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Highly Stereocontrolled Synthesis of Enantiomeric 4-Methoxy Trinems *via* Resolution of Scalemic Enol Phosphates.

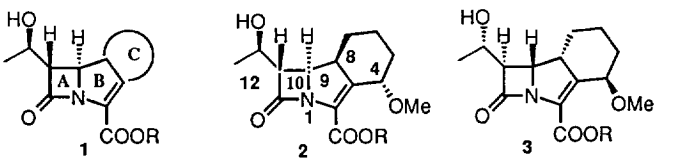
Mauro Panunzio[a]*, Roberto Camerini[a], Roberta Pachera[a] Daniele Donati[b]*, Carla Marchioro[b] and Alcide Perboni[b]

a: Dipartimento di Chimica "G. Ciamician", C.S.F.M.-C.N.R. Via Selmi 2, 40126 Bologna, Italy
b: Glaxo Wellcome S.p.A., Medicines Research Centers, Via A. Fleming 4, 37100 Verona, Italy

Abstract: Stereocontrolled syntheses of 4-methoxy trinem **2** and its enantiomer **3** were achieved using the ester enolate *N*-trimethylsilylimine approach. The key step was the resolution of racemic enolphosphates derived from ephedrine.

As new β-lactam antibiotics are constantly being sought to meet the ongoing challenges of bacterial resistance to existing drugs, the most promising means to oppose bacterial infections is to use new potent β-lactam antibiotics. Among those reported are the recently designed novel β-lactam antibiotics which have been developed by GlaxoWellcome laboratories.[1-13] (Fig. 1)

Fig. 1



This new family of totally synthetic β-lactam antibiotics is characterised by the novel feature of a tricyclic skeleton and has been prepared *via* (3*R*, 4*R*, 1'*R*)-(+)-4-acetoxy-[1'-(*tert*-butyldimethylsilyl)oxy]ethyl-2-azetidin-2-one. Although this procedure allows the preparation of the target, in a few high yielding steps, sufficiently concise methods of preparing epimeric compounds for pharmaceutical applications have been elusive. Improvements are needed to develop an attractive synthesis which allows the preparation of **2**, as well as different 4 and 10 substituted derivatives (see Fig. 1 for trinems numbering). Particularly desirable is the synthesis of **3**, the enantiomer of **2** which has been the subject of considerable study due to its antibacterial activity, resistance to β-lactamases and stability to renal dehydropeptidase.

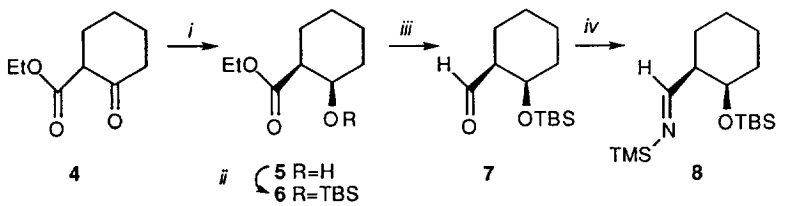
We sought to investigate approaches to building the trinem structure **2**, as well as **3**, which would accomplish this goal in a few overall steps. The key intermediate in our approach is the racemic azetidinone **11** (For the sake of simplicity only one enantiomer in Scheme 1 and 2 has been reported) (Scheme 2). By carefully designing this intermediate, it possesses most of the carbon atoms needed to construct the tricyclic nucleus. Additionally, this type of azetidinone can also incorporate the functionality and stereochemistry needed for the possible biological activity.

In a previous study,[14] we have shown that the β-silyloxy-*N*- trimethylsilylimine **8** may be utilised, in the ester enolate-imine condensation route to azetidinones[15-17] as a chiral building block. In this way the

correct stereochemistry is induced in the target while presenting the necessary functionality for further elaboration of the azetidinone and of the cyclohexyl substituent in a non-immolative fashion. After demonstrating the ability of our approach to produce racemic trinems, we then sought to explore the downstream chemistry to establish that such racemic azetidinones could be independently elaborated to both enantiomers **2** and **3**. Here we report the details of our synthesis.

Our strategic plan starts from the cyclohexyl-2-*tert*-butyldimethylsilyloxy-1-methane-(*N*-trimethylsilyl) imine **8** obtained from the corresponding commercially available 2-ethoxycarbonyl-cyclohexanone **4** following the procedure depicted in Scheme 1.

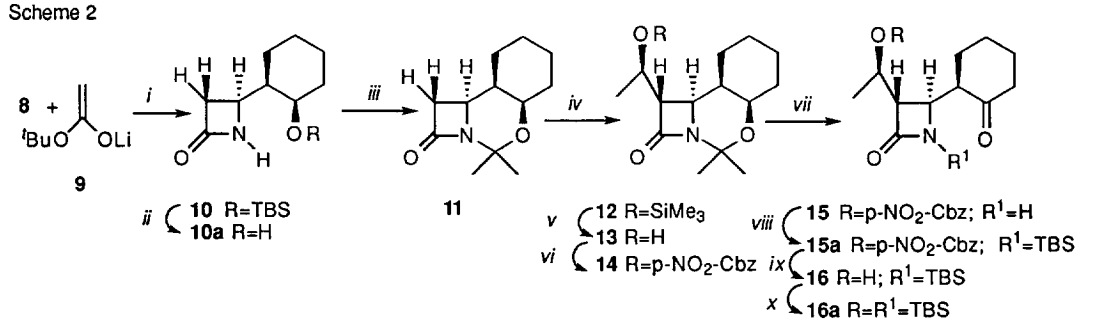
Scheme 1



Reagents and conditions: *i*: H_2/PtO_2 / EtOH/60 Atm, 80%; *ii*: TBSCl, Imidazole, DMF, r.t., 94%; *iii*: DIBAH, Ether, -78°C, 70%; *iv*: LiHMDSA, THF, -20°C.

Reaction of the racemic imine **8** with the lithium enolate[18] of *t*-butyl acetate **9** afforded, after crystallization, the azetidinone **10** in 57%, overall yield from the aldehyde, as a single diastereoisomer. Introduction of the hydroxy ethyl side chain was realised according to the well established Merck procedure.[19] To this aim the TBS (*tert*-butyldimethylsilyl) group was removed and the hydroxy-azetidinone **10a** thus obtained was converted to the acetonide derivative **11**, in almost quantitative yield, by treatment with DMP (dimethoxypropane) in the presence of a catalytic $BF_3(Et_2O)$.

