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Synthetic studies on amphidinolides C and F: synthesis of the C18–C29 segment of amphidinolide F

Alan Armstrong *, Constantina Pyrkotis

Department of Chemistry, Imperial College London, South Kensington, London SW7 2AZ, UK

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ABSTRACT

The C18–C29 segment of amphidinolide F is synthesised in 12 steps from 1,4-butanediol. Key steps include a mono-Sharpless dihydroxylation of a dienoate, iodocyclisation to construct the *trans*-THF ring and an *E*-selective Wittig reaction to introduce the C25–C26 olefin.

The amphidinolides[1] are a structurally diverse family of cytotoxic marine compounds which occur naturally in only minute amounts; total synthesis therefore becomes an important potential source. Although successful routes to several members of the family have been reported,[1,2] this feat has not yet been accomplished for the closely related amphidinolides C[3] and F[4] (Fig. 1). Amphidinolide C, in particular, exhibits highly potent cytotoxic activity against L1210 and KB cells in vitro (values of 0.0058 and 0.0046 μg/ml, respectively), making a synthetic route to amphidinolides of this class an important goal. To date, three groups have reported studies towards the synthesis of fragments of these compounds.[3b,d,5] Here we describe our own approach, leading to a concise synthesis of the C18–C29 THF unit of amphidinolide F.

We envisaged key bond disconnections across the diene at C9–C10 and the macrolactone, as well as at C17–C18. These led us to require the THF fragment **1** (Scheme 1), which could be obtained by appropriate manipulation of the α-hydroxy-diester **2**. Diester **2** could in principle be accessed directly via a desymmetrising mono-Sharpless AD/Michael reaction on symmetrical dienoate **3**. In the forward sense, this process would raise interesting questions of regio- and stereocontrol (vide infra), but it would potentially provide a highly concise route to the key intermediate **2**.

We first required an efficient route for the synthesis of diene dioate **3**. Of several methods evaluated, the two proving most efficient in our hands are shown in Scheme 2. Hydrolysis of 2,5-dimethoxytetrahydrofuran **4** gave the dialdehyde **5** which underwent double Wittig reaction to give **3**[6] in 36% overall yield (*E*,*E*:*E*,*Z* = 92:8) from **4**. The low yield is believed to be at least partly due to the volatility and water miscibility of **5**. A higher overall yield was obtained in a sequential oxidation/olefination process using methodology recently reported by Graham and co-workers.[7] Thus, in situ MnO_2 monooxidation/olefination of diol **6** afforded **7**, which was isolated and purified before application of a second oxidation/olefination step, this time using PCC as oxidant, to give **3** (65% overall) with similar stereoselectivity (*E*,*E*:*E*,*Z* = 92:8).

With dienoate **3** in hand, we could now study the key conversion to THF **2**. Ideally, this would be effected directly via a novel

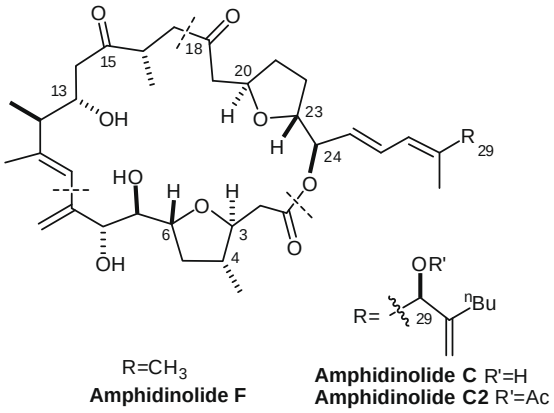

Figure 1. Structures of Amphidinolides C, C2 and F.

* Corresponding author. Fax: +44 0 20 75945804.
E-mail address: a.armstrong@imperial.ac.uk (A. Armstrong).

