[1] the first example of a naturally occurring carbapenem, was the beginning of an exciting new era in the search for effective antibacterials containing the β-lactam motif. Since then many advances have been made in the synthesis, chemical modification, and biology of these fascinating molecules.[2] The increased stability of the 1-substituted analogs (**1**, R_1 = Me), both chemically and to dehydropeptidases,[3] is just one example of the advantages of such a structural modification.

Continuing our studies in the synthesis of β-lactam containing molecules,[4] we became interested in exploring methods for the stereocontroled construction of tricyclic β-lactams. Although limited data has been published in this area,[5] a successful and clinically promising drug candidate has emerged with Glaxo S.p.A.'s 4α-methoxy-tribactam **2** (Figure 1).[6] Prompted by recent reports on the synthesis of structural variants of these "tribactams,"[7] we now wish to report our efforts in this area, exemplified by the synthesis and preliminary biological evaluation of the 5α-methoxy-tribactam **3** (Figure 1) as well as the 5β-methoxy epimer.

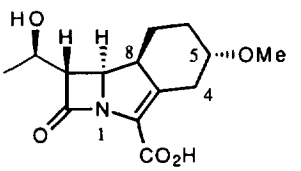
Figure 1



1
Thienamycin - type
(carbapenem)
R_1 = H, Me, etc.



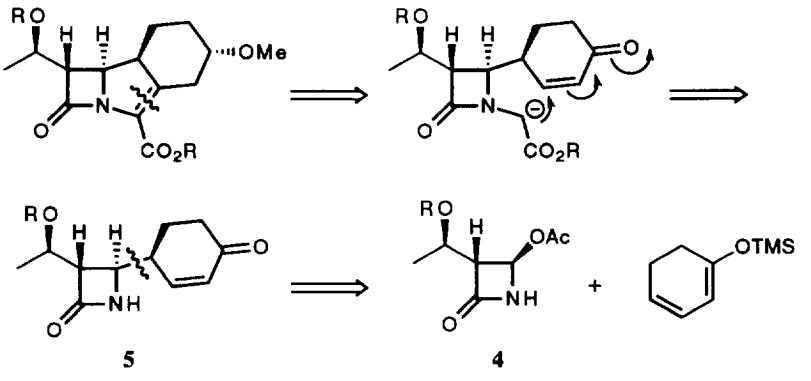
2
Glaxo's tribactam
(4α - methoxy)



3
Positional isomer
(5α - methoxy)

Analysis of our target structure led us to consider the two major disconnections shown in Scheme 1. The formation of the five membered ring was envisaged through a Michael type ring closure,[4f] and the generation of the requisite enone was expected to arise from the coupling of the commercially available acetoxyazetidinone derivative **4** [4i] with an appropriate enolate or silylenol ether.

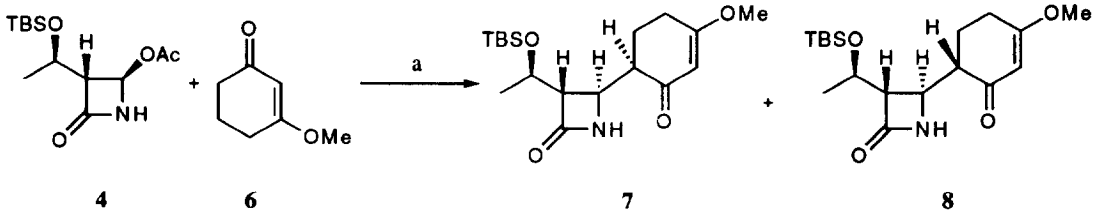
Scheme 1



Preliminary studies on the synthesis of the desired enone **5** involved the Lewis acid catalyzed coupling of the acetoxyazetidinone **4** and 1-trimethylsilyloxy 1,3-cyclohexadiene. Slow addition of a dichloromethane solution of the silyloxydiene to the acetoxyazetidinone **4** in the presence of 20% $ZnCl_2$ provided the γ-coupling product **5** and its epimer[8] as an inseparable 17 to 83 mixture of diastereomers in modest yield (43%) in addition to the undesired α-coupling product (30%). Clearly, this approach lacked the requisite stereo- and site-selectivity.

