β-Lactams. IX. The synthesis of 7-β-phenylacetamido-3′-hydroxybenzo-[3,4]-*O*-2-isocephem, a weak antibacterial β-lactam antibiotic

GEORGE JUST, YOULA S. TSANTRIZOS, AND ANTONIO UGOLINI[1]
Department of Chemistry, McGill University, Montreal, P.Q., Canada H3A 2K6
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The synthesis of the title compound is described.

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La synthèse du produit nommé est décrite.

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As part of a continuing program to prepare nonclassical β-lactam antibiotics (for rationale, see ref. 1), in which a phenolic group replaces the carboxylic function of penicillins and cephalosporins, we wish to describe the synthesis of title compound **18** and its nitro analogues. Recently, Doyle (2) has described a similar compound differing from **18** only in the nature of the side-chain and the position of the phenolic hydroxy group, which was attached *para* to the ether function.

o-Aminophenol **1** and 2-aminoresorcinol **4** were transformed to their dimethyl-*tert*-butylsilyl ethers **2** and **5**. Amines **2** and **5** were converted to their cinnamylidene Schiff bases **3** and **6**, and, without purification, treated with azidoacetyl chloride and triethylamine at −20°C.

β-Lactams **7**, mp 84–85°C, and **8**, mp 95–96°C, were obtained in good yield after column chromatography and crystallization. The presence of the azide and β-lactam functions was confirmed by ir absorption bands at 2100, and 1760 and 1770 cm^{-1} respectively. The stereochemistry could not be assigned at this point because of overlapping signals in the ^{1}Hmr spectrum. However, all ^{1}Hmr spectra of compounds **9**–**21** showed $J_{3,4} \simeq 5$ Hz, indicating that the substituents on the β-lactam ring were *cis* (3).

Ozonolysis of **7** in methanol at −78°C, followed by sodium borohydride reduction (−40° → +20°C), gave alcohol **9**, mp 77°C. Alcohol **9** was converted with little difficulty to the corresponding mesylate **11**, and, by means of thionyl chloride – pyridine in boiling benzene, to chloride **13**.

In order to study the cyclization reaction, mesylate **11** and chloride **13** were used as model compounds. Treatment of a tetrahydrofuran solution of either mesylate **11** or chloride **13** with freshly prepared tetra-*n*-butylammonium fluoride (4) gave instantaneously a quantitative yield of tricyclic azide **15**, mp 77–78°C.

This sequence was then applied to the disilylazido-β-lactam **8**. Ozonolysis of **8** in methanol at −78°C as described for monosilyl-β-lactam **7** proceeded in very poor yield. However, when the reaction was carried out in ethanol – methylene chloride (4:1) at −78°C, and the crude ozonide reduced with sodium borohydride (−40° → +20°C), alcohol **10** was obtained in good yield. Treatment of **10** with methanesulfonyl chloride and triethylamine in methylene chloride at −78°C gave mesylate **12**.

Reaction of mesylate **12** with exactly one equivalent of tetra-*n*-butylammonium fluoride in dry tetrahydrofuran gave tricyclic azide **16**, mp 69–70°C. Since the amount of fluoride added turned out to be extremely critical, and the reaction was virtually a titration with no easily determined end-point except by tlc, a more controllable set of reaction conditions was sought. Treatment of an acetonitrile solution of disilylether **12** with 1.2 equiv. of potassium fluoride and 0.3 equiv. of 18-crown-6 effected the same transformation to **16** in about 6 hours, permitting easy monitoring of the reaction. The reaction conditions turned out not to be critical, and the amounts of 18-crown-6 and potassium fluoride could be varied with impunity.

Tricyclic azido-β-lactam **15** exhibited a clean, nearly first-order ^{1}Hmr spectrum in deuterobenzene at 100 MHz for protons A–D. Proton A appeared at 4.18 ppm (J_{AB} = 5.0 Hz). Proton B (3.10 ppm) was coupled to A (J_{BA} = 5.0 Hz), C (J_{BC} = 3.5 Hz), and D (J_{BD} = 10 Hz). Protons C (3.36 ppm) and D (3.87 ppm) showed geminal coupling of 10 Hz, giving the spectrum a deceptively simple appearance reproduced below (Fig. 1). Hydrogen

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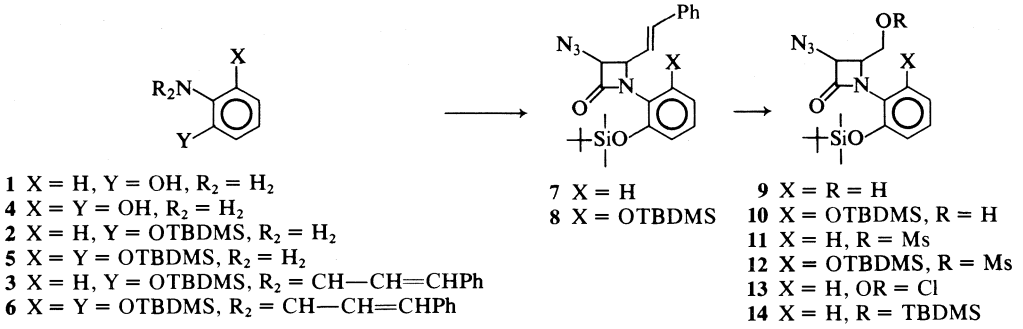
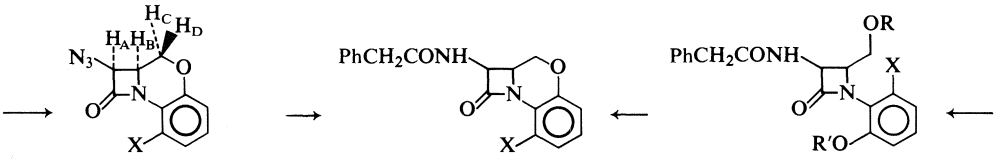


1 X = H, Y = OH, $R_2 = H_2$
4 X = Y = OH, $R_2 = H_2$
2 X = H, Y = OTBDMS, $R_2 = H_2$
5 X = Y = OTBDMS, $R_2 = H_2$
3 X = H, Y = OTBDMS, R_2 = CH—CH=CHPh
6 X = Y = OTBDMS, R_2 = CH—CH=CHPh

