# Easy Access to (±)-Schefflone and Espintanol

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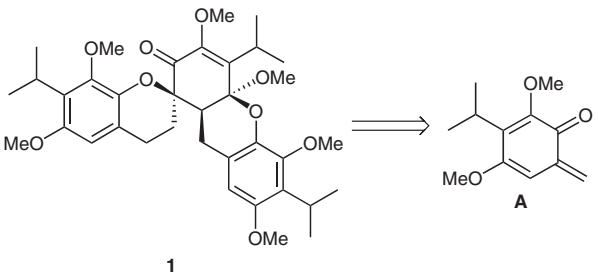
**Abstract:** Oxidation of espintanol by silver oxide gives trimeric monoterpenoid (±)-schefflone via *ortho*-quinone methide intermediate. The heating of 6-[(dibenzylamino)methyl]-3-isopropyl-2,4-dimethoxyphenol also results in *ortho*-quinone methide intermediate which is trapped by 3-(dimethylamino)-5,5-dimethylcyclohex-2-en-1-one or benzotriazole.

**Key words:** (±)-schefflone, *ortho*-quinone methide, espintanol, trimerization, Diels–Alder reaction

(±)-Schefflone (**1**) is the trimeric monoterpenoid containing the fragment of spiro[chromene-2,1′-xantene]. It was isolated from the root barks of *Uvaria scheffleri* (Annonaceae) by Nkunya and co-workers[1] and was also found in antimalarial extract of the *U. scheffleri* which is commonly used in traditional African medicine.[2]




**Scheme 1** Retrosynthetic analysis of (±)-schefflone

Retrosynthetic analysis of (±)-schefflone shows that it can be regarded as a trimer of the relevant *ortho*-quinone methide (*o*-QM), 3-isopropyl-2,4-dimethoxy-6-methylenecyclohexa-2,4-dienone (**A**; Scheme 1). During preparation of this manuscript another paper by Lei and co-workers appeared, describing the successful realization of this retrosynthesis.[3]

It is well known that in the absence of nucleophiles and dienophiles *o*-QMs undergo oligomerization reaction via the oxo-Diels–Alder reaction to form a complex mixture of products. However, some reactions stop on the stage of trimeric product formation.[4] As precursors of *o*-QMs phenolic Mannich bases, quaternary ammonium salts, 2-halo- and 2-thiomethylphenols, salicylic alcohols, etc. are usually used.[5]

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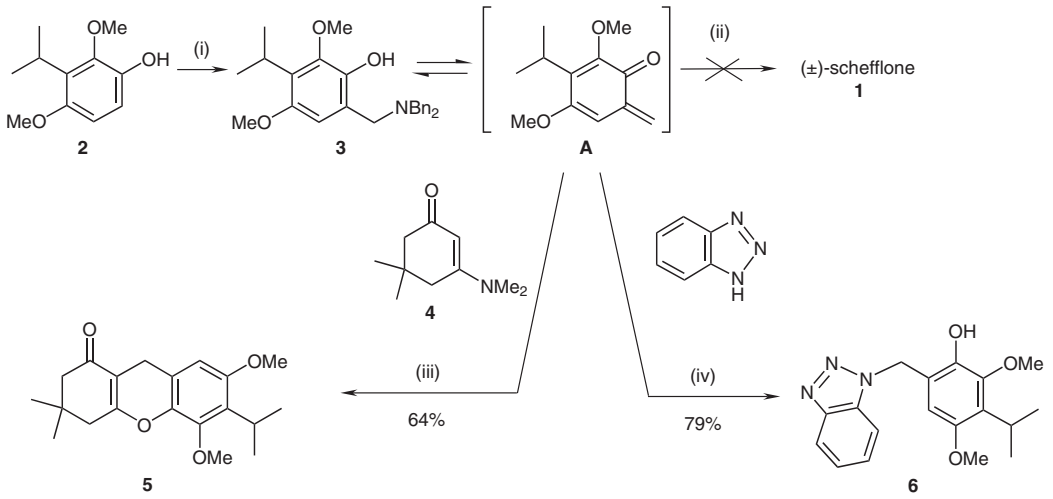
Recently we have shown that thermolysis of 3-(1-adamantyl)-2-hydroxy-5-methylbenzyl(trimethyl)ammonium iodide in refluxing DMF leads to the trimeric product in 85% yield.[6] So, we tried to synthesize the relevant quaternary salt as a precursor of *o*-QM **A** from 3-isopropyl-2,4-dimethoxyphenol (**2**). However, the aminomethylation of phenol **2** by aqueous dimethylamine and formaldehyde in ethanol or bis(dimethylamino)methane in dioxane gave a complex mixture of deeply colored unidentified products. On the other hand, using of dibenzylamine gave Mannich base **3** in 88% yield.[7] Next, we attempted to quaternize the Mannich base **3** by excess of MeI under reflux as described in our earlier work.[6] However, only Mannich base **3** was isolated even at 100 °C under pressure. Attempts to prepare quaternary ammonium salt in polar aprotic solvents (DMF, acetone) also failed. This can be explained by the sterical hindrance of benzyl groups and the existence of the strong intramolecular hydrogen bond.