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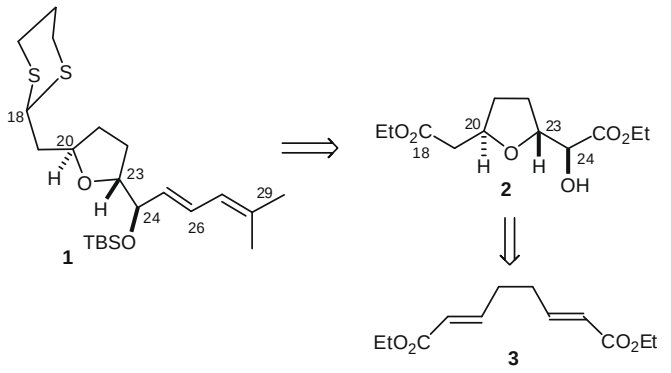
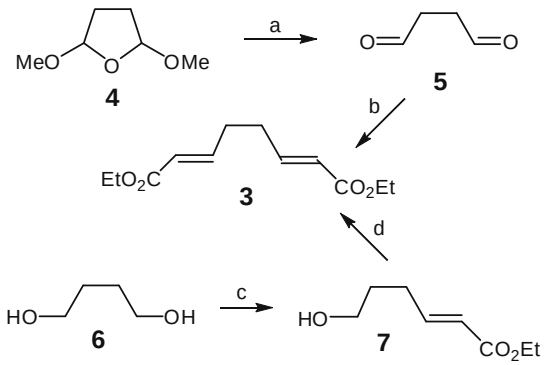


Scheme 1.



Scheme 2. Reagents and Conditions: (a) HCl (aq), THF, reflux, 2 h; (b) $Ph_3P{=}CHCO_2Et$, 3 Å MS, CH_2Cl_2, rt, 36 h, 36%; (c) MnO_2, $Ph_3P{=}CHCO_2Et$, 48 h, 95%; (d) PCC, imidazole, $Ph_3P{=}CHCO_2Et$, 19 h, 65%.

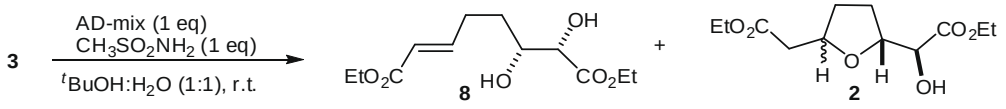
one-pot Sharpless AD/Michael reaction. Mono- versus bis-dihydroxylation of the diene was a potential concern. While we could not find direct literature precedent for selective mono-AD on 2,6-dienoates, there was literature precedent for mono-dihydroxylation of this type of substrate under Upjohn conditions.[8] Additionally, we hoped that in situ Michael reaction of the initially formed AD product would remove the potentially reactive second alkene before any second dihydroxylation could take place.

For the cyclisation step, we envisaged that the desired 5-*exo*-trig cyclisation mode would be kinetically preferred over the alternative possible 6-*exo*-trig.[9] A further key question involved stereoselectivity in the Michael reaction, given the lack of stereocentres in the linking chain between C20 and C23. In one relevant precedent, Kobayashi observed non-diastereoselective cyclisation in a Michael reaction as part of his synthesis of the amphidinolide C17–C29 fragment.[3d] While this was not encouraging, we hoped that use of alternative cyclisation conditions would allow improved stereocontrol. Application of standard Sharpless AD conditions[10] to **3** with 1 equivalent of AD-mix-β (Table 1, entry 1) in the presence of methanesulfonamide effected complete reaction in <2 h. The diol **8** was isolated in 85% yield together with 10% of the THF **2**, which was obtained as a 3:2 mixture of diastereoisomers according to ^{1}H NMR analysis. The enantiomeric excess of diol **8** was determined by chiral HPLC and found to be 73%. For comparison, AD was also carried out with AD-mix-α (entry 2). Interestingly, this gave diol *ent*-**8** of lower ee (57% ee), despite the fact that the quinidine and quinine-derived ligands in the two AD-mixes usually behave as 'pseudoenantiomers', giving products of similar enantiomeric excess. We next attempted the AD reaction in the presence of additional base in an attempt to promote the cyclisation reaction (entries 3 and 4). While conversion was high and the THF **2** was now the major product, the yield was low, suggesting base-mediated decomposition. Moreover, the diastereoselectivity was consistently low (3:2). Since we had been able to isolate only low amounts of THF **2**, but good yields of diol **8**, we decided to investigate the cyclisation step separately. Treatment of **8** with 1 equiv of EtONa in EtOH/THF for 2 h gave **2** in 50% yield, again as a 3:2 mixture of diastereoisomers. Aprotic conditions (LHMDS in THF) gave very low conversion and an unchanged stereoisomeric ratio. We were able to separate small quantities of the two diastereomers, and resubmission of these to base allowed us to tentatively conclude that the minor *cis*-diastereomer was thermodynamically preferred. We therefore decided to abandon the Michael addition and investigate alternative methods for THF formation.

