Nuclear analogs of β-lactam antibiotics. XV.[1] Synthesis of 6-substituted 2-methylpenem-3-carboxylic acids

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The synthesis of 6-substituted 2-methylpenem-3-carboxylic acids is described. The dianion **6** was prepared *in situ* from 2-methylpenem-3-carboxylic acid (**5**) by the addition of two equivalents of *n*-butyllithium in THF at −78°C. This dianion reacted with deuterated acetic acid, acetone, acetaldehyde, benzaldehyde, and methyl thiomethylsulfonate to give 6-deuterio-, 6-(2′-hydroxy-2′-propyl)-, 6-(1′-hydroxyethyl)-, 6-(1′-hydroxybenzyl)-, 6-methylthio-2-methylpenem-3-carboxylic acids and their sodium or potassium salts, **7–11**, respectively. The stereochemistry of the products is also discussed.

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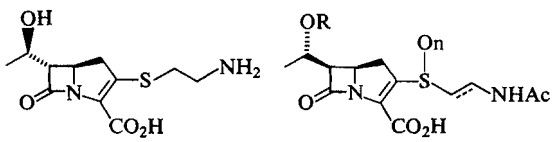
On décrit la synthèse d'acides méthyl-2 penèmecarboxyliques-3 substitués en position 6. On a préparé le dianion **6** *in situ* à partir de l'acide méthyl-2 penèmecarboxylique-3 (**5**) par l'addition de deux équivalents de *n*-butyllithium dans le THF à −78°C. Les réactions de ce dianion avec l'acide acétique deutéré, l'acétone, l'acétaldehyde, le benzaldéhyde et le thiométhylsulfonate de méthyle conduisent respectivement aux acides deutéro-6, (hydroxy-2 propyl-2)-6, (hydroxy-1′ éthyl)-6, (hydroxy-1′ benzyl)-6 et méthylthio-6 méthyl-2 penèmecarboxyliques-3 (**7–11**) aussi qu'à leurs sels de sodium ou de potassium. On discute aussi de la stéréochimie des produits.

[Traduit par le journal]

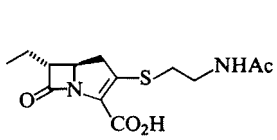
Naturally occurring carbapenem antibiotics, isolated from *streptomyces* species, were shown to differ markedly from the classical penicillins and cephalosporins in the composition of their side chain at position 6: thienamycin (**1**) (1) and the olivanic acids (**2**) (2) possess a 1-hydroxyethyl moiety while PS-5 (**3**) (3) and carpetimycins (or C-19393) (**4**) (4) carry a simple ethyl group and a 2-hydroxypropyl group respectively as a substituent.

In order to assess the influence of the side chain on the biological activity of the analogous penems, members of a new class of totally synthetic antibiotics (5), we prepared a series of 6-substituted penem-3-carboxylic acids (6). In this paper[3] we report the most direct and most desirable approach to 6-substitution: a one-step introduction of the 6-substituent onto a preformed 6-unsubstituted 2-substituted penem-3-carboxylic acid by metallation and subsequent reaction with electrophiles.



1

2 (R = H, SO_3H)



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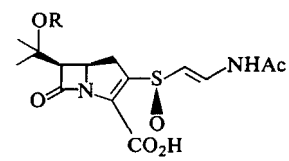

4 (R = H, SO_3H)

Although metallation of monocyclic β-lactams is well documented (7–9) and this method has been used in the total synthesis of thienamycin (10) and in the synthesis of 6-substituted penem acids (5*e*, 6*c*), a direct metallation on 6-unsubstituted penem acid has not been reported. Furthermore, electrophilic additions to enolates of the penam and the cephem nuclei have been achieved (11, 12) but, because of the lability of the penem system, especially toward strong bases, it was generally assumed (5*e*) that such a process would not be possible with the penem nucleus.

The dianion **6** was prepared from 2-methylpenem-3-carboxylic acid (**5**) (6*a*) by the addition of two equivalents of *n*-butyllithium in the presence or absence of diisopropylamine (2 equiv.) in THF at −78°C. This species was stable enough at −78°C to react with a variety of electrophiles to give the 6-substituted penem acids. Thus, the dianion, so prepared, reacted with CD_3CO_2D, acetone, acetaldehyde, benzaldehyde, or methyl thiomethylsul-

[1]For Part XIV see ref. 17.

