Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 1037–1043

TETRAHEDRON: *ASYMMETRY*

Diastereoselective synthesis of protected 4-*epi*-vancosamine from (*S*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinal

Alberto Avenoza,* Jesús H. Busto, Francisco Corzana, Jesús M. Peregrina,* David Sucunza and María M. Zurbano

Departamento de Química, Universidad de La Rioja, Grupo de Síntesis Química de La Rioja, U.A.-C.S.I.C., 26006 Logroño, Spain

Received 5 December 2002; accepted 28 January 2003

Abstract—An efficient diastereoselective synthesis of methyl *N*,*O*-dibenzoyl-L-4-*epi*-vancosamine is described. The key step involves Sharpless asymmetric dihydroxylation of a *Z* olefin derived from (*S*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinal.

1. Introduction

During the last decade, glycopeptide antibiotics have been the subject of intensive investigation.[1] Two glycopeptide antibiotics, vancomycin and teicoplanin, are in clinical use and are of great utility in the treatment of infections by bacteria that are resistant to many other classes of antibiotics. Indeed, vancomycin is considered to be the last line of defense for many severe bacterial infections.

However, resistance to vancomycin is unfortunately now on the increase.[2] Although the SAR of the glycopeptide antibiotics has been extensively studied,[3] the modifications necessary to improve the resistance situation are not clear. Because of this, many investigations aimed at enhancing the activity of the vancomycin group of glycopeptide antibiotics are in progress.[4]

In this sense, different vancomycin derivatives are currently under investigation; for example A82846B (vancomycin plus one additional carbohydrate substituent: 4-*epi*-vancosamine) and LY333328 (a vancomycin derivative that features both the chlorobiphenyl side chain and the additional sugar substituent of A82846B) are highly efficient against vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) and are now undergoing clinical trials.[5] The structure of vancomycin is shown in Fig. 1 and consists of a disaccharide moiety (a glucose and a vancosamine) attached to a rigid cyclic heptapeptide framework aglycon. The structures of the vancomycin derivatives previously mentioned are also shown.

Taking into account the importance of glycopeptide antibiotics,[6] and in order to construct combinatorial libraries of vancomycin analogs for biological screening, the synthesis of vancosamine donors has been the focus of many researchers. To this end, several stereoselective syntheses of protected vancosamines have been described.[7] Nevertheless, the synthesis of 4-*epi*-vancosamine derivatives has received little attention. In fact, although some derivatives have been isolated from several antibiotics,[8] they have only been synthesized de novo on a few occasions[9] and these approaches have involved three methodologies.[10–12]

2. Results and discussion

In this context, we wished to explore the chemistry of our chiral building block (*S*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinal[13] **1** for the asymmetric synthesis of suitably protected 4-*epi*-vancosamine. Our synthesis started with the Wittig olefination of α-amino aldehyde

* Corresponding authors. Tel./fax: +34-941-299655; e-mail: alberto.avenoza@dq.unirioja.es; jesusmanuel.peregrina@dq.unirioja.es

0957-4166/03/$ - see front matter
doi:10.1016/S0957-4166(03)00119-8

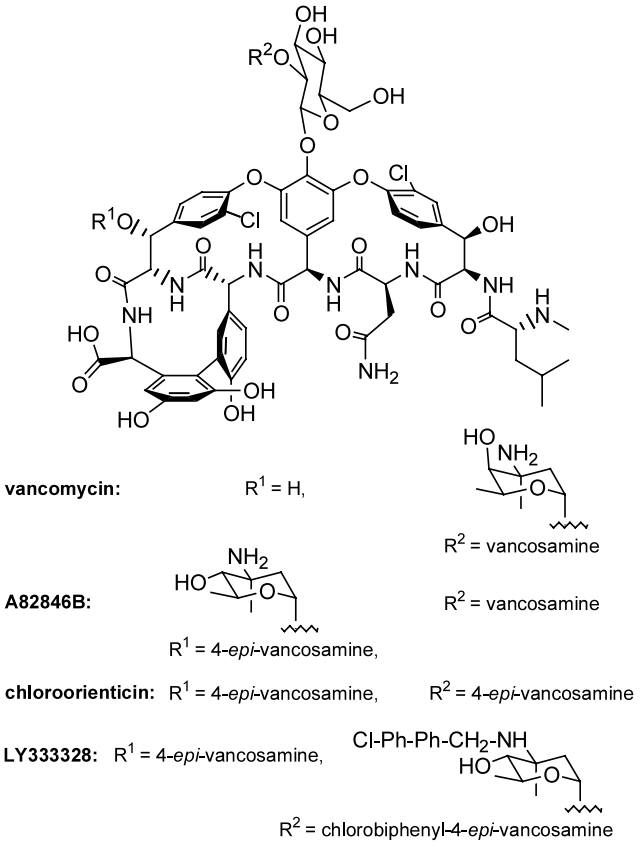


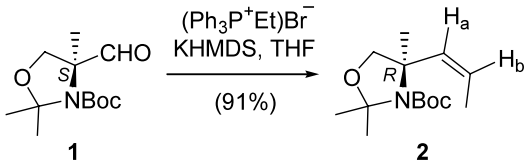
Figure 1. Important glycopeptide antibiotics corresponding to the vancomycin group.

1, using ethyltriphenylphosphonium bromide and potassium bis(trimethylsilyl)amide (KHMDS) as base, to give the olefin **2** in 91% yield (Scheme 1).

