

Syntheses of *epi*-aigialomycin D and *deoxy*-aigialomycin C via a diastereoselective ring closing metathesis macrocyclization protocol

Naval Bajwa and Michael P. Jennings*

Department of Chemistry, 250 Hackberry Lane, The University of Alabama, Tuscaloosa, AL 35487-0336, United States

Received 5 October 2007; accepted 5 November 2007

Available online 26 November 2007

Abstract—Syntheses of *epi*-aigialomycin D and *deoxy*-aigialomycin C are described via a remote stereocontrolled RCM macrocyclization.

© 2007 Elsevier Ltd. All rights reserved.

First isolated and disclosed in 2002 by Isaka and co-workers, aigialomycin D (**1**) was shown to exhibit modest anti-malarial activities (IC₅₀: 6.6 µg/ml) against *Plasmodium falciparum* K1, as well as, cytotoxicity towards the KB and Vero cancer cell lines at 3.0 and 1.8 µg/ml (IC₅₀), respectively.¹ In addition, aigialomycin D has recently been shown to bind to HSP90, but does not function as an indiscriminate ATP antagonist. Also, Winssinger has demonstrated that **1** is a selective kinase inhibitor for CDK1/cyclin and CDK5/p25 (5.7–5.8 µM).² From this data, it can be inferred that aigialomycin D and other resorcinol based natural products show promise as a valuable class of compounds for chemical genetics (Fig. 1).

Based on the biological data of aigialomycin D and other structurally similar resorcinol natural products, it is not surprising that there has been great interest in these compounds.³ The first total synthesis of **1** was reported by the Danishefsky group in 2004 and utilized a ring-closing metathesis (RCM) reaction to forge the

macrocycle at the C7'–C8' linkage and a very elegant late stage Diels–Alder reaction for the construction of the aromatic core.⁴ A second synthesis was reported by She and Pan in which they employed a Julia–Kocienski olefination reaction for the construction of both double bonds and a Yamaguchi macrolactonization finished the targeted compound **1**.⁵ Most recently, a macrocyclic RCM strategy at the C7'–C8', similar to the Danishefsky effort, was recently utilized by Winssinger for the completion of **1** and structurally related analogues via both solution and solid phase protocols.²

Our synthetic blueprint of **1** was envisioned to feature a highly chemoselective RCM protocol for the completion of the 14-membered macrocycle as shown in Figure 2. While RCM had been utilized by both Danishefsky and Winssinger for the C7'–C8' olefin formation, our approach to **1** relied on a disconnection at the C1'–C2'

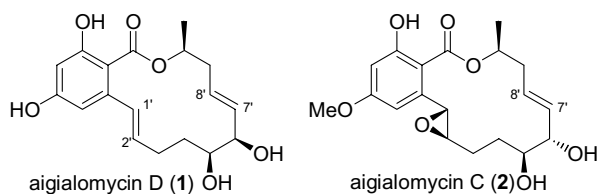


Figure 1. Structures of aigialomycin D (**1**) and aigialomycin C (**2**).

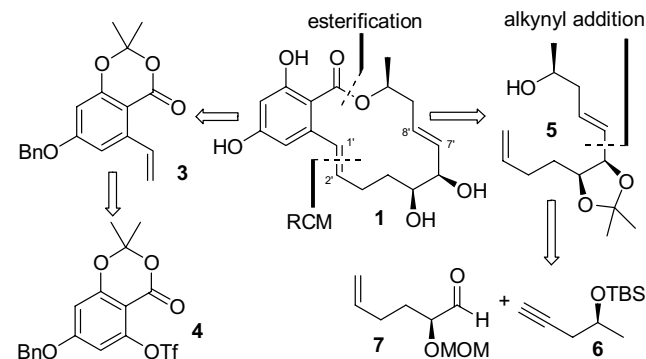
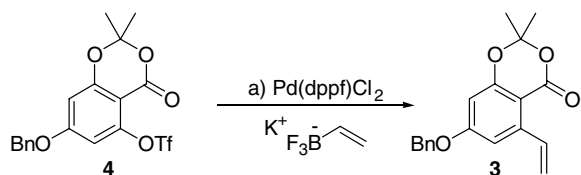


Figure 2. Retrosynthetic analysis of **1**.