7 X = H
8 X = OTBDMS

9 X = R = H
10 X = OTBDMS, R = H
11 X = H, R = Ms
12 X = OTBDMS, R = Ms
13 X = H, OR = Cl
14 X = H, R = TBDMS



15 X = H
16 X = OTBDMS
16*a* X = OTBDMS, $N_3 = NH_2$

17 X = OTBDMS
18 X = OH

19 X = H, R = R′ = TBDMS
20 X = H, R = R′ = H
21 X = OTBDMS, R = Ms, R′ = TBDMS

sulfide – triethylamine reduction of **16** followed by acylation with phenylacetyl chloride, gave amide **17** in 54% yield, based on **8**. Removal of the silyl group gave tricyclic amide **18**, mp 194–195°C. The same compound could be obtained using the alternate route **12** → **21** → **17** → **18**. It should be noted that the potassium fluoride/18-crown-6 cyclization method could not be used for the transformation **21** → **17**, and the tetra-*n*-butylammonium fluoride method had to be employed.

For comparison purposes, alcohol **9** was silylated, and the resulting silyl ether **14** transformed by the methods described to the phenylacetamido-β-lactam **19**, which was hydrolyzed to **20**. Whereas bicyclic β-lactam **20** showed no biological activity, when tested against a variety of microorganisms in concentrations up to 256 μg/mL (MIC), tricyclic β-lactam **18** inhibited the growth of *S.aureus* (Q74-1) and *S.lutea* (PCl-1001) at 128 and 64 μg/mL respectively.

High anti-bacterial activity has usually been associated with chemical reactivity of the β-lactam ring, which is normally induced by steric strain. In a system such as **18**, increased reactivity of the β-lactam ring can, in principle, be induced by substituting the phenyl ring with an electron-withdrawing substituent such as a nitro group. In order to obtain a tricyclic β-lactam in which a nitro group is substituted *para* to the β-lactam nitrogen (see **15**), one would have to use as starting material an *o*,*o*′-disilyloxy-*p*-nitroaniline. We have shown

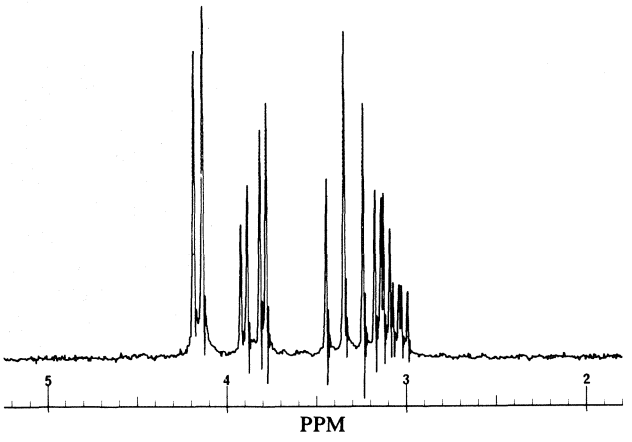
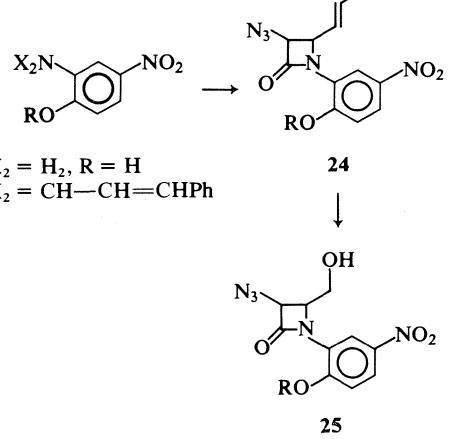


FIG. 1



22 $X_2 = H_2$, R = H
23 X_2 = CH—CH=CHPh

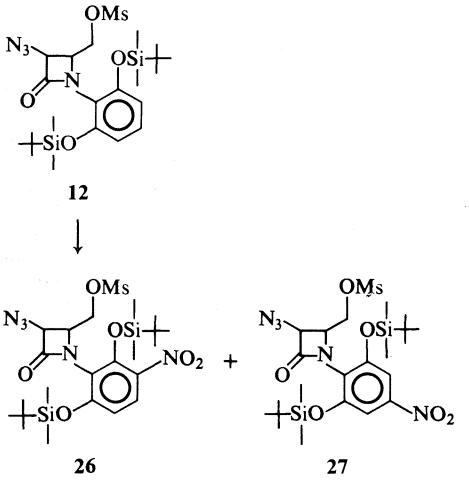
24

25

a, R = *t*-BuSiMe_2
b, R = *t*-BuSiPh_2

that *o*-dimethyl-*tert*-butylsilyloxy-*p*-nitroaniline is converted to the corresponding *trans*-fused β-lactam only (5).

We therefore used 2-hydroxy-5-nitroaniline **22** as model. Silylation with either *tert*-butyldimethyl or *tert*-butyldiphenylsilyl chloride gave silyl ethers **22***a* and **22***b*, which were converted via their cinnamylidene derivatives **23***a* and **23***b* to β-lactams **24***a* and **24***b*. Both **24***a* and **24***b* were extremely labile to reductive ozonolysis reaction conditions, and little **25** could be isolated, the side-products being silanol and other unidentified products. Because of the lability of the *p*-nitrosilyl ethers to reductive ozonolysis conditions, we next investigated the nitration of the relatively unstrained β-lactam **12**, and cyclization of the resulting nitro derivatives, **26** and **27**.



12 → **26** + **27**

β-Lactam **12** was treated with nitronium tetrafluoroborate at −20°C and, as expected, two compounds (**26** and **27**) were detected in the reaction mixture. Attempts to purify the mixture, which was well separated on thin layer chromatography, proved unsuccessful, resulting in complete decomposition of **27** and extensive desilylation of **26**.

It is known that *p*-nitrophenols (pK_A = 7.2) (7) behave almost like carboxylic acids, and it is therefore to be expected that the *p*-nitrosilyl ether **26** would be extremely unstable to hydrolysis, as are silyl esters. In **27**, the nitro substituent *para* to the β-lactam ring introduces so much chemical reactivity that the amide linkage is easily hydrolyzed on contact with silica gel.