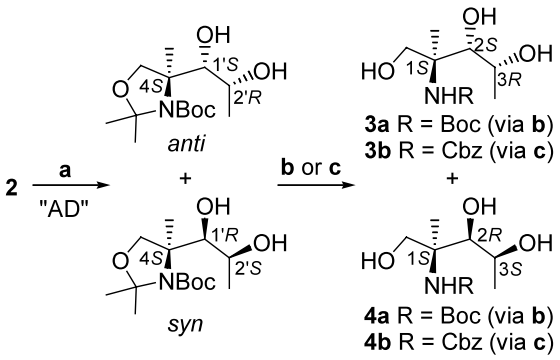
As one would expect in the Wittig reaction with non-stabilized ylides,[14] the stereochemistry of olefin **2** was assigned as *Z* on the basis of the coupling constants ($J_{a-b}=11.1$ Hz and 12.3 Hz) observed for the ^{1}H NMR signals corresponding to the vinylic protons H_a of the two conformers that appear in solution as a result of the slow interconversion around the *N*-Boc bond.[15]

Taking into account the *Z* stereochemistry of this olefin, the best method to obtain the required diol of 1′*R*,2′*S* configuration involved asymmetric *cis*-dihydroxylation of olefin **2** (Scheme 2). However, when the dihydroxylation of **2** was carried out with RuO_4 the reaction occurred with low stereoselectivity (*anti*/*syn* = 48/52, 86%).[16] Given this poor result, we decided to assess the double asymmetric induction using the Sharpless asymmetric dihydroxylation (AD)[17] on this olefin. Nevertheless, the treatment of olefin **2** with AD-mix-β gave the 'mismatched pair', with poor stereoselectivity obtained once again (*anti*/*syn* = 51/49, 77%). Fortunately, the use of AD-mix-α provided good stereoselection in favor of the *syn* diol (*anti*/*syn* = 20/80, 82%).

The *anti* and *syn* diols could not be separated by column chromatography and all attempts to carry out selective deprotection of their acetonide moiety failed. For these



Scheme 1. Synthesis of olefin **2** by Wittig olefination of serinal **1**.



Scheme 2. *Reagents and conditions*: (a) i. AD-mix-α, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 0°C, 12 h; (b) i. $HCl_{c.}$/THF (2:3), 25°C, 2 h, ii. Boc_2O (1.3 equiv.), $Na_2CO_3\cdot10H_2O$ (2.5 equiv.), H_2O/THF (1:5), 25°C, 24 h, 79%; (c) i. $HCl_{c.}$/THF (2:3), 25°C, 2 h, ii. CbzCl (1.3 equiv.), $Na_2CO_3\cdot10H_2O$ (2.5 equiv.), H_2O/THF (1:5), 25°C, 24 h, 51%.

reasons the mixture of diols, without purification, was transformed into compounds **3a** and **4a** (79% from olefin **2**) by acid hydrolysis using hydrochloric acid and subsequent treatment of the corresponding amino alcohols with Boc_2O in the presence of sodium carbonate (Scheme 2).

Compounds **3a** and **4a** were easily separated by column chromatography and, in order to determine the absolute configuration of their stereogenic centers by X-ray analysis, we attempted to crystallize them. Unfortunately, monocrystals could not be obtained in this way so we changed the carbamate group by hydrolyzing the mixture of diols and treating the resulting material with CbzCl in sodium carbonate to give compounds **3b** and **4b** (Scheme 2). These compounds were separated by column chromatography and a monocrystal of the minor compound **3b** could now be obtained and studied by X-ray analysis, which showed the stereochemistry to be 1*S*,2*S*,3*R*. The stereochemistry of the major compound, **4a**, is therefore 1*S*,2*R*,3*S* (Fig. 2).[†]

[†] Crystal data: $C_{14}H_{21}NO_5$, $M_w=283.32$, colorless prism of 0.68×0.25×0.22 mm, $T=173(2)$ K, orthorhombic, space group $P2_12_12_1$, $Z=4$, $a=6.1566(3)$, $b=12.9469(7)$, $c=18.8239(9)$ Å, $V=1500.43(13)$ Å^3, $d_{calcd}=1.254$ g cm^{-3}, $F(000)=608$, $\lambda=0.71073$ Å (Mo, Kα), $\mu=0.095$ mm^{-1}, Nonius Kappa CCD diffractometer, θ range 1.91–27.89°, 5867 collected reflections, 3312 unique ($R_{int}=0.0349$), full-matrix least-squares (SHELXL97[a]), $R_1=0.0530$, $wR_2=0.1153$, ($R_1=0.0834$, $wR_2=0.1319$ all data), goodness of fit = 1.043, residual electron density between 0.237 and −0.220 e Å^{-3}. Hydrogen atoms were located from mixed methods (electron-density maps and theoretical positions). Further details on the crystal structure are available on request from Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, UK on quoting the depository number 198872. (a) Sheldrick, G. M. SHELXL97. Program for the refinement of crystal structures. University of Göttingen, Germany, 1997.

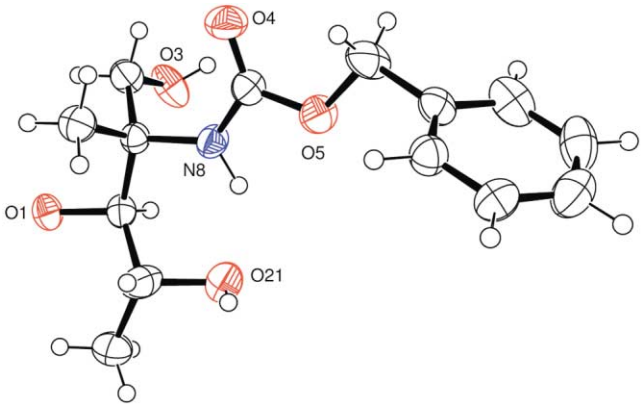
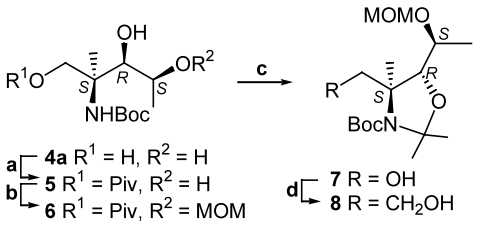


Figure 2. ORTEP drawing (arbitrary numbering of the heteroatoms) of the molecular structure of compound **3b**.



