Tetrahedron Vol. 45, No. 4, pp. 941 to 950, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00

HIGHLY STEREOSELECTIVE FREE RADICAL C-6-ALLYLATION OF PENAMS - SYNTHESIS OF A NOVEL β-LACTAMASE INHIBITOR.

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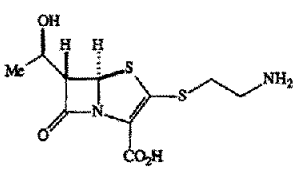
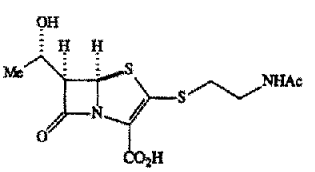
(*Received in Japan* 4 *November* 1988)

Summary - Highly efficient radical-induced C-allylation is possible with 6-bromo and 6,6-dibromopenams with excellent chemo- and stereoselectivity. 6-β-Allyl penicillin 1,1-dioxide sodium salt is a novel β-lactamase inhibitor.

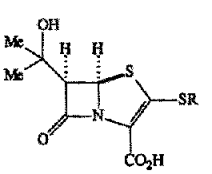
Thienamycin,[1] olivanic acid[2] and carpetimycin[3] are relative newcomers to the large arsenal of naturally occurring classical β-lactam antibiotics.[4] They are unique with regard to the traditional penicillins in that the C-6 amino group is replaced by a carbon substituent, and the thiazolidine ring is in fact a dihydropyrrole (carbapenem).[5] Thienamycin, which is one of the most potent antibiotics in this series, contains an α-orientated (1R)-hydroxyethyl side chain. This unusual substitution pattern has fostered intense efforts aimed at producing hybrid molecules that combine certain features from different classes of β-lactam antibiotics. Interesting examples, are FCE 22101[6] and related penems[7], which incorporate a penem ring structure as well as an α-(1R)-hydroxyethyl side-chain, with the consequence of much enhanced antibacterial activity.



THIENAMYCIN



OLIVANIC ACID



CARPETIMYCIN

Although much effort has been made toward the synthesis of penems[8] and carbapenems,[5] relatively few methods exist for the stereocontrolled introduction of alkyl, alkenyl and related side-chains at C-6 of the penam, penem or carbapenem nucleus. Some of the existing methods are the aldol-type condensation of β-lactam enolates,[9] the sigmatropic rearrangement of allylammonium derivatives,[10] the reaction of 6-diazopenicillanates with allyl sulfides, selenides and bromide followed by free radical desulfuration or debromination,[11] and the hydrogenation of an alkylidene derivative.[12] Free radical cleavage of 6-alkyl-6-isocyanopenams[13] and carbapenems[14] has also been reported as an entry into 6-substituted systems. The formation of 6-α- or 6-β-orientated derivatives depends on the method used. For example in all previously reported free radical mediated reactions, the alkyl chain adopts a β-orientation, since the reduction of the halo or phenylthio groups with tributyltin hydride takes place from the least hindered convex side of the bicyclic β-lactams.[11,13]

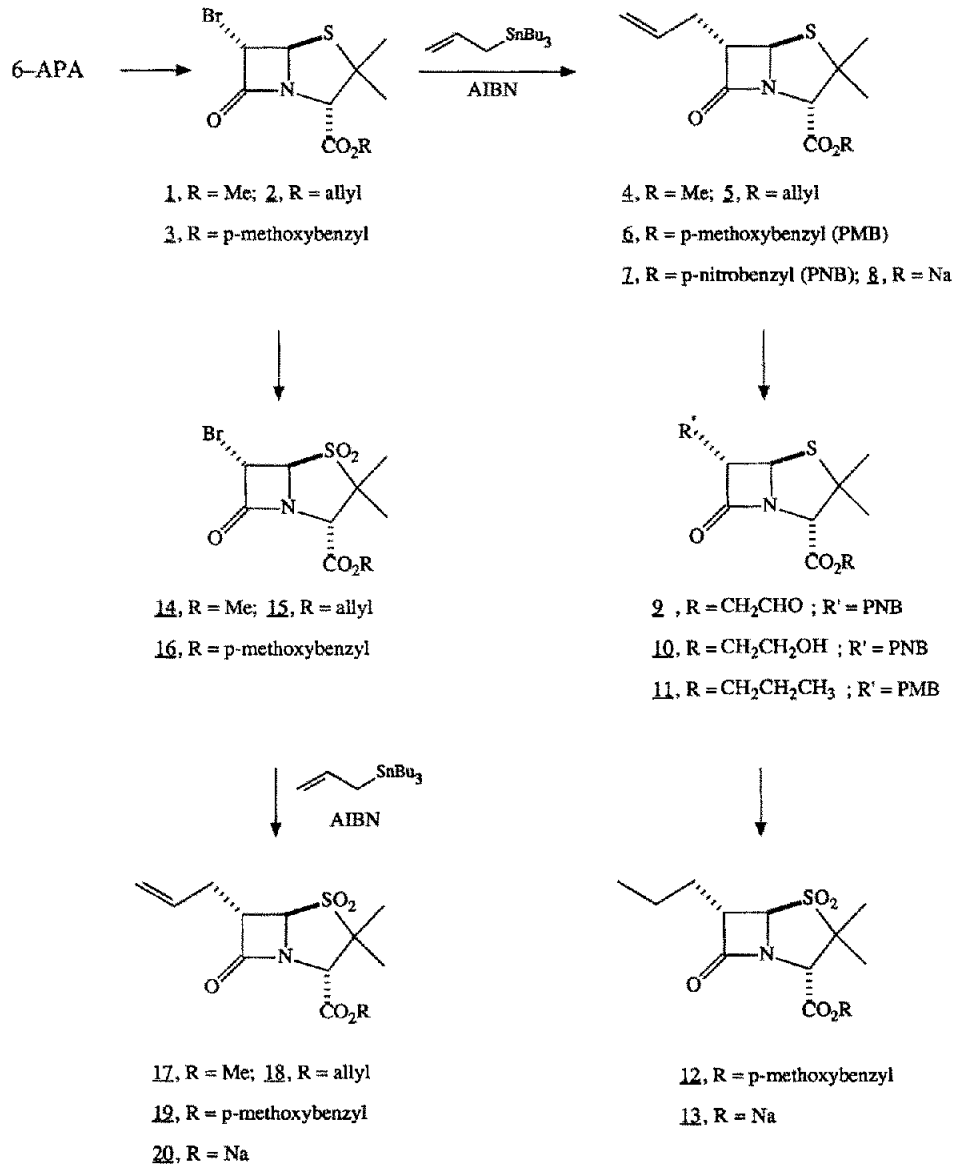
In view of the importance of this type of transformation, and the potential for discovering novel derivatives with antibacterial and/or β-lactamase inhibiting activity,[15] we explored a novel method for the introduction of the versatile allyl group at C-6 of the penam nucleus.[16,17] Free radical reactions[18] are relatively tolerant of a number of functional groups, as evidenced by previously demonstrated compatibility with penams,[11,13,16] 2-azetidinones[14,19] and related systems.[18] To this

end, we studied the direct free-radical allylation of a number of 6-bromo and 6,6-dibromopenicillanates with allyl tributyltin[16] in the presence of a catalytic amount of AIBN.[20] The reactions proved to be highly chemo- and stereoselective and provided access to 6-α- and 6-β-allylpenicillins with or without additional C-6 substitution.