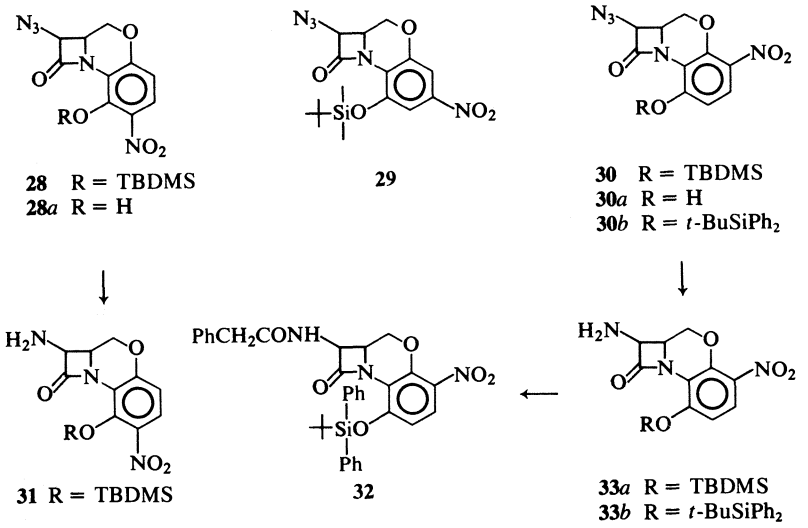
Nitration of silyloxy azido-β-lactam **16** showed very similar complications. The ^{1}Hmr spectrum of the crude reaction mixture clearly showed the presence of three compounds (**28**, **29**, and **30**), characterized by three sets of doublets, two having a large coupling constant (J = 9 Hz), as would be expected for *ortho* protons (**28**, **30**), and one set at about 7.4 ppm with the two doublets overlapping and a small coupling constant of 3 Hz indicating *meta* protons (**29**). Attempts to separate the three compounds by chromatography lead to complete decomposition of **29** and some desilylation of **28** and **30**. The latter were found to be sensitive to moisture and traces of acid, even after crystallization. The ^{1}Hmr spectra of **28** and **30** in deuterobenzene were virtually identical. However, in deuterochloroform the two methyl groups attached to silicon appeared in **28** as two 3H singlets at approximately 0.2 ppm downfield from the corresponding 6H singlet in **30**, indicating hindered rotation of the silyloxy group in **28**. This assignment was further corroborated by mass spectrometric data: *o*-nitro substituted phenyl ethers and amines are characterized by intense ions of mass $M^{+\cdot} - OR^{\cdot}$ (6).

The very intense peak at *m/e* 260 ($M^{+\cdot}$ − $OSiMe_2$-*tert*-butyl$^{\cdot}$) seen in the mass spectrum of compound **28** is almost completely absent from the spectrum of **30**.

Both compounds show intense ions at *m/e* 334 (base peak, $M^{+\cdot}$ − *tert*-butyl$^{\cdot}$), 306 (334 − N_2, from the azide group), 251 (334 − 83, 83 = COCH—N_3), and 205 (251 − NO_2).

A mixture of **28** and **30** was reacted with hydrogen sulfide – triethylamine to obtain the unstable amines **31** and **33***a* in good yield. Further reaction of **31** or **33***a* with phenylacetyl chloride was unsuccessful, initially leading to hydrolysis of the silyl ether, followed by hydrolysis of the β-lactam ring, as evidenced by ^{1}Hmr, which showed the presence of silanol, and ir, which showed a decrease in intensity of the β-lactam absorption with time.

We then thought that protection of the phenol group with diphenyl-*tert*-butylsilyl chloride would give a more stable β-lactam. It was found that treatment of phenol **30***a* with diphenyl-*tert*-butylsilyl chloride – triethylamine gave compound **30***b* which was well characterized by its ^{1}Hmr spectrum. However, phenol **28***a* was unreactive under the same conditions, further confirming that the phenolic group was sterically hindered by the presence of an *ortho* nitro substituent. The azide function of diphenyl-*tert*-butylsilyl ether **30***b* was then reacted with hydrogen sulphide – triethylamine and the progress of the reaction was followed by the disappearance of the infrared absorption of the azide. Upon complete formation of amine **33***b*,



an equivalent of triethylamine was added along with an equivalent of phenylacetyl chloride to form final product **32**.

The ^{1}Hmr spectrum of **32** clearly showed the presence of all expected proton resonances: a singlet at 3.5 ppm (—COCH_2Ph), a multiplet at 3.3–3.6 ppm due to H_B, two sets of doublets at 3.8 to 4.6 ppm, coupled to each other and each integrating to one proton (H_C and H_D). H_A was found as a doublet of doublets at 5.1 to 5.3 ppm with one of its coupling constants equal to that of the broad doublet (due to NH) at 8.0 ppm. Finally, two doublets (6.6 and 8.7 ppm) were seen coupled to each other by a large coupling constant of 9 Hz, characteristic of the *ortho* protons on the nitrobenzene ring.

The infrared spectrum of **26** was also consistent with the structure given, with an absorption of 1790 cm^{-1} for the carbonyl group of the β-lactam.

Unfortunately, mass spectrometry and elemental analysis could not be used to further support the structure of **32** due to the extreme instability of this compound. It was observed through ^{1}Hmr and ir studies that even the traces of moisture or acid found in DMSO-d_6 would cause rapid decomposition of the silyl ether, followed by hydrolysis of the β-lactam ring, within half an hour.

Biological studies of these compounds were inconclusive due to complete decomposition of these compounds within a short time. We therefore showed that a nitro substituent introduces greater reactivity than desired and perhaps replacement of this group with a less electron withdrawing substituent such as an ester might lead to more stable and perhaps biologically active products.

Experimental

Thin-layer chromatography (tlc) was performed on Merck Silica Gel 60 F_{254} aluminum-backed plates. Flash chromatography was done on Woelm Silica (32–63 μ). Melting points (mp) were measured on a Gallenkamp block and are uncorrected, unless specified otherwise. The nmr spectra were recorded on Varian T-60, T-60A, and where noted, HA-100 and XL-200 spectrometers. Infrared (ir) spectra were recorded on Pye Unicam SP-1000, Perkin Elmer 257 and 297 spectrophotometers. Mass spectra (ms) were obtained on HP 5984A or LKB 9000 spectrometers, in the direct inlet mode unless indicated otherwise. Elemental analyses were performed by Midwest Microlab Ltd., Indianapolis.

