Pergamon

Tetrahedron Letters 43 (2002) 761–766

TETRAHEDRON LETTERS

Cyclative cleavage via solid-phase supported stabilized sulfur ylides: synthesis of macrocyclic lactones

Elena La Porta,[a] Umberto Piarulli,[a,b] Francesca Cardullo,[c] Alfredo Paio,[c] Stefano Provera,[c] Pierfausto Seneci[d] and Cesare Gennari[a,*]

[a]*Dipartimento di Chimica Organica e Industriale, Università di Milano, Centro CNR per lo Studio delle Sostanze Organiche Naturali, via G. Venezian 21, I-20133 Milano, Italy*

[b]*Dipartimento di Scienze Chimiche, Fis. e Mat., Università dell'Insubria, via Valleggio 11, I-22100 Como, Italy*

[c]*Glaxo-SmithKline, Med. Res. Centre, via Fleming 4, I-37135 Verona, Italy*

[d]*Nucleotide Analog Design AG, Landsbergerstrasse 50, D-80339 Munich, Germany*

Received 31 October 2001; accepted 26 November 2001

Abstract—A new synthesis of macrolactones bearing a cyclopropyl ring condensed to the macrocycle is reported via a cyclization-release strategy making use of solid-phase supported stabilized sulfur ylides.

The convenient purification procedures and the other known advantages associated with solid-phase synthesis make it a powerful tool for the preparation of combinatorial libraries, a fundamental element of contemporary drug discovery processes. In this context, cyclization-release techniques[1] present distinct advantages over more conventional approaches to solid-phase synthesis:

(a) Most traditional solid-phase methods incorporate a heteroatom within a device that links the substrate to the polymer support. Cleavage is achieved by 'deprotecting' the heteroatom which, however, remains as a vestigial stub on the final molecule. This is not a problem in cyclative-cleavage approaches, where release from the polymer support is obtained as a consequence of the natural reactivity of the connecting functionality, leaving no traces on the target molecules.

(b) Since detachment from the resin is a step associated with the correct reaction sequence, *only* substrates

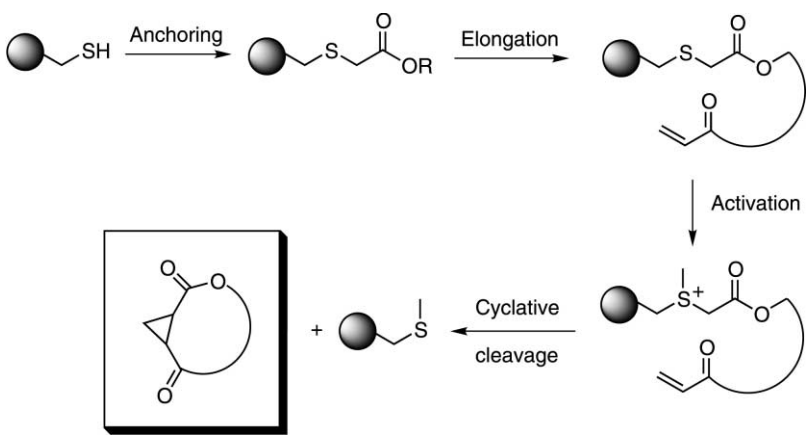


Figure 1. Synthesis of macrocyclic lactones via the cyclative release strategy, using solid-phase supported stabilized sulfur ylides.

Keywords: solid-phase synthesis; macrocycles; cyclopropanes; sulfonium salts.

* Corresponding author. Tel. +39-025835.4091; fax: +39-025835.4072; e-mail: cesare.gennari@unimi.it