Scheme 3. *Reagents and conditions*: (a) PivCl (1.1 equiv.), TEA (1.1 equiv.), CH_2Cl_2, 25°C, 12 h, 65%; (b) MOMCl (3.0 equiv.), DIEA (3.0 equiv.), CH_2Cl_2, 25°C, 24 h, 88%; (c) i. DMP (13.0 equiv.), *p*-TsOH (0.02 equiv.), toluene, reflux, 4 h, ii. DIBAL-*H* (2.2 equiv.), CH_2Cl_2, −78°C, 12 h, 84%; (d) i. Dess–Martin periodinane (1.5 equiv.), CH_2Cl_2, 25°C, 6 h, ii. $(Ph_3P^+Me)Br^-$ (3.0 equiv.), KHMDS (3.0 equiv.), THF, 25°C, 15 h, iii. BH_3–THF complex (2.0 equiv.), $LiBH_4$ (0.3 equiv.), THF, 25°C, 12 h, iv. H_2O/20% NaOH/30% H_2O_2 (1:1:1), 25°C, 3 h, 67%.

Once the major compound **4a** had been separated, we continued to explore a variety of protective groups to orthogonally protect the three hydroxyl groups. It has been reported that PivCl is an excellent reagent for selective reaction with primary hydroxyl groups in the presence of secondary ones.[18] We therefore carried out the reaction of triol **4a** with PivCl (1.1 equiv.) using triethylamine (TEA) as base. This reaction gave the triol protected at the primary alcohol, i.e. compound **5** with excellent selectivity (Scheme 3).

The reagent selected to protect the two secondary alcohols was chloromethyl methyl ether (MOMCl), since the MOM group is stable to the conditions required for deprotection the Piv group.[19] With this strategy in mind, we investigated the reaction of diol **5** with MOMCl (3.0 equiv.) in the presence of DIEA. This reaction led to the formation of compound **6** in which, curiously, only one hydroxyl group was protected. The structure of this compound was determined by X-ray analysis of a monocrystal obtained by crystallization from chloroform/hexane (Fig. 3).[‡]

Having established the structure of **6**, the NH and OH groups were protected simultaneously as the oxazolidine by addition of 2,2-dimethoxypropane (DMP) and catalytic amounts of *p*-TsOH under reflux. The resulting compound was treated with DIBAL-*H* at −78°C,

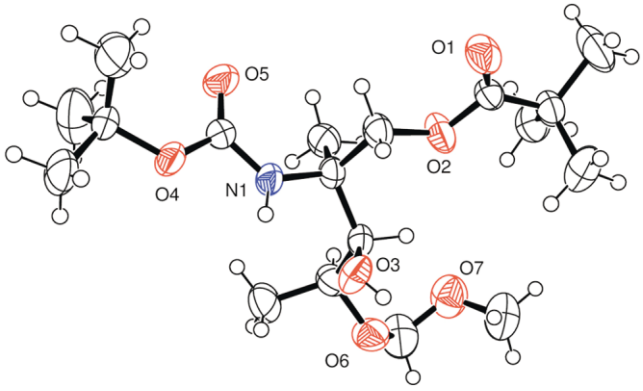


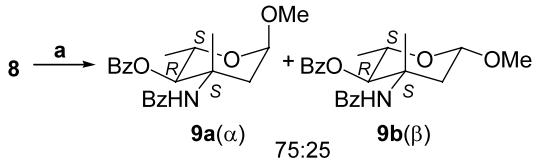
Figure 3. ORTEP drawing (arbitrary numbering of the heteroatoms) of the molecular structure of compound **6**.

without prior purification, in order to deprotect the primary alcohol and give alcohol **7** in an 84% yield (Scheme 3).

In order to synthesize the required 4-*epi*-vancosamine skeleton from compound **7**, we needed to increase the chain length by one additional carbon. The transformation of the CH_2OH group into the CH_2CH_2OH group was investigated by several methods. The best results were obtained upon using the following reaction sequence: oxidation of the alcohol to the aldehyde (Dess–Martin periodinane),[20] followed by Wittig methylenation of this aldehyde (methyltriphenylphosphonium bromide and KHMDS) and regioselective hydroboration/oxidation of the terminal olefin to give primary alcohol **8** (BH_3–THF complex combined with $LiBH_4$ as a borane reagent followed by oxidation with hydrogen peroxide and sodium hydroxide) (Scheme 3).

Finally, suitably protected enantiomerically pure 4-*epi*-vancosamine **9** was obtained from compound **8** in three steps (Scheme 4). The first step involved oxidation of

[‡] Crystal data: (a) $C_{18}H_{35}NO_7$, $M_w = 377.47$, colorless prism of 0.63×0.25×0.25 mm, $T = 298$ K, monoclinic, space group $P21$, $Z = 2$, $a = 9.1497(3)$, $b = 10.0060(4)$, $c = 12.0612(6)$, $\beta = 100.5353(17)°$, $V = 1085.61(8)$ Å^3, $d_{calcd} = 1.155$ g cm^{-3}, $F(000) = 412$, $\lambda = 0.71073$ Å (Mo Kα), $\mu = 0.088$ mm^{-1}, Nonius Kappa CCD diffractometer, θ range 3.04–27.94°, 3992 unique reflections, full-matrix least-squares (SHELXL97[a]), $R_1 = 0.0444$, $wR_2 = 0.1132$, ($R_1 = 0.0544$, $wR_2 = 0.1177$ all data), goodness of fit = 1.465, residual electron density between 0.278 and -0.201 e Å^{-3}. Hydrogen atoms fitted at theoretical positions. Further details on the crystal structure are available on request from Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, UK on quoting the depository number 198873. (a) Sheldrick, G. M. SHELXL97. Program for the refinement of crystal structures. University of Göttingen, Germany, 1997.