*Di-*tert*-butyldimethylsilyl-2-aminoresorcinol 5*

A suspension of 2-nitroresorcinol (15 g, 97 mmol) and PtO_2 (1 g) in absolute ethanol (250 mL) was hydrogenated in a Parr apparatus at 40 psi. Filtration through Celite and evaporation of the rapidly darkening filtrate afforded 12 g of amine **4** as a brown solid. This amine was added to *tert*-butyldimethylsilyl chloride (32 g, 211 mmol) and imidazole (33 g, 485 mmol) in dry DMF (75 mL), and let stir overnight at room temperature. Then water (300 mL) was added and the solution extracted thrice with ether (300, 50, 50 mL). The ether extract was washed with water (3 × 100 mL), then brine (100 mL), then dried ($MgSO_4$) and evaporated. Chromatography of the residue on SiO_2 (250 g) afforded 20 g (59%) of amine **5** as a brownish oil; ^{1}Hmr ($CDCl_3$) δ: 0.2 (s, 12H, $SiMe_2$), 1.0 (s, 18H, *t*-BuSi), 3.47 (bs, 2H, NH_2), 6.27 (s, 3H, C_6H_3).

β-Lactam Azide 8

Amine **5** (14.2 g, 40 mmol) and cinnamaldehyde (5.6 g, 42 mmol), in benzene (150 mL), with a trace of *p*-TsOH, were refluxed overnight using a Dean–Stark trap. Evaporation of the solvent afforded Schiff base **6** as a thick brown oil. To this Schiff base, in CH_2Cl_2 (250 mL) containing triethylamine (5.3 g, 52 mmol), at −20°C was added dropwise azidoacetyl chloride (6.2 g, 52 mmol) in CH_2Cl_2 (50 mL), over 1 h. The red-brown solution was stirred for an additional hour at −20°C, and then allowed to warm up. Washing with water (2 × 150 mL) and brine (150 mL), then drying ($MgSO_4$) and evaporation of the solvent afforded, after chromatography on SiO_2 (300 g, $CHCl_3$), 13 g (59%) of β-lactam **8** as a thick brown oil, which crystallized upon trituration with

petroleum ether, mp 95–96°C; ir (film) ν_{max}: 2900, 2100 (N_3), 1770 (β-lactam), 1580 cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 0.24, 0.3 (2s, 12H, $SiMe_2$), 1.03 (s, 18H, *t*-BuSi), 4.8–5.0 (m, 2H, CH—CHN_3), 6.4–7.3 (m, 10H, C_6H_3 and CH=CH—C_6H_5).

β-Lactam Azide **7** was prepared as described for **8**; 63% yield, mp 84–85°C; ir ($CHCl_3$) ν_{max}: 2100 (N_3), 1760 (β-lactam) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 0.28 (s, 6H, $SiMe_2$), 1.03 (s, 9H, *t*-BuSi), 4.88 (d, 1H, CHN_3), 5.02 (dd, 1H, C*H*—CHN_3), 6.1 (dd, 1H, C*H*=CH—Ph, *J* = 7, 15 Hz), 6.57 (d, 1H, C*H*—Ph, *J* = 15 Hz), 6.6–7.5 (m, 9H, C_6H_5 and C_6H_4).

Azido Alcohol 10

Ozone was bubbled through a solution of β-lactam **8** (7 g, 12.7 mmol) in EtOH (200 mL) and CH_2Cl_2 (50 mL) at −78°C. Excess ozone was flushed out with N_2 and $NaBH_4$ (0.95 g, 25 mmol) was added at −40°C. After warming to room temperature, pH 4.5 buffer (200 mL) was added and the ethanol removed under reduced pressure. The aqueous residue was extracted with ether (3 × 100 mL) and the ether washed with brine (100 mL), dried ($MgSO_4$), and evaporated to a yellow oil, which was chromatographed on SiO_2 to give 4.5 g (74%) of a viscous pale yellow oil. Crystallization was induced, by addition of a little pentane, giving β-lactam **10** as white needles, mp 99.5–100°C; ir (film) ν_{max}: 3500 (OH), 2100 (N_3), 1765 (β-lactam), 1590 cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 0.26, 0.30 (2s, 12H, $SiMe_2$), 1.05 (s, 18H, *t*-BuSi), 2.5 (bs, 1H, OH), 3.8 (bs, 2H, CH_2), 4.1 (dt, 1H, C*H*—CH_2—OH, *J* = 5, 5 Hz), 4.7 (d, 1H, CH—N_3, *J* = 5 Hz), 6.4–7.2 (m, 3H, C_6H_3).

Azido Alcohol **9** was prepared as described for **10**; 88% yield, mp 77–77.5°C; ^{1}Hmr ($CDCl_3$) δ: 0.25 (s, 6H, $SiMe_2$), 0.98 (s, 9H, *t*-BuSi), 2.30 (bt, 1H, OH), 3.83 (bdd, 2H, CH_2), 4.46 (dt, 1H, C*H*—CH_2, *J* = 4, 5 Hz), 4.87 (d, 1H, CHN_3, *J* = 5 Hz), 6.7–7.7 (m, 4H, C_6H_4).

Azido Mesylate 12

To alcohol **10** (4 g, 8.4 mmol) in CH_2Cl_2 (100 mL) and Et_3N (1 g, 10 mmol) at −78°C was added dropwise MsCl (1.1 g, 10 mmol) in CH_2Cl_2 (10 mL). The solution was stirred for 0.5 h at −78°C and allowed to warm to room temperature. After 1 h the solution was washed with water (2 × 75 mL), then brine (75 mL), dried ($MgSO_4$), and evaporated to give a pale yellow oil, which crystallized *in vacuo*. Trituration with petroleum ether yielded 4.4 g (95%) of mesylate **12** as white crystals, mp 69–70.5°C; ir (film) ν_{max}: 2900, 2100 (N_3), 1780 (C=O) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 0.24, 0.27 (2s, 12H, 2$SiMe_2$), 1.0 (s, 18H, 2*t*-BuSi), 2.86 (s, 3H, SCH_3), 4.45 (bm, 3H, CH—CH_2), 4.94 (m, 1H, CHN_3), 6.4–7.2 (m, 3H, C_6H_3).

