Oxidation of 3-alkylidene-β-lactams. A preparation of 3-alkenyl-3-hydroxy-β-lactams

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Hydroxylation of the enolates of several 3-alkylideneazetidin-2-ones with MoOPH leads to the formation of 3-hydroxy-3-alkenylazetidin-2-ones in fair to good yields. The products were formed with *trans* stereochemistry in the alkenyl moiety and a presumed *trans* relationship between the hydroxyl substituent and a 4-substituent. Hydrogenation leads to 3-alkyl-3-hydroxyazetidin-2-ones. The prerequisite 3-alkylideneazetidin-2-ones were formed from 3-trimethylsilylazetidin-2-ones and aldehydes via a Peterson olefin synthesis.

WILLIAM W. OGILVIE et TONY DURST. Can. J. Chem. **66**, 304 (1988).

L'hydroxylation des énolates de plusieurs alkylidène-3 azétidinones-2 par le MoOPH conduit à la formation d'hydroxy-3 alcènyl-3 azétidinones-2, avec des rendements qui vont de moyens à bons. Les produits qui se forment présentent une stéréochimie *trans* dans la portion alcènyle et une relation que l'on croit *trans* entre le substituant hydroxyle et un substituant en position 4. Une hydrogénation conduit à la formation d'alkyl-3 hydroxy-3 azétidinones-2. On a obtenu les alkylidène-3 azétidinones-2 de départ à partir des triméthylsilyl-3 azétidinones-2 et des aldéhydes par le biais d'une synthèse d'oléfine suivant Peterson.

[Traduit par la revue]

Introduction

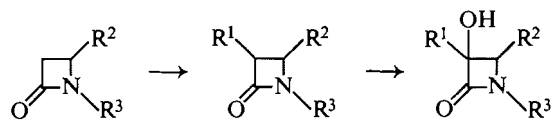
Several monobactams have been described that contain a 3-hydroxy or 3-alkoxy-β-lactam moiety, such as Sulfazecin **1** (1), Tabtoxin **2** (2), and the related microbial product **3** (2*a*). As part of a study directed towards the synthesis of monobactams of this type, we required an entry into 3-hydroxy-3-alkyl-β-lactams, which we envisaged could be readily obtained from 3-hydroxy-3-alkenyl-β-lactams. Compounds of type **4** (R^1 = Me, Ph) had previously been produced by photolysis of α-oxo amides (3), photolytic reaction of benzoylformate in the presence of imines (4), and by the [2 + 2] cycloaddition of imines with ketenes derived with hydroxyacetic acid derivatives (5, 6) to give products of type **4** (R^1 = H, Ph). However, no general route to **4** (R^1 = alkenyl) was apparent in the literature.

We would like to report a straightforward method for the preparation of 3-alkenyl-3-hydroxy-β-lactams via oxygenation of the anion derived from 3-alkenyl-β-lactams. Hydrogenation of these compounds should readily give the above mentioned 3-alkyl-3-hydroxy-β-lactams.

We briefly investigated the addition of organolithiums to 3-oxo-β-lactams as a route to 3-hydroxy-3-alkyl-β-lactam derivatives. Previous literature work indicated that such 3-oxo-β-lactam derivatives react with nucleophilic species such as hydride (7*a*), cyanide (7*a*), and Wittig reagents (7*b*,*c*) to give the expected products. In our hands the reaction of 3-oxo-4-phenyl-1-*p*-methoxyphenylazetidin-2-one, prepared from 3-ethylidene-4-phenyl-1-*p*-methoxyphenylazetidin-2-one, with several organolithiums gave complex mixtures of products, which were not further investigated.

Results and discussion

The formation of β-lactam enolates is a well-known and convenient method of introducing a variety of substituents onto position 3 of the azetidin-2-one ring. We therefore envisaged the formation of **4** by enolate hydroxylation of 3-alkylazetidin-2-ones (eq. [1]), since methods for hydroxylations

[1] 

of carbanions have previously been described (8, 9). Initial attempts to hydroxylate 3-alkylazetidin-2-ones directly were unsuccessful, mainly due to difficulties in generating the required carbanions. Thus treatment of 3-methyl-4-phenylazetidin-2-one **5**, prepared in 70% yield from 4-phenyl-*N*-pyrrolidinomethyl-azetidin-2-one (10), with LDA at −78°C followed by quenching with methyl iodide resulted in recovery of the starting lactam. A similar result was observed using trimethylsilyl chloride as the electrophile, thus indicating that no enolate formation had taken place under these conditions.

Anion formation from **5** did occur upon treatment with LDA in the presence of one equivalent of tetramethylethylenediamine (TMEDA), based upon isolation of the *cis* 3,4-disubstituted lactam **6** and the formation of the 3,3-dimethylazetidin-2-one **7**.

Quenching of this enolate with CH_3I gave a mixture of 3,3-dimethyl product **7** (36%) as well as smaller amounts of **5** and **6**. The product **7** was characterized by the appearance of two methyl signals at δ 1.49 and 0.77 in the proton nmr. The signal

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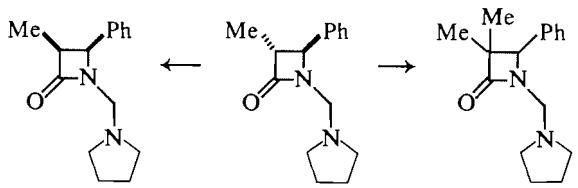
for the 3-methyl group in the *cis* isomer **6** was located 0.63 ppm upfield of the 3-methyl signal in **5**. Correspondingly, the signal for the α-hydrogen in **6** was 0.52 ppm downfield from the 3-hydrogen in **5**. These differences are explained by the anisotropic effect of the phenyl ring on the *cis* methyl group of **6** and on the *cis* H of **5**. In addition, the coupling constant for H-3 and H-4 of **6** was much larger (5.0 Hz) than the respective coupling in **5** (2.2 Hz), verifying that **6** had the *cis* 3,4 stereochemistry. This geometry was expected since **6** would arise by protonation of the enolate of **5**, which should preferentially occur *trans* to the 4-phenyl group.

