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Trimethylsilyltriflate-Promoted Addition of 2-Trimethylsilyloxyfuran to a Chiral Cyclic Nitrone; a Short Synthesis of [1S(1α,2β,7β,8α,8aα)]-1,2-Di(*t*-butyldiphenylsilyloxy)-indolizidine-7,8-diol

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Abstract—The trimethylsilyl triflate promoted addition of 2-trimethylsilyloxyfuran to (3***S***,4***S***)-3,4-dihydro-3,4-di(***t***-butyldiphenylsilyloxy)-2H-pyrrole 1-oxide, derived from (***R***,***R***)-tartaric acid, displays complete facial selectivity, affording two diastereomeric butenolides in excellent overall yield. The major adduct undergoes silica-gel induced ring-closure to give in almost quantitative yield [4***S***(4**α**,5**β**,5a**β**,5-b**α**,8a**α**)]-hexahydro-4,5-di(***t***-butyldiphenylsilyloxy)-pyrrolo [1,2-***b***]furo[2,3***d***] isoxazol-7(3H)one; reduction with DIBAH followed by hydrogenolysis on $Pd(OH)_2$/C affords the partially protected 1,2,7,8-indolizidinetetrol.

Glycosidases and glycosyltransferases are widespread enzymes present in almost all organisms. They are essential for the processing of oligo- and polysaccharides and complex carbohydrates such as glycolipids and glycoproteins.[1] The inhibition of this family of hydrolases represents a powerful solution on the one hand to control obesity, diabetes and other metabolic disorders,[2] and on the other hand to block infection, inflammation and metastasis by preventing the biogenesis of membrane glycoproteins in fungi, bacteria and viruses.[3] A number of polyhydroxylated piperidines, pyrrolidines, indolizidines and pyrrolizidines, isolated from natural sources, are powerful and specific inhibitors of α- and β-glycosidases, and an even larger number of isomers and congeners have been synthesised and assayed for biological activity. A few of them display outstanding inhibition levels.[4] Among polyhydroxylated indolizidine alkaloids, besides naturally occurring lentiginosine, swainsonine and castanospermine (Fig. 1), a number of stereoisomers and analogues have been synthesised and tested in order to get information on structure–activity relationships.[5] For example, among 1,2,7,8-indolizidinetetrols, the stereoisomers **1a**,[6] **1b**[7] and **1c**[7] have been synthesised and tested for biological activity.

Here we propose a route to the skeleton of [1*S*(1α,2β,7β,8α,8aα)]-1,2,7,8-indolizidinetetrol (**1d**) and of *ent*-**1d** by applying to a chiral cyclic five-membered ring nitrone deriving from tartaric acid, an efficient protocol previously developed by us for the synthesis of 2-substituted 3,4-piperidinediols starting from aldonitrones (Scheme 1).[8]

The key reaction is the trimethylsilyl triflate (TMSOTf)-catalysed condensation of 2-trimethylsilyloxyfuran with an aldonitrone **2** to give an intermediate butenolide **3**, which, in the presence of fluoride, undergoes cyclisation to **4**.[9] These bicyclic compounds are successfully transformed into piperidines **6** in a two-reductive step sequence involving DIBAH reduction to lactol **5** and, finally, hydrogenolysis to the target piperidine.[8]

Five-membered cyclic nitrones derived from tartaric acid[10] have been successfully manipulated to indolizidines by Brandi[11] and Wightman[12] exploiting 1,3-dipolar cycloaddition reactions. The results obtained by applying our preceding protocol to nitrone **2a** are summarised in Scheme 2.

Condensation of **2a** and 2-trimethylsilyloxyfuran in the presence of TMSOTf (10%) in dichloromethane at −20°C displayed complete facial selectivity and afforded butenolides **3a** and **3b** possessing the 2′*S*,5*S* and 2′*S*,5*R* absolute stereochemistry, respectively, in 82/18 ratio and in 71% overall yield. Bulky *t*-butyldiphenylsilyl protecting group (TBDPS) in **2a** proved to be an optimum choice forcing the nucleophilic attack of 2-trimethylsilyloxyfuran only on