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[3]Following papers will describe the synthesis of 6-substituted penems where the 6-substituents are introduced at an earlier stage in the sequence. See also ref. 6*c*.

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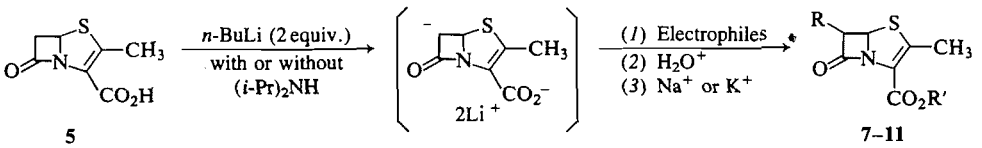


5 6 7–11

SCHEME 1

fonate to yield 6-substituted 2-methylpenem-3-carboxylic acids or the corresponding sodium or potassium salts, **7–11**, in 6–60% yield. Most of the penem acid products were immediately converted to their sodium or potassium salts, **8***a*, **9**, **10**, and **11***a*. 6-(1′-Hydroxyethyl) or 6-(1′-hydroxybenzyl) derivatives could not be isolated in the acid form without serious decomposition.

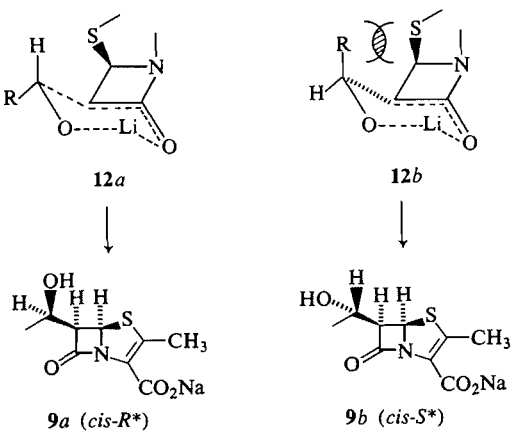
The infrared spectrum of each product showed a strong β-lactam carbonyl band in the 1750–1793 cm^{-1} region. The ultraviolet spectrum of each product exhibited a maximum at around 300 nm. These data indicated that the penem ring system had been retained.

Examination of the ^{1}Hmr spectrum of each product revealed that the reaction of this dianion with the above electrophiles produced a mixture of *cis* and *trans* 6-substituted penem acids or the corresponding salts. The *cis–trans* ratio varied from 4:1 to 3:7 as listed in Table 1. The relative stereochemistry at C5—C6 of each product was determined based on the fact that *cis* β-lactam coupling constants (~4 Hz) were larger than *trans* coupling constants (~2 Hz) (13). Deuterated acetic acid, acetaldehyde, and methyl thiomethylsulfonate gave the *cis* isomers as the major product. Among these, the smallest electrophile, CD_3CO_2D, produced the highest ratio of the *cis* isomer (80% *cis*). This preferential formation of the sterically more hindered *cis* isomers is quite unusual, although there are a few examples in similar systems (8, 12). However, when bulkier electrophiles such as acetone were employed, steric hindrance between the incoming electrophile and the thiazoline ring was large enough to force the electrophile to come from the other side of the thiazoline group, yielding the *trans* isomer as the major product. In the case of benzaldehyde the situation was well balanced, giving a 1:1 mixture of *cis* and *trans* isomers. Two diastereomers were found in the *trans* isomer and only one diastereomer in the *cis* isomer.

Although acetone and methyl thiomethylsulfonate gave a mixture of *cis* and *trans* isomers, we were able to isolate each pure *trans* isomer (**8***b* and **11***b*) in the acid form by crystallization.