In an alternative approach, addition of the lithium enolate of 3-methoxy-2-cyclohexen-1-one (**6**) to the acetoxyazetidinone **4** afforded a 1:1 mixture of **7** and **8** in 50% yield, that were separable by column chromatography (Scheme 2).[9] Reduction of **7** with DiBAlH, followed by hydrolysis of the enol ether during workup, provided the desired enone **5** in 80% yield. None of the undesired α-coupling product was observed under these conditions. Initial attempts to enrich the proportion of the desired *syn* diastereomer **7** by transmetalation of the lithium enolate of **6** to the triisopropoxytitanium enolate[5d] led to poor yields (15 - 20%) under a variety of conditions. Attempts to convert the undesired **8** to **7**, using the conditions worked out by Bender *et al.*,[10] were also unsuccessful in this case.

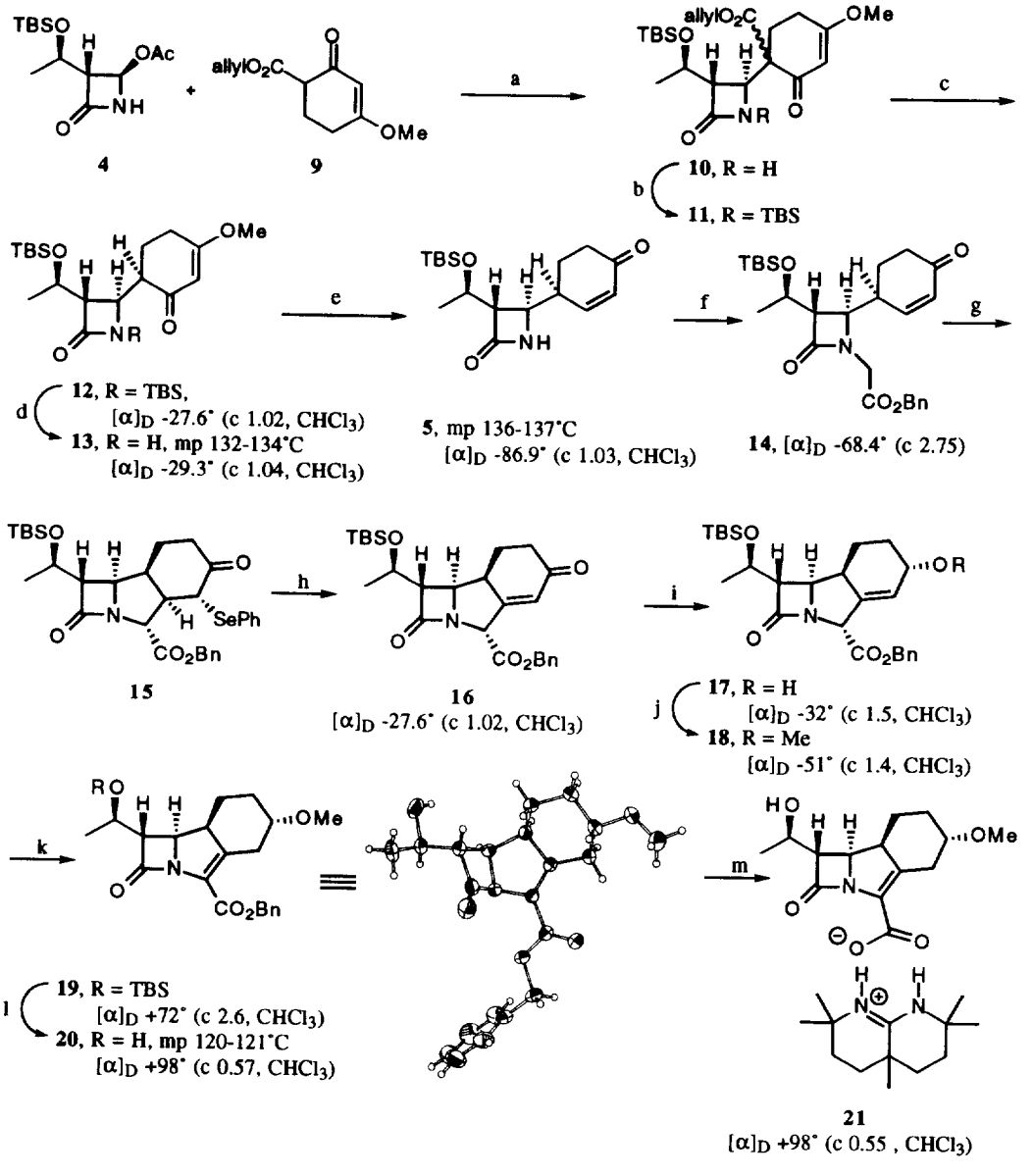
Scheme 2



(a) i. LDA (2.5 eq), -78 °C, THF, then add **4**, -78 °C, 2h. (50%).

We then turned our attention towards the decarboxylation of a β ketoester intermediate as a means of controlling the stereochemistry at C8 (Scheme 3). As an extension of the methods recently developed by Miura *et al.*[11] and Choi *et al.*,[12] the sodium salt of the β ketoester **9** was condensed with the acetoxyazetidinone **4** to provide the coupling product **10** as a 3:2 mixture of diastereomers. Protection of the nitrogen using TBS triflate followed by treatment with formic acid and a catalytic amount of palladium acetate[13] provided the desired N-TBS protected