Scheme 4. *Reagents and conditions*: (a) i. Dess–Martin periodinane (1.5 equiv.), CH_2Cl_2, 25°C, 6 h, ii. 6N HCl/MeOH (2:3), 25°C, 3 h, iii. BzCl (4.0 equiv.), pyridine, 25°C, 20 h, 60%.

the primary alcohol group of compound **8** to the aldehyde using the Dess–Martin periodinone. In the second step, this aldehyde was treated with methanol in acidic medium, in order to cleave the *N*,*O*-acetal, to hydrolyze the *N*-Boc group to NH_2, to recover the OH group from the OMOM protecting group and to form the corresponding *arabino*-hexose skeleton. The last step involved the protection of the OH and NH_2 groups with benzoyl chloride in the presence of pyridine. In this way, methyl *N*,*O*-dibenzoyl-4-*epi*-vancosamine was obtained as a mixture of the two anomers **9a** (α) and **9b** (β) in a 75:25 ratio from compound **8** with an overall yield of 60% (11% from serinal **1**). These anomers could be separated by column chromatography.

3. Conclusions

In summary, we have developed a diastereoselective synthesis of an important *C*-branched sugar with an amine-bearing C-3 quaternary center—i.e. the protected 4-*epi*-vancosamine **9**—which will be used as a 4-*epi*-vancosamine donor in order to construct different combinatorial libraries of vancomycin analogs for biological screening. The L-*arabino*-hexose skeleton, L-2,3,6-trideoxy-3-*C*-methyl-3-aminohexopyranose (L-4-*epi*-vancosamine or L-eremosamine), has been prepared by Sharpless AD on a *Z* olefin derived from (*S*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinal followed by functional group transformations.

4. Experimental

4.1. General procedures

Melting points are uncorrected. All the manipulations with air-sensitive reagents were carried out under a dry argon atmosphere using standard Schlenk techniques. Solvents were purified according to standard procedures. The chemical reagents were purchased from the Aldrich Chemical Co. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using Kieselgel 60 (230–400 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and, when necessary, concentrated under reduced pressure using a rotary evaporator. ν_{max} (cm^{-1}) of IR spectra are given for the main absorption bands. NMR spectra were recorded at 300 MHz (^1H) and at 75 MHz (^{13}C) and are reported in ppm downfield from TMS. Mass spectra were obtained by electronic impact (EI) and electrospray ionization (ESI).

4.1.1. (*R*)-(*Z*)-2,2,4-Trimethyl-4-propenyloxazolidine-3-carboxylic acid *tert*-butyl ester, 2. Ethyltriphenylphosphonium bromide (4.63 g, 12.3 mmol) was suspended in THF (60 mL) at 25°C and KHMDS (0.5 M in toluene, 24.7 mL, 12.3 mmol) was added. The resulting red suspension was stirred at 25°C for 1 h. Then, it was cooled to −78°C and a solution of aldehyde (*S*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinal **1** (1.01 g, 4.2 mmol) in THF (20 mL) was added dropwise. The cooling bath was removed, the mixture allowed to reach rt over 2 h and then warmed to 35°C for a further 12 h. The reaction was quenched with MeOH (10 mL) and the resulting mixture was poured into a solution of saturated potassium sodium tartrate and water (1:1, v/v, 75 mL). Extraction with ethyl ether (2×50 mL), drying and evaporation of the solvent gave a pale oil which was purified by flash chromatography (hexane:ethyl acetate, 9.5:0.5) to give compound **2** as a colorless liquid (0.97 g, 3.81 mmol); yield: 91%. $[\alpha]_D^{25} = -48.0$ (*c* 1.28, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.44–1.59 (m, 18H), 1.66 (d, 3H, $J=7.2$ Hz), 3.83–3.94 (m, 2H), 5.35–5.50 (m, 1H), 5.56, 5.72 (2d, 1H, $J=11.1$ Hz, $J=12.3$ Hz). ^{13}C NMR ($CDCl_3$): δ 14.0, 24.0, 24.8, 25.3, 25.7, 26.2, 27.5, 28.5, 62.9, 63.5, 74.8, 75.1, 79.5, 79.8, 94.1, 95.0, 123.5, 123.9, 134.2, 135.2, 151.3, 151.8. MS (EI) (m/z) = 41, 57, 140, 184, 255. ESI^+ (m/z) = 256. Anal. calcd for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.49. Found: C, 65.53; H, 9.91; N, 5.52.

4.1.2. (1*S*,2*S*,3*R*)-(2,3-Dihydroxy-1-hydroxymethyl-1-methylbutyl)carbamic acid *tert*-butyl ester, 3a and (1*S*,2*R*,3*S*)-(2,3-dihydroxy-1-hydroxymethyl-1-methylbutyl)carbamic acid *tert*-butyl ester, 4a. A round-bottomed flask was charged with *tert*-butylic alcohol (27 mL), water (27 mL), AD-mix-α (7.35 g) and methanesulfonamide (0.50 g). The mixture was stirred at rt until both phases were clear, and then cooled to 0°C, whereupon the inorganic salts partially precipitated. Olefin **2** (1.34 g, 5.25 mmol) was added and the heterogeneous slurry was stirred vigorously at 0°C for 12 h. The reaction was quenched at 0°C by addition of sodium sulphite (7.88 g) and then stirred for 1 h. The reaction mixture was extracted with ethyl acetate (3×30 mL) and then dried and concentrated to give a mixture of both diols (*syn* and *anti*) with a diastereoselectivity of 4:1 in favor of the diol *syn*. Without further purification the mixture was dissolved in THF (15 mL) and concentrated HCl (10 mL) was added. The solution was stirred at 25°C for 2 h. Then, HCl was removed to give the corresponding mixture of amino alcohols, which were dissolved in water/THF (1/5, 60 mL) and $Na_2CO_3 \cdot 10H_2O$ (3.76 g, 13.14 mmol) and Boc_2O (1.42 g, 6.31 mmol) were added. The mixture was stirred at 25°C for 24 h and then, quenched with saturated NH_4Cl (20 mL) and extracted with ethyl acetate (3×30 mL). The combined organic layers were dried and concentrated. The residue was purified by column chro-

