Chemical Transformation of (+)-Dehydroabietic Acid Leading to a Formal Synthesis of (+)-Coleon A

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(*R*)-6-Hydroxy-7-isopropyl-3-(3-methoxypropyl)-3,4-dimethylnaphtho[2,3-*b*]furan-2(3*H*)-one (3), prepared from (+)-dehydroabietic acid (2), was converted into (*R*)-9-acetoxy-6-benzoyloxy-7-isopropyl-3-(3-methoxypropyl)-3,4-dimethylnaphtho[2,3-*b*]furan-2,5,8(3*H*)-trione (10) and its 9-acetyl compound (11) by a series of reactions: sodium borohydride reduction, acetylation, alkaline hydrolysis, benzoyl peroxide oxidation, Jones oxidation, and *m*-chloroperbenzoic acid oxidation. The trione 10 was further transformed into (*R*)-5,6,8,9-tetraacetoxy-7-isopropyl-3-(3-methoxypropyl)-3,4-dimethylnaphtho[2,3-*b*]furan-2(3*H*)-one (15) by alkaline hydrolysis and reductive acetylation. Since the conversion of 15 into coleon A (1) has already been reported, the present work can be regarded as a new formal synthesis of coleon A.

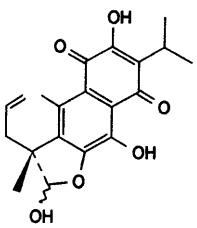
Keywords coleon A; synthesis; highly oxygenated 1,10-secoabietane; *Coleus igniarius* (Labiatae); diterpene; benzoyl peroxide oxidation; naphthol derivative

Coleon A (**1**), a rare highly oxygenated 1,10-secoabietane derivative, has been isolated from the leaves of *Coleus igniarius* SCHWEINF (Labiatae) by Eugster *et al.*[1-3] In previous papers,[4,5] we have reported the novel conversion of (+)-dehydroabietic acid (**2**) into coleon A (**1**) *via* the lactone intermediate, (*R*)-6-hydroxy-7-isopropyl-3-(3-methoxypropyl)-3,4-dimethylnaphtho[2,3-*b*]furan-2(3*H*)-one (**3**). In order to obtain further information on the introduction of oxygen functions into the naphthol skeleton, we have recently investigated the oxidation of some simple naphthol compounds with benzoyl peroxide, and these results were also reported in the preceding paper.[6] As an extension of the previous work, we now describe a new synthetic route to coleon A which involves the oxidation of highly substituted naphthol compounds with benzoyl peroxide.

The lactone **3** prepared from **2** was reduced with sodium borohydride in ethanol and the resulting mixture of C-2 epimeric alcohols (**4**) was immediately treated with acetic anhydride in the presence of boron trifluoride etherate to give the corresponding 2,6-diacetoxy-9-acetyl derivative (**5**). The infrared (IR) spectrum of **5** indicated the presence of acetoxyl (1748 cm^{-1}) and acetyl (1672 cm^{-1}) groups, and its proton nuclear magnetic resonance (^{1}H-NMR) spectrum showed singlet signals at δ 2.68 (3H) due to an acetyl group and at δ 7.58 (1H) and 8.36 (1H) due to the C-5 and C-8 aromatic protons. Hydrolysis of the acetoxyl groups in **5** with sodium hydrogencarbonate in refluxing aqueous methanol afforded the hemiacetal derivative (**6**). This was oxidized with benzoyl peroxide in chloroform at room temperature and then with Jones reagent to give two bis(benzoyloxy) keto lactones (**7** and **8**) in 30% and 8% yields from **3**. The ^{1}H-NMR spectrum of **7** showed a singlet signal due to a C-8 olefinic proton at δ 7.15, while that of **8** showed the corresponding signal at a lower filed (δ 7.54). These spectral data suggested that the C-7 and C-8 double bond in **8** is conjugated with a carbonyl group. Thus, the structures of **7** and **8** were assigned to be (*R*)-9-acetyl-6,6-bis(benzoyloxy)-7-isopropyl-3-(3-methoxypropyl)-3,4-dimethylnaphtho[2,3-*b*]furan-2,5(3*H*,6*H*)-dione and (*R*)-9-acetyl-5,5-bis(benzoyloxy)-7-isopropyl-3-(3-methoxypropyl)-3,4-dimethylnaphtho[2,3-*b*]furan-2,6(3*H*,5*H*)-dione, respectively.