0040-4039/02/$ - see front matter
PII: S0040-4039(01)02258-4

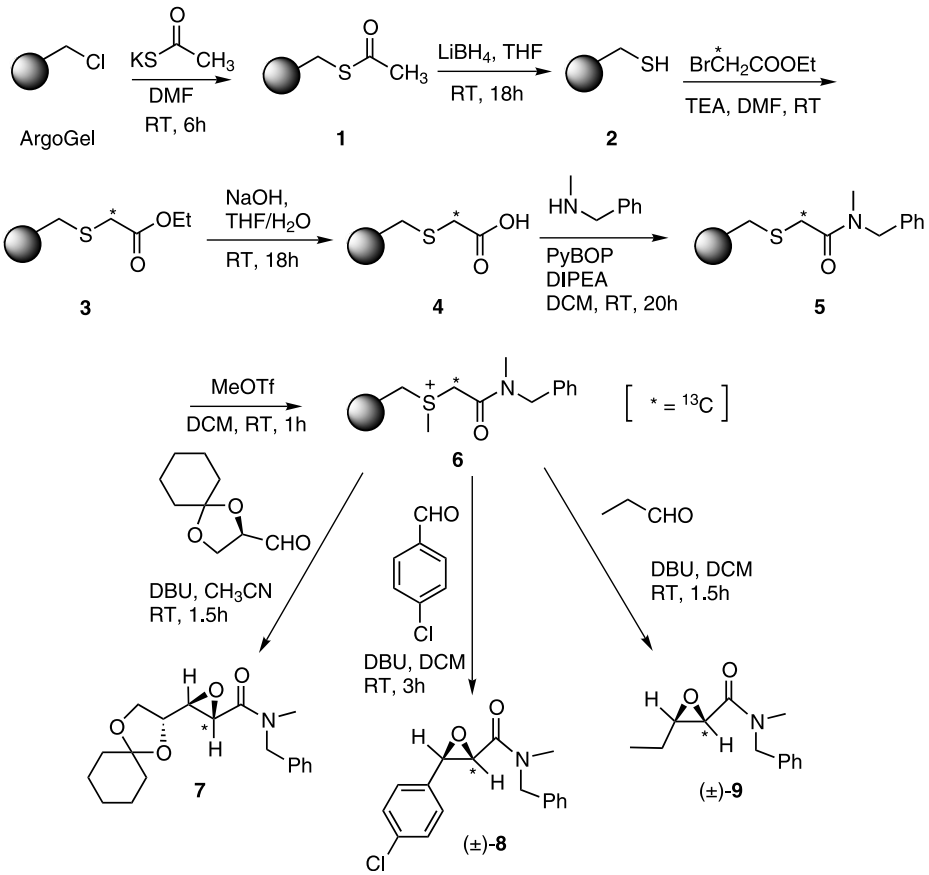
which possess the correct functionality and react in the expected way are released into the solution in high purity, leaving all unreacted systems and by-products on the solid-phase.

(c) The cyclization step takes place while the substrate is anchored on the polymer support, taking advantage of the functional group isolation granted by the resin and thus eliminating the risk of intermolecular reactions and the need of high dilution conditions. The ring closing metathesis (RCM),[1] the Wittig–Horner reaction,[2] the Stille[3] and Suzuki[4] couplings have recently been adapted to fit this scheme as carbon–carbon bond forming cyclization processes in a cyclorelease from the solid-phase.

We recognized in sulfur ylides[5] a functional arrangement with suitable characteristics for an original cyclorelease strategy, featuring an activation phase prior to the actual cyclization event, in a way reminiscent of the principle of safety catch linkers. In particular, we focused on sulfur ylides stabilized by electron-withdrawing groups,[6,7] which can be generated under extremely mild conditions[8] and are therefore suitable for intramolecular reactions. Following the anchoring of the ylide precursor onto the solid support and elongation with a chain containing a Michael acceptor terminal moiety (Fig. 1), the cyclative release from the solid-phase is made possible by alkylation of the sulfur atom to the sulfonium salt, the immediate precursor to ylide formation and reaction.

Here we describe the application of this new cyclization-release strategy to the synthesis of macrolactones bearing a cyclopropyl system condensed to the macrocyclic ring.[9]