* Corresponding author. Tel.: +1 205 348 0351; fax: +1 205 348 9104; e-mail: jenningsm@bama.ua.edu



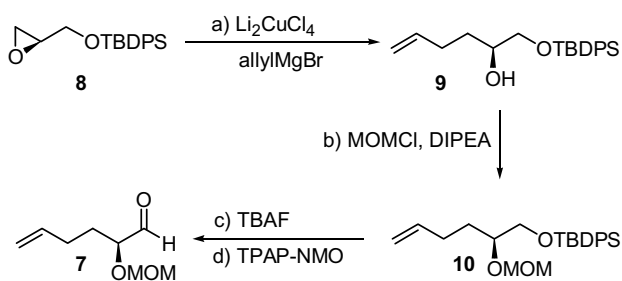
Scheme 1. Synthesis of intermediate **3**: Reagents and conditions: (a) potassium vinyl trifluoroborate (1.1 equiv), Et₃N (1.3 equiv), Pd(dppf)Cl₂ (10 mol %), EtOH, 80 °C, 16 h, 77%.

styrene linkage, which would require a highly chemo-selective macrocyclization versus a six-membered ring formation, *vide infra*.

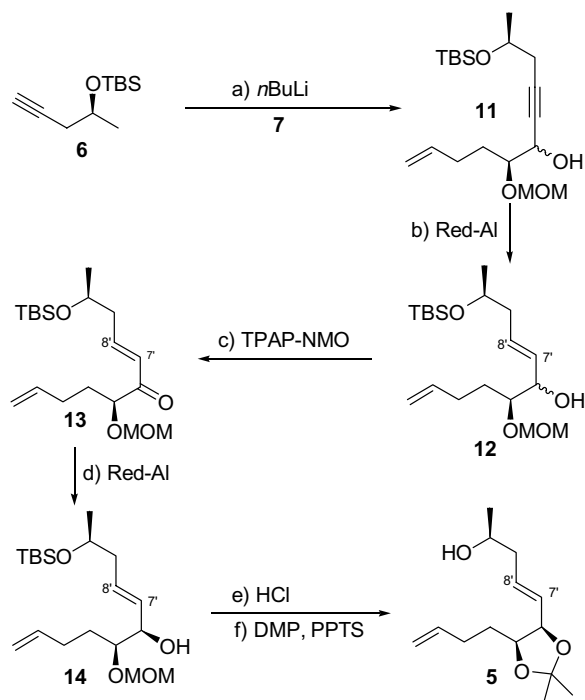
Our synthetic outline to **1** required the synthesis of the substituted styrene **3** as highlighted in **Scheme 1**. Hence, a subsequent Suzuki–Miyaura coupling of the aryl triflate **4**⁶ with potassium vinyl trifluoroborate and Pd(dppf)Cl₂ utilizing Molander's procedure⁷ readily provided substituted styrene **3** in 77% yield.⁸

With the aromatic segment readily in hand and in gram quantities, we next focused our effort on the completion of the aliphatic portion of **1** as delineated in **Schemes 2, 3**. Thus, treatment of the previously reported TBDPS protected glycidol derivative **8** with allyl magnesium bromide and 2 mol % of dilithio-tetrachlorocuprate readily provided the olefinic alcohol intermediate **9** in 87% yield.⁹ Protection of the free hydroxyl group resident in **9** with MOMCl and Hunig's base furnished the protected olefinic diol **10** in 93% yield and subsequent selective removal of the silyl ether with TBAF afforded the free primary alcohol which was further oxidized with TPAP-NMO to furnish the MOM protected chiral α -hydroxy aldehyde **7** in 74% yield over two steps from **10**.¹⁰

With **7** in hand, we next focused our attention on the completion of **5** via an alkynyl addition to the aldehyde moiety. With this in mind, treatment of the known TBS protected propargylic alcohol **6**¹¹ with *n*BuLi provided the lithium alkynyl nucleophile which smoothly underwent addition to the aldehyde moiety of **7** to afford **11** which represented the entire carbon framework of the aliphatic portion of **1**. We initially surmised that the



