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A Stereocontrolled Synthesis of a C_{19}–C_{32} / C_{17}–C_{30} Segment for Swinholide A and Misakinolide A, Cytotoxic Dimeric Macrolides from *Theonella Swinhoei*.

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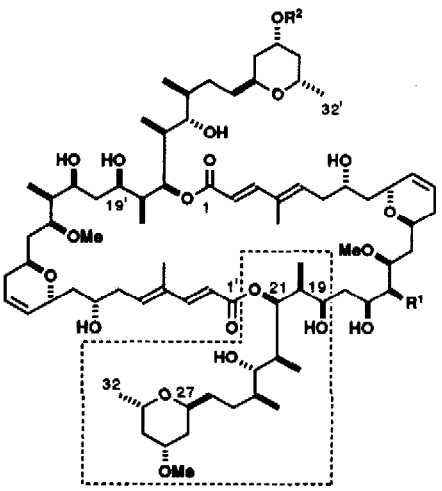
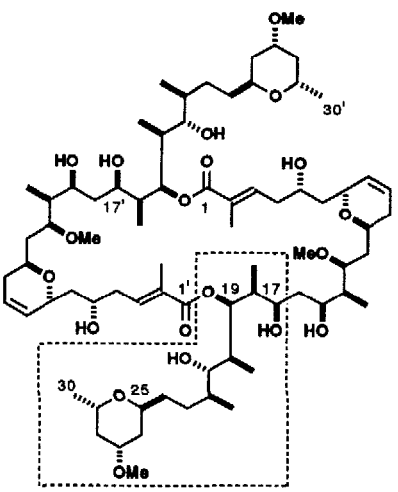
Abstract: The C_{19}–C_{32} / C_{17}–C_{30} segment (–)–**5** of swinholide A / misakinolide A was prepared in 15 steps (6% yield) from (±)–**13**. Key steps include the Sharpless epoxidation, **13** → **14**, the acetal allylation, **12** → **16**, the *anti* aldol, **17** + **11** → **9**, and the alkene hydroboration, **19** → **20**.

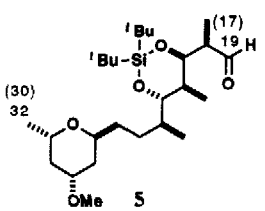
Swinholide A, a novel cytotoxic macrolide isolated from marine sponges of the genus *Theonella swinhoei*, was first reported by Carmely and Kashman in 1985.[1] While originally misassigned as a monomeric macrolide,[1] more recent mass spectroscopic[2a] and X-ray crystallographic[2b-d] studies showed it to be a symmetrical dimer having the 44-membered dilactone structure **1** (**Scheme 1**). Several other dimeric macrolides have also been isolated from *Theonella*, including the desmethyl analogues swinholides B (**2**) and C (**3**),[2e] and the closely related 40-membered dilactone, misakinolide A (**4**)[3a-c] (≡ bistheonellide A[3b,d]). These are all characterised by potent cytotoxicity, *e.g.* swinholide A has an IC_{50} of 0.04 and 0.03 μg/ml against KB and L1210 tumour cells *in vitro*.[2a,d] All of these marine macrolides have identical stereostructures,[4] determining their conformation and possibly the cytotoxic activity.[2d] As part of our synthetic studies towards swinholide A and misakinolide A, we now report the enantiocontrolled synthesis of the C_{19}–C_{32} / C_{17}–C_{30} segment **5**.



swinholide A (**1**): R^1 = R^2 = Me
swinholide B (**2**): R^1 = H, R^2 = Me
swinholide C (**3**): R^1 = Me, R^2 = H



misakinolide A (**4**)
(bistheonellide A)