Azido Mesylate β-Lactam **11** was prepared as described for **12**; 85% yield; ir (film) ν_{max}: 2110 (N_3), 1770 (β-lactam) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 0.28 (s, 6H, $SiMe_2$), 1.02 (s, 9H, *t*-BuSi), 2.87 (s, 3H, SO_2CH_3), 4.47 (m, 2H, CH_2), 4.80 (m, 1H, C*H*—CH_2), 5.10 (d, 1H, CHN_3, *J* = 4.5 Hz), 6.8–7.8 (m, 4H, C_6H_4).

Chloro β-Lactam 13

Alcohol **9** (0.5 g, 1.4 mmol) was refluxed for 2 h in benzene (25 mL), containing thionyl chloride (0.2 g, 1.7 mmol) and pyridine (0.14 g, 1.7 mmol). This mixture was added to ether (25 mL) and then washed with water (2 × 30 mL) and brine (30 mL). Treatment with charcoal and drying ($MgSO_4$), followed by filtration and evaporation of the solvent afforded 0.46 g (87%) of chloride **13** as a white solid, mp 77–78°C (Et_2O–hexane); ir (film) ν_{max}: 2110 (N_3), 1765 (β-lactam) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 0.32 (s, 6H, $SiMe_2$), 1.03 (s, 9H, *t*-BuSi), 3.75 (m, 2H, CH_2), 4.75 (m, 1H, C*H*—CH_2), 5.05 (d, 1H, CHN_3, *J* = 4.5 Hz), 6.8–7.8 (m, 4H, C_6H_4).

Disilyl Ether **14** was prepared according to the procedure described by Corey and Venkoteswarlu (8); ^{1}Hmr ($CDCl_3$) δ: −0.10, −0.15 (2s, 6H, $SiMe_2$), 0.20 (s, 6H, $SiMe_2$), 0.75, 0.92 (2s, 18H, 2*t*-BuSi), 3.75 (d, 2H, CH_2, *J* = 5 Hz), 4.40 (dt, 1H, C*H*—CH_2, *J* = 5,5 Hz), 4.65 (d, 1H, C*H*N_3, *J* = 5 Hz), 6.6–7.6 (m, 4H, C_6H_4).

β-Lactam Amide **19** was prepared as described for **21**; ir ($CHCl_3$) ν_{max}: 3400 (NH), 1755 (β-lactam), 1680 (amide) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: −0.37, −0.23 (2s, 6H, $SiMe_2$), 0.20, 0.24 (2s, 6H, $SiMe_2$), 0.80, 0.95 (2s, 18H, 2*t*-BuSi), 3.52 (s, 2H, CH_2Ph), 3.72 (broad *ABX*, 2H, CH_2O), 4.47 (bd, 1H, C*H*—CH_2, *J* = 5.5 Hz), 5.60 (dd, 1H, C*H*—NH, *J* = 5.5, 10 Hz), 6.5–7.9 (m, 10H, C_6H_4, C_6H_5, NH).

Tricyclic β-Lactam **15** was prepared from **11** or **13** as described for **16**, mp 77–78°C; ir (KBr) ν_{max}: 2120 (N_3), 1780 (β-lactam) cm^{-1}; ^{1}Hmr 100 MHz (C_6D_6) δ: 3.10 (ddd, 1H, C*H*—CH_2, *J* = 3.5, 5.0, 10 Hz), 3.36 (dd, 1H, CH—C*H*H, *J* = 10,10 Hz), 3.87 (dd, 1H, CH—CH*H*, *J* = 3.5, 10 Hz), 4.18 (d, 1H, CHN_3, *J* = 5.0 Hz), 6.6–7.4 (m, 4H, C_6H_4); ms (70 eV, 30°C), *m/e* (‰): 216 (330, $M^{+\cdot}$), 188 (250, $M^{+\cdot} - N_2$), 135 (1000), 133 (455, $M^{+\cdot}$ − O=C=CH—N_3), 84.4 (M*, 216 → 135).

Tricyclic β-Lactam 16

To mesylate **12** (400 mg, 0.72 mmol) in dry THF (30 mL) at 0°C was added dropwise *n*-Bu_4NF (0.76 mmol) in dry THF (10 mL), over 15 min. Dilution with pH 4.5 buffer (KH_2PO_4, 40 mL) and extraction with ether (3 × 50 mL) afforded, after chromatography of the residue on SiO_2 (CH_2Cl_2), 226 mg (91%) of tricyclic β-lactam **16** as a pale yellow oil which crystallized on standing, mp 69–70°C; ir (film) ν_{max}: 2900, 2100 (N_3), 1775 (C=O) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 0.22, 0.30 (2s, 6H, $SiMe_2$), 1.0 (s, 9H, *t*-BuSi), 3.95 (m, 2H, CH_2), 4.56 (m, 1H, C*H*—CH_2), 5.24 (d, 1H, CHN_3, *J* = 5 Hz), 6.55–6.94 (m, 3H, C_6H_3).

Procedure B

To mesylate **12** (3.42 g, 6.2 mmol) in dry CH_3CN (80 mL) was added anhydrous KF (0.43 g, 7.4 mmol) and 18-crown-6 (0.49 g, 1.9 mmol). Upon completion of the reaction, as indicated by tlc (6–8 h), the solution was diluted with water (100 mL) and extracted with CH_2Cl_2 (3 × 80 mL), which was then washed with brine (100 mL), dried ($MgSO_4$), and evaporated to give 2.0 g (95%) of tricyclic β-lactam **16**, after chromatography.