First of all, we investigated the preparation of resin-bound thioglycolic acid on Argogel® resin, the stability of the resin-bound sulfonium salt and the reactivity of the resin-bound ylide with aldehydes.[6] Argogel®-Cl resin was reacted with potassium thioacetate according to a published procedure,[10] and the supported thioester **1** was successfully reduced with $LiBH_4$ in THF to give Argogel®-SH resin **2**, which was characterized by MAS–^{1}H NMR and FT-IR (Scheme 1). Argogel®-SH resin **2** was then reacted with ^{13}C-enriched (99%) ethyl bromoacetate and triethylamine in DMF at room temperature. The supported ester **3** was characterized by ^{13}C-gel phase NMR (32.0 ppm) and FT-IR (νC=O, 1730 cm^{-1}). The ethyl ester was then saponified (NaOH, THF–H_2O), and the resulting acid **4** was characterized by MAS–^{1}H NMR, FT-IR (νC=O 1720 cm^{-1}), ^{13}C-gel phase NMR (34.6 ppm) and transformed into the *N*-benzyl,*N*-methylamide **5** characterized by MAS–^{1}H NMR, FT-IR (νC=O 1636 cm^{-1}) and ^{13}C-gel phase

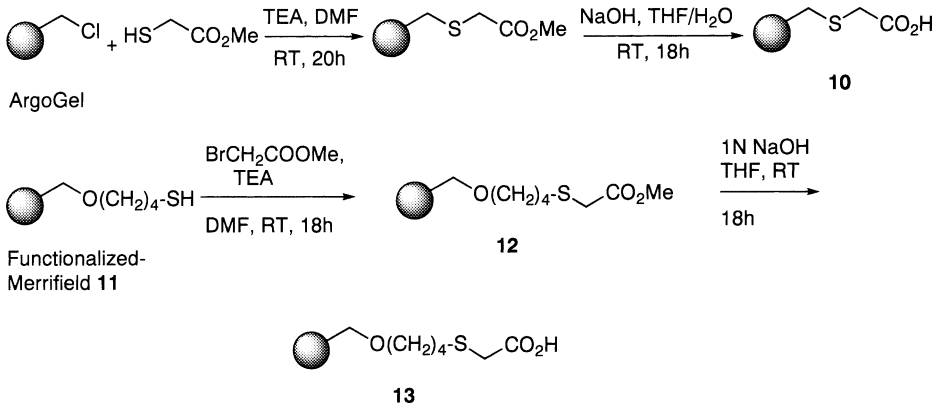


Scheme 1. Investigation on the stability of the resin-bound sulfonium salt **6** and on the reactivity of the resin-bound ylide with aldehydes.

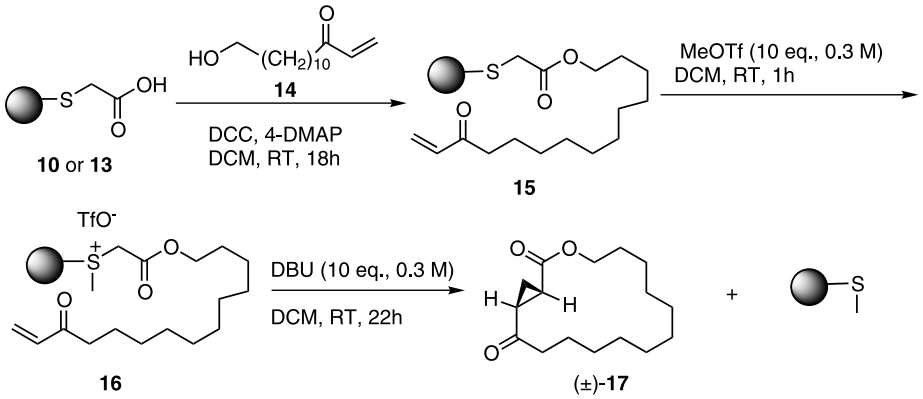
NMR (33.9 ppm). Sulfonium salt **6** was synthesized by treatment of sulfide **5** with 0.3 M MeOTf in DCM (room temperature, 1 h). The solid-supported sulfonium salt **6** was shown to be stable to washings and storage, and characterized by MAS–^{1}H NMR, FT-IR (νC=O 1646 cm^{-1}) and ^{13}C-gel phase NMR (48.5 ppm). Finally, it was reacted with DBU and protected glyceraldehyde[6] in CD_2Cl_2 at room temperature: the reaction was followed by ^{13}C NMR in the gel phase-NMR tube (coaxial insert), by disappearance of the sulfonium–carbon peak at 48.5 ppm and appearance of the new epoxide–carbon peak at 52.4/52.7 ppm (two peaks because of the tertiary amide present in **7**). The same reaction was run successfully on a preparative scale employing different aldehydes (*p*-chlorobenzaldehyde, propionaldehyde and protected glyceraldehyde) and solvents (DCM and CH_3CN), as reported in Scheme 1. Flash-chromatography of the crudes deriving from the washings of the resin allowed the isolation and characterization of the desired epoxyamides **7** (41%), (±)-**8** (10%), and (±)-**9** (20%).[6] Overall yields were calculated based on the initial loading of Argogel®-Cl resin (0.44 mmol/g).

