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Toward the total synthesis of vineomycin B_2: application of an efficient glycosylation methodology using 2,3-unsaturated sugars

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Abstract—The application of an efficient glycosylation methodology using 2,3-unsaturated sugars to synthesize critical precursors required for the total synthesis of an antibiotic, vineomycin B_2 (**1**), was demonstrated. The required disaccharide, the acurosyl rhodinose derivative of **1**, was prepared by chemoselective glycosylation using a 2,3-saturated glycosyl acetate corresponding to the rhodinose moiety and a 2,3-unsaturated glycosyl acetate corresponding to the acurose portion. Further, the right-hand side chain of **1**, consisting of β-oxo-*tert*-alcohol and rhodinose, was constructed by a powerful glycosylation approach using a 2,3-unsaturated glycosyl acetate in an ionic liquid under reduced pressure.

Many structurally complex oligosaccharides are found in naturally occurring bioactive compounds such as antibiotics, and it is known that these oligosaccharides play very important roles in biological events. Much effort by synthetic organic chemists to effectively synthesize such complex oligosaccharides[1] has highlighted the need to develop an efficient glycosylation methodology in order to address these challenging tasks.[2] In this context, we have recently developed a chemoselective and powerful glycosylation methodology using 2,3-unsaturated sugars.[3] Our previous work demonstrated that glycosylation using a 2,3-unsaturated sugar and the corresponding 2,3-saturated sugar proceeded chemoselectively to provide a disaccharide possessing a hex-2-enosyl hexose structure. Furthermore, the tertiary alcohols, which show low reactivity, underwent efficient glycosylation using 2,3-unsaturated sugars. As expected, the 2,3-unsaturated glycosides obtained are synthetically equivalent to the 2,3-dideoxy glycosides. Based on these earlier findings, the aim of the present study was to synthesize critical building blocks required for the total synthesis of vineomycin B_2 in order to demonstrate the usefulness and generality of this glycosylation methodology using 2,3-unsaturated sugars.

Vineomycin B_2 (**1**), an anthracycline antibiotic, was isolated by Ōmura et al. from the culture broth of *Streptomyces matensis* subsp. *Vineus*. Vineomycin B_2 is active against Gram-positive bacteria and against sarcoma 180 solid tumors in mice.[4] Compound **1** has a hexenosyl hexose disaccharide (acurosyl rhodinose) at the C4 position of olivose and at the C3 position of the right-hand side chain moiety. Although elegant syntheses of the aglycon moiety, vineomycinone B_2 methyl ester (**2**), were reported by four groups,[5] the complete synthesis of **1** has not been reported to date. One of the most difficult aspects in the synthesis is the introduction of the glycon moiety to the aglycon moiety, which involves the introduction of the highly deoxygenated sugar, rhodinose, into the β-oxo-*tert*-alcohol at the side chain. It has been reported that even β-oxo-*sec*-alcohols are difficult to be glycosylated due to stabilization by intramolecular hydrogen bonds between the hydroxy group and the carbonyl oxygen.[6] Herein, we report the successful application of our previously reported glycosylation methodology using 2,3-unsaturated sugars to the synthesis of critical vineomycin B_2 building blocks, and demonstrate the effective construction of vineomycin B_2 glycoside structures (see Fig. 1).

The retrosynthetic analysis for **1**, outlined in Figure 2, is based on the disconnections of the disaccharide, acurosyl rhodinose **4**, and the monosaccharide, acurose precursor **5**, from **1**. The Diels–Alder reaction of the known bromo naphthoquinone **6**[7] and the ketene silyl

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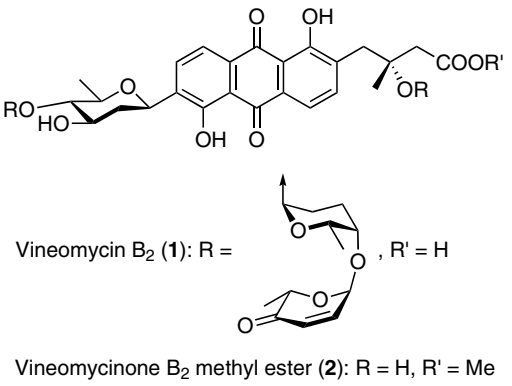


Figure 1. Vineomycin B_2 and vineomycinone B_2 methyl ester.

acetal derived from **7** would proceed with debrominational aromatization to afford anthraquinone **3**;[5d,8] this synthesis would be preceded by glycosylation of β-oxo-*tert*-alcohol **8** with the rhodinose equivalent **9** to afford glycoside **7**.

