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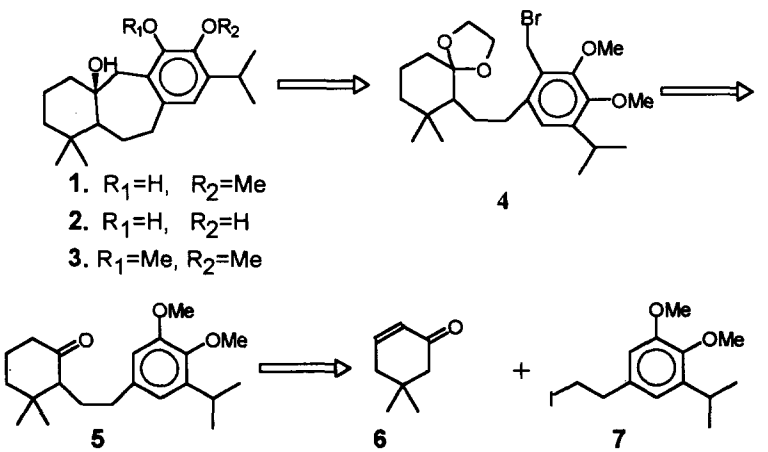
The First Total Synthesis of (±)-Demethyl Salvicanol

Xuechao Wang, Xinfu Pan*, Yuxin Cui and Yaozu Chen

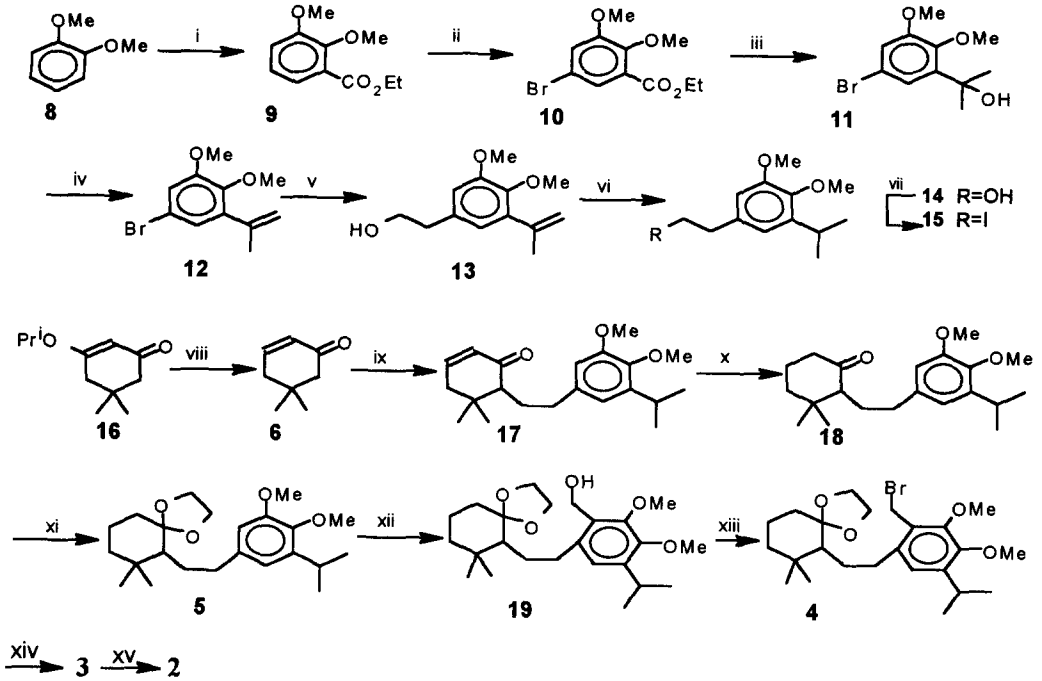
Department of Chemistry,National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

Abstract: Demethyl salvicanol, a novel rearranged 9(10→20)-*abeo*-8, 11, 13-triene diterpene, has been synthesize for the first time. The zinc-promoted coupling reaction of benzyl bromide with ketone and the alkylation of ketone with iodide are the key steps. Copyright © 1996 Elsevier Science Ltd

Salvicanol (**1**) and demethyl salvicanol (**2**), representing a group of rare naturally-occurring rearranged 9(10→20)-*abeo*-8, 11, 13-triene diterpenoids[1], have been recently isolated from the roots of *S. canaviensis*[2] and *S. apiana*[3] and characterized by Fraga and Gonzalez respectively. A number of partial and total syntheses of these types of diterpenoids, such as (±)-isopisiferin, (±)-pisiferin and barbatusol, have been described[4]. As a part of our synthetic studies on natural products, we have been devoting our efforts to synthesize these types of compounds[5]. Herein we wish to report the first total synthesis of (±)-demethyl salvicanol **2**.