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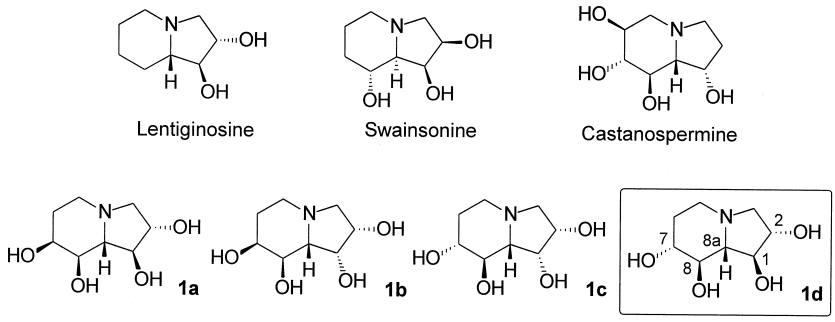
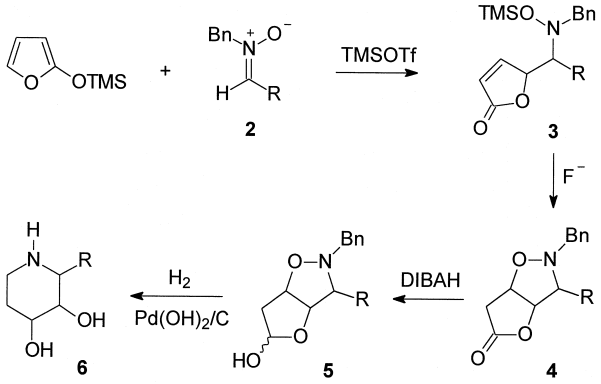


Figure 1.



Scheme 1.

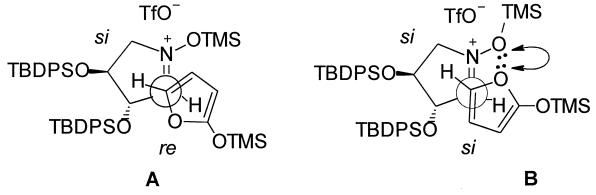
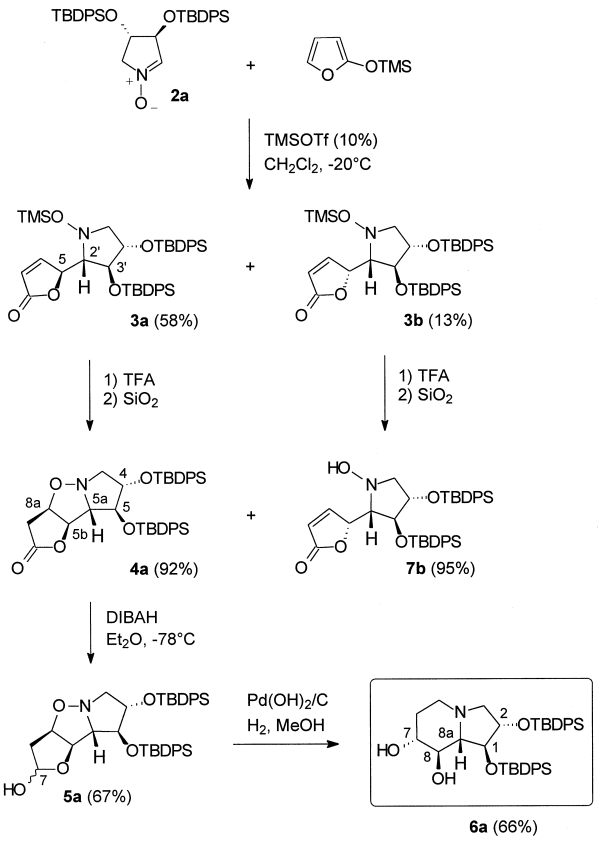


Figure 2.



Scheme 2.

the less encumbered *si* face of the nitrone **2a**. Formation of the 2′*S*,5*S* relationship is favoured (d.e. 64%) according to synclinal approach **A** in Fig. 2, which involves the *re* face of 2-trimethylsilyloxyfuran. Anti approach **B** is disfavoured both by unfavourable dipolar interactions and by oxygen atoms lone pairs repulsion. Butenolides **3a** and **3b** were easily separated by silica-gel flash-chromatography and treated with diluted trifluoroacetic acid (TFA) in order to remove the trimethylsilyl group chemoselectively. Silica-gel chromatographic purification of the crude residue led, in one case, to complete cyclisation to **4a**, as we observed previously on simple aldonitrones,[9a] in the other case to the almost quantitative recovery of **7b**. The absence of the corresponding tricyclic product deriving from **3b** was probably due to steric compression in the *cis–syn–cis* triquinane-type nucleus. Such a dramatically different behaviour allowed us to develop a shorter and more efficient procedure for the synthesis of **4a**; after condensation of 2-trimethylsilyloxyfuran with **2a**, the crude reaction mixture was directly treated with dilute aqueous TFA, then, after water extraction and solvent concentration, the residue was eluted through a silica-gel column affording **4a** (56%) and **7b** (12%).

