Synthesis of Hydroxylated Pyrrolizidines Related to Alexine using Cycloaddition Reactions of Functionalized Cyclic Nitrones

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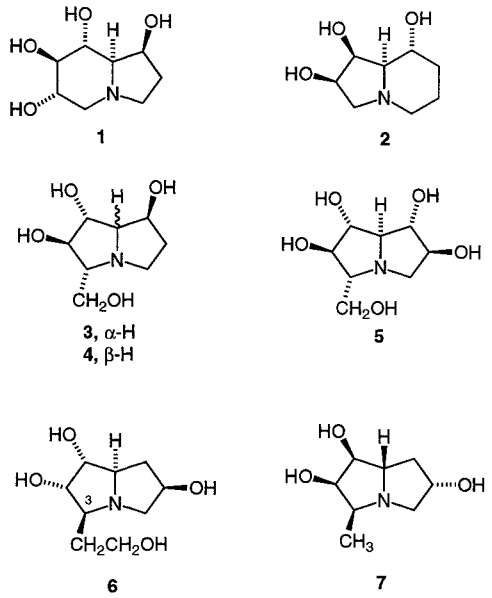
Received 11 September 1996

Abstract: Cycloaddition reactions of the functionalized Δ^1-pyrroline-*N*-oxides **10** and **19** have been used to prepare the hydroxylated pyrrolizidines **6** and **7** respectively, which are related to the natural products alexine and australine.

In recent years there has been much interest in the synthesis of polyhydroxylated indolizidines such as castanospermine (**1**) swainsonine (**2**), and their stereoisomers,[1] sustained by the potential of such compounds as medicinal agents as a consequence of their ability to inhibit glycosidases.[2] Additionally, polyhydroxylated pyrrolizidines such as australine (**3**), alexine (**4**) and various of their stereoisomers have been isolated,[3] and australine and two of its stereoisomers have demonstrated antiviral activity, including against HIV.[4] Further such structures continue to emerge, as illustrated by the recent report of the pentahydroxylated pyrrolizidine casuarine (**5**).[5]



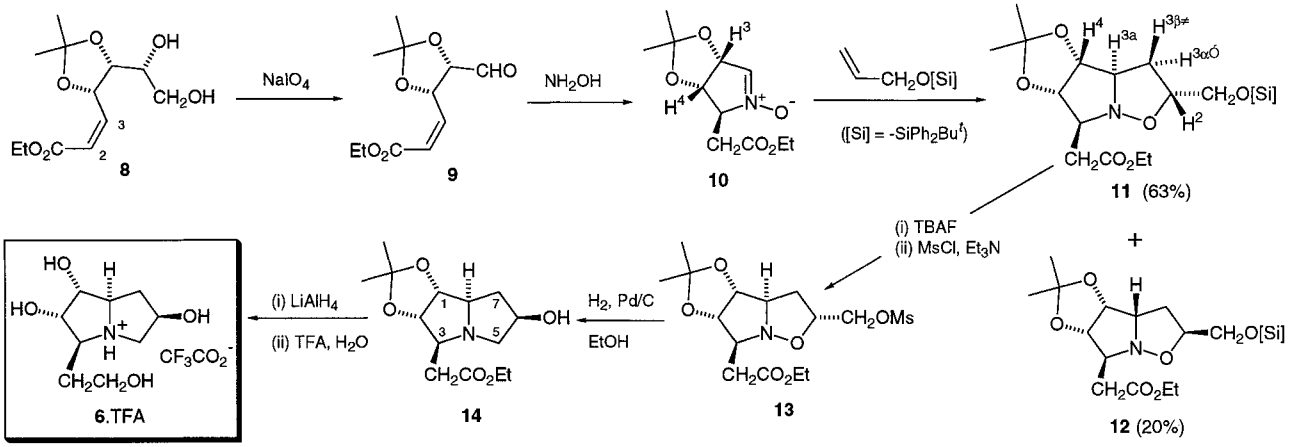
In this letter we illustrate the use of 1,3-dipolar cycloaddition reactions of oxygenated cyclic nitrones[6] to gain access to pyrrolizidines **6** and **7** having a carbon substituent at C-3, as is characteristic of the australine/alexine class of pyrrolizidine alkaloids.[7]