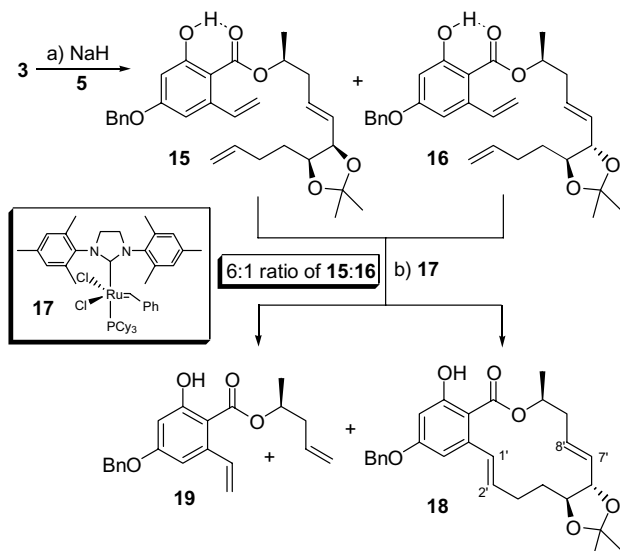
Scheme 2. Synthesis of intermediate **7**: Reagents and conditions: (a) Li₂CuCl₄ (2 mol %), allylMgBr (1.2 equiv), THF, –30 °C, 0.25 h, 87%. (b) MOMCl (2.0 equiv), DIPEA (1.5 equiv), CH₂Cl₂, rt, 8 h, 93%. (c) TBAF (1.5 equiv), THF, rt, 16 h, 96%. (d) TPAP (10 mol %), NMO (3.0 equiv), CH₂Cl₂, 0 °C, 1.5 h, 74%.



Scheme 3. Synthesis of intermediate **5**: Reagents and conditions: (a) *n*BuLi (1.1 equiv), **6** (1.0 equiv), THF, –78 °C, 1.5 h, then **7** (0.7 equiv), THF, –78 °C, 1.5 h, 71%. (b) Red-Al (3.2 equiv), THF, 0 °C, 48 h, 72%. (c) TPAP (10 mol %), NMO (3.0 equiv), CH₂Cl₂, 0 °C, 1.5 h, 92%. (d) Red-Al (1.2 equiv), toluene, 0 °C, 0.5 h, 84%. (e) HCl (two drops concd), MeOH, 50 °C, 0.5 h, 100%. (f) DMP (25 equiv), PPTS (2 mol %), CH₂Cl₂, rt, 5.0 h, 62%.

nucleophilic addition to **6** might display modest selectivity for the anti-Cram product due to the ability of the MOM group to undergo chelation controlled additions. Somewhat surprisingly, the addition of **6** to **7** gave rise to a 2:1 diastereomeric ratio (dr) favoring the Cram product **11**.¹² Ensuing diastereoselective reduction of the acetylene moiety of **11** was accomplished upon the addition of Red-Al via chelation-hydroalumination to selectively ($\geq 15:1$, *E:Z*) afford the allylic alcohol **12** in 72% yield, while maintaining the 2:1 dr at the hydroxyl group. With the olefin geometry set, attention was turned to final induction of the required diol stereochemistry of **5**. Thus, oxidation of the allylic alcohol resident in **12** with TPAP-NMO readily removed the redundant 2:1 dr at C6' and provided the α,β -unsaturated ketone **13**¹³ in 92% yield which set the stage for a chelation controlled reduction in anticipation of forming the *cis*-diol **14**.