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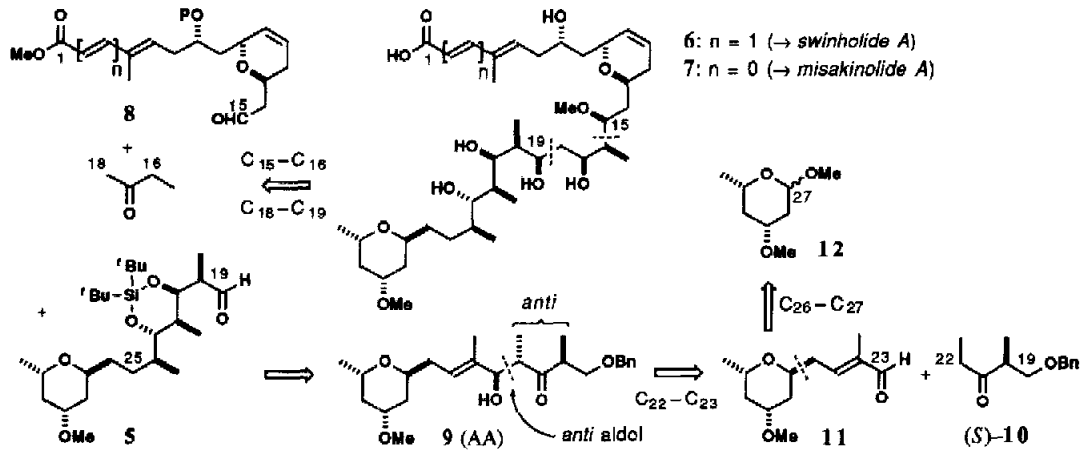
Scheme 1

Scheme 2 summarises our strategy for the synthesis of the monomeric secoacid **6**[5] for swinholide A (together with the secoacid **7** for misakinolide A), involving aldol-type disconnections at the C_{15}–C_{16} and C_{18}–C_{19} bonds to afford the key segments **5** and **8**. Segment **5**, containing the C_{19}–C_{25} stereopentad and the tetrahydropyran ring, should then be attainable using our general synthetic approach[6a] to such polypropionate systems. In this case, an *anti-anti* aldol reaction[6b] between the ethyl ketone (*S*)-**10**[6] and the chiral aldehyde **11** is required to control the C_{22} and C_{23} stereocentres in **9**. The aldehyde component **11** should be available in turn from the cyclic acetal **12** by a suitable alkylation reaction at C_{27}.