For the synthesis of **6** (Scheme 1), 2,3-*O*-isopropylidene-β-D-ribofuranose[8] was treated with carboethoxymethylene triphenylphosphorane (CH_2Cl_2, 18 h) to give the *cis*-enoate **8** ($J_{2,3}$ 11.5 Hz) which, without rigorous purification, underwent reaction with $NaIO_4$ in aqueous methanol to give the somewhat unstable aldehyde **9** (71% overall). When **9** was treated with hydroxylamine hydrochloride and NaOAc (H_2O-EtOH, r.t., 18 h), the nitrone **10**[9] was obtained (83%) as a single epimer. The stereochemistry of **10** was indicated by the small coupling (1.3 Hz) observed between H-4 and H-5 in the ^{1}H-nmr spectrum, and confirmed by the observation of strong n.O.e effects between H-3, H-4 and both protons of the CH_2 group of the sidechain.

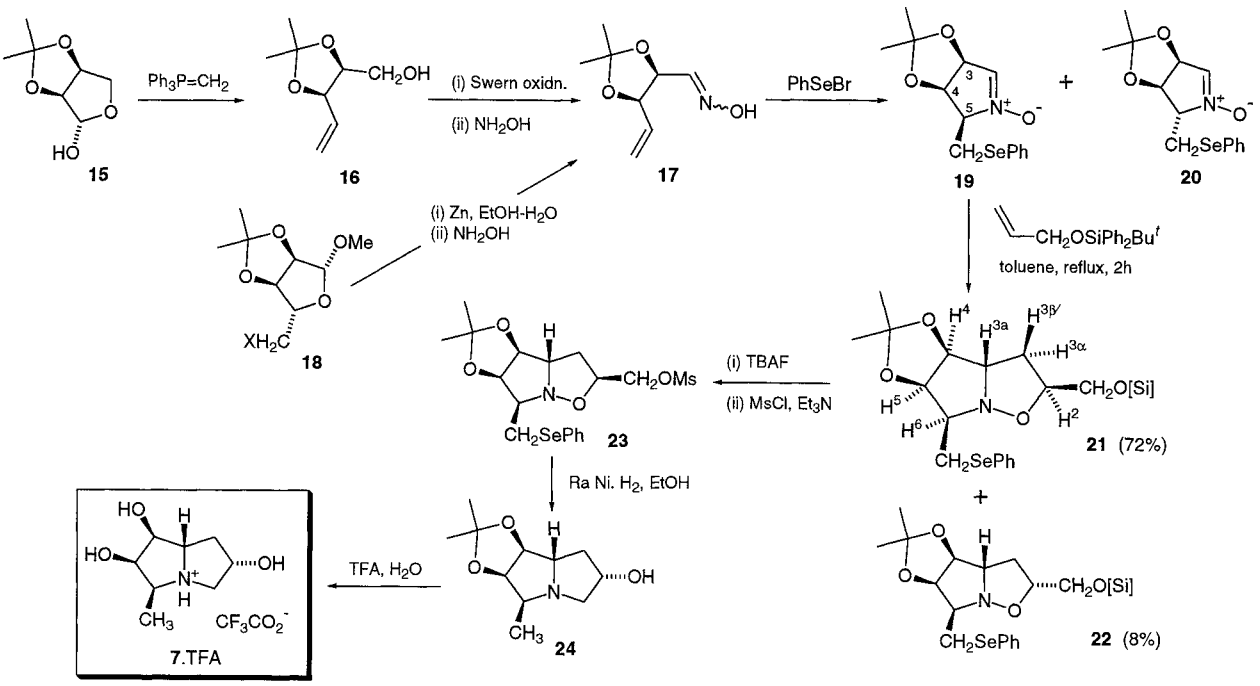
Cycloaddition of **10** and allyl *t*-butyldiphenylsilyl ether (toluene, reflux) led to the isolation of two cycloadducts in a combined yield of 83% and an isomer ratio of *ca.* 3:1. The major cycloadduct was assigned structure **11**[9] on the basis of nmr experiments; in particular, irradiation of the signal for 3α-H (δ 2.29) caused enhancements of the signals for 3a-H (δ 3.79) and both of the protons of the CH_2O[Si] unit, whilst irradiation of the signal for 3β-H (δ 2.40) caused enhancements of the signals for 2-H (δ 4.10) and 4-H (δ 4.48). In a similar way, the structure **12** could be assigned to the minor stereoisomer. Both isomers therefore arise by reaction via *exo*-transition states, as is well documented for cycloadditions of cyclic nitrones,[10] with the major isomer **11** arising from reaction on the more sterically-accessible face of the nitrone, *trans*- to the isopropylidenedioxy group.