Scheme 2



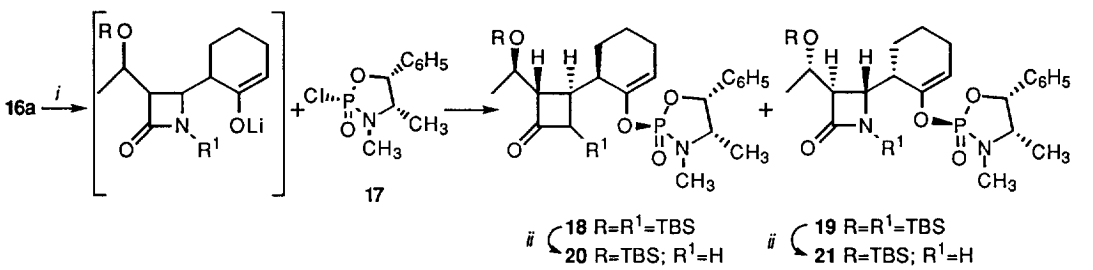
Reagents and Conditions: *i*: THF, -78°C then r.t. 12 h, 55%; *ii*: LiHMDSA, TBAF, THF, 8h, 74%; *iii*: DMP, BF_3Et_2O, CH_2Cl_2, r.t. 84%; *iv*: LDA, $CH_3COSiMe_3$ then ^tBuOK, ^tBuOH , 97%; *v*: HF_{aq}; *vi*: p-NO_2BnOCOCl, DMAP, CH_2Cl_2 , 63%; *vii*: Jones, acetone 74%; *viii*: TBSCl, Et_3N, CH_2Cl_2, 86%; *ix*: H_2/Pd, 72%; *x*: TBSCl, Imidazole, DMF, 94%.

The racemic acetonide **11** presents the correct stereochemistry on the C_8 and C_9 stereocenters (see Fig. 1) as determined by careful analysis of the 500-MHz ^1H NMR spectra. Introduction of the hydroxyethyl side chain was achieved by treatment with LDA and trimethylacetylsilane followed by Brooke rearrangement with potassium *t*-butoxide[19]. The TMS-group of the hydroxy ethyl side chain was removed to give the free hydroxy group which was then protected by the more stable p-nitro benzyloxycarbonyl group.[20] Finally the so obtained compound **14** was converted into azetidinone **15** by Jones oxidation.[21]

The key step in the present approach has been the resolution and elaboration of racemic **16a** to enantiomerically pure β-lactams **24** and **25** *via* chiral enolphosphates **20** and **21**.

Treatment of the racemic azetidinone **16a** with LiHMDSA affords a racemic mixture of lithium enolates. Reaction of these enolates with a dialkyl phosphochlorydrate furnishes the corresponding enantiomeric enol phosphates.[22] However, if the dialkylphosphochlorydrate used contains one or more stereogenic centre, then a mixture of diastereomers will result. Welch[23] and Wiemer[24] reported the synthesis of enolphosphate derivatives of ephedrine. In taking advantage of their results, we have succeeded in preparing diastereomeric enol phosphates **18** and **19** in 82% overall yield by reacting the *enantiomeric* lithium enolates of **16** with ephedrine phosphochlorydrate[25,26] **17.** Although the phosphoenolates **18** and **19** may be isolated by careful flash chromatography, a better separation has been achieved via the corresponding *N-H* derivatives **20** and **21.** To this aim the diastereomeric mixture was treated with potassium fluoride in methanol to give **20** and **21** through a selective *N*-deprotection.

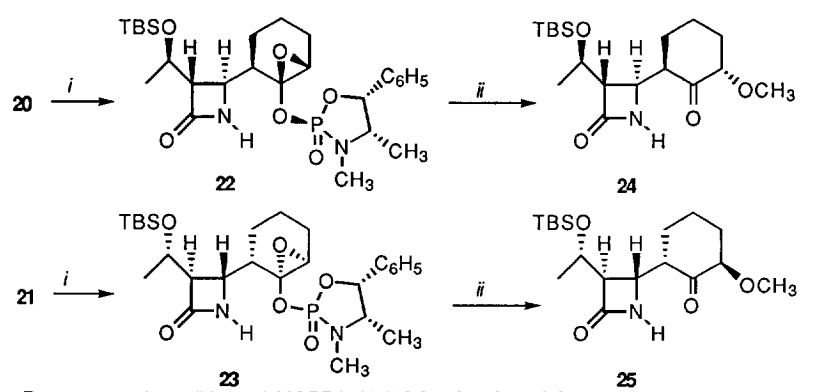
Scheme 3



Reagents and Conditions: *i:* LDA, THF, -78°C, 82%; *ii*: KF, MeOH, 70%.

After chromatographic separation, MCPBA oxidation gave rise to the epoxides **22** and **23** with complete diastereoselectivity. Since the NMR data don't allow the unequivocally assignment of the stereochemistry, *the reported epoxide-stereochemistry has been tentatively assigned on the basis of the final compounds* **24** and **25.**

Scheme 4

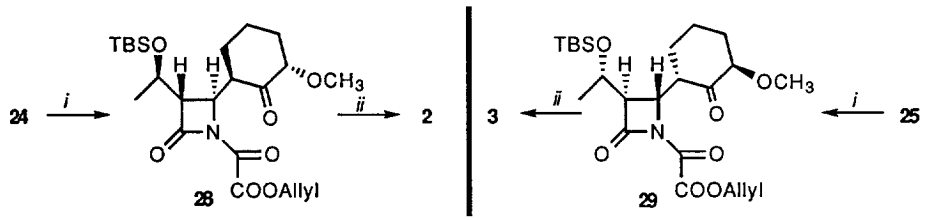


Reagents and conditions: *i:* MCPBA, $NaHCO_3$, CH_2Cl_2, 0° C 30 min then 3 h, r.t.;
ii: MeOH, 40° C, 3hr.