Disaccharide **4** was synthesized following the retrosynthetic analysis, as summarized in Scheme 1. Both the armed glycosyl donor **5** and the disarmed glycosyl donor **14** were synthesized from the known *p*-methoxyphenyl (MP) glycoside **10**.[9] Thus, silylation of the allylic alcohol of **10** with the TPS group, followed by deprotection of the MP group with CAN in the presence of $NaHCO_3$, gave the hemiacetal **12** which was subsequently subjected to acetylation to give the armed glycosyl donor **5**, corresponding to the acurose moiety. The addition of $NaHCO_3$ in the CAN-oxidation reaction was important because the resulting hemiacetal was acid-sensitive and thus transformed into the corresponding δ-hydroxy-α,β-unsaturated aldehyde possessing an *E*-olefin. Subsequent hydrogenation of the olefin in **5**, catalyzed by Rh/Al_2O_3 in a mixture of EtOAc and toluene, gave the hexopyranosyl acetate **13**;[10] deprotection of the TPS group of **13** using TBAF yielded the disarmed glycosyl donor **14** corresponding to the rhodinose moiety. The efficiency of our chemoselective glycosylation methodology using 2,3-unsaturated and 2,3-saturated sugars was demonstrated in the next step of the synthesis. Glycosylation of the 2,3-unsaturated sugar **5** (1.0 equiv) and the 2,3-saturated sugar **14** (1.5 equiv) using TBSOTf as an activator[11] chemoselectively proceeded at −98 °C to give the disaccharide **15** in high yield (82%) and with high stereoselectivity (α/β = 1:0).[3] Disaccharide **15** was then converted into the fully functionalized acurosyl rhodinose segment **4**[12] by appropriate deprotection and oxidation reactions, while retaining the OAc leaving group at the C-1 position.

The synthesis of **7** was achieved as summarized in Schemes 2 and 3. The 1,4-addition of a vinyl cuprate to the known enone **16**[13] according to Roush's protocol[14] provided *anti*-adduct **17** in moderate yield, which was then subjected to aldol reaction with EtOAc to afford **18**. Diastereo-induction in the aldol reaction was not observed and the resulting diastereomers were inseparable at this stage; therefore, they were derived into hemiacetals **22** and **23** by sequential deprotection and protection reactions followed by Swern oxidation via **19**–**21**. Hemiacetals **22** and **23** were separable, and their configurations were confirmed by NOE experiments on the acetate derivatives **24** and **25**. Although reduction of

