A Novel Approach to the Synthesis of Precursors of Tricyclic β-Lactam Antibiotics

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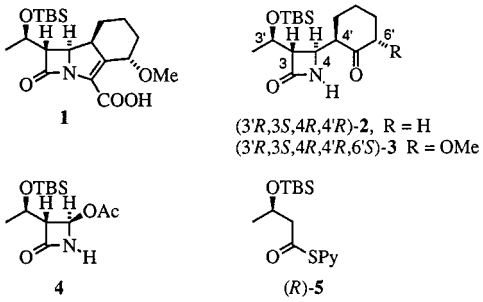
The stereoselective synthesis of two precursors of tricyclic β-lactam antibiotics (trinems) has been attempted by a novel approach that involves a highly stereoselective azetidinone ring-forming reaction followed by the reduction of a functionalized aromatic substituent at C-4 of the β-lactam nucleus.

Introduction

Tricyclic β-lactam antibiotics, generally referred to as trinems,[1] are a new class of synthetic antibacterial agents featuring both a broad spectrum of activity against Gram-positive and -negative bacterial strains, and good resistance to β-lactamases and dehydropeptidases. Sanfetrinem **(1)** (Figure 1),[2] developed by GlaxoWellcome, has emerged among trinems because of its excellent biological profile and is currently in Phase II clinical trials.



Abbreviations: TBS = t-BuMe$_2$Si; Py = 2-Pyridyl

Figure 1. Structures of Sanfetrinem and its precursors

Several syntheses of β-lactam **1** have been reported,[1−3] all of which are centered on the preparation of ketones **2** or **3** (Figure 1). These are generally obtained by displacement of the acetoxy group of the commercially available azetidinone **4**[4] by different precursors of the methoxycyclohexanone moiety.[5] Only two formal syntheses of Sanfetrinem that do not start from β-lactam **4** have been described. One generates the racemic ketone **2**, which is then resolved after formation of its diastereoisomeric enolphosphate derivatives.[6] The other exploits the stereocenter of (*S*)-2-methoxycyclohexanone[5c] to establish the remaining stereocenters of compound **3**.[7]

Over the last few years we have developed a one-pot synthesis of β-lactams that is based on the condensation of the trichlorotitanium enolate of 2-pyridylthioesters with imines.[8] Among the large number of thioesters used in this reaction, compound (*R*)-**5** was found to condense, with high stereoselectivity, with *N*-4-methoxyphenyl (PMP) imines derived from aromatic aldehydes, to afford β-lactams having the correct absolute and relative configuration at C-3 and C-4 (see Figure 1 for numbering) required by the trinem antibiotics such as **1**.[9]

We decided to attempt a new synthesis of adducts **2** and **3** starting from the thioester (*R*)-**5**, with the aim of exploiting its stereocenter to control the stereochemistry of the remaining stereocenters. We report here the results of this work.

Results and Discussion

The imine **6** (Scheme 1) was prepared in two simple steps from 2-hydroxy-3-methoxybenzaldehyde by allylation[10] and subsequent reaction with 4-methoxyaniline. Condensation with the trichlorotitanium enolate of thioester **5**[9][11] gave isolated β-lactams **7** in 96% yield.[12] These compounds were obtained as a 93:7 mixture of diastereoisomers, the ratio of which was determined by ^{1}H NMR spectroscopic analysis of the crude reaction products. The *trans*/*cis* relative stereochemistry at C-3 and C-4 of the azetidinone ring was inferred from the coupling constant values (J_{trans} = 2.0−3.0 Hz; J_{cis} = 5.0−6.0 Hz). The assignment of the relative configuration at C-3 and C-3′ was based on comparison of NMR spectroscopic data for compound **7** with those of similar substrates of known stereochemistry,[8][9] and confirmed by chemical correlation (see below). Thus, the C-3,C-4-*trans*/C-3,C-3′-*anti* configuration (**ta**) was assigned to the major isomer **7ta** and the C-3,C-4-*trans*/C-3,C-3′-*syn* (**ts**) one to the minor product **7ts**. Pure **7ta** was obtained by flash chromatography.

Removal of the PMP and allyl protecting groups from **7ta** was then accomplished in this sequence:[13] treatment with [Ce(NH$_4$)$_2$(NO$_3$)$_6$·(CAN)] in acetonitrile/water,[14] and then reaction with triethylammonium formate in ethanol/water in the presence of a catalytic amount of Pd(OAc)$_2$ and PPh$_3$.[15] Compound **8** was thus obtained in 56% overall yield.

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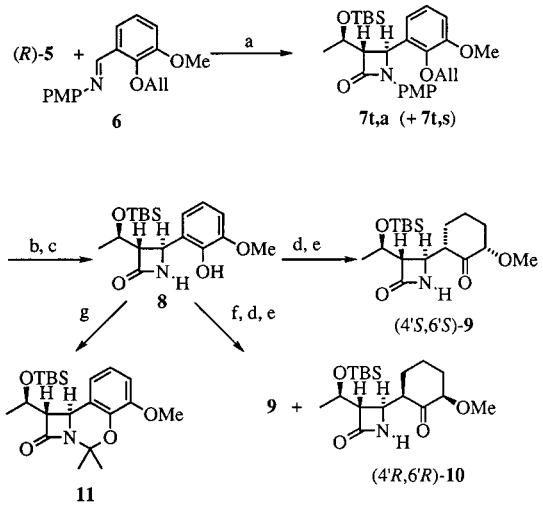


Abbreviations: PMP = 4-methoxyphenyl; All = $CH_2CH=CH_2$. Reagents: a, $TiCl_4/Et_3N$, CH_2Cl_2; b, CAN, MeCN, H_2O; c, HCO_2H, Et_3N, EtOH, H_2O, PPh_3, $Pd(OAc)_2$; d, H_2, Rh/C, AcOEt; e, $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2; f, Cs_2CO_3; g, $BF_3{\cdot}OEt_2$, $(MeO)_2CMe_2$.