Scheme 2

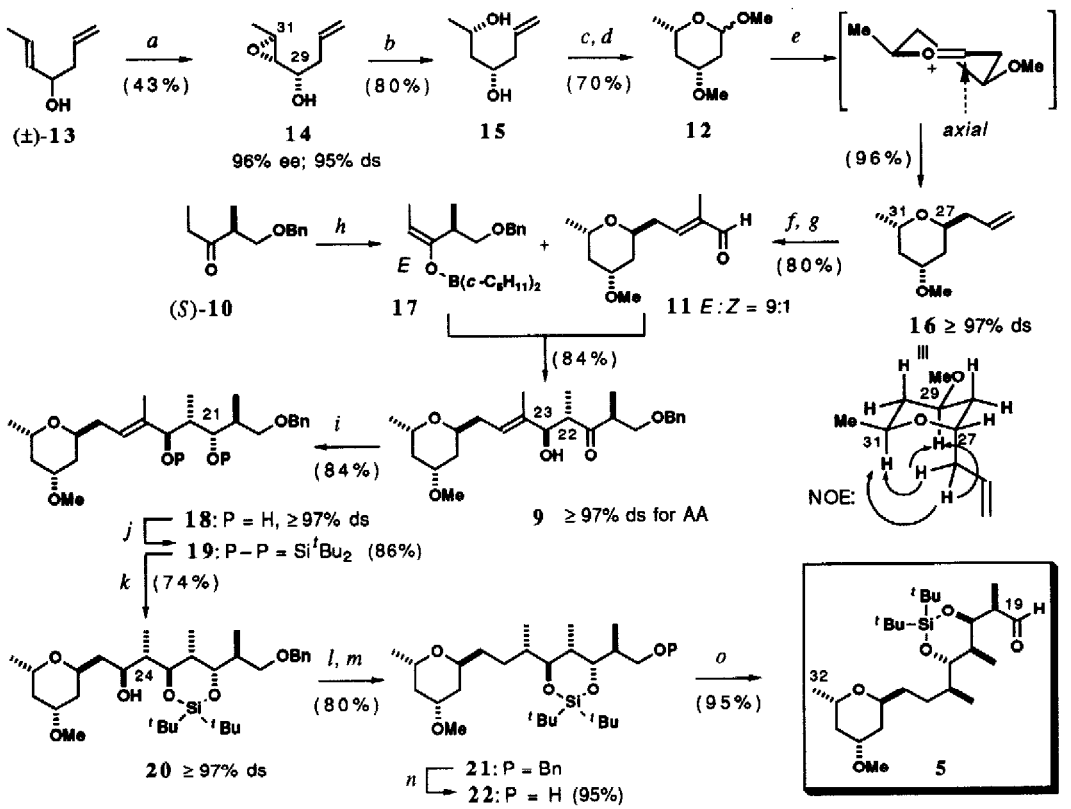
The synthesis of this C_{19}–C_{32} segment **5** starting from (*E*)-1,5-heptadien-4-ol (**13**)[7] is shown in **Scheme 3** and outlined below. Catalytic Sharpless asymmetric epoxidation[8a] of (±)-**13** with kinetic resolution gave the (*S*,*S*,*S*) epoxide **14**[8b] (96% ee by ^{1}H NMR analysis of the Mosher ester formed from (*R*)-(+)-MTPA) in 43% yield with 95% ds. Directed reductive opening of the epoxide **14** was achieved using Red-al®[9] giving the 1,3-diol **15**,[10] $[\alpha]_D^{20}$ = +20.7° (*c* 2.9, $CHCl_3$). Ozonolysis of **15** in MeOH, followed by acidic workup and *O*-methylation, then gave the cyclic acetal **12** in 70% yield as a mixture of anomers, which were not separated. Treatment of **12** with allyltrimethylsilane in MeCN at –20 °C under Me_3SiOTf catalysis[11] led, *via* kinetically controlled *axial* attack on the oxonium ion, to the rapid (< 2 min) and clean formation of the *trans*-substituted tetrahydropyran **16**,[10] $[\alpha]_D^{20}$ = –62.3° (*c* 3.8, $CHCl_3$), in 96% yield with ≥ 97% ds. ^{1}H NMR decoupling and NOE difference experiments on **16** confirmed the relative stereochemistry at C_{27} and suggested a preferred chair conformation with the allyl group *axially* disposed. A similar chair conformation is found for the tetrahydropyran containing segments of swinholide A.[2b,d] Ozonolysis of **16** then gave the corresponding aldehyde, which underwent a stereoselective Wittig reaction[12] to give the required (*E*)-enal **11**, $[\alpha]_D^{20}$ = –5.7° (*c* 1.0, $CHCl_3$), in preparation for the forthcoming aldol chain-extension.

Using our standard conditions with equimolar amounts of the two reactants,[6b] the key *anti*-selective boron aldol reaction between (*S*)-**10** and the aldehyde **11** proceeded well. A high level of substrate-based stereocontrol at the C_{22} and C_{23} centres was achieved from the *E*-dicyclohexylenol borinate **17**,[6b] giving the *anti-anti* (AA) isomer **9**,[10] $[\alpha]_D^{20}$ = –18.4° (*c* 2.0, $CHCl_3$), in 84% yield with ≥ 97% ds (no other aldol isomers detected). This was followed by introduction of the C_{21} stereocentre using reduction[13] with $Me_4BH(OAc)_3$ to give the *anti*-1,3-diol **18**, $[\alpha]_D^{20}$ = +1.7° (*c* 1.8, $CHCl_3$), with ≥ 97% ds, which was converted to its di-*tert*-butylsilylene derivative **19** in 72% overall yield.