Scheme 1



Scheme 2

Reaction conditions: i, a) BuLi, b) $ClCO_2Et$; ii, Br_2, AcOH; iii, MeMgBr, Et_2O; iv, PTSA, benzene; v, a) BuLi, b) ethylene oxide; vi, H_2, 10%Pd-C; vii, I_2, imidazole; viii, $NaBH_4$, MeOH; ix, a) LDA, b) followed by addition of 15; x, Li-ammonia; xi, ethylene glycol; xii, a) BuLi, b) $(CH_2O)_n$; xiii, PBr_3; xiv, a) H^+, acetone, b) Zn, DMF; xv, NaH, EtSH.

The synthetic strategy was developed based on a retro-synthetic analysis of the natural products (scheme 1). The desired ester **9** was readily available in 79% yield from veratrol **8** by lithiation followed by treatment with ethyl chloroformate [6]. Regiospecific bromination of **9** with bromine in glacial acetic acid gave **10** in a yield of 90%[7]. Treatment of **10** with an excess of methylmagnesium bromide furnished the alcohol **11** in a yield of 98%. Compound **12**, readily obtained in 95% yield from alcohol **11** by dehydration using a catalytic amount of *p* - TsOH, was lithiated with butyllithium, followed by treatment with ethylene oxide to give alcohol **13** in 85% yield[8]. Compound **14**, readily obtained by hydrogenation of **13** on 10% Pd-C in a quantitative yield, was converted in an excellent yield to desired iodide **15** by Corey's method[9].

Isopropyl enol **16**[10], was reduced with sodium borohydride in anhydrous ethanol followed by acid hydrolysis to give enone **6** in 80% yield. Enone **6** was deprotonated with LDA and alkylated with iodide **15** to afford enone **17** in 51% yield. Ketone **18**, obtained from enone **17** by selective reduction with lithium in liquid-ammonia in 91% yield, was protected as ketal **5** in 84% yield.

Regiospecifically lithiation of **5** with butyllithium followed by treatment with paraformaldehyde furnished

the desired alcohol **19** in a yield of 86%. Ketal-bromide **4**, obtained from alcohol **19** by bromination with phosphorus tribromide in 90% yield, was deprotected in aq. HCl, followed by treatment with zinc dust in DMF to give desired 11-methoxysalvicanol **3** in an overall yield of 73%. Demethylation with sodium hydride in ethanethiol furnished the target compound **2** in a yield of 56%[4a]. The NMR, infrared and mass spectra were identical with those reported[2,3].

EXPERIMENTAL

Mass spectra were recorded on a ZAB-HS spectrometer, ^{1}H NMR, ^{13}C NMR, spectra were obtained on a Bruker AM-400 instrument in $CDCl_3$ with TMS as the internal standard. IR spectra were recorded on an FT-170SX spectrometer. Elemental analyses were performed on a Carlo Erba-1106 instrument. All compounds were purified by flash chromatography (FC) on silica gel H(200-300 mesh) from Qingdao Marine Chemical Factory, eluting with the solvent mixture of petroleum ether and ethyl acetate.

Ethyl 2, 3-dimethoxybenzonate 9

To a stirred solution of **8** (13.8g, 100mol) in anhydrous THF (40ml) at r.t. under nitrogen was added dropwise a solution of butyllithium (1.8M;60ml) in ether. The mixture solution was stirred for 3h. The resulting yellowish solution was cooled to -78°C before a solution of ethyl chloroformate (12.5g, 110mmol) in anhydrous THF (15ml) was added dropwise. The mixture was then stirred for another 2h at -78°C and then at r.t. overnight. The reaction was quenched with saturated solution of NH_4Cl (25ml), and the resulting solution was extracted with ether (3x80ml). The standard ethereal workup and FC gave the desired **9** (15.6g, 79%). MS: m/z(%), 210(M^+, 38), 165(72), 163(100), 137(7), 122(21), 107(32); ^{1}H NMR: δ=7.30(dd, J=2.0Hz, 7.3Hz, 1H), 7.04(m, 2H), 4.38(q, J=7.1Hz, 2H), 3.90(s, 3H), 3.87(s, 3H), 1.38(t, J=7.1Hz, 3H); IR(cm^{-1}): 3078, 2981, 1765, 1725, 1582, 1479, 1310, 1059, 766.