Scheme 1. Synthesis of ketones **9** and **10**

With this compound in hand the reduction of the aromatic ring was attempted,[16] with the reasonable expectation that hydrogen addition would occur from the side of the hydrogen atom at C-4 and deliver the desired (*R*)-configuration at C-4′ as in ketone **3**.[17] However, when β-lactam **8** was treated with H_2 (70 bar) over 5% Rh/C in AcOEt and the crude cyclohexanol was oxidized by the Swern procedure[18][19] to the corresponding ketone, (4′*S*, 6′*S*)-**9** was obtained as the sole reaction product in 40% yield.[20][21] It should be noted that **9** differs from **3** only in the configuration at C-4′.

Since attack from the less hindered face of the aromatic ring (*i.e.* from the side of the H at C-4) appeared most likely,[17] the stereochemical outcome of the reduction suggested that compound **8** mainly existed, and possibly reacted, in a conformation in which the phenolic OH is transoid to the β-lactam nitrogen to form a hydrogen bond with the oxygen at C-3′ oriented as in **A** (Figure 2). Molecular mechanics calculations[22] carried out on a model compound confirmed this hypothesis showing that the H-bonded conformation **B** is more stable than **C** by about 4 kJ/mol (Figure 2).

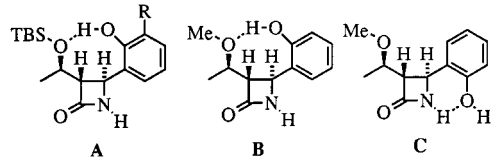


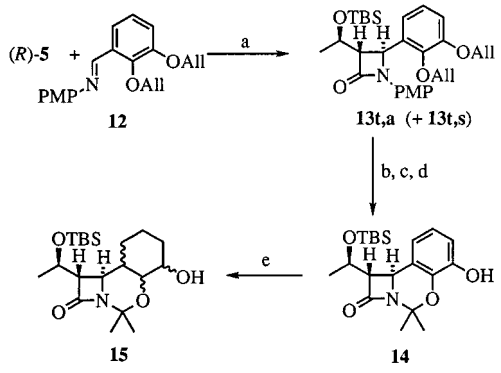
Figure 2. Conformations of 4-(2-hydroxyphenyl) substituted azetidinones

Since the reduction of the aromatic ring of **8** led to the formation of the wrong epimer at C-4′, we were faced with two possibilities to obtain the desired stereoisomers: i) to invert the configuration at C-4′ of **9**; ii) to run the reduction on a rotamer of **8** conformationally restricted to exist mainly as in **C**.

Epimerization at C-4′ of ketone **9** was attempted by several enolization/reprotonation procedures. These involved the use of strong bases such as LTMP, LDA, LHMDS, KH or NaH, and of combinations of weak bases [Et_3N, Et-N(iPr)$_2$] and Lewis acids ($TiCl_4$, $SnCl_4$, TBSOTf). The first set of reagents led to some decomposition and mostly gave back the unchanged starting materials. The second set of reagents did not induce any epimerization when used in stoichiometric amounts below or at room temperature and led to extensive decomposition when used in excess and/or under more drastic conditions.

Prompted by these disappointing results, we turned our attention to the possibility of forcing phenol **8** to adopt, and undergo reduction in, a conformation such as **C**. To this end, hydrogenation of **8** was carried out in the presence of a threefold molar excess of Cs_2CO_3. This salt is known to generate phenoxide ions effectively.[23] In the present case this should result in the replacement of the H-bond between the OH and the OTBS groups by a new bond between the β-lactam NH and the negatively charged phenoxide oxygen. This strategy was only partially successful, since Swern oxidation of the crude reduction products gave a 75:25 mixture of ketone (4′*S*, 6′*S*)-**9** and its (4′*R*, 6′*R*)-isomer **10** in 34% overall yield (50% based on recovered **8**).

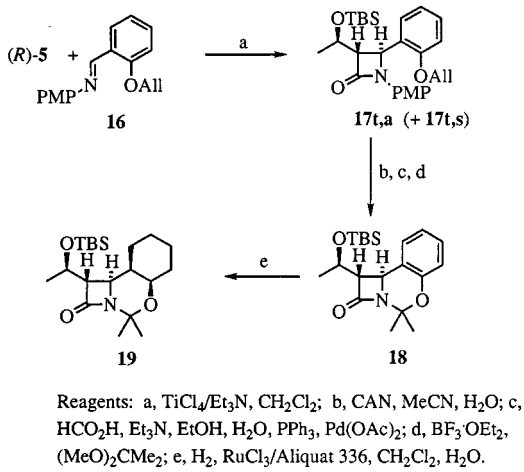
To more firmly lock **8** in a **C**-type conformation, this compound was transformed into the acetonide **11**, but this product proved to be extremely resistant to hydrogenation under both heterogeneous and homogeneous conditions.[21] However, the acetonide **14**, prepared in 43% overall yield following the reaction sequence reported in Scheme 2 from the thioester **5** and the bisallyl-protected imine **12** via adduct **13ta** (97% yield, **13ta/13ts** ratio 92:8), could be reduced with H_2 (60 bar) in the presence of $RuCl_3$ and trioctylamine in ethyl acetate/water. From this reaction, adduct **15** was isolated as a 50:50 mixture of (4′*R*,5′*S*,6′*R*)- and (4′*S*,5′*R*,6′*S*)-isomers in 31% yield (43% based on recovered **14**).



Reagents: a, $TiCl_4/Et_3N$, CH_2Cl_2; b, CAN, MeCN, H_2O; c, HCO_2H, Et_3N, EtOH, H_2O, PPh_3, $Pd(OAc)_2$; d, $BF_3{\cdot}OEt_2$, $(MeO)_2CMe_2$; e, $RuCl_3$/trioctylamine, AcOEt, H_2O.

