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Tetrahedron Letters 45 (2004) 7899–7902
Tetrahedron Letters

Towards the total synthesis of amphidinolide E: an enantioselective synthesis of C12–C29 fragment

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Received 19 July 2004; revised 16 August 2004; accepted 24 August 2004
Available online 11 September 2004

Abstract—An enantioselective synthesis of the C12–C29 fragment of amphidinolide E is described. Key transformations include an intramolecular mercuriocyclization reaction, stereoselective introduction of methyl group at the C2 position, and Stille coupling for the introduction of the diene side chain.

The family of amphidinolides was isolated from the marine dinoflagellates *Amphidinium* sp.[1] and characterized by a significant anti-tumor activity against a variety of NCI tumor cell lines. Among them, amphidinolide E **1** has a unique feature of a 19-membered macrocyclic structure, which was elucidated by 2D NMR data[2] while the relative stereochemistry of eight chiral centers positioned at C2, C7, C8, C13, C16, C17, C18 and C19 were confirmed by a combination of the *J*-based configuration method and detailed NOESY experiments. The absolute stereochemistry of **1** was determined by the exciton chirality method coupled with Mosher's method.[3] Because of its unique structural features, notable biological activity, and limited availability, the amphidinolide group of molecules represents attractive targets for total synthesis. Herein, we report an enantioselective synthesis of the C12–C29 fragment of amphidinolide E **1** starting from D-glucose.

Our retrosynthetic analysis for the synthesis of the C12–C29 fragment of amphidinolide E **1** is illustrated in Scheme 1. The four chiral centers at C16–C19 were to be obtained from D-glucose while the stereo-controlled off-template construction of the tetrahydrofuran ring was predicted by utilizing the mercuriocyclization protocol on the 4-alkenol derivative **6**. The side-chain installation was to employ the Stille coupling reaction between the triflate **3** and the dienyl-stannane intermediate **8** (Scheme 1).

The reported[4] intermediate **6** was prepared from D-glucose by a modified protocol in which the Grignard reaction was carried out in ether by reverse addition of Grignard reagent at 0 °C to improve the diastereoselectivity (9:1) in favor of **6**. Compound **6** was isolated from the reaction mixture by crystallization in 80% yield. The oxymercuration reaction[5] of **6** gave a *cis–trans* mixture of tetrahydrofuran derivatives with 3:1 selectivity but conveniently separated by flash chromatography to obtain the pure *cis*-tetrahydrofuran **11**. The stereochemistry of **11** was unambiguously determined by X-ray crystallography (Fig. 1).[6] The demercuration[7] reaction of **11** was carried out under a stream of oxygen in the presence of $NaBH_4$ to give **12**, which was benzylated to form **13** (Scheme 2).

Our next concern was the introduction of a methyl group at C2 for which compound **12** was heated under reflux for a prolonged period with methanol and Amberlyst IR120 H^+ resin followed by chromatography to give the pure β-glycosides **14**. The β-glycoside **14** showed in its ^1H NMR spectrum a characteristic singlet at δ 4.78, corresponding to H1. The secondary hydroxyl group present in **14** was oxidized with IBX[8] in DMSO to give the 2-ulose derivative **15**, which was subjected to one carbon homologation with $Ph_3P{=}CH_2$ to produce the olefin **16**. The hydrogenation of the double bond in the presence of 10% Pd–C gave **5** exclusively. The

