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Total Synthesis of (±)-Boschnialactone and (±)-Tetrahydroanhydrodesoxyaucubigenin

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A total synthesis of (±)-boschnialactone (**1**) and (±)-tertahydroanhydrodesoxyaucubigenin (**2**) is described and trisubstitued cyclopentenoid **3** is a key intermediate.

INTRODUCTION

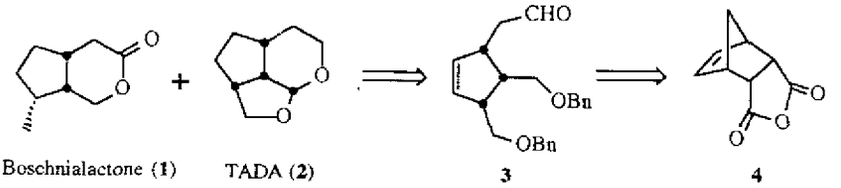
Recently, a remarkable number of oxygenated monoterpenoids which belong to the group of compounds containing a trialkyl substituted cyclopentanoid carbon skeleton, have been isolated.[1] Several of these have been proved to possess some interesting biological activities and stimulate the challenge of constructing cyclopentanoid derivatives. In this report, we describe the total synthesis of boschnialactone (**1**) and tetrahydroanhydrodesoxyaucubigenin (TADA) (**2**), both of which have *cis*-fused ring junctions and contiguous stereogenic centers. The key intermediate, trisubstituted cyclopentenoid **3**, was obtained in high yield *via* photolytic cleavages[2,3] of the bicyclo[2.2.1]heptanone. Iridoid boschnialactone (**1**) was isolated from *Boschniakiarossica* Hult. and assigned the cyclopentapyranone skeleton with three contiguous stereogenic centers by Sakan and his co-workers.[4] The physiological activities toward cats and insecticidal properties are the focal points of the synthetic approaches.[5-15] TADA (**2**) with an unique tricyclic cage acetal ring system, is the most important derivative of aucubin glycoside in a preliminary finding.[16] Our synthetic strategy is outlined in Scheme I, and dibenzyl aldehyde **3** is a reasonable precursor for the synthesis of boschnialactone (**1**) and TADA (**2**).

RESULTS AND DISCUSSION

Aldehyde **3** which was easily prepared from the known *endo* anhydride **4** by a series of functional group transformations, was chosen as starting material.[17] As shown in Scheme II, oxidation of aldehyde **3** with Jones reagent gave an acid which was further reacted with diazomethane to furnish the corresponding ester **5**. Hydrogenation of unsaturated ester **5** with a mixture of 4-toluenesulfonyl hydrazine and sodium acetate gave saturated ester **6**. Hydrogenolysis of dibenzyl ester **6** with palladium on activated carbon as catalyst in ethanol gave lactone **7**.[15] Finally, tosylation of the alcohol **7** gave tosylate **8**, and subsequent treatment with zinc and sodium iodide led to boschnialactone (**1**).[11,15] The synthesis of boschnialactone (**1**) comprised 10 steps, starting with anhydride **4**, and a total yield > 38%.

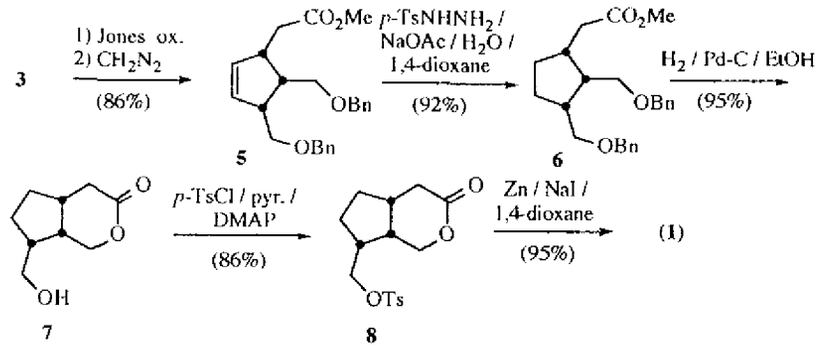
The synthesis of racemic TADA (**2**) is shown in Scheme III. Protection of aldehyde **3** with ethylene glycol in the presence of catalytic amount of *p*-toluenesulfonic acid furnished ketal **9**. Further debenzylation of ketal **9** with Stock solution of lithium naphthalenide gave diol **10** in 88% yield.[18] Swern oxidation of diol **10** produced dialdehyde.[19,20] Without purification, treatment of the dialdehyde with methanol containing a catalytic amount of *p*-toluenesulfonic acid caused cyclization to give a mixture of epi-