It is well known that highly reactive *o*-QMs are trapped by nucleophiles or electron-rich dienophiles such as the enamines.[5b,8] The possibility of generation of the *o*-QM **A** from the Mannich base **3** was observed by heating of **3** with two trapping compounds. Using 3-(dimethylamino)-5,5-dimethylcyclohex-2-en-1-one[9] (**4**) and benzotriazole as a dienophile and nucleophile, respectively, resulted in tetrahydro-1*H*-xanten-1-one (**5**) and product of aza-Michael reaction[10] **6** (Scheme 2).

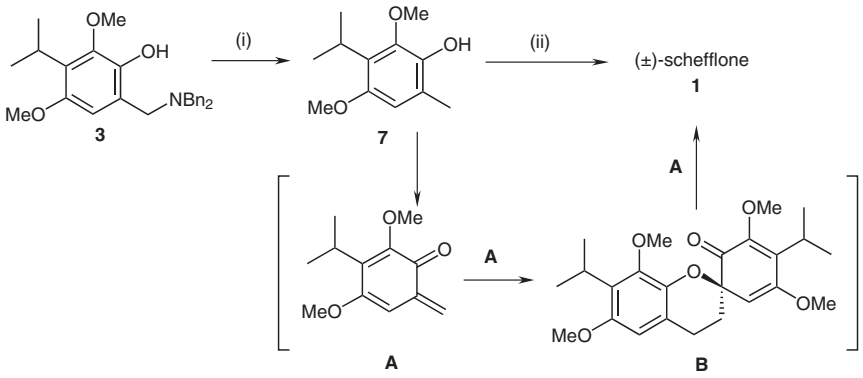
However, the thermolysis of the Mannich base **3** in DMF at reflux even after 20 hours did not show any trace amount of (±)-schefflone.[11] It is assumed that the reaction rate of oxo-Diels–Alder dimerization of *o*-QM **A** is slower than that of the reversible Michael addition of highly nucleophilic dibenzylamine.

Since all our approaches to the synthesis of (±)-schefflone were not successful, a search for another synthetic route was necessary. Oxidation of *ortho*-alkylphenols by one-electron oxidants ($Ag_2O$, $K_3[Fe(CN)_6]$, $PbO_2$) is one of the methods for generating *o*-QMs.[4a,5] Nkunya suggested that 3-isopropyl-2,4-dimethoxy-6-methylphenol (espintanol; **7**) can be biogenetic precursor of (±)-schefflone.[1] This process occurs via the oxidative formation of *o*-QM **A**. It should be noted that espintanol has also been isolated from *U. scheffleri*.[1]

Several multistep routes to the synthesis of espintanol from different substrates such as dimethyl 2-isopropyl-3-oxoglutarate, dimethyl squarate, ethyl 3-ethoxybut-2-enoate and carvacrol have been described.[12]




**Scheme 2** Preparation of Mannich base **3** and its thermolysis. *Reagents and conditions*: (i) $Bn_2NH$, 30% aq HCHO, MeOH, r.t., 24 h; (ii) DMF, heat, 20 h; (iii) DMF, heat, 4 h; (iv) solvent-free, 170 °C, 1 h.




