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

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

First isolated and disclosed in 2002 by Isaka and co-workers, aigialomycin D (**1**) was shown to exhibit modest anti-malarial activities (IC_{50}: 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 (IC_{50}), 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 CDK/5p25 (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′

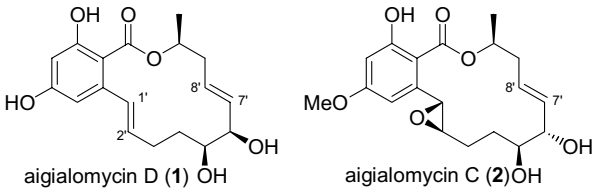

Figure 1. Structures of aigialomycin D (**1**) and aigialomycin C (**2**).

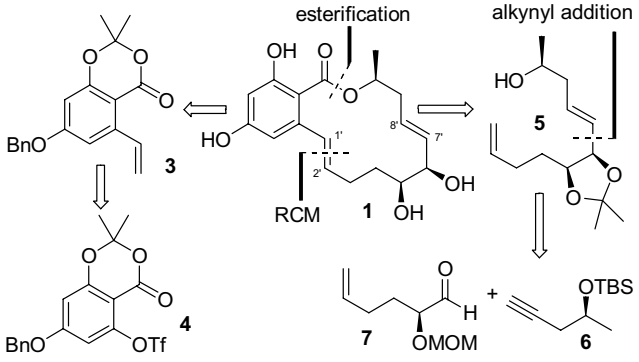

Figure 2. Retrosynthetic analysis of **1**.

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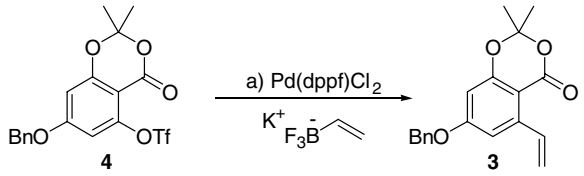


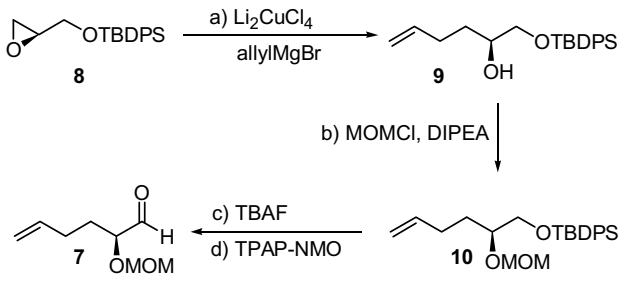
Scheme 1. Synthesis of intermediate **3**: Reagents and conditions: (a) potassium vinyl trifluoroborate (1.1 equiv), Et_3N (1.3 equiv), Pd(dppf)Cl_2 (10 mol %), EtOH, 80 °C, 16 h, 77%.

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

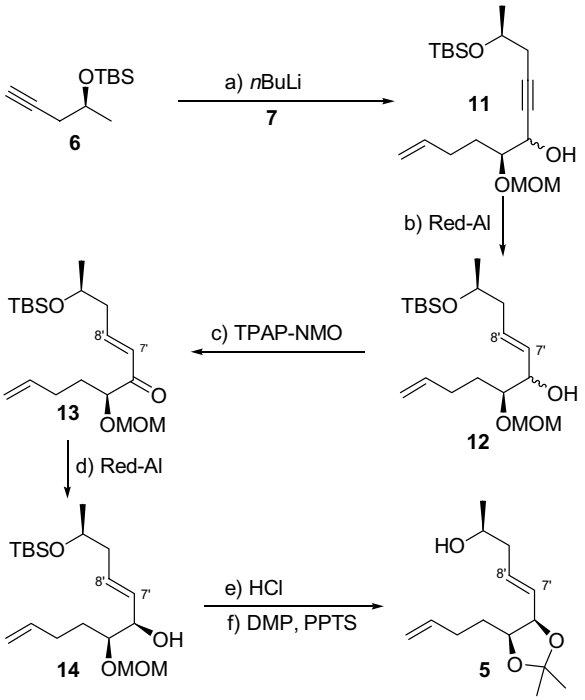
Our synthetic outline to **1** required the synthesis of the substituted styrene **3** as highlighted in Scheme 1. Hence, a subsequent Suzuki–Miyaura coupling of the aryl triflate **4**[6] with potassium vinyl trifluoroborate and Pd(dppf)Cl_2 utilizing Molander's procedure[7] readily provided substituted 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 sub sequent 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 71% 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