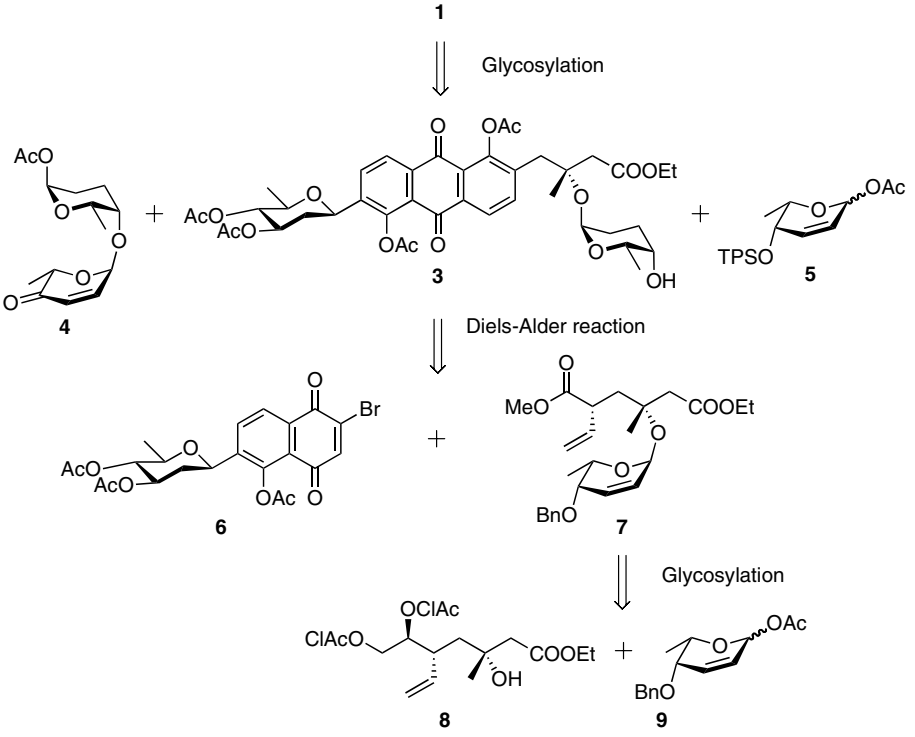
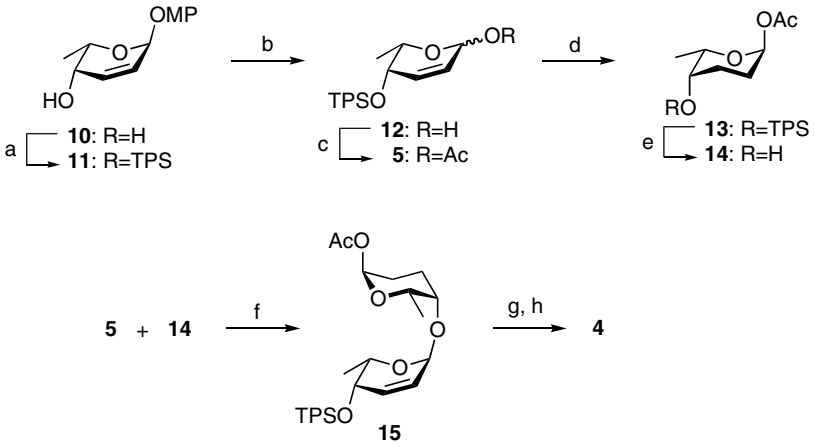
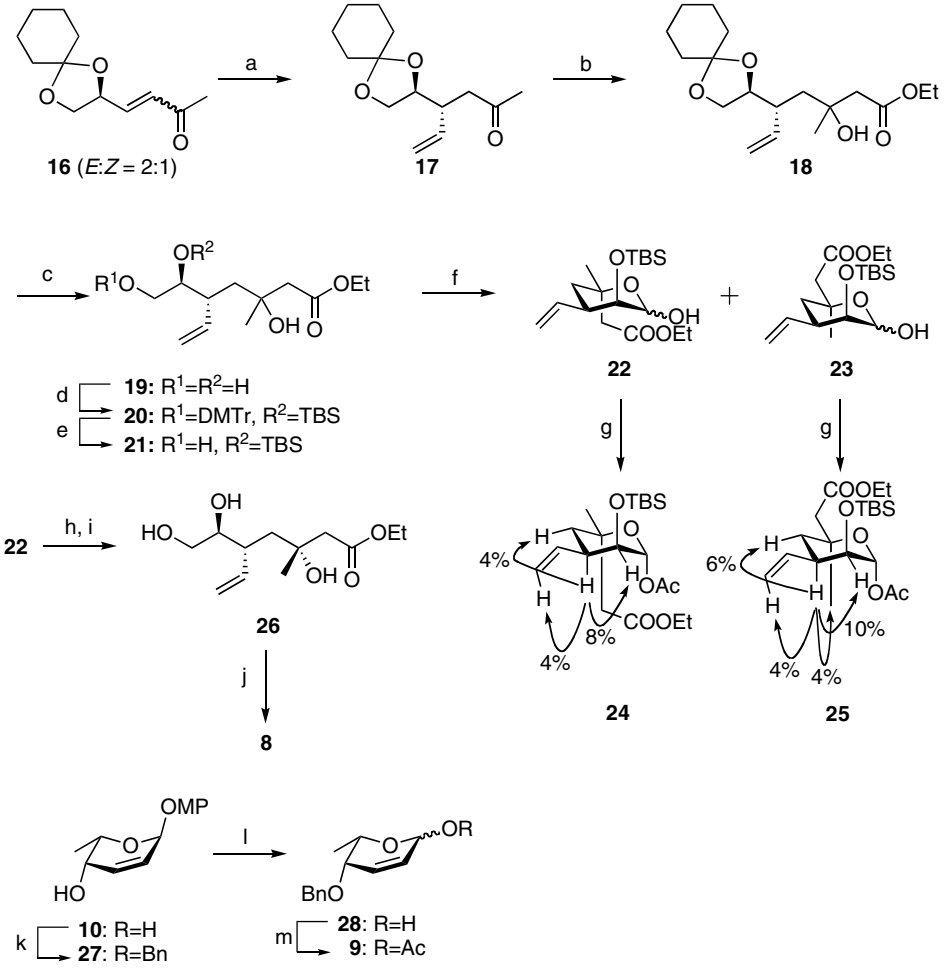