**Scheme 3** Synthesis of espintanol and (±)-schefflone. *Reagents and conditions*: (i) $NaBH_3CN$, *i*-BuOH, heat, 4 h; (ii) $Ag_2O$, $CHCl_3$, heat, 2 h.

Herein, we report a two-step synthesis of espintanol[13] (**7**) from 2-isopropyl-1,3-dimethoxyphenol[14] (**2**). The aminomethylation of phenol **2** and the reduction of Mannich base **3** by sodium cyanoborohydride resulted in the espintanol in 91% yield. The further oxidation of **7** by freshly prepared silver oxide in refluxing chloroform led to (±)-schefflone.[15] There is a high correlation of spectral data between the natural and synthetic samples.[1,3] In this reaction other non-nucleophilic solvents can be used instead of chloroform, e.g. oxidation of espintanol in benzene gives (±)-schefflone in comparable yield.[3] The reaction is a cascade process involving two sequentially occurring oxo-Diels–Alder reactions. Formation of trimer is rationalized by assumption that the hydrogen atom abstraction in espintanol gives *o*-QM **A** which undergoes self-condensation to form the spirodimer **B** (Scheme 3). Attack of a third molecule of *o*-QM **A** on dimer **B** produces the trimer. Probably, the driving force of the reaction is the rearomatization of two carbocyclic moieties.

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## References and Notes

(1) Nkunya, M. H. H.; Jonker, S. A.; de Gelder, R.; Wachira, S. W.; Kihampa, C. *Phytochemistry* **2004**, *65*, 399.
(2) Kokwaro, J. O. *Medicinal Plants of East Africa*, 3rd ed.; University of Nairobi Press: Nairobi, **2009**, 43.
(3) Liao, D.; Li, H.; Lei, X. *Org. Lett.* **2012**, *14*, 18.
(4) (a) Dean, F. M.; Orabi, M. O. A. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2617. (b) Bavoux, C.; Perrin, M. *J. Chem. Soc., Perkin Trans. 2* **1989**, 2059. (c) Tarli, A.; Wang, K. K. *J. Org. Chem.* **1997**, *62*, 8841. (d) Xiong, Y.; Xia, H.; Moore, H. W. *J. Org. Chem.* **1995**, *60*, 6460. (e) Qiao, G. G.; Lenghaus, K.; Solomon, D. H.; Reisinger, A.; Bytheway, I.; Wentrup, C. *J. Org. Chem.* **1998**, *63*, 9806. (f) Faure, R.; Thomas-David, G.; Bartnik, R.; Cebulska, Z.; Graca, E.; Lesniak, S. *Bull. Soc. Chim.* **1991**, 378.
(5) (a) Bolon, D. A. *J. Org. Chem.* **1970**, *35*, 715. (b) Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367.
(6) Osyanin, V. A.; Popova, Y. N.; Klimochkin, Y. N. *Russ. J. Org. Chem.* **2011**, *47*, 958.
(7) **6-[(Dibenzylamino)methyl]-3-isopropyl-2,4-dimethoxyphenol (3)**: To a mixture of 3-isopropyl-2,4-

 