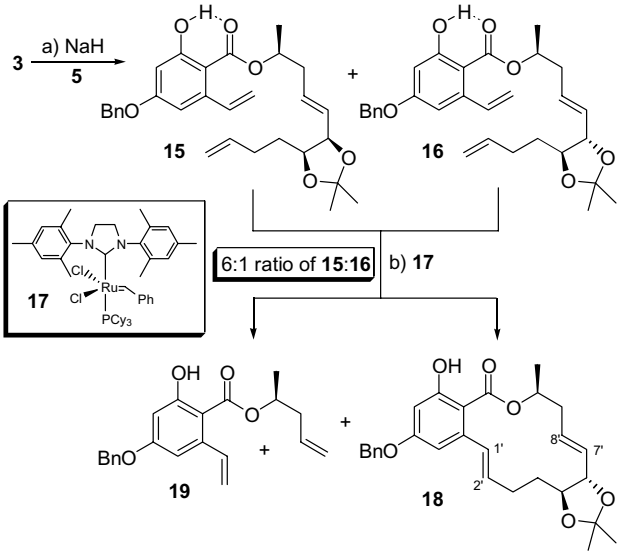
Scheme 2. Synthesis of intermediate **7**: Reagents and conditions: (a) Li_2CuCl_4 (2 mol %), allylMgBr (1.2 equiv), THF, −30 °C, 0.25 h, 87%. (b) MOMCl (2.0 equiv), DIPEA (1.5 equiv), CH_2Cl_2, rt, 8 h, 93%. (c) TBAF (1.5 equiv), THF, rt, 16 h, 96%. (d) TPAP (10 mol %), NMO (3.0 equiv), CH_2Cl_2, 0°C, 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), CH_2Cl_2, 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 %), CH_2Cl_2, 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 ($\geqslant$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, $LiBH_4$ 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

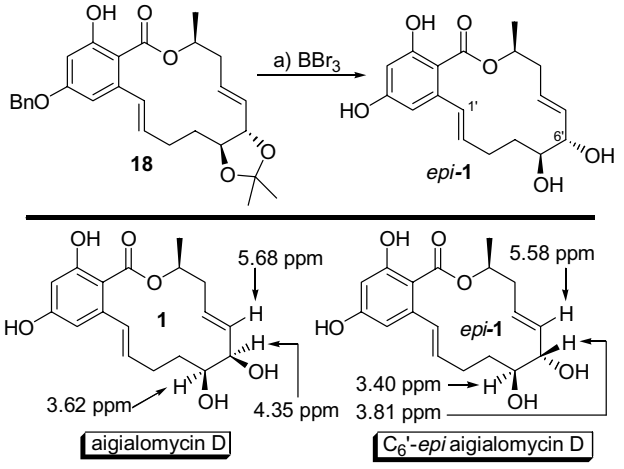


Scheme 4. Synthesis of intermediate **18**: Reagents and conditions: (a) NaH (1.2 equiv), **5** (1.3 equiv), THF/DMF 1:1, rt, 5 h, 78%. (b) **17** (5 mol %), CH_2Cl_2, 50 °C, 16 h, 13% of **18** and 84% of **19.**

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 ^{1}H 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.