Treatment of the major cycloadduct **11** with tetrabutylammonium fluoride (THF, r.t., 1h) gave the corresponding alcohol {m.p. 55-57 °C, $[\alpha]_D$-126° (*c* 1.45, $CHCl_3$)} in quantitative yield, and this was converted routinely to the mesylate **13** {m.p. 65-6 °C, $[\alpha]_D$ -95.3° (*c* 1.48, $CHCl_3$)}. Hydrogenolysis of the N-O bond was accompanied by cyclization to give the pyrrolizidine **14**[9] (83%). Reduction of the ester with $LiAlH_4$, followed by hydrolysis of the resultant diol with aqueous TFA then gave (69%) the tetraol **6**, isolated as its trifluoroacetate salt.[9]

The synthesis of the pyrrolizidine **7** is indicated in Scheme 2. Treatment of 2, 3-*O*-isopropylidene-L-erythrose (**15**) (prepared from L-arabinose without purification of intermediates[11]) with methylene



Scheme 1



Scheme 2

triphenylphosphorane gave the alkene **16**.[12] Oxidation of this [$(COCl)_2$, DMSO, CH_2Cl_2, -60 °C, then Et_3N] followed by direct trapping of the volatile aldehyde with hydroxylamine gave the oxime **17** (80%) as a mixture of isomers (*E*:*Z* , 5:2). Alternatively, **17** could be prepared[13] from the D-ribose derivatives **18** (X = Br or I), using Bernet-Vasella fragmentation,[14] followed by direct oximation, but in our hands this route proceeded in poorer overall yield and was less convenient than the route from L-arabinose; additionally, the use of arabinose as starting material permits access to the enantiomeric series from D-arabinose by the use of the same chemistry.

When oxime **17** was treated with phenyl selenenyl bromide in dichloromethane, followed by neutralization with $K_2C\,O_3$,[15] electrophile-induced cyclization occurred to give a moderate yield (45%) of two isomeric nitrones **19** and **20**, in a ratio of ~1:1.[16] Although **19** and **20** were readily separable by chromatography, the lack of stereoselectivity in the cyclization was disappointing; based on the precedent of related electrophilic cyclizations of 4-alkenyl alcohols with an oxygen substituent at the allylic position[17] we had anticipated a predominance of the all-*cis*-isomer **19**. The structures of **19** and **20**[18] were evident from nmr data ; ^{1}H-spectra showed $J_{4,5}$ = 6.0 Hz for **19**, whilst the equivalent compling was virtually zero in the spectrum of **20.** Additionally the signals for C-3, C-4, C-5 and the methylene carbon all appeared at higher field in **19** than in **20**, as would be expected on the basis of stereocompression.[19]

Cycloaddition of the all-*cis* nitrone **19** with allyl *t*-butyldiphenylsilyl ether gave as major product the isoxazolidine **21** (72%)[18] with lesser amounts (8%) of the epimer **22**.[20] The structure of **21** was clear from n.O.e experiments. In particular, irradiation of 5-H (δ 4.81) gave major enhancements of 4-H (δ 4.60) and 6-H (δ 3.05), confirming the all-*cis*- stereochemistry of the nitrone precursor, whilst irradiation of 2-H (δ 4.22) led to enhancement of 6-H as well as 3α-H (δ 1.83), a result which is in accordance only with the stereochemistry shown. Additional confirmatory n.O.e effects were observed between 3α-H, 2-H and 4-H. Isomer **21** is thus the product of reaction on the more accessible face of nitrone **19,** via an *exo*-transition state. It is interesting that significant amounts of **22,** formed via an *endo*-transition state, are also isolated, since the parent nitrone, Δ^1-pyrroline-*N*-oxide, gives exclusively the *exo*-adduct.[10b] However, modelling indicates that the fusion of the isopropylidenedioxy group onto the pyrroline ring leads to a flattening of the structure which makes non-bonding intractions in the *endo*- transition state less severe.