Both lithium and sodium borohydrides failed to exhibit selectivity as the product alcohol was isolated in good yields (80–88%). Unfortunately and contrary to Burke's report, LiBH₄ appeared not to undergo a chelation controlled addition as a modest amount of the Cram alcohol was isolated (2:1).¹⁴ Attempted reduction of **13** with LAH in THF (0 °C) provided the desired alcohol **14** in very high yield. However, the selectivity for the LAH reduction just simply replicated the dr from the addition of **6** to **7**. With the LAH result in hand, it appeared that aluminum 'ate' based reducing reagents

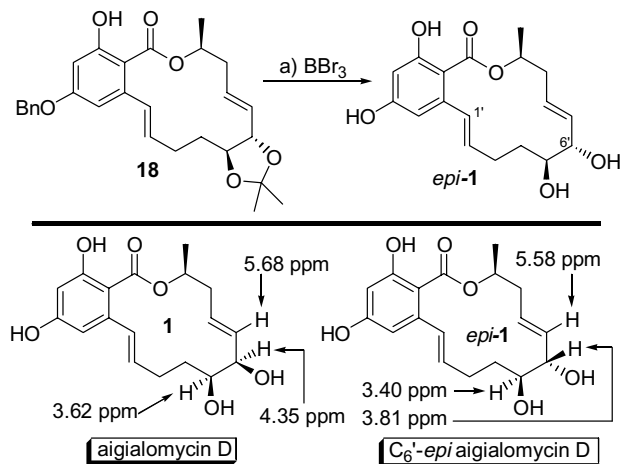


Scheme 4. Synthesis of intermediate **18**: Reagents and conditions: (a) NaH (1.2 equiv), **5** (1.3 equiv), THF/DMF 1:1, rt, 5 h, 78%. (b) **17** (5 mol %), CH₂Cl₂, 50 °C, 16 h, 13% of **18** and 84% of **19**.

showed a propensity for a chelation controlled reduction of ketone **13**. Based on this observation, we decided to investigate Red-Al as a chelating reagent for the reduction of **13** to **14**. Much to our delight, treatment of **13** with Red-Al in toluene at 0 °C readily afforded alcohol **14** with a satisfactory level of dr (6:1 by ¹H NMR of the crude product) in a very acceptable 84% yield. With **14** in hand, only a couple of protecting group removals and a selective reprotection of the 1,2-diol subunit as the acetonide was left to complete the aliphatic portion of **1**. Hence, treatment of the protected triol **14** with concd HCl in refluxing methanol readily cleaved both the silyl ether, as well as the MOM protecting group to provide the triol intermediate. Ensuing acetal formation of the *cis*-diol functionality to afford the acetonide protected compound **5** was accomplished via 2,2-dimethoxypropane and PPTS as the acid catalyst in a 62% yield over two steps from **15**. The absolute configuration of the *cis*-diol moiety was unequivocally defined as illustrated in **Scheme 3** via NOE enhancements between the C5' and C6' hydrogen atoms.

With the two subunits readily in our hands, we proceeded to couple advanced intermediates **3** and **5** as described in **Scheme 4**. Thus, deprotonation of **5** with NaH in 1:1 THF/DMF at 0 °C proceeded to provide the alkoxide anion which was then esterified with the aromatic compound **3** to afford the macrocyclic precursors **15** and **16** as an inseparable 6:1 ratio of diastereomers.

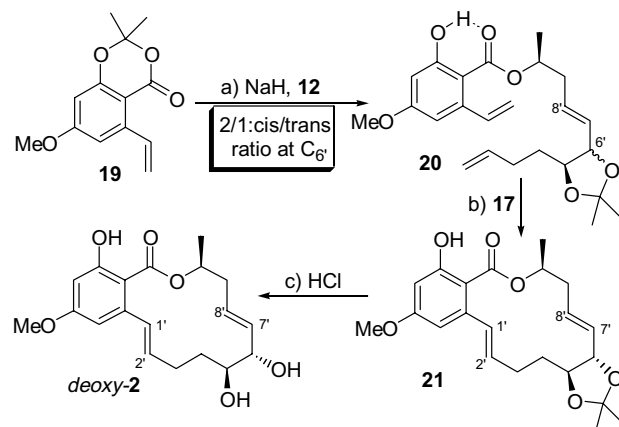
With the two subunits coupled, the stage was finally set for our proposed macrocyclization via a chemoselective RCM reaction. Much to our surprise, treatment of **15** and **16** with Grubbs' 2nd generation catalyst (**17**)¹⁵ in refluxing CH₂Cl₂ (0.0002 M) led to the formation of a 14-membered macrocycle **18** and the acyclic compound **19** in 13% and 84% yields, respectively. Finally, treatment of **18** with 4 equiv of BBr₃ at –78 °C in CH₂Cl₂



