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TETRAHEDRON: *ASYMMETRY*

Determination of the absolute configuration of an unexpectedly stable *N*-silylated isomer isolated en route to the trinem antibiotic GV129606

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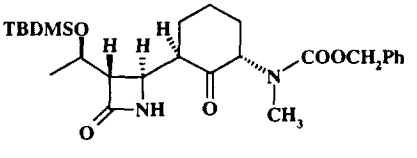
Abstract

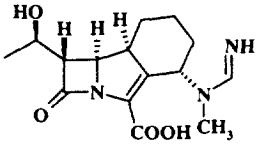
The unexpected (3*S*,4*R*)-3-[(*R*)-1-(hydroxy)ethyl]-4-[(2′*R*,6′*S*)-1′-oxo-2′-(*N*-benzyloxy-*N*-methyl)aminocyclohexen-6′-yl]-1-(*t*-butyl-dimethylsilyl)azetidin-2-one was one of the main reaction products of the Lewis acid catalysed condensation of (3*S*,4*R*)-3-[(*R*)-1-(*t*-butyl-dimethylsilyloxy)ethyl]-4-acetoxyazetidin-2-one with 1-trimethylsilyloxy-6-(*N*-benzyloxycarbonyl-*N*-methylamino)cyclohexene. Its absolute configuration was established by NMR experiments on the corresponding, conformationally rigid, acetonide derivative.

The bicyclic compound GV158943X **1** (Fig. 1) is the key synthetic intermediate en route to GV129606X **2**,[1] a potent and broad spectrum trinem[2] antibiotic. As part of a wider program aimed at the definition of a more practical and scaleable synthetic route to **2**, we approached the synthesis of the intermediate **1** via the single-step Lewis acid catalysed aldol-type condensation between (3*S*,4*R*)-3-[(*R*)-1-(*t*-butyl-dimethylsilyloxy)ethyl]-4-acetoxyazetidin-2-one **3** and 1-trimethylsilyloxy-6-(*N*-benzyloxycarbonyl-*N*-methylamino)cyclohexene **4** (Scheme 1).[3]

Preliminary results show that the Lewis acids effectively producing the desired isomer **1** also gave variable amounts of an unexpected[4] *N*-silylated isomer **5**[5] (Scheme 1) and, in some cases, this latter



1 (GV158943X)



2 (GV129606X)

Fig. 1.

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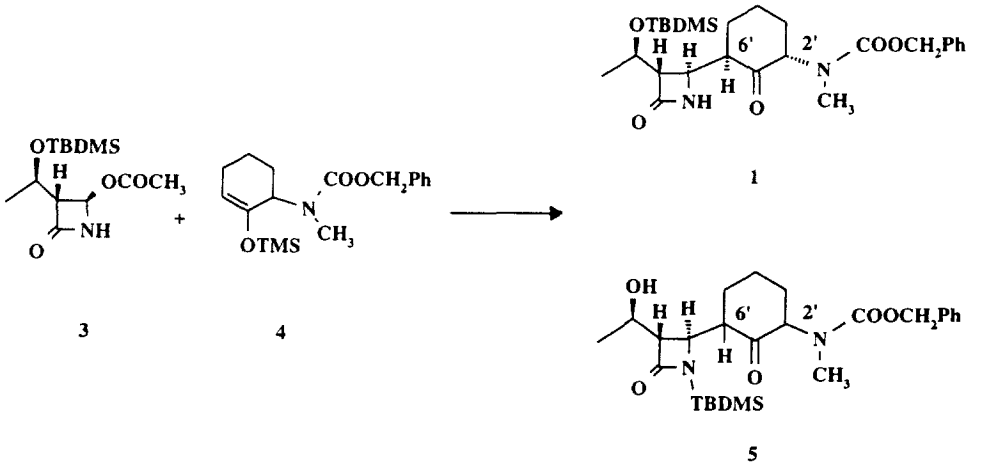
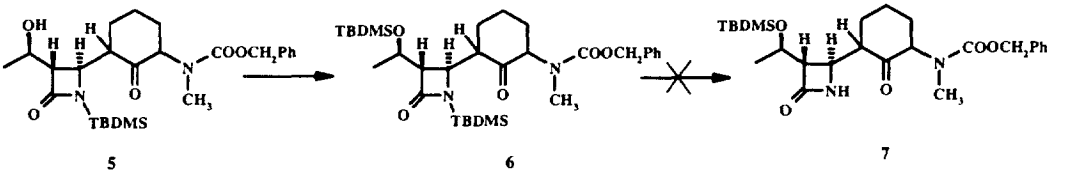