Ethyl 5-bromo-2, 3-dimethoxybenzonate 10

To a stirred solution of **9** (10.5g, 50mmol) and anhydrous sodium acetate (10g, 122mmol) in glacial acetic acid (200ml), was added dropwise slowly bromine (8g, 50mmol) in glacial acetic acid (40ml) at r.t.. The resulting solution was stirred until the brown colour disappeared, and then the solvent was removed under reduced pressure. The residue was poured into water (100ml), and extracted with ether (3x50ml). The standard workup and FC furnished the desired **10** (13.3g, 90%). MS: m/z(%), 290(M^+, 43), 288(43), 245(73), 243(100); ^{1}H NMR: δ=7.41(d, J=2.1Hz, 1H), 7.08(d, J=2.1Hz, 1H), 4.36(q, J=7.1Hz, 2H), 3.91(s, 3H), 3.86(s, 3H), 1.37(t, J=7.1Hz, 3H); IR(cm^{-1}): 3085, 2982, 2940, 2905, 1735, 1576, 1474, 1415, 1389, 1365, 1272, 1180, 1057,

1007, 805, 663.

2-(5-bromo-2, 3-dimethoxyphenzyl)isopropyl alcohol 11

To a solution of **10** (14.5g, 50mmol) in anhydrous ether (60ml) stirred at refluxing tempreture under nitrogen, a solution of MeMgBr [prepared by bromomethane (14.1g, 150mmol) and magnesium (4g, 167mmol)] in anhydrous ether (100ml) was added dropwise. The result mixture was refluxed overnight. Then the reaction was quenched by addition of saturated solution of NH_4Cl (60ml). The standard ethereal workup and FC gave alcohol **11** (11.3g, 98%). MS: m/z(%), 276(M^+, 10), 274(10), 261(35), 259(35), 196(30), 181(100), 139(25); ^1H NMR: δ=7.03(d, J=1.9Hz, 1H), 6.91(d, J=1.9Hz, 1H), 3.96(s, 3H), 3.84(s, 3H), 1.62(s, 6H); IR(cm^{-1}): 3454(br), 3080, 2971, 2937, 1580, 1474, 1365, 1297, 1265, 1224, 1055, 1004, 956, 746.

2-(5-bromo-2, 3-dimethoxyphenzyl)isopropene 12

A mixture solution of alcohol **11** (13.8g, 50mmol) and catalitic ammount of *p*-toluenesulfonic acid was refluxed in benzene to remove water azeotropically. After no more water was separated, the resulting mixture was cooled to r.t., and washed successively with aqueous 5% sodium hydroxide (2x15ml), aqueous 5% HCl (2x10ml), brine (3x15ml) and dried over anhydrous sodium sulfate. Evaporation of the solvent, the crude residue was purified by FC to give desired **12** (12.3g, 95%). MS: m/z(%), 258(M^+, 76), 256(81), 178(87), 163(100), 135(64); ^1H NMR: δ=6.98(d, J=2.1Hz, 1H), 6.90(d, J=2.1Hz, 1H), 5.11(m, 2H), 3.88(s, 3H), 3.81(s, 3H), 2.21(s, 3H); IR(cm^{-1}): 3078, 2958, 2933, 2834, 1636, 1597, 1471, 1263, 1228, 1152, 1064, 1009, 837, 752.