Scheme 5. Synthesis of *epi*-aigialomycin D: Reagents and conditions: (a) BBr₃ (4.0 equiv), CH₂Cl₂, –78 °C, 1.0 h, 74%.

furnished the macrocycle *epi*-**1** in a respectable 74% yield, as shown in **Scheme 5**. Unfortunately, the spectral data (¹H NMR, 360 MHz; ¹³C NMR, 90 MHz) were not in agreement with the natural sample **1**.¹ As delineated in **Scheme 5**, close investigation of the ¹H NMR of *epi*-**1** and **1** coupled with the comparison of the structural data of aigialomycin C suggested that the synthesized compound was that of *epi*-*C*₆' aigialomycin D.^{1,16} The methine proton of *C*₆' possessed a dramatic upfield shift of 3.81 ppm versus that of 4.35 ppm in **1**. In addition, both protons α - to the *C*₆' methine displayed an upfield shift with respect to that of **1**.

Thus, it appeared that the stereochemistry resident at *C*₆' influenced macrocyclization by means of a classical resolution of the two diastereomers (**15** and **16**) by Grubbs' catalyst **17**. The initial insertion of **17** must have taken place at the more accessible terminal alkene moiety of **15** and **16** followed either by six- or 14-membered ring formation via RCM. The formation of the *cis*-acetonide protected cyclohexene diol appeared to be favored over



Scheme 6. Synthesis of *deoxy*-2: Reagents and conditions: (a) NaH (1.2 equiv), **12** (1.3 equiv), THF/DMF 1:1, rt, 5.0 h, 78%. (b) **17** (5 mol %), CH₂Cl₂, 50 °C, 16 h, 31%. (c) HCl (two drops concd), MeOH, rt, 1 h, 69%.

macrocyclization (also leading to the production of **19**). However, the construction of the trans-substituted six-membered ring was not readily viable, and RCM of **16** exclusively lead to the desired macrocyclic framework.

As shown in Scheme 6, we took advantage of such a diastereoselective RCM reaction to also synthesize deoxy-aigialomycin C. As described above, esterification of **12** (2/1 ratio at C₆') with styrene **19**¹⁷ provided **20** in good yield. A subsequent RCM with **17** furnished the macrocycle **21** in virtually quantitative yield with respect to the *trans*-dioxolane diastereomer. Final deprotection of the acetonide moiety with HCl provided deoxy-aigialomycin C **2** in 69% yield.¹⁸

In conclusion, the syntheses of *epi*-aigialomycin D and deoxy-aigialomycin C have been described via a remote stereocontrolled RCM macrocyclization. Future work in this area will focus on the completion of both **1** and **2** by means of site-selective RCM.

Acknowledgments

Support was provided by the University of Alabama and the NSF (CHE-0115760) for the departmental NMR facility.