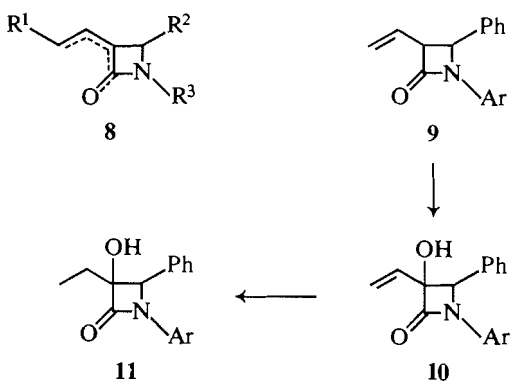
Reaction of the enolate of **5**, generated as above, with TMS chloride gave no incorporation of a trimethylsilyl group, and resulted only in the recovery of starting material **5** and isomerization product **6**. Attempted oxidation of the **5** enolate with 2-sulfonyloxaziridine (11) or with molecular oxygen failed to give oxidation products and resulted only in the recovery of **5** and **6**.



6 **5** **7**

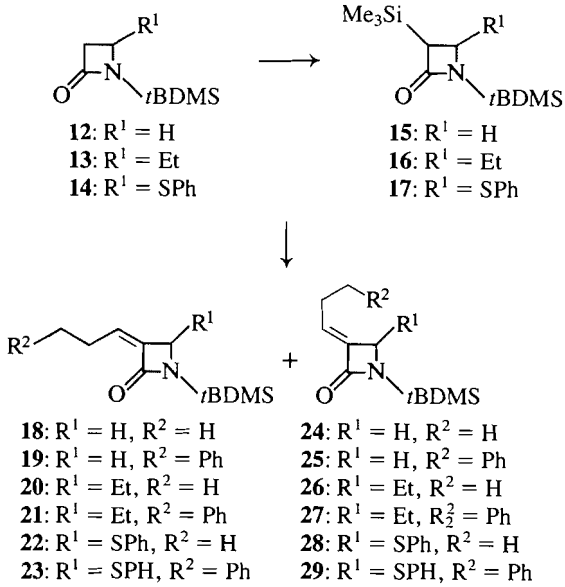
To enhance anion formation at C-3 we decided to employ a vinylogous carbanion of type **8**. Since allyl anions are known to preferentially add hard electrophiles in the α position rather than at the γ-carbon (see ref. 12 for leading references), we felt that the control of regiochemistry in the hydroxylation reaction would not be a problem.

As an initial test of our hypothesis, we treated the lithium enolate of **9** (13) with oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide (MoOPH) (8, 14, 15). After flash chromatography, 3-hydroxy-β-lactam **10** was isolated in 67% yield. The product **10** was also obtained in 30% yield upon treatment of the enolate of **9** with O_2. Compound **10** exhibited an infrared absorption at 1750 cm^{-1} indicating the presence of a β-lactam. The nmr spectrum showed a clear ABX pattern at δ 5.59 (H_A), δ 5.47 (H_B), and at δ 5.18 (H_X). Presumably the hydroxyl group and phenyl group are *trans*, since alkylations of β-lactam enolates at position 3 are known to proceed *anti* to any large group at position 4. Unfortunately, this conclusion could not be corroborated spectroscopically. This compound was smoothly hydrogenated over PtO_2 to give a highly crystalline solid, mp 129–130°C, which was identified as **11**.



8 **9** **11** **10**

Ar = *p*-methoxyphenyl



12: R^1 = H; **13**: R^1 = Et; **14**: R^1 = SPh

15: R^1 = H; **16**: R^1 = Et; **17**: R^1 = SPh

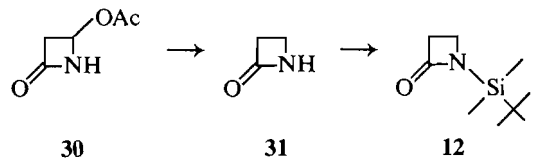
18: R^1 = H, R^2 = H; **19**: R^1 = H, R^2 = Ph; **20**: R^1 = Et, R^2 = H; **21**: R^1 = Et, R^2 = Ph; **22**: R^1 = SPh, R^2 = H; **23**: R^1 = SPH, R^2 = Ph

24: R^1 = H, R^2 = H; **25**: R^1 = H, R^2 = Ph; **26**: R^1 = Et, R^2 = H; **27**: R^1 = Et, R^2 = Ph; **28**: R^1 = SPh, R^2 = H; **29**: R^1 = SPH, R^2 = Ph

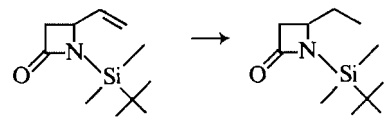
SCHEME 1

Compounds such as **11** are thus easily accessible via the route described above. The prerequisite 3-alkenylazetidin-2-ones are readily available via Peterson olefination starting with 3-trimethylsilylazetidin-2-ones and ketones (16), and presumably also aldehydes.