Figure 2. Retrosynthetic analysis of vineomycin B_2.

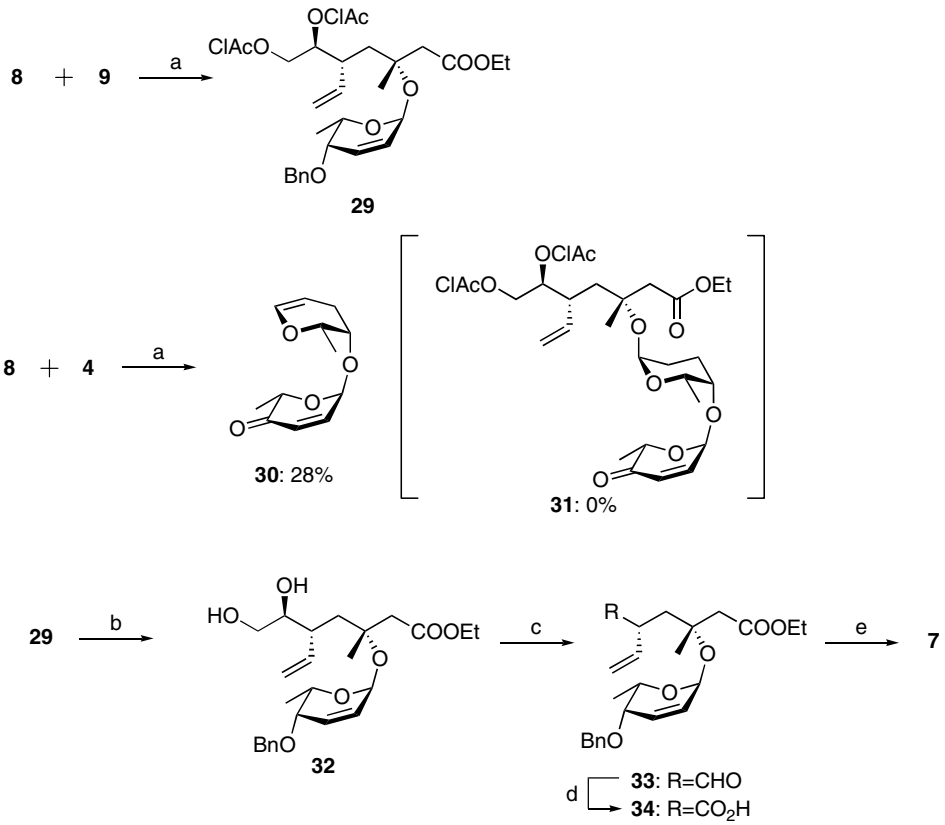


Scheme 1. Reagents and conditions: (a) TPSCl, imidazole, CH_2Cl_2, 0 °C, 98%; (b) CAN, $NaHCO_3$, MeCN/H_2O (9:1), 0 °C, 56%; (c) Ac_2O, DMAP, pyridine, 0 °C, 85% (α:β = 8:1); (d) H_2, Rh/Al_2O_3, EtOAc/toluene (9:1), 0 °C, 89%; (e) TBAF, THF, 40 °C, 87%; (f) TBSOTf, Et_2O, MS 5A, −98 °C, 82%; (g) TBAF, AcOH, THF, 40 °C, 99%; (h) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 25 °C, 94%.



