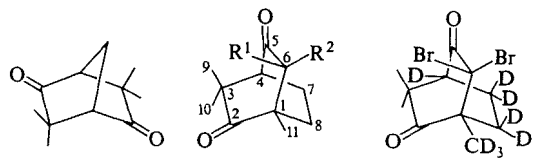
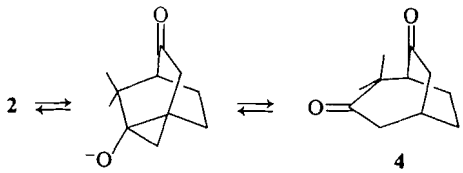


1 2 3

a, $R^1 = R^2 = H$
b, $R^1 = R^2 = Br$



SCHEME 1

bridgehead methyl. A possible candidate is 2,2-dimethylbicyclo[3.2.2]nonane-3,7-dione (**4**) (Scheme 1). We are currently investigating the homoenolization of other methylated bicyclo-[2.2.2]octanones and bicyclo[3.2.2]octanediones to establish the reason for the facile homoenolizations.

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A highly asymmetric synthesis of the *O*-2-isocephem class of β-lactam antibiotics

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This paper is dedicated to Prof. Raymond U. Lemieux on the occasion of his 60th birthday

SHEILA M. TENNESON and BERNARD BELLEAU. Can. J. Chem. **58**, 1605 (1980).

Starting from D-threonine, an asymmetric synthesis of the dextrorotatory bioactive enantiomer of 3-methyl-7-phenylacetamido-*O*-2-isocephem was accomplished. The key step, where asymmetric cycloaddition of azidoacetyl chloride to the cinnamylidene Schiff base of protected D-threonine is induced, generates the desired *cis*-β-lactam in 90% optical yield. The absolute configuration of the final product was confirmed by comparing its antimicrobial activity with that of its corresponding racemate.

SHEILA M. TENNESON et BERNARD BELLEAU. Can. J. Chem. **58**, 1605 (1980).

En partant de la D-thréonine, on a réalisé une synthèse asymétrique de l'énantiomère dextrogyre biologiquement actif du méthyl-3 phénylacétamido-7 *O*-isocéphème-2. L'étape principale implique la cycloaddition asymétrique du chlorure d'azidoacétyle sur la base de Schiff de la cinnamaldéhyde avec la D-thréonine protégée et elle engendre la β-lactame *cis* désirée avec un rendement optique de 90%. On a confirmé la configuration absolue du produit final en comparant son activité antimicrobienne à celle du racémate correspondant. [Traduit par le journal]

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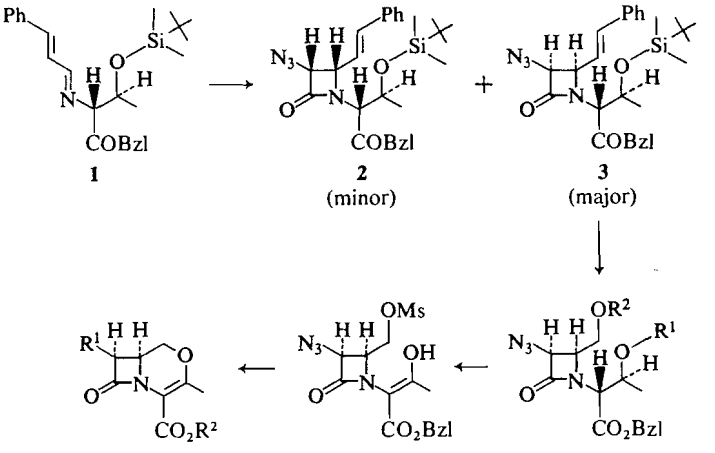
Efficient and stereospecific syntheses of isocephems and the analogous *O*- and *N*-2-isocephems were recently reported by the Bristol Canada group (1). The *O*-2-isocephems in particular constitute a new class of β-lactam antibiotics whose effectiveness against some common pathogenic bacteria compare favorably with analogous cephalosporins currently in use. As is the case of all β-lactam antibiotics, antibacterial activity of a prototype *O*-2-isocephem was associated exclusively with one of the enantiomers (dextrorotatory) of the synthetic racemix mixture (1*f*). A single key step of the synthesis, the cycloaddition of azidoacetyl chloride to a cinnamylidene Schiff base introduces simultaneously the only two asymmetric centers appearing in the final product. However, only one racemate is obtained owing to the exclusive *cis*-stereospecificity of the cycloaddition. For obvious reasons of economics, a synthetic process leading mainly to the bioactive enantiomer from inexpensive starting materials became an important goal. Such an asymmetric process demands that the steric course of the cycloaddition be sensitive to chirality effects about an appropriate α-aminoester Schiff base. Although the chiral α-carbon of an aminoacid Schiff base is not proximal to the reacting aldimine carbon, preliminary observations by the Bristol group some time ago[1] strongly indicated that asymmetric cycloaddition was induced in some degree using a protected L-threonine Schiff base as the reaction partner. However, similar experiments by Just and Liak (2), but with a protected L-serine cinnamylidene Schiff base, led only to racemic material and thus could not yield any information on the possibility of asymmetric induction during the cycloaddition. This provided an additional incentive to reexamine, but in detail, the use of a protected enantiomer of a threonine Schiff base as a potential inducer of asymmetry. Mechanistic considerations allowed the prediction that, for the bioactive enantiomer of the end-product to be obtained, the D-isomer of threonine should be used as staring material. Thus, starting from D-threonine benzyl ester, the synthesis of optically pure (+)-3-methyl-7-phenyl-acetamido-*O*-2-isocephem of *cis*-configuration was accomplished as shown in Scheme 1.