Keywords: Mercuriocyclization; Stille coupling; Wittig reaction; Hydroboration–oxidation.
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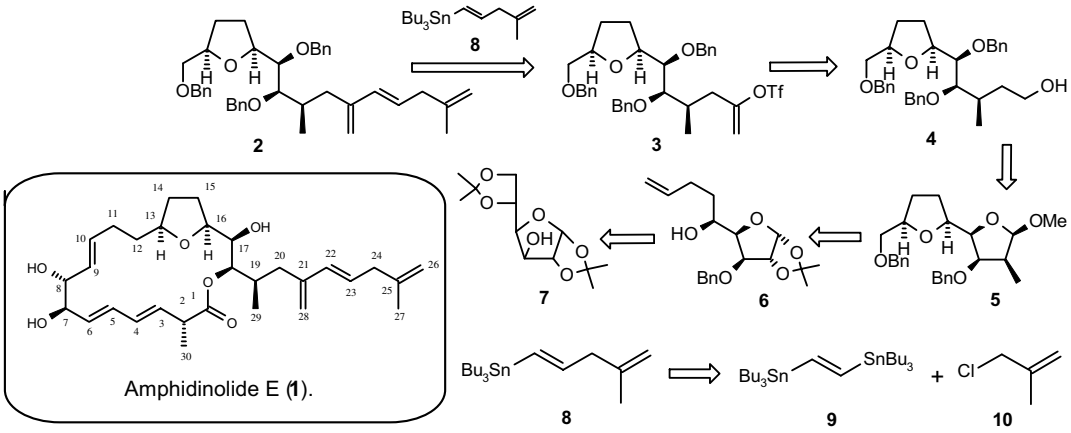
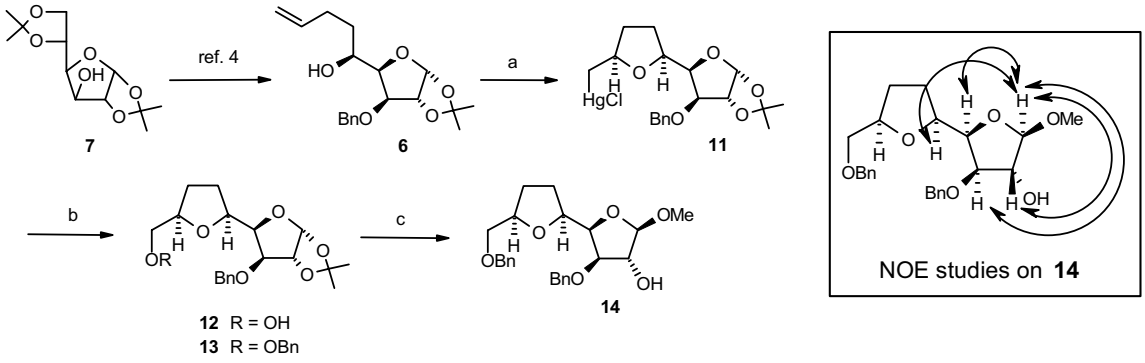
doi:10.1016/j.tetlet.2004.08.143



Scheme 1.



Scheme 2. Reagents and conditions: (a) $HgCl_2$, H_2O, 1 h, rt, 90%; (b) (1) O_2, $NaBH_4$, DMF, 4 h, rt, 81%; (2) NaH, BnBr, DMF, 3 h, rt, 94%; (c) Amberlyst IR 120, MeOH, 9 h, reflux, 86%.