Since a number of penicillin sulfones (1,1-dioxides) have been shown to inhibit β-lactamases,[15,21,22] we opted to prepare sulfone derivatives also and to evaluate their biological activity. It was therefore necessary to prepare a number of esters in order to assess their suitability for deprotection to the corresponding penicillins.

In view of the ready availability of 6-bromopenams from 6-aminopenicillanic acid,[22] we first explored the radical-mediated allylation of several such esters using the methyl ester[23] as a prototype for exploratory studies (Scheme 1). Treatment of the methyl, allyl or p-methoxybenzyl[24] esters 1-3 individually with a slight excess of allyltributyltin and a catalytic quantity of AIBN (henceforth designated as standard conditions), in refluxing benzene, gave high yields of the

Scheme 1



1, R = Me; 2, R = allyl

3, R = p-methoxybenzyl

4, R = Me; 5, R = allyl

6, R = p-methoxybenzyl (PMB)

7, R = p-nitrobenzyl (PNB); 8, R = Na

14, R = Me; 15, R = allyl

16, R = p-methoxybenzyl

9, R = CH_2CHO ; R' = PNB

10, R = CH_2CH_2OH ; R' = PNB

11, R = $CH_2CH_2CH_3$; R' = PMB

17, R = Me; 18, R = allyl

19, R = p-methoxybenzyl

20, R = Na

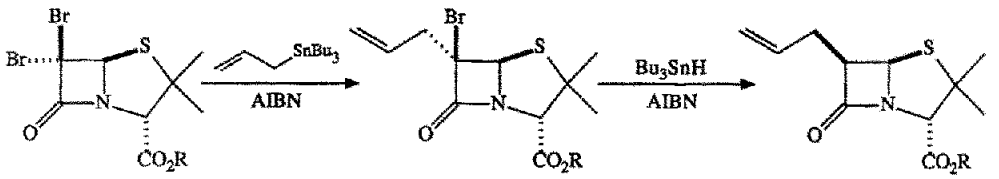
12, R = p-methoxybenzyl

13, R = Na

corresponding 6-α-allylpenicillanates 4-6. The sodium salt 8 was prepared from the allyl ester following established methodology.[25] Since the p-nitrobenzyl ester function was found to be incompatible with the conditions of C-allylation (a notable exception!), this ester was prepared indirectly. Thus, the sodium salt 8 was prepared and treated with p-nitrobenzyl bromide to give the desired ester 7 as an oil. The p-nitrobenzyl and p-methoxybenzyl esters 6 and 7 were then utilized as substrates for the preparation of the 6-α-formylmethyl, 6-α-[(1R)-hydroxyethyl], and 6-α-propylpenicillanates 9-11 respectively by oxidation-reduction sequences. Oxidation of 11 to the sulfone and subsequent ester cleavage[24] using aluminum trichloride gave 6-α-propylpenicillanic acid 1,1-dioxide sodium salt 13. In another sequence of reactions, C-allylation was performed on the 6-α-bromopenicillanate 1,1-dioxide esters 14-16 to give the 6-α-allylpenicillanate 1,1-dioxide esters 17-19. The sodium salt 20, needed for biological testing was prepared from the allyl 18 or p-methoxybenzyl esters.

From the above examples, it was clear that free radical allylation of 6-α-bromopenicillanates occurred with high chemo- and stereoselectivity to give α-C-allylpenams exclusively. Access to 6-β-C-allylpenams with or without a bromine substituent was envisaged next using 6,6-dibromopenicillanates as substrates[9,23] (Scheme 2). When a slight excess of allyltributylstannane was used under the standard conditions only one allyl group was introduced to give the 6-α-allyl-6-β-bromopenicillanates 25 and 26. Reduction with tributyltin hydride gave the corresponding 6-β-allylpenicillanates 27 and 28

Scheme 2



21, R = H; 22, R = Me;

23, R = allyl;

24, R = p-methoxybenzyl;

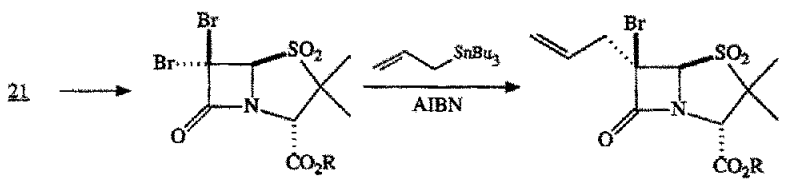
25, R = Me;

26, R = allyl;

27, R = Me;

28, R = allyl;

29, R = Na;



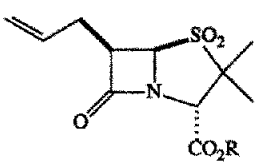
30, R = H;

31, R = allyl;

32, R = p-methoxybenzyl;

33, R = allyl;

15, 16

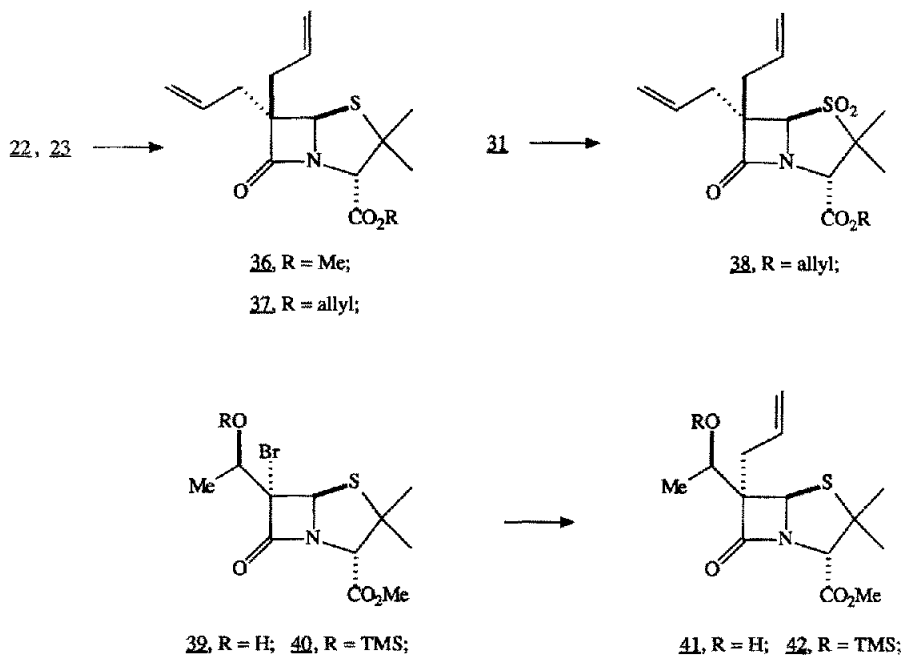


34, R = allyl; 35, R = Na;

respectively. As expected, hydride was delivered from the least hindered α-side of the penam nucleus.[11,16] Ivor John, Thomas and coworkers[11,18] had previously reported the formation of 2,2,2-trichloroethyl 6-α-allyl-6-β-bromopenicillanate from the reaction of the 6-diazopenicillanate with allyl bromide in the presence of $Cu(acac)_2$. The reportedly unstable product, a pale green oil,[11] was reduced with tributyltin hydride to the corresponding 6-β-allylpenicillanate. In related work,[13] the same authors had also reported on the reduction of benzyl 6-β-allyl-6-α-phenylselenopenicillanate to benzyl-6-β-allylpenicillanate. None of these derivatives were de-esterified to the parent 6-β-allyl penicillin. In our hands, attempted allylation of 2,2,2-trichloroethyl 6-α-bromopenicillanate (benzene reflux, 10h) led to concomitant allylation of the ester function.