*Amino β-Lactam 16*a

Into azide **16** (2.1 g, 6.1 mmol) dissolved in CH_2Cl_2 (80 mL) and Et_3N (0.61 g, 6.1 mmol) at 0°C was bubbled H_2S for 10 min. The solution was allowed to warm, and after stirring for 1 h at room temperature, nitrogen was bubbled through the solution for 0.5 h. The solution was then washed with H_2O (2 × 50 mL) and brine (50 mL), then dried ($MgSO_4$), and evaporated. The oily residue was flash chromatographed on silica gel, using ethyl acetate – petroleum ether (3:1), affording 1.65 g (85%) of amine **16***a* as a white solid, mp 135–136°C (recrystallized from ether); ir (film) ν_{max}: 3400 and 3330 (NH_2), 2900, 1765 (C=O) cm^{-1}; ^{1}Hmr (C_6D_6) δ: 0.22, 0.30 (2s, 6H, $SiMe_2$), 0.9 (bs, 2H, NH_2), 1.13 (s, 9H, *t*-BuSi), 3.15 (ddd, 1H, O—CH_2—C*H*, *J* = 3.5, 4.6, 10 Hz), 3.5 (dd (apparent triplet), 1H, O—C*H*H—CH, *J* = 10, 10 Hz), 3.95 (bs, 1H, C*H*NH_2), 4.1 (dd, 1H, O—CH*H*—CH, *J* = 3.5, 10 Hz), 6.4–6.9 (m, 3H, C_6H_3); ms (70 eV, 51°C), *m/e* (‰): 320 (22, $M^{+\cdot}$), 305 (54, $M^{+\cdot} - CH_3$), 292 (428), 263 (1000, $M^{+\cdot} - 57$), 248 (290, $M^{+\cdot} - 15 - 57$), 235 (314), 216.2 (M*, 320 → 263), 189.1 (M*, 292 → 235). *Anal.* calcd. for $C_{16}H_{24}N_2O_3Si$: C 59.97, H 7.55, N 8.74; found: C 59.59, H 7.61, N 8.74.

β-Lactam Amide 17

To amine **16***a* (640 mg, 2 mmol) and Et_3N (242 mg, 2.4 mmol)

in CH_2Cl_2 (20 mL) at 0°C was added dropwise phenylacetyl chloride (370 mg, 2.4 mmol) in CH_2Cl_2 (5 mL), over a period of 5 min. The solution was allowed to warm and, after stirring for 1 h at room temperature, was washed with pH 4.5 buffer (20 mL) and H_2O (20 mL), dried ($MgSO_4$), and evaporated. Chromatography of the residue on SiO_2, eluting successively with CH_2Cl_2, $CHCl_3$, and ether, afforded 750 mg (86%) of amide **17** as fine needles from ether, mp 161–162°C; ir (film) ν_{max}: 3300 (NH), 2900, 1780 (β-lactam), 1670 (amide) cm^{-1}; ^{1}Hmr 200 MHz ($CDCl_3$) δ: 0.15, 0.22 (2s, 6H, $SiMe_2$), 0.96 (s, 9H, *t*-BuSi), 3.56 (s, 2H, CH_2Ph), 3.62 (dd, 1H, C*H*H—CH, *J* = 10, 10 Hz), 3.93 (ddd, 1H, CH_2CH, *J* = 3.5, 5.0, 10 Hz), 4.38 (dd, 1H, CH*H*—CH, *J* = 3.5, 10 Hz), 5.46 (dd, 1H, C*H*NH, *J* = 5, 7 Hz), 6.4 (2 dd, 2H, C*H*—CH—C*H* on C_6H_3, *J* = 1, 8 Hz), 6.53 (bd, 1H, NH, *J* = 7 Hz), 6.83 (dd, 1H, CH—C*H*—CH, on C_6H_3, *J* = 8, 8 Hz), 7.25 (m, 5H, C_6H_5); ms (70 eV, 91°C), *m/e* (‰): 438 (311, $M^{+\cdot}$), 423 (26, $M^{+\cdot} - CH_3^{\cdot}$), 381 (130, $M^{+\cdot} - t$Bu$^{\cdot}$), 264 (1000), 206 (732), 159.1 (M*, 438 → 264), 111.4 (M*, 381 → 206).

Phenol β-*Lactam* ***18***

To silyl ether **17** (240 mg, 0.55 mmol) in dry THF (15 mL) at 0°C was added *n*-Bu_4NF (0.61 mL, 1 *M*), in dry THF (4 mL), dropwise over 10 min. After stirring for 15 min, pH 4.5 buffer (15 mL) was added, and half the THF removed under reduced pressure. Extraction with ethyl acetate (30 mL) followed by evaporation afforded 92 mg (52%) of phenolic β-lactam **18** as fine needles, mp 194–195°C, from ethyl acetate – petroleum ether; ir (Nujol) ν_{max}: 3280 (NH, OH), 1760 (β-lactam), 1655 (amide) cm^{-1}; ^{1}Hmr 200 MHz ($OC(CD_3)_2$) δ: 3.62 (s, 2H, CH_2Ph), 4.07 (dd, 1H, C*H*HCH, *J* = 10, 10 Hz), 4.18 (ddd, 1H, CH_2CH, *J* = 3.3, 4.5, 10 Hz), 4.47 (dd, 1H, CH*H*CH, *J* = 3.3, 10 Hz), 5.66 (dd, 1H, C*H*NH, *J* = 4.5, 8 Hz), 6.50 (2dd, 2H, C*H*—CH—C*H* on C_6H_3, *J* = 1, 8 Hz), 6.92 (dd, 1H, CH—C*H*—CH on C_6H_3, *J* = 8, 8 Hz), 7.32 (m, 5H, C_6H_5), 7.99 (bd, 1H, NH, *J* = 8 Hz); ms (70 eV), *m/e*(‰): 324 (103, $M^{+\cdot}$), 205 (12, $M^{+\cdot} - PhCH_2CO^{\cdot}$), 175 (30), 149 (54), 150 (1000), 91 (398).