Having established the stability of the resin-bound sulfonium salt and the reactivity of the resin-bound ylide, we turned our attention to the preparation of two different resins bearing a thioglycolic acid unit. In the case of Argogel® resin, a more straightforward route was developed (Scheme 2) starting from methyl thioglycolate and leading in two steps to the desired functionalized resin **10**. In the case of Merrifield resin (chloromethylated polystyrene crosslinked with 1% divinylbenzene, 1.09 mmol/g), this was transformed to the functionalized thiol resin **11**, using a 1,4-butanediol spacer according to a published procedure.[11] Thiol-resin **11** was then reacted with methyl bromoacetate and triethylamine in DMF. The supported ester **12** was characterized by MAS–^{1}H NMR and FT-IR (νC=O, 1739 cm^{-1}) and then saponified (NaOH, THF–H_2O) to the desired functionalized resin **13** (νC=O, 1730 cm^{-1}) (Scheme 2).

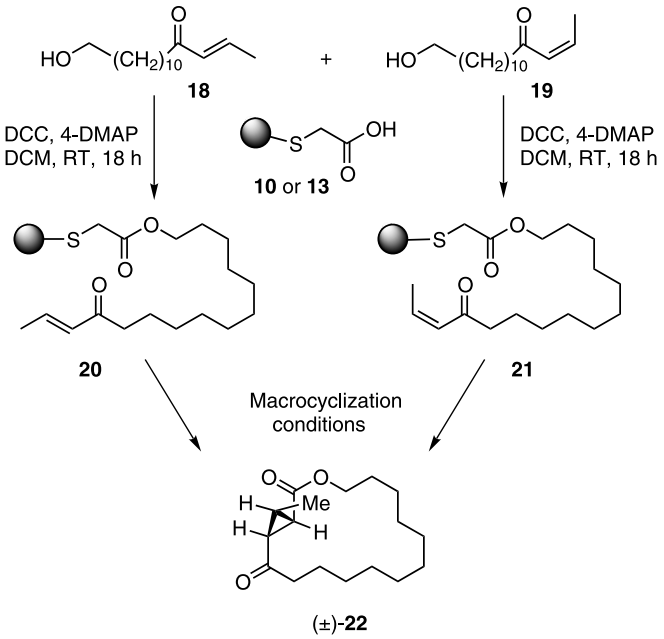
Functionalized resins **10** or **13** were reacted with ω-hydroxy vinylketone **14**[12] using DCC and DMAP in DCM to give supported vinylketone **15** (Scheme 3). The thioether of **15** was activated with MeOTf in DCM to the corresponding resin bound sulfonium salt **16**, which was purified by filtration and washings. Treatment of **16** with DBU generated the stabilized sulfur ylide which underwent cyclative cleavage to give the macrocyclic lactone (±)-**17**, bearing a cyclopropyl ring[7] condensed to the macrocycle, in good yield and purity as a single diastereoisomer (*trans*).[15]



Scheme 2. Preparation of resins **10** and **13**, functionalized as thioglycolic acid.



Scheme 3. Solid-phase synthesis and cyclative release of macrocyclic lactone (±)-**17**.



Scheme 4. Solid-phase synthesis and cyclative release of macrocyclic lactone (±)-**22**.

The scope of the cyclative cleavage reaction was investigated using propenylketones **18** (*E*)[16] and **19** (*Z*),[16] following the same procedure described above for vinylketone **14**. Macrocyclic lactone (±)-**22** was obtained as a single diastereoisomer from either *E* (**20**) or *Z* (**21**) resin-bound propenylketone in poor yield[17] (Scheme 4). Thus, the cyclization reaction seems quite sensitive to enone β-substitution.