Scheme 3



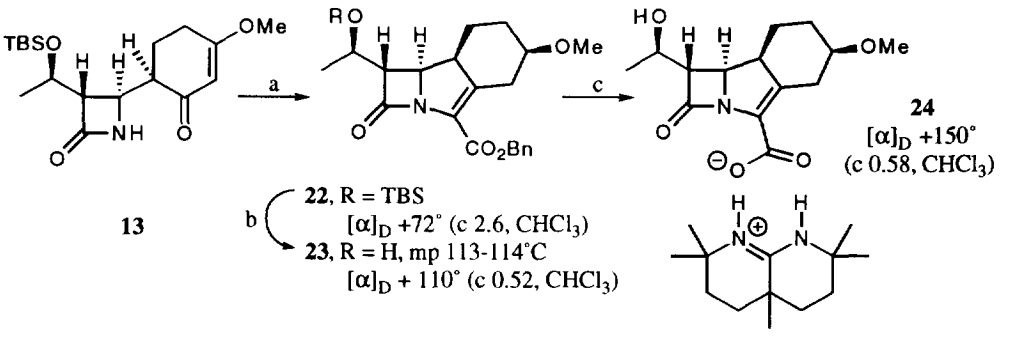
(a) i. NaH (2.5 eq), 0 °C, THF; ii. add **4** -78 °C to 0 °C, 2h; (b) TBDMSOTf, 2,6-lutidine, 0 °C, CH_2Cl_2, 30 min, 84%; (c) $Pd(OAc)_2$ (1mol%), Ph_3P, (5mol%), formic acid (3 eq), reflux, EtOAc, 2.5h, 80%; (d) HOAc (2 eq), TBAF (1 eq), rt, THF, 30 min, 98% (e) i. DiBAlH, -78 °C, THF, 1.5h; ii. aqueous workup with 10% HCl, 80%. (f) i. NaHMDS (1 eq), -78 °C, THF; ii. benzyl 2-bromoacetate (1.2 eq), -78 °C, 30 min, 72%; (g) i. NaHMDS (1.1 eq), -78 °C, THF; ii. $ZnCl_2$, -78 °C, 30 min; iii. PhSeBr (1.1 eq), -78 °C, 15 min, 70%; (h) mCPBA (2 eq), -78 °C, CH_2Cl_2, 30 min, 80%; (i) $NaBH_4$ (1.1 eq), -78 °C, MeOH, 30 min, 75%; (j) MeI (solvent), Ag_2O (3 eq), rt, 10 h, 63%; (k) DBU (1 eq), rt , CH_2Cl_2, 12 h, 92%; (l) TBAF (3 eq), HOAc (4 eq), rt, THF, 4 days, 85%; (m) 3,3,6,9,9-pentamethyl-2,10-diazabicyclo[4.4.0]dec-1-ene, H_2, Pd(C), rt, dioxane, 1h, 93%.

derivative **12** in a 67% overall yield from the acetoxyazetidinone. N-Deprotection with TBAF-HOAc, followed by reduction with DiBAlH led to the desired γ coupling product **5** needed for the Michael addition reaction.