Desilylation of **21** occured quantitatively on treatment with tetrabutyl ammonium fluoride in THF, and the resultant alcohol was converted conventionally to the mesylate **23** {m.p. 109 °C $[\alpha]_D$ +125.2° (*c* 1.15, CH_2Cl_2)} in 92% yield. Since Raney nickel is known to be effective both for the hydrogenolysis of N-O bonds[21] and for reductive deselenation of phenylselenyl ethers,[22] it seemed likely that this reagent could transform isoxazolidine **23** into the selenium-free pyrrolizidine **24**. This proved to be the case, with **24** being obtained in ~65% yield, but only if the reaction was carried out in an atmosphere of hydrogen; use of a nitrogen atmosphere gave the product of reduction of just the selenoether. Treatment of **24** with aqueous trifluoroacetic acid led to the deprotected pyrrolizidine **7**[18] isolated as its trifluoroacetate salt.

Acknowledgements - We thank EPSRC for financial support (studentship to KPM) and for access to facilities for mass spectrometry at the University of Wales, Swansea.

References and Notes

(1) Synthesis of castanospermine and isomers: Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045 and refs. therein; synthesis of hydroxylated indolizidines: Herczegh, P.; Kovács, I.; Sztaricskai, F. in *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products;* Lucacs, G., Ed.; Springer Verlag: Berlin, 1993; p. 751.

(2) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2,* 199.

(3) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Girdhar, A.; Ramsden, N. G.; Peach, J. M.; Hegarty, M. P.; Schofield, A. M. *Phytochemistry* **1990**, *29*, 111, and refs. therein.

(4) Taylor, D. L.; Nash, R.; Fellows, L. E.; Kang, M.S.; Syms, A. S. *Antiviral Chem. Chemother.* **1992**, *3*, 273.

(5) Nash, R. J.; Thomas, P. I.; Waigh, R. D.; Fleet, G. W. J.; Wormald, M. R.; Lilley, P. M. de Q.; Watkin, D. J. *Tetrahedron Lett.* **1994**, *35,* 7849.

(6) For earlier work on the use of cycloadditions of such nitrones to prepare hydroxylated pyrrolizidines and indolizidines see: McCaig, A. E.; Wightman, R. H. *Tetrahedron Lett.* **1993**, *34*, 3939; Herczegh, P.; Kovács, I.; Szilágyi, L.; Varga, T.; Dinya, Z.; Sztaricskai, F. *Tetrahedron Lett.* **1993**, *34*, 1211; Cordero,

F. M.; Cicchi, S.; Goti, A., Brandi, A. *Tetrahedron Lett.* **1994,** *35*, 949; Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.,* **1995**, *60,* 4743; Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60,* 6806; Goti, A.; Cardona, F.; Brandi, A. *Synlett* **1996**, 761.

(7) For previous synthetic work on australine and its stereoisomers, see: Fleet, G. W. J.; Haraldsson, M.; Nash, R. J.; Fellows, L. E. *Tetrahedron Lett.* **1988**, *29,* 5441; Pearson, W. H.; Hines, J. V. *Tetrahedron Lett.* **1991**, *32*, 5513; Choi, S.; Bruce, I.; Fairbanks, A. J.; Fleet, G. W. J.; Jones, A. H.; Nash, R. J.; Fellows, L. E. *Tetrahedron Lett.* **1991**, *32*, 5517; Ikota, N, *Tetrahedron Lett.* **1992**, *33*, 2553.

(8) Hughes, N. A.; Speakman, P. R. H. *Carbohydr. Res.* **1965,** *1*, 171.