Since sulfone derivatives were a prime objective in this work, we carried out the alkylation on the 6,6-dibromo sulfone 31, which provided allyl 6-α-allyl 6-β-bromopenicillanate. Reduction with tributyltin hydride and de-esterification led to the sodium salt 35. It is of interest that treatment of the dibromosulfone derivatives 31 and 32 with ethylmagnesium bromide led to reductive debromination[9] to give the 6-α-bromo esters 15 and 16 respectively.

Scheme 3



With methodology capable of introducing the C-allyl group at C-6 of the penam nucleus with a high degree of stereocontrol, we turned our attention to the prospects of geminal C-substitution (Scheme 3). Treatment of the dibromo esters 23 and 24 with a three-fold excess of allyltributyltin under the standard conditions led to the 6,6-di-C-allyl esters 36 and 37 in 84% and 76% yield respectively. Finally, allylation of methyl 6-β-[(1R)-hydroxyethyl]-6-α-bromopenicillanate[26] 39 (or the TMS derivatives 40) gave the corresponding 6-α-allyl derivative 41 (or 42) in 75% yield. The stereochemistry at C-6 was ascertained from N.O.E. studies.

It is therefore clear from our studies that radical-induced C-allylation of 6-bromo-, 6,6-dibromo, and 6-bromo-6-alkylpenicillanates (or 1,1-dioxides) is a highly chemo- and stereoselective reaction. Introduction of the allyl radical takes place from the less hindered side of the penam nucleus and the reactions conditions are tolerant not only of the penam nucleus, but a variety of functional groups as well (with the exception of the p-nitrobenzyl and 2,2,2-trichloroethyl ester groups).

Finally, it should be pointed out that in preliminary experiments, 6-β-allylpenicillin 1,1-dioxide sodium salt, 35, was found to be a potent β-lactamase inhibitor.[27] The 6-α-allyl isomer, as well as several of the other sulfones reported herein were found to be inactive. Thus, the β-orientation of the allyl group in 35 must play a crucial role in its interaction with the enzymes.

EXPERIMENTAL

Melting points are uncorrected. ^1H n.m.r. spectra were recorded in $CDCl_3$ on Brucker 90 MHz and 400 MHz spectrometers. Infrared spectra were obtained as neat films from syrups, or with 781 spectrometer. Optical rotations were measured at room temperature with a Perkin Elmer model 141 polarimeter. Mass spectra were obtained on a VG-1212 low resolution and Kratos-50 high resolution spectrometers by the chemical ionization technique. Work-up in the usual manner signifies, washing the organic phase with water or di. hydrochloric acid, washing with aq. bicarbonate, brine, water, drying ($MgSO_4$) and evaporation to dryness under vacuo. Chromatography was done by the flash column technique.[28] AIBN (azobisisobutyronitrile).

Methyl 6-α-Allylpenicillanate, 4. Allyltributyltin (2g; 6.04 mmol) and AIBN (100 mg) were added to a solution of 1.2 g (4.08 mmol) of methyl 6-α-bromopenicillanate in 50 mL of benzene. The resulting mixture was refluxed under argon for 5 hours. Flash chromatography (230-400 mesh silica, n-hexane then n-hexane/ethyl acetate mixtures as eluants) of the crude mixture allowed the isolation of the title compound as a colorless oil (905 mg; 87%); $[\alpha]_D$ + 237° (c 4.1 $CHCl_3$); IR (film), 1780, 1755, 1645 cm^{-1}; $CDCl_3$ MH^+ 256, (MH^+ - C_5H_6O) 174; NMR (400 MHz, $CDCl_3$): δ: 1.46 (3H, s); 1.63 (3H, s); 2.50 (2H, m); 3.39 (1H, m); 3.76 (3H, s); 5.06 (1H, d,J=1.6 Hz) 5.11-5.16 (2H, m); 5.85 (1H, m).

Allyl 6-α-Allylpenicillanate, 5. Starting from allyl 6-α-bromopenicillanate and following the same procedure as described for the analogous penicillin methyl ester, the title product was obtained as a colorless oil (85%); $[\alpha]_D$ +213° (c 2.7 $CHCl_3$); IR (film) 3080, 1775, 1745 cm^{-1}; MH^+ 282 (MH^+- C_5H_6O); NMR (400 MHz, $CDCl_3$); δ: 1.47 (3H, s); 1.64 (3H, s); 2.53-2.67 (2H, m); 3.87 (1H, m); 4.49 (1H, s); 4.65 (2H, d, J=5.8 Hz); 5.06 (1H, d, J=1.5 Hz); 5.14 (1H, s); 5.15 (1H, dd, J=1.3 and 8.4 Hz); 5.29 (1H, dd, J=1.3 and 8.3 Hz) 5.38 (1H, dd, J=1.4 and 17.1 Hz) 5.79-5.97 (2H, m).

p-Methoxybenzyl 6-α-Allylpenicillanate, 6. Starting from p-methoxybenzyl 6-α-bromopenicillanate and following a procedure similar to that described above, the title product was obtained as colorless oil (81% yield); IR ($CHCl_3$) 1765, 1745 cm^{-1};M^+ 361 NMR ($CDCl_3$, 90 MHz); δ: 1.34 (3H, s); 1.58 (3H, s); 2.57 (2H, m); 3.35 (1H, m); 3.78 (3H, s); 4.44 (1H, s); 5.02 (1H, d, J < 2 Hz); 5.1-5.4 (2H, m); 5.11 (2H, s); 5.6-6.0 (1H, m); 6.87 (2H, d, J=8.5 Hz); 7.30 (2H, d, J=8.5 Hz)

p-Nitrobenzyl 6-α-Allylpenicillanate, 7. A solution of allyl 6-α-allylpenicillanate 5 (2.8 g) in dry THF (50 mL) was treated with sodium ethylhexanoate (1.7 g), triphenylphosphine (200 mg) and tetrakis(triphenylphosphine) palladium(0) (200 mg) and stirred 2h at room temperature under nitrogen. Solvent was removed under vacuum and the residue was dissolved in dry DMF (70 ml) and treated with p-nitrobenzyl bromide (2.8 g). After stirring 2h at room temperature. The reaction mixture was poured into EtOAc/ice-water. The organic phase was dried and evaporated. Flash chromatography of the residue afforded the title product as a light yellow oil (3g; 80% yield); $[\alpha]_D$ + 168° (c 0.98, $CHCl_3$) IR ($CHCl_3$) 1775-1750 cm^{-1} ; M^+ 376; NMR ($CDCl_3$, 90 MHz); δ: 1.45 (3H, s); 1.65 (3H, s); 2.62 (2H, m); 3.42 (1H, m); 4.54 (1H, m); 5.05 (1H, d, J < 2Hz); 5.1-5.4 (2H, m); 5.29 (2H, s); 5.6-6.1 (1H, m); 7.24 (2H, d, J=8.5 Hz); 8.27 (2H, d, J=8.5 Hz).