The remaining stereocentre at C_{24} was installed by a hydroboration reaction on **19**, again relying on substrate-based[14] stereocontrol. Use of thexylborane gave, after oxidation, the alcohol **20**, $[\alpha]_D^{20}$ = –45.3°

(*c* 2.2, $CHCl_3$), in 74% yield with ≥ 97% ds. The surplus secondary hydroxyl group at C_{25} was then efficiently removed by reduction[15] of the derived thiocarbonylimidazolide with $^nBu_3SnH$, as in **20** → **21** (80%). Finally, hydrogenolysis of the benzyl ether in **21** and subsequent Swern oxidation of **22** gave the desired aldehyde **5**, $[\alpha]_D^{20} = -75.9°$ (*c* 1.3, $CHCl_3$), in 90% overall yield. The assigned structure was verified using ^1H NMR (COSY, NOE).[10]

This completes a synthesis of a common C_{19}–C_{32} / C_{17}–C_{30} segment **5** for swinholide A and misakinolide A (15 steps from (±)–**13**, in 6% overall yield and 75% diastereoselectivity), using a combination of cyclic and acyclic stereocontrol strategies to set up seven of the eight stereogenic centres. In summary, this relies on a single *reagent*-controlled reaction, the Sharpless epoxidation **13** → **14**, and a series of *substrate*-controlled reactions, (*i*) the acetal allylation, **12** → **16**, (*ii*) the boron-mediated aldol reaction, **17** + **11** → **9**, (*iii*) the ketone reduction, **9** → **18**, and (*iv*) the alkene hydroboration, **19** → **20**. Studies towards the elaboration of aldehyde **5** into the antitumour macrolides swinholide A and misakinolide A are underway.



Scheme 3 (*a*) (+)-DIPT (15 mol %), $Ti(O^iPr)_4$ (10 mol %), ^{t}BuOOH (50 mol %), 4Å sieves, CH_2Cl_2, –25 °C, 20 h; Me_2S, 20 °C, 16 h; (*b*) Red-al®, THF, 20 °C, 18 h; (*c*) O_3, MeOH, –20 °C, 10 min; Me_2S, 20 °C; 1 *M* HCl(aq), 3 h; (*d*) NaH, MeI, THF, 20 °C, 6 h; (*e*) $H_2C{=}CHCH_2SiMe_3$, Me_3SiOTf (10 mol %), MeCN, –20 °C, 2 min; (*f*) O_3, 3:1 CH_2Cl_2/MeOH, $NaHCO_3$(s), –78 °C, 10 min; Me_2S, 20 °C; (*g*) $Ph_3P{=}C(Me)CHO$, PhH, reflux, 18 h; (*h*) $(c\text{-}C_6H_{11})_2BCl$, Et_3N, Et_2O, 0 °C, 2 h; **11**, –78 → –20 °C, 14 h; H_2O_2, pH7 buffer, MeOH, 0 °C, 1 h; (*i*) $Me_4NBH(OAc)_3$, 1:1 AcOH/MeCN, –20 °C, 19 h; (*j*) $^tBu_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2, 20 °C, 17 h; (*k*) thexylborane, THF, 20 °C, 3 h; H_2O_2/NaOH, 20°C, 1 h; (*l*) $(imid)_2C{=}S$, THF, 60 °C, 16 h; (*m*) $^nBu_3SnH$, PhMe, reflux, 50 min; (*n*) H_2, 10% Pd/C, EtOH, 20 °C, 5 h; (*o*) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1 h; Et_3N, –78 → –25 °C, 30 min.

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References and Notes

1. Carmely, S.; Kashman, Y. *Tetrahedron Lett.* **1985**, *26*, 511.

2. (a) Kobayashi, M.; Tanaka, J.; Katori, T.; Matsuura, M.; Kitagawa, I. *Tetrahedron Lett* **1989**, *30*, 2963; (b) Kitagawa, I.; Kobayashi, M.; Katori, T.; Yamashita, M.; Tanaka, J.; Doi, M.; Ishida, T. *J. Am. Chem. Soc.* **1990**, *112*, 3710; (c) Kobayashi, M.; Tanaka, J.; Katori, T.; Matsuura, M.; Yamashita, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1990**, *38*, 2409; (d) Doi, M.; Ishida, T.; Kobayashi, M.; Kitagawa, I. *J. Org. Chem.* **1991**, *56*, 3629; (e) Kobayashi, M.; Tanaka, J.; Katori, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1990**, *38*, 2960.