Similarly, (*R*)-9-acetyl-6-hydroxy-7-isopropyl-3-(3-methoxypropyl)-3,4-dimethylnaphtho[2,3-*b*]furan-2(3*H*)-one (**9**),[5] prepared from **3**, was also oxidized with benzoyl peroxide in dichloromethane at room temperature to give **7** and **8** in 75% and 9% yields, respectively. In order to introduce oxygen functions at the C-8 and C-9 positions, a mixture of the acetyl compounds (**7** : **8** = *ca.* 8/1) was refluxed with *m*-chloroperbenzoic acid and *p*-toluenesulfonic acid monohydrate in dichloromethane. Purification of the crude product gave two *p*-quinones, **10** and **11**, in 18% and 13% yields, respectively. Each of **7** and **8** was also oxidized with *m*-chloroperbenzoic acid to give a similar result. The IR spectrum of **10** showed absorption bands at 1813 (γ-lactone), 1770 (acetoxyl), 1739 (benzoyloxyl), and 1660 cm^{-1} (*p*-quinone). The spectrum of **11** showed absorption bands at 1812 (γ-lactone), 1738 (benzoyloxyl), 1702 (acetyl), and 1662 cm^{-1} (*p*-quinone). Hydrolysis of the acetyl *p*-quinone (**11**) with sodium hydrogencarbonate in refluxing aqueous methanol produced the corresponding hydroxy *p*-quinone (**12**),[5] which was then submitted to reductive acetylation with zinc powder and acetic anhydride in pyridine to give the corresponding triacetate (**13**). Transformation of **13** into the desired tetraacetoxy lactone (**15**) by Baeyer–Villiger oxidation using *m*-chloroperbenzoic acid was attempted, but only the starting **13** was recovered. Subsequently, the acetoxy *p*-quinone (**10**) was also hydrolyzed with sodium hydrogencarbonate in refluxing aqueous methanol and the resulting dihydroxy *p*-quinone (**14**) was then treated with zinc powder and acetic anhydride in pyridine to give the tetraacetoxy lactone (**15**) in 79% yield from **10**.

Since the conversion of **15** into coleon A (**1**) has already



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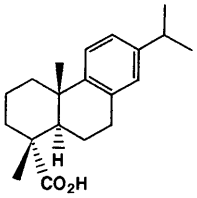

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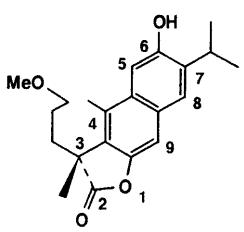

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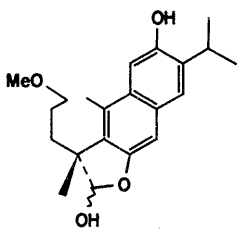

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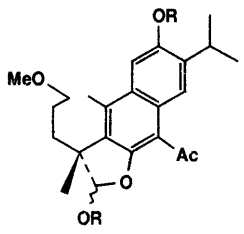
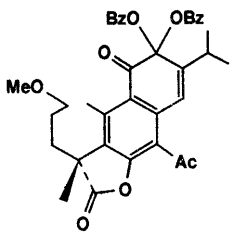


5 : R=H
6 : R=Ac



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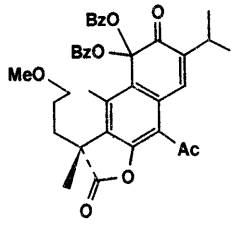

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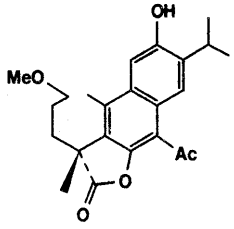