matography (hexane/ethyl acetate, 3:7) to give **3a** (0.19 g, 0.77 mmol) as a white solid and the required diol **4a** (0.85 g, 3.42 mmol) as a white solid; yield of **4a**: 62%. Overall yield: 79%. Compound **3a**: mp: 67°C. $[\alpha]_D^{25} = -2.4$ (*c* 1.23, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 3H), 1.35 (d, 3H, $J = 6.3$ Hz), 1.42 (s, 9H), 3.29 (m, 1H), 3.53 (d, 1H, $J = 12.0$ Hz), 3.69 (d, 1H, $J = 12.0$ Hz), 3.71–3.81 (m, 1H), 4.78 (br s, 1H), 5.18 (br s, 1H), 5.55 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 20.5, 21.2, 28.2, 59.0, 68.4, 80.0, 80.3, 157.4. ESI$^+$ (m/z) = 250. Anal. calcd for $C_{11}H_{23}NO_5$: C, 52.99; H, 9.30; N, 5.62. Found: C, 52.82; H, 9.22; N, 5.60%. Compound **4a**: mp: 74°C. $[\alpha]_D^{25} = -1.3$ (*c* 0.87, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.26–1.28 (m, 6H), 1.40 (s, 9H), 3.62–3.88 (m, 5H), 4.25 (br s, 1H), 4.62 (br s, 1H), 5.27 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 19.6, 20.1, 28.3, 58.8, 67.2, 68.5, 78.2, 80.2, 156.7. ESI$^+$ (m/z) = 250. Anal. calcd for $C_{11}H_{23}NO_5$: C, 52.99; H, 9.30; N, 5.62. Found: C, 52.78; H, 9.25; N, 5.58%.

4.1.3. (1*S*,2*S*,3*R*)-(2,3-Dihydroxy-1-hydroxymethyl-1-methylbutyl)carbamic acid benzyl ester, 3b and (1*S*,2*R*,3*S*)-(2,3-dihydroxy-1-hydroxymethyl-1-methylbutyl)carbamic acid benzyl ester, 4b. A round-bottomed flask was charged with *tert*-butylic alcohol (12 mL), water (12 mL), AD-mix-α (3.29 g) and methanesulfonamide (0.21 g). The mixture was stirred at rt until both phases are clear, and then cooled to 0°C, whereupon the inorganic salts partially precipitate. Olefin **2** (0.6 g, 2.35 mmol) was added and the heterogeneous slurry was stirred vigorously at 0°C for 12 h. The reaction was quenched at 0°C by addition of sodium sulphite (3.53 g) and then stirred for 1 h. The reaction mixture was extracted with ethyl acetate (3×20 mL) and then dried and concentrated to give a mixture of both diols (*syn* and *anti*) with a diastereoselectivity of 4:1 in favor of the diol *syn*. Without further purification the mixture was dissolved in THF (7 mL) and concentrated HCl (7 mL) was added. The solution was stirred at 25°C for 2 h. Then, HCl was removed to give the corresponding mixture of amino alcohols, which were dissolved in water/THF (1/5, 30 mL) and $Na_2CO_3{\cdot}10H_2O$ (1.68 g, 5.88 mmol) and $ClCO_2CH_2Ph$ (0.46 mL, 3.06 mmol) were added. The mixture was stirred at 25°C for 48 h and then, quenched with saturated NH_4Cl (10 mL) and extracted with ethyl acetate (3×15 mL). The combined organic layers were dried and concentrated. The residue was purified by column chromatography (hexane/ethyl acetate, 3:7) to give **3b** as a white solid (67 mg, 0.23 mmol) and **4b** as an oil (270 mg, 0.96 mmol); yield of **4b**: 41%. Overall yield: 51%. Compound **3b**: mp: 88°C. $[\alpha]_D^{25} = +1.4$ (*c* 0.90, MeOH). ^{1}H NMR ($CDCl_3$): δ (ppm): 1.30 (s, 3H), 1.35 (d, 3H, $J = 6.0$ Hz), 3.36 ('t', 1H, $J = 6.0$ Hz), 3.60–3.83 (m, 3H), 4.20 (br s, 1H), 5.05 (d, 1H, $J = 12.3$ Hz), 5.10 (d, 1H, $J = 12.3$ Hz), 5.81 (br s, 1H), 7.36 (s, 5H). ^{13}C NMR ($CDCl_3$): δ (ppm): 20.3, 21.6, 59.3, 67.0, 68.2, 68.5, 79.3, 128.0, 128.3, 128.6, 136.1, 157.4. ESI$^+$ (m/z) = 284. Anal. calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.27; H, 7.46; N, 4.92%. Compound **4b**: $[\alpha]_D^{25} = -0.4$ (*c* 1.36, MeOH). ^{1}H NMR ($CDCl_3$): δ (ppm): 1.20–1.30 (m, 6H), 3.62–3.97 (m, 6H), 5.06 (s, 2H), 5.57 (s, 1H), 7.34 (br s, 5H). ^{13}C NMR ($CDCl_3$): δ (ppm): 19.5, 19.6, 58.9, 66.9, 67.3, 68.5, 78.2, 128.0, 128.2, 128.5, 136.0, 156.7. ESI$^+$ (m/z) = 284. Anal. calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.25; H, 7.45; N, 4.92%.