dimethoxyphenol (**2**; 1 g, 5.1 mmol) and dibenzylamine (1.01 g, 5.1 mmol) in MeOH (10 mL) 30% aq formaldehyde (0.53 g, 5.3 mmol) was added and the solution was stirred at r.t. for 24 h. The solvent was evaporated under vacuum. Recrystallization of the residue from MeOH yielded the pure product. Yield: 1.82 g (88%); colorless crystals; mp 102–104 °C. IR (KBr): 3100–2400 (OH), 2984, 2951, 2926, 2870, 2833, 1477, 1449, 1396, 1323, 1238, 1130, 1103, 1069, 827, 746, 696 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.31 [d, *J* = 7.1 Hz, 6 H, $CH(CH_3)_2$], 3.50 [sept, *J* = 7.1 Hz, 1 H, $CH(CH_3)_2$], 3.62 (s, 4 H, 2 × $CH_2Ph$), 3.69 (s, 2 H, $CH_2$), 3.72 (s, 3 H, $CH_3O$), 3.86 (s, 3 H, $CH_3O$), 6.32 (s, 1 H, H-5), 7.25–7.40 (m, 10 H, 2 × Ph), 10.32 (br s, 1 H, OH). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 21.4 [$CH(CH_3)_2$], 25.2 [$CH(CH_3)_2$], 56.4 ($CH_3O$-2), 57.3 ($CH_2$), 58.1 ($CH_2$), 60.8 ($CH_3O$-4), 107.8 (CH-5), 119.6 (C-3), 127.7, 128.7, 129.7 (CH-2′,3′,4′), 130.0 (C-6), 137.0 (C-1′), 144.7, 146.4 (C-1,2), 151.3 (C-4). Anal. Calcd for $C_{26}H_{31}NO_3$ (405.53): C, 77.01; H, 7.71; N, 3.45. Found: C, 77.11; H, 7.67; N, 3.39.

(8) Osyanin, V. A.; Klimochkin, Y. N. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2011**, *47*, 242.

(9) Kowalski, C. J.; Fields, K. W. *J. Org. Chem.* **1981**, *46*, 197.

(10) **6-Isopropyl-5,7-dimethoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (5)**: A mixture of 3-dimethylamino-5,5-dimethyl-2-cyclohexen-1-one (**4**; 0.1 g, 0.6 mmol) and **3** (0.25 g, 0.6 mmol) in DMF (2 mL) was refluxed for 4 h. The reaction mixture was poured into 5% AcOH (10 mL) to yield a solid product, which was filtered, washed with $H_2O$, dried and recrystallized from EtOH. Yield: 0.13 g (64%); orange crystals; mp 155–157 °C. IR (KBr): 2959, 2924, 2851, 1647 (C=O), 1616, 1574, 1512, 1454, 1420, 1389, 1254, 1231, 1134, 1076, 1049, 1034, 854, 841 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.11 [s, 6 H, $C(CH_3)_2$], 1.28 [d, *J* = 7.1 Hz, 6 H, $CH(CH_3)_2$], 2.32 (s, 2 H, $CH_2$), 2.48 (s, 2 H, $CH_2$), 3.45 (s, 2 H, 9-$CH_2$), 3.47 [sept, *J* = 7.1 Hz, 1 H, $CH(CH_3)_2$], 3.76 (s, 3 H, $CH_3O$), 3.83 (s, 3 H, $CH_3O$), 6.36 (s, 1 H, 5-H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 21.2 [$CH(CH_3)_2$], 21.4 ($CH_2$), 25.1 [$CH(CH_3)_2$], 28.5 (2 × $CH_3$), 32.2 (C), 41.7 ($CH_2$), 50.8 ($CH_2$), 55.8 (4-$CH_3O$), 61.8 (2-$CH_3O$), 106.5 (8-CH), 108.3 (C), 119.0 (C), 128.0 (C), 137.7 (C), 146.6 (C), 155.0 (C), 164.9 (C), 198.1 (C=O). Anal. Calcd for $C_{20}H_{26}O_4$ (330.42): C, 72.70; H, 7.93. Found: C, 72.79; H, 7.87.