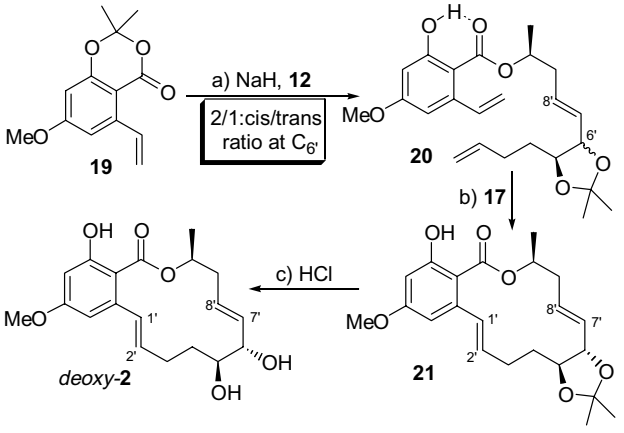
With the two subunits coupled, the stage was finally set for our proposed macrocyclization via a chemoselective RCM reaction. Much to our surprise, treatment of **15** and **16** with Grubbs' 2nd generation catalyst (**17**)[15] in refluxing CH_2Cl_2 (0.0002 M) led to the formation of a 14-membered macrocycle **18** and the acyclic compound **19** in 13% and 84% yields, respectively. Finally, treatment of **18** with 4 equiv of BBr_3 at −78 °C in CH_2Cl_2



Scheme 5. Synthesis of *epi*-aigialomycin D: Reagents and conditions: (a) BBr_3 (4.0 equiv), CH_2Cl_2, −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 (^{1}H NMR, 360 MHz; ^{13}C NMR, 90 MHz) were not in agreement with the natural sample **1**.[1] As delineated in Scheme 5, close investigation of the ^{1}H 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 a 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 %), CH_2Cl_2, 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 C_6') 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

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10. *Data for aldehyde* **7**: ^{1}H NMR (360 MHz, $CDCl_3$) 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). ^{13}C NMR (90 MHz, $CDCl_3$) δ 202.9, 137.2, 115.9, 96.9, 81.8, 56.1, 29.3, 28.9. IR (CH_2Cl_2): 3053, 2986, 2305, 1733, 1422, 1374, 1265, 1046, 895, 735, 705, 421, 410, 404 cm^{-1}. $R_f = 0.33$, 20% EtOAc in hexanes. $[\alpha]_D^{24}$ 23.3° (*c* 0.012 g/mL, CH_2Cl_2). HRMS (EI) calcd for $C_8H_{14}O_3$ $[M-H]^+$: 157.0865; found, 157.0863.
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13. *Data for ketone* **13**: ^{1}H NMR (360 MHz, $CDCl_3$) 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). ^{13}C NMR (90 MHz, $CDCl_3$) 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 (CH_2Cl_2): 3054, 2986, 1733, 1422, 1373, 1265, 1046, 895, 739, 705 cm^{-1}. $R_f = 0.48$, 20% EtOAc in hexanes. $[\alpha]_D^{24}$ −3.3° (*c* 0.046 g/mL, CH_2Cl_2). HRMS (EI) calcd for $C_{19}H_{36}O_4Si$ $[M-C_4H_9]^+$: 299.1679; found, 299.1681.
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16. *Data for epi*-**1**: ^{1}H 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). ^{13}C 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. $[\alpha]_D^{24}$ +19.6° (*c* 0.0056 g/mL, MeOH). HRMS (EI) calcd for $C_{18}H_{22}O_6$ $[M]^+$: 334.1416; found, 334.1410.
17. Styrene **19** was synthesized in the same manner as compound **3**. Data for compound **19**: ^{1}H NMR (360 MHz, $CDCl_3$) 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). ^{13}C NMR (90 MHz, $CDCl_3$) 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 (CH_2Cl_2): 4450, 3065, 2985, 1720, 1427, 1158, 895, 740, 705 cm^{-1}. $R_f = 0.64$, 50% EtOAc in hexanes. HRMS (EI) calcd for $C_{13}H_{14}O_4$ $[M]^+$: 234.0892; found, 234.0900.
18. *Data for deoxy*-**2**: ^{1}H NMR (360 MHz, $CDCl_3$) 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). ^{13}C NMR (90 MHz, $CDCl_3$) 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 (CH_2Cl_2): 3420, 3000, 1720, 1560, 1216, 1080, 890, 705, 667 cm^{-1}. $R_f = 0.31$, 50% EtOAc in hexanes. $[\alpha]_D^{24}$ +25.4° (*c* 0.054 g/mL, CH_2Cl_2). HRMS (EI) calcd for $C_{19}H_{24}O_6$ $[M]^+$: 348.1573; found, 348.1573.