It is worth mentioning that the aldol condensation of the dianion **6** with acetaldehyde gave only a single diastereomer of *cis*-6-(1′-hydroxyethyl)-penem as was the case for benzaldehyde. In both cases, the other diastereomer was not detected on the scale on which our reactions were performed. We presumed this diastereomer was a *cis-R**[4] isomer because we expected that in the transition state depicted by **12** (14), **12***a* will form in preference to **12***b* because of the severe repulsive interaction between the R-group of the electrophiles and the thiazoline ring in **12***b* (11). This *cis-R** stereochemistry in the product was unambiguously confirmed by total synthesis of both isomers (*cis-R**, **9***a* and *cis-S**, **9***b*)[5] from *N-tert*-butyldimethyl-(*cis-R** and *cis-S**)-3-(1′-hydroxyethyl-4-tritylthioazetidin-2-ones (**13***a* and **13***b*) (6*c*). This will be reported in a forthcoming publication.[6]

R = Me or Ph



SCHEME 2

[4]All compounds described here are racemic. All structural formulae and stereochemical designations refer to the enantiomer related to natural products, such as the penicillins and thienamycin.

[5]Examination of ^{1}Hmr spectra of the two diastereomers **9***a* and **9***b* revealed that although $J_{6-1'}$ or δ_{6-H} were not different enough to allow the two isomers to be distinguished from one another, $\delta_{1'-Me}$ was distinctly different for the two compounds. The signal for *cis-R** methyl (1.23 ppm) appeared at higher field than the signal for *cis-S** methyl (1.31 ppm).

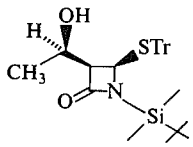
[6]See footnote 3.

TABLE 1. 6-Substituted 2-methylpenem-3-carboxylic acids and their salts **7–11**

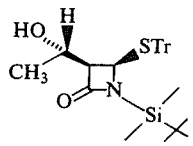
Penems	Electrophiles	R	R′	Yield (%)	*cis*/*trans*[a]
7	CD_3CO_2D	D	H	60	4/1
8*a*	CH_3COCH_3		K	26	3/7
8*b*	CH_3COCH_3		H	23	*trans* only
9	CH_3CHO		Na	9	*cis* major
10	PhCHO		K	20	1/1
11*a*	$CH_3SSO_2CH_3$	CH_3S	K	28	5/3
11*b*	$CH_3SSO_2CH_3$	CH_3S	H	6	*trans* only

[a]À *cis*/*trans* ratio was determined from integration of C5–H signals in the ^{1}Hmr spectra.

Since the aldol condensation with acetaldehyde, unlike the reaction with benzaldehyde, did not give a sufficient amount of the *trans* isomer, after isolation as the sodium salt, we were unable to measure the *cis*–*trans* ratio in the product. An attempt to obtain more of the *trans* isomer using $ZnCl_2$, a chelate stabilizing agent which is known to change the stereochemistry of aldol products (14*a*), was not successful. No penem product was isolated in this reaction.

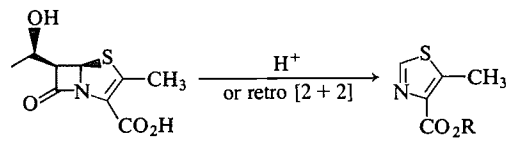


13*a*



13*b*

A major acidic by-product in the reaction with acetaldehyde was identified as 5-methylthiazole-4-carboxylic acid (**14**) based on a singlet at 2.63 ppm which was assigned to 5-Me protons and a broad singlet at 8.63 ppm, assigned to 2-H. More of this thiazole **14** was found when the crude product was left in the acid form. This indicates that the thiazole **14** may have formed during the work-up by the acid-catalyzed decomposition of the penem nucleus or by the retro [2 + 2] process as shown in Scheme 3 (5*a*). Separation of sodium salt **9** from the crude product (which was contaminated with thiazole sodium salt **15**) was achieved in two ways. The



16

14: R = H
15: R = Na

SCHEME 3

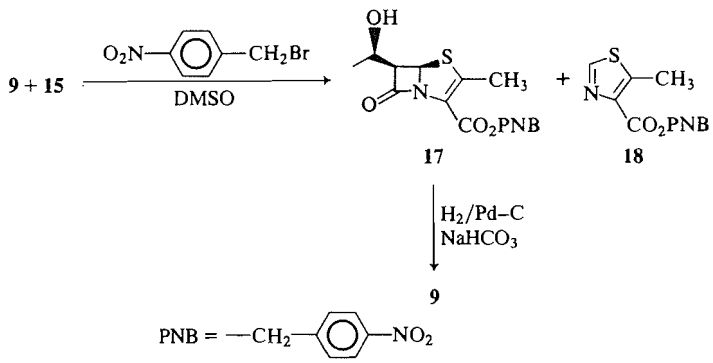
first involved several steps as shown in Scheme 4. A mixture of the crude material was converted to the *p*-nitrobenzyl esters, **17** and **18**, which were separated by chromatographic means. Catalytic hydrogenation of **17** gave the corresponding sodium salt **9**. Alternatively, the salt **9** precipitated out without contamination of thiazole **15** by addition of sodium 2-ethylhexanoate to the crude acid in EtOAc. When Et_2O was used as a solvent, both salts (**9** and **15**) precipitated.