4.1.4. (2′*S*,3′*R*,4′*S*)-2,2-Dimethylpropionic acid 2′-*tert*-butoxycarbonylamino-3′,4′-dihydroxy-2′-methylpentyl ester, 5. Triol **4a** (1.22 g, 4.89 mmol) was dissolved in dichloromethane (30 mL) and triethylamine (TEA) (0.75 mL, 5.38 mmol) and pivaloyl chloride (0.66 mL, 5.38 mmol) were added at 25°C. The reaction was stirred for 12 h and then, quenched with water (20 mL) and extracted with ethyl acetate (40 mL). The organic layer was dried and concentrated. The residue was purified by column chromatography (hexane/ethyl acetate, 3:2) to give compound **5** as a white solid (1.06 g, 3.18 mmol); yield: 65%. Mp: 129°C. $[\alpha]_D^{25} = -2.5$ (*c* 1.04, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.21 (s, 9H), 1.29 (d, 3H, $J = 6.3$ Hz), 1.34 (s, 3H), 1.41 (s, 9H), 3.50–3.54 (m, 1H), 3.84–3.90 (m, 1H), 4.24 (d, 1H, $J = 11.1$ Hz), 4.43 (d, 1H, $J = 11.1$ Hz), 4.74–4.80 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 19.3, 21.6, 27.1, 28.2, 38.9, 57.8, 66.0, 68.3, 77.9, 80.5, 156.4, 178.2. MS (EI) (m/z) = 28, 57, 100, 144, 281. ESI$^+$ (m/z) = 334. Anal. calcd for $C_{16}H_{31}NO_6$: C, 57.64; H, 9.37; N, 4.20. Found: C, 57.52; H, 9.35; N, 4.18%.

4.1.5. (2′*S*,3′*R*,4′*S*)-2,2-Dimethylpropionic acid 2′-*tert*-butoxycarbonylamino-3′-hydroxy-4′-methoxymethoxy-2′-methylpentyl ester, 6. Compound **5** (500 mg, 1.50 mmol) was dissolved in dichloromethane (25 mL) and diisopropylethylamine (DIEA) (0.78 mL, 4.50 mmol) and methoxymethyl chloride (MOMCl) (0.34 mL, 4.50 mmol) were added at 25°C. The reaction was stirred for 24 h and then, quenched with water (20 mL) and extracted with ethyl acetate (40 mL). The organic layer was dried and concentrated. The residue was purified by column chromatography (hexane/ethyl acetate, 4:1) to give compound **6** as a white solid (498 mg, 1.32 mmol); yield: 88%. Mp: 82°C. $[\alpha]_D^{25} = -7.1$ (*c* 0.95, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.19 (s, 9H), 1.26 (d, 3H, $J = 6.3$ Hz), 1.34 (s, 3H), 1.39 (s, 9H), 3.35 (s, 3H), 3.57–3.61 (m, 1H), 3.78–3.82 (m, 1H), 4.20–4.30 (br s, 1H), 4.21 (d, 1H, $J = 10.8$ Hz), 4.36 (d, 1H, $J = 10.8$ Hz), 4.60 (d, 1H, $J = 6.9$ Hz), 4.67 (d, 1H, $J = 6.9$ Hz), 4.83 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 16.0, 21.3, 27.1, 28.2, 38.8, 55.6, 57.5, 65.9, 74.0, 76.5, 80.1, 94.9, 156.0, 178.0. MS (EI) (m/z) = 45, 57, 114, 144, 158, 304. ESI$^+$ (m/z) = 378. Anal. calcd for $C_{18}H_{35}NO_7$: C, 57.27; H, 9.35; N, 3.71. Found: C, 57.01; H, 9.31; N, 3.69%.

4.1.6. (1′*S*,4*S*,5*R*)-4-Hydroxymethyl-5-(1′-methoxy-methoxyethyl)-2,2,4-trimethyloxazolidine-3-carboxylic acid *tert*-butyl ester, 7. A solution of **6** (550 mg, 1.46 mmol), 2,2-dimethoxypropane (DMP) (2.33 mL, 18.9 mmol) and *p*-TsOH (6 mg, 0.03 mmol) in toluene (20 mL) was heated under reflux for 2 h and then slowly distilled over 15 min to eliminate the MeOH formed. DMP (2.33 mL, 18.9 mmol) was added and the procedure was repeated until TLC showed no starting material remained. The solvent was removed and the residue partitioned between water (10 mL) and ethyl acetate

(50 mL). The organic layer was dried (Na_2SO_4), concentrated and the crude was dissolved in dichloromethane (15 mL). The solution was cooled to −78°C before addition of DIBAL-*H* (1.0 M in dichloromethane, 3.2 mL, 3.2 mmol). The reaction was stirred for 12 h at −78°C and then quenched by addition of MeOH (5 mL). The mixture was warmed to rt, poured into a solution of potassium sodium tartrate (5 g) in water (15 mL) and the biphasic mixture was stirred vigorously for 2 h. The phases were separated and the aqueous layer was extracted with diethyl ether (2×25 mL). The combined organic layers were dried and concentrated. The residue was purified by column chromatography (hexane/ethyl acetate, 4:1) to give **7** (408 mg, 1.23 mmol) as a colorless oil; yield: 84%. $[\alpha]_D^{25}=+4.0$ (*c* 1.37, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.25–1.29 (m, 6H), 1.39–1.51 (m, 15H), 3.36 (s, 3H), 3.42 (d, 1H, $J=8.1$ Hz), 3.63 (d, 1H, $J=6.9$ Hz), 3.76–3.84 (m, 1H), 3.95–4.01 (m, 1H), 4.57 (d, 1H, $J=6.9$ Hz), 4.71 (d, 1H, $J=6.9$ Hz), 4.72 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.9, 18.0, 25.2, 28.2, 28.4, 56.1, 67.2, 67.6, 72.3, 80.1, 80.7, 92.9, 95.1, 153.2. MS (EI) (m/z)=45, 57, 170, 202, 318. ESI$^+$ (m/z)=334. Anal. calcd for $C_{16}H_{31}NO_6$: C, 57.64; H, 9.37; N, 4.20. Found: C, 57.27; H, 9.30; N, 4.25%.