Silylation (3) of D-Thr-ObzL·Hcl (4) (mp 126.5–127.5°C; $[\alpha]_D^{23}$ +10.1 (*c* 4.5, MeOh) in HMPT with *tert*-butyldimethylsilyl chloride gave the *O*-silyl ether[2] which was converted to Schiff base **1** on reaction with cinnamaldehyde (1*a*). The crude Schiff base plus triethylamine (1.3 equiv.) in dry CH_2Cl_2 was treated at −10°C with azidoacetyl chloride (1.2 equiv.) according to published procedures (1) to give β-lactams **2** and **3** (60% from D-Thr-ObzL·HCl), the azidoacetyl amide of protected threonine (~ 30%), and small amounts of unidentified material. The β-lactam fraction was submitted to hplc (Spherisorb, Si 100, 10 μm; MeOh–EtOAc–hexane (0.1:5:95)) to give pure **3** ($[\alpha]_D^{23}$ −150 (*c* 2.5, hexane)) and **2** ($[\alpha]_D^{23}$ +80 (*c*



SCHEME 1

[1]B. Belleau, J. L. Douglas, and D. E. Horning, unpublished results.

[2]For all substances the spectra (ir, pmr, and ms) were in agreement with the assigned structures. Satisfactory microanalyses were obtained for key products. All rotations are for $CHCl_3$ solution unless stated otherwise.

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1.5, hexane)) in a ratio of 9:1. That both **3** and **2** had *cis*-stereochemistry was inferred from their respective 200 MHz pmr spectra ($CDCl_3$)(**3**: $\delta = 4.90$ (d, $J = 5.3$ Hz, 1H, H-3) and 4.92 (dd, $J = 5.3$ and 8.8 Hz, 1H, H-4) ppm; **2**: $\delta = 4.89$ (d, $J = 5.2$ Hz, 1H, H-3) and 4.80 (dd, $J = 5.2$ and 8.8 Hz, 1H, H-4) ppm). Hence, the cycloaddition reaction proceeds asymmetrically to give a *cis* β-lactam in 90% optical yield.

The major β-lactam **3** was submitted to ozonolysis (CH_2Cl_2–MeOH, 9:1) at −70°C followed by reductive workup with $NaBH_4$–Alox (5) to give **4** (90%, $[\alpha]_D^{23}$ −158 (*c* 3.7)). Mesylation (6), then hydrolysis of the silyl ether with 95% TFA afforded alcohol mesylate **6** (85% from **4**, mp 100–101°C, $[\alpha]_D^{23}$ −112 (*c* 3) which on oxidation with Jones' reagent (7) (1.1 equiv.) at 15–20°C gave the enol mesylate **7** (1*b*) plus unreacted **6** which was recycled.[3] Without further purification, **7** was treated with triethylamine in refluxing CH_2Cl_2 (2.5 h) to give *O*-2-isocephem derivative **8** (1*b*) ($[\alpha]_D^{23}$ −22 (*c* 2.4)). Hydrogenation of **8** over Pt gave the amine **9** (1*b*) which was coupled with phenylacetic acid using EEDQ (8) to give the ester amide **10** (65% from **8**) ($[\alpha]_D^{23}$ +154 (*c* 0.6)). Hydrogenolysis (10% Pd/C) of **10** in EtOH–Thf (10:7) gave the *O*-2-isocephem acid **11**, (mp 95–105°C (dec.); $[\alpha]_D^{23}$ +155 (*c* 1, acetone)).

The respective *in vitro* antimicrobial activity (expressed as MIC's) of **11** and its corresponding racemate BC-L30 (9) against 5 typical strains of bacteria were as follows: *Streptococcus pneumoniae*, 0.25 and 0.5; *Streptococcus pyrogenes*, 0.5 and 0.5; *Staphylococcus aureus*, 0.5 and 1.0; *Escherichia coli*, 32 and 125; *Proteus mirabilis*, 8 and 16. These results establish the absolute configuration of **11** and its precursors. It appears to be the first time that a highly asymmetric cycloaddition on a Schiff base has been developed successfully for the production of the bioactive enantiomer of a β-lactam antibiotic. The mechanistic implications of this asymmetric cycloaddition, as well as other pertinent applications of this approach, will be described later.

[3]The oxidation was monitored by tlc and stopped at about 50% at which point side reactions became significant.

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