**6-(1*H*-1,2,3-Benzotriazol-1-ylmethyl)-3-isopropyl-2,4-dimethoxyphenol (6)**: A mixture of benzotriazole (0.08 g, 0.67 mmol) and **3** (0.25 g, 0.6 mmol) in DMF (2 mL) was heated at 170 °C for 1 h under solvent-free conditions. The reaction mixture was diluted with EtOH (1 mL). The formed precipitate was filtered, washed with $H_2O$ and recrystallized from EtOH. Yield: 0.16 g (79%); colorless crystals; mp 178–179 °C. IR (KBr): 3300–3100 (OH), 2986, 2957, 2932, 2874, 2837, 1487, 1454, 1423, 1344, 1180, 1130, 1096, 1059, 1005, 750 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.31 [d, *J* = 7.1 Hz, 6 H, $CH(CH_3)_2$], 3.31 [sept, *J* = 7.1 Hz, 1 H, $CH(CH_3)_2$], 3.63 (s, 3 H, $CH_3O$), 3.74 (s, 3 H, $CH_3O$), 5.80 (br s, 1 H, OH), 5.83 (s, 2 H, $CH_2$), 6.51 (s, 1 H, 5-H), 7.33, 7.43 (t, *J* = 8.2 Hz, 2 H, 5′-H, 6′-H), 7.68, 8.03 (t, *J* = 8.2 Hz, 2 H, 4′-H, 7′H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 20.9 [$CH(CH_3)_2$], 26.1 [$CH(CH_3)_2$], 46.2 ($CH_2$), 55.8 (4-$CH_3O$), 62.1 (2-$CH_3O$), 108.2 (CH), 110.4 (CH), 118.1 (C), 119.9 (CH), 123.9 (CH), 127.2 (CH), 130.3 (C), 133.0 (C), 141.0 (C), 145.4 (C), 146.1 (C), 152.8 (4-C). Anal. Calcd for $C_{18}H_{21}N_3O_3$ (327.38): C, 66.04; H, 6.47; N, 12.84. Found: C, 65.96; H, 6.52; N, 12.90.

(11) According to mass spectrometric data.

(12) (a) Zúñiga, A. C.; Romero-Ortega, M.; Zárraga, J. G. A. *Synthesis* **2005**, 527. (b) Tomooka, C. S.; Liu, H.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 6009. (c) Wadsworth, D. J.; Losch, S. *Tetrahedron* **1994**, *50*, 8673. (d) Hocquemiller, R.; Cortes, D.; Arango, G. J.; Myint, S. H.; Cave, A. *J. Nat. Prod.* **1991**, *54*, 445. (e) Söderberg, B. C.; Fields, S. L. *Org. Prep. Proced. Int.* **1996**, *28*, 221.

(13) **3-Isopropyl-2,4-dimethoxy-6-methylphenol(espintanol) (7)**: A mixture of **3** (0.96 g, 2.37 mmol) and sodium cyanoborohydride (0.90 g, 14.29 mmol) in *i*-BuOH (10 mL) was stirred at reflux under argon atmosphere for 4 h. The cooled reaction mixture was quenched with 2 N HCl (10 mL), poured into $H_2O$ (20 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The organic layer was separated, washed with sat. $NaHCO_3$ (10 mL), $H_2O$ (5 mL), dried ($Na_2SO_4$), filtered and concentrated. The residue was purified by column chromatography on silica gel (15 g) eluting with $CCl_4$. Yield: 0.45 g (91%); colorless oil. IR (KBr): 3500–3350 (OH), 2988, 2955, 2938, 2874, 2835, 1489, 1458, 1416, 1358, 1211, 1188, 1130, 1067, 1009, 833 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.32 [d, *J* = 7.1 Hz, 6 H, $CH(CH_3)_2$], 2.23 (s, 3 H, $CH_3$), 3.32 [sept, *J* = 7.1 Hz, 1 H, $CH(CH_3)_2$], 3.74 (s, 3 H, $CH_3O$), 3.75 (s, 3 H, $CH_3O$), 5.43 (br s, 1 H, OH), 6.45 (s, 1 H, 5-H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 15.8 ($CH_3$), 21.3 [$CH(CH_3)_2$], 25.9 [$CH(CH_3)_2$], 55.9 (4-$CH_3O$), 61.9 (2-$CH_3O$), 110.1 (5-C), 121.4 (3-C), 126.9 (6-C), 141.2 (1-C), 144.9 (2-C), 152.1 (4-C). MS (70 eV): *m/z* (%) = 210 (66) $[M]^+$, 195 (100) $[M - CH_3]^+$, 180 (28) $[M - 2 \times CH_3]^+$, 147 (11), 139 (17), 91 (13) $[C_7H_7]^+$. Anal. Calcd for $C_{12}H_{18}O_3$ (210.27): C, 68.54; H, 8.63. Found: C, 68.60; H, 8.57.