The preparation of the required alkenyl-β-lactams is shown in Scheme 1. The 4-unsubstituted β-lactam **12**, was obtained from the readily available 4-acetoxyazetidin-2-one **30** (17). Pfaendler and Hoppe (18) had reported that treatment of **30** with KBH_4 in H_2O gave **31** in 69% yield. We found that $NaBH_4$ in ethanol gave **31** in 84% yield from a nonaqueous work-up. This compound was readily protected as **12** with *tert*-butyldimethylsilyl chloride in DMF in 61% yield. 4-Ethylazetidin-2-one **13** was obtained by hydrogenation of 4-vinyl-1-*tert*-butyldimethylsilylazetidin-2-one **32** (19).



30 **31** **12**



32 **13**

Both derivatives were smoothly converted to the 3-trimethylsilyl products **15** and **16** by treatment with LDA followed by addition of trimethylsilyl chloride. The thiophenyl derivative **17** was prepared in a similar manner from 4-thiophenylazetidin-2-one (20). Compounds **16** and **17** were obtained in pure form by flash chromatography while **15** was used without further purification.

The lithium enolate of **15**, prepared by treatment with LDA at −78°C, was reacted with propionaldehyde to give a mixture of **18** and **24** in 66% overall yield. These isomers could be easily separated by flash chromatography and were readily distinguished by ^1H nmr. The vinyl hydrogen of **18** appeared at δ 5.52, upfield of the vinyl hydrogen of **24** at δ 6.11.

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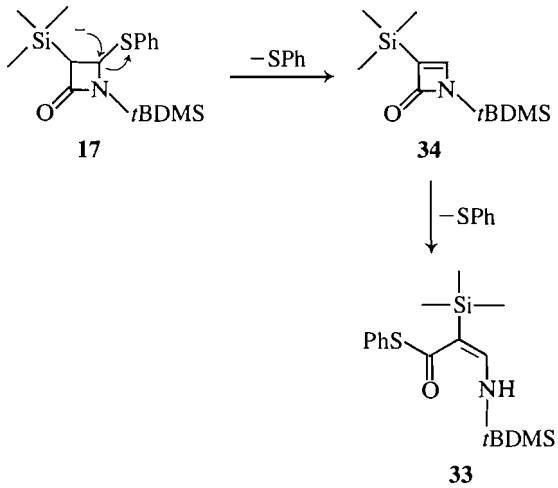
Additionally, the vinylic methylene group of **18** was downfield of the analogous CH_2 group in **24**. The assignment of stereochemistry was based on observations noted previously (21). Reaction of **15** with hydrocinnamaldehyde gave **19** and **25** in 58% overall yield. As with **18** and **24**, the *Z*-isomer **19** was easily distinguished from the *E*-isomer **25** by the chemical shift differences in the olefinic hydrogens of each isomer.

In a similar manner, **16** and propionaldehyde gave **20** and **26** in yields similar to those obtained by the reaction of **15** with propionaldehyde. Reaction of the anion of **16** with hydrocinnamaldehyde gave a good yield of **21** and **27**. In all reactions, the *Z*-ene-lactams **18–21** were eluted before the corresponding *E*-isomers upon flash chromatography, and were obtained in higher proportions.

The reaction of the enolate of **17** with propionaldehyde at −78°C gave a disappointing yield of **22** and **28**. The reaction mixture smelled strongly of thiophenol and we isolated as the major product, in 30% yield, a crystalline material assigned structure **33** on the basis of spectroscopic data. An infrared spectrum showed signals at 1605 and 1551 cm^{-1} only, indicating that the β-lactam was no longer intact. Aside from signals for thiophenoxy, trimethylsilyl, and *tert*-butyldimethylsilyl groups, compound **33** showed only a doublet at δ 6.67 (J = 15.25) and a broad singlet at δ 9.0. A HOMCOR spectrum of this material indicated that the signals at δ 6.67 and δ 9.0 were coupled, as expected for a structure such as **33**.

This compound could arise by elimination of thiophenoxide to give the unsaturated β-lactam **34** followed by attack at the carbonyl group by thiophenoxide to afford thioester **33** (eq. [2]). The yield of desired products **22** and **28** could be

[2]

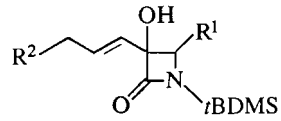


17 **34** **33**

increased to 37 and 28% respectively by allowing only 1 min for the formation of the enolate of **17**. The reaction of the enolate of **17** with hydrocinnamaldehyde using the normal reaction time gave **33** as the major product, with **23** and **29** being formed in smaller amounts. Using the short enolate formation time, **23** and **29** were obtained in 35 and 26% yield respectively.

Generation of the allylic enolates of **18–21** with LDA followed by addition of solid MoOPH at −78°C and subsequent warming until the solution had cleared gave crude products that were purified by flash chromatography to give the desired 3-hydroxy-3-alkenyl-β-lactams **35–38** in yields of 31–53%. Attempted oxidation of the 3-alkenyl-4-thiophenoxyazetidin-2-ones **22** and **23** was unsuccessful, possibly due to the instability of the anion. The crude reaction mixture smelled strongly of thiophenol.