Another point of interest regards the introduction of a more funtionalized chain in the macrocyclic ring. (+)-*t*-Butyl-(D)-lactate was coupled to Argogel® resin **10** (DIC, 4-DMAP) to give resin-bound *t*-butylester **23** which was hydrolized (TFA, DCM) to resin-bound acid **24**. Coupling with ω-hydroxy vinylketone **25**[18] gave cyclization precursor **26**, which underwent cyclative cleavage under the usual conditions to give macrocyclic lactones **27** and **28** (1:1)[19] (Scheme 5).

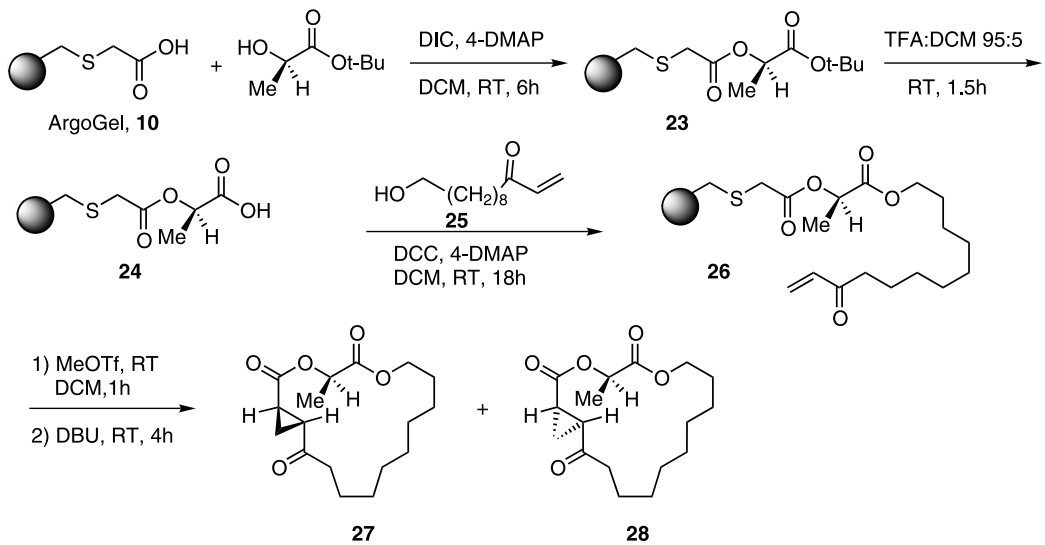
After optimization, this methodology will be employed for the synthesis of a library of macrocyclic lactones with potential biological interest, bearing the uncommon 'condensed-cyclopropyl' functionality.[9]

Acknowledgements

A graduate fellowship is gratefully acknowledged by E. La Porta (Glaxo-SmithKline, Verona, Italy). We thank Dr. Sergio Lociuro (Glaxo-SmithKline) for support and helpful discussions.

References

1. Nicolaou, K. C.; Vorloumis, D.; Li, T.; Pastor, J.; Winssinger, N.; He, Y.; Ninkovic, S.; Sarabia, F.; Vallberg, H.; Roschangar, F.; King, N. P.; Finlay, R. M. V.; Giannakakou, P.; Verdier-Pinard, P.; Hamel, E. *Angew. Chem.* **1997**, *109*, 2181–2187; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2097–2103.
2. Nicolaou, K. C.; Pastor, J.; Winssinger, N.; Murphy, F. *J. Am. Chem. Soc.* **1998**, *120*, 5132–5133.
3. Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Murphy, F. *Angew. Chem.* **1998**, *110*, 2677–2680; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2534–2537.
4. Li, W.; Burgess, K. *Tetrahedron Lett.* **1999**, *40*, 6527–6530.
5. Trost, B. M.; Melvin, L. S. *Sulfur Ylides*; Academic Press: New York, 1975.
6. *N*,*N*-Dimethyl-2-(dimethylsulfuranilidene) acetamide reacts with chiral aldehydes and ketones with high stereoselectivity to form *trans* 2,3-epoxy-amides, see: (a) Valpuesta-Fernández, M.; Durante-Lanes, P.; López-Herrera, F. J. *Tetrahedron* **1990**, *46*, 7911–7922; (b)



Scheme 5. Solid-phase synthesis and cyclative release of macrocyclic lactones **27** and **28**.