Further studies are in progress to completely elucidate the absolute stereochemistry as well as the reaction-epoxidation mechanism. The epoxide-compounds **22** and **23** were subjected to a fast elaboration to the end products **24** and **25** because their relative stability *via* opening of the epoxide-ring by methanol (Scheme 4). The absolute stereochemistry of these compounds, which show superimposable IR, ^1H and ^{13}C NMR, were established by comparison with an authentic sample of **24**, obtained from GlaxoWellcome laboratories. A crucial role from the yield and diastereomeric point of view, seems to be played by the *NH* group: as a matter of fact oxidation of the *N-TBS* protected azetidinone **18** gives rise to a complex mixture containing diastereomeric epoxy-azetidinones. Finally azetidinones **24** and **25** could be ultimately elaborated

to Sanfetrinem (GV 104326) and its enantiomer following the well established GlaxoWellcome procedure[2]. (Scheme 5).

Scheme 5



Reagents and Conditions: *i*: K_2CO_3, ClCOOAllyl, TEA, CH_2Cl_2; *ii*: Triethyl Phosphite, Xylene, Reflux. Ref. 1,2

Acknowledgement: We thank Dr. M. Hamdan of GlaxoWellcome for mass spectral data, Dr. A. Mazzoni for his valuable contributions and Dr. T. Rossi for helpful discussions. These studies were financially assisted by GlaxoWellcome S.p.A-Verona Italy.

Experimental Section

General: Melting points are uncorrected. All reactions were conducted under an argon atmosphere. THF was distilled from Na/benzophenone ketyl and CH_2Cl_2 was distilled from P_2O_5. ^{1}H- and ^{13}C-NMR spectra were recorded at 300, 400, 500 and 75 MHz in $CDCl_3$ using TMS or residual $CHCl_3$ as internal reference or in D_2O using dioxane as external reference.

Ethyl ester of *cis* 2-Hydroxy-cyclohexanoic acid 5.

Ethyl-cyclohesanone-2-carboxylate **4** (34g, 200 mmoli) in ethanol (70 mL) was hydrogenated in pressurised vat at 60 atm in the presence of PtO_2 (10mmoli) at r.t.. After 72 h the reduction was complete, the catalyst was filtered off and the solvent removed in vacuo. The target alcohol was obtained in 80% yield, the rest 20% being trans isomer. I.R. (film) 3450, 1730 cm^{-1}. ^{1}HNMR ($CDCl_3$): 4.18 (2H, m); 4.16 (1H, m); 3.22 (1H, d, J=3.57); 2.48 (1H, ddd, J=3.6, J=3.6, J=10.98); 1.86 (2H, m); 1.65 (3H, m); 1.49 (1H, m); 1.14 (1H, m); 1.33 (1H, m); 1.25 (3H, t). ^{13}C NMR ($CDCl_3$) 170.51; 66.48; 60.27; 46.49; 31.59; 24.52; 23.57; 19.84; 13.89. MS: 172 (M+); 155 (3); 145 (5); 144 (50); 127 (11); 115 (16); 101 (100); 98 (27); 81 (49); 73 (68); 70 (20); 69 (13).

Ethyl ester of *cis* 2-(*tert*-butyldimethylsilyloxy)-cyclohesanoic acid. 6

5 (32g,186 mmoli), imidazole (26g, 386mmoli) and *tert*-butyldimethylsilyl chloride (31g, 210 mmoli) were dissolved in DMF (180mL). After 12 h at r.t. the reaction was complete. The mixture was quenched rapidly with cold 0.1 N HCl and extracted with ethyl acetate (3x300 mL). The organic phase was dried (Na_2SO_4) and the solvent removed to give sufficiently pure **6** for further elaboration. Yield 94%. I.R. (Film) 3450, 1740 cm^{-1}. ^{1}H NMR ($CDCl_3$): 4.39 (1H, m); 4.09 (2H, m); 2.31 (1H, m); 1.9-1.3 (8H, m); 1.25 (3H, t); 0.86 (9H, s); 0.04 (3H, s); 0.02 (3H, s). ^{13}C NMR ($CDCl_3$) 173.75; 68.26; 60.02; 48.43; 33.46; 25.63; 24.86; 21.86; 19.54; 17.94; 14.10; -4.44; -5.39. MS: 271 (M-15); 241 (2); 229 (85); 201 (30); 183 (26); 155 (7); 115 (8); 103 (27); 75 (100). E.A. Calcd. for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.56 Found: C, 62.80; H, 10.00.

***Cis* 2-(*tert*-butyldimethylsilyloxy)-cyclohexan-carboxaldheyde. 7**

DIBALH (5.2 mmoli) was slowly added at -78°C to **6** (1g, 3.5 mmol) in anhydrous Et_2O (10mL). The mixture was stirred for 40 min, poured in potassium sodium tartrate aqueous satured solution and vigorously stirred for 1h. The ethereal phase was separated, the aqueous phase was washed with ether (3x50 mL). The combined organic phase were washed with brine, dried (Na_2SO_4), the solvent evaporated and the residue purified by flash chromatography to give **7** in 70% yields. I.R. (Film) 3450, 1730 cm^{-1}.^{1}H NMR

($CDCl_3$): 9.70 (1H, d); 4.39 (1H, m); 2.23 (1H, m); 1.88 (1H, m); 1.7-1.20 (7H, m); 0.88 (9H, s); 0.08 (3H, s); 0.03 (3H, s). GC*m/e*: : 227 (M-15); 186 (13); 185 (90); 167 (3); 155 (24); 143 (6); 117 (78); 107 (10); 93 (11); 75 (100). E.A. Calcd. for $C_{13}H_{26}O_2Si$: C, 64.42; H, 10.82; Found: C, 64.50; H, 10.17.