In all cases the regenerated alkene moiety was shown to have an *E*-configuration as indicated by the large (approximately 15 Hz) coupling of the olefin protons. As mentioned above, the relative 3,4 stereochemistry could not be assigned on the basis of spectroscopic evidence. However, as with **10**, it is presumed that the hydroxyl group enters *trans* to the substituent at position 4.



35: R^1 = H, R^2 = H
36: R^1 = H, R^2 = Ph
37: R^1 = Et, R^2 = H
38: R^1 = Et, R^2 = Ph

Experimental

Melting and boiling points are uncorrected. Nuclear magnetic resonance spectra were measured with a Varian XL-300 spectrometer in $CDCl_3$ solution. Values are given as δ values in ppm downfield from TMS. Infrared spectra were recorded with a Perkin–Elmer 783 spectrometer; values are given in cm^{-1}. Mass spectra were obtained on a VG 7070E. Column chromatography was performed using 60–200 mesh silica gel (Baker) and flash chromatography was done with Merck type 9385 silica gel (Terochem). In both cases ethyl acetate – hexane mixtures were used for elution.

CH_2Cl_2 was distilled from P_2O_5. THF was dried over benzophenone ketyl. DMF and diisopropylamine were distilled from CaH_2. Butyllithium was used as received from Aldrich after titration with diphenylacetic acid.

4-Phenyl-2-pyrrolidinomethylazetidin-2-one

4-Phenylazetidin-2-one (8.16 g) was refluxed in 45 mL of ethanol containing 6.4 mL of formalin and 5.5 mL of pyrrolidine for 7 h. The solvent was then removed under reduced pressure and the residue distilled (155°C/0.8 Torr; 1 Torr = 133.3 Pa) to give 9.6 g (75%) of 4-phenyl-2-pyrrolidinomethylazetidin-2-one as a pale yellow liquid; ir ($CHCl_3$): 1748; ^{1}H nmr δ: 7.40–7.36 (m, 5H), 4.72–4.69 (bs, 1H), 4.25 (d, J_{AB} = 13.12, 1H), 3.59 (d, J_{AB} = 13.12, 1H), 3.41 (dd, J = 5.25, 14.85, 1H), 2.85 (dd, J = 2.40, 15.00, 1H), 2.62–2.55 (m, 4H), 1.76–1.72 (m, 4H); ms: 230 (M^+), 70 (base peak) (M^+ − 160).

trans-*3-Methyl-4-phenyl-2-pyrrolidinomethylazetidin-2-one* ***5***

To a solution of 1.2 equivalents of LDA in THF at −78°C was added 3.0 g of 4-phenyl-2-pyrrolidinomethylazetidin-2-one in THF. The resulting deep orange solution was stirred at −78°C for 10 min and then 2 mL of MeI was added all at once. This solution was stirred at −78°C for an additional 10 min and then quenched with saturated NH_4Cl solution. The mixture was extracted with CH_2Cl_2, washed with water, and dried over $MgSO_4$. Removal of solvent followed by flash chromatography gave 2.2 g of **5** as a pale yellow oil (69%); ir (thin film): 1750; ^{1}H nmr δ: 7.25 (s, 5H), 4.21 (d, J_{AB} = 12.90, 1H), 3.55 (d, J_{AB} = 12.90, 1H), 4.22 (d, J = 2.2, 1H), 2.98 (dq, J_q = 7.4, J_d = 2.2, 1H), 2.70–2.41 (m, 4H), 1.90–1.52 (m, 4H), 1.41 (d, J = 7.4, 3H); ms: 244 (M^+).

cis-*3-Methyl-4-phenyl-2-pyrrolidinomethylazetidin-2-one* ***6***

To a solution of 1 equivalent of LDA and 1 equivalent of TMEDA in THF at −78°C was added 117 mg of **5** in THF. The solution was stirred for 10 min and 0.2 mL of freshly distilled trimethylsilyl chloride was added. Stirring was continued at −78°C for a further 20 min. Then the reaction mixture was quenched with saturated NH_4Cl, extracted with ether, washed with water, and dried over $MgSO_4$. Flash chromatography gave 38 mg of **6** as a pale yellow oil (33%); ir (thin film): 1745; ^{1}H nmr δ: 7.18 (m, 5H), 4.84 (d, J = 5.0, 1H), 4.28 (d, J_{AB} = 13.30, 1H), 3.50 (dq, J_q = 7.8, J_d = 5.0, 1H), 3.65 (d, J_{AB} = 13.30, 1H), 2.7–2.4 (m, 4H), 1.9–1.6 (m, 4H), 0.78 (d, J = 8.0, 3H); ms: 244 (M^+).

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3,3-Dimethyl-4-phenyl-1-pyrrolidinomethylazetidin-2-one 7

Azetidin-2-one **5** (106 mg) in 2 mL of THF was added to a solution of 1 equivalent of LDA in 5 mL THF containing 1 equivalent of TMEDA at −78°C. The reaction mixture was stirred for 20 min, 0.2 mL of MeI was added, and the resulting solution stirred for a further 20 min at −78°C. The reaction mixture was then quenched with saturated NH_4Cl, extracted with ether, washed with water, and dried over $MgSO_4$. Removal of solvent and flash chromatography gave 40 mg of 7 as a pale yellow oil (36%); ir (thin film): 1750; ^1H nmr δ: 7.4–7.1 (m, 5H), 4.5 (s, 1H), 4.32 (d, J_{AB} = 12.25, 1H), 3.70 (d, J_{AB} = 12.25, 1H), 2.7–2.4 (m, 4H), 1.9–1.6 (m, 4H), 1.49 (s, 3H), 0.77 (s, 3H); ms: 258 (M^+).