Transformation of the hexahydropyrrolo[1,2-*b*]furo[2,3-*d*]-isoxazol-7(3H)one ring system of **4a** into an indolizidine was easily accomplished via DIBAH reduction of **4a** to **5a** followed by hydrogenolysis of **5a** in the presence of $Pd(OH)_2$. The N–O bond cleavage was followed by spontaneous intramolecular reductive amination to [1*S*(1α,2β,7β,8α,8aα)]-1,2-di(*t*-butyldiphenylsilyloxy)-indolizidine-7,8-diol (**6a**).

Regioselectively protected **6a** offers interesting opportunities since it allows the hydroxyl groups to be orthogonally manipulated to generate further stereoisomers.

Experimental

General

^{1}H NMR and ^{13}C NMR spectra in deuterated solvents were recorded at 300 and 75 MHz, respectively, using a Varian Gemini 300 spectrometer. Chemical shifts are reported in ppm relative to internal standard Me_4Si. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Water content of anhydrous solvents used was measured with a Karl-Fisher titrator Mettler DL18. Reactions were performed in oven-dried glassware under argon. Hydrogenations were performed at 45 psi on a Parr apparatus. 2-Trimethylsilyloxyfuran and moist 20% $Pd(OH)_2$ on carbon (Degussa type E101) were purchased from Aldrich. Nitrone **2a** was synthesised from (*R*,*R*)-tartaric acid diethyl ester according to the procedure reported by Brandi et al.[11] Melting points are uncorrected.

5-[1′-Trimethylsilyloxy-3′,4′-di(*t*-butyldiphenylsilyloxy)-2′-pyrrolidinyl]-2(5H)-furanones (3a, 3b). 2-Trimethylsilyloxyfuran (0.19 mL, 1.1 mmol) was added to a solution of **2a** (0.6 g, 1 mmol) in CH_2Cl_2 (2 mL) and the solution was cooled to −20°C. TMSOTf (0.018 mL, 0.1 mmol) was added and the reaction mixture was stirred at −20°C for 1.5 h. The reaction was quenched with aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3×5 mL). Silica gel was directly added to the combined organic layers and the solvent was evaporated at reduced pressure. The solid residue was loaded on a silica gel column. Elution with cyclohexane/ethyl acetate (95/5) afforded 0.43 g (58%) of **3a** as a white solid and 0.1 g (13%) of **3b** as an oil.

[2′*S*-[2′α,3′α,4′β(5*R)]]-3a:** m.p. 98–100°C; $[\alpha]_D^{22}$=−11.0 (*c*=0.21 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 9H, $SiMe_3$), 0.93 (s, 9H, Si*t*Bu), 0.97 (s, 9H, Si*t*Bu), 2.95 (dd, *J*=4.2/11.0 Hz, 1H, H-5′), 3.01 (br d, *J*=11.0 Hz, 1H, H-5′), 3.19 (br dd, *J*≈1.5/6.0 Hz, 1H, H-2′), 4.20–4.30 (m, 2H, H-3′+H-4′), 4.99 (dt, *J*=2.0/6.0 Hz, 1H, H-5), 5.87 (dd, *J*=2.0/5.5 Hz, 1H, H-3), 7.20–7.62 (m, 21H, ArH+H-4); ^{13}C NMR ($CDCl_3$) δ −0.3 ($SiCH_3$), 19.0 (Si*C*Me_3), 19.1 (Si*C*Me_3), 26.7 (SiC*Me*$_3$), 26.8 (SiC*Me*$_3$), 64.8 (C-5′), 78.4, 78.9, 79.5, 81.9 (C-5, C-2′, C-3′, C-4′), 121.7 (C-3), 127.6, 127.7, 128.0, 129.6, 129.7, 129.8, 129.9, 132.8 (Cquat), 133.0 (Cquat), 133.1 (Cquat), 133.6 (Cquat), 135.7, 135.8, 154.7 (C-4), 172.6 (C=O). Anal. Calcd. for $C_{43}H_{55}NO_5Si_3$: C, 68.85; H, 7.39; N, 1.87. Found: C, 68.53; H, 7.42; N, 1.85.