6-α-Allylpenicillanic Acid Sodium Salt, 8. Allyl 6-α-allylpenicillanate (300 mg) was dissolved in dry THF (3 mL) at room temperature under argon. Sodium ethylhexanoate (185 mg) was added immediately followed by PPh_3 (15 mg) and tetrakis-(triphenylphosphine) palladium(0) (15 mg). The solution was stirred at room temperature. After concentration of the solvent to a small volume, diethyl ether (12 mL) was added and the resulting mixture was stirred 10 minutes. The precipitate was isolated by centrifugation. The crude material was dissolved in a small amount of water and passed through a reverse-phase column (Merck LiChroprep C-18) eluting with distilled water, then with water-acetone mixtures. The fractions containing the product were freeze-dried to afford the title product as a white powder (190 mg; 68%); IR (KBr) 1760, 1605 cm^{-1}; NMR (200 MHz, D_20): δ: 1.50 (3H, s); 1.62 (3H, s); 2.55-2.64 (2H, m); 3.47 (1H, m); 4.25 (H, s); 5.13 (1H, d, J=1.5 Hz); 5.13-5.25 (2H, m); 5.96 (1H, m).

p-Nitrobenzyl 6-α-Formylmethylpenicillanate, 9. A solution of p-nitrobenzyl 6-α-allylpenicillanate (3 g) in dichloromethane (140 mL) and 99% EtOH (70 mL) was cooled to -78°C and ozonized until thin layer chromatography indicated complete consumption of starting material. Dimethylsulphide (4 mL) was added and the reaction mixture was allowed to warm to room temperature. The solution was concentrated and the residue purified by flash-chromatography eluting with n-hexane/ethyl acetate mixtures). The title product was obtained as a foam (1.9 g); [α] + 164° (c 1.16,$CHCl_3$); IR ($CHCl_3$) 1775, 1755, 1730 cm^{-1}; M^+ 378; NMR $CDCl_3$, 90 MHz). δ: 1.42 (3H,s); 1.64 (3H, s); 3.03 (2H, m); 3.68 (1H, m); 4.53 (1H, s); 5.03 (1H, d, J=1.6 Hz); 5.27 (2H, s); 7.55 (2H, d, J=8.5 Hz); 8.25 (2H, d, J=8.5 Hz); 9.82 (1H, s).

p-Nitrobenzyl 6-α-(2-hydroxyethyl)penicillanate, 10. To a solution of p-nitrobenzyl 6-α-formylmethylpenicillanate (900 mg) in dry THF (60 mL), were added acetic acid (500 μl) and sodium-cyanoborohydride (1 g). The mixture was vigorously stirred for 30 minutes at room temperature, then concentrated under vacuum. The residue was taken-up with ethyl acetate and washed with water, 2N hydrocloric acid, 4% aqueous $NaHCO_3$ then water. After drying over sodium sulphate the organic solvent was removed. The title hydroxy compound was obtained in quantitative yield as a foam; $[\alpha]_D$ + 175° (c 1.5, $CHCl_3$); IR ($CHCl_3$) 1745 (broad) cm^{-1}; M^+ 380; NMR ($CDCl_3$, 90 MHz); δ: 1.43 (3H, s); 1.63 (3H, s); 2.0-2.2 (2H, m); 3.45 (1H,m); 3.67-3.80 (2H, m); 3.41 (1H, s); 4.52 (1H, s); 5.13 (1H, d, J=1.6 Hz); 5.29 (2H, s); 7.58 (2H, d, J=8 Hz); 8.25 (2H, d, J=8 Hz).

p-Methoxybenzyl 6-α-Propylpenicillanate, 11. A solution of p-methoxybenzyl 6-α-allylpenicillanate (500 mg) in EtOAc (25 mL) and EtOH (25 mL) was treated with 5% Pd/C (200 mg) and hydrogenated at room temperature for 2h. Filtration of the catalyst, removal of the solvent and flash chromatography of the residue gave the title product as a colorless

oil (quantitative yield);$[\alpha]_D$ + 163° (c 0.43, $CHCl_3$); IR ($CHCl_3$) 1795, 1750 cm^{-1}; M^+ 363; NMR ($CDCl_3$, 90 MHz). δ: 0.90 (3H, t, J=7.0 Hz); 1.33 (3H, s); 1.56 (3H, s); 1.2-2.3 (4H,m); 3.23 (1H, m); 3.43 (3H,s); 4.41 (1H,s); 4.99 (1H,d, J < 2 Hz); 5.08 (2H, s); 6.85 (2H, d, J=8.5 Hz); 7.28 (2H, d, J=8.5 Hz).

p-Methoxybenzyl 6-α-Propylpenicillanate 1,1-Dioxide, 12. A solution of p-methoxybenzyl 6-α-propylpenicillanate (200 mg) in $CHCl_3$ (5 mL) was treated with 80% m-chloroperbenzoic acid (350 mg) and stirred 5h at room temperature. The precipitate was filtered and the filtrate was washed with aqueous $NaHSO_3$ then with aqueous $NaHCO_3$. Removal of the solvent and flash chromatography of the residue gave the title product as a colorless oil (quantitative yield) which crystallized on standing, mp 58-60°C; $[\alpha]_D$ + 153° (c 1,1, $CHCl_3$); IR ($CHCl_3$) 1795, 1750 cm^{-1}; NMR ($CDCl_3$, 90 MHz). δ: 0.97 (3H,t, J=7Hz); 1.25 (3H,s); 1.52 (3H,s); 1.2-2.1 (4H, m; 3.68 (1H, m); 3.82 (3H, s); 4.30 (1H, d, J < 2Hz); 4.35 (1H, s); 5.15 (2H, ABq, J=11 Hz); 6.89 (2H, d, j=8.5 Hz); 7.31 (2H, d, J=8.5 Hz).
Anal. calcd. for $C_{19}H_{25}NO_6S$: C 57.70, H, 6.37; N, 3.54; S, 8.11. Found, C, 57.60; H, 6.30; N, 3.49; S, 7.74.

6-α-Propylpenicillanic Acid 1,1-Dioxide Sodium Salt, 13. A solution of p-methoxybenzyl 6-α-propylpenicillanate 1,1-dioxide (200 mg) in anisole (13 mL) and methylene chloride (1.5 mL) was cooled to -40°C. Aluminum trichloride (300 mg) was added and the resulting mixture was stirred 1h at -40°C. 1M Phosphate buffer (40 mL) and $NaHCO_3$ (1.2 g) were added and the mixture was stirred 10 minutes at room temperature then filtered, washed with ethyl acetate and concentrated under vacuum. The residue was dissolved in the minimum amount of water, and passed through a reverse-phase column (Merck LiChroprep C-18) eluting with water, then water-acetone mixtures. The product-containing fractions were freeze-dried to afford the title product as a white powder (90mg); IR (KBr) 1760, 1615 cm^{-1}.