3. (a) Sakai, R.; Higa, T.; Kashman, Y. *Chem. Lett.* **1986**, 1499; (b) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Sakai, R.; Higa, T.; Kashman, Y. *Tetrahedron Lett* **1987**, *28*, 6225; (c) Tanaka, J.; Higa, T.; Kobayashi, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1990**, *38*, 2967; (d) Kobayashi, J.; Tsukamoto, S.; Tanabe, A.; Sasaki, T.; Ishibashi, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2379.

4. This stereochemical homology also extends to the scytophycins, monomeric macrolides from the blue-green alga *Scytonema pseudohofmanni*, see: Ishibashi, M.; Moore, R. E.; Patterson, G. M. L.; Xu, C.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5300.

5. The monomeric acid **6** (= pre-swinholide A) has been isolated from *Theonella swinhoei*, collected in Papua New Guinea, see: Todd, J. S.; Alvi, K. A.; Crews, P. *Tetrahedron Lett.* **1992**, *33*, 441.

6. (a) Paterson, I.; Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, 797; (b) Paterson, I.; Goodman, J. M; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121; (c) Paterson, I.; Lister, M. A. *Tetrahedron Lett.* **1988**, *29*, 585.

7. (*E*)-1,5-heptadien-4-ol (**13**) was prepared by the method of Shono *et al.* in 80% yield from crotonaldehyde and allyl bromide, see: Shono, T.; Ishifune, M.; Kashimura, S. *Chem. Lett.* **1990**, 449.

8. (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765; (b) Roush, W. R.; Brown, R. J. *J. Org. Chem.* **1983**, *48*, 5093.

9. (a) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378; (b) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719.