Scheme 2. Synthesis of acetonide **5**

From the experiments described in Schemes 1 and 2 it was concluded that the simultaneous establishment of both stereocenters at C-4′ and at C-6′ in the required configuration was not possible by this approach.[24] Therefore we turned our attention to the acetonide **18** obtained by the reaction sequence reported in Scheme 3. Condensation of (*R*)-**5** with imine **16** gave adducts **17ta** and **17ts** in 91% yield (**ta**:**ts** ratio = 91:9). Pure **17ta**, obtained after flash chromatography, was transformed into **18** as described above (51% overall yield). This β-lactam was reduced under mild conditions with H_2 (1 bar) in the presence of $RuCl_3$-Aliquat 336 as catalyst[25] to give adduct **19** as a single (4′*S*)-isomer in 65−70% yield.[26] Conversion of **19** to **2** can be carried out following literature methods.[27]



Scheme 3. Synthesis of acetonide **19**

In conclusion, two Sanfetrinem precursors were synthesized using the stereocenter of thioester (*R*)-**5** as the sole element of stereocontrol. Although this approach cannot compete with the highly convergent and stereoselective synthesis currently employed for the industrial preparation of **1**, it compares favorably with other available methods, especially in terms of the low cost of starting materials and of the reduced number of steps required to prepare the precursors **2** and **3**. The extension of this new route to the preparation of differently substituted derivatives of the trinem class is currently under investigation in our laboratories.

Experimental Section

2-Allyloxy-[28] and 2-allyloxy-3-methoxybenzaldehyde[29] are known compounds. 2,3-Diallyloxybenzaldehyde was obtained in 99% yield according to the published procedure.[29] The oily product was purified by flash chromatography with a 80:20 hexane/Et_2O mixture as eluent. IR: 1685 cm^{-1}. − ^1H NMR (80 MHz): δ = 10.45 (s, 1 H), 7.00−7.50 (m, 3 H), 5.80−6.20 (m, 2 H), 5.10−5.50 (m, 4 H), 4.50−4.90 (m, 4 H). − $C_{13}H_{14}O_3$: calcd. C 71.54, H 6.47; found C 71.38, H, 6.40. Imines **6**, **12**, and **16** were prepared by overnight stirring of an equimolar mixture of aldehyde and 4-methoxyaniline in CH_2Cl_2 at room temperature in the presence of excess $MgSO_4$. They were used as crude products.

Synthesis of β-Lactams 7, 13, and 17. − General Procedure: To a stirred 0.1M solution of thioester **5** (1−10 mmol) in CH_2Cl_2 at −78°C and kept under nitrogen were added dropwise in this order a 1M solution of $TiCl_4$ (1.05 mol equiv.) in CH_2Cl_2, and triethylamine (1.1 mol equiv.). After 15 min stirring at −78°C, a 0.1M solution of imine (0.5 mol equiv.) in CH_2Cl_2 was added dropwise in 5 min, and the reaction mixture was stirred at −78°C for a further 5 h. It was then allowed to warm to room temperature overnight. A saturated aqueous solution of $NaHCO_3$ was added, and the resulting mixture filtered through a celite cake, which was washed several times with CH_2Cl_2. The organic phase was separated and the aqueous phase extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuum. The crude residue was dissolved in THF and treated with a twofold molar excess of 1M aqueous KOH for 2 h at room temperature. This procedure hydrolyzed the unchanged **5** and greatly simplified the ^1H NMR analysis of the crude product to determine the diastereoisomeric ratio without affecting it. Diethyl ether was then added and the aqueous phase was separated. The organic phase was dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography with a 70:30 hexanes/Et_2O mixture as eluent. Yields and diastereoisomeric ratios are reported in the text.

3-(1-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}ethyl)-1-(4-methoxyphenyl)-4-[3-methoxyphenyl-2-(propen-2-yloxy)]azetidin-2-one (7ta): Isolated as an oil. − $[\alpha]_D^{23}$ = + 13.0 (*c* = 0.15 in $CHCl_3$). − IR: 1743, 1265 cm^{-1}. − $C_{28}H_{39}NO_5Si$: calcd., C 67.57, H 7.90, N 2.81; found C 67.61, H 7.97, N 2.87. − ^1H NMR(**7ta**): δ = 6.73−7.27 (m, 7 H, aromatic protons), 6.10−6.25 (m, 1 H, *CH*=CH_2), 5.51 (d, 1 H, *J* = 2.0 Hz, H−C4), 5.20−5.46 (m, 2 H, CH=*CH*$_2$), 4.53−4.70 (m, 2 H, CH_2−O), 4.37 (dq, 1 H, *J* = 2.0, 6.5 Hz, H−C3′), 3.87 (s, 3 H, CH_3O), 3.72 (s, 3 H, CH_3O), 3.11 (t, 1 H, *J* = 2.0 Hz, H−C3), 1.26 (d, 3 H, *J* = 6.5 Hz, CH_3−C3′), 0.76 (s, 9 H, *t*Bu), 0.07 (s, 3 H, CH_3Si), 0.02 (s, 3 H, CH_3Si). ^1H NMR (**7ts**): δ = 6.73−7.27 (m, 7 H, aromatic protons), 6.15−6.30 (m, 1 H, *CH*=CH_2), 5.23 (d, 1 H, *J* = 2.0 Hz, H−C4), 5.20−5.41 (m, 2 H, CH=*CH*$_2$), 4.60−4.75 (m, 2 H, CH_2−O), 4.37 (dq, 1 H, *J* = 2.0, 6.5 Hz, H−C3′), 3.86 (s, 3 H, CH_3O), 3.72 (s, 3 H, CH_3O), 3.10 (t, 1 H, *J* = 2.0 Hz, H−C3), 1.37 (d, 3 H, *J* = 6.5 Hz, CH_3−C3′), 0.75 (s, 9 H, *t*Bu), 0.06 (s, 3 H, CH_3Si), 0.02 (s, 3 H, CH_3Si). − ^{13}C NMR (**7ta**) (when different, the data for **7ts** are reported in parentheses): δ = 166.1 (165.8), 155.6, 152.6 (152.9), 145.4 (145.6), 134.0, 132.2, 124.5, 118.7, 118.3, 118.2, 118.1, 114.2, 111.8, 74.1 (74.2), 66.3 (66.8), 66.1 (64.7), 55.7, 55.4, 51.9 (50.4), 25.6, 21.5 (22.3), 17.9 (17.8).