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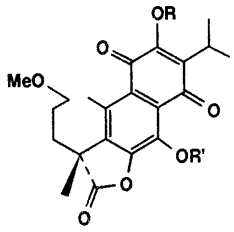
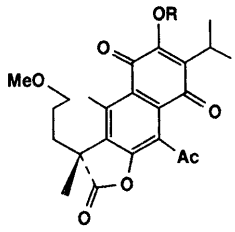
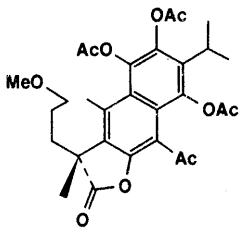


10 : R=Bz, R'=Ac
14 : R=R'=H



11 : R=Bz
12 : R=H



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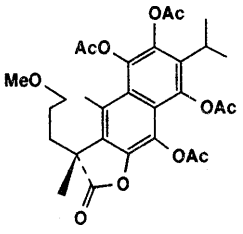

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been reported,[5] the present work can be regarded as a new formal synthesis of (+)-coleon A.

Experimental

The IR spectra and optical rotations were measured in chloroform, and the ^{1}H-NMR spectra in deuteriochloroform at 90 MHz with tetramethylsilane as an internal standard, unless otherwise stated. The column chromatography was performed using Merck silica gel (0.063 mm).

The C-2 Epimeric Mixture of 9-Acetyl-2,3-dihydro-7-isopropyl-3-(3-methoxypropyl)-3,4-dimethylnaphtho[2,3-*b*]furan-2,6-diol (6) Sodium borohydride (0.83 g) was added portionwise to a stirred solution of (*R*)-6-hydroxy-7-isopropyl-3-(3-methoxypropyl)-3,4-dimethylnaphtho[2,3-*b*]-furan-2(3*H*)-one (**3**)[5] (3.41 g) in ethanol (140 ml) with cooling in an ice-water bath. The mixture was stirred at this temperature for 1 h and then at room temperature for 15 h. After the excess hydride had been decomposed with acetone, the mixture was concentrated *in vacuo*, poured into dilute hydrochloric acid, and extracted with chloroform. The chloroform extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give a mixture of the crude C-2 epimeric alcohols (**4**) (3.40 g). IR (Nujol): 3350 (br) cm^{-1}.

Boron trifluoride etherate (3.40 ml) was added to a stirred solution of the crude **4** (3.40 g) in acetic anhydride (68 ml) at −5 °C over a period of 5 min. The mixture was stirred at room temperature for 5 min, poured into a mixture of ice and aqueous sodium hydrogencarbonate, and extracted with chloroform. The chloroform extract was washed with brine, dried, and evaporated *in vacuo* to give a crude epimeric mixture (*ca.* 3 : 1) at C-2 of the 2,6-diacetoxy-9-acetyl derivative (**5**) (3.92 g). IR: 1748, 1672 cm^{-1}. ^{1}H-NMR δ: 1.27 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.46 (minor) and 1.55 (major) (3H, each s, C_3-CH_3), 2.07 (major) and 2.10 (minor) (3H, each s, C_2-$OCOCH_3$), 2.37 (3H, s, C_6-$OCOCH_3$), 2.62 (3H, s, C_4-CH_3), 2.68 (3H, s, C_9-$COCH_3$), 3.09 (1H, m, $-C\underline{H}(CH_3)_2$), 3.23 (major) and 3.28 (minor) (3H, each s, $-OCH_3$), 3.27 (major) and 3.33 (minor) (2H, each t, J=6 Hz, $-C\underline{H}_2OCH_3$), 6.47 (minor) and 6.57 (major) (1H, each, s, C_2-H), 7.58 (1H, s, C_5-H), 8.36 (1H, s, C_8-H).

A mixture of the crude **5** (3.92 g) and sodium hydrogencarbonate (4.20 g) in methanol (390 ml) and water (84 ml) was refluxed for 2 h. The mixture was concentrated *in vacuo* to *ca.* 100 ml, diluted with brine, and extracted with ether. The ether extract was washed with brine, dried, and evaporated *in vacuo* to give a crude epimeric mixture (**6**) (3.40 g), which was used without purification in the next reaction. IR: 3600, 3320 (br), 1658 cm^{-1}.