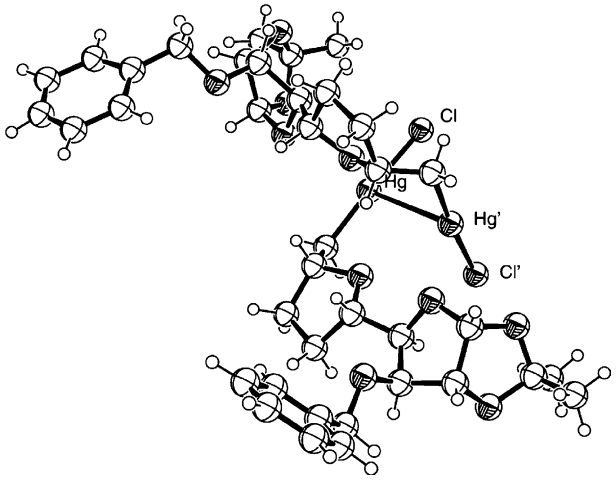


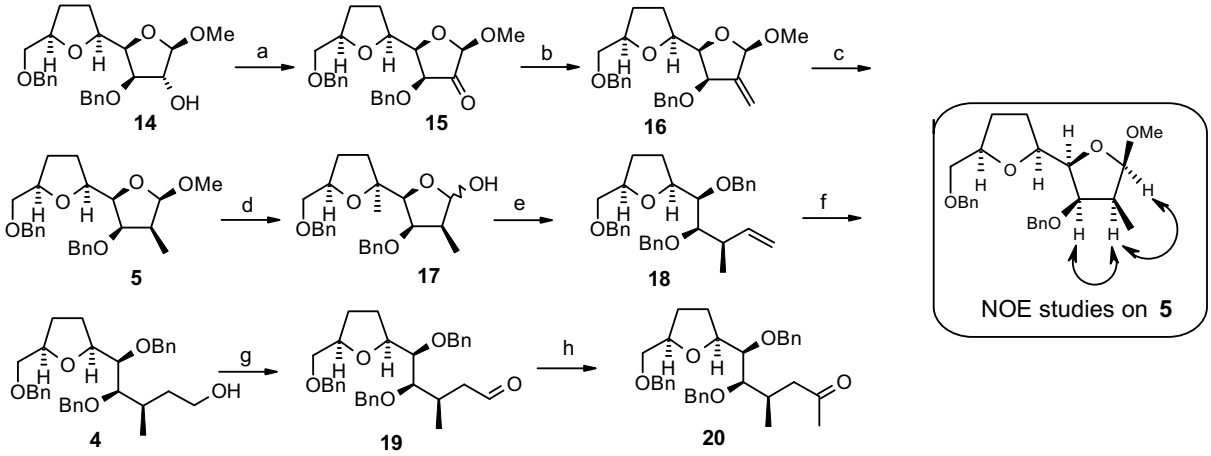
Figure 1. ORTEP diagram of **11**.

structure of **5** was confirmed by NOESY experimental data. In order to convert **5** into the primary hydroxyl derivative **4** successive hydrolysis,[9] Wittig reaction, benzylation, and hydroboration–oxidation reactions[10] were carried out (Scheme 3). Compound **4** was oxidized using the Dess–Martin periodinane (DMP)[11] and then the derived aldehyde **19** was subjected to a Grignard reaction with MeMgI and oxidation with DMP to give the ketone **20**. The structure of **20** was confirmed by ^1H, ^{13}C NMR, mass, and elemental analysis.

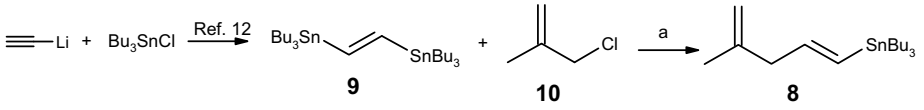
The stannane derivative **8** was not known, so designing its synthesis became our priority. Amongst several protocols that could be envisaged, a Pd-catalyzed C–C bond forming approach[12,13] was chosen for its simplicity. Bis-ethylene distannane **9** was reacted with methallyl chloride **10** in the presence of $PdCl_2(CH_3CN)_2$ followed by distillation to give **8**, which was analyzed by ^1H, ^{13}C NMR, mass, and elemental analysis (Scheme 4).

Compound **20** was first enolated with LDA and then treated with *N*-(2-pyridyl)-triflimide[14] to give rise to the O-Tf derivative **3**. It was immediately reacted with **8** by the modified Stille coupling reaction[15] to afford the target fragment **2** (Scheme 5). The structure of compound **2** was confirmed by its ^1H, ^{13}C NMR, mass spectra, and microanalysis.[16]

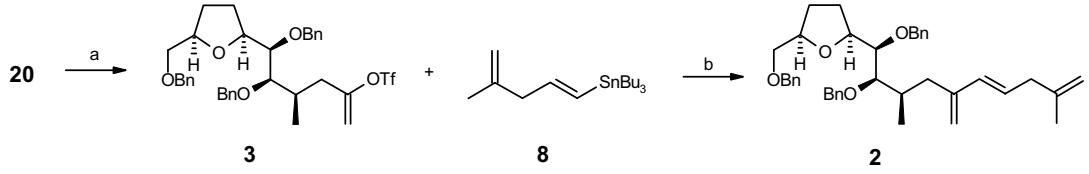
In conclusion, we have synthesized an advance C12–C29 segment of amphidinolide E **1** and further work leading to the total synthesis of **1** is under extensive investigation.