We also attempted the direct introduction of 6-substituents on the methoxymethyl ester of **5** by the method described above using, in this case, one equivalent of *n*-butyllithium in the presence of diisopropylamine (with or without HMPA). In this experiment, we expected that the monoanion, generated *in situ*, would react more cleanly with electrophiles to give 6-substituted penem esters. In fact this reaction gave a complex mixture in which the desired product was not detected. This is presumably due to the fact that lithium diisopropylamide reacts, in the absence of HMPA, with the α,β-unsaturated ester moiety to give the Michael adduct (15). The deprotonation at the γ-position of this unsaturated ester moiety also creates more complications in the reaction with LDA-HMPA.

In summary, we have described here the synthesis of 6-substituted 2-methylpenem-3-carboxylic acids by direct metallation on 6-unsubstituted penem acid followed by the reaction with electrophiles, producing a mixture of *cis* and *trans* isomers, the ratio varying from *cis*-major to *trans*-major.

Experimental

Melting points were determined on a Gallenkamp melting point apparatus and are not corrected. The infrared spectra were recorded on a Perkin–Elmer 267 Grating Infrared spectrophotometer.



SCHEME 4

The ^{1}H nuclear magnetic resonance spectra were taken with either a Varian EM-360A (60 MHz) or a Varian CFT-20 (80 MHz) nmr spectrometer. Tetramethylsilane (for solution other than deuterium oxide) and sodium 4,4-dimethyl-4-silapentane-1-sulfonate (for solutions of deuterium oxide) were used as internal standards and chemical shifts are reported in parts per million (δ) relative to the internal standards.

The ultraviolet spectra were recorded on either an Unicam SP-800 or SP 8-100 uv spectrophotometer. Tetrahydrofuran was freshly distilled from $LiAlH_4$.

Commercial CH_3CHO was distilled prior to use. Diisopropylamine was distilled from CaH_2 and stored over NaOH. *n*-Butyllithium in hexane (Aldrich) and CD_3CO_2D (99.5%, MSD) were used as supplied. 2-Methylpenem-3-carboxylic acid (**5**) was prepared as described before (6*a*). Methyl thiomethylsulfonate was prepared by the procedure of Slusarchyk *et al.* (16).

6-Deuterio-2-methylpenem-3-carboxylic acid (7)

To a stirred solution of 2-methylpenem-3-carboxylic acid (**5**) (50 mg, 0.27 mmol) in THF (10 mL) was added at −78°C under a nitrogen atmosphere a solution of *n*-butyllithium in hexane (1.66 *M*, 0.36 mL, 0.60 mmol). After a half minute, CD_3CO_2D (0.4 mL, a large excess) was injected. The yellow reaction mixture was stirred (−78°C, N_2) for 5 min and then diluted with EtOAc (15 mL). This was washed with brine (×2), dried (Na_2SO_4), and evaporated, yielding 45 mg of yellow solid. This solid was rinsed with a small amount of anhydrous Et_2O to obtain 30 mg (0.16 mmol, yield 60%) of the title compound **7** as a mixture of the *cis* and *trans* isomers in a ratio of 4:1. This material was contaminated with a small amount of **5**, mp 113–117°C (dec.); ir (KBr disc) ν_{max}: 2400–3100 (CO_2H), 1775 (β-lactam), and 1670 (CO_2H) cm^{-1}; uv (EtOH) λ_{max}: 262 (ε 4330) and 305 nm (ε 6680); ^{1}Hmr (acetone-d_6; CFT-20) δ: 2.34 (3H, s, 2-Me), 3.41 (1/5 H, dt, $J_{6-5\,trans}$ = 2 Hz, J_{H-D} = 2 Hz, H-6), 3.81 (4/5 H, dt, $J_{6-5\,cis}$ = 4 Hz, J_{H-D} = 2 Hz, H-6), and 5.71 ppm (1H, 2d, $J_{5-6\,cis}$ = 4 Hz and $J_{5-6\,trans}$ = 2 Hz, H-5; the both isomers appeared at the same place). The signals for **5** appeared at 3.40 (dd, J = 2 Hz, J_{gem} = 16.5 Hz, H-6) and 3.85 ppm (dd, J = 4 Hz, J_{gem} = 16.5 Hz, H-6).