Methyl 6-α-Bromopenicillanate 1,1-Dioxide,14. Methyl 6-α-bromopenicillanate (735 mg; 2.5 mmol) in $CHCl_3$ (40 mL) at 0° was treated with 80% m-chloroperbenzoic acid (1.5 g; 7 mmol) and stirred 30 min. at 0°C then 4h at room temperature. After stirring with aqueous $NaHSO_3$ and aqueous $NaHCO_3$ the organic phase were stirred over $MgSO_4$ then concentrated under reduced pressure. Flash chromatography of the crude product afforded white crystals (660 mg; 81%); mp 142-144°; [α] + 168° (c 2,3, $CHCl_3$); IR (KBr), 1800, 1755 cm^{-1}.

Allyl 6-α-Bromopenicillanate 1,1-Dioxide, 15. A solution of allyl 6,6-dibromopenicillanate 1,1-dioxide (2.6 g; 6.03 mmol) in dry THF (100 mL) was cooled to -78°C. 2M Ethylmagnesium bromide in ether (2M solution, 3.05 mL = 6.1 mmol) was added dropwise in five minutes. After stirring for 10 min., saturated aq.NH_4Cl (10 mL) was added. The resulting mixture was partitioned between ether and sat.aq.NH_4Cl. After drying over MgSO4, removal of the solvent gave a light yellow waxy solid (2.0 g; 94%). A sample was purified by flash chromatography (n-hexane-ethyl acetate mixtures); [α] + 162° (c 1.8, $CHCl_3$); IR (KBr) 1800, 1755 cm^{-1}; M^+ 351; MH^+ 352 ($MH^+ - SO_2$); NMR ($CDCl_3$, 400 MHz). δ: 1.43 (3H, s); 1.63 (3H, s); 4.44 (1H, s); 4.70 (1H, d, J=1.3 Hz); 4.71 (2H, m); 5.16 (1H, d, J=1.3 Hz); 4.71 (2H, m); 5.16 (1H, d, J=1.3 Hz); 5.35 (1H, dd, J=0.9 and 10.4 Hz); 5.40 (1H, dd, J=1.1 and 17.1 Hz) 5.85-5.97 (1H, m).

p-Methoxybenzyl 6-α-Bromopenicillanate 1,1-Dioxide, 16. Following the same methodology as described above and starting from p-methoxybenzyl 6,6-dibromopenicillanate 1,1-dioxide, the title compound was obtained as white crystals in 83% yield; m.p. 81-83°; $[\alpha]_D$ + 155° (c 1.53, $CHCl_3$); IR (KBr) 1805, 1750 cm^{-1}; NMR ($CDCl_3$, 90 MHz). δ: 1.23 (3H, s); 1.52 (3H, s); 3.78 (3H, s); 4.39 (1H, s); 4.66 (1H, d, J < 2Hz); 5.15 (2H, s); 5.18 (1H, d, J < 2 Hz); 6.87 (2H, d, J=8.5 Hz); 7.31 (2H, d, J=8.5 Hz).
Anal. calcd. for $C_{16}H_{18}NO_6SBr$; C, 44.46; H, 4.20; N, 3.24; S, 7.42; Br, 18.48. Found, C. 44.56, H, 4.24; N. 3.30; 5, 7.32; Br, 18.61.

Methyl 6-α-Allylpenicillanate 1,1-Dioxide, 17. A solution of methyl 6-α-bromopenicillanate 1,1-dioxide (245 mg; 0.75 mmol), allyltributyltin (400 mg; 1.2 mmol) and AIBN (15 mg) in benzene (6 mL), was heated at reflux under argon for 5h. The cooled solution was passed through a short pad of silica gel (230-400 mesh) packed with n-hexane. Eluting with n-hexane then n-hexane-ethyl acetate mixture provided a white solid (200 mg; 93%), m.p. 93-5°; $[\alpha]_D$ + 169° (c 1.5 $CHCl_3$); IR (KBr) 1800, 1750, 1640 cm^{-1}; MH(+) 288, ($MH^+ - C_5H_6O$) 206; NMR ($CDCl_3$, 400 MHz). δ: 1.40 (3H, s); 1.60 (3H, s); 2.61-2.72 (2H,m); 3.81 (1H, m); 3.82 (3H, s); 4.36 (1H, d, J=1.8 Hz); 4.39 (1H, s); 5.18-5.23 (2H, m); 5.78-5.85 (1H, m).

Allyl 6-α-Allylpenicillanate 1,1-Dioxide, 18. A solution of allyl 6-α-bromopenicillanate 1,1-dioxide (1.8 g), allyltributyltin (2.2 mL) and AIBN (50 mg) in benzene (20 mL) was refluxed under nitrogen for 8h. The cooled solution was directly passed through a silica gel column packed with cyclohexane. Eluting with cyclohexane then with cyclohexane/EtOAc mixtures afforded a crude product which was freed from traces of tin derivatives by partitioning between n-hexane and acetonitrile. Acetonitrile was removed under vacuum affording the title compound as a colorless oil (1.1 g; 69%); $[\alpha]_D$ + 153° (c 1.2 $CHCl_3$); IR ($CHCl_3$) 1800, 1755 cm^{-1}; M^+ 313; NMR ($CDCl_3$, 90 MHz). d: 1.37 (3H, s); 1.58 (3H, s); 2.63 (2H, m); 3.75 (1H, m); 4.32 (1H, d, J < 2 Hz); 4.37 (1H, s); 4.65 (2H, d, J=7 Hz); 5.0-5.5 (4H, m); 5.6-6.1 (2H, m).

p-Methoxybenzyl 6-α-Allylpenicillanate 1,1-Dioxide, 19. Starting from p-methoxybenzyl 6-α-bromopenicillanate 1,1-dioxide and following the same methodology as described in the previous example gave the title product as a colorless oil (76% yield) which crystallized on standing, mp 59-60°C; $[\alpha]_D$ + 155° (c 1.21, $CHCl_3$); IR ($CHCl_3$) 1790, 1750 cm^{-1}; NMR ($CDCl_3$, 90 MHz). δ: 1.22 (3H, s); 1.49 (3H, s); 2.61 (2H, m); 3.73 (1H, m); 3.77 (3H, s); 4.28 (1H, d, J=2Hz); 4.32 (1H, s); 5.12 (2H, ABq, J=11 Hz); 5.0-5.3 (2H, m); 5.6-6.1 (1H, m); 6.86 (2H, d, J=8.5 Hz); 7.28 (2H, d, J=8.5 Hz).
Anal. calcd. for $C_{19}H_{22}NO_{65}$: C, 57.99; H, 5.89; N, 3.56, S, 8.15. Found, C, 58.01, H, 5.99; N, 3.55; S, 8.06.