Scheme 1.

derivative was the predominant reaction product. The isomer **5** was the only *N*-silylated derivative observed under different reaction conditions and its *N*–silicon bond proved to be unusually stable, surviving both acid work-up conditions and elution on silica gel. The molar ratio **1**:**5** obtained was essentially related to the nature of the catalyst employed in the reaction.[3]

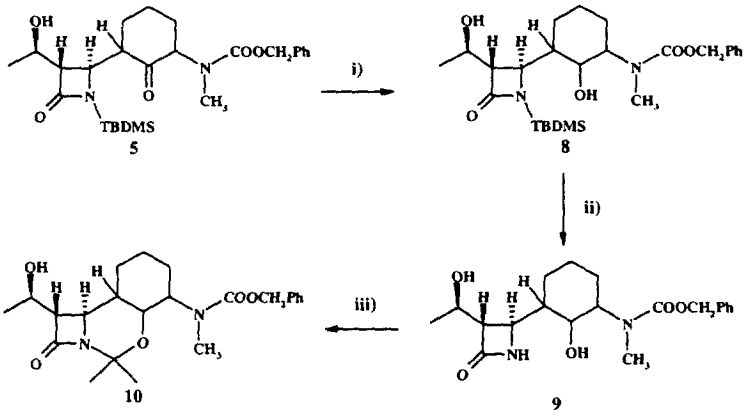
For a better understanding of the factors affecting the diastereoselection of the condensation reaction, we judged it necessary to determine the absolute configuration of this novel *N*-silylated derivative. However, due to an unfavourable overlap of the signals, it was not possible to obtain a straightforward assignment of the absolute configuration of the C-2′ and C-6′ stereocentres in **5** by means of NMR techniques. Attempts to convert **5** into the corresponding, and possibly more easily interpretable, *O*-silylated derivative **7** (Scheme 2) failed due to the surprising stability of the *N*–silicon bond in the bis-silylated derivative **6**[6] that caused a preferential or, at least simultaneous, removal of the protecting group on the oxygen (Scheme 2).



Scheme 2.

The absolute configuration of **5** was eventually determined by converting it into the conformationally more rigid acetonide derivative **10** (Scheme 3) to obtain an unambiguous NOE pattern. Consequently, the reduction of **5** by means of $NaBH_4$ gave the alcohol **8** as a single isomer, this was in turn desilylated with tetrabutylammonium fluoride and reacted with 2,2-dimethoxypropane to form **10**.[7]

The NOE data were obtained for compounds **8**, **9** and **10**. While for compounds **8** and **9** the measured NOEs resulted in more than one solution, the NMR studies on compound **10** allowed an unambiguous determination of the stereochemistry on the basis of the NOE effects observed between H-11, H-9 and H-4 together with the enhancement from H-5 to H-10 (Fig. 2). As a consequence, the stereochemistry of the C-2′ and C-6′ stereocentres in **5** (Fig. 2) were determined as 2′*R*,6′*S*, i.e. the opposite to that observed in the isomer **1**. A convincing rationale for the formation of a stable *N*-silylated derivative only in the (2′*R*,6′*S*)-isomer has yet to be found and further work on this subject is in progress.



i)$NaBH_4$, EtOH/H_2O 9/1, 0°C; ii) TBAF, THF, r.t.; iii) dimethoxypropane, r.t.

Scheme 3.