Scheme 3. Reagents and conditions: (a) IBX, DMSO, 3 h, rt, 92%; (b) $Ph_3P{=}CH_2$, THF–Et_2O, 4 h, rt, 78%; (c) Pd–C, H_2, MeOH, 20 min, rt, 92%; (d) 20% AcOH, 4 h, 80 °C, 76%; (e) (1) $Ph_3P{=}CH_2$, THF–Et_2O, 4 h, rt, 86%; (2) NaH, BnBr, DMF, 3 h, rt, 93%; (f) 9-BBN, NaOH, H_2O_2, 5 h, rt, 90%; (g) Dess–Martin periodinane, DCM, 30 min, rt, 96%; (h) (1) MeMgI, Et_2O, 2 h, rt, 87%; (2) Dess–Martin periodinane, DCM, 30 min, rt, 95%.



Scheme 4. Reagents and conditions: (a) $PdCl_2(CH_3CN)_2$, methallyl chloride, THF, 5 h, 50 °C, 84%.



Scheme 5. Reagents and conditions: (a) LDA, *N*-(2-pyridyl)-triflimide, DME, −78 °C, 3 h, 81%; (b) $Pd(PPh_3)_4$, LiCl, CuCl, DMSO, 6 h, 60 °C, 92%.

Acknowledgements

S.M. is thankful to CSIR, New Delhi, for providing financial assistance in the form of a research fellowship.

References and notes

1. (a) Ishbashi, M.; Kobayashi, J. *Heterocycles* **1997**, *44*, 543–572; (b) Chakraborty, T. K.; Das, S. *Curr. Med. Chem. Anti Cancer Agents* **2001**, *1*, 131–149; (c) Kobayashi, J.; Shimbo, K.; Kubota, T.; Tsuda, M. *Pure Appl. Chem.* **2003**, *75*, 337.
2. Kobayashi, J.; Ishibashi, M.; Murayama, T.; Takamatsu, M.; Iwamura, M.; Ohizumi, Y.; Sasaki, T. *J. Org. Chem.* **1990**, *55*, 3421–3423.
3. Kubota, T.; Tsuda, M.; Kobayashi, J. *J. Org. Chem.* **2002**, *67*, 1651–1656.
4. Bertrand, P.; Sukkari, H. E.; Gesson, J. P.; Renoux, B. *Synthesis* **1999**, *2*, 330–335.
5. (a) Speziale, V.; Roussel, J.; Lattes, A. *J. Heterocycl. Chem.* **1974**, *11*, 771; (b) Vincens, M.; Dumont, C.; Vidal, M. *Can. J. Chem.* **1979**, *57*, 2314.
6. CCDC 244671, X-ray crystal data: single crystals of the complex were grown by slow evaporation of the solution in dichloromethane. Colorless needle of approximate size $0.37 \times 0.18 \times 0.08$ mm, was used for data collection on Bruker SMART APEX CCD diffractometer using Mo K_α radiation with fine focus tube with 50 kV and 30 mA. Crystal to detector distance 6.05 cm, 512×512 pixels/frame, Quadrant data acquisition. Total scans = 4, total frames = 2424, oscillation/frame −0.3°, exposure/frame = 20.0 s/frame, maximum detector swing angle = −30.0°, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, θ range = 2.13 to 28.31°, completeness to θ of 28.31° is 94.9%. SADABS correction applied, $2(C_{19}H_{25}O_5HgCl)$. 0.5 H_2O, $M = 1156.88$. Crystals belong to orthorhombic, space group $P2_1$, $a = 10.987(2)$, $b = 20.206(3)$, $c = 11.125(2)$ Å, $V = 2414.0(6)$ Å^3, $Z = 2$, $D_c = 1.592$ mg m^{-3}, μ (Mo K_α) = 6.511 mm^{-1}, $T = 295(2)$ K, 27,288 reflections measured, 11,013 unique [$I > 2\sigma(I)$], R value 0.0373, wR2 = 0.0865. All the data were corrected for Lorentzian, polarization, and absorption effects. SHELX-97 (ShelxTL) was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. Compound crystallizes with half molecules of water as solvent of crystallization (Sheldrick, G. M. SHELX-97 Program for Crystal Structure Solution and Refinement, University of Gottingen, Germany, 1997).