6-α-Allylpenicillanic Acid 1,1-Dioxide Sodium Salt,20 - From 18 - Allyl 6-α-allylpenicillanate 1,1-dioxide (500 mg) was dissolved in dry THF (6 mL) at room temperature under argon. Sodium ethylhexanoate (300 mg), triphenylphosphine (70 mg) and tetrakis (triphenylphosphine) palladium(0) (70 mg) were added sequentially. The solution

was stirred 20 minutes at room temperature then diethyl ether (30 mL) was added. The precipitate was isolated by centrifugation then dissolved in a small amount of water and passed through a reverse phase column (Merck LiChroprep C-18) eluting with water and water/acetone mixtures. Fractions containing the product were pooled and freeze-dried to afford the title compound as a white powder (300 mg; 70%); IR (KBr) 1760, 1610 cm^{-1}; NMR (200 MHz, D_2O; 1.43 (3H, s); 1.58 (3H, s); 2.68 (2H, m); 3.84, (2H, m); 4.21 (1H, s); 4.86 (1H, d, J=1.7 Hz); 5.2-5.3 (2H, m); 5.94 (H, m)..

6-α-Allylpenicillanic Acid 1,1-Dioxide Sodium Salt, 20. From 19 - Starting from p-methoxybenzyl 6-α-allylpenicillanate 1,1-dioxide and following the same procedure as described for 13, the title product was obtained as white powder in 62% yield; IR (KBr) 1760, 1610 cm^{-1}.

Methyl 6-α-Allyl-6-β-Bromopenicillanate, 25. Methyl 6,6-dibromopenicillanate (1.0 g) was dissolved in benzene (35 mL) then treated with allyltributyltin (1.0 g) and a catalytic amount of AIBN. The mixture was heated at reflux for 4h under argon, then concentrated under reduced pressure. Flash chromatography over silica-gel (eluting with n-hexane then n-hexane-ethyl acetate) allowed the separation of three products. The faster running product (TLC: n-hexane - ethyl acetate 1/2) was shown to be methyl 6,6-diallylpenicillanate (103 mg; 13%). The second eluted product was unreacted starting material (260 mg; 26%). The slower running fraction afforded the title compound as a light yellow oil (474 mg; 53%); $[\alpha]_D$ + 211° (c 1.1 $CHCl_3$); IR (film) 1790, 1750 cm^{-1}; M^+ 333; NMR (400 MHz, $CDCl_3$). δ: 1.46 (3H, s); 1.67 (3H, s); 3.03 (2H, m); 3.78 (3H, s); 4.51 (1H, s); 5.24-5.31 (2H, m); 5.33 (1H, s); 5.88 (1H, m).

Allyl 6-α-Allyl-6-β-Bromopenicillanate, 26. Starting from allyl 6,6-dibromopenicillanate and following the same procedure as described in the above example, the title product was obtained as a colorless oil (55%); $[\alpha]_D$ + 194° (c 5.6 $CHCl_3$); IR (film) 1790, 1745 cm^{-1}; M^+ 359; NMR (400 MHz, $CDCl_3$). δ: 1.47 (3H, s); 1.67 (3H, s); 3.03 (2H, m); 4.52 (1H, s); 4.66 (2H, m); 5.25-5.41 (4H, m); 5.33 (1H, s); 5.84-5.93 (1H, m).

Methyl 6-β-Allylpenicillanate, 27. Tributyltinhydride (270 ml) and a catalytic amount of AIBN were added to a solution of methyl 6-α-allyl-6-β-bromopenicillanate (280 mg) in benzene (15 mL). The mixture was stirred 1h at room temperature, then concentrated under vacuum. Chromatography on silica gel (n-hexane then n-hexane-ethyl acetate as eluants) afforded a colorless oil (185 mg); $[\alpha]_D$ + 163° (c 1.0 $CHCl_3$); IR ($CHCl_3$) 1810, 1755 cm^{-1}; MH^+ 256;NMR (90 MHz, $CDCl_3$). δ: 1.45 (3H, s); 1.65 (3H, s); 3.09 (2H, d, J=7 Hz); 4.52 (1H, s); 4.53 (1H, s); 4.72 (2H, d, J=6 Hz); 5.20-5.60 (4H, m); 5.71-6.27 (2H, m).

Allyl 6-β-Allylpenicillanate, 28. Starting from allyl 6-α-allyl-6-β-bromopenicillanate and following the same procedure as described in the previous example, gave a colorless oil, corresponding to the title product, in 83% yield; $[\alpha]_D$ + 86° (c 5.0 $CHCl_3$); IR (film) 1755, 1745 cm^{-1}; MH^+ 282; NMR (400 MHz, $CDCl_3$). δ: 1.48 (3H, s); 1.65 (3H, s); 2.54 (2H, m); 3.69 (1H, dt, J=4.3 and 7.2 Hz); 4.38 (1H, s); 4.66 (2H, m); 5.06-5.13 (2H, m); 5.29 (1H, dd, J-1.1 and 10.3 Hz) 5.37 (1H, dd, J=1.3 and 17.2 Hz); 5.43 (1H, d, J=4.3 Hz); 5.74 -5.81 (1H, m); 5.88-5.96 (1H, m).

6-β-Allylpenicillanic Acid Sodium Salt, 29. Allyl 6-β-allylpenicillanate (2.0g) was dissolved in dry THF (20 mL) at room temperature. Sodium ethyl hexanoate (1.25 g), triphenylphosphine (400 mg) and tetrakis (triphenylphosphine) palladium(0) (60 mg) were added sequentially. The solution was stirred 35 minutes at room temperature, then diethyl ether (200 mL) was added. The precipitate was collected by centrifugation, dissolved in a small amount of water, and passed through a reverse phase column (Merck LiChroprep C-18) eluting with water and water/acetonitrile mixtures. The product-containing fractions were pooled and freeze-dried to afford the title product as a white powder (1.48 g); IR (KBr) 1760, 1610 cm^{-1}; NMR (200 MHz, D_2O); 1.52 ($3H_2S$); 1.65 (3H, s), 2.5-2.6 (2H, m); 3.86 (1H, t, J=4.2, 8.4 Hz); 4.17 (1H, s); 5.1-5.2 (2H, m); 5.49 (1H, d, J=4.2 Hz); 5.90 (1H, m).

Allyl 6,6-Dibromopenicillanate 1,1-Dioxide, 31. 6,6-Dibromopenicillanic acid 1,1-dioxide (15.6 g) was dissolved in DMF (150 mL) and treated with triethylamine (7 mL) and allyl bromide (4.3 mL). The resulting mixture was stirred for 4h at room temperature, then poured into EtOAc/ice-water. The organic phase was washed twice with water then dried and concentrated. The residue was crystallized from diisopropylether-n-hexane to afford the title product as white crystals (13 g; 76%); $[\alpha]_D$ + 172° (c 4.9 $CHCl_3$); m.p. 80-82°; IR (KBr) 1810, 1755 cm^{-1}; NMR ($CDCl_3$, 400 MHz). δ: 1.42 (3H, s); 1.63 (3H, s); 4.53 (1H, s); 4.72 (2H, m); 5.02 (1H, s); 5.35 (1H, dd, J=0.8 and 10.3 Hz); 5.41 (1H, dd J=1.3 and 16.9 Hz); 5.89-5.96 (1H, m).
Anal. calcd. for $C_{11}H_{13}NO_5SBr_2$; C, 30.65; H, 3.04; N, 3.25; S, 7.44; Br, 37.06. Found. C, 31.37; H, 3.15; N, 3.35; S, 7.25; Br, 38.05.