[2′*S*-[2′α,3′α,4′β(5*S)]]-3b:** $[\alpha]_D^{22}$=+2.0 (*c*=0.11 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.13 (s, 9H, $SiMe_3$), 0.87 (s, 9H, Si*t*Bu), 0.97 (s, 9H, Si*t*Bu), 2.99–3.03 (m, 2H, H-5′), 3.58–3.64 (m, 1H, H-2′), 3.80–3.97 (m, 1H, CHOSi), 4.02–4.08 (m, 1H, CHOSi), 5.06 (dt, *J*=2.0/5.1 Hz, 1H, H-5), 5.92 (dd, *J*=2.0/7.8 Hz, 1H, H-3), 7.10–7.70 (m, 21H, ArH+H-4); ^{13}C NMR ($CDCl_3$) δ −0.17 ($SiCH_3$), 19.0 (Si*C*Me_3), 19.1 (Si*C*Me_3), 26.8 (SiC*Me*$_3$), 63.7 (C-5′), 77.6, 77.9, 78.1, 82.1 (C-5, C-2′, C-3′, C-4′), 122.0 (C-3), 127.7, 127.9, 129.6, 129.8, 129.9, 132.1, 132.2, 133.2, 133.9, 135.5, 135.7, 135.9, 155.5 (C-4), 172.5 (C=O). Anal. Calcd. for $C_{43}H_{55}NO_5Si_3$: C, 68.85; H, 7.39; N, 1.87. Found: C, 68.66; H, 7.44; N, 1.83.

[4*S*(4α,5β,5aβ,5bα,8aα)]-Hexahydro-4,5-di(*t*-butyldiphenylsilyloxy)-pyrrolo[1,2-*b*]furo[2,3-*d*] isoxazol-7(3H)one (4a). 0.65 M Trifluoroacetic acid in H_2O (0.23 mL, 0.15 mmol) was added to a solution of **3a** (0.18 g, 0.23 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature for 45 min, then quenched with aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried (Na_2SO_4) and solvent was evaporated to dryness. Chromatography of the residue on silica gel using cyclohexane/ethyl acetate (95/5) yielded 0.144 g (92%) of pure **4a**: $[\alpha]_D^{22}$=+46.0 (*c*=0.20 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 9H, Si*t*Bu), 0.96 (s, 9H, Si*t*Bu), 2.58 (dd, *J*=4.8/18.6 Hz, 1H, H-8), 2.66 (br dd, *J*≈0.9/18.6 Hz, 1H, H-8), 3.11 (br dd, *J*≈0.6/14.7 Hz, 1H, H-3), 3.66 (dd, *J*=4.2/14.7 Hz, 1H, H-3), 3.86 (br s, 1H, H-5a), 4.22–4.28 (m, 2H, H-4+H-5), 4.77 (br dd, *J*≈1.6/4.5 Hz, 1H, H-5b), 4.92 (m, 1H, H-8a; upon irradiation of H-8 the signal collapses into a doublet with *J*=4.5 Hz), 7.22–7.58 (m, 20H, ArH); ^{13}C NMR ($CDCl_3$) δ14.2 (C-8), 19.1 (Si*C*Me_3), 26.8 (SiC*Me*$_3$), 27.0 (SiC*Me*$_3$), 34.0 (C-3), 63.9 (C-5a), 78.2, 78.3, 79.1, 81.3, (C-4, C-5, C-5b, C-8a), 127.8, 127.9, 128.0, 130.0 (Cquat), 130.2 (Cquat), 131.9 (Cquat), 132.3 (Cquat), 135.5, 135.6, 173.5 (C=O). Anal. Calcd. for $C_{40}H_{47}NO_5Si_2$: C, 70.86; H, 6.99; N, 2.07. Found: C, 70.95; H, 6.91; N, 2.16.

H-5a/H-5b *trans* and a H-5a/H-5 *trans* stereorelationships were assigned on the basis of n.O.e. measurements. Upon irradiation of H-5a, similar enhancements for both H-5b (3.0%) and H-5 (4.6%) were observed; moreover, irradiation of H-5b caused a strong enhancement of H-5 (10.5%) and a smaller response of H-5a (4.7%).