4[2-(*tert*butyldimethylsilyloxy)-cyclohexyl]azetidin-2-one. 10

In a predried flask, **7** (3g, 12.39 mmol) was dissolved in anhydrous THF (60 mL). LiHMDSA (14.25 mL of 1M solution in THF) was added dropwise at -78°C. The temperature was left to rise -20°C (1h). I.r. test showed the disappearance of the aldehydic C=O stretching (1720 cm^{-1}) and the appearance of the iminic (1680 cm^{-1}) stretching as probe of the formation of **8**. In a separate flask the lithium enolate of the *tert*-butyl acetate **9** (71.2 mmol) was prepared adding at -78°C, under stirring, LiHMDSA (61.95 mL of 1M solution in THF) to a THF solution of *tert*-butylacetate. The solution containing imine **8** was added dropwise to the enolate at -78°C under vigorously mechanical stirring. The stirring was continued overnight while the temperature was left to reach spontaneously r.t.. Canonic work-up of the reaction followed by precipitation by diethyl ether-pentane yielded the target **10** in 57% yield as single isomer. M.P.= 151-154°C. IR (nujol): 3182; 1757, 1732 cm^{-1}. ^1H NMR ($CDCl_3$): 5.79 (1H, bs); 3.95 (1H, m); 3.57 (1H, ddd, J=2.52, J=4.84, J=7.4); 2.99 (1H, ddd, J=2.16, J=4.96, J=14.66); 2.65 (1H, ddd, J=1.3, J=2.48, J=14.68); 1.78 (2H, m); 1.62 (1H, m); 1.53 (1H, m); 1.5-1.36 (4H, m); 1.25 (1H, m); 0.91 (9H, s); 0.07 (3H, s); 0.03 (3H, s). ^{13}C NMR ($CDCl_3$) : 168.47; 68.09; 50.31; 47.27; 41.82; 33.44; 25.71; 24.95; 22.69; 19.66; 17.94; -4.40; -5.10. MS: 268(M-15); 226(26); 185(18); 184(100); 167(7); 155(19); 116(6); 100(6); 88(4); 75(83). E.A. Calcd. for $C_{15}H_{29}NO_2Si$: C, 63.56; H, 10.32; N, 4.49. Found: C, 63.36 ; H, 10.35; N, 4.52.

4[2-hydroxy-cyclohexyl]azetidin-2-one. 10a

To a LiHMDSA (5.48 mL 1M in THF) solution at -78°C was added **10** (4.98 mmol) in anhydrous THF (30mL). After 20 min at 0°C TBAF (9.96 mL of 1M Solution in THF) was added. The stirring was continued overnight at r.t. The solution was acidified (AcOH), extracted with ethyl acetate and dried on Na_2SO_4. Short flash chromatography yielded the target in 74%. M.P. 151-153°C. IR (nujol): 3400; 3186;1727; 1683 cm^{-1}. ^1H NMR ($CDCl_3$): 5.87 (1H, bs); 4.02 (1H, s); 3.70 (1H, m); 3.02 (1H, ddd, J =5.1, J=14.8); 2.71 (1H, ddd, J=2.5, J=14.8); 1.80 (2H, m); 1.63-1.48 (5H, m); 1.30-1.125 (2H,m); 1.17 (1H,m). ^{13}C NMR ($CDCl_3$): 163.03; 68.67; 50.58; 44.97; 41.44; 33.78; 24.92; 21.30; 19.57. MS: 126 (17); 108 (93); 98 (55); 93 (64); 88 (15); 82 (100); 67 (80); 54 (37). E.A. Calcd. per $C_9H_{15}NO_2$: C, 54.8; H, 7.67; N, 7.11. Found: C, 54.85; H, 7.68 ; N, 7.08.

3,3-Dimethyl-octaidro-4-oxa-2a-aza-cyclobuta[a]-naftalen-2-one. 11

Azetidinone **10a** (1.9 g, 11.24 mmol) in anhydrous CH_2Cl_2 (2 mL) was treated with BF_3OEt_2 (0.16g 1.12 mmol). After 5 min DMP (dimethoxypropane) (22.48 mmol) was added. The solution was stirred for 90min, the solvent was removed in vacuo, ethyl acetate (50 mL) was added and the resulting solution was washed twice with brine. Organic layers were dried (Na_2SO_4). Short column flash chromatography furnished **11** in 84% yield. M.P.=80-84°C. IR (nujol): 1740 cm^{-1}. ^1H NMR ($CDCl_3$): 4.00 (1H, m); 3.74 (1H, m); 2.88 (1H, dd, J =2.5, J=14.5); 2.83 (1H, dd, J=5, J=14.5); 1.9-1.8 (2H, m); 1.78 (3H, s); 1.7-1.42 (7H, m); 1.42 (3H, s); 1.30 (1H, m). ^{13}C NMR ($CDCl_3$): 163.8; 82.63; 66.13; 47.41; 38.14; 35.74; 31.76; 26.37; 24.82; 22.88; 19.45; 18.98 MS: 210 (M+1); 194 (100); 180 (1); 166 (2); 152 (62); 135 (8); 124 (2); 110 (9); 93 (11); 84 (26); 67 (12). HRMS *m/e* 210.149404 Calcd for $C_{12}H_{20}NO_2$ Found 210.15060 (M+1). E.A. Anal. Calcd. for $C_{12}H_{19}NO_2$: C, 68.85; H, 9.16; N, 6.70. Found: C, 68.75; H, 9.18; N, 7.08.

1-(1-trimethylsilyloxy ethyl)-3,3-Dimethyl-octaidro-4-oxa-2a-aza-cyclobuta[a]-naftalen-2-one. 12

To a solution of LDA (1.5 mmmol) in THF (3 mL) at -78°C °C was added dropwise **11** (0.270g 1.3 mmol) in THF (4mL). After 30 min acetyltrimethylsilane (1.5 mmol) in THF (2 ml) was added. The reaction evolution was tested by t.l.c.. When the formation of trimethylsilyl carbinol was complete (15 min), KO^{t}Bu (1.6 mmol) in ^{t}BuOH (3 mL) was added. The temperature was raised to 0 °C. After 1 h the reaction mixture was worked-up in the usual way. The target **12** was obtained without further purification as single isomer in quantitative yield. IR (nujol) 1734 cm^{-1}. ^1H NMR ($CDCl_3$): 4.13 (1H, m); 3.97 (1H, s); 3.69 (1H, m); 3.09 (1H, dd, J=1.9, J=5.2); 1.85 (1H, m); 1.74 (3H, s); 1.6-1.4 (6H, m); 1.25 (1H, m); 1.20 (3H, d, J=6.8). ^{13}C NMR ($CDCl_3$): 164.07; 82.74; 66.31; 65.51; 58.51; 50.92; 35.85; 31.80; 26.58; 24.89; 22.97;

21.57; 19.98; 19.55; 0.28; -5.56. E.A. Calcd. for $C_{17}H_{31}NO_3Si$: C, 62.73; H, 9.61; N, 4.31. Found: C, 62.91; H, 9.58; N, 4.32.