7. Sih, J. C.; Graber, D. R. *J. Org. Chem.* **1982**, *47*, 4919–4927.
8. Frigeno, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022.
9. Kruse, C. G.; Jonkers, F. L.; Dert, V.; Gen, A. V. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 371.
10. Brown, H. C.; Knights, E. F.; Scouten, C. G. *J. Am. Chem. Soc.* **1974**, *96*, 7765–7770.
11. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
12. Bottaro, J. C.; Hanson, R. N.; Seitz, D. E. *J. Org. Chem.* **1981**, *46*, 5221–5222.
13. Naruse, Y.; Esaki, T.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 4747–4756.
14. Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299–6301.
15. Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605.
16. Spectral data of compound **11**: $[\alpha]_D$ −29.3 (*c* 3.35, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 6.02 (d, 1H, J = 3.8 Hz), 4.67 (d, 1H, J = 11.9 Hz), 4.58 (d, 1H, J = 3.8 Hz), 4.45 (d, 1H, J = 11.9 Hz), 4.34 (m, 1H), 4.18 (q, 1H, J = 7.4, 14.1 Hz), 4.02 (dd, 1H, J = 3.3, 6.5 Hz), 3.86 (d, 1H, J = 3.3 Hz), 2.34 (dd, 1H, J = 5.3, 12.5 Hz), 2.13 (m, 1H), 2.05 (m, 1H), 1.96 (m, 1H), 1.65 (m, 1H), 1.49 (s, 3H), 1.42 (m, 1H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 128.5, 128.0, 127.9, 111.7, 105.3, 83.2, 83.0, 82.0, 78.7, 77.9, 71.8, 38.3, 35.3, 28.8, 27.0, 26.5; Anal. Calcd for $C_{19}H_{25}O_5HgCl$: C, 40.07; H, 4.42. Found: C, 40.32; H, 4.78.
Spectral data of compound **13**: $[\alpha]_D$ −45.1 (*c* 4.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 10H), 5.96 (d, 1H, J = 3.5 Hz), 4.65 (d, 1H, J = 11.4 Hz), 4.58 (d, 1H, J = 3.5 Hz), 4.54 (s, 2H), 4.41 (d, 1H, J = 11.4 Hz), 4.12 (m, 2H), 4.06 (dd, 1H, J = 3.2, 6.9 Hz), 3.85 (d, 1H, J = 3.4 Hz), 3.54 (dd, 1H, J = 4.4, 9.3 Hz), 3.46 (dd, 1H, J = 4.4, 9.3 Hz), 1.94 (m, 1H), 1.81 (m, 2H), 1.50 (m, 1H), 1.45 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 137.1, 128.2, 128.0, 127.7, 127.5, 127.3, 127.2, 111.3, 105.31, 83.3, 82.5, 81.7, 78.3, 78.0, 73.1, 73.0, 72.4, 71.4, 28.0, 27.2, 26.7, 26.3; Anal. Calcd for $C_{26}H_{32}O_6$: C, 70.88; H, 7.32. Found: C, 71.12; H, 7.14.
Spectral data of compound **14**: $[\alpha]_D$ −38.0 (*c* 2.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.32 (m, 10H), 4.78 (s, 1H), 4.65 (d, 1H, J = 11.9 Hz), 4.53 (br s, 2H), 4.46 (d, 1H, J = 11.9), 4.24 (br s, 1H), 4.12 (m, 2H), 4.06 (t, 1H, J = 6.3 Hz), 3.84 (dd, 1H, J = 3.0, 6.3 Hz), 3.56 (dd, 1H, J = 4.8, 9.8 Hz), 3.45 (dd, 1H, J = 4.8, 9.8 Hz), 3.40 (s, 3H), 1.94 (m, 2H), 1.75 (m, 1H), 1.53 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 137.8, 128.4, 128.3, 127.9, 127.8, 127.7, 127.5, 109.6, 83.8, 83.4, 79.3, 78.6, 78.4, 73.4, 72.9, 72.1, 55.7, 28.6, 27.6; Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.29; Found: C, 69.43; H, 7.42.