Azetidin-2-one 31

To an ethanolic solution of 3.44 g of **30** at 0°C was added 1.01 g of $NaBH_4$ and the resulting solution stirred for 1 h at 0°C until the evolution of hydrogen had ceased. An excess of acidic Amberlite resin was then added at once and this suspension stirred for 1/2 h at 0°C. The resin was then filtered off and the ethanol removed under reduced pressure. The resulting white solid was washed with ethyl acetate to remove boron compounds, filtered, and the ethyl acetate removed under reduced pressure. This process was repeated with CH_2Cl_2 to give 1.60 g (84%) of **31** as white crystals, mp 72°C (lit. (22) mp 73–74°C).

*1-*tert*-Butyldimethylsilylazetidin-2-one 12*

A solution of 1.60 g of **31**, 3.72 g of *tert*-butyldimethylsilyl chloride and 3.76 mL of triethylamine in 20 mL DMF was stirred at 0°C for 1/2 h. The amine hydrochloride was filtered off and 40 mL of water added to the filtrate. This solution was extracted with ether (4 × 50 mL) and the combined ether fractions washed with water. Drying over $MgSO_4$ followed by removal of solvent under reduced pressure gave a pale yellow oil, which was distilled (75–77°C/1 Torr) to give 2.54 g (61%) of **12** as a colorless liquid; ir (thin film): 1745; ^1H nmr δ: 3.22 (t, J = 4.90, 2H), 3.00 (t, J = 4.90, 2H), 0.93 (s, 9H), 0.21 (s, 6H); ms: 185 (M^+), 128 (base peak) (M^+ − 57). *Anal.* calcd. for $C_9H_{19}NOSi$: C 58.38, H 10.27, N 7.57; found: C 58.02, H 10.24, N 7.33.

*4-Ethyl-1-*tert*-butyldimethylsilylazetidin-2-one 13*

4-Vinylazetidin-2-one **32** (2.87 g) was stirred in methanol with 100 mg of 10% Pd/C under H_2 at atmospheric pressure until 333 mL of H_2 had been consumed (2 h). The solution was then filtered and the methanol removed under reduced pressure. The pale yellow oil containing residual catalyst was purified by column chromatography to give 91% of **13** as a clear, colorless liquid; ir (thin film): 1750; ms: 213 (M^+), 156 (base peak) (M^+ − 57). *Anal.* calcd. for $C_{11}H_{23}NOSi$: C 61.97, H 10.80, N 6.57; found: C 62.07, H 10.66, N 6.44.

*General procedure for the preparation of 3-trimethylsilyl-1-*tert*-butyldimethylsilylazetidin-2-ones: 15, 16, 17*

A solution of *tert*-butyldimethylsilylazetidin-2-one (**12**, **13**, **11**) in THF was added to 1.2 equivalents of LDA generated *in situ* from diisopropylamine and *n*-butyllithium (ca. 2.5 M in hexane) in THF at −78°C. After 10 min, 1.2 equivalents of freshly distilled trimethylsilyl chloride was introduced and the mixture stirred at −78°C for an additional 10–20 min. The solution was then quenched with saturated NH_4Cl and extracted twice with ether. The combined extracts were washed with H_2O and dried over $MgSO_4$ before the solvent was removed under reduced pressure.

*3-Trimethyl-1-*tert*-butyldimethylsilylazetidin-2-one 15*

A portion of **12** (1.07 g) was treated as described above to give 1.49 g (96%) of **15** as a clear colorless oil. This material was used without further purification; ir (thin film): 1730; ^1H nmr δ: 3.26 (t, J = 5.93, 1H), 2.94–2.86 (m, 2H), 0.92 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H), 0.09 (s, 9H); ms: 257 (M^+), 242 (M^+ − 15), 200 (M^+ − 57).

*3-Trimethylsilyl-4-ethyl-1-*tert*-butyldimethylsilylazetidin-2-one 16*

Compound **13** (525 mg) gave 585 mg (83%) of **16** after flash chromatography; ir (thin film): 1730; ^1H nmr δ: 3.21–3.18 (m, 1H), 2.42 (d, J = 2.63, 1H), 1.90–1.80 (m, 1H), 1.40–1.30 (m, 1H), 0.93 (s, 9H), 0.85 (t, J = 7.44, 3H), 0.18 (s, 3H), 0.17 (s, 3H), 0.09 (s, 9H); ms (chemical ionization (CI)): 286 (base peak) (M^+ + 1). *Anal.* calcd. for $C_{14}H_{31}NOSi$: C 58.95, H 10.88, N 4.91; found: C 59.23, H 10.69, N 4.63.

*3-Trimethylsilyl-4-thiophenyl-1-*tert*-butyldimethylsilylazetidin-2-one 17*

Azetidin-2-one **11** (1.04 g) gave 980 mg (75%) of **17** after flash chromatography (75%); ir (thin film): 1740, 1580; ^1H nmr δ: 7.46–7.43 (m, 2H), 7.34–7.30 (m, 3H), 4.64 (d, J = 2.38, 1H), 2.89 (d, J = 2.39, 1H), 0.98 (s, 9H), 0.25 (s, 3H), 0.23 (s, 3H), −0.03 (s, 9H). *Exact Mass* (hrms) calcd. for $C_{12}H_{26}NOSi$: 256.1552; found: 256.1532 (M^+ − 109).