Potassium 6-(2′-hydroxy-2′-propyl)-2-methylpenem-3-carboxylate (8a)

To a solution of diisopropylamine (0.098 mL, 0.699 mmol) in THF (2 mL) *n*-butyllithium in hexane (1.6 *M*, 0.44 mL, 0.70 mmol) was added at −78°C under a nitrogen atmosphere and stirred (−78°C, N_2) for 30 min. To this solution was added a solution of 2-methylpenem-3-carboxylic acid (**5**) (116 mg, 0.627 mmol) in THF (4 mL) and the mixture was stirred for 5 min at −78°C, followed by successive addition of diisopropylamine (0.098 mL; 0.699 mmol) and *n*-butyllithium in hexane (1.6 *M*, 0.44 mL, 0.70 mmol) at −78°C. It was then stirred for 10 min at −78°C and treated rapidly with acetone (5 mL). After 10 min at −78°C, it was acidified (pH 2) with 1% HCl, diluted with EtOAc (40 mL), and the organic layer was washed with brine (3 × 20 mL), dried (Na_2SO_4), and evaporated to give a crude residue which was taken up in CH_2Cl_2. The crude acid (yield 90 mg) was dissolved in cold methylisobutylketone (2 mL) and treated dropwise with a solution of potassium 2-ethylhexanoate in *n*-BuOH (50%). After addition of anhydrous Et_2O, it gave 36.4 mg (0.13 mmol, yield 20.6%) of the title compound as a mixture of the *cis* and *trans* isomers in a ratio of 7:3; ir (Nujol mull) ν_{max}: 3600–3100 (OH), 1765 (β-lactam), and 1582 (—CO_2^-) cm^{-1}; uv (EtOH) λ_{max}: 257 (ε 3920) and 300 nm (ε 4020); ^{1}Hmr (DMSO-d_6) δ: 1.32, 1.35 (2s, di-Me), 1.40, 1.47 (2s, di-Me), 2.34 (3H, s, CH_3), 3.50 (br s, OH), 3.62 (d, $J_{6-5\,trans}$ = 2 Hz, H-6), 3.93 (d, $J_{6-5\,cis}$ = 4 Hz, H-6), 5.55 (1 × 7/10 H, d, $J_{5-6\,trans}$ = 2 Hz, H-5), and 5.60 ppm (1 × 3/10 H, d, $J_{5-6\,cis}$ = 4 Hz, H-5).

trans-*6-(2′-Hydroxy-2′-propyl)-2-methylpenem-3-carboxylic acid (8b)*

To a stirred solution of 2-methylpenem-3-carboxylic acid (**5**) (50 mg, 0.27 mmol) in THF (4 mL) diisopropylamine (0.08 mL, 0.58 mmol) was added at 0–5°C under a nitrogen atmosphere. The mixture was cooled to −78°C and *n*-butyllithium (0.38 mL, 1.6 *M* in hexane, 0.60 mmol) was added. After 5 min at −78°C, acetone (0.5 mL) was injected into this orange mixture. The resulting yellow mixture was stirred for 10 min at −78°C. This was neutralized with 0.1 *N* HCl (12 mL) and extracted with EtOAc (3 × 20 mL). The EtOAc extracts were washed with brine, dried (Na_2SO_4), and evaporated to yield 59 mg of a crude oil. This oil was extracted with Et_2O, removing the insoluble material to give 53 mg of an oily solid. This was characterized by ^{1}Hmr as a mixture of the *cis* and *trans* isomers in a ratio of 7:3; ^{1}Hmr ($CDCl_3$) δ: 3.75 (7/10 H, d, J = 1.5 Hz, 6-H_{trans}), 4.00 (3/10 H, d, J = 4 Hz, 6-H_{cis}), 5.62 (d, J = 1.5 Hz, 5-H_{trans}) and 5.70 ppm (d, J = 4 Hz, 5-H_{cis}). This oily solid was triturated with a small amount of $CHCl_3$ and Et_2O to yield 15 mg (0.062 mmol, yield 23%) of the title compound **8***b* as white crystals, mp 117–121°C; ir (Nujol mull) ν_{max}: 3500 (OH), 1765 (β-lactam), and 1660 (CO_2H) cm^{-1}; uv (EtOH) λ_{max}: 265 (ε 3400) and 309 nm (ε 5700); ^{1}Hmr (acetone-d_6) δ: 1.30 (3H, s, 2′-CH_3), 1.35 (3H, s, 2′-CH_3), 2.35 (3H, s, 2-CH_3), 3.77 (1H, d, J = 1.8 Hz, 6-H), and 5.63 ppm (1H, d, J = 1.8 Hz, 5-H).