Iodocyclisation has been widely employed for THF synthesis[11] and was an attractive option. This was first attempted with the 'unnatural' diol, *ent*-**8** (Scheme 3), affording a 3:1 mixture of *trans*- and *cis*- tetrahydrofurans *ent*-**9b** and *ent*-**9a**. Separation of the two diastereoisomers using flash chromatography gave the *trans*-diastereoisomer *ent*-**9b** as a pale yellow semi-crystalline solid, recrystallisation of which resulted in enhanced ee (93%) according to chiral HPLC analysis. X-ray crystallography[12] verified both the relative and the absolute configuration of *ent*-**9b**.

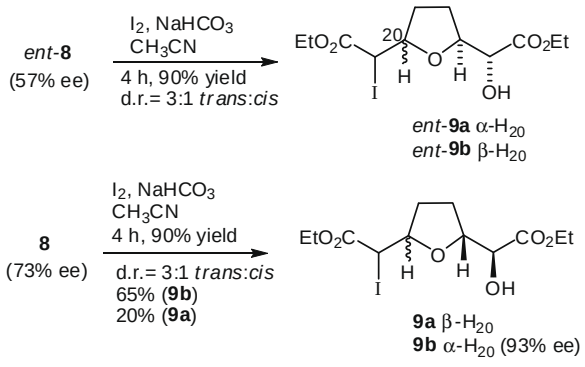
We repeated the iodocyclisation with **8** itself (Scheme 3) to obtain **9b**. Resolution during recrystallisation again resulted in enrichment from 73% to over 93% ee.[13] The improved cyclisation diastereoselectivity (albeit in a still-moderate 3:1 ratio), the significantly increased overall yield and the opportunity to improve the enantiomeric excess via resolution during the recrystallisation meant that the iodocyclisation approach towards the synthesis of this fragment was preferable to the earlier, base-mediated cyclisation.

Table 1
Dihydroxylation/Cyclisation of Dienoate **3**

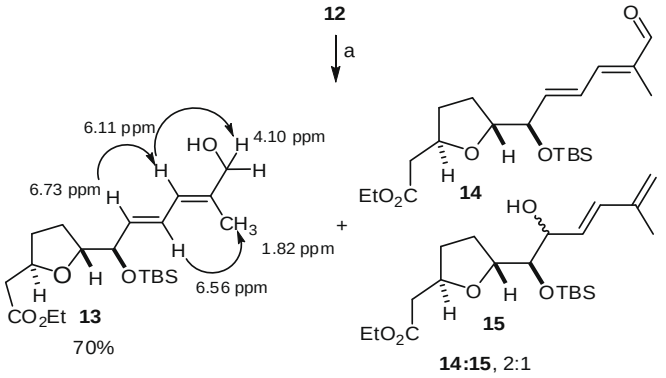


Entry	AD-mix	Additive	Time (h)	Yield **8** (%)	Yield **2** (%)	**2** *trans:cis*[a]
1	β	—	2	85	10	3:2
2[b]	α	—	2	82	12	3:2
3	β	DBU (2 equiv)	18	—	35	3:2
4	β	NaOH (2 equiv)	8	—	40	3:2

[a] Determined by ^{1}H NMR analysis. Major isomer is the *trans*-THF by correlation with products from the iodocyclisation route.
[b] *Ent*-**8** and *ent*-**2** obtained in this experiment.