General procedure for the preparation of 3-alkylideneazetidine-2-ones 18–29

To a solution of 1.2 equivalents of LDA in THF (prepared as above) was added a solution of 3-trimethylsilyl-1-*tert*-butyldimethylsilyl-azetidin-2-one (**15**, **16**, **17**) in THF at −78°C. After stirring for 10 min, 1.5 equivalents of aldehyde was added to the golden yellow solution via syringe. The resulting mixture was stirred for 10–20 min and then quenched with saturated NH_4Cl, extracted twice with ether, washed with water, and dried over $MgSO_4$. Removal of solvent under reduced pressure gave a syrup, which was purified by flash chromatography. In all cases, the *Z*-isomers **18–23** were eluted before the *E*-isomers **24–29**.

From 664 mg of **15** and 50% excess propionaldehyde was obtained 203 mg (33%) of **18** and 181 mg (31%) of **24** as clear colorless oils. For **18**: ir (thin film): 1730; ^1H nmr δ: 5.52 (t, J = 8.4, 1H), 3.60 (s, 2H), 2.48 (quint, J = 8.5, 2H), 1.02 (t, J = 8.4, 3H), 0.92 (s, 9H), 0.20 (s, 6H); ms: 225.1 (M^+), 168 (base peak) (M^+ − 57). *Anal.* calcd. for $C_{12}H_{25}NOSi$: C 64.00, H 10.22, N 6.22; found: C 64.12, H 10.08, N 6.19. For **24**: ir (thin film): 1740; ^1H nmr δ: 6.11 (t, J = 7.5, 1H), 3.75 (s, 2H), 2.10 (quint, J = 7.5, 2H), 1.05 (t, J = 7.5, 3H), 0.95 (s, 9H), 0.24 (s, 6H); ms: 225.1 (M^+), 168 (base peak) (M^+ − 57). *Anal.* calcd. for $C_{12}H_{23}NOSi$: C 64.00, H 10.22, N 6.22; found: C 64.09, H 10.29, N 6.07.

From 164 mg of **15** and 50% excess hydrocinnamaldehyde was obtained 57.2 mg (35%) of **19** and 38.6 mg (23%) of **25**, both as clear colorless oils. For **19**: ir (CH_2Cl_2): 1720; ^1H nmr δ: 7.29–7.16 (m, 5H), 5.54 (t, J = 8.5, 1H), 3.59 (s, 2H), 2.84–2.75 (m, 4H), 0.93 (s, 9H), 0.22 (s, 6H); ms: 301 (M^+), 244 (89.2) (M^+ − 57). *Exact Mass* (hrms) calcd. for $C_{18}H_{27}NOSi$: 301.1860; found: 301.1870. For **25**: ir (CH_2Cl_2): 1730; ^1H nmr δ: 7.24–7.09 (m, 5H), 6.08 (t, J = 8.3, 1H), 3.44 (s, 2H), 2.71 (t, J = 8.4, 2H), 2.31 (q, J = 8.4, 2H), 0.87 (s, 9H), 0.16 (s, 6H); ms: 301 (M^+), 244 (base peak) (M^+ − 57). *Anal.* calcd. for $C_{18}H_{27}NOSi$: C 71.76, H 8.97, N 4.65; found: C 71.89, H 9.11, N 4.93.

From 547 mg of **16** and 50% excess propionaldehyde was obtained 180 mg (37%) of **20** and 145 mg (30%) of **26**, both as clear colorless oils. For **20**: ir (thin film): 1735; ^1H nmr δ: 5.53 (dt, J = 1.08, 7.70, 1H), 3.91 (dd, J = 2.39, 8.30, 1H), 2.48 (quint, J = 7.65, 2H), 1.80–1.77 (m, 1H), 1.60–1.53 (m, 1H), 1.03 (t, J = 7.52, 3H), 0.95 (s, 9H), 0.93 (t, J = 7.46, 3H), 0.24 (s, 3H), 0.19 (s, 3H); ms: 253 (M^+), 196.1 (base peak) (M^+ − 57). *Anal.* calcd. for $C_{14}H_{27}NOSi$: C 66.40, H 10.67, N 5.53; found; C 62.66, H 11.01, N 5.56. For **26**: ir (thin film): 1740; ^1H nmr δ: 6.03 (dt, J = 1.50, 7.66, 1H), 4.25 (b, 1H), 2.06 (quint, J = 7.56, 2H), 1.82–1.74 (m, 2H), 1.03 (t, J = 7.52, 3H), 0.948 (s, 9H), 0.90 (t, J = 7.37, 3H), 0.27 (s, 3H), 0.18 (s, 3H); ms: 253 (M^+), 196 (base peak) (M^+ − 57). *Exact Mass* (hrms) calcd. for $C_{14}H_{27}NOSi$: 253.1860; found: 253.1850.