1-(1-Hydroxy ethyl)-3,3-Dimethyl-octaidro-4-oxa-2a-aza-cyclobuta[a]-naftalen-2-one. 13

To a solution of **12** (4.18 mmol) in acetonitrile (20 mL) was added at 0°C HF (4.18 mmol of 1/10 40% solution). After 10 min 5 ml of 5% $NaHCO_{3aq}$, were added. Acetonitrile was removed in vacuo and to the crude reaction mixture ethyl acetate (30 mL) was added. The organic layers were washed with brine and dried to give pure **13** in quantitative yield. I.R. (Film) 3450, 1735 cm^{-1}. ^1H NMR ($CDCl_3$): 4.11 (1H, m); 3.97 (1H, s); 3.72 (1H, m); 3.08(1H, dd, J=1.9, J=5.9); 1.8 (1H m); 1.74 (3H, s); 1.62-1.38 (7H, m); 1.40 (3H, s); 1.20 (3H, d, J=6.6). ^{13}C NMR ($CDCl_3$) 164.16; 82.55; 66.41; 65.74; 58.79; 50.51; 36.00; 31.84; 26.57; 24.98; 22.80; 21.57; 19.9; 19.54. E.A. Calcd. for $C_{14}H_{23}NO_3$: C, 66.36; H, 9.16; N, 5.53. Found: C, 66.40; H, 9.14; N, 5.48.

1-(1-p-nitrobenzyloxycarbonyl-ethyl)-3,3-Dimethyl-octaidro-4-oxa-2a-aza-ciclobuta[a]-naftalen-2-one.14

To a solution of **13** (4.62 mmol) in anhydrous CH_2Cl_2 (20 mL) were added dropwise consecutively at 0°C DMAP (9.24 mmol), p-nitrobenzyl-chloroformiate (2 g, 9.24 mmol) in CH_2Cl_2 (4mL). After 3h at r.t. the reaction mixture was poured into ice/water and pH adjusted at 3 by means of diluted HCl. Extraction with CH_2Cl_2 followed by washing the organic layers with 5% $NaHCO_{3aq}$ and brine and purification by flash chromatography on silica gel (ether/cyclohexane 6/4 eluting) yielded **14** in 63 %. IR ($CDCl_3$) 1747 cm^{-1}. ^1H NMR ($CDCl_3$): 8.23 (2H, m); 7.54 (2H, m); 5.23 (2H, m); 5.03 (1H, m); 3.93 (1H, m); 3.64(1H, dd); 3.23 (1H, dd); 1.87 (1H, dd); 1.79 (1H, m); 1.74 (3H, s); 1.7-1.5 (2H, m); 1.5-1.3 (3H, m); 1.42 (3H, d); 1.39 (3H, s); 1.23 (1H, m). ^{13}C NMR ($CDCl_3$): 162.01; 154.11; 142.26; 128.41; 123.85; 82.87; 74.05; 67.93; 66.12; 55.99; 52.25; 35.67; 31.68; 26.55; 24.88; 22.92; 19.80;19.44; 18.68. HRMS *m/e* 432.189651 Calcd per $C_{22}H_{29}N_2O_7$ found (M^{+1}) 433.194240. E.A. Calcd. for $C_{22}H_{28}N_2O_7$: C, 61.08; H, 6.53; N, 6.48. Found: C, 60.89; H, 6.55; N, 6.52.

3(1-p-nitrobenzyloxycarbonyl-ethyl)4-(2-oxo-cyclohexyl)-azetidin-2-one. 15

Jones reagent (2 mL) was added at r.t. to **14** (0,7g 4.14 mmol) dissolved in acetone (150 mL). After 30 min *sec*-butyl alcohol was added. The solvent was removed in vacuo, ethyl acetate was added and the mixture filtered on Florisil. Short column flash chromatography yielded **15** in 74%. IR (film) : 3342 , 1747, 1709 cm^{-1}. ^1H NMR ($CDCl_3$): 8.24 (2H, d, J=8.8); 7.57 (2H, d, J=8.8); 5.78 (1H, bs); 5.26 (2H, s); 5.18 (1H, m); 3.97 (1H, dd, J=2.4, J=5.6); 3.07 (1H, dd, J=2, J=7.6); 2.54-2.28 (3H, m); 2.20-1.92 (3H, m); 1.80-1.40 (3H, m);1.47 (3H, d, J=6.4). ^{13}C NMR ($CDCl_3$): 210.93; 166.17; 142.36; 128.51; 128.43; 123.79; 73 26; 67.99; 58.87; 53.16; 51.28; 42.26; 28.74; 27.67; 24.53; 18.24. HRMS *m/e* 391.150526 Calcd for $C_{19}H_{23}N_2O_7$ Found 391.149550 (M^{+1}). Anal. Calcd. per $C_{19}H_{22}N_2O_7$: C, 58.44; H, 5.68; N, 7.18. Found: C, 58.40; H, 5.69; N, 7.21.

***N-tert*-butyldimethylsilyl-3(1-p-nitrobenzyloxycarbonyl-ethyl)4-(2-oxo-cyclohexyl)-azetidin-2-one. 15a**

To a solution of **15** (2.83 mmol) in CH_2Cl_2 (15 mL) a 0°C were added TEA (4.2 mmol) and TBSCl (3.11 mmol). After 20 h at r.t. the reaction was poured in acidic (HCl_{dil}) H_2O and extracted with CH_2Cl_2. The organic layers were washed with brine, the solvent removed and the residue chromatographed (SiO_2, cyclohexane/ethyl acetate eluting) to give **15a** in 86%. IR (nujol) : 1745, 1620 cm^{-1}. ^1H NMR ($CDCl_3$): 8.24 (2H, d, J=8.5); 7.54 (2H, d, J=8.5); 5.24 (2H, m); 5.08 (1H, m); 3.87 (1H, m); 3.31 (1H, dd, J=2.5, J=6.5); 2.60 (1H, m); 2.42 (1H, m); 2.30 (1H, m); 2.10 (1H, m); 2.1-1.9 (2H, m); 1.81 (3H, m); 1.42 (3H, d, J=6.5); 0.95 (9H, s); 0.27 (3H, s); 0.09 (3H, s). ^{13}C NMR ($CDCl_3$): 209.65; 171.59; 154.16; 142.37; 130.87; 128.32; 123.81; 73.79; 68.13; 67.82; 59.03; 53.28; 42.53; 38.69; 29.60; 27.22; 25.01; 18.86; 18.44; -4.93; -5.26. HRMS *m/e* 505.237005 Calcd per $C_{25}H_{36}N_2O_7Si$: Found 505.236480 (M^{+1}). E.A. Calcd. for $C_{25}H_{36}N_2O_7Si$: C, 59.5; H, 7.2; N, 5.55. Found: C, 59.65; H, 7.18; N, 5.52.