4.1.7. (1′*S*,4*S*,5*R*)-4-(2″-Hydroxyethyl)-5-(1′-methoxymethoxyethyl)-2,2,4-trimethyloxazolidine-3-carboxylic acid *tert*-butyl ester, 8. Compound **7** (200 mg, 0.60 mmol) was dissolved in dichloromethane (6 mL) and Dess–Martin periodinane (380 mg, 0.90 mmol) was added, at 25°C. The reaction was stirred for 6 h and then, quenched with a solution of NaOH 1 M (5 mL) and extracted with diethyl ether (15 mL). The organic layer was dried and concentrated. The residue, without further purification, was used in next reaction. Methyltriphenylphosphonium bromide (656 mg, 1.80 mmol) was suspended in THF (10 mL) at rt and KHMDS (0.5 M in toluene, 3.6 mL, 1.80 mmol) was added. The resulting yellow suspension was stirred at rt for 1 h. Then, it was cooled to −78°C and a solution of aldehyde achieved after Dess–Martin reaction in THF (5 mL) was added dropwise. The cooling bath was removed and the mixture was allowed to reach 25°C over 15 h. The reaction was quenched with MeOH (2 mL) and the resulting mixture was poured into a solution of saturated potassium sodium tartrate and water (1:1, v/v, 15 mL). Extraction with ethyl ether (2×15 mL), drying and evaporation of the solvent gave a pale oil which was purified by flash chromatography (hexane/ethyl acetate, 9.5:0.5) to give the corresponding olefin (160 mg, 0.49 mmol, 82%) which was dissolved in THF (5 mL) at −25°C. Lithium borohydride (72 μl of 2 M in THF, 0.15 mmol) and the BH_3–THF complex (0.97 mL of 1 M in THF, 0.97 mmol) were added dropwise. After the reaction mixture was stirred overnight at 25°C, it was carefully quenched with water (0.3 mL) followed by 20% NaOH (0.3 mL) and 30% hydrogen peroxide solutions (0.3 mL), stirred for an additional 3 h and extracted with ethyl acetate (2×15 mL). The combined organic layers were dried and concentrated. The residue was purified by column chromatography (hexane/ethyl acetate, 7:3) to give **8** (140 mg, 0.40 mmol) as a colorless oil; yield: 67%. $[\alpha]_D^{25}=+13.8$ (*c* 0.80, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.23–1.30 (m, 6H), 1.46 (s, 12H), 1.53 (s, 3H), 2.06–2.13 (m, 2H), 3.38 (s, 3H), 3.60–3.90 (m, 4H), 4.60 (d, 1H, $J=6.9$ Hz), 4.73 (d, 1H, $J=6.9$ Hz). ^{13}C NMR ($CDCl_3$): δ 18.0, 19.5, 20.6, 24.3, 25.2, 27.0, 28.5, 38.2, 38.5, 56.2, 59.0, 64.4, 72.7, 79.9, 80.5, 92.6, 95.1, 151.7. MS (EI) (m/z)=28, 57, 111, 170, 232, 332. ESI$^+$ (m/z)=348. Anal. calcd for $C_{17}H_{33}NO_6$: C, 58.77; H, 9.57; N, 4.03. Found: C, 58.28; H, 9.41; N, 4.22%.

4.1.8. α- and β-Methyl *N*,*O*-dibenzoyl-L-4-*epi*-vancosamine, 9. Compound **8** (90 mg, 0.26 mmol) was dissolved in dichloromethane (5 mL) and Dess–Martin periodinane (160 mg, 0.39 mmol) was added at 25°C. The reaction was stirred for 6 h and then, quenched with a solution of NaOH 1 M (5 mL) and extracted with diethyl ether (10 mL). The organic layer was dried and concentrated. Without further purification the mixture were dissolved in methanol (3 mL) and HCl 6N (2 mL) was added. The solution was stirred at 25°C for 3 h. Then, HCl was removed to give the corresponding methyl L-4-*epi*-vancosamine, which was dissolved in pyridine (5 mL) and BzCl (0.12 mL, 1.04 mmol) was added. The reaction mixture was stirred for 20 h at 25°C. Ethyl acetate (15 mL) was added and the solution was washed with HCl 1N (7 mL) and saturated aqueous $NaHCO_3$ (7 mL). The organic layer was dried and concentrated. The residue was purified by silica gel flash column chromatography (dichloromethane/ethyl acetate, 9.5:0.5) to give the two isomeric *N*,*O*-dibenzoyl methylglycosides **9a**(α) and **9b**(β) (60 mg, 0.16 mmol) with a relationship α/β of 75:25; Overall yield: 60%. A further silica gel column chromatography (dichloromethane/ethyl acetate, 9.5:0.5) allowed the separation of both compounds. The physical data are identical to that described in the literature.[8b] In the ^{1}H NMR spectra of each compound, recorded at 25°C, it was observed the presence of two conformers, due to the ring interconversion.

Acknowledgements

We thank the Ministerio de Ciencia y Tecnología (project PPQ2001-1305), the Gobierno de La Rioja (project ANGI2001/30 and grant of D.S.) and the Universidad de La Rioja (project API-01/B02). F.C. thanks the Ministerio de Educación y Cultura for a grant.

References

1. (a) Nicolaou, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2097–2152; (b) Williams, D. H.; Bardsley, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1173–1193.
2. (a) Walsh, C. T.; Fisher, S. L.; Park, I. S.; Prahalad, M.; Wu, Z. *Chem. Biol.* **1996**, *3*, 21–28; (b) Courvalin, P. *Antimicrob. Agents Chemother.* **1990**, *38*, 1675–1677.