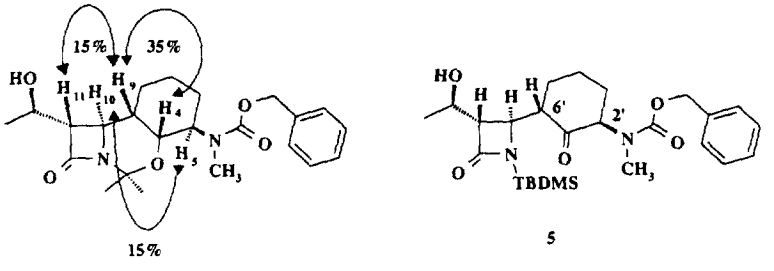


Fig. 2.

Acknowledgements

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References

1. (a) Di Modugno, E.; Broggio, R.; Erbetti, I.; Lowther, J. *Antimicrob. Agents Chemother.* **1997** *41*, 2742; (b) Biondi, S. Trinems: Synthesis and Antibacterial Activity of a New Generation of Antibacterial beta-Lactams. In *Anti-Infective: Recent Advances in Chemistry and Structure–Activity Relationship*; Bentley, P. H. and O'Hanlon, P. J., Eds; The Royal Society of Chemistry, 1997, p. 86.
2. This class of compounds was formerly referred to as tribactams. See Gaviraghi, G. *Eur. J. Med. Chem.* **1995**, *30*, 467.
3. Preliminary results on the preparation of **1** by single-step reaction of **3** with **4** will be published in due course.
4. The aldol-type condensations of the azetidinone **3** with different nucleophiles have been extensively used during the studies related to the syntheses of several penem and carbapenem antibiotics (see: Wild, H. In *The Organic Chemistry of Beta-Lactams*; Georg, G. I., Ed.; VCH: New York, NY, 1993, Chapter 2) but no products such as **5** were previously reported.
5. To a suspension of $FeCl_3$ (324 mg, 2 mmol) in dry dichloromethane (10 ml), stirred under nitrogen and at 0°C, was added a solution of the azetidinone **3** (574 mg, 2 mmol) and silyl enol ether **4** (2 g, 6 mmol) in dry dichloromethane (15 ml). The reaction mixture was stirred for 30 min at 0°C, then quenched with a saturated solution of $NaHCO_3$ (40 ml) and extracted with AcOEt (2×40 ml). The combined organic extracts were dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate:cyclohexane=1:1) yielding ca. 220 mg each of compounds **1** and **5**. Compound **5** showed: IR ($CDCl_3$, cm^{-1}): 1738 C=O β-lactam; 1693 C=O; ^{1}H-NMR ($CDCl_3$): 7.4 (5H, m, –Ph); 6.16 (1H, bs, –OH); 5.17, 5.07 (2H, m, $-CH_2Ph$); 4.57 (1H, bm, H2′); 4.16 (1H, m, H5); 3.81 (1H, m, H4); 2.89 (3H, s, $-NCH_3$); 2.72 (1H, m, H3); 2.58 (1H, bm, H6′); 2.18–1.80 (6H, m, H3′+H4′+H5′); 1.25 (3H, d,

J=6.0 Hz, Me); 0.88 (9H, s, $-C(CH_3)_3$); 0.09 (3H, s, $-Si(Me)_2$); 0.07 (3H, s, $-Si(Me)_2$); MS: 489 (M+H), 431; Anal. calcd for $C_{26}H_{40}N_2O_5Si$: C, 63.17; H, 8.13; N, 5.84. Found: C, 63.89; H, 8.27; N, 5.73.