***N-tert*-butyldimethylsilyl-3(1-hydroxyethyl)4-(2-oxo-cyclohexyl)-azetidin-2-one. 16**

Azetidinone **15a**, (0.3g, 0.6mmol) dissolved in ethylacetate (7 mL) was hydrogenated under gentle pressure of H_2 in the presence of catalytic Pd/C 10% at r.t.. After 90 min the reduction was complete: the catalyst was filtered off and the solvent removed in vacuo. The crude reaction mixture dissolved in DMF, (6

mL) imidazole (2 eq) and TBSCl (1.5 eq) were added. After 12 h at r.t. the reaction was complete. The mixture was quenched rapidly with cold 0.1 N HCl and extracted with ethyl acetate (3x30 mL). The organic phase was dried (Na_2SO_4), the solvent removed and the residue chromatographed to give the title compound in 72% yield. IR ($CDCl_3$): 3450, 1735, 1705 cm^{-1}. ^1H NMR ($CDCl_3$): 4.09-4.00 (1H, m); 3.71 (1H, dd, J=2.4, J=6.5); 2.89 (1H, dd, J=2.4, J=8.2); 2.62-2.56 (1H, m); 2.45-2.10 (4H, m); 1.95 (1H, m); 1.73-1.50 (2H, m); 1.55-1.42 (1H, m); 1.30 (3H, d, J=6.1); 0.97 (9H, s); 0.23 (3H, s); 0.15 (3H, s). ^{13}C NMR ($CDCl_3$): 212.00; 158.00; 68.34; 61.09, 54.15; 51.85; 42.80; 27.54; 26.44; 26.27; 24.69; 20.79; 18.73; -5.47; -5.54.

***N*-*tert*-butyldimethylsilyl-3(1-*tert*-butyldimethylsilyl-oxyethyl)4-(2-oxo-cyclohexyl)-azetidin-2-one. 16a**

Azetidinone **16** (140 mg, 0,43 mmol) was dissolved in DMF (6 mL). Imidazole (58 mg, 0.86 mmol) and TBSCl (98 mg, 0.65 mmol) were added at 0°C. The reaction was stirred overnight at r.t. then poured in satured solution of NH_4Cl and extracted with CH_2Cl_2. Flash chromatography of the residue yielded the title compound in 94% yield. IR (nujol): 1735, 1710 cm^{-1}. ^1H NMR ($CDCl_3$): 4.12-4.00 (1H, m); 3.99 (1H, m); 3.05 (1H, dd, J=2.8, J=7.5); 2.62-2.56 (1H, m); 2.45-2.38 (1H, m); 2.30-2.22 (1H, m); 2.12-1.95 (2H, m); 1.73-1.50 (4H, m); 1.24 (3H, d, J=6.2); 0.95 (9H, s); 0.85 (9H, s); 0.26 (3H, s); 0.08 (3H, s); 0.06 (3H, s); 0.05 (3H, s). ^{13}C NMR ($CDCl_3$): 210.72; 174.65; 68.61; 63.03, 53.71; 53.14; 43.39; 29.68; 27.98; 27.41; 26.86; 26.02; 23.92; 19.92; 18.95; -3.39; -3.45; -3.69; -4.10.

***(2S,4R,5S)* 2-chloro-2-oxy-3,4-dimethyl -5-phenyl 1,3,2- oxazaphospholan. 17**

To a solution of (*1R,2S*)-ephedrine (30 mmol, 5g) in CH_2Cl_2 (100mL), while stirring, at -30°C were added TEA (1.2 eq) and $POCl_3$ (1.1 eq). The reaction mixture was left under stirring for 2 h, after that the temperature was left to reach spontaneously r.t.. The crude reaction mixture was poured into NH_4Cl saturated ice/water solution. The mixture was extracted with methylene chloride and the organic layers dried on $MgSO_4$. Removal of the solvent followed by flash chromatography on silica gel (cyclohexane/ethyl acetate 1/1) yielded the pure diastereomer **17** in 61%. M.P. 95°C. $[\alpha]_D^{20}$= -23.3 (1.73, $CHCl_3$) I.R. (nujol) 1458, 1340, 1275, 1210, 1190, 1060 cm^{-1}. ^1H NMR ($CDCl_3$): 7.43-7.27 (5H, m); 5.87 (1H; d, J=6.2); 3.85 (1H, m); 2.84 (3H, d, J=12.5); 0.84 (3H, d, J=6.8). ^{13}C NMR ($CDCl_3$): 134.64 (J=8.5); 128.68; 125.53; 82.84; 60.36 (J=13.6); 28.85 (J=5.5); 11.71. GC*m/e*: : 245 (M^+); 230 (16); 210 (6); 192 (5); 154 (5); 139 (100); 117 (16); 105 (21); 91 (18); 77 (25).

Synthesis of Enolphosphates.

To a solution of LiHMDSA (4.5 mL of 1 M THF solution) and anhydrous THF (10 mL) was added dropwise at -78°C the azetidinone **16** (3.2 mmol) dissolved in THF (5mL). The reaction mixture was allowed to react for 1h at -78°C, after that **17** (4 mmol, in 5 mL of THF) was added dropwise. After 1h the reaction mixture was left to rise -20 and stirred overnight. The mixture was poured into NH_4Cl saturated ice/water solution and extracted with ethyl acetate. After drying and removing the solvent in vacuo, the crude was purified by flash chromatography (cyclohexane 5/ CH_2Cl_2 4/ acetone 1) to give **18** and **19** in 82% overall yield.