(*R*)-9-Acetyl-6,6-bis(benzoyloxy)-7-isopropyl-3-(3-methoxypropyl)-3,4-dimethylnaphtho[2,3-*b*]furan-2,5(3*H*,6*H*)-dione (7) and (*R*)-9-Acetyl-5,5-bis(benzoyloxy)-7-isopropyl-3-(3-methoxypropyl)-3,4-dimethylnaphtho[2,3-*b*]furan-2,6(3*H*,5*H*)-dione (8) a) A solution of the above crude **6** (3.40 g) and benzoyl peroxide (4.67 g) in chloroform (46 ml) was stirred at room temperature for 26 h. After the addition of ether (200 ml), acetic acid (2.0 ml), and aqueous potassium iodide (20%, 50 ml), the mixture was further stirred at room temperature for 3 h and then washed successively with water, aqueous sodium thiosulfate, aqueous sodium hydrogencarbonate, and brine. The dried solution was evaporated *in vacuo*. The residue was dissolved in acetone (150 ml) and then oxidized with Jones reagent (2.5 mol dm^{-3}, 16 ml) at 0—5 °C for 15 min. After the usual work-up, the crude product was chromatographed on silica gel (500 g), using ether–benzene (3 : 97) as an eluent, to give oily **7** (1.87 g, 30.1% yield from **3**), $[\alpha]_D$ +39° (c=2.44). IR: 1809, 1725, 1690 cm^{-1}. ^{1}H-NMR δ: 1.12 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$, 1.66 (3H, s, C_3-CH_3), 2.69 (6H, s, C_4-CH_3 and C_9-$COCH_3$), 2.88 (1H, m, $-C\underline{H}(CH_3)_2$), 3.22 (3H, s, $-OCH_3$), 3.26 (2H, t, J=6 Hz, $-C\underline{H}_2OCH_3$), 7.15 (1H, br s, C_8-H), *ca.* 7.3—7.7 (6H, m) and 8.07 (4H, dd, J=2, 8 Hz) (2-C_6H_5). MS *m/z*: 624 (M^+). *Anal.* Calcd for $C_{37}H_{36}O_9$: C, 71.14; H, 5.81. Found: C, 70.97; H, 5.88.

Further elution gave oily **8** (0.52 g, 8.4% yield from **3**), $[\alpha]_D$ +54° (c=1.85). IR: 1810, 1732, 1688 cm^{-1}. ^{1}H-NMR δ: 1.24 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.51 (3H, s, C_3-CH_3), 2.69 (6H, s, C_4-CH_3 and C_9-$COCH_3$), 2.80 (3H, s, $-OCH_3$), 3.00 (2H, m, $-C\underline{H}_2OCH_3$), 3.12 (1H, m, $-C\underline{H}(CH_3)_2$), 7.35—7.75 (6H, m), 8.04 and 8.06 (4H, each dd, J=2, 8 Hz) (2-C_6H_5), 7.54 (1H, d, J=1.5 Hz, C_8-H). MS *m/z*: 624 (M^+). *Anal.* Calcd for $C_{37}H_{36}O_9$: C, 71.14; H, 5.81. Found: C, 71.41; H, 5.96.

b) A solution of (*R*)-9-acetyl-6-hydroxy-7-isopropyl-3-(3-methoxypropyl)-3,4-dimethylnaphtho[2,3-*b*]furan-2(3*H*)-one (**9**)[5] (3.76 g) and benzoyl peroxide (5.33 g) in dichloromethane (110 ml) was stirred at room temperature for 54 h. After work-up as described in a), the crude product was chromatographed on silica gel (600 g), using ether–benzene (2 : 98) as an eluent, to give oily **7** (4.55 g, 74.5%) and **8** (0.56 g, 9.2%). The IR and ^{1}H-NMR spectra of **7** and **8** were identical with those of authentic samples.