(9) Selected data for compounds in Scheme 1: **10**, syrup, $[\alpha]_D$ -14.4° (*c* 1.04, $CHCl_3$); ν_{max} (film) 1732, 1579 and 1458 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.20 (3H, t, ester), 1.32 and 1.41 (each 3H, s, C*Me*$_2$), 2.92 (1H, dd, *J* 17.6 and 4.2 Hz, CH_2[a]), 3.05 (1H, dd, *J* 17.6 and 6.1 Hz, CH_2[b]), 4.07 (2H, q, ester), 4.18 (1H, m, 5-H), 4.80 (1H, dd, $J_{4,3}$ 6.5 Hz, $J_{4,5}$ 1.3 Hz, 4-H), 5.30 (1H, dt, *J* 6.5, 1.5 and 1.5 Hz, 3-H), 6.87 (1H, br. s, 2-H).
11, syrup, $[\alpha]_D$ -49.5° (*c* 1.03, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.02 (9H, s, *t*-Bu), 1.21 (3H, t, ester), 1.31 and 1.50 (each 3H, s, C*Me*$_2$), 2.29 (1H, dt, *J* 12.8, 7.0 and 7.0 Hz, 3_α-H), 2.40 (1H, ddd, *J* 13.0, 7.5 and1.4 Hz, 3_β-H), 2.70 (1H, dd, *J* 15.7, 6.5 Hz, *CH*$_2$CO$_2$Et), 2.88 (1H, dd, *J* 15.7, 7.9 Hz, *CH*$_2$CO$_2$Et), 3.50 (1H, dd, *J* 10.4, 5.7 Hz, *CH*$_2$OSi), 3.66 (1H, q, J~7.4 Hz, 6-H), 3.74 (1H, dd, *J* 10.4, 6.5 Hz, *CH*$_2$OSi), 3.79 (1H, m, 3a-H), 4.10 (1H, m, 2-H), 4.13 (2H, q, ester), 4.48 (1H, dd, $J_{4,5}$ 6.6, $J_{4,3a}$ 3.3 Hz, 4-H), 4.69 (1H, t, *J* ~7Hz, 5-H), 7.35-7.45 (6H, m, Ar), 7.61-7.65 (4H, m, Ar) (assignments supported by COSY spectrum).
14: oil, $[\alpha]_D$ -24.4° (*c* 2.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.25 (3H, t, ester), 1.30 and 1.50 (each 3H, s, C*Me*$_2$), 1.70 (1H, dt, *J* 13.4, 5.2 and 5.2 Hz, 7_α-H), 2.44 (1H, dt, *J* 13.4, 7.6 and 7.6 Hz, 7_β-H), 2.57 (1H, dd, *J* 9.8 and 5.0 Hz, 5-H), 2.61 (1H, dd, *J* 15.0 and 9.0 Hz, CH_2CO_2Et), 2.69 (1H, dd, *J* 15.0 and 6.0 Hz, *CH*$_2$CO$_2$Et), 3.37 (2H, m, 3-H, 7a-H), 4.17 (2H, q, ester), 4.40 (1H, dq, *J* 7.2 and 5.2(x3), 6-H), 4.55 (2H, m, 1-H, 2-H); δ_C ($CDCl_3$) 14.0 (OCH$_2$*Me*), 25.3 and 27.4 (C*Me*$_2$), 36.0 (CH_2), 38.3 (CH_2), 55.5 (C-5), 60.7 (O*CH*$_2$Me), 64.1, 69.1, 72.2, 84.9 and 86.1 (each CH), 114.0 (*C*Me$_2$), 171.2 (C=O).
6. TFA: m.p. 116-119 °C, $[\alpha]_D$ -48.6° (*c* 1.38, H_2O); δ_H (400 MHz, D_2O), 1.90 (1H, dt, *J* 14.0, 7.0 and 7.0 Hz, 7-H), 2.10 (2H, m), 2.61 (1H, ddd, *J* 14.0, 8.8 and 5.8 Hz, 7'-H), 3.20 (1H, dd, *J* 12.2 and 6.4 Hz, 5-H), 3.60 (1H, dd, *J* 12.2 and 5.3 Hz, 5'-H), 3.80 (3H, m, C*H*$_2$OH, 7a-H), 4.18 (1H, t, *J* 8.2 Hz, 3-H), 4.30 (1H, d, *J* 4.6 Hz, 2-H), 4.44 (1H, dd, *J* 8.0 and 4.6 Hz, 1-H), 4:51 (1H, quintet, *J*~6 Hz, 6-H); δ_C ($CDCl_3$) 29.3 (C-7), 36.4 (*C*H$_2$CH$_2$OH), 54.1 (C-5), 59.2 (CH$_2$OH), 62.7 and 69.3 (C-3, C-7a), 72.1 72.7 and 73.3 (C-1, C-2, C-6).