Sodium cis-*6-(1′-hydroxyethyl)-2-methylpenem-3-carboxylate (9)*

To a stirred solution of 2-methylpenem-3-carboxylic acid (**5**) (1.00 g, 5.40 mmol) in THF (80 mL) *n*-butyllithium (7.00 mL, 1.6 *M* in hexane, 11.2 mmol) was added dropwise at −78°C under a nitrogen atmosphere. After 1 min CH_3CHO (1.2 mL) was added to this reddish mixture and the resulting pale yellow

mixture was stirred (−78°C, N_2) for 10 min. To this mixture was added saturated NH_4Cl (100 mL) followed by brine (50 mL). The aqueous layer was collected and washed with EtOAc (2 × 60 mL). This aqueous layer, mixed with EtOAc (60 mL), was cooled in an ice-bath and acidified carefully with a cold 0.1 *N* HCl solution (120 mL), saturated with NaCl, and extracted quickly with EtOAc (3 × 60 mL). The EtOAc extracts were washed with brine, dried (Na_2SO_4), and evaporated to reduce the volume to ca. 25 mL. To this was added sodium 2-ethylhexanoate in *n*-BuOH (10% w/w, 2.1 mL) and the precipitate was collected by a centrifuge and washed with EtOAc to yield 123 mg (0.490 mmol, yield 9.1%) of the title compound **9** as a yellow powder; ir (Nujol mull) ν_{max}: 3350 (OH), 1750 (β-lactam), and 1590 (CO_2Na) cm^{-1}; uv (H_2O) λ_{max}: 252 (ε 4200) and 297 nm (ε 3400); ^{1}Hmr (D_2O) δ: 1.23 (3H, d, J = 6 Hz, 1′-CH_3), 2.28 (3H, s, 2-CH_3), 3.85 (1H, dd, $J_{6-5\,cis}$ = 4 Hz, $J_{6-1'}$ = 8 Hz, 6-H), and 5.65 ppm (1H, d, $J_{5-6\,cis}$ = 4 Hz, 5-H).

To the supernatant solution was added Et_2O and the precipitate was collected by a centrifuge and washed with Et_2O to give 145 mg of a mixture of the title compound **9** and sodium 5-methylthiazole-4-carboxylate (**15**) as a white solid; ^{1}Hmr (D_2O) δ: thiazole peaks at 2.63 (3H, s, 5-Me) and 8.63 ppm (1H, s, 2-H). This material was purified as follows.