Valpuesta, M.; Durante, P.; López-Herrera, F. J. *Tetrahedron* **1993**, *49*, 9547–9560; (c) López-Herrera, F. J.; Sarabia-Garcia, F.; Pedraza-Cebrian, G. M.; Pino-Gonzalez, M. S. *Tetrahedron Lett*. **1999**, *40*, 1379–1380; (d) Imashiro, R.; Yamanaka, T.; Seki, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2845–2851; (e) For chiral sulfur ylides, see: Zhou, Y.-G.; Hou, X.-L.; Dai, L.-X.; Xia, L.-J.; Tang, M.-H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 77–80.

7. Dimethylsulfonium phenacylide and ethyl(dimethylsulfuranilidene)acetate (EDSA) are reported to react with a variety of Michael acceptors to form cyclopropyl derivatives, see: (a) Trost, B. M. *J. Am. Chem. Soc*. **1967**, *89*, 138–142; (b) Payne, G. B. *J. Am. Chem. Soc*. **1965**, *87*, 3351–3355; (c) Ma, D.; Cao, Y.; Yang, Y.; Cheng, D. *Org. Lett*. **1999**, *1*, 285–287; (d) Ma, D.; Cao, Y.; Wu, W.; Jiang, Y. *Tetrahedron* **2000**, *56*, 7447–7456; (e) Ma, D.; Jiang, Y. *Tetrahedron: Asymmetry* **2000**, *11*, 3727–3736.
8. (a) Collado, I.; Dominguez, C.; Ezquerra, J.; Pedregal, C.; Monn, J. A. *Tetrahedron Lett*. **1997**, *38*, 2133–2136; (b) Nozaki, H.; Tunemoto, D.; Matubara, S.; Kondô, K. *Tetrahedron* **1967**, *23*, 545–551.
9. For a macrocyclic antibiotic containing an α-ketocyclopropyl functionality (tolypomicin), see: Bellomo, P.; Brufani, M.; Marchi, E.; Mascellani, G.; Melloni, W.; Montecchi, L.; Stanzani, L. *J. Med. Chem*. **1977**, *20*, 1287–1291. For a review on cyclopropane containing natural products, see: Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589–8627.
10. Kobayashi, S.; Hachiya, I.; Suzuki, S.; Moriwaki, M. *Tetrahedron Lett*. **1996**, *37*, 2809–2812.
11. Vanier, C.; Lorgé, F.; Wagner, A.; Mioskowski, C. *Angew. Chem*. **2000**, *112*, 1745–1749; *Angew. Chem., Int. Ed. Engl*. **2000**, *39*, 1679–1683. A modified procedure was followed in one of the synthetic steps: PBr_3, THF, 0°C to rt was used instead of MsCl, Et_3N, CH_2Cl_2, rt. We thank Dr. Wagner for exchange of experimental procedures and helpful discussions.
12. ω-Hydroxy vinylketone **14** was prepared as follows: commercially available 12-hydroxylauric acid was protected at the terminal hydroxy group (TBDPS-Cl, imidazole, DMF, rt, 1 h, 67%). The ω-OTBDPS-protected acid was transformed into the Weinreb amide (*N*,*O*-dimethylhydroxylamine hydrochloride, 1,1′-carbonyldiimidazole, DCM, rt, 4 h, 91%) and subsequently reduced to aldehyde (DIBAl-H, THF, 0°C, 45 min, 80%). The aldehyde was then treated with vinylmagnesium bromide (THF, −75 to 0°C, 1.5 h, 60%) to give the allylic alcohol, which was in turn oxidized to the vinylketone [Dess Martin Periodinane (DMP),[13] DCM, rt, 1 h, 92%]. The ω-OTBDPS-protected vinylketone was deprotected (TBAF, *p*-TsOH–H_2O, THF, 0°C to rt, 80 h, 80%)[14] to give the ω-hydroxy vinylketone **14**.
13. Dess Martin Periodinane (DMP): (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277–7287; (b) Ireland, R. E.; Liu, L. *J. Org. Chem*. **1993**, *58*, 2899–2899.
14. Hitchcock, S. A.; Houldsworth, S. J.; Pattenden, G.; Pryde, D. C.; Thomson, N. M.; Blake, A. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3181–3206.