2-(3-Isopropenyl-4, 5-dimethoxyphenyl)ethanol 13

To a solution of **12** (10g, 38.9mmol) in anhydrous THF (50ml) stirred at -78°C under nitrogen was added dropwise a solution of butyllithium (1.8M;22ml) in ether. The resulting mixture solution was stirred at -78°C for 1.5h, then allowed to warm to r.t. and stirred for another 3h. After the mixture solution was cooled to -78°C, ethylene oxide (2g, 40.1mmol) in ether (5ml) was added dropwise. The mixture was stirred at -78°C for 2h, then was allowed to warm slowly to r.t., and stiirred for another 4h. Saturated solution of NH_4Cl (40ml) was added. The standard ethereal workup and FC furnished **13** (7.3g, 84%).MS: m/z(%), 222(M^+, 37), 191(100), 161(7), 91(9); ^1H NMR: δ=6.88(d, J=2Hz, 1H), 6.82(d, J=2Hz, 1H), 5.06(m, 2H), 3.87(s, 3H), 3.82(s, 3H), 3.78(t, J=8.1Hz, 2H), 2.85(t, J=8.1Hz, 2H), 2.10(s, 3H);IR(cm^{-1}): 3376, 3079, 2999, 2879, 1633, 1600, 1403, 1226, 1174, 1066, 963, 898, 749, 640.

2-(3-Isopropyl-4, 5-dimethoxyphenyl)ethanol 14

A mixture of **13** (10g, 45mmol) and catalitic ammount of 10% Pd-C in anhydrous ethanol (60ml) was stirred at r.t. under hydrogen atmosphere of until the reaction was completed. The catalyst was then removed by filtration.

After the solvent was evaporated, the residue was purified by FC to give **14** (10g, 99%). MS: m/z(%), 224(M^+, 47), 193(100), 163(18), 91(18), 91(15), 77(10); ^{1}H NMR: δ=6.81(d, J=2.2Hz, 1H), 6.79(d, J=2.2Hz, 1H), 3.88(s, 3H), 3.86(s, 3H), 3.77(t, J=6.9Hz, 2H), 3.41(sept, J=6.9Hz, 1H), 2.86(t, J=8.1Hz, 2H), 1.25(d, J=6.9Hz, 6H); IR(cm^{-1}): 3371, 2081, 2958, 2864, 1658, 1594, 1449, 1286, 1187, 1151, 1096, 1058. Anal. Calcd for $C_{13}H_{20}O_3$: C,69.61; H,8.99. found: C, 69. 63; H,8.85.

5, 5-Dimethyl-2-cyclohexen-1-one 6

To an ice-cooled, stirred solution of **16** (10g, 54.3mmol) in anhydrous ethanol (150ml) was added portionwise sodium borohydride (1.85g, 54.3mmol). After the reaction mixture was stirred for 4h, saturated aqueous NH_4Cl solution (50ml) was added to quench the reaction. The resulting mixture was extracted with ether (3x60ml). The combined ethereal extracts were washed with 5% HCl (3x15ml) and brine (3x20ml), and evaporated. The residue was dissolved in THF (100ml). Aqueous 10% HCl (25ml) was added. The mixture was refluxed for 3h. The standard ethereal workup and FC gave **6** (5.4g, 80%). MS: m/z(%), 124(M^+, 16), 109(31), 68(100); ^{1}H NMR: δ=6.75(m, 1H), 5.98(m, 1H), 2.25(m, 4H); IR(cm^{-1}): 2958, 2828, 2870, 1710, 1679, 1618, 1466, 1389, 1242, 1163, 902, 734.

5-(2-(3-Isopropyl-4, 5-dimethoxyphenyl)ethyl)-5, 5-dimethyl-2-cyclohexen-1-one 17