(*R*)-9-Acetoxy-6-benzoyloxy-7-isopropyl-3-(3-methoxypropyl)-3,4-dimethylnaphtho[2,3-*b*]furan-2,5,8(3*H*)-trione (10) and (*R*)-9-Acetyl-6-benzoyloxy-7-isopropyl-3-(3-methoxypropyl)-3,4-dimethylnaphtho[2,3-*b*]-furan-2,5,8-(3*H*)-trione (11) a) A solution of a mixture of **7** and **8** (*ca.* 8 : 1 ratio, 1.220 g), *m*-chloroperbenzoic acid (90%, 1.23 g), and *p*-toluenesulfonic acid monohydrate (244 mg) in dichloromethane (60 ml) was refluxed for 8 h. The solution was cooled, diluted with ether, and then washed successively with aqueous potassium iodide, aqueous sodium thiosulfate, aqueous sodium hydrogencarbonate, and brine. The dried solution was evaporated *in vacuo*. The residue was chromatographed on silica gel (100 g), using ether–benzene (2 : 98) as an eluent, to give oily **10** (192 mg, 18.4%), $[\alpha]_D$ +36° (c=1.95). IR: 1813, 1770, 1739, 1660 cm^{-1}. ^{1}H-NMR δ: 1.28 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.63 (3H, s, C_3-CH_3), 2.46 (3H, s, C_9-$OCOCH_3$), 2.67 (3H, s, C_4-CH_3), 3.19 (3H, s, $-OCH_3$),

3.22 (2H, t, $J=6$ Hz, $-C\underline{H}_2OCH_3$), 3.30 (1H, m, $-C\underline{H}(CH_3)_2$), *ca.* 7.4—7.8 (3H, m) and 8.18 (2H, dd, $J=2$, 8 Hz) ($-C_6H_5$). *Anal.* Calcd for $C_{30}H_{30}O_9$: C, 67.40; H, 5.66. Found: C, 67.11; H, 5.93.

Further elution gave oily **11** (133 mg: 13.1%), $[\alpha]_D$ +21° ($c=1.72$). IR: 1812, 1738, 1702, 1662 cm^{-1}. ^{1}H-NMR δ: 1.28 (6H, d, $J=7$ Hz, $-CH(C\underline{H}_3)_2$), 1.61 (3H, s, C_3-CH_3), 2.60 (3H, s, C_9-$COCH_3$), 2.70 (3H, s, C_4-CH_3), 3.18 (3H, s, $-OCH_3$), 3.22 (2H, t, $J=6$ Hz, $-C\underline{H}_2OCH_3$), 3.29 (1H, m, $-C\underline{H}(CH_3)_2$), *ca.* 7.4—7.8 (3H, m) and 8.17 (2H, dd, $J=2$, 8 Hz) ($-C_6H_5$). *Anal.* Calcd for $C_{30}H_{30}O_8$: C, 69.48; H, 5.83. Found: C, 69.52; H, 6.01.

b) A solution of **7** (1.690 g), *m*-chloroperbenzoic acid (90%, 1.86 g), and *p*-toluenesulfonic acid monohydrate (169 mg) in chloroform (85 ml) was refluxed for 17 h to give **10** (212 mg, 14.7%) and **11** (167 mg, 11.9%).

c) A solution of **8** (192.7 mg), *m*-chloroperbenzoic acid (90%, 212.6 mg), and *p*-toluenesulfonic acid monohydrate (193 mg) in chloroform (9.6 ml) was refluxed for 17 h to give **10** (24.6 mg, 14.9%) and **11** (6.5 mg, 4.1%).

(*R*)-9-Acetyl-6-hydroxy-7-isopropyl-3-(3-methoxypropyl)-3,4-dimethylnaphtho[2,3-*b*]furan-2,5,8-(3*H*)-trione (12) A mixture of **11** (253.4 mg) and sodium hydrogencarbonate (845 mg) in methanol (50 ml) and water (10 ml) was refluxed for 15 min. After removal of the methanol *in vacuo*, the residue was diluted with brine and extracted with ether. The ether extract was washed with brine and evaporated *in vacuo*. The residue was dissolved in methanol (18 ml) and dilute hydrochloric acid (6 mol dm^{-3}, 3.6 ml) was then added. The mixture was refluxed for 15 min, concentrated *in vacuo*, and extracted with ether. The ether extract was washed with brine, dried, and evaporated *in vacuo*. The crude product was chromatographed on silica gel (20 g), using ether–benzene (6.94) as an eluent, to give oily **12**[5] (61.5 mg, 30.4%), $[\alpha]_D$ +26° ($c=0.35$). IR: 3360, 1820, 1712, 1652 cm^{-1}. *Anal.* Calcd for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.40; H, 6.30.