References and notes

- Isaka, M.; Suyarnsestakorn, C.; Tanticharoen, M.; Kongsaeree, P.; Thebtaranonth, Y. *J. Org. Chem.* **2002**, *67*, 1561.
- Barluenga, S.; Dakas, P.-Y.; Ferandin, Y.; Meijer, L.; Winessinger, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 3951.
- (a) Delmotte, P.; Delmotte-Plaquee, J. *Nature* **1953**, *171*, 344; (b) Ellestad, G. A.; Lovell, F. M.; Perkinson, N. A.; Hargreaves, R. T.; McGahren, W. J. *J. Org. Chem.* **1978**, *43*, 2339; (c) Ayer, W. A.; Lee, S. P.; Tsuneda, A.; Hiratsuka, Y. *Can. J. Microbiol.* **1980**, *26*, 766; (d) Ayer, W. A.; Pena-Rodriguez, L. *Phytochemistry* **1987**, *26*, 1353; (e) Sugawara, F.; Kim, K. W.; Kobayashi, K.; Uzawa, J.; Yoshida, S.; Murofushi, N.; Takahashi, N.; Strobel, G. A. *Phytochemistry* **1992**, *31*, 1987; (f) Sharma, S. V.; Agatsuma, T.; Nakano, H. *Oncogene* **1998**, *16*, 2639.
- Geng, X.; Danishefsky, S. J. *Org. Lett.* **2004**, *6*, 413.
- Lu, J.; Ma, J.; Xie, X.; Chen, B.; She, X.; Pan, X. *Tetrahedron: Asymmetry* **2006**, *17*, 1066.
- Dushin, R. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 655.
- Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, *4*, 107.
- Bajwa, N.; Jennings, M. P. *J. Org. Chem.* **2006**, *71*, 3646.
- Dixon, D. J.; Ley, S. V.; Reynolds, D. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3622.
- Data for aldehyde 7*: ¹H NMR (360 MHz, CDCl₃) δ 9.7 (d, *J* = 1.8 Hz, 1H), 5.8 (m, 1H), 5.1 (m, 2H), 4.8 (dd, *J* = 14.8, 7.0 Hz, 2H), 4.0 (t, *J* = 5.7 Hz, 1H), 3.5 (s, 3H), 2.2 (m, 2H), 1.8 (m, 2H). ¹³C NMR (90 MHz, CDCl₃) δ 202.9, 137.2, 115.9, 96.9, 81.8, 56.1, 29.3, 28.9. IR (CH₂Cl₂): 3053, 2986, 2305, 1733, 1422, 1374, 1265, 1046, 895, 735, 705, 421, 410, 404 cm⁻¹. *R*_f = 0.33, 20% EtOAc in hexanes. [α]_D²⁴ 23.3° (c 0.012 g/mL, CH₂Cl₂). HRMS (EI) calcd for C₈H₁₄O₃ [M-H]⁺: 157.0865; found, 157.0863.
- Romo, D.; Rzasa, R. M.; Shea, H. A.; Park, K.; Langenhan, J. M.; Sun, L.; Akhiezer, A.; Liu, J. O. *J. Am. Chem. Soc.* **1998**, *120*, 12237.
- Mead, K. T. *Tetrahedron Lett.* **1987**, *28*, 1019.
- Data for ketone 13*: ¹H NMR (360 MHz, CDCl₃) δ 7.0 (m, 1H), 6.4 (dt, *J* = 15.7, 1.4 Hz, 1H), 5.8 (m, 1H), 5.1 (m, 2H), 4.7 (dd, *J* = 15.4, 6.8 Hz, 2H), 4.2 (dd, *J* = 7.7, 5.5 Hz, 1H), 4.0 (dd, *J* = 11.8, 5.9 Hz, 1H), 3.4 (s, 3H), 2.3 (m, 2H), 2.2 (m, 2H), 1.8 (m, 2H), 1.2 (d, *J* = 6.1 Hz, 3H), 0.90 (s, 9H), 0.10 (d, *J* = 3.9 Hz, 6H). ¹³C NMR (90 MHz, CDCl₃) δ 199.8, 146.1, 137.7, 127.6, 115.8, 96.5, 80.8, 67.8, 56.3, 43.2, 32.0, 30.0, 26.0, 24.1, 18.3, -4.3, -4.6. IR (CH₂Cl₂): 3054, 2986, 1733, 1422, 1373, 1265, 1046, 895, 739, 705 cm⁻¹. *R*_f = 0.48, 20% EtOAc in hexanes. [α]_D²⁴ -3.3° (c 0.046 g/mL, CH₂Cl₂). HRMS (EI) calcd for C₁₉H₃₆O₄Si [M-C₄H₉]⁺: 299.1679; found, 299.1681.