Scheme 3.

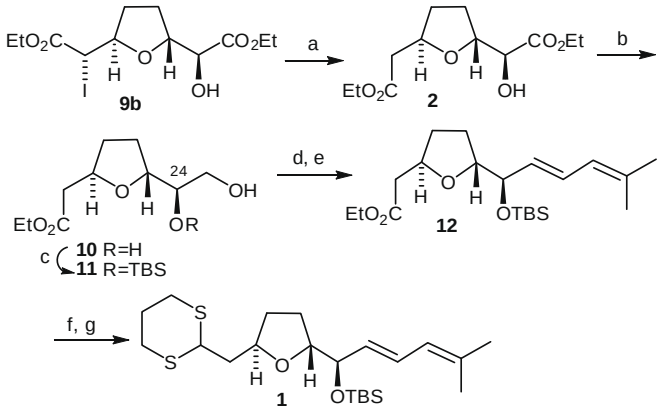


Scheme 5. (a) SeO_2, ^tBuOOH, CH_2Cl_2, rt, overnight.

Having desymmetrised the diene dioate **3**, we were now in a position to install the required functionality at either side of the THF unit (Scheme 4). Deiodination of **9b** could be effected efficiently using either tributyltin hydride/cat. AIBN in toluene at 50 °C or with indium hydride,[14] generated from $NaBH_4$/cat. $InCl_3$. Differentiation of the two ethyl esters was now accomplished by selective reduction of the α-hydroxy ester[15] using $BH_3{\cdot}SMe_2$/cat. $NaBH_4$. Hydroxy group differentiation was achieved by *bis*-TBS ether formation and selective primary deprotection, affording **11**. Dess-Martin oxidation in the presence of 1 equiv of H_2O[16] afforded an unstable aldehyde in 80% yield which was then subjected to an *E*-selective olefination[17] with a tributylphosphonium ylide to provide **12**[18] (43% from alcohol **11**; 87:13, *E*:*Z*). The *E*-isomer was distinguished from the minor *Z*-isomer by coupling constant analysis (*J* H25–H26 = 15.1 vs 11.3 Hz). Reduction of the ethyl ester with DIBAL-H gave the corresponding aldehyde which was then converted to the 1,3-dithiane **1**.[19] Use of $BF_3{\cdot}OEt_2$ as Lewis acid in this step afforded **1** in only moderate yields due to competitive cleavage of the TBS ether. However, use of the milder Lewis acid $MgBr_2{\cdot}OEt_2$ solved this problem, leading to formation of **1** (87:13, *E*:*Z*) in 75% yield (over two steps).

Finally, we have performed preliminary studies demonstrating the feasibility of converting the amphidinolide F side-chain into that of amphidinolide C, via selective allylic oxidation at C29 (Scheme 5). We could find little literature precedent for SeO_2-mediated allylic oxidation[20] of acyclic 1,3-dienes, and this process could potentially result in a mixture of regioisomeric products. In the event, **12** underwent SeO_2 allylic oxidation to give, after chromatography, the desired allylic alcohol **13**[21] (ca. 70%; *E*,*E*-configuration confirmed by NOE analysis), along with a 2:1 mixture assigned tentatively by ^1H NMR as aldehyde **14** and regioisomeric allylic alcohols **15**. This key transformation potentially allows access into amphidinolide C and analogues bearing unnatural side-chains at C29.

In conclusion, we have achieved a synthesis of the C18–C29 fragment 1 of amphidinolide F in 12 steps starting from commercially available butane-1,4-diol 6. We have also demonstrated potential for further elaboration to amphidinolide C and analogues via oxidation at C29. Further studies towards these targets are currently underway.