The material containing **9** and **15** (total 201 mg) was converted to the mixture of the corresponding *p*-nitrobenzyl ester by treating it with *p*-nitrobenzyl bromide (104 mg, 0.9 mmol) in dimethylsulfoxide (2 mL) at room temperature overnight (21 h). The crude products were separated by preparative tlc (E. Merck silica gel 60F-254, benzene–Et_2O 1:1), collecting 40 mg (0.14 mmol) of *p*-nitrobenzyl 5-methylthiazole-4-carboxylate (**18**) as white crystals (fast moving band), mp 128–130°C; ir (Nujol mull) ν_{max}: 1720 (ester), 1603, 1520 (NO_2), and 1350 (NO_2) cm^{-1}; uv (EtOH) λ_{max}: 256 nm (ε 12 500); ^{1}Hmr ($CDCl_3$) δ: 2.80 (3H, s, 5-CH_3), 5.47 (2H, s, —CH_2—), 7.53–7.68–8.15–8.30 (2H, $A_2'B_2'$, aromatic H's), and 8.60 ppm (1H, br s, 2-H); and 41 mg (0.11 mmol) of **17** as white crystals (slow moving band), mp 140–143°C; ir (Nujol mull) ν_{max}: 3400 (OH), 1770 (β-lactam), and 1705 (ester) cm^{-1}; uv (EtOH) λ_{max}: 265 (ε 12 000) and 309 nm (ε 9200); ^{1}Hmr ($CDCl_3$) δ: 1.25 (3H, J = 6 Hz, 1′-CH_3), 2.40 (3H, s, 2-CH_3), 3.78 (1H, dd, J_{6-5} = 4 Hz, $J_{6-1'}$ = 9 Hz, 6-H), 4.35 (1H, m, 1′-H), 5.03–5.27–5.37–5.60 (2H, AB type, —CH_2Ar), 5.61 (1H, d, J_{5-6} = 4 Hz, 5-H), and 7.52–7.67–8.13–8.24 ppm (2H, $A_2'B_2'$, aromatic H's).

A solution of **17** (40 mg, 0.11 mmol) in THF (4 mL) was mixed with Et_2O (8 mL), H_2O (4 mL), $NaHCO_3$ (9.5 mg, 0.11 mmol), and 30% Pd–Celite (45 mg; Engelhard) and hydrogenated at room temperature (H_2, 30 psi) for 3 h. After filtration of the catalyst over Celite, the filtrate and the washings were combined. The aqueous layer was washed once with Et_2O and lyophilized to yield 24 mg (0.096 mmol, yield 87%) of the title compound (**9**) as a greyish powder; ir (Nujol mull) ν_{max}: 3350 (OH), 1760 (β-lactam), and 1585 (CO_2Na) cm^{-1}; uv (H_2O) λ_{max}: 297 (ε 3000) and 254 nm (ε 2900); ^{1}Hmr (DMSO-d_6) δ: 1.03 (3H, d, J = 6 Hz, 1′-CH_3), 2.20 (3H, s, 2-CH_3), 3.53 (1H, dd, J = 4 Hz, J = 9 Hz, 6-H), 3.9 (1H, m, 1′-H), and 5.40 ppm (1H, d, J = 4 Hz, 5-H).

*Potassium 6-(1′-hydroxybenzyl)-2-methylpenem-3-carboxylate (**10**)*

To a solution of diisopropylamine (0.084 mL, 0.599 mmol) in THF (2 mL) was added at −78°C under a nitrogen atmosphere 1.6 *M* *n*-butyllithium in hexane (0.380 mL, 0.608 mmol) and stirred (−78°C, N_2) for 30 min. To this solution was added dropwise a solution of 2-methylpenem-3-carboxylic acid (**5**) (100 mg, 0.54 mmol) in THF (6 mL) and the mixture stirred for 5 min at −78°C, followed by successive addition of diisopropylamine (0.084 mL, 0.599 mmol) and 1.6 *M* *n*-butyllithium in hexane (0.380 mL, 0.608 mmol). It was then stirred for 7 min at −78°C and treated rapidly with benzaldehyde (0.3 mL). The mixture was allowed to react at −78°C for 20 min. It was acidified with 1% HCl (pH ≃ 2), diluted with EtOAc (40 mL), washed with H_2O–brine (1:1, 3 × 20 mL) and brine (1 × 20 mL). It was dried over Na_2SO_4 and evaporated to give a residue which was dissolved in methylisobutylketone (2 mL). This was treated dropwise with a solution of potassium 2-ethylhexanoate in *n*-BuOH to give 35 mg (0.11 mmol, yield 20%) of the title compound **10** as a diastereomeric mixture (*cis*–*trans* ≃ 1:1); ir (Nujol mull) ν_{max}: 3600–3100 (OH), 1760 (β-lactam), and 1590 (CO_2K) cm^{-1}; uv (H_2O) λ_{max}: 262 (ε 5100) and 296 nm (ε 3000); ^{1}Hmr (DMSO-d_6) δ: 2.35 (3H, 2s, CH_3), 3.65 (br s, OH), 3.90 (m, H-6), 4.25 (dd, $J_{6-5\,cis}$ = 4 Hz, $J_{6-1'}$ = 10 Hz, H-6), 5.0 (m, H-1′), 5.35 (d, $J_{5-6\,cis}$ = 4 Hz, H-5), 5.45 (d, $J_{5-6\,trans}$ = 1.5 Hz, H-5), 5.57 (d, $J_{5-6\,trans}$ = 1.5 Hz, H-5), and 7.95 ppm (5H, s, aromatic H's).