Hydroxy Phenol β-*Lactam* **20** was prepared as described for **18**, 97% yield, mp 174–175°C dec. (corr.); ir (CH_3CN) ν_{max}: 3400 (OH, NH), 1720 (β-lactam), 1680 (amide) cm^{-1}; ^{1}Hmr ($OC(CD_3)_2$) δ: 3.1 (b, 2H, 2 OH), 3.80 (s, 2H, CH_2Ph), 4.07 (*ABCX*, 2H, CH_2OH, *J* = 2.5, 3.0, 12.5 Hz), 4.75 (ABC*X*, 1H, C*H*—CH_2, *J* = 2.5, 3.0, 5.0 Hz), 5.72 (ABC*X*, dd, 1H, C*H*—NH, *J* = 5.0, 10 Hz), 6.8–7.7 (m, 10H, C_6H_4, C_6H_5, NH); gc–ms (TMS derivative) (70 eV), *m/e* (‰): component 1: 542 (4, $M^{+\cdot}$, tri-TMS derivative), 527 (17, $M^{+\cdot} - CH_3^{\cdot}$), 439 (30, $M^{+\cdot}$ – TMS—O—$CH_2^{\cdot}$), 335 (210, $M^{+\cdot}$ – TMS—O—Ar—N=C=O); component 2: 470 (56, $M^{+\cdot}$, di-TMS derivative), 455 (24, $M^{+\cdot} - CH_3^{\cdot}$), 296 (1000, $M^{+\cdot} - 174$).

Amide Mesylate ***21***

Hydrogen sulfide was bubbled through a solution of azido mesylate **12** (796 mg, 1.4 mmol) and Et_3N (0.2 mL, 1.4 mmol) in CH_2Cl_2 (75 mL) at 0°C for 10 min. The cooling bath was removed and stirring continued for 1 h, then nitrogen was flushed through the solution for 0.5 h. To this solution at 0°C was added Et_3N (0.26 mL, 1.8 mmol) followed by dropwise addition of phenylacetyl chloride (287 mg, 1.8 mmol) over 5 min. After stirring for 1 h at ambient temperature, the solution was washed with H_2O (3 × 50 mL) and brine (50 mL), then treated with $MgSO_4$ and charcoal, filtered, and evaporated to give 735 mg (79%) of crystalline amide **21**, upon trituration with hexane, mp 129–130°C; ir (CH_2Cl_2) ν_{max}: 3310 (NH), 1775 (β-lactam), 1685 (amide) cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 0.20 (s, 12H, $SiMe_2$), 0.95 (s, 18H, *t*-BuSi), 2.80 (s, 3H, CH_3SO_2), 3.68 (s, 2H, CH_2Ph), 4.15–4.60 (m, 3H, CH_2CH), 5.35 (dd, 1H, C*H*NH, *J* = 4.4, 7 Hz), 6.0 (bd, 1H, NH, *J* = 7 Hz), 6.4–7.2 (m, 3H, C_6H_3), 7.37 (s, 5H, C_6H_5); ms (70 eV, 116°C), *m/e* (‰): 537 (8), 512 (23, $M^{+\cdot} - t$Bu$^{\cdot} - SO_2CH_3^{\cdot}$), 495 (131), 322 (1000).

Azido β-*Lactam* ***24***a

2-*tert*-Butyldimethylsiloxy-5-nitroaniline (7.5 g, 28 mmol) and cinnamaldehyde (4.1 g, 31 mmol), in benzene (100 mL) containing a trace of *p*-TsOH, were refluxed for 2 days using a Dean–Stark trap. The solvent was then evaporated and replaced by CH_2Cl_2 (250 mL). To this solution, at −20°C, was added triethylamine (3.7 g, 36 mmol) followed by dropwise addition of azidoacetyl chloride (4.3 g, 36 mmol), in CH_2Cl_2 (50 mL), over 1 h. The red-brown solution was stirred for an additional hour at −20°C, then allowed to warm up. Washing with water (2 × 200 mL), brine (200 mL), and drying ($MgSO_4$), then treating with charcoal and evaporating the solvent afforded 6.9 g (53%) of β-lactam ***24a*** as a pale yellow solid; mp 109–110°C (ether – petroleum ether); ir (film) ν_{max}: 2100 (N_3), 1770 (β-lactam) cm^{-1}; ^{1}Hmr (C_6D_6) δ: 0.10 (s, 6H, $SiMe_2$), 0.93 (s, 9H, *t*-BuSi), 4.35 (d, 1H, CH—N_3, *J* = 5.5 Hz), 4.58 (dd, 1H, C*H*—CHN_3, *J* = 5.5, 7.0 Hz), 5.9–6.7 (m, 2H, CH=CH), 6.42 (d, 1H, C_6H_3), 7.16 (m, 5H, C_6H_5), 7.60 (dd, 1H, C_6H_3), 8.46 (d, 1H, C_6H_3).

Azido β-*Lactam* ***24***b

tert-Butyldiphenylsilyl ether β-lactam ***24b*** was obtained, using the same procedure as for ***24a***, in 58% yield as fine white crystals, mp 159.5–160°C corr. (ether – petroleum ether); ir (film) ν_{max}: 2100 (N_3), 1780 (β-lactam) cm^{-1}; ^{1}Hmr (C_6D_6) δ: 1.22 (s, 9H, *t*-BuSi), 4.50 (m, 2H, CH—CHN_3), 6.33 (m, 3H, CH=CH, and C_6HH_2), 7.16 and 7.76 (2m, 16H, 3 C_6H_5 and C_6HH_2), 8.16 (d, 1H, C_6H_3).

Nitro Derivatives: 28 and 30

To a solution of **16** (574 mg, 1.6 mmol) in dry acetonitrile (20 mL) under nitrogen atmosphere at −20°C, nitronium tetrafluoroborate (3.2 mL, 0.5 *M* solution in sulfolane) was added dropwise. After 1 h, dry benzene (10 mL) was added and the mixture was stirred for 10 more minutes. The reaction mixture was then poured (while still very cold) into 30 mL of pH 4.5 buffer and extracted twice, dried ($MgSO_4$), and evaporated. The *ortho*-, *nitro*-, and *para*-nitrosilyl ether compounds were isolated and crystallized, after flash chromatography. The remaining mixture of nitrophenols was separated from sulfolane via Kugelrohr distillation, resilylated, and purified by flash chromatography to afford more of the desired products.