6. Compound **6** showed: IR ($CDCl_3$, cm^{-1}): 1738 C=O β-lactam; 1693 C=O; ^{1}H-NMR ($CDCl_3$): 7.34 (5H, m, –Ph); 5.11 (2H, bs, $-CH_2Ph$); 4.56 (1H, bm, H2′); 4.22–4.04 (2H, m, H5+H4); 2.94 (1H, m, H3); 2.87 (3H, s, $-NCH_3$); 2.74 (1H, bm, H6′); 2.02–1.78–1.80 (6H, m, H3′+H4′+H5′); 1.10 (3H, bd, Me); 0.95 (9H, s, $-C(CH_3)_3$); 0.87 (9H, s, $-C(CH_3)_3$); 0.20 (3H, s, $-Si(Me)_2$); 0.17 (3H, s, $-Si(Me)_2$); 0.06 (3H, s, $-Si(Me)_2$); 0.04 (3H, s, $-Si(Me)_2$); MS: 603 (M+H), 545.
7. The *N*-silylated derivative **5** (1 g) was dissolved at 0°C in 50 ml of an ethanol:water (9:1) mixture and treated portionwise with 2.5 molar equiv. of $NaBH_4$. After stirring for a further 1 hour at room temperature, the reaction mixture was diluted with water (20 ml), concentrated to ca. 20 ml, acidified with 0.1 N HCl and extracted with ethyl acetate. The organic layer was washed with brine (2×20 ml), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by silica gel chromatography (EtOAc, 100%) to give **8** in 75% yield. ^{1}H-NMR ($CDCl_3$): 7.4–7.3 (5H, m, –Ph); 6.30 (1H, bs, 1′-OH); 5.15 (2H, m, $-CH_2Ph$); 4.20 (1H, bm, H2′); 4.23 (1H, m, H5); 3.89 (2H, m, H4+H1′); 2.85 (3H, s, $-NCH_3$); 2.75 (1H, bm, H3); 2.2 (1H, m, H6′); 1.80–1.40 (6H, m, H3′+H4′+H5′); 1.23 (3H, d, J=6.2 Hz, Me); 0.88 (9H, s, $-C(CH_3)_3$); 0.08 (6H, s, $-Si(Me)_2$); MS: 491 (M+H), 433. Anal. calcd for $C_{26}H_{42}N_2O_5Si$: C, 62.32; H, 8.59; N, 5.50. Found: C, 62.62; H, 8.64; N, 5.71. Compound **8** (50 mg, 0.1 mmol) was dissolved in dry tetrahydrofuran (3 ml) and treated with 2 equiv. of tetrabutylammonium fluoride. The reaction mixture was stirred for 3 hours at room temperature, the solvent was evaporated *in vacuo* and the crude mixture purified by chromatography on silica gel (EtOAc:MeOH=9:1) to give 25 mg of **9** (yield=66%). IR ($CDCl_3$, cm^{-1}): 1749 C=O β-lactam; 1691 C=O; ^{1}H-NMR ($CDCl_3$): 7.4–7.3 (5H, m, –Ph); 6.60 (1H, bs, NH); 5.13 (2H, m, $-CH_2Ph$); 4.27 (1H, bm, H2′); 4.15 (1H, m, H5); 3.9 (2H, m, H4+H1′); 2.96 (1H, bm, 1′–OH); 2.84 (3H, s, $-NCH_3$); 2.85 (1H, bm, H3); 2.2 (1H, m, H6′); 1.80–1.40 (6H, m, H3′+H4′+H5′); 1.32 (3H, bm, Me); MS: 377 (M+H). Compound **9** (20 mg) was dissolved in 2,2-dimethoxypropane and the reaction mixture was stirred at room temperature for 2 hours. The solvent was removed *in vacuo* and the residue diluted with ethyl acetate (20 ml) and washed successively with saturated $NaHCO_3$ (20 ml) and brine (20 ml). The organic layer was dried over Na_2SO_4, the solvent evaporated and the crude product purified by chromatography on silica gel (EtOAc 100%) to give 18 mg of the compound **10** (yield=78%). IR ($CDCl_3$, cm^{-1}): 1738 C=O β-lactam; 1690 C=O; ^{1}H-NMR ($CDCl_3$): 7.3 (5H, m, –Ph); 5.14 (2H, m, $-CH_2Ph$); 4.45 (1H, bm, H5); 4.17 (1H, bm, H12); 3.96 (1H, dd, J=5.4, 11.70 Hz, H4); 3.65 (1H, bm, H10); 2.88 (3H, s, $-NCH_3$); 2.77 (1H, dd, J=5.8, 1.8 Hz, H11); 2.10 (1H, m, H9); 2.01 (1H, m, –OH); 1.78 (2H, m); 1.65 (3H, s, –Me); 1.7–1.4 (3H, m); 1.30 (1H, m); 1.30 (3H, s, Me); 1.29 (3H, d, J=5.8 Hz, Me); MS: (M+H) 603.