4-[2,3-Bis(propen-2-yloxy)phenyl]-3-(1-{[(1,1-dimethylethyl)-dimethylsilyl]oxy}ethyl)-1-(4-methoxyphenyl)azetidin-2-one (13ta): Isolated as an oil. − $[\alpha]_D^{23}$ = + 14.9 (*c* = 0.8 in $CHCl_3$). − IR: 1741, 1224 cm^{-1}. − $C_{30}H_{41}NO_5Si$: calcd. C 68.80, H 7.89; N 2.67; found C 68.51, H 7.74, N 2.53. − ^1H NMR (**13ta**): δ = 6.73−7.24 (m, 7 H, aromatic protons), 6.02−6.25 (m, 2 H, C*H*=CH_2), 5.53 (d, 1 H, *J* = 2.5 Hz, H−C4), 5.25−5.47 (m, 4 H, CH=C*H*$_2$), 4.56−4.72 (m, 4 H, CH_2−O), 4.37 (dq, 1 H, *J* = 2.5, 6.5 Hz, H−C3′), 3.70 (s, 3 H, CH_3O), 3.10 (t, 1 H, *J* = 2.5 Hz, H−C3), 1.26 (d, 3 H, *J* = 6.5 Hz, CH_3−C3′), 0.77 (s, 9 H, *t*Bu), 0.08 (s, 3 H, CH_3Si), 0.03 (s, 3 H, CH_3Si). ^1H NMR (**13ts**): δ = 6.73−7.24 (m, 7 H, aromatic protons), 6.02−6.25 (m, 2 H, C*H*=CH_2), 5.24 (d, 1 H, *J* = 3.0 Hz, H−C4), 5.26−5.48 (m, 4 H, CH=C*H*$_2$), 4.56−4.72 (m, 4 H, CH_2−O), 4.37 (dq, 1 H, *J* = 3.0, 6.5 Hz, H−C3′), 3.72 (s, 3 H, CH_3O), 3.10 (t, 1 H, *J* = 3.0 Hz, H−C3), 1.37 (d, 3 H, *J* = 6.5 Hz, CH_3−C3′), 0.76 (s, 9 H, *t*Bu), 0.07 (s, 6 H, CH_3Si). − ^{13}C NMR (**13ta**) (when different, the data for **13ts** are reported in parentheses): δ = 165.1 (165.9), 151.5 (151.8), 145.6

(146.0), 134.0 (133.9), 133.0, 132.9 (131.4), 124.3, 118.5 (118.9), 118.0, 117.5, 113.3, 73.9 (74.0), 69.4, 66.3 (66.6), 66.1 (64.6), 55.2, 52.1 (50.4), 25.5, 21.6 (22.4), 17.8 (17.7).

3-(1-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}ethyl)-1-(4-methoxyphenyl)-4-[2-(propen-2-yloxy)phenyl]azetidin-2-one (17ta): Isolated as an oil. − $[\alpha]_D^{23}$ = −42.5 (*c* = 1 in $CHCl_3$). − IR: 1745, 1265 cm^{-1}. − $C_{27}H_{37}NO_4Si$: C 69.34, H 7.97, N 2.99; found C 69.11, H 8.07, N 2.87. − ^1H NMR **(17ta)**: δ = 6.73−7.30 (m, 8 H, aromatic protons), 6.02−6.15 (m, 1 H, *CH*=CH_2), 5.57 (d, 1 H, *J* = 2.5 Hz, H−C4), 5.25−5.50 (m, 2 H, CH=*CH_2*), 4.57−4.68 (m, 2 H, CH_2−O), 4.38 (dq, 1 H, *J* = 2.5, 6.0 Hz, H−C3′), 3.71 (s, 3 H, CH_3O), 3.09 (t, 1 H, *J* = 2.5 Hz, H−C3), 1.25 (d, 3 H, *J* = 6.0 Hz, CH_3−C3′), 0.77 (s, 9 H, *t*Bu), 0.09 (s, 3 H, CH_3Si), 0.04 (s, 3 H, CH_3Si). ^1H NMR **(17ts)**: δ = 6.73−7.30 (m, 8 H, aromatic protons), 6.02−6.15 (m, 1 H, *CH*=CH_2), 5.27 (d, 1 H, *J* = 2.5 Hz, H−C4), 5.25−5.50 (m, 2 H, CH=*CH_2*), 4.57−4.68 (m, 2 H, CH_2−O), 4.38 (dq,1 H, *J* = 2.5, 6.0 Hz, H−C3′), 3.70 (s, 3 H, CH_3O), 3.06 (t, 1 H, *J* = 2.5 Hz, H−C3), 1.39 (d, 3 H, *J* = 6.0 Hz, CH_3−C3′), 0.77 (s, 9 H, *t*Bu), 0.09 (s, 3 H, CH_3Si), 0.04 (s, 3 H, CH_3Si). − ^{13}C NMR **(17ta)** (when different, the data for **17ts** are reported in parentheses): δ = 165.8 (165.0), 156.0, 132.9 (133.1), 129.0, 127.0, 126.4, 121.2, 117.4, 111.6, 68.8 (69.0), 66.7 (66.3), 64.9 (65.9), 55.2, 50.4 (52.2), 25.8, 22.3 (21.7), 17.8.