p-Methoxybenzyl 6,6-Dibromopenicillanate 1,1 Dioxide, 32. A solution of 6,6-dibromopenicillanic acid 1,1-dioxide (47 g) in dry DMF (220 mL) was treated with triethylamine (26.4 mL) at 0°C. p-Methoxybenzylchloride (27.8 mL) and sodium iodide (20 g) were added and the resulting mixture was stirred overnight. The slurry was slowly poured onto ice-water under vigorous stirring. The precipitate was filtered, washed with water then dried in vacuo. Crystallization from methanol gave white crystals (49 g; 85%). m.p. 130-131°C; [α] + 169° (c 0.91, $CHCl_3$); IR (KBr) 1815, 1745 cm^{-1}; (NMR ($CDCl_3$, 90 MHz). δ: 1.19 (3H, s); 1.51 (3H, s); 3.78 (3H, s); 4.46 (1H, s); 4.94 (1H, s); 5.16 (2H, ABq, J=10 Hz); 6.87 (2H, d, J=8.5 Hz); 7.28 (2H, d, J=8.5 Hz).
Anal. calcd. for $C_{16}H_{17}NO_6Br_2$, C, 37.59; H, 3.35; N, 2.74; S, 6.27. Found, C, 38.08, H. 3.48: N N 2.70; S, 6.27.

Allyl 6-α-Allyl-6-β-Bromopenicillanate 1,1-Dioxide, 33. Starting from allyl 6,6-dibromopenicillanate 1,1-dioxide and following the same procedure as described for compound 25 the title product was obtained as a yellowish oil (55%); $[\alpha]_D$ + 163° (c 1.0 $CHCl_3$); IR ($CHCl_3$) 1810, 1755 cm^{-1}; M^+ 391; NMR (90 MHz, $CDCl_3$). δ: 1.45 (3H, s); 1.65 (3H, s); 3.09 (2H, d, J=7 Hz); 4.52 (1H, s); 4.53 (1H, s); 4.72 (2H, d, J=6 Hz); 5.20-5.60 (4H, m); 5.71-6.27 (2H, m).

Allyl 6-β-Allylpenicillanate 1,1-Dioxide, 34. Starting from allyl 6-α-allyl-6-β-bromopenicillanate 1,1-dioxide, and following the procedure described for compound 27, the title product was obtained as a colorless oil (88%); $[\alpha]_D$ + 192° (c 1.0 $CHCl_3$); IR ($CHCl_3$) 1810, 1755 cm^{-1}; M^+ 313; NMR (90 MHz, $CDCl_3$). δ: 1.43 (3H, s); 1.62 (3H, s); 2.5-3.3 (2H,m); 3.92 (1H, m); 4.48 (1H, s); 4.63 (1H, d, J=4.5 Hz); 4.71 (2H, d, J=6 Hz); 5.1-5.6 (4H, m); 5.65-6.25 (2H, m).

6-β-Allylpenicillanic Acid 1,1-Dioxide Sodium Salt, 35. Starting from allyl 6-β-allylpenicillanate 1,1-dioxide and following the same procedure as described for 20, the title product was obtained in 54% as white powder; IR (KBr) 1770, 1750, 1605 cm^{-1}; NMR (200 MHz, D_2O). δ: 1.41 (3H, s); 1.54 (3H, s); 2.50-2.96 (2H, m); 4.21 (1H, m); 4.26 (1H, s); 5.07 (1H, d, J=4.1 Hz); 5.14-5.26 (2H, m); 5.92 (1H, m).

Methyl 6,6-Diallylpenicillanate, 36. A solution of methyl 6,6-dibromopenicillanate (120 mg; 0.32 mL) was treated with AIBN (10 mg) and refluxed 6h under argon. After removal of the solvent, the crude product was chromatographed on silica gel (n-hexane then n-hexane-ethyl acetate as eluants), small amounts of tributyltin derivatives were removed by partitioning between n-hexane and acetonitrile. Evaporation of the lower layer afforded the title product as a colorless oil (79 mg; 84%);.$[\alpha]_D$ +256° (c 0.5 $CHCl_3$); IR (film) 1770, 1750 cm^{-1}, MH^+ 296, (MH^+ - $C_8H_{10}O$) 174; NMR (400 MHz, $CDCl_3$). δ: 1.46 (3H, s); 1.64 (3H, s); 2.57 (4H, m); 3.76 (3H, s); 4.40 (1H, s); 5.15 (1H, s); 5.13-5.22 (4H, m); 5.72-5.91 (2H, m).

Allyl 6,6-Diallylpenicillanate, 37. Starting from allyl 6,6-dibromopenicillanate and following the same procedure for the analogous penicillin methyl ester, the title product was obtained as oil (76%); $[\alpha]_D$ + 246° (c 3.3 $CHCl_3$); IR (film) 3080, 1770, 1750, 1640 cm^{-1}; NMR (400 MHz, $CDCl_3$); δ: 1.48 (3H, s); 1.64 (3H, s); 2.55 (4H, m); 4.4l (1H, s); 4.65 (2H, d, J=6.0H); 5.15 (1H, s); 5.14-5.20 (2H, m); 5.27 (1H, dd, J=1.2 and 10.3 Hz); 5.36 (1H, dd, J=1.5 and 17.0 Hz); 5.72-5.93 (2H, m). MH^+ 322, (MH^+ - $C_8H_{10}O$) 200.

Allyl 6,6-Diallylpenicillanate 1,1-Dioxide, 38. Starting from allyl 6,6-dibromopenicillanate 1,1-dioxide and following the same procedure to that described before the title product was obtained as a colorless oil (72%);. $[\alpha]_D$ + 185° (c 1.3 $CHCl_3$); IR ($CHCl_3$) 1785, 1750 cm^{-1}; NMR (90 MHz, $CDCl_3$). δ 1.37 (3H, s); 1.58 (3H, s); 2.49 (1H, dd, J=7.5 and 14 Hz); 2.62 (2H, d, J=7.5 Hz); 2.80 (2H, dd, J=7 Hz); 4.24 (1H, s); 4.43 (1H, s); 4.43 (1H, s), 4.67 (2H, d, J=6 Hz); 5.07-5.50 (6H, m); 5.56-6.10 (3H, m).

Methyl 6-α-Bromo-6-β-[(1R)trimethylsilyloxyethyl]-Penicillanate, 40. Methyl 6-α-bromo-6-β-[(1R)-hydroxyethyl]penicillanate (3.37 g; 10 mmol) in dry DMF (30 mL) at room temperature was treated with imidazole (2.04 g; 30 mmol) and trimethylchlorosilane (2.54 ml; 20 mmol). The resulting mixture was stirred overnight. The mixture was worked-up by pouring into water/n-hexane. The organic phase was dried over Na_2SO_4 and concentrated to a small volume. Flash chromatography of the mixtures crude product (n-hexane-ethyl acetate mixtures as eluants) gave a colorless oil which crystallized upon standing (3.89 g; 95%); $[\alpha]_D$ + 192° (c 8.8 $CHCl_3$); mp 64-65°.