Scheme 4. Reagents and Conditions: (a) AIBN, nBu$_3$SnH, toluene, reflux, 1 h, 95% *or* cat. $InCl_3$, $NaBH_4$, CH_3CN, 3 h, 73%; (b) (i) $BH_3{\cdot}SMe_2$/THF, rt; (ii) $NaBH_4$; (iii) EtOH, TsOH, 60% (+18% starting material); (c) (i) TBSCl, imidazole DMF, rt, overnight, 81%; (ii) HF.pyridine, pyridine, THF, rt, 8 h, 86%; (d) Dess-Martin periodinane, CH_2Cl_2 (wet), rt, 5–15 min; (e) $Me_2C{=}CHCH_2P^+Bu_3Br^-$, nBuLi (in hexanes), DMSO, toluene, −78 °C to 0 °C, 43% (over two steps), 87:13 *E*:*Z*; (f) DIBAL-H, THF, −78 °C, 1 h; (g) $HS(CH_2)_3SH$, $MgBr_2{\cdot}OEt_2$, CH_2Cl_2, rt, 1 h, 75% (over two steps).

Acknowledgements

We thank Merck Sharpe and Dohme and Pfizer for support of our work. C.P. thanks the A.G. Leventis Foundation for a fellowship.

References and notes

1. (a) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77–93; (b) Kobayashi, J. *J. Antibiot.* **2008**, *61*, 271–284; (c) Kobayashi, J.; Kubota, T. *J. Nat. Prod.* **2007**, *70*, 451–460.
2. For reviews, see: (a) Chakraborty, T. K.; Das, S. *Curr. Med. Chem.-Anti-Cancer Agents* **2001**, *1*, 131–149; (b) Hiersemann, M. *Nachr. Chem.* **2006**, *5*, 534–537; (c) Colby, E. A.; Jamison, T. F. *Org. Biomol. Chem.* **2005**, *3*, 2675–2684; (d) Furstner, A.; Bouchez, L. C.; Funel, J. A.; Liepins, V.; Poree, F. H.; Gilmour, R.; Beaufils, F.; Laurich, D.; Tamiya, M. *Angew. Chem. Int. Ed* **2007**, *46*, 9265–9270. and references therein..
3. (a) Kobayashi, J.; Ishibashi, M.; Walchli, M. R.; Nakamura, H.; Hirata, Y.; Takuma, S.; Ohizumi, Y. *J. Am. Chem. Soc.* **1988**, *110*, 490–494; (b) Ishiyama, H.; Ishibashi, M.; Kobayashi, J. *Chem. Pharm. Bull.* **1996**, *44*, 1819–1822; (c) Kubota, T.; Tsuda, M.; Kobayashi, J. *Org. Lett.* **2001**, *3*, 1363–1366; (d) Kubota, T.; Tsuda, M.; Kobayashi, J. *Tetrahedron* **2003**, *59*, 1613–1625; (e) Kubota, T.; Tsuda, M.; Kobayashi, J. *Tetrahedron* **2001**, *57*, 5975–5977.
4. Kobayashi, J.; Tsuda, M.; Ishibashi, M.; Shigemori, H.; Yamasu, T.; Hirota, H.; Sasaki, T. *J. Antibiot.* **1991**, *44*, 1259–1261.
5. (a) Shotwell, J. B.; Roush, W. R. *Org. Lett.* **2004**, *6*, 3865–3868; (b) Bates, R. H.; Shotwell, J. B.; Roush, W. R. *Org. Lett.* **2008**, *10*, 4343–4346; (c) Mohapatra, D. K.; Rahaman, H.; Chorghade, M. S.; Gurjar, M. K. *Synlett* **2007**, 567–570; Synthesis of an amphidinolide U fragment: Mohapatra, D. K.; Rahaman, H. *Synlett* **2008**, 837–840.
6. Sato, K.; Inoue, S.; Ota, S.; Fujita, Y. *J. Org. Chem.* **1972**, *37*, 462–464.
7. (a) Phillips, D. J.; Pillinger, S. K.; Li, W.; Taylor, A. E.; Graham, A. E. *Chem. Commun.* **2006**, 2280–2282; (b) Phillips, D. J.; Pillinger, S. K.; Li, W.; Taylor, A. E.; Graham, A. E. *Tetrahedron* **2007**, *63*, 10528–10533.
8. Saito, S.; Morikawa, Y.; Moriwake, T. *Synlett* **1990**, 523–524.
9. Guindon, Y.; Delorme, D.; Law, K. C.; Zamboni, R. *J. Org. Chem.* **1988**, *53*, 267–275.
10. Reviews: (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547; (b) Zaitsev, A. B.; Adolfsson, H. *Synthesis* **2006**, 1725–1756.
11. For examples of Sharpless AD/iodocyclization for THF synthesis, see: (a) Zhang, H.; Mootoo, R. D. *J. Org. Chem.* **1995**, *60*, 8134–8135; (b) Zhang, H.; Seepersaud, M.; Seepersaud, S.; Mootoo, R. D. *J. Org. Chem.* **1998**, *63*, 2049–2052.