Scheme 2. Reagents and conditions: (a) $CH_2CHMgBr$, $CuBr{\cdot}SMe_2$, TMSCl, THF, −78 °C, 64%; (b) EtOAc, LDA, THF, −78 °C to 0 °C, 91%; (c) IR-120, MeOH/H_2O (1:1), 60 °C, 84%; (d) DMTrCl, TEA, DMF, 25 °C, then, TBSCl, imidazole, 25 °C, 89%; (e) montmorillonite K-10, CH_2Cl_2/MeOH (9:1), 25 °C, 91%; (f) $(COCl)_2$, DMSO, TEA, −78 °C to −20 °C, 40% for **22**, 40% for **23**; (g) Ac_2O, DMAP, pyridine, 0 °C, 82% for **24**, 63% for **25**; (h) $NaBH_4$, MeOH, 0 °C; (i) TBAF, THF, 25 °C, 86% (two steps); (j) ClAcCl, pyridine, CH_2Cl_2, −78 °C, 99%; (k) BnBr, NaH, DMF, 25 °C, 99%; (l) CAN, $NaHCO_3$, MeCN/H_2O (9:1), 0 °C, 78%; (m) Ac_2O, DMAP, pyridine, 0 °C, 69% (α:β = 17:3).

the desired hemiacetal **22** with $NaBH_4$ took place with migration of the TBS group, producing two alcohols, both isomers could lead to the triol **26** by deprotection of the TBS group using TBAF. Finally, protection of the diol in **26** with chloroacetyl (ClAc) groups furnished glycosyl acceptor **8**. The 2,3-unsaturated glycosyl acetate



Scheme 3. Reagents and conditions: (a) HOTf (0.5 mol % to IL), C_6mim[OTf], 25 °C, 2 mm Hg, 98% for **29**; (b) pyridine/H_2O (1:1), 25 °C, 91%; (c) $NaIO_4$, CH_2Cl_2/H_2O (1:1), 25 °C; (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O (4:1), 25 °C, 84% (two steps); (e) $TMSCHN_2$, CH_2Cl_2/MeOH (20:3), 25 °C, 99%.

9 was prepared using a route similar to that used for **5**, except that a benzyl group was used as the C-4 protecting group instead of the TPS group.

With both the β-oxo-*tert*-alcohol acceptor **8** and the glycosyl donor **9** in hand, we next examined the glycosylation reaction using these key segments (Scheme 3). After several attempts, we found that the glycosylation of **8** (1.0 equiv) with **9** (2.0 equiv) proceeded smoothly at 25 °C under reduced pressure (2 mm Hg) in the ionic liquid 1-hexyl-3-methylimidazolium trifluoromethanesulfonate (C_6mim[OTf]) containing the protic acid HOTf (0.5 mol % to the ionic liquid). The desired glycoside **29** was obtained in high yield (98%) and with high stereoselectivity ($\alpha/\beta = 1{:}0$).[15,16] These results confirmed that the use of non-volatile C_6mim[OTf] under reduced pressure provided significant advantages for the glycosylation reaction. A volatile by-product, HOAc, could be removed from the reaction mixture during the reaction, and the side-reaction between HOAc and the glycosyl cation intermediate was prevented. To the best of our knowledge, this is the first successful example of chemical glycosylation for constructing the glycosidic linkage between a highly deoxygenated sugar and a β-oxo-*tert*-alcohol. In contrast, when the 2,3-saturated glycosyl donor **4** was employed under the same conditions, the glycal **30** was produced and the desired glycoside **31** was not detected. This result indicated that the double bond installed at the C2 position of the glycosyl donor worked well to prevent the oxocarbenium intermediate from being derivatized into the corresponding glycal. Deprotection of the di-ClAc groups of **29** in aqueous pyridine, and oxidative cleavage of the resulting diol **32**, afforded the unstable aldehyde **33**. Subsequent immediate oxidation using $NaClO_2$ followed by methylation using $TMSCHN_2$ gave **7**,[17] which is the precursor of the diene segment for the Diels–Alder reaction.