From 214 mg of **16** and 50% excess hydrocinnamaldehyde was obtained 114 mg (46%) of **21** and 73 mg (29%) of **27**, both as clear colorless oils. For **21**: ir (thin film): 1730; ^1H nmr δ: 7.27 (m, 5H), 5.22 (t, J = 7.2, 1H), 3.84 (m, 1H), 2.81–2.75 (m, 4H), 1.75–1.70 (m, 1H), 1.45–1.40 (m, 1H), 0.94 (s, 9H), 0.869 (t, J = 7.4, 3H), 0.23 (s, 3H), 0.19 (s, 3H); ms: 329 (M^+), 272 (16) (M^+ − 57). *Anal.* calcd. for $C_{20}H_{31}NOSi$: C 72.95, H 9.42, N 4.26; found: C 72.25,

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H 9.56, N 4.35. For **27**: ir (thin film): 1740; ^{1}H nmr δ: 7.29–7.20 (m, 5H), 6.06 (t, J = 7.8, 1H), 4.02 (s, 1H), 2.76–2.69 (m, 2H), 2.37–2.33 (m, 2H), 0.93 (s, 9H), 0.811 (t, J = 7.41, 3H), 0.24 (s, 3H), 0.16 (s, 3H); ms: 329 (M^+), 272 (base peak) ($M^+ - 57$). *Exact Mass* (hrms) calcd. for $C_{16}H_{22}NOSi$: C 272.1469; found: 272.1492 ($M^+ - 57$).

From 340 mg of **17** and 50% excess propionaldehyde was obtained 45 mg (15%) of **22** and 43 mg (14%) of **28**, both as clear colorless oils. Eluting in the fastest fractions was 102 mg (30%) of **33**, which was recrystallized from methanol, mp 102°C. For **22**: ir (thin film): 1740; ^{1}H nmr δ: 7.43–7.27 (m, 5H), 5.52 (t, J = 9.3, 1H), 5.30 (s, 1H), 2.34 (quint, J = 9.0, 2H), 0.97 (s, 9H), 0.91 (t, J = 7.51, 3H), 0.30 (s, 3H), 0.025 (s, 3H); ms (CI): 334 ($M^+ + 1$), 224 (60) ($M^+ - 109$). *Anal.* calcd. for $C_{18}H_{27}NOSSi$: C 64.86, H 8.11, N 4.20; found: C 64.69, H 8.35, N 4.20. For **28**: ir (thin film): 1750; ^{1}H nmr δ: 7.43–7.38 (m, 2H), 7.29–7.27 (m, 3H), 5.98 (t, J = 8.0, 1H), 5.40 (s, 1H), 2.17 (quint, J = 8.03, 2H), 0.99 (t, J = 7.45, 3H), 0.96 (s, 9H), 0.30 (s, 3H), 0.25 (s, 3H); ms (CI): 334 ($M^+ + 1$), 224 (63) ($M^+ - 109$). *Exact Mass* (hrms) calcd. for $C_{12}H_{22}NOSi$: 224.1469; found: 224.1493 ($M^+ - 109$). For **33**: ir ($CHCl_3$): 3600, 1605, 1551; ^{1}H nmr δ: 9.0 (b, 1H), 7.45–7.36 (m, 5H), 6.77 (d, J = 15.25, 1H), 0.86 (s, 9H), 0.30 (s, 9H), 0.14 (s, 3H); ms (CI): 366 ($M^+ + 1$). *Exact Mass* (hrms) calcd. for $C_{12}H_{26}NOSi_2$: 356.1552; found: 256.1532 ($M^+ - 109$).

From 468 mg of **17** and 50% excess hydrocinnamaldehyde was obtained 81 mg (15%) of **23** and 61 mg (12%) of **27**, both as clear colorless oils; 127 mg of **33** (27%) was also obtained in the fastest fractions. For **23**: ir (thin film): 1740; ^{1}H nmr δ: 7.42–7.36 (m, 5H), 7.28–7.20 (m, 5H), 5.54 (t, J = 7.8, 1H), 5.24 (s, 1H), 2.83–2.73 (m, 4H), 0.96 (s, 9H), 0.29 (s, 3H), 0.245 (s, 3H); ms (CI): 410 ($M^+ + 1$), 300 (base peak) ($M^+ - 109$). *Exact Mass* (hrms) calcd. for $C_{18}H_{26}NOSi$: 300.1782; found: 300.1760 ($M^+ - 109$). For **27**: ir (thin film): 1750; ^{1}H nmr δ: 7.42–7.36 (m, 10H), 6.00 (t, J = 8.1, 1H), 4.98 (s, 1H), 2.80–2.45 (m, 4H), 0.93 (s, 9H), 0.26 (s, 3H), 0.22 (s, 3H); ms (CI): 410 ($M^+ + 1$), 300 (base peak) ($M^+ - 109$). *Exact Mass* (hrms) calcd. for $C_{18}H_{26}NOSi$: 300.1782; found: 300.1775 ($M^+ - 109$).

General procedure for MoOPH hydroxylations

To a solution of LDA (1.2 equivalents) in THF at −78°C was added a solution of 3-alkylidene-1-*tert*-butyldimethylsilylazetidin-2-one **10**, **18**, **19**, **20**, **21** in THF. After stirring for 10 min, 1.5 equivalents of MoOPH was added at once. The solutions immediately turned orange or blue. Following MoOPH addition, the acetone bath was removed and the solution stirred until clear (10–15 min). Once MoOPH dissolution was complete, the solution was quenched with 10% Na_2SO_3, extracted twice with ether, washed with 10% HCl, dried over $MgSO_4$, and the solvent removed under reduced pressure. Products were purified by flash chromatography.