12. We thank Dr. A. J. P. White, Department of Chemistry, Imperial College, London, for determination of this crystal structure.
13. Data for **9b**: pale yellow crystalline solid, mp = 58–60 °C, ee = 93% (chiral HPLC, Chiralcel OD, 10% ^{i}PrOH/hexane, 0.05 mL/min, 254 nm) **9b** (153.8 min), *ent*-**9b** (164.0 min); **9b**; R_f 0.75, (50% EtOAc/petrol); $[\alpha]_D^{20}$ −22.7 (*c*. 1.06, EtOH); IR ($CHCl_3$): ν_{max} 3436, 2982, 1736, 1281, 469 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.43 (td, *J* 7.6, 2.0 Hz, 1H), 4.38–4.31 (m, 1H), 4.30–4.12 (m, 4H), 4.02 (d, *J* 2.0 Hz, 1H), 2.93 (d, *J* 8.4 Hz, 1H), 2.44–2.36 (m, 1H), 2.17–2.01 (m, 2H), 1.87–1.78 (m, 1H), 1.68 (br s, 1H), 1.27 (t, *J* 7.2 Hz, 3H), 1.25 (t, *J* 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.5, 169.6, 80.84, 80.75, 72.4, 61.77, 61.75, 32.2, 27.5, 25.7, 14.1, 13.7; HRMS (CI) *m*/*z* calcd for $C_{12}H_{23}NO_6I$ (MNH_4^+), 404.0570, found: 404.0574.
14. Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 906–907.
15. (a) Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R.; Fujii, T.; Nomizu, S.; Moriwake, T. *Chem. Lett.* **1984**, 1389–1392; (b) Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067–4086.
16. Meyer, D. S.; Schreiber, S. *J. Org. Chem.* **1994**, *59*, 7549–7552.
17. Tamura, R.; Saegusa, K.; Kakihana, M.; Oda, D. *J. Org. Chem.* **1988**, *53*, 2723–2728.
18. Data for **12** (87:13, *E*:*Z*) R_f 0.82 (20% EtOAc/petrol); $[\alpha]_D^{25}$ −32.0 (*c*. 1.04, EtOH); IR ($CHCl_3$): ν_{max} 1739, 1659, 1463, 1430, 1379, 1254 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.49 (dd, *J* 15.1, 11.1 Hz, $1H_{major}$), 6.23 (app t, *J* 11.3 Hz, $1H_{minor}$), 6.10 (d, *J* 11.3 Hz, $1H_{minor}$), 5.85 (d, *J* 10.8 Hz, $1H_{major}$), 5.56 (dd, *J* 15.1, 5.5 Hz, $1H_{major}$), 5.30 (app t, *J* 10.6 Hz, $1H_{minor}$), 4.38–4.28 (m, 1H), 4.23 (t, *J* 5.5 Hz, 1H), 4.15 (q, *J* 7.1 Hz, 2H), 4.00 (dt, *J* 7.1, 5.5 Hz, 1H), 2.61 (dd, *J* 15.0, 7.1 Hz, 1H), 2.43 (dd, *J* 15.0, 6.3 Hz, 1H), 2.15–2.03 (m, 1H), 1.95–1.85 (m, 1H), 