10. All new compounds gave spectroscopic data in agreement with the assigned structures. **16** had ^{1}H NMR δ ($CDCl_3$, 400 MHz) 5.75 (1H, dddd, J = 17.1, 10.0, 7.1, 7.0 Hz, C<u>H</u>=CH_2), 5.05 (1H, d, J = 17.1 Hz, CH=C<u>H$_A$</u>H$_B$), 5.03 (1H, d, J = 10.0 Hz, CH=CH$_A$<u>H$_B$</u>), 4.05 (1H, m, H_{27}), 3.73 (1H, dqd, J = 9.4, 6.2, 2.9 Hz, H_{31}), 3.50 (1H, m, H_{29}), 3.30 (3H, s, OMe), 2.43 (1H, m, C<u>H$_A$</u>H$_B$CH=C), 2.19 (1H, m, CH$_A$<u>H$_B$</u>CH=C), 1.95 (1H, m, H_{30eq}), 1.84 (1H, m, H_{28eq}), 1.52 (1H, ddd, J = 12.9, 10.2, 5.4 Hz, H_{28ax}), 1.19 (1H, buried m, H_{30ax}), 1.18 (3H, d, J = 6.2 Hz, Me_{32}); ^{13}C NMR δ ($CDCl_3$, 100 MHz) 135.0, 117.0, 72.9, 71.4, 65.1, 55.2, 38.4, 36.7, 33.7, 21.6; HRMS (CI, NH_3) $[M+H]^+$ found 171.1385, $C_{10}H_{19}O_2$ requires 171.1385; **9** had ^{1}H NMR δ ($CDCl_3$, 400 MHz) 7.36-7.27 (5H, m, Ph), 5.45 (1H, dd, J = 6.8, 6.6 Hz, H_{25}), 4.52 & 4.47 (2H, AB_q, J_{AB}= 12.1 Hz, C<u>H$_2$</u>Ph), 4.18 (1H, dd, J = 9.3, 2.7 Hz, H_{23}), 4.05 (1H, m, H_{27}), 3.72 (1H, m, H_{31}), 3.68 (1H, dd, J = 8.9, 8.7 Hz, H_{19A}), 3.53 (1H, m, H_{29}), 3.45 (1H, dd, J = 8.9, 5.0 Hz, H_{19B}), 3.34 (3H, s, OMe), 3.10 (1H, dqd, J = 8.7, 7.0, 5.0 Hz, H_{20}), 2.88 (1H, dq, J = 9.3, 7.1 Hz, H_{22}), 2.62 (1H, s, OH), 2.45 (1H, m, H_{26A}), 2.21 (1H, m, H_{26B}), 1.99 (1H, m, H_{30eq}), 1.85 (1H, m, H_{28eq}), 1.63 (3H, s, C_{24}Me), 1.57 (1H, ddd, J = 12.9, 10.3, 5.5 Hz, H_{28ax}), 1.20 (1H, m, H_{30ax}), 1.19 (3H, d, J = 6.2 Hz, Me_{32}), 1.06 (3H, d, J = 7.0 Hz, C_{20}Me), 0.92 (3H, d, J = 7.1 Hz, C_{22}Me); ^{13}C NMR δ ($CDCl_3$, 100 MHz) 217.2, 137.8, 136.1, 128.4, 127.7, 127.6, 125.6, 80.0, 73.3, 73.1, 72.3, 71.8, 65.2, 55.3, 49.5, 45.8, 38.6, 34.0, 30.5, 21.7, 13.7, 13.6, 11.0; HRMS (CI, NH_3) $[M+NH_4]^+$ found 436.3063, $C_{25}H_{42}O_5N$ requires 436.3063; **5** had ^{1}H NMR δ (C_6D_6, 400 MHz) 9.97 (1H, d, J = 2.6 Hz, CHO), 4.31 (1H, dd, J = 9.1, 3.6 Hz, H_{21}), 4.02 (1H, m, H_{27}), 3.70 (1H, dd, J = 4.8, 4.6 Hz, H_{23}), 3.60 (1H, m, H_{31}), 3.38 (1H, m, H_{29}), 3.19 (3H, s, OMe), 2.46 (1H, dqd, J = 9.1, 7.0, 2.6 Hz, H_{20}), 1.89 (2H, m, H_{22}, H_{28eq}), 1.84 (2H, m, H_{26A}, H_{30eq}), 1.74 (1H, m, H_{28ax}), 1.61 (2H, m, H_{24}, H_{25A}), 1.51 (1H, m, H_{25B}), 1.30 (1H, m, H_{30ax}), 1.25 (3H, d, J = 6.4 Hz, Me_{32}), 1.16 (19H, s + buried m, H_{26B}, ^{t}Bu), 0.95 (3H, d, J = 6.7 Hz, C_{24}Me), 0.91 (3H, d, J = 7.3 Hz, C_{22}Me), 0.79 (3H, d, J = 7.0 Hz, C_{20}Me); ^{13}C NMR δ (C_6D_6, 100 MHz) 203.2, 82.3, 75.4, 73.6, 71.0, 64.8, 55.0, 49.3, 38.9, 38.5, 36.7, 35.6, 29.3, 28.3, 27.9, 26.9, 22.2, 22.0, 16.1, 13.9, 10.8; HRMS (CI, NH_3) $[M+H]^+$ found 471.3501, $C_{26}H_{51}O_5Si$ requires 471.3506.

11. Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383.

12. Trippett, S.; Walker, D. M. *J. Chem. Soc.* **1961**, 1266.

13. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

14. (a) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487; (b) Paterson, I.; Perkins, M. V. *Tetrahedron Lett.* **1992**, *33*, 801.

15. (a) Rasmussen, J. R.; Slinger, C. J.; Kordish, R. J.; Newman-Evans, D. D. *J. Org. Chem* **1981**, *46*, 4843; (b) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

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