To a stirred, ice-cooled solution of alcohol **14** (6.23g, 27.8mmol), triphenyl phosphine (9g, 34.4mmol) and imidazole (2.5g, 37mmol) in acetonitrile (20ml) and anhydrous ether (35ml) was slowly added iodine (10.2g, 37.2mmol), The mixture was stirred for 1h before being diluted with ether (300ml) and washed sequentially with satursted aqueous $Na_2S_2O_3$(2x50ml), saturated aqueous $CuSO_4$ (2x50ml) and water(3x50ml). the organic layer was then dried over anhydrous sodium sulfate, filtered, concentrated and purified by FC to give pure iodide **15** was furnished quantitatively, which was used directly in the next reaction. A solution of **6** (5g, 40.3mmol) in anhydrous THF (25ml) was added dropwise to a stirred, cooled (-78°C) solution of LDA [prepared from diisopropyl amide (8ml) in anhydrous THF (20ml) and butyllithium in ether (1.8M;23ml) at -20 °C] under nitrogen. After stirred for another 1h the mixture was allowed to warm to r.t., and stirred for another 2h. The mixture solution was cooled to -78°C, before a solution of the iodide **15** (10g, 27.8mmol) in anhydrous THF (15ml) was added dropwise. The mixture was then stirred at -78°C for 3h, and at r.t. for 24h. The reaction was quenched with saturated solution of NH_4Cl (50ml) at -20°C—0°C. The resulting mixture was extracted with ether (4x50ml). The standard ethereal workup and FC furnished **17** (4.98g, 54%).MS: m/z(%), 330(M^+, 33), 287(25), 193(100), 123(85); ^{1}H NMR: δ=6.92(d, J=2.1Hz, 1H), 6.83(d, J=2.1Hz, 1H), 6.71(m. 1H), 5.62(m, 1H), 3.89(s, 3H), 3.86(s, 3H), 3.31(sept, J=6.8Hz, 1H), 2.83(t, J=8Hz, 2H), 2.28(d, J=17.3Hz, 1H), 2.17(d, J=17.3Hz, 1H0, 1.28(d, J=6.8Hz, 6H), 1.07(s, 6H); IR(cm^{-1}): 3035, 2984, 2955, 2877, 1714, 1681,

1658, 1440, 1337, 1083.

2-(2-(3-Isopropyl-4, 5-dimethoxyphenyl)ethyl)-5, 5-dimethyl-cyclohexan-1-one 18

A solution of **17** (5g, 15.2mmol) in anhydrous ether (5ml) was added to distilled liquid ammonia (100ml). Lithium pieces (0.12g, 17.1mmol) was then added portionwise. The resulting mixture was stirred for 2h. After the ammonia was evaporated, a solution of saturated NH_4Cl (30ml) was added, followed by extraction with ether (4x40ml). The standard ethereal workup and FC gave **18** (4.68g, 91%). MS: m/z(%), 332(M^+, 25), 317(22), 289(34), 193(100), 125(77); ^1H NMR: δ=6.94(d, J=2Hz, 1H), 6.84(d, J=2.1Hz, 1H), 3.88(s, 3H), 3.86(s, 3H), 3.30(sept, J=7Hz, 1H), 2.82(t, J=8.1Hz, 2H), 2.72(t, J=7.8Hz, 2H), 2.24(m, 2H), 1.56(t, J=7.8Hz, 2H), 1.29(d, J=7Hz, 6H), 1.06(s, 6H); IR(cm^{-1}): 3034, 2980, 2955, 2877, 1730, 1657, 1443, 1335, 1085; Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. found: C, 75.62; H, 9.75.

Compound 5

A mixture solution of **18** (4g, 15.1mmol), ethylene glycol (1.24g, 20mmol) and boron trifluoride etherate (22ml) in anhydrous ether (50ml) was stirred at r.t. for 24h. After evaporation of the solvent, the residue was purified by FC to give **5** (3.8g, 84%). MS: m/z(%), 376(M^+, 28), 333(27), 261(13), 232(31), 193(100); ^1H NMR: δ=6.91(d, J=2.1Hz, 1H), 6.85(d, J=2.1Hz, 1H), 3.99(s, 4H), 3.87(s, 3H), 3.31(sept, J=7Hz, 1H), 2.85(t, J=8.1Hz, 2H), 2.24(m, 2H), 2.04(t, J=7.8Hz, 2H), 1.53(t, J=7.8Hz, 2H), 1.28(d, J=7Hz, 6H), 1.07(s, 6H); IR(cm^{-1}): 3031, 2988, 2877, 1468, 1335, 1072. Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.63. found: C, 73.52; H, 9.68.

Alcohol 19

To a solution of **5** (3.5g, 9.3mmol) in anhydrous THF (15ml) stirred at r.t. under nitrogen, was added a solution of butyllithium (1.8M; 5.6ml) in ether. After being stirred for 5h, the mixture was cooled to -20°C and paraformaldehyde (0.5g, 16.7mmol) was added portionwise. Stirring was continued at this temperature for 2h then at r.t. overnight. A solution of saturated NH4Cl (40ml) was added. The standard ethereal workup and FC furnished alcohol **19** (3.5g, 86%). MS: m/z(%), 406(M^+, 48), 391(32), 362(21), 223(85), 207(100); ^1H NMR: δ=6.84(s, 1H), 4.65(s, 2H), 4.02(s, 4H), 3.88(s, 3H), 3.85(s, 3H), 3.29(sept, J=7Hz, 1H), 2.86(t, J=8.1Hz, 2H), 2.23(m, 2H), 2.01(t, J=7.9Hz, 2H), 1.55(t, J=7.9Hz, 2H), 1.29(d, J=7.2Hz), 1.05 (s, 6H); IR(cm^{-1}): 3389, 3031, 2967, 2887, 1470, 1336, 1274, 1172, 1069. Anal Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. found: C, 71.02; H, 9.51.