1.79 (s, 3H), 1.77 (s, 3H), 1.65–1.38 (m, 2H), 1.28 (t, *J* 7.1 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3, 137.0 (*Z*), 135.0 (*E*), 129.6 (*E*), 128.5 (*Z*), 127.5 (*E*), 125.7 (*Z*), 124.7 (*E*), 120.3 (*Z*), 82.3, 75.7, 75.1, 60.4, 40.9, 31.9, 26.9, 26.0, 25.9 (3 × C), 18.2 (2 × C), 14.2, −4.7 (2 × C); HRMS (CI) *m*/*z* calcd for $C_{21}H_{42}NO_4Si$ (MNH_4^+), 400.2883, found: 400.2883.
19. Data for **1**: R_f 0.52 (10% EtOAc/petrol); $[\alpha]_D^{25}$ −25.3 (*c*. 1.02, EtOH); IR ($CHCl_3$): ν_{max} 1654, 1462, 1378, 1264, 1063 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.29 (app t, *J* 14.3 Hz, 1H), 5.87 (br d, *J* 11.1 Hz, 1H), 5.50–5.37 (m, 1H), 4.34–4.26 (m, 1H), 4.24–4.19 (m, 1H), 4.18–4.11 (m, 1H), 4.10–4.00 (m, 1H), 2.95–2.73 (m, 4H), 2.70–2.55 (m, 2H), 2.14–1.77 (m, 4H), 1.80 (s, 3H), 1.78 (s, 3H), 1.62–1.34 (m, 2H), 0.94 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.6 (C_Z), 135.5 (C_E), 129.9 (CH_Z), 129.2 (CH_E), 128.0 (CH_E), 125.3 (CH_Z), 124.4 (CH_E), 122.9 (CH_Z), 81.3, 80.5, 76.1, 44.4, 41.8, 37.4, 33.5, 31.3, 30.4, 26.0, 25.6, 23.9, 20.8, 18.5, −3.6; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{25}OS_2$ ($M-OTBS^+$), 297.1347, found: 297.1374.
20. (a) McMurry, J. E.; Rico, J. G.; Shih, Y. *Tetrahedron Lett.* **1989**, *30*, 1173–1176; (b) Ichige, T.; Okano, Y.; Kanoh, N.; Nakata, M. *J. Am. Chem. Soc.* **2007**, *129*, 9862–9863; (c) Kim, M.; Kleckley, T. S.; Wiemer, A. J.; Holstein, S. A.; Holh, R. J.; Wiemer, D. F. *J. Org. Chem.* **2004**, *69*, 8186–8193.
21. Data for **13**: R_f 0.76 (50% EtOAc/petrol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.56 (ddd, *J* 15.1, 11.1, 1.4 Hz, 1H), 6.11 (d, *J* 11.1 Hz, 1H), 5.73 (dd, *J* 15.1, 5.1 Hz, 1H), 4.37–4.27 (m, 2H), 4.17 (q, *J* 7.1 Hz, 2H), 4.11 (d, *J* 4.1 Hz, 2H), 4.06–4.00 (m, 1H), 2.61 (dd, *J* 15.0, 7.1 Hz, 1H), 2.45 (dd, *J* 15.0, 6.2 Hz, 1H), 2.12–1.84 (m, 2H), 1.82 (s, 3H), 1.83–1.72 (m, 1H), 1.58–1.36 (m, 2H), 1.29 (t, *J* 7.1 Hz, 3H), 0.93 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H).