- Burke, S. D.; Deaton, D. N.; Olsen, R. J.; Armistead, D. M.; Blough, B. E. *Tetrahedron Lett.* **1987**, *28*, 3905.
- Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
- Data for epi-1*: ¹H NMR (360 MHz, acetone-*d*₆) δ 11.7 (s, 1H), 9.2 (br s, 1H), 7.2 (dt, *J* = 15.9, 1.8 Hz, 1H), 6.6 (d, *J* = 2.5 Hz, 1H), 6.3 (d, *J* = 2.5 Hz, 1H), 6.2 (dt, *J* = 15.9, 5.0 Hz, 1H), 6.0 (m, 1H), 5.6 (m, 2H), 4.0 (d, *J* = 3.0 Hz, 1H), 3.9 (d, *J* = 3.6 Hz, 1H), 3.8 (m, 1H), 3.4 (m, 1H), 2.5 (m, 4H), 2.2 (m, 1H), 1.6 (m, 1H), 1.4 (d, *J* = 6.6 Hz, 3H). ¹³C NMR (90 MHz, acetone-*d*₆) δ 171.2, 165.1, 162.3, 143.3, 135.6, 132.4, 129.5, 127.0, 106.7, 103.4, 101.7, 76.8, 72.6, 71.7, 37.0, 30.4, 26.9, 17.8. IR (acetone): 3413, 3003, 1714, 1575, 1418, 1361, 1222, 1091, 901, 667 cm⁻¹. *R*_f = 0.31, 7% MeOH in DCM. [α]_D²⁴ +19.6° (c 0.0056 g/mL, MeOH). HRMS (EI) calcd for C₁₈H₂₂O₆ [M]⁺: 334.1416; found, 334.1410.
- Styrene **19** was synthesized in the same manner as compound **3**. *Data for compound 19*: ¹H NMR (360 MHz, CDCl₃) δ 7.7 (dd, *J* = 17.5, 10.9 Hz, 1H), 6.8 (d, *J* = 2.0 Hz, 1H), 6.4 (d, *J* = 2.0 Hz, 1H), 5.7 (d, *J* = 17.5 Hz, 1H), 5.4 (d, *J* = 10.9 Hz, 1H), 3.8 (s, 3H), 1.7 (s, 6H). ¹³C NMR (90 MHz, CDCl₃) δ 165.0, 160.2, 158.7, 144.0, 135.5, 117.6, 108.6, 105.1, 103.9, 100.8, 55.7, 25.6. IR (CH₂Cl₂): 4450, 3065, 2985, 1720, 1427, 1158, 895, 740, 705 cm⁻¹. *R*_f = 0.64, 50% EtOAc in hexanes. HRMS (EI) calcd for C₁₃H₁₄O₄ [M]⁺: 234.0892; found, 234.0900.
- Data for deoxy-2*: ¹H NMR (360 MHz, CDCl₃) δ 11.8 (s, 1H), 7.1 (d, *J* = 15.9 Hz, 1H), 6.6 (d, *J* = 2.7 Hz, 1H), 6.4 (d, *J* = 2.7 Hz, 1H), 6.2 (dt, *J* = 15.9, 5.2 Hz, 1H), 6.0 (m, 1H), 5.6 (m, 2H), 3.9 (t, *J* = 8.4 Hz, 1H), 3.8 (s, 3H), 3.5 (m, 1H), 3.5 (s, 1H), 2.6 (m, 2H), 2.4 (m, 2H), 2.1 (m, 1H), 2.1 (s, 1H), 1.6 (m, 1H), 1.4 (d, *J* = 6.6 Hz, 3H). ¹³C NMR (90 MHz, CDCl₃) δ 171.2, 165.2, 163.9, 142.7, 134.1, 132.3, 129.8, 128.6, 106.7, 104.0, 99.8, 73.0, 71.4, 55.4, 37.3, 30.7, 27.0, 18.6. IR (CH₂Cl₂): 3420, 3000, 1720, 1560, 1216, 1080, 890, 705, 667 cm⁻¹. *R*_f = 0.31, 50% EtOAc in hexanes. [α]_D²⁴ +25.4° (c 0.054 g/mL, CH₂Cl₂). HRMS (EI) calcd for C₁₉H₂₄O₆ [M]⁺: 348.1573; found, 348.1573.