Methyl 6-α-Allyl-6-β-[(1R)-hydroxymethyl]-Penicillanate, 41. Allyltributyltin (157 mg; 0.47 mmol), methyl 6-α-bromo-6-β-[(1R)hydroxyethyl]-penicillanate (80 mg; 0.237 mmol) and AIBN (5 mg) in benzene (10 mL) were refluxed for 35h under argon. The crude reaction mixture was chromatographed on silica gel eluting with n-hexane, then n-hexane-ethyl acetate mixtures allowing the isolation of the title product as colorless oil (58 mg; 82%); $[\alpha]_D$ + 202° (c 1.0 $CHCl_3$); IR (film) 3500, 1750 cm^{-1}; MH^+ - $C_7H_9O_2$) 174; NMR (400 MHz, $CDCl_3$); δ: 1.16 (3H, d, J=6.2 Hz); 1.47 (3H, s); 1.66 (3H, s); 2.40 (1H, dd, J=8.4 and 14.5 Hz); 2.59 (1H, d, J= 2Hz), exch. D_2O) 2.86 (1H, dd, J=6.3 and 14.5 Hz); 3.77 (3H, s); 4.43 (1H, s); 4.46 (1H, dd, J=2 and 6.2 Hz); 5.19 (1H, s); 5.19-5.27 (2H, m); 5.82-5.92 (1H, m).

Methyl 6-α-Allyl-6-β-[(1R)trimethylsilyloxyethyl]-Penicillanate, 42. Methyl 6-α-bromopenicillanate (250 mg; 0.61 mmol) was dissolved in dry benzene (20 mL) and treated with allyltributyltin (331 mg; 1.0 mmol) and a catalytic amount of AIBN (10 mg). The resulting mixture was refluxed under argon for 4h. After concentration, the residue was purified by flash chromatography (eluted with n-hexane, n-hexane-ethyl acetate). Traces of tributyltin derivatives were removed by partitioning in n-hexane/CH_5CN and evaporating the lower layer. The title product was obtained as colorless oil (170 mg; 75%);.$[\alpha]_D$ + 195° (c O.5 $CHCl_3$) IR (film) 1775, 1750 cm-1; MH^+ 372, (MH^+-$C_{10}H_{18}O_2Si$) 174; NMR (400 MHz, $CDCl_3$). δ: 0.12 (9H, s); 1.1. (3H, d, J=6.2 Hz); 1.44 (3H, s); 2.35 (1H, dd, J=8.6 and 14.4 Hz); 2.88 (1H, dd, J=6.1 and 14.4 Hz); 3.74 (3H, s); 4.40 (1H, 9, J=6.2 Hz); 5.16 (1H, dd, J=0.8 and 9.1 Hz); 5.19 (1H, dd, J=1.4 and 15.2 Hz); 5.87 (1H, m).

GENERAL PROCEDURE FOR THE REMOVAL OF THE ALLYL ESTER[25]

The allylpenicillanate (1 mmol) was dissolved in dry THF (6 ml) at room temperature under argon. Sodium ethylhexanoate (1.2 mmol) was added immediately followed by PPh_3 (0.1 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.02 mmol). The solution was stirred 1h at room temperature. After concentration of the solvent to small volume, diethyl ether (20 mL) was added and the resulting mixture was stirred 10 minutes at room temperature. The precipitated solid was isolated by centrifugation. The crude material was dissolved in a small amount of water and passed through a reverse-phase column (Merck Lichroprep C-18) eluting with distilled water then with water/acetone mixtures. The product containing fractions were freeze-dried to afford the sodium penicillanate as white powder (45/80% yield).

6-β-Allylpenicillanic acid sodium salt (68%). IR (KBr) 1755, 1595 cm^{-1}); NMR (200 MHz, D_2O). δ: 1.52 (3H, s); 1.66 (3H, s); 2.53 (2H, m); 3.86 (1H, m); 4.17 (1H, s); 5.11-5.21 (2H, m); 5.49 (1H, d, J=4.2 Hz); 5.87 (1H, m).

6,6-Diallylpenicillanic acid sodium salt, (49%). IR (KBr) 1730, 1640-1610 cm^{-1}; NMR (200 MHz, D_2O). δ: 1.52 (3H, s); 1.64 (3H, s); 2.53-2.65 (4H, m); 4.18 (1H, s); 5.24 (1H, d, J=10 Hz); 5.25 (1H, s); 5.26 (1H, dd, J=2 and 16 Hz); 5.89 (1H, m).

6-α-Allyl-6-β-bromopenicillanic acid sodium salt (69%). IR (KBr) 1750, 1600 cm^{-1}; NMR (200 MHz, D_2O). δ: 1.52 (3H, s); 1.65 (3H, s); 3.08 (2H, d, J=7Hz); 4.32 91H, s); 5.31 (1H, d, J=9 Hz); 5.34 (1H, d, J=17 Hz); 5.47 (1H, s); 5.96 (1H, m).

6-α-Allylpenicillanic acid sodium salt (74%). IR (KBr) 1760, 1605 cm^{-1}; NMR (200 MHz, D_2O). δ: 1.50 (3H, s); 1.62 (3H, s); 2.55-2.64 (2H, m); 3.47 (1H, m); 4.25 (1H, s); 5.13 (1H, d, J=1.5 Hz); 5.13-5.25 (2H, m); 5.96 (1H, m).

6,6-Allylpenicillanic acid 1,1-dioxide sodium salt (59%). IR (KBr) 1780, 1630 cm^{-1}; NMR (200 MHz, D_2O); δ: 1.42 (3H, s); 1.56 (3H, s); 2.51 (1H, d, J=6.5 and 16 Hz); 2.77 (2H, d, J=7.0 Hz); 3.00 (1H, dd, J=6.5 and 16 Hz); 2.77 (2H, d, J=7.0 Hz); 3.00 (1H, dd, J=6.5 and 16 Hz); 4.28 (1H, s); 5.25 91H, d, J=2Hz); 5.28 (1H, dd, J=1.8 and 9.2 Hz); 5.29 (1H, d, J=16.5 Hz); 5.87 (1H, m).

6-α-Allyl-6-β-bromopenicillanic acid 1,1-dioxide sodium salt (63%). IR (KBr) 1780, 1620 cm^{-1}; NMR, 200 MHz, D_2O). δ: 1.44 (3H, s); 1.58 (3H, s); 3.16 (2H, d, J=7Hz); 4.35 (1H, s); 5.16 (1H, s); 5.37 (1H, dd, J=0.9 and 9.6 Hz); 5.39 (1H, dd, J=1.4 and 17.6 Hz); 5.96 (1H, m).

6-β-Allylpenicillanic acid 1,1 dioxide sodium salt (57%). IR (KBr) 1770, 1750, 1605 cm^{-1}; NMR (200 MHz, D_2O). δ: 1.41 (3H, s); 1.54 (3H, s); 2.50-2.96 (2H, m); 4.21 (1H, m); 4.26 (1H,s); 5.07 (1H, d, J=4.1 Hz); 5.14-5.26 (2H, m); 5.92 (1H, m).

ACKNOWLEDGEMENTS

We thank Farmitalia-Carlo Erba for a sabbatical leave to M.A. and for financial assistance. We thank the Mass spectrometry and NMR laboratories at the Université de Montréal and Farmitalia Carlo Erba for spectroscopic services. We especially thank the biological division of FCE for the β-lactamase inhibition tests.

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