(10) e.g. Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396; Tufariello, J. J.; Puglis, J. M. *Tetrahedron Lett.* **1986**, *27*, 1265.

(11) Thompson, D. K.; Hubert, C. N.; Wightman, R.H. *Tetrahedron*, **1993**, *49*, 3827.

(12) Gypser, A.; Flasche, M.; Scharf, H.-D. *Liebigs Ann. Chem.* **1994**, 775.

(13) Gallos, J. K.; Goga, E. G.; Koumbis, A. E. *J. Chem. Soc., Perkin Trans 1* **1994**, 613.

(14) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990, 2400 and 2411.

(15) Grigg, R.; Hadjisoteriou, M.; Kennewell, P.; Markandu, J. *J. Chem. Soc., Chem. Commun.* **1992**, 1537; see also ref. 16 for later observations concerning the mechanism of such cyclizations.

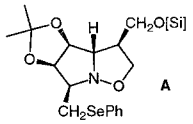
(16) Cyclizations using iodine (Grigg, R.; Hadjisoteriou, M.; Kennewell, P.; Markandu, J.; Thornton-Pett, M. *J. Chem. Soc., Chem. Commun.* **1993**, 1340) gave two iodomethyl nitrones analogous to **19** and **20** (ratio 3:5), but in poorer combined yield.

(17) Chamberlin, A. R.; Mulholland, R. L., Jr.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672 and refs therein; see in particular: Nicotra, F.; Panza, L.; Ronchetti, F.; Toma, L. *Tetrahedron Lett.* **1984**, *25*, 5937; Freeman, F.; Robarge, K.D. *Carbohydr. Res.* **1985**, *137*, 89.