Spectral data of compound **5**: $[\alpha]_D$ +33.2 (*c* 5.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.30–7.23 (m, 10H), 4.70 (d, 1H, J = 5.4 Hz), 4.56 (m, 2H), 4.51 (m, 2H), 4.08 (m, 1H), 4.04 (t, 1H, J = 3.7 Hz), 3.85 (m, 1H), 3.80 (dd, 1H, J = 2.2, 6.7 Hz), 3.38 (m, 2H), 3.37 (s, 3H), 2.18 (m, 1H), 1.90–1.71 (m, 4H), 1.05 (d, 3H, J = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 138.5, 128.3, 127.8, 127.7, 127.6, 107.1, 85.6, 80.7, 80.4, 78.6, 73.4, 73.0, 72.2, 55.5, 42.1, 28.5, 27.4, 7.8; Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.52; H, 7.64.
Spectral data of compound **4**: $[\alpha]_D$ +14.6 (*c* 1.3, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.30–7.15 (m, 15H), 4.71 (m, 3H), 4.56 (m, 3H), 4.14 (m, 2H), 3.69 (m, 1H), 3.54 (dd, 1H, J = 3.2, 7.7 Hz), 3.52 (m, 3H), 3.45 (dd, 1H, J = 3.2, 7.7 Hz), 2.09 (m, 1H), 1.92 (m, 3H), 1.78 (m, 3H), 1.61 (m, 1H), 1.00 (d, 3H, J = 3.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.6, 138.4, 128.3, 128.2, 127.8, 127.6, 127.5, 84.0, 81.0, 80.2, 77.8, 74.2, 73.3, 60.2, 34.3, 31.5, 28.5, 27.6, 18.0; Anal. Calcd for $C_{32}H_{40}O_5$: C, 76.15; H, 7.98. Found: C, 76.04; H, 7.85.
Spectral data of compound **20**: $[\alpha]_D$ −15.8 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.25 (m, 15H), 4.71 (m, 3H), 4.55 (s, 2H), 4.43 (d, 1H, J = 11.6 Hz), 4.14 (m, 2H), 3.54 (m, 3H), 3.39 (m, 1H), 2.87 (dd, 1H, J = 3.6, 16.9 Hz), 2.46 (m, 1H), 2.27 (m, 1H), 1.99 (s, 3H), 1.89–1.66 (m, 4H), 0.94 (d, 3H, J = 6.98 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.0, 138.9, 138.7, 128.3, 128.2, 128.0, 127.8, 127.6, 127.5, 127.4, 83.9, 82.0, 81.0, 77.9, 74.2, 73.4, 73.2, 46.5, 30.7, 30.3, 29.7, 28.4, 18.8; Anal. Calcd for $C_{33}H_{40}O_5$: C, 76.71; H, 7.80. Found: C, 76.41; H, 7.52.
Spectral data of compound **8**: bp = 120–125 °C/1 mm; ^1H NMR (200 MHz, $CDCl_3$) δ 5.95 (t, 2H, J = 8.33 Hz), 4.74 (m, 2H), 2.85 (s, 2H), 1.74 (s, 3H), 1.49 (m, 6H), 1.34 (m, 6H), 0.92 (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.7, 144.0, 129.5, 110.9, 46.9, 29.3, 27.4, 22.2, 13.7, 9.48; Anal. Calcd for $C_{18}H_{36}Sn$: C, 58.24; H, 9.78. Found: C, 58.46; H, 9.84.
Spectral data of compound **2**: $[\alpha]_D$ +11.2 (*c* 0.3, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.26 (m, 15H), 6.04 (d, 1H, J = 15.6 Hz), 5.78 (dt, 1H, J = 6.6, 15.6 Hz), 4.95 (s, 1H), 4.83 (s, 1H), 4.77 (d, 2H, J = 12.8 Hz), 4.73 (s, 1H), 4.70 (d, 1H, J = 2.8 Hz), 4.66 (s, 1H), 4.54 (m, 3H), 4.15 (m, 2H), 3.59 (t, 1H, J = 4.8 Hz), 3.54 (dd, 1H, J = 4.8, 9.5 Hz), 3.46 (m, 2H), 2.71 (d, 2H, J = 7.1 Hz), 2.31 (m, 1H), 1.91 (m, 3H), 1.72 (s, 3H), 1.66 (s, 3H), 0.87 (d, 3H, J = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 144.6, 139.0, 138.9, 138.6, 133.6, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 115.0, 110.7, 84.8, 82.0, 80.1, 77.6, 73.8, 73.7, 73.3, 73.1, 41.4, 34.4, 33.4, 28.4, 27.9, 22.4, 17.3; Anal. Calcd for $C_{39}H_{48}O_4$: C, 80.65; H, 8.33. Found: C, 80.51; H, 8.42.