(*R*)-5,6,8-Triacetoxy-9-acetyl-7-isopropyl-3-(3-methoxypropyl)-3,4-dimethylnaphtho[2,3-*b*]furan-2(3*H*)-one (13) A mixture of **12** (220.1 mg), acetic anhydride (0.6 ml), and zinc powder (100 mg) in pyridine (1.0 ml) was stirred at 0—5 °C for 1 h. The mixture was diluted with ether and washed successively with aqueous sodium hydrogencarbonate, dilute hydrochloric acid, and brine. The dried solution was evaporated *in vacuo*. The residue was chromatographed on silica gel (25 g), using ether–benzene (2 : 8) as an eluent, to give oily **13** (56.3 mg, 19.5%), $[\alpha]_D$ +16° ($c=1.11$). IR: 1815, 1784, 1712 cm^{-1}. ^{1}H-NMR δ: 1.26 (6H, d, $J=7$ Hz, $-CH(C\underline{H}_3)_2$), 1.60 (3H, s, C_3-CH_3), 2.28 (3H, s) and 2.35 (6H, s) (3-$OCOCH_3$), 2.59 (3H, s, C_9-$COCH_3$), 2.68 (3H, s, C_4-CH_3), 3.05 (1H, m, $-C\underline{H}(CH_3)_2$), 3.18 (3H, s, $-OCH_3$), 3.22 (2H, t, $J=6$ Hz, $-C\underline{H}_2OCH_3$). *Anal.* Calcd for $C_{29}H_{34}O_{10}$: C, 64.19; H, 6.32. Found: C, 64.07; H, 6.37.

(*R*)-5,6,8,9-Tetraacetoxy-7-isopropyl-3-(3-methoxypropyl)-3,4-dimethylnaphtho[2,3-*b*]furan-2(3*H*)-one (15) A mixture of **10** (192.1 mg) and sodium hydrogencarbonate (302 mg) in methanol (38 ml) and water (7.5 ml) was refluxed for 15 min. The mixture was cooled, acidified with dilute hydrochloric acid, and then refluxed for 15 min. After removal of the methanol *in vacuo*, the residue was extracted with ether. The ether extract was washed successively with aqueous sodium hydrogencarbonate and brine, dried, and evaporated *in vacuo* to give crude (*R*)-6,9-dihydroxy-7-isopropyl-3-(3-methoxypropyl)-3,4-dimethylnaphtho[2,3-*b*]furan-2,5,8-(3*H*)-trione (**14**) (142.7 mg). IR: 3340, 1812, 1650, 1622 cm^{-1}.

A solution of the crude **14** (142.7 mg) and acetic anhydride (2.5 ml) in pyridine (2.5 ml) was stirred at room temperature for 30 min and then cooled in an ice-water bath. After the addition of zinc powder (42 mg), the mixture was further stirred at this temperature for 5 min and at room temperature for 1 h, diluted with ether, and then filtered. The filtrate was washed successively with aqueous sodium hydrogencarbonate, dilute hydrochloric acid, and brine. The dried solution was evaporated *in vacuo*. The residue was chromatographed on silica gel (20 g), using ether–benzene (15 : 85) as an eluent, to give **15** (158.0 mg, 78.7% yield from **10**), mp 243 °C (from methanol), $[\alpha]_D$ +12° ($c=0.65$). IR: 1809, 1775, 1648 cm^{-1}. ^{1}H-NMR δ: 1.27 (6H, br d, $J=7$ Hz, $-CH(C\underline{H}_3)_2$), 1.63 (3H, s, C_3-CH_3), 2.35 and 2.40 (each 6H and s, 4-$OCOCH_3$), 2.66 (3H, s, C_4-CH_3), 3.17 (3H, s, $-OCH_3$), 3.21 (2H, t, $J=6$ Hz, $-C\underline{H}_2OCH_3$), 3.21 (1H, m, $-C\underline{H}(CH_3)_2$). The IR and ^{1}H-NMR spectra of **15** were identical with those of an authentic sample.[5] *Anal.* Calcd for $C_{29}H_{34}O_{11}$: C, 62.35; H, 6.14. Found: C, 62.56; H, 6.17.

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