15. The loading of cyclization precursor **15** (0.35 mmol/g for Argogel® resin; 0.81 mmol/g for Merrifield resin) was calculated from the original loading of the commercial resin (0.44 mmol/g for Argogel®-Cl resin; 1.09 mmol/g for Merrifield resin) and considering a 100% yield for each solid-phase synthetic step preceding the cyclization. The overall yield for the solid-phase synthesis of macrocycle (±)-**17** was calculated based on the above loading values: 52% from Argogel® precursor **15** (31% after flash chromatography); 20% from Merrifield precursor **15** (10% after flash chromatography). Lactone (±)-**17** was also synthesized in solution-phase, following the same chemistry described in Scheme 3 but using *S*-ethyl thioglycolic acid instead of resins **10** or **13**. Sulfonium salt formation (1.5 equiv. MeOTf, DCM, rt, 1 h) and macrocyclization (2 equiv. DBU) under high dilution conditions (10^{-3} M in DCM, rt, 20 h) gave lactone (±)-**17**, which was purified by flash-chromatography (60% yield) and characterized as follows. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20–1.45 (14H, bs), 1.40–1.56 (2H, m), 1.60–1.75 (4H, m), 2.10 (1H, ddd, $J_1=9.2$ Hz, $J_2=5.9$ Hz, $J_3=3.7$ Hz), 2.35 (1H, ddd, $J_1=14.1$ Hz, $J_2=8.0$ Hz, $J_3=6.3$ Hz), 2.51 (1H, ddd, $J_1=9.1$ Hz, $J_2=5.7$ Hz, $J_3=3.7$ Hz), 2.70–2.80 (1H, m), 3.85–3.95 (1H, m), 4.53 (1H, ddd, $J_1=11.1$ Hz, $J_2=7.0$ Hz, $J_3=4.2$ Hz). ^{13}C NMR ($CDCl_3$, 50.13 MHz): δ 16.2, 24.9, 28.7, 24.3–27.8 (7C), 44.1, 64.6, 209.0. HRMS [EI (70 eV)] calcd for $[C_{16}H_{26}O_3]^+$ 266.1882, found 266.1825.
16. ω-Hydroxy propenylketones **18** and **19** were prepared as described in Ref. 12 for ω-hydroxy vinylketone **14** but using propenylmagnesium bromide instead of vinylmagnesium bromide (THF, −75 to 0°C, 2.5 h, 70%). The allylic alcohols (*E*+*Z*) were in turn oxidized to the propenylketones [DMP,[13] DCM, rt, 1.5 h, 77%]. The ω-OTBDPS-protected propenylketones were separated by flash-chromatography (*E*:*Z*=1:1) and deprotected (TBAF, *p*-TsOH–H_2O, THF, 0°C to rt, 20 h, 84%)[14] to give the ω-hydroxy propenylketones **18** and **19**.
17. The loading of cyclization precursor **20** or **21** (0.34 mmol/g for Argogel® resin; 0.81 mmol/g for Merrifield resin) was calculated from the original loading of the commercial resin (0.44 mmol/g for Argogel®-Cl resin; 1.09 mmol/g for Merrifield resin) and considering a 100% yield for each solid-phase synthetic step preceding the cyclization. The overall yield for the solid-phase synthesis of macrocycle (±)-**22** was calculated based on the above loading values: 15% from Argogel® precursor **20** or **21** (8% after flash chromatography); 5% from Merrifield precursor **20** or **21** (2% after flash chromatography). Lactone (±)-**22** was also synthesized in solution-phase, following the same chemistry described in Scheme 4 but using *S*-ethyl thioglycolic acid instead of resins **10** or **13**. Sulfonium salt formation (1.5 equiv. MeOTf, DCM, rt, 1 h) and macrocyclization (2 equiv. DBU) under high dilution conditions (10^{-3} M in DCM, rt, 20 h) gave lactone (±)-**22** which was purified by flash-chromatography (10% yield) and characterized as follows. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20–1.40 (17H, bs), 1.60–1.70 (4H, m), 1.91–2.03 (1H, m), 2.20 (1H, dd, $J_1=9.5$ Hz, $J_2=4.4$ Hz), 2.33 (1H, ddd, $J_1=13.5$ Hz, $J_2=8.1$ Hz, $J_3=6.0$ Hz), 2.47 (1H, dd, $J_1=5.8$ Hz, $J_2=4.4$ Hz), 2.75 (1H, ddd, $J_1=13.5$ Hz, $J_2=7.3$ Hz, $J_3=5.9$ Hz), 3.87 (1H, ddd, $J_1=10.8$ Hz, $J_2=6.8$ Hz, $J_3=3.5$ Hz), 4.59 (1H, ddd, $J_1=10.8$ Hz, $J_2=7.4$ Hz, $J_3=3.5$ Hz). The relative stereochemistry was assigned based on the coupling constants and on a COSY NMR spectrum ($CDCl_3$, 400 MHz).