Deprotection of 7ta, 13ta, and 17ta. − General Procedure for the *N*-Deprotection: To a stirred 0.015 M solution of β-lactam (1−3 mmol) in MeCN at −30°C was added dropwise a solution of CAN (4 mol equiv.) in water (final $MeCN/H_2O$ = 3/1). The mixture was stirred at −30°C for 35 min and then Et_2O and saturated aqueous solutions of $NaHCO_3$ and Na_2SO_3 were added in this order. The mixture was allowed to warm to room temperature and then filtered through a celite cake. The phases were separated and the aqueous layer was extracted twice with Et_2O. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuum to give the product, which was purified by flash chromatography with a 50:50 hexanes/Et_2O mixture as eluent.

The compound obtained from **7ta** (78% yield) had m.p. 136−139°C. − $[\alpha]_D^{23}$ = −3.9 (*c* = 0.4 in $CHCl_3$). − IR: 1752 cm^{-1}.

The compound obtained from **13ta** (70% yield) had m.p. 98−100°C. − $[\alpha]_D^{23}$ = +0.2 (*c* = 0.2 in $CHCl_3$). − IR: 1756 cm^{-1}.

The compound obtained from **17ta** (73% yield) had m.p. 143−144°C. − $[\alpha]_D^{23}$ = −17.7 (*c* = 1.8 in $CHCl_3$). − IR: 1755 cm^{-1}.

General Procedure for the Deallylation: To a stirred solution of N-unprotected β-lactam (1−2 mmol) in absolute EtOH were added in this order $Pd(OAc)_2$ (0.1 mol equiv.) and PPh_3 (0.4 mol equiv.) . To this solution a mixture of formic acid (1.5 mol equiv.) and triethylamine (1.5 mol equiv.) in 4:1 $EtOH/H_2O$ (half the volume of the original EtOH) was added at once, and the stirring was continued for two days at room temperature. EtOH was then evaporated in vacuum, H_2O was added, and the resulting mixture was extracted three times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuum to give the product, which was purified by flash chromatography with a 20:80 hexanes/Et_2O mixture as eluent.

3-(1-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}ethyl)-4-(2-hydroxyphenyl)azetidin-2-one: (79% yield), m.p. 165−6°C. − $[\alpha]_D^{23}$ = −80.7 (*c* = 0.5 in $CHCl_3$). − IR: 1755, 1215 cm^{-1}. − $C_{17}H_{27}NO_3Si$: C 63.51, H 8.46, N 4.36; found C 63.11, H 8.27, N 4.57. − ^1H NMR: δ = 6.85-7.21 (m, 4 H, aromatic protons), 6.69 (br. s, 2 H, NH and OH), 4.76 (d, 1 H, *J* = 2.5 Hz, H−C4), 4.31 (dq,1 H, *J* = 2.0, 6.0 Hz, H−C3′), 3.13 (dd, 1 H, *J* = 2.0, 2.5 Hz, H−C3), 1.37 (d, 3 H, *J* = 6.0 Hz, CH_3−C3′), 0.93 (s, 9 H, *t*Bu), 0.17 (s, 3 H, CH_3Si), 0.16 (s, 3 H, CH_3Si).

3-(1-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}ethyl)-4-(2-hydroxy-3-methoxyphenyl)azetidin-2-one 8: (72% yield), m.p. 156−8°C. − $[\alpha]_D^{23}$ = −22.0 (*c* = 0.3 in $CHCl_3$). − IR: 1762, 1265 cm^{-1}. − $C_{18}H_{29}NO_4Si$: C 61.50, H 8.32, N 3.98; found C 61.36, H 8.19, N 3.87. − ^1H NMR: δ = 6.80-6.97 (m, 3 H, aromatic protons), 5.94 (br. s, 2 H, NH and OH), 5.07 (d, 1 H, *J* = 2.0 Hz, H−C4), 4.30 (dq,1 H, *J* = 4.0, 6.0 Hz, H−C3′), 3.89 (s, 3 H, CH_3O), 3.16 (dd, 1 H, *J* = 2.0, 4.0 Hz, H−C3), 1.28 (d, 3 H, *J* = 6.0 Hz, CH_3−C3′), 0.90 (s, 9 H, *t*Bu), 0.10 (s, 3 H, CH_3Si), 0.09 (s, 3 H, CH_3Si). − ^{13}C NMR: δ = 169.3, 146.5, 143.0, 125.7, 119.7, 118.8, 110.0, 66.6, 65.3, 56.0, 48.0, 25.7, 22.3, 18.0.

4-(2,3-Dihydroxyphenyl)-3-(1-{[(1,1-dimethylethyl)dimethylsilyl]-äoxy}ethyl)azetidin-2-one: (61% yield), m.p. 148−150°C. − $[\alpha]_D^{23}$ = −74.1 (*c* = 0.8 in $CHCl_3$). − IR: 1755, 1214 cm^{-1}. − $C_{17}H_{27}NO_4Si$: C 60.50, H 8.06, N 4.15; found C 60.32, H 8.24, N 4.23. − ^1H NMR: δ = 6.68-6.88 (m, 3 H, aromatic protons), 5.94 (br. s, 3 H, NH and 2 OH), 4.76 (d, 1 H, *J* = 2.0 Hz, H−C4), 4.31 (dq,1 H, *J* = 4.0, 6.0 Hz, H−C3′), 3.11 (dd, 1 H, *J* = 2.0, 4.0 Hz, H−C3), 1.36 (d, 3 H, *J* = 6.0 Hz, CH_3−C3′), 0.93 (s, 9 H, *t*Bu), 0.18 (s, 3 H, CH_3Si), 0.17 (s, 3 H, CH_3Si).