***(3S,4R)N*-*tert*-butildimethylsilyl-4[(2*R*, 4*R*, 5*S*)2-3,4-Dimethyl-2-oxo-5-phenyl-[1,3,2]oxazaphospholidin-2-yl-oxy)(*S*)cyclohexen-2-enyl]-3-[1(*R*)*tert*-butyldimethylsilyl-oxy-ethyl] azetidin-2-one. 18**

Y%=43. $[\alpha]_D^{20}$= -57 (0.434, $CHCl_3$). I.R. (film) 2970, 2930, 2840, 1737, 1679 cm^{-1}. ^1H NMR ($CDCl_3$): 7.39-7.25 (5H, m); 5.66 (1H, d, J=6.2); 5.60 (1H, m); 4.19-4.01 (1H, m); 3.93 (1H, t, J=2.6); 3.77-3.53 (1H, m); 3.18 (1H, dd, J=2.7, J=5.8); 2.79 (3H, d, J=9.9); 2.76 (1H, m); 2.1 (2H, m); 1.93-1.65 (3H, m); 1.24 (3H, d, J=6.1); 1.24 (1H, m); 0.96 (9H, s); 0.84 (9H, s); 0.78 (3H, d, J=6.4); 0.27 (3H, s); 0.23 (3H, s); 0.05 (3H, s); 0.04 (3H, s). ^{13}C NMR ($CDCl_3$): 173.81; 148.63 (d, J=9.5); 135.56 (d, J=8.3); 128.23; 127.96; 123.54; 113.03 (d, J=4.9); 80.79 (d, J=23); 66.56; 61.43; 59.91 (d, J=13.6); 54.43; 40.52 (d, J=3.4); 29.89 (d, J=4.1); 26.44; 25.76; 23.68; 22.47; 19.90; 18.66; 17.79; 13.56; -4.31; -4.81; -5.05; -5.16.

(3*R*,4*S*)*N*-*tert*-butildimethylsilyl-4[(2*R*, 4*R*, 5*S*)2-3,4-Dimethyl-2-oxo-5-phenyl-[1,3,2]oxazaphospholidin-2-yl-oxy)(*R*)cyclohexen-2-enyl]-3-[1(*S*)*tert*-butyldimethylsilyl-oxy-ethyl] azetidin-2-one. 19

Y%=39. $[\alpha]_D^{20}$= -36.5 (0.12, $CHCl_3$). I.R. (film) 2970, 2930, 2840, 1737, 1679 cm^{-1}. ^1H NMR ($CDCl_3$): 7.43-7.27 (5H, m); 5.70 (2H; m); 4.15 (2H, m); 3.70 (1H, m); 3.10 (1H, m); 2.80 (3H, d, J=9.9); 2.76 (1H, m); 2.1 (2H, m); 1.93-1.65 (3H, m); 1.24 (3H, d, J=6.1); 1.24 (1H, m); 0.96 (9H, s); 0.84 (9H, s); 0.78 (3H, d, J=6.4); 0.27 (3H, s); 0.23 (3H, s); 0.05 (3H, s); 0.04 (3H, s) . ^{13}C NMR ($CDCl_3$): 173.85; 148.63 (d, J=9.5); 135.56 (d, J=8.3); 128.23; 127.96; 123.54; 113.03 (d, J=4.9); 81.01 (d, J=23); 66.18; 61.50; 60.00 (d, J=13.6); 53.43; 40.22 (d, J=3.4); 29.71 (d, J=4.1); 26.69; 26.00; 23.89; 22.63; 20.18; 18.88; 13.96; -4.04; -4.68; -4.72; -4.88.

(3*S*,4*R*)-4[(2*R*, 4*R*, 5*S*)2-3,4-Dimethyl-2-oxo-5-phenyl-[1,3,2]oxazaphospholidin-2-yl-oxy)(*S*)cyclohexen-2-enyl]-3-[1(*R*)*tert*-butyldimethylsilyloxy-ethyl] azetidin-2-one. 20

To a solution of **18** (110 mg, 0.169 mmol) in MeOH were added 2 eq of KF. The mixture was stirred for 90 min, MeOh was removed in vacuo. Ethyl acetate (50 ml) and ice-water (20 ml) were added. The organic layers separated and dried over $MgSO_4$. Flash chromatography of the residue (ethyl acetate 9/ cyclohexane 1) yielded the target in 70 %. $[\alpha]_D^{20}$= -35 (1.18, $CHCl_3$). I.R. (nujol) 2930, 2850, 1751, 1437, 1374, 1258, 1190, 1128, 1105, 1062, 977 cm^{-1}. ^1H NMR ($CDCl_3$): 7.40-7.25 (5H, m); 6,5 (1H, bs); 5.75 (2H, m); 4.18 (1H, quintet, J=6.0); 4.14 (1H, m); 3.7 (1H, m); 3.06 (1H, dd, J=5.0; J=2.2); 2.77 (3H, J=10.2); 2.60 (1H, m); 2.1 (2H, m); 1.90-1.60 (3H, m); 1.23 (1H, m); 1.23 (3H, d, J=6.3); 0.85 (9H, s); 0.78 (3H, d, J=6.6); 0.61 (6H, s).^{13}C NMR ($CDCl_3$): 168.18, 147.85 (d, J=10.5); 135.11 (d, J=8.1); 128.47; 128.28; 125.64; 114.32 (d, J=4.6); 81.22, 65.89, 59.58 (d, J=13.0); 59.38, 50.14, 39.26 (d, J=2.7); 29.31 (d, J=4.9); 25.71; 23.68; 22.83; 20.37; 17.89; 13.30; -4.35; -4.92.