18. Prepared from 1,10-decanediol via the following sequence of reactions: (a) monoprotection (TBDPSCl, imidazole, DMF, rt, 24 h, 80%); (b) oxidation to aldehyde (DMP, DCM, rt, 1.5 h, 71%);[13] (c) addition of vinylmagnesium bromide (THF, 0°C, 1.5 h, 68%); (d) oxidation of the allylic alcohol to the vinylketone (DMP, DCM, rt, 1.5 h, 92%);[13] (e) TBDPS deprotection (TBAF, *p*-TsOH–H_2O, THF, 0°C to rt, 70 h, 77%).[14]
19. The loading (0.33 mmol/g) of Argogel® resin cyclization precursor **26** was calculated from the original loading of commercial Argogel®-Cl resin (0.44 mmol/g) and considering a 100% yield for each solid-phase synthetic step preceding the cyclization. The overall yield for the solid-phase synthesis of macrocycle **27** and **28** was calculated based on the above loading value: 33% (18% after flash chromatography). Lactones **27** and **28** were also synthesized in solution-phase, following the same chemistry described in Scheme 5 but using *S*-ethyl thioglycolic acid instead of resin **10**. Sulfonium salt formation (1.5 equiv. MeOTf, DCM, rt, 1 h) and macrocyclization (2 equiv. DBU) under high dilution conditions (10^{-3} M in DCM, rt, 20 h) gave lactones **27** and **28** which were separated by flash-chromatography (63% combined yield) and characterized as follows. ^{1}H NMR ($CDCl_3$, 400 MHz) **27** (or **28**): δ 1.28–1.45 (10H, bs), 1.49 (3H, d, $J=7.0$ Hz), 1.50–1.54 (2H, m), 1.61–1.71 (3H, m), 1.82–1.92 (1H, m), 2.15 (1H, ddd, $J_1=10.3$ Hz, $J_2=6.2$ Hz, $J_3=3.9$ Hz), 2.39–2.49 (1H, m), 2.70–2.80 (2H, m), 4.14–4.28 (2H, m), 5.07 (1H, q, $J=7.0$ Hz). ^{13}C NMR DEPT ($CDCl_3$, 100.6 MHz): δ 16.4, 17.1, 24.4, 25.4, 24.6–28.1 (5C), 28.4, 29.0, 43.3, 65.9, 69.8. ^{1}H NMR ($CDCl_3$, 400 MHz) **28** (or **27**): δ 1.20–1.45 (10H, bs), 1.48–1.52 (2H, m), 1.53 (3H, d, $J=7.0$ Hz), 1.60–1.72 (3H, m), 1.85–1.95 (1H, m), 2.26 (1H, ddd, $J_1=9.0$ Hz, $J_2=5.7$ Hz, $J_3=3.8$ Hz), 2.44 (1H, ddd, $J_1=15.5$ Hz, $J_2=8.1$ Hz, $J_3=4.9$ Hz), 2.60 (1H, ddd, $J_1=8.8$ Hz, $J_2=5.9$ Hz, $J_3=3.8$ Hz), 2.75 (1H, ddd, $J_1=15.5$ Hz, $J_2=8.5$ Hz, $J_3=4.8$ Hz), 4.10–4.29 (2H, m), 5.27 (1H, q, $J=7.0$ Hz). HRMS [EI (70 eV)] calcd for $[C_{17}H_{26}O_5]^+$ 310.1780, found 310.1758.