Synthesis of Ketones 9 and 10:[1,5b] Dearomatization: To a 0.01 M solution of compounds **8** (0.1−0.5 mmol) in AcOEt was added freshly opened 5% Rh/C (half the weight amount of the starting material). The suspension was then transferred to a steel pressure vessel and hydrogenated under 70 bar of H_2 for two days at room temperature with continuous shaking. The mixture was then filtered through a celite cake, and the solvent evaporated under vacuum. The crude product was subjected to a Swern oxidation as previously described[30] to afford the products. The obtained diastereoisomeric mixture could be separated during product purification by flash chromatography. The ketones are known compounds and showed ^1H NMR spectroscopic data identical to those previously reported.[1,5b]

Synthesis of Acetonides 11, 14 and 18: These compounds were prepared according to a published procedure.[27] Acetonide **11** was isolated as an oil, which was purified by flash chromatography with a 60:40 hexanes/Et_2O mixture as eluent. − $[\alpha]_D^{23}$ = −58.3 (*c* = 2.5 in $CHCl_3$). − IR: 1762 cm^{-1}. − $C_{21}H_{33}NO_4Si$: C 64.41, H 8.49, N 3.58; found C 64.09, H 8.27, N 3.57. − ^1H NMR: δ = 6.67-6.93 (m, 3 H, aromatic protons), 4.62 (d, 1 H, *J* = 2.0 Hz, H−C4), 4.28 (dq, 1 H, *J* = 4.0, 6.5 Hz, H−C3′), 3.83 (s, 3 H, CH_3O), 2.89 (dd, 1 H, *J* = 2.0, 4.0 Hz, H−C3), 2.00 (s, 3 H, CH_3−C−N), 1.43 (s, 3 H, CH_3−C−N), 1.33 (d, 3 H, *J* = 6.5 Hz, CH_3−C3′), 0.91 (s, 9 H, *t*Bu), 0.10 (s, 6 H, CH_3Si). − ^{13}C NMR: δ = 168.0, 149.3, 141.7, 122.1, 120.8, 118.2, 110.5, 84.7, 65.9, 64.8, 56.0, 46.0, 25.7, 25.1, 24.3, 22.7, 18.0.

Acetonide **14** was isolated as an oil which was purified by flash chromatography with a 50:50 hexanes/Et_2O mixture as eluent. − $[\alpha]_D^{23}$ = −13.0 (*c* = 0.45 in $CHCl_3$). − IR: 1752 cm^{-1}. − $C_{20}H_{31}NO_4Si$: C 63.62, H 8.28, N 3.71; found C 63.38, H 8.13, N 3.59. − ^1H NMR: δ = 6.61-6.86 (m, 3 H, aromatic protons), 4.64 (d, 1 H, *J* = 2.0 Hz, H−C4), 4.33 (dq, 1 H, *J* = 4.0, 6.0 Hz, H−C3′), 2.92 (dd, 1 H, *J* = 2.0, 4.0 Hz, H−C3), 1.99 (s, 3 H, CH_3−C−N), 1.43 (s, 3 H, CH_3−C−N), 1.33 (d, 3 H, *J* = 6.0 Hz, CH_3−C3′), 0.92 (s, 9 H, *t*Bu), 0.10 (s, 6 H, CH_3Si). ^{13}C NMR: δ = 168.2, 145.6, 139.1, 121.7, 121.4, 117.2, 113.5, 96.0, 65.8, 64.7, 46.1, 25.7, 25.0, 24.5, 22.8, 17.9.

Acetonide **18** was purified by flash chromatography with a 60:40 hexanes/Et_2O mixture as eluent. − m.p. 62−64°C. − $[\alpha]_D^{23}$ =

−104.0 (c = 1.26 in $CHCl_3$). − IR: 1760 cm^{-1}. − $C_{20}H_{31}NO_3Si$: C 66.44, H 8.64, N 3.87; found C 66.19, H 8.57, N 3.64. − ^1H NMR: δ = 6.73-7.25 (m, 4 H, aromatic protons), 4.65 (d, 1 H, J = 2.0 Hz, H−C4), 4.30 (dq, 1 H, J = 2.0, 6.0 Hz, H−C3′), 2.90 (t, 1 H, J = 2.0 Hz, H−C3), 1.95 (s, 3 H, CH_3−C−N), 1.45 (s, 3 H, CH_3−C−N), 1.31 (d, 3 H, J = 6.0 Hz, CH_3−C3′), 0.90 (s, 9 H, tBu), 0.08 (s, 6 H, CH_3Si).

Reduction of 14 to 15: A suspension of β-lactam **14** (0.043 g, 0.114 mmol), $RuCl_3$ monohydrate (0.050 g, 0.240 mmol) and trioctylamine (0.120 g, 0.342 mmol) in 6 mL of a 5:1 AcOEt/H_2O mixture was hydrogenated under 60 bar of H_2 for 60 h at room temperature with continuous shaking. The crude mixture was then filtered through a celite cake, and the filtrate was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by two flash chromatographies with different eluents (50:50 hexanes/Et_2O, then pure Et_2O, then 95:5 Et_2O/MeOH) to afford compound **15** as a mixture of two isomers. − IR: 1760 cm^{-1}. − $C_{20}H_{37}NO_4Si$: C 62.62, H 9.72, N 3.65; found C 62.49, H 9.58, N 3.53. − ^1H NMR (3′R,3S,4R,4′R,5′S,6′R)-**15**: δ = 4.19 (dq, 1 H, J = 2.5, 6.0 Hz, H−C3′), 4.05−4.07 (m, 1 H, HC−O−CMe_2), 3.82 (dd, 1 H, J = 2.0, 3.5 Hz, H−C4), 3.48−3.58 (m, 1 H, CH−OH), 3.04 (dd, 1 H, J = 2.0, 2.5 Hz, H−C3), 1.50−1.80 (m, 7 H, other cyclohexyl protons), 1.77 (s, 3 H, CH_3−C−N), 1.43 (s, 3 H, CH_3−C−N), 1.18 (d, 3 H, J = 6.0 Hz, CH_3−C3′), 0.89 (s, 9 H, tBu), 0.09 (s, 3 H, CH_3Si), 0.08 (s, 3 H, CH_3Si). ^1H NMR (3′R,3S,4R,4′S,5′R,6′S)-**15**: δ = 4.17 (dq, 1 H, J = 2.0, 6.0 Hz, H−C3′), 3.83 (t, 1 H, J = 3.0 Hz, HC−O−CMe_2), 3.31 (t, 1 H, J = 2.0 Hz, H−C4), 3.45−3.58 (m, 1 H, CH−OH), 2.82 (dd, 1 H, J = 2.0, 2.5 Hz, H−C3), 1.50−1.80 (m, 7 H, other cyclohexyl protons), 1.72 (s, 3 H, CH_3−C−N), 1.41 (s, 3 H, CH_3−C−N), 1.21 (d, 3 H, J = 6.0 Hz, CH_3−C3′) 0.89 (s, 9 H, tBu), 0.09 (s, 3 H, CH_3Si), 0.08 (s, 3 H, CH_3Si). The configurations at C4′, C5′, and C6′ were established by 2D NMR experiments.