ortho-Silyl ether **28**, mp 109–110°C; ir (film) ν_{max}: 2100 (N_3), 1795 (β-lactam) cm^{-1}; ^{1}Hmr (C_6D_6) δ: 0.2 (s, 3H, $SiCH_3$), 0.3 (s, 3H, $SiCH_3$), 1.1 (s, 9H, *t*-Bu), 2.6–2.9 (ddd, 1H, CH_2—C*H*), 2.9–3.3 (dd, 1H, CH*H*—CH, *J* = 10, 10 Hz), 3.8–4.0 (dd, 1H, C*H*H—CH, *J* = 3, 10 Hz), 4.05 (d, 1H, CHN_3, *J* = 4.5 Hz), 6.15 (d, 1H, C_6HH, *J* = 9 Hz), 7.43 (d, 1H, C_6HH, *J* = 9 Hz); ms, *m/e*: 334 ($M^{+\cdot} - t$-Bu$^{\cdot}$), 306 ($M^{+\cdot} - t$-Bu$^{\cdot} - N_2^{\cdot}$), 260 ($M^{+\cdot}$ – $OSi(CH_3)_2C(CH_3)_3^{\cdot}$), 251 ($M^{+\cdot} - t$-Bu$^{\cdot}$ – O=C=CHN_3).

para-Silyl ether **30**, mp 122–123°C; ir (film) ν_{max}: 2100 (azide), 1785 (β-lactam) cm^{-1}; ^{1}Hmr (C_6D_6) δ: 0.03 (s, 3H, $SiCH_3$), 0.15 (s, 3H, $SiCH_3$), 1.7 (s, 9H, *t*-Bu), 2.66–3.0 (ddd, 1H, CH_2—C*H*, *J* = 4, 5, 10 Hz) 3.15–3.45 (dd, 1H, C*H*H—CH, *J* = 10, 10 Hz), 3.7–3.9 (dd, 1H, CH*H*—CH, *J* = 4, 10 Hz), 4.1 (d, 1H, CHN_3, *J* = 5 Hz), 6.15 (d, 1H, C_6HH, *J* = 9 Hz), 7.35 (d, 1H, C_6HH, *J* = 9 Hz); ms *m/e*: 334 ($M^{+\cdot} - t$-Bu$^{\cdot}$), 306 ($M^{+\cdot} - t$-Bu$^{\cdot} - N_2^{\cdot}$), 251 ($M^{+\cdot}$ – *t*-Bu$^{\cdot}$ – O=C=CHN_3). *Anal.* calcd. for $C_{16}H_{21}N_5O_5Si$: C 49.10, H 5.37, N 17.90; found: C 48.91, H 5.50, N 17.72.

p-*Nitro Silyl Ether* ***30***b

A mixture of *ortho*- and *para*-nitrophenols ***28a*** and ***30a*** (138 mg, 0.5 mmol), *tert*-butyldiphenylsilyl chloride (165 mg, 0.6 mmol), and imidazole (82 mg, 1.2 mmol), in dry dimethylformamide (5 mL) was stirred at room temperature for 15–20 h.

The reaction mixture was then added to ethyl ether (100 mL), washed with water and brine, dried ($MgSO_4$), and evaporated to dryness to give crude product **30***b* which was crystallized from CH_2Cl_2 – petroleum ether (100 mg, 45%), mp 153–154°C. The water–brine layer was further extracted with ethyl acetate in order to isolate *ortho*-nitrophenol **28***a* and decomposition products; ^{1}Hmr (C_6D_6) δ: 1.1 (s, 9H, $C(CH_3)_3$), 3.15–3.5 (ddd, 1H, CH_2—C*H*, J = 4, 5, 10 Hz), 3.65–4.0 (dd, 1H, C*H*H—CH, J = 10, 10 Hz), 4.3–4.55 (dd, 1H, CH*H*—CH, J = 4, 10 Hz), 4.65 (d, 1H, CHN_3, J = 5 Hz), 6.47 (d, 1H, C_6HH, J = 9 Hz), 7.2–7.7 (m, 11H, C_6HH, 2Ph).

β-*Lactam Amines* ***31*** *and* ***33***a

Hydrogen sulphide was bubbled into a solution of azides **28** and **30** (mixture) (170 mg, 0.45 mmol) and triethylamine (49 mg, 0.5 mmol) in dry methylene chloride (10 mL) at 0°C. After 1 h of stirring at room temperature the solution was purged with nitrogen, washed with water (2 × 10 mL), dried, and evaporated to give a crude yellow oily product (140 mg); ir (film) ν_{max}: 3350 (amine), 1780 (β-lactam) cm^{-1}; ^{1}Hmr (acetone-d_6) δ: 0.3 (2s, 6H, $Si(CH_3)_2$), 1.0 (s, 9H, $C(CH_3)_3$), 2.9 (bs, 2H, NH_2), 4.0–4.3 (m, 2H), 4.7–4.9 (m, 1H), 5.5–5.6 (dd, 1H, C*H*NH_2), 6.5–6.7 (2d, 1H, C_6HH), 7.6 (d, 1H, C_6HH).

Phenylacetamido Silyl Ether ***32***

Hydrogen sulphide was bubbled into a solution of azide **30***b* (140 mg, 0.3 mmol) and triethylamine (0.05 mL) in methylene chloride (10 mL) at 0°C for 3–5 min. After 1 h, the solution was purged with nitrogen. To the crude product **33***b*, in methylene chloride (10 mL) and triethylamine (0.05 mL) at 0°C, was added dropwise phenylacetyl chloride (0.06 g, 0.4 mmol). After stirring for 1 h the solution was washed with pH 4.5 buffer (10 mL), water (10 mL), dried ($MgSO_4$), and concentrated. The crude product **32** was crystallized from ethyl acetate – petroleum ether several times to obtain 100 mg (60%) of pale yellow crystalline product, mp 190–191°C; ir (film) ν_{max}: 1790 (β-lactam), 1710 (amide) cm^{-1}; ^{1}Hmr (DMSO-d_6) δ: 1.1 (s, 9H, $C(CH_3)_3$), 3.5 (s, 2H, $COCH_2Ph$), 3.3–3.7 (m, 1H, CH_2—C*H*), 3.8–4.2 (dd, 1H, C*H*H—CH, J = 10, 10 Hz), 4.3–4.6 (dd, 1H, CH*H*—CH, J = 4, 10 Hz), 5.1–5.3 (dd, 1H, C*H*—NHCO, J = 5, 8 Hz), 6.6 (d, 1H, C_6HH, J = 9 Hz), 7.2 (s, 10H, $SiPh_2$), 7.2–7.7 (m, 5H, —CH_2Ph), 8.0 (bd, 1H, NH, J = 8 Hz), 8.7 (d, 1H, C_6HH, J = 9 Hz).

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