The β-lactam was N-alkylated with benzyl 2-bromoacetate and the product **14** was converted to the Na enolate. Addition of $ZnCl_2$ and trapping the ketone enolate formed by phenylselenyl bromide provided **15** in 72% yield. The role of the $ZnCl_2$ is two fold: it enhances the Michael-type ring closure reaction, and it allows the formation of the phenylseleno compound as a single diastereomer with the configuration required for elimination and regeneration of the enone.[14] Oxidation and elimination of the phenylseleno group was carried out with mCPBA to afford the enone **16**, which was reduced with $NaBH_4$ in methanol at -78 °C to provide the alcohol **17** as a single diastereomer. Methylation and migration of the double bond with DBU[15] gave the fully protected 5-methoxytribactam **19**. Desilylation of the hydroxyethyl side-chain afforded the crystalline alcohol **20**, whose structure and absolute stereochemistry was confirmed by single X-ray analysis (Scheme 3). Hydrogenolysis of the benzyl ester in the presence of a bulky base[4a,16] led to the desired tricyclic β-lactam **21**.

In order to study the effect the stereochemistry of the methoxy substituent on the antibacterial activity, the corresponding 5β-methoxy-tribactam **24** was also prepared (Scheme 4). Reduction of the double bond in the enone **13** followed by cyclization mediated by triethylphosphite[17] afforded a 1:1 mixture of α- and β-methoxy epimers, which could be separated by careful column chromatography. The β-methoxy isomer was then deprotected as before to afford the tricyclic β-lactam isolated as its amidinium salt **24**.

Scheme 4



(a) i. H_2, Pd(C)(cat.), EtOAc, 2h; ii. benzyl oxalylchloride, pyridine, CH_2Cl_2, 0 ° to rt, 2h; iii. $P(OEt)_3$, xylene, 155 °C, overnight. iv, chromatography, β-isomer 24%, total 48%; (b) TBAF (3 eq), HOAc (4 eq), rt, THF, 4 days, 83%; (c) 3,3,6,9,9-pentamethyl-2,10-diazabicyclo[4.4.0]dec-1-ene, H_2, Pd(C), rt, dioxane, 1h, 100%.

Preliminary data on the anitbacterial activity of **21** and **24** are provided in Table 1. Except for Pseudomonas aeruginosa and anaerobes, the activity of the α-methoxyisomer **21** compares favorably with imipenem in contrast to the β-epimer **24**. Results pertaining to the stability to dehydropeptidases will be reported in due course.

Table 1

Organism[a]	**21**	**24**	Imipenem
S. aureus 663E[b]	0.25	1	0.13
S. aureus 853E[c]	0.5	1	0.13
S. aureus 113I[d]	32	>32	4
S. aureus COL[d]	>32	>32	>32
E. faecalis 850	4	>32	1
H. influenzae 49247	0.5	16	1
E. coli DC_0[e]	1	16	0.5
E. coli DC_2[f]	1	0.5	0.5
E. coli DC_2 TEM1[g]	1	1	0.5
E. cloacae 3647	1	16	2
P. mirabilis 355g	4	32	1
P. aeruginosa 1911E	>32	>32	4
P. aeruginosa 2032E WT	>32	>32	4
P. aeruginosa 2033E[h]	1	16	0.5
C. perfringens 615E	0.5	8	0.06
B. fragilis 2017E	1	32	0.13

a. MIC values were determined by conventional dilution techniques in microtiter broth using the procedures as laid down by NCCLS and are defined as the lowest concentration (μg/mL) giving no visible growth after 16-20 h. b. Pen, sens.; c. β-lactamase prod. strain; d. methicillin resist.; e. wild; f. permeable; g. permeable, β-lactamase prod. strain; h. permeable mutant

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