In conclusion, we synthesized three key segments, **4**, **5** and **7**, of vineomycin B_2. The key steps were the preparation of the acurosyl rhodinose segment **4** by reduction of the hex-2-enopyranosyl acetate **5** using Rh/Al_2O_3, and the chemoselective glycosylation of the 2,3-unsaturated sugar **5** with the 2,3-saturated sugar **14**. Furthermore, the diene precursor **7** was synthesized by a powerful glycosylation approach in which the β-oxo-*tert*-alcohol acceptor **8** and the 2,3-unsaturated glycosyl donor **9** were reacted in an ionic liquid. Studies toward the total synthesis of vineomycin B_2 using these segments are now in progress in our laboratories.

Acknowledgments

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12. ^{1}H NMR (300 MHz, $CDCl_3$): (δ, $SiMe_4$; *J* Hz) δ 6.88 (1H, dd, $J_{2',3'} = 10.2$, $J_{1',2'} = 3.3$, H-2′), 6.16 (1H, br dd, $J_{1,2} = 1.8$, H-1), 6.11 (1H, d, $J_{2',3'} = 10.2$, H-3′), 5.25 (1H, d, $J_{1',2'} = 3.3$, H-1′), 4.57 (1H, q, $J_{4',5'} = 6.6$, H-5′), 4.05 (1H, qd, $J_{5,6} = 6.3$, $J_{4,5} = 1.5$, H-5), 3.68 (1H, br ddd, $J_{4,5} = 1.5$, H-4), 2.10 (3H, s, $C(O)CH_3$), 2.17–1.91 (3H, m), 1.67–1.60 (1H, m), 1.39 (3H, d, $J_{5',6'} = 6.6$, H-6′), 1.22 (3H, d, $J_{5,6} = 6.3$, H-6); ^{13}C NMR (75 Hz, $CDCl_3$): (δ, $CDCl_3$) δ 196.6, 169.6, 142.8, 127.3, 95.3, 92.0, 75.8, 70.5, 68.3, 24.3, 23.1, 21.2, 17.1, 15.1; Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 58.96; H, 7.23.
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17. ^{1}H NMR (300 MHz, $CDCl_3$): (δ, $SiMe_4$; *J* Hz) δ 7.37–7.23 (5H, m, ArH), 6.09 (1H, dd, $J_{2',3'} = 10.2$, $J_{3',4'} = 4.8$, H-3′), 5.85 (1H, dd, $J_{2',3'} = 10.2$, $J_{1',2'} = 3.3$, H-2′), 5.80 (1H, ddd, $J_{1'',2''E} = 17.1$, $J_{1'',2''Z} = 9.9$, $J_{2,1''} = 7.8$, H-1″), 5.33 (1H, d, $J_{1',2'} = 3.3$, H-1′), 5.14 (1H, d, $J_{1'',2''E} = 17.1$, H-2″*E*), 5.07 (1H, d, $J_{1'',2''Z} = 9.9$, H-2″*Z*), 4.64 and 4.54 (2H, ABq, $J = 12.0$, $ArCH_2$), 4.14 (1H, qd, $J_{5',6'} = 6.6$, $J_{4',5'} = 2.4$, H-5′), 4.11 (2H, q, $J = 6.9$, OCH_2CH_3), 3.62 (3H, s, OMe), 3.48 (1H, dd, $J_{3',4'} = 4.8$, $J_{4',5'} = 2.4$, H-4′), 3.32 (1H, ddd, $J_{2,3} = 9.6$, $J_{2,1''} = 7.8$, $J_{2,3} = 3.6$, H-2), 2.78 and 2.70 (2H, ABq, $J = 14.4$, H-5), 2.25 (1H, dd, $J_{3,3} = 14.4$, $J_{2,3} = 9.6$, H-4), 1.89 (1H, dd, $J_{3,3} = 14.4$, $J_{2,3} = 3.6$, H-4), 1.41 (3H, s, CH_3), 1.31 (3H, d, $J_{5',6'} = 6.6$, H-6′), 1.25 (3H, t, $J = 6.9$, OCH_2CH_3); ^{13}C NMR (75 Hz, acetone-d_6): (δ, acetone-d_6) δ 174.7, 170.9, 140.3, 138.4, 131.3, 129.0 (×2), 128.3 (×2), 128.1, 127.5, 116.3, 89.7, 77.1, 71.0, 70.4, 67.2, 60.7, 51.9, 46.5, 44.9, 42.9, 24.2, 16.7, 14.5; Anal. Calcd for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67. Found: C, 67.10; H, 7.71.