3. Nagarajan, R. *J. Antibiot*. **1993**, *46*, 1181–1195.
4. Ritter, T. K.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2001**, *40*, 3508–3533.
5. (a) Biavasco, F.; Vignaroli, C.; Lupidi, R.; Manso, E.; Facinelli, B.; Varaldo, P. E. *Antimicrob. Agents Chemother*. **1997**, *41*, 2165–2172; (b) Rodriguez, M. J.; Snyder, N. J.; Zweifel, M. J.; Wilkie, S. C.; Stack, D. R.; Cooper, R. D. G.; Nicas, T. I.; Mullen, D. L.; Butler, T. F.; Thompson, R. C. *J. Antibiot*. **1998**, *51*, 560–569.
6. Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576–1624.
7. (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Vega, J. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2525–2529; (b) Kirschning, A.; Jesberger, M.; Schöning, K.-U. *Synthesis* **2001**, 507–540; (c) Cutchins, W. W.; McDonald, F. E. *Org. Lett*. **2002**, *4*, 749–752 and references cited therein.
8. (a) Gause, G. F.; Brazhnikova, M. G.; Lomakina, N. N.; Berdnikova, T. F.; Fedorova, G. B.; Tokareva, N. L.; Borisova, V. N.; Batta, G. Y. *J. Antibiot*. **1989**, *42*, 1790–1799; (b) Hunt, A. H.; Molloy, R. M.; Debono, M.; Occolowitz, J. L. *Tetrahedron Lett*. **1988**, *29*, 1223–1226; (c) Olsufyeva, E. N.; Backinowsky, L. V. *Tetrahedron Lett*. **1990**, *31*, 4805–4808; (d) Chatterjee, S.; Vijayakumar, E. K. S.; Nadkarni, S. R.; Patel, M. V.; Blumbach, J.; Ganguli, B. N.; Fehlhaber, H.-W.; Kogler, H.; Vertesy, L. *J. Org. Chem*. **1994**, *59*, 3480–3484.
9. Hauser, F. M.; Ellenberger, S. R. *Chem. Rev*. **1986**, *86*, 35–67.
10. Condensation of a dialdehyde, obtained from oxidation of methyl α-L-rhamnopyranoside, with basic nitroethane: (a) Brimacombe, J. S.; Doner, L. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 62–65; (b) Brimacombe, J. S.; Mengech, A. S.; Saeed, M. S. *Carbohydr. Res*. **1979**, *75*, C5–C7; (c) Brimacombe, J. S.; Mengech, A. S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2054–2060; (d) Ahmad, H. I.; Brimacombe, J. S.; Mengech, A. S.; Tucker, L. C. N. *Carbohydr.Res*. **1981**, *93*, 288–293.
11. Synthesis of both enantiomers of 4-*epi*-vancosamine from L- and D-hexos-3-ulose intermediates: (a) Yoshimura, J.; Matsuzawa, M.; Sato, K.-I.; Funabashi, M. *Chem. Lett*. **1977**, 1403–1406; (b) Yoshimura, J.; Matsuzawa, M.; Sato, K.-I.; Nagasawa, Y. *Carbohydr. Res*. **1979**, *76*, 67–78; (c) Yoshimura, J.; Matsuzawa, M.; Funabashi, M. *Bull. Chem. Soc. Jpn*. **1978**, *51*, 2064–2067; (d) Brimacombe, J. S.; Saeed, M. S.; Weakley, J. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2061–2064.
12. Synthesis of the *N*-benzoyl derivatives of 4-*epi*-vancosamine from a chiral diol, prepared in fermenting baker's yeast from α-methylcinnamaldehyde and acetaldehyde: (a) Fronza, G.; Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G. *Tetrahedron Lett*. **1981**, *22*, 5073–5076; (b) Fronza, G.; Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G. *J. Carbohydr. Chem*. **1983**, *2*, 225–248.
13. Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *J. Org. Chem*. **1999**, *64*, 8220–8225.
14. Jurczak, J.; Golebiowski, A. *Chem. Rev*. **1989**, *89*, 149–164.
15. This duplication of signals in the NMR spectra has also been observed in other compounds that incorporate carbamate groups, see: (a) Ref. 13; (b) Parthasarthy, R.; Paul, B.; Korytnyk, W. *J. Am. Chem. Soc*. **1976**, *98*, 6634–6643; (c) Garner, P.; Park, J. M. *J. Org. Chem*. **1987**, *52*, 2361–2364; (d) Monache, G. D.; Di Giovanni, M. C.; Maggio, F.; Misiti, D.; Zappia, G. *Synthesis* **1995**, 1155–1158.
16. Shing, T. K. M.; Tam, E. K. W.; Tai, V. W.-F.; Chung, I. H. F.; Jiang, Q. *Chem. Eur. J*. **1996**, *2*, 50–57.
17. (a) Kolb, H. C.; VanNiewenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483–2547; (b) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 1059–1070.
18. (a) Nagaoka, H.; Rutsch, W.; Schmid, G.; Ilio, H.; Johnson, M. R.; Kishi, Y. *J. Am. Chem. Soc*. **1980**, *102*, 7962–7965; (b) Boschelli, D.; Takemasa, T.; Nishitani, Y.; Masamune, S. *Tetrahedron Lett*. **1985**, *26*, 5239–5242; (c) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453–461.
19. (a) Hatakeyama, S.; Matsumoto, H.; Fukuyama, H.; Mukugi, Y.; Irie, H. *J. Org. Chem*. **1997**, *62*, 2275–2279; (b) Linderman, R. J.; Jaber, M.; Griedel, B. D. *J. Org. Chem*. **1994**, *59*, 6499–6500.
20. Other attempts at oxidation, such as Swern conditions, failed.