Reduction of 18 to 19: This was accomplished as described in the literature[25] carrying out the reaction with 23 mg of compound **18**. The crude reaction mixture was filtered through a celite cake, and the organic phase was separated. The aqueous phase was extracted twice with CH_2Cl_2, and the combined organic phases were dried and concentrated in vacuum. The crude residue was purified by flash chromatography with a 50:50 Et_2O/hexanes mixture as eluent to give the product[27] in 65−70% yield as a low-melting material. − $[\alpha]_D^{23}$ = 218.0 (c = 0.1 in CH_2Cl_2). − IR: 1760 cm^{-1}. − ^1H NMR: δ = 4.16 (dq, 1 H, J = 4.5, 6.0 Hz, H−C3′), 3.76−3.83 (m, 1 H, HC−O−CMe_2), 3.24 (t, 1 H, J = 2.0 Hz, H−C4), 2.78 (dd, 1 H, J = 2.0, 4.5 Hz, H−C3), 1.40−1.90 (m, 9 H, cyclohexyl protons), 1.69 (s, 3 H, CH_3−C−N), 1.40 (s, 3 H, CH_3−C−N), 1.21 (d, 3 H, J = 6.0 Hz, CH_3−C3′) 0.90 (s, 9 H, tBu), 0.09 (s, 6 H, CH_3Si). The configurations at C4′, and C5′ were established by 2D NMR experiments.

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[1] Review: C. Ghiron, T. Rossi, *The Chemistry of Trinems* in *Targets in Heterocyclic Systems - Chemistry and Properties* (Eds.: O. A. Attanasi, D. Spinelli), Societa′ Chimica Italiana, Rome, vol. 1, pp. 161−186, **1997**; and references therein.

[2] Review: J. Ngo, J. Castañer, *Drugs of the Future* **1996**, *21*, 1238−1245; and references therein.

[3] References 1 and 2 list all the reported syntheses of compound **1**. For more recent reports see: [3a] T. Murayama, S. Mitsuhashi, T. Miura, European Patent Application 97400458−2, 1998. − [3b] Y. Iso, Y. Nishitani, *Heterocycles* **1998**, *48*, 2287−2308. See also: − [3c] S. Hanessian, B. Reddy, *Tetrahedron* **1999**, *55*, 3427- 3443.

[4] Almost thirty different syntheses of **4** have been reported. For a review see: [4a] A. H. Berks, *Tetrahedron* **1996**, *52*, 331−375. For a synthesis based on the use of thioester **5** see: [4b] F. Cozzi, R. Annunziata, M. Cinquini, L. Poletti, A. Perboni, B. Tamburini, *Chirality*, **1998**, *10*, 91−94.

[5] These precursors can be achiral, racemic or enantiomerically pure. For examples see:

[5a] T. Rossi, S. Biondi, S. Contini, R. J. Thomas, C. Marchioro, *J. Am. Chem. Soc.* **1995**, *117*, 9604−9605. − [5b] S. Hanessian, M. J. Rozema, *J. Am. Chem. Soc.* **1996**, *118*, 9884−9491. − [5c] T. Rossi, C. Marchioro, A. Paio, R. J. Thomas, P. Zarantonello, *J.Org. Chem.* **1997**, *62*, 1653−1661.

[6] [6a] M. Panunzio, R. Camerini, R. Pachera, D. Donati, C. Marchioro, A. Perboni, *Tetrahedron: Asymmetry* **1996**, *7*, 2929−2938. − [6b] M. Panunzio, R. Camerini, A. Mazzoni, D. Donati, C. Marchioro, R. Pachera, *Tetrahedron: Asymmetry* **1997**, *8*, 15−18.

[7] P. M. Jackson, S. M. Roberts, S. Davalli, D. Donati, C. Marchioro, A. Perboni, S. Provera, T. Rossi, *J. Chem. Soc., Perkin Trans. 1* **1996**, 2029−2039.

[8] For recent papers in this series see ref.[4b] and: [8a] R. Annunziata, M. Benaglia, A. Chiovato, M. Cinquini, F. Cozzi, *Tetrahedron* **1995**, *51*, 10025−10032. − [8b] V. Molteni, R. Annunziata, M. Cinquini, F. Cozzi, M. Benaglia, *Tetrahedron Lett.* **1998**, *39*, 1257−1260.

[9] R. Annunziata, M. Cinquini, F. Cozzi, P. G. Cozzi, *J. Org. Chem.* **1992**, *57*, 4155−4162. (*R*)-**5** was obtained in three simple steps from ethyl (*R*)-3-hydroxy butanoate in 83% yield. It is a white solid that can be stored at −20°C for at least six months without decomposition.