(18) Selected data for compounds in Scheme 2: **19:** $[\alpha]_D$ +120° (*c* 0.65, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 1.34 and 1.41 (each 3H, s, C*Me*$_2$), 3.15 (1H, dd, *J* 12.5 and 11.4 Hz, CH_2), 3.70 (1H, dd, *J* 12.5 and 3.8 Hz, CH_2), 4.12 (1H, m, 5-H), 4.96(1H, t, *J* 6.0 Hz, 4-H), 5.19 (1H, dd, *J* 6.1 and 1.7 Hz, 3-H), 6.87(1H, d, *J* 1.9 Hz, 2-H), 7.15-7.3 (3H, m), 7.5-7.6 (2H, m); δ_C (50 MHz, $CHCl_3$) 21.5 (CH_2), 25.8 and 27.0 (C*Me*$_2$), 74.7, 75.1 and 77.0 (C-3, C-4, C-5), 112.1 (*C*Me$_2$) 129.2 (C-2).
20: $[\alpha]_D$ -44.3° (*c* 1.45, $CHCl_3$); δ_H (200 MHz, $CHCl_3$) 1.32 and 1.43 (each 3H, s, C*Me*$_2$), 3.33 (1H, dd, *J* 13.5 and 6.7 Hz, CH_2), 3.48 (1H, dd, *J* 13.5 and 3.6 Hz, CH_2), 4.35 (1H, m, 5-H), 4.65 (1H, d, $J_{4,3}$ 6.4 Hz, 4-H), 5.30 (1H, dd, *J* 6.4 and 1.6 Hz, 3-H), 6.90 (1H, d, *J* 1.2 Hz, 2-H), 7.15-7.25 (3H, m), 7.50-7.65 (2H, m); δ_C (50 MHz, $CDCl_3$) 25.5 and 27.0 (C*Me*$_2$), 27.1 (CH_2), 78.2, 78.4 and 79.0 (C-3, C-4, C-5), 111.9 (*C*Me$_2$), 129.3 (C-2).
21: $[\alpha]_D$ +96.8° (*c* 3.6, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 1.05 (9H, s, CMe$_3$), 1.30 and 1.50 (each 3H, s, C*Me*$_2$), 1.83 (1H, dt, *J* 12.8, 9.5 and 9.5 Hz, 3_α-H), 2.35 (1H, ddd, J_{gem} 12.8, $J_{3\beta,3a}$ 8.9, $J_{3\beta,2}$ 4.3 Hz, 3_β-H), 3.05 (1H, dt, *J* 9.5, 5.0 and 5.0 Hz, 6-H), 3.25-3.35 (2H, m, CH_2SePh), 3.62 (2H, d, *J* 4.5 Hz, CH_2OSi), 3.78 (1H, t, *J* 9.3 Hz, 3a-H), 4.22 (1H, dq, $J_{2,3\alpha}$ 9.0, *J* 4.5 Hz(x3), 2-H), 4.60 (1H, d, *J* $_{4,5}$ 6.5 Hz, $J_{4,3a}$~0, 4-H), 4.81 (1H, dd, *J* 6.5 and 5.0 Hz, 5-H), 7.15-7.70 (15H, m, Ar).
24: m.p. 124 °C, $[\alpha]_D$ ~0; δ_H (200 MHz, $CDCl_3$) 1.14 (3H, d, *J* 6.6 Hz, Me), 1.28 and 1.49 (each 3H. s, C*Me*$_2$), 1.50 (1H, m, 7-H), 2.21 (1H, dt, *J* 13.0, 7.5 and 7.5 Hz, 7'-H), 2.78 (1H, dd, *J* 13.1 and 2.5 Hz, 5-H), 3.05 (1H, dd, *J* 13.1 and 6.0 Hz, 5'-H), 3.2 (1H, br s, OH), 3.25 (1H, dq, *J* 6.5 (x3) and 4.2 Hz, 3-H), 3.42 (1H, br t, $J_{7a,7}$ ~ $J_{7a,7'}$ ~ 8 Hz, $J_{7a,1}$ ~ 0, 7a-H), 4.45 (1H, m, 6-H), 4.57 (1H, d, $J_{1,2}$ 6.6 Hz, 1-H), 4.62 (1H, dd, *J* 6.2 and 4.2, 2-H).
7 .TFA: m.p. 134-139 °C, $[\alpha]_D$ -3.3° (*c* 1.0, H_2O); δ_H (200 MHz, D_2O), 1.40 (3H, d, *J* 6.8 Hz, CH_3), 2.20 (1H, dd, J_{gem} 13.9, $J_{7,7a}$ 1.0, $J_{7,6}$~0, 7-H), 2.32 (1H, ddd, J_{gem} 14.4, $J_{7',7a}$ 9.2, $J_{7',6}$ 4.4 Hz, 7'-H), 3.38 (2H, m, 5-H_2), 3.89 (1H, dq, *J* 6.8 and 2.3 Hz, 3-H), 4.08 (1H, dt, *J* 9.0, 9.0 and 2.5 Hz, 7a-H), 4.17 (1H, dd, $J_{1,7a}$ 8.8, $J_{1,2}$ 3.7 Hz, 1-H), 4.68 (1H, dt, *J* 4.4, 4.4 and 2.1 Hz, 6-H); δ_C (50 MHz, D_2O) 9.7 (CH_3), 35.4 (C-7), 57.2 (C-5), 67.3 and 68.0 (C-3, C-7a), 71.5, 73.2 and 76.2 (C-1, C-2, C-6).

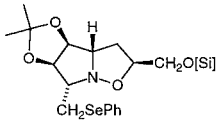
(19) e.g. Ohrui, H.; Jones, G. H.; Moffatt, J. G.; Maddox, M. L.; Christensen, A. T.; Byram, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 4602.

(20) Additionally, very small amounts (~1%) of a third cycloadduct were isolated to which the regioisomeric structure **A** is assigned by nmr.

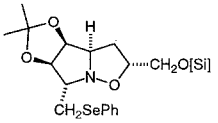


A

Cycloaddition of the *cis-trans* -nitrone **20** with allyl TBDPS ether gave two cycloadducts **B** and **C** (68% total yield), in a ratio of 4:3.



B



C

(21) e.g. Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024.

(22) Clive, D. L. J.; Chittattu, G. J.; Farina, V.; Kiel, W. A.; Menchen, S. M.; Russell, C. G.; Singh, A.; Wong, C. K.; Curtis, N. J. *J. Am. Chem. Soc.* **1980**, *102*, 4438.