Bromide 4

To a stirred solution of **19** (2.3g, 5.7mmol) in anhydrous dichloromethane (20ml) was added dropwise tribromide phosphorous (1.6g, 5.8mmol) at r.t.. The mixture was stirred for another 1h. Then some wet sodium

hydrogen carbonate was added portionwise until the pH=8--9. The resulting mixture was filtered through anhydrous magnesium carbonate. After the evaporation of the solvent, the residue was purified by FC to give **4** (2.4g, 90%). MS: m/z(%), 470(M^+, 23), 468(23), 455(9), 426(35), 389(81), 207(100); ^{1}H NMR: δ=6.85(s, 1H), 4.59(s, 2H), 4.05(s, 4H), 3.86(s, 3H), 3.84(s, 3H), 3.29(sept, J=7Hz, 1H), 2.81(t, J=8.1Hz, 2H), 2.21(m, 2H), 2.01(t, J=7.9Hz, 2H), 1.55(t, J=7.9Hz, 2H), 1.28(d, J=7.2Hz), 1.03(s, 6H); IR(cm^{-1}): 3034, 2968, 2874, 1335, 1220, 1053.

11-Methoxysalvicanol 3

A miture of **4** (2.35g, 5mmol), THF(25ml), acetone(10ml) and 10% aqueous HCl (5ml) was refluxed until the reaction was completed. After cooling, ether (150ml) was added, and the resulting mixture was washed successively with saturated aqueous sodium hydroxide (2x20ml) and brine (2x20ml), and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was dissolved in distilled DMF (10ml), and then zinc small chips (480mg, 7.5mmol) was added at r.t.. The resulting mixture was stirred for 1h. The mixture was poured into a saturated solution of NH_4Cl (50ml). The standard ethereal workup and FC gave **3** (1.27g, 73%). MS: m/z(%), 346(M^+, 20), 330(13), 327(25), 314(11), 299(15), 235(31), 220(73), 207(40), 149(70), 69(78), 57(100); ^{1}H NMR: δ=6.74(s, 1H), 3.84(s, 3H), 3.81(s, 3H), 3.26(d, J=14Hz, 1H), 3.23(sept, J=7.0Hz, 1H), 2.51(d, J=14.0Hz, 1H), 1.20(d, J=7.0Hz, 6H), 0.92(s, 3H), 0.88(s, 3H); IR(cm^{-1}): 3518, 2961, 2918, 2845, 1443, 1358, 1084, 1020, 994, 923. Anal Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. found: C, 76.32; H, 9.91.

Demethyl salvicanol 2

Ethanethiol (2.7ml) was added dropwise to a suspension of sodium hydride (0.415g, 17.6mmol) in anhydrous DMF (6ml) stirred under nitrogen. Ether **3** (1g, 2.89mmol) in anhydrous DMF (6ml) was then added. The resulting mixture was heated at reflux for 5h. After cooling, the mixture was diluted with water (5ml), Acidification and the standard ethereal workup followed by FC gave desired **2** (0.51g, 55.5%).MS: m/z(%), 318(M^+, 12), 300(68), 285(11), 271(5), 257(8), 232(19), 192(100), 177(32), 69(16), 55(26); ^{1}H NMR: δ=6.55(s, 1H), 5.64(br, s), 3.16(sept, J=7.0Hz, 1H), 3.03(d, J=14.4Hz, 1H), 2.68(m, 2H), 2.57(d, J=14.4Hz, 1H), 1.22(d, J=7Hz, 6H), 0.92(s, 3H), 0.85(s, 3H); IR(cm^{-1}): 3618, 3515, 2922, 2851, 1437, 1358, 1081, 1023, 1007, 986, 965. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. found: C, 75.51; H, 9.46.

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