[10] The allyl protecting group was selected among a few other tested groups (benzyl, trimethylsilyl, acetyl) because of its stability under the reaction conditions as well as its mild and selective removal.

[11] For leading references to the generation of trichlorotitanium enolates by this procedure see: D. A. Evans, M. T. Bilodeau, T. C. Somers, J. Clardy, D. Cherry, Y. Kato, *J. Org. Chem.* **1991**, *56*, 5750−5752; and references therein.

[12] Best yields and stereoselectivities were obtained with 2 mol equiv. of **5** per mol equiv. of imine on maintaining the condensation temperature at −78°C for 5 h and then allowing the temperature to rise to room temp. overnight. Other stoichiometries and reaction conditions were tested with less success. For instance, when 1 mol equiv. of titanium enolate was employed, the yield dropped to 60%. When the condensation was started at −78°C and then immediately warmed to room temp. the yield of **7** remained unchanged (96%) but minor amounts (ca. 10%) of a 3,4-*cis* isomer were obtained.

[13] When the deallylation reaction was attempted on the *N*-protected β-lactams these were quantitatively recovered.

[14] G. I. Georg, J. Kant, H. S. Gill, *J. Am. Chem. Soc.* **1987**, *109*, 1129−1135.

[15] D. M. Rudkevich, Z. Brzozka, M. Palys, H. Visser, W. Verboom, D. N. Reinhoudt, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 467−468.

[16] For a recent review on the stereoselective reduction of aromatic compounds see: T. J. Donohue, R. Garg, C. A. Stevenson, *Tetrahedron: Asymmetry* **1996**, *7*, 317−344.

[17] Reductions of double bonds have been widely exploited in the synthesis of 1-β- methylcarbapenems and were shown to produce, with high selectivity, a β methyl group at C-4′. For a list of examples see ref.[4a] For other references describing attack from the side of the H at C-4 on a trigonal carbon at C-4′ in β-lactams see: [17a] R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, F. Ponzini, *J. Org. Chem.* **1993**, *58*, 4746−4748. − [17b] C. Palomo, A. Arrieta, F. P. Cossio, J. M. Aizpurua, A. Mielgo, N. Aurrekoetxea, *Tetrahedron Lett.* **1990**, *31*, 6429−6432.

[18] While the Swern oxidation proceeded smoothly (typical yield 70 to 80%), the reduction was sluggish. Generally, recovery of the unchanged phenols was possible.

[19] Solvents more polar than AcOEt are known to accelerate the hydrogenation; for examples see: J. H. Stocker, *J. Org. Chem.* **1962**, *27*, 2288−2289; J. C. Sircar, A. I. Meyers, *J. Org. Chem.*

1965, *30*, 3206−3207. In our case however, their use resulted in extensive substrate decomposition.
[20] The configuration at the OH bearing C-5′ of the cyclohexanol obtained by reduction of **8** was determined to be (*S*) by comparison of its ^{1}H NMR spectra with those of the compounds prepared by us by $NaBH_4$ reduction of the ketone generously provided by GlaxoWellcome.
[21] Other reducing systems such as $RuCl_3$/trioctylamine: [21a] F. Fache, S. Lehuede, M. Lemaire, *Tetrahedron Lett*. **1995**, *36*, 885−888; and $[RuCl_2(\eta^6\text{-}C_6Me_6)(PPh_3)]$: [21b] M. A. Bennet, T.-N. Huang, T. W. Turney, *J. Chem. Soc., Chem. Commun.* **1979**, 312−313 reported inferior results in terms of chemical yield. Birch-type reductions led to N−C4 bond cleavage.
[22] The Macromodel/Batchmin package was used: [22a] F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440−467; two thousand steps of Pseudo-Systematic Monte Carlo search were performed: [22b] J. M. Goodman, W. C. Still, *J. Comput. Chem.* **1991**, *12*, 1110−1117; four torsions (around the Me/O, C-3/C-3′, C-4/C-4′, and HO/C bonds were set as variables with the standard resolution and chirality check on the stereocenters to avoid epimerization; energy minimization with MM2 force field: [22c] U. Burkert, N. L. Allinger, *Molecular Mechanics*, ACS Monograph 177, American Chemical Society; Washington D.C., **1982**; and Truncated Newton conjugated gradient: [22d] J. W. Ponder, F. M. Richards, *J. Comput. Chem.* **1987**, *8*, 1016−1024) was subsequently performed, and duplicate conformers eliminated. Only unique conformations within 25 kJ/mol from the global minimum were saved. All conformations were sampled several times, thus ensuring the convergence of the search.
[23] B. J. VanKeulen, R. M. Kellogg, O. Piepers, *J. Chem. Soc., Chem. Commun.* **1979**, 285−286.
[24] It must be noted, however, that the epimerization at C-6′ of ketone **10** to give **3** has been described in ref.[5b]
[25] J. Blum, I. Amer, K. P. C. Vollhardt, H. Schwartz, G. Höhne, *J. Org. Chem.* **1987**, *52*, 2804−2813. This catalyst was ineffective in the reduction of **11** and **14**.
[26] For a recent synthesis of a compound similar to **19** by aromatic ring reduction see: M. Anada, S. Hashimoto, *Tetrahedron Lett.* **1998**, *39*, 9063−9066.
[27] R. DiFabio, T. Rossi, R. J. Thomas, *Tetrahedron Lett.* **1997**, *38*, 3587−3590.
[28] S. F. Martin, T. H. Cheavens, *Tetrahedron Lett.* **1989**, *30*, 7017−7020.
[29] S. F. Martin, P. J. Garrison, *J. Org. Chem.* **1981**, *46*, 3567−3568.
[30] B. Bertani, R. DiFabio, C. Ghiron, A. Perboni, T. Rossi, R. J. Thomas, P. Zarantonello, *Tetrahedron*, **1997**, *53*, 15011−15028.

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