10: From 100 mg of **9** was obtained 71 mg (67%) of **10** as a white solid, which was recrystallized from ethyl acetate, mp 145°C; ir (thin film): 3600, 1750; ^{1}H nmr δ: 7.33–7.17 (m, 5H), 7.24 (d, J_{AB} = 9.07, 2H), 6.78 (d, J_{AB} = 9.07, 2H), 5.59 (dd, J_{AB} = 17.34, J_{AX} = 11.10, 1H), 5.47 (dd, J_{AB} = 17.34, J_{BX} = 0.92, 1H), 5.18 (dd, J_{AX} = 11.10, J_{BX} = 0.92, 1H), 5.10 (s, 1H), 3.74 (s, 3H); ms: 295 (M^+). *Exact Mass* (hrms) calcd. for $C_{18}H_{17}NO_3$: 295.1207; found: 295.1244.

35: From 95 mg of **18** was obtained 41.2 mg (41%) of **35** as a clear colorless oil; ir (CH_2Cl_2): 3550, 1642; ^{1}H nmr δ: 5.96 (dq, J_q = 6.47, J_d = 15.50, 1H), 5.67 (dd, J = 1.74, 15.50, 1H), 3.33 (d, J_{AB} = 6.05, 1H), 3.28 (d, J_{AB} = 6.05, 1H), 1.73 (dd, J = 1.59, 6.47, 3H), 0.93 (s, 9H), 0.24 (s, 3H), 0.21 (s, 3H); ms (CI): 242 (base peak) ($M^+ + 1$). *Anal.* calcd. for $C_{12}H_{23}NO_2Si$: C 59.75, H 9.54, N 5.81; found: C 59.86, H 9.56, N 6.00.

36: From 161.5 mg of **19** was obtained 52 mg (31%) of **36** as a clear colorless oil; ir ($CHCl_3$): 3500, 1740; ^{1}H nmr δ: 7.29–7.14 (m, 5H), 6.12 (dt, J_d = 15.57, J_t = 6.75, 1H), 5.72 (dt, J_d = 15.54, J_t = 1.54, 1H), 3.41 (dd, J = 6.05, 2H), 3.34 (d, J_{AB} = 6.11, 1H), 3.30 (d, J_{AB} = 6.11, 1H), 2.78 (s, 1H), 0.91 (s, 9H), 0.24 (s, 3H), 0.21 (s, 3H); ms (CI): 318 ($M^+ + 1$). *Anal.* calcd. for $C_{18}H_{27}NO_2Si$: C 68.14, H 8.52, N 4.42; found: C 67.99, H 8.93, N 4.38.

37: From 159 mg of **20** was obtained 90 mg (53%) of **37** as a white solid, mp 99°C. Recrystallization from hexanes did not change the melting point; ir ($CHCl_3$): 3500, 1740; ^{1}H nmr δ: 5.95 (dq, J_d = 15.62, J_q = 6.53, 1H), 5.59 (dd, J = 1.65, 15.62, 1H), 3.45 (dd, J = 3.17, 11.45, 1H), 2.64 (s, 1H), 1.77 (dd, J = 1.60, 6.51, 3H), 1.7–1.6 (m, 1H), 1.5–1.4 (m, 1H), 0.94 (s, 9H), 0.88 (t, J = 7.35, 3H), 0.25 (s, 3H), 0.22 (s, 3H); ms: 269 (M^+), 212 (9.3) ($M^+ - 57$). *Anal.* calcd. for $C_{14}H_{27}NO_2Si$: C 62.45, H 10.04, N 5.20; found: C 62.65, H 10.22, N 5.20.

38: From 290 mg of **21** was obtained 100 mg (33%) of **38** as a white solid, which was recrystallized from hexane, mp 101°C; ir ($CHCl_3$): 3300, 1730; ^{1}H nmr δ: 7.30–7.21 (m, 5H), 6.11 (dt, J_d = 15.56, J_t = 6.62, 1H), 5.61 (dt, J_d = 15.61, J_t = 1.55, 1H), 3.48–3.42 (m, 3H), 2.60 (s, 1H), 1.7–1.6 (m, 1H), 1.4–1.3 (m, 1H), 0.92 (s, 9H), 0.86 (t, J = 7.41, 3H), 0.24 (s, 3H), 0.21 (s, 3H); ms: 345 (M^+), 288 (10) ($M^+ - 57$). *Anal.* calcd. for $C_{20}H_{31}NO_2Si$: C 69.56, H 8.98, N 4.06; found: C 69.30, H 8.98, N 3.92.

3-Ethyl-3-hydroxy-4-phenyl-1-(4-methoxyphenyl)-azetidin-2-one ***11***

Compound **10** (71 mg) in THF was stirred with 21 mg of 10% PtO_2 under an atmosphere of H_2 at atmospheric pressure for 1 h. The solution was then filtered through a pad of Celite and the solvent removed under reduced pressure to give 73 mg (100%) of **11** as a white solid melting at 130°C. Recrystallization from ethyl acetate did not change the melting point; ir (KBr): 3400, 1720; ^{1}H nmr δ: 7.33–7.23 (m, 5H), 7.21 (d, J_{AB} = 9.04, 2H), 6.77 (d, J_{AB} = 9.04, 2H), 4.99 (s, 1H), 3.73 (s, 3H), 1.57 (sextet, J = 7.45, 1H), 1.37 (sextet, J = 7.27, 1H), 0.84 (t, J = 7.45, 3H); ^{13}C nmr δ: 168.68 (s), 156.20 (s), 134.27 (s), 130.45 (s), 128.67 (d), 128.25 (d), 126.98 (d), 119.15 (d), 114.19 (d), 87.93 (s), 69.50 (d), 55.33 (q), 25.08 (t), 6.84 (q). *Exact Mass* (hrms) calcd. for $C_{18}H_{19}NO_3$: 297.1363; found: 297.1367.

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