*Potassium 6-methylthio-2-methylpenem-3-carboxylate (**11**a)*

A solution of 2-methylpenem-3-carboxylic acid (**5**) (100 mg, 0.54 mmol) in THF (5 mL) was added dropwise to a cold (−78°C) THF (2 mL) solution of lithium diisopropylamide, made from diisopropylamine (0.084 mL, 0.599 mmol) and 1.6 *M* *n*-butyllithium – hexane (0.380 mL, 0.608 mmol). The mixture was stirred for 7–8 min, followed by successive addition of diisopropylamine (0.084 mL, 0.599 mmol) and 1.6 *M* *n*-butyllithium – hexane (0.380 mL, 0.608 mmol). It was then stirred for 7 min at −78°C and treated rapidly with methyl thiomethylsulfonate (0.30 mL, excess). The mixture was allowed to react at −78°C for 5 min. It was acidified with 1% HCl (pH ≃ 2), diluted with EtOAc (40 mL), washed with 1:1 H_2O–brine (3 × 20 mL) and then brine (20 mL). The organic solution was dried (Na_2SO_4) and evaporated to give a residue which was dissolved in cold methylisobutylketone (2 mL). To this solution was added dropwise a solution of potassium 2-ethylhexanoate in *n*-BuOH (50% w/w). The precipitate was collected to yield 40 mg (0.15 mmol, yield 28%) of the title compound **11***a* as a 5:3 mixture of *cis* and *trans* isomers, mp 115–120°C (dec.); ir (Nujol mull) ν_{max}: 1770 (β-lactam) and 1600 (CO_2K) cm^{-1}; uv (H_2O) λ_{max}: 252 (ε 4200) and 297 nm (ε 3700); ^{1}Hmr (DMSO-d_6) δ: 2.25 (s, SCH_3), 2.33 (s, CH_3), 2.37 (s, SCH_3), 3.42 (br s, OH), 4.72 (1H, d, $J_{6-5\,trans}$ = 1.5 Hz, H-6), 4.87 (1H, d, $J_{6-5\,cis}$ = 4 Hz, H-6), 5.57 (1H, d, $J_{5-6\,trans}$ = 1.5 Hz, H-5), and 5.85 ppm (1H, d, $J_{5-6\,cis}$ = 4 Hz, H-5).

trans-*6-Methylthio-2-methylpenem-3-carboxylic acid (**11**b)*

Diisopropylamine (1.16 g, 11.4 mmol) was added at 5°C to a solution of 2-methylpenem-3-carboxylic acid (**5**) (1.00 g, 5.40 mmol) in THF (800 mL). The mixture was cooled to −78°C and treated with 2.52 *M* *n*-butyllithium – hexane (4.4 mL, 11.1 mmol). After stirring at −78°C for 5 min, methyl thiomethylsulfonate (750 mg, 5.90 mmol) was added and it was stirred at −78°C for an additional 10 min. Then the reaction mixture was poured into a saturated NH_4Cl solution, extracted with CH_2Cl_2, acidified to pH 3 with dilute HCl, and again extracted with CH_2Cl_2. The organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a mixture of *cis*- and *trans*-6-methylthio-2-methylpenem-3-carboxylic acids. However, crystallization from Et_2O afforded 75 mg (0.32 mmol, yield 6%) of the pure *trans* isomer **11***b*, mp 109–112°C; ir (CH_2Cl_2) ν_{max}: 1793 (β-lactam) and 1681 (CO_2H) cm^{-1}; uv (EtOH) λ_{max}: 303 nm (ε 4348); ^{1}Hmr ($CDCl_3$) δ: 2.24 (3H, s, —SCH_3), 2.37 (3H, s, —CH_3), 4.56 (1H, d, J = 1.6 Hz, H-6), and 5.49 ppm (1H, d, J = 1.6 Hz, H-5).

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