[2′,*S*-[2′α,3′α,4′β(5*S)]]-5-[1′-Hydroxy-3′,4′-di(*t*-butyldiphenylsilyloxy)-2′-pyrrolidinyl]-2(5H)-furanone (7b).** TFA treatment of **3b** followed by silica gel chromatography brought about the chemoselective deprotection of the trimethylsilyl group affording **7b** in almost quantitative yield. $[\alpha]_D^{22}$=+21.9 (*c*=0.62 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 9H, Si*t*Bu), 0.97 (s, 9H, Si*t*Bu), 3.12 (dd, *J*=3.6/10.5 Hz, 1H, H-5′), 3.16-3.26 (m, 2H, H-5′+H-2′), 3.98–4.05 (m, 1H, H-4′), 4.20 (dd, *J*=1.5/3.0 Hz, 1H, H-3′), 4.83 (ddd, *J*=1.5/2.1/6.6 Hz, 1H, H-5), 5.86 (dd, *J*=2.1/5.7 Hz, 1H, H-3), 6.81 (dd, *J*=1.5/5.7 Hz, 1H, H-4), 7.20–7.70 (m, 20H, ArH); ^{13}C NMR ($CDCl_3$) δ 19.0 (Si*C*Me_3), 19.1 (Si*C*Me_3), 26.8 (SiC*Me*$_3$), 62.8 (C-5′), 77.8, 78.4, 78.8, 83.1 (C-5, C-2′, C-3′, C-4′), 121.8 (C-3), 127.6, 127.7, 127.8, 127.9, 129.8, 129.9, 130.0, 132.6 (Cquat), 132.7 (Cquat), 132.9 (Cquat), 133.4 (Cquat), 135.58, 135.63, 135.9, 154.2 (C-4), 172.7 (C=O). Anal. Calcd. for $C_{40}H_{47}NO_5Si_2$: C, 70.86; H, 6.99; N, 2.07. Found: C, 70.94; H, 7.10; N, 2.11.

[1*S*(1α,2β,7β,8α,8aα)]-1,2-di(*t*-butyldiphenylsilyloxy)-indolizidine-7,8-diol (6a). 1 M DIBAH in hexane (0.55 mL, 0.55 mmol) was added dropwise at −78°C to a solution of **4a** (0.24 g, 0.35 mmol) in anhydrous diethyl ether (8 mL). The reaction mixture was stirred for 4 h at −78°C and then quenched with ice. Seignette salt was added in order to dissolve aluminum salts and, after stirring for 1 h, the solution was carefully extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was filtered

affording 0.16 g (67%) of crude **5a** as a mixture of epimers at C-7: ^{1}H NMR ($CDCl_3$) two broad triplets at δ 5.63 and δ 4.90 with $J\approx$4.0 Hz, due to H-7; ^{13}C NMR ($CDCl_3$) δ 89.9 and 98.9 (C-7).

Crude lactol **5a** (0.16 g, 0.24 mmol) and 20% $Pd(OH)_2$ on carbon (0.035 g) in anhydrous methanol (10 mL) was hydrogenated for 12 h at 45 psi. The solution was filtered over Celite and the solvent was removed at reduced pressure. The residue was purified by flash-chromatography on silica gel using cyclohexane/ethyl acetate (95/5) yielding **6a** (0.106 g, 66%) as a viscous oil: $[\alpha]_D^{22}=+8.4$ (c=0.62 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.89 (s, 9H, Si*t*Bu), 1.06 (s, 9H, Si*t*Bu), 1.61 (br dq, $J\approx$5.1/12.6 Hz, 1H, H-6), 1.78–1.86 (m, 1H, H-6), 1.97–2.11 (m, 2H, H-5+H-8a), 2.18 (dd, J=5.4/9.9 Hz, 1H, H-3), 2.56–2.62 (m, 1H, H-5), 2.63 (d, J=9.9 Hz, 1H, H-3), 3.24–3.35 (m, 2H, H-7+H-8), 4.29 (d, J=5.1 Hz, 1H, CHOSi), 4.39 (d, J=5.1 Hz, 1H, CHOSi), 7.27–7.78 (m, 20H, ArH); ^{13}C NMR ($CDCl_3$, APT) δ 19.1 (Si*C*Me_3), 19.2 (Si*C*Me_3), 26.7 (SiC*Me*$_3$), 27.0 (SiC*Me*$_3$), 31.0 (C-6), 47.9 (C-5), 59.0 (C-3), 73.5, 74.8, 76.4, 81.0, 85.8, (C-1, C-2, C-7, C-8, C-8a), 127.2, 127.5, 127.6, 127.7, 129.3, 129.5, 129.7, 129.8, 133.4 (Cquat), 133.5 (Cquat), 133.6 (Cquat), 134.7 (Cquat), 135.6, 135.9. Anal. Calcd. for $C_{40}H_{51}NO_4Si_2$: C, 72.14; H, 7.72; N, 2.10. Found: C, 72.18; H, 7.65; N, 2.13.