(14) Burnell, R. H.; Caron, S. *Can. J. Chem.* **1992**, *70*, 1446.

(15) **4′,6′,7-Triisopropyl-3′,4a′,5′,6,7′,8-hexamethoxy-3,4,9′,9a′-tetrahydrospiro[chromene-2,1′-xanthen]-2′(4a′*H*)-one [(±)-Schefflone] (1)**: To a solution of espintanol (**7**; 69 mg, 0.33 mmol) in anhyd $CHCl_3$ (2 mL), silver oxide (125 mg, 0.54 mmol) was added and the mixture was stirred at reflux for 2 h. The solution was filtered and evaporated under vacuum. Recrystallization of the residue from MeOH yielded the pure product. Yield: 52 mg (76%); colorless crystals; mp 215–217 °C. IR (KBr): 2994, 2959, 2932, 2872, 2839, 1695 (C=O), 1618, 1481, 1456, 1423, 1341, 1273, 1240, 1130 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.09 (d, *J* = 7.1 Hz, 3 H, $CH_3$), 1.27–1.33 (m, 15 H, 5 × $CH_3$), 2.12 (ddd, *J* = 14.2, 11.0, 5.0 Hz, 1 H), 2.51 (ddd, *J* = 16.0, 10.6, 5.6 Hz, 1 H), 2.55 (dd, *J* = 16.0, 12.4 Hz, 1 H), 2.69 (ddd, *J* = 16.5, 5.0, 4.6 Hz, 1 H), 2.77 (ddd, *J* = 14.2, 10.1, 5.0 Hz, 1 H), 2.90 (dd, *J* = 12.4, 5.0 Hz, 1 H), 3.04 [sept, *J* = 7.1 Hz, 1 H, $CH(CH_3)_2$], 3.25 (dd, *J* = 16.0, 5.0 Hz, 1 H), 3.40 (s, 3 H, $CH_3O$), 3.47 [sept, *J* = 7.1 Hz, 1 H, $CH(CH_3)_2$], 3.53 [sept, *J* = 7.1 Hz, 1 H, $CH(CH_3)_2$], 3.67 (s, 3 H, $CH_3O$), 3.72 (s, 6 H, 2 × $CH_3O$), 3.87 (s, 3 H, $CH_3O$), 3.92 (s, 3 H, $CH_3O$), 6.28 (s, 1 H, ArH), 6.33 (s, 1 H, ArH). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 20.4 ($CH_3$), 21.3 ($CH_3$), 21.4 (3 × $CH_3$), 21.5 ($CH_3$), 22.0 ($CH_2$), 25.2 (2 × CH), 26.1 ($CH_2$), 27.6 (CH), 28.8 ($CH_2$), 43.3 (CH), 49.6 ($CH_3O$), 56.0 (2 × $CH_3O$), 59.0 ($CH_3O$), 61.2 ($CH_3O$), 61.4 ($CH_3O$), 81.2 (C), 102.4 (C), 105.9 (CH), 106.6 (CH), 118.4 (C), 121.1 (C), 128.9 (C), 129.0 (C), 140.6 (C), 141.2 (C), 146.4 (C), 146.4 (C), 148.1 (C), 148.6 (C), 151.9 (C), 152.9 (C), 194.1 (C=O). MS (70 eV): *m/z* (%) = 624 (<1) $[M]^+$, 593 (3) $[M - CH_3O]^+$, 416 (21) $[C_{24}H_{32}O_6]^+$, 208 (48) $[C_{12}H_{16}O_3]^+$, 193 (62) $[C_{12}H_{16}O_3 - CH_3]^+$, 178 (32) $[C_{12}H_{16}O_3 - 2 \times CH_3]^+$, 165 (54) $[C_{12}H_{16}O_3 - C_3H_7]^+$, 136 (60), 43 (100) $[C_3H_7]^+$. Anal. Calcd for $C_{36}H_{48}O_9$ (624.76): C, 69.21; H, 7.74. Found: C, 69.17; H, 7.79.