(3*R*,4*S*)-4[(2*R*, 4*R*, 5*S*)2-3,4-Dimethyl-2-oxo-5-phenyl-[1,3,2]oxazaphospholidin-2-yl-oxy)(*R*)cyclohexen-2-enyl]-3-[1(*S*)*tert*-butyldimethylsilyloxy-ethyl] azetidin-2-one. 21

Obtained in 72% yield following the procedure reported for **20**. $[\alpha]_D^{20}$= -56.0 (0.332, $CHCl_3$). I.R. (nujol) 2930, 2850, 1756, 1456, 1374, 1250 , 1190, 1128, 1105, 1062, 977cm^{-1}. ^1H NMR ($CDCl_3$): 7.40-7.25 (5H, m); 6,06 (1H, bs); 5.65 (2H, m); 4.15 (2H, m); 3.71 (1H, m); 3.05 (1H, m); 2.80 (3H, J=10.1); 2.67 (1H, m); 2.15 (2H, m); 1.90-1.60 (3H, m); 1.23 (1H, m); 1.23 (3H, d, J=6.3); 0.85 (9H, s); 0.78 (3H, d, J=6.6); 0.62 (3H, s); 0.49 (3H, s) .^{13}C NMR ($CDCl_3$): 168.46, 147.87 (d, J=10.4); 135.81 (d, J=8.1); 128.46; 128.18; 125.64; 114.80 (d, J=4.9); 81.00, 65.66, 60.04 (d, J=13.0); 59.91, 50.05, 39.71 (d, J=1.7); 29.66 (d, J=4.9); 25.72; 23.80; 23.41; 22.60; 17.80; 13.50; -4.36; -4.95.

Method B.

Alternatively the crude mixture of enolphosphates, after aqueous work-up, was processed as described for the preparation of **20.** Chromatography of the reaction mixture, yielded **20** and **21** in 30 and 27% yield respectively starting from chetone **16a**.

Synthesis of Epoxyphosphates.

To a solution of enolphosphate (3.5 mmol) in anhydrous CH_2Cl_2 (30mL) were added consecutively at 0°C solid $NaHCO_3$ (2 eq) and MCPBA (5 eq, 50% in H_2O). The suspension was stirred at the same temperature for 30 min and then 3 h at r.t. The mixture was poured into an ice cold 3% aqueous sulphite solution. The organic layers were washed with saturated solution $NaHCO_3$, water and brine, dried and evaporated to give the epoxyphosphonates which were utilized for the next step without further purification. An aliquot was purified for analytical purpose. Spectral data as follows.

(3*S*, 4*R*) 4-[1-[(2*R*, 4*R*, 5*S*)3,4-dimethyl-2-oxo-5-phenyl-[1,3,2]oxazaphospholidin-2-yl-oxy]-(1*S*)-7-oxa-bicyclo[4.1.0.]hept-2-yl]-3-(1(*S*)-*tert*-butyldimethylsilyloxy-ethyl)-azetidin-2-one. 22

Y%=90. I.R. (film) 1756 cm^{-1}. ^1H NMR ($CDCl_3$): 7.40-7.25 (5H, m); 6,05 (1H, bs); 5.68 (1H, d, J=6.3); 4.33-4.29 (2H, m); 3.75 (1H, d, J= 3.8); 3.65 (1H, m); 3.12 (1H, m); 2.77 (3H, J=10.2); 2.55 (1H, m); 1.95 (2H, m); 1.90-1.60 (3H, m); 1.23 (1H, m); 1.25 (3H, d, J=6.3); 0.85 (9H, s); 0.68 (3H, d, J=6.6); 0.61 (6H, s).

(3*R*, 4*S*) 4-[1-[(2*R*, 4*R*, 5*S*)3,4-dimethyl-2-oxo-5-phenyl-[1,3,2]oxazaphospholidin-2-yl-oxy]-(1*R*)-7-oxa-bicyclo[4.1.0.]hept-2-yl]-3-(1(*R*)-*tert*-butyldimethylsilyloxy-ethyl)-azetidin-2-one. 23

Y%=80. I.R. (film) 1754 cm^{-1}. ^1H NMR ($CDCl_3$): 7.40-7.25 (5H, m); 5.96 (1H, s); 5.67 (1H, d, J=6.3); 4.33-4.29 (2H, m); 3.80 (1H, d, J= 3.8); 3.65 (1H, m); 3.09 (1H, m); 2.76 (3H, J=10.2); 2.62 (1H, m); 2.01 (2H, m); 1.80-1.60 (3H, m); 1.23 (1H, m); 1.25 (3H, d, J=6.3); 0.85 (9H, s); 0.77 (3H, d, J=6.6); 0.088 (3H, s); 0.073 (3H, s).

Syntheses of 4-Methoxy Ketones.

A solution of the epoxy-phosphate (0.18 mmol) in methanol (10 mL) was stired for 2h at r.t. and for further 3h at 40°C. Methanol was removed in vacuo and the residue purified by flash chromatography (ethyl acetate).

(3*S*,4*R*)-3[(*R*)-(1-*tert*-butyldimethylsilyloxy-ethyl)-4-[(2'*S*,6'*S*)-6'-methoxy-1-oxo-cyclohex-2-'yl]-azetidin-2-one. 24

Y% =70. $[\alpha]_D^{20}$= +20.8 (0.148, $CHCl_3$). I.R. (nujol) 1457 cm^{-1}. ^1H NMR ($CDCl_3$): 5.85 (1H; bs); 4.20 (1H, m); 4.02 (1H, m); 3.60 (1H, m); 3.30 (3H, s); 3.10 (1H, m); 2.89 (1H, dd, J=6.5, J=3); 2.24 (1H, m); 2.11 (1H, m); 2.01 (1H, m); 1.69 (1H, m); 1.66 (1H, m); 1.56 (1H, m); 1.25 (3H, d, J=6.0); 0.88 (s, 9H); 0.08 (s, 3H); 0.07 (s, 3H). ^{13}C NMR ($CDCl_3$): 166.16; 154.15; 142.35; 128.57; 128.42; 123.79; 83.88; 72.98; 67.97; 59.13; 56.94; 51.01;49.22; 33.39; 29.51; 18.95; 18.23. HRMS *m/e* 355.217887 Calcd per $C_{18}H_{33}NO_4Si$: Found 355.217899 . E.A. Calcd. for $C_{18}H_{33}NO_4Si$: C, 60.81; H, 9.36; N, 3.94. Found: C, 60.85; H, 9.58; N, 3.54.

(3*R*,4*S*)-3[(*S*)-(1-*tert*-butyldimethylsilyloxy-ethyl)-4-[(2'*R*,6'*R*)-6'-methoxy-1-oxo-cyclohex-2'-yl]-azetidin-2-one. 25

Y%=67. $[\alpha]_D^{20}$= -18.3 (0.24, $CHCl_3$).

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