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References

1. Elbein, A. D. In *Comprehensive Medicinal Chemistry*, Sammes, P. G. Ed.; Pergamon: New York, 1990; 2, pp 365–381.
2. Robinson, K. M.; Begovic, M. E.; Rhinehart, B. L.; Heineke, E. W.; Ducep, J.-B.; Kastner, P. R.; Marshall, F. N.; Danzin, C. *Diabetes* **1991**, *40*, 825.
3. (a) Elbein, A. D. *Ann. Rev. Biochem.* **1987**, *56*, 497. (b) Taylor, D. L.; Nash, R.; Fellows, L. E.; Kang, M. S.; Tyms, A. S. *Antiviral Chem. Chemother.* **1992**, *3*, 273. (c) Taylor, D. L.; Kang, M. S.; Brennan, T. M.; Bridges, C. G.; Sunkara, P. S.; Tyms, A. S. *Antimicrob. Agents Chemother.* **1994**, *38*, 1780. (d) Gross, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clinical Cancer Res.* **1995**, *1*, 935.
4. (a) Wong, C.-H.; Halcomb, R. L.; Ichihawa, Y.; Kajimoto, T. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 521. (b) Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1.
5. (a) Carretero, J. C.; Arrayás, R. G. *J. Org. Chem.* **1998**, *63*, 2993 and references quoted therein. (b) Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045.
6. Furneaux, R. H.; Gainsford, G. J.; Mason, J. M.; Tyler, P. C.; Hartley, O.; Winchester, B. G. *Tetrahedron* **1995**, *51*, 12611.
7. Davis, B.; Bell, A. A.; Nash, R. J.; Watson, A. A.; Griffiths, R. C.; Jones, M. G.; Smith, C.; Fleet, G. W. *J. Tetrahedron Lett.* **1996**, *37*, 8565.
8. Degiorgis, F.; Lombardo, M.; Trombini, C. *Synthesis* **1997**, 1243. See also Degiorgis, F.; Lombardo, M.; Trombini, C. *Org. Prep. Proced. Int.* **1997**, *29*, 485.
9. (a) Camiletti, C.; Poletti, L.; Trombini, C. *J. Org. Chem.* **1994**, *59*, 6843. (b) Castellari, C.; Lombardo, M.; Pietropaolo, G.; Trombini, C. *Tetrahedron: Asymmetry* **1996**, *7*, 1059. (c) Degiorgis, F.; Lombardo, M.; Trombini, C. *Tetrahedron* **1997**, *53*, 11721.
10. (a) Ballini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1992**, *57*, 1316. (b) Cicchi, S.; Höld, I.; Brandi, A. *J. Org. Chem.* **1993**, *58*, 527.
11. (a) Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806. (b) Goti, A.; Cardona, F.; Brandi, A.; Picasso, S.; Vogel, P. *Tetrahedron: Asymmetry* **1996**, *7*, 1659. (c) Goti, A.; Cardona, F.; Brandi, A. *Synlett* **1996**, 761. (d) Cardona, F.; Valenza, S.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **1997**, *38*, 8097. (e) Cicchi, S.; Numes, Jr., J.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **1998**, 419. (f) Cardona, F.; Valenza, S.; Picasso, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1998**, *63*, 7311.
12. (a) McCaig, A. E.; Wightman, R. H. *Tetrahedron Lett.* **1993**, *34*, 3939. (b) McCaig, A. E.; Meldrum, K. P.; Wightman, R. H. *Tetrahedron* **1998**, *54*, 9429.