Scheme I

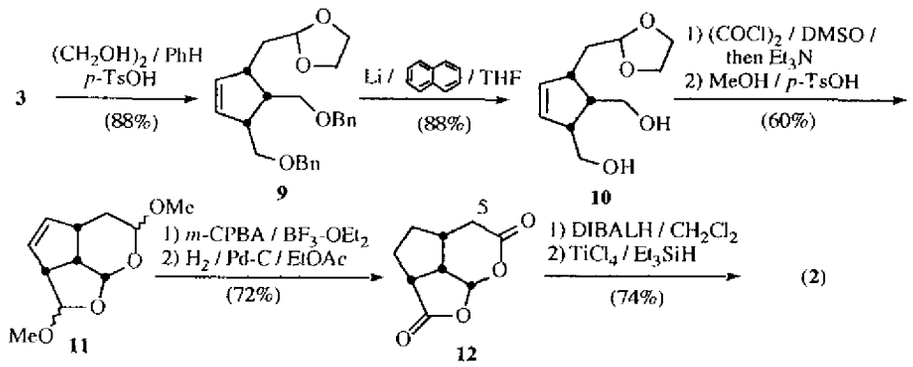


Boschnialactone (**1**) TADA (**2**) **3** **4**

Scheme II



Scheme III



meric acetal **11**. The tricyclic acetal **11** was oxidized with a mixture of *m*-chloroperoxybenzoic acid and boron trifluoride etherate to produce an unstable bislactone.[21] Without purification, the olefinic moiety of bislactone was reduced in ethyl acetate to give saturated bislactone **12**. Finally, reduction of the bislactone **12** with diisobutylaluminum hydride in methylene chloride, followed by treatment of the crude products with titanium tetrachloride in the presence of triethylsilane provided TADA (**2**).[22,23] The above procedures constitute a new approach to the synthesis of boschnialactone (**1**) and TADA (**2**).

EXPERIMENTAL SECTION

General

Diethyl ether and tetrahydrofuran were distilled before use from a deep-blue solution of benzophenone and sodium. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out in a dry nitrogen atmosphere with magnetic stirring. Organic solution of products were dried with anhydrous magnesium sulfate before concentration *in vacuo*.

Methyl-2-[4,5-di(benzyloxymethyl)-2-cyclopentenyl]acetate (5)

To a solution of aldehyde **3** (1.0 g, 2.9 mmol) in acetone (20 mL) at 0 °C was added excess Jones reagent. The mixture was stirred for 15 min and treated with 2-propanol (2 mL) to destory the unreacted oxidation reagent. After the solvent was removed, the residue was diluted with water and extracted with ethyl acetate (4 × 25 mL). The organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was dissolved in diethyl ether (30 mL) and treated with diazomethane. After 15 min, nitrogen was bubbled into the solution to remove excess diazomethane. The ether solution was concentrated, then purified by chromatography on silica gel (hexane/ethyl acetate = 10/1) to give dibenzyl ester **5** (0.95 g, 86%) as a colorless oil: IR (neat) 1044, 1730, 2913, 3039 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.25 (dd, J = 15.6, 9.6 Hz, 1H), 2.56 (dd, J = 15.6, 6.0 Hz, 1H), 2.70-2.82 (m, 1H), 2.94-3.00 (m, 1H), 3.12-3.22 (m, 1H), 3.37-3.62 (m, 4H), 3.61 (s, 3H), 4.35-4.46 (m, 4H), 5.73-5.76 (m, 1H),

5.83-5.86 (m, 1H), 7.26-7.35 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.0, 41.8, 42.7, 47.0, 51.3, 67.9, 70.5, 73.1, 73.2, 127.5 (2×), 127.6 (2×), 127.7 (2×), 128.2 (4×), 132.3, 135.0, 138.2, 138.3, 173.5; HRMS calcd $C_{24}H_{28}O_4$ 380.1988, found 380.1988. Anal. Calcd for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42. Found: C, 75.74; H, 7.32.

Methyl-2-[2,3-di(benzyloxymethyl)cyclopentenyl]acetate (6)

To a solution of unsaturated ester **5** (1.0 g, 2.6 mmol) and 4-toluenesulfonyl hydrazine (2.5 g, 13.4 mmol) in 1,4-dioxane (20 mL) warmed under reflux was added a solution of sodium acetate (3.4 g, 25.0 mmol) in 10 mL of water over a 4 h period. The mixture was cooled to 25 °C, poured into 10 mL of water and extracted with dichloromathane (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to afford crude saturated ester. The crude products were purified by chromatography on silica gel (hexane/ethyl acetate = 10/1) to give ester **6** (0.92 g, 92%) as a colorless oil: IR (neat) 1733 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40-1.47 (m, 2H), 1.75-1.90 (m, 2H), 2.12-2.54 (m, 5H), 3.40-3.50 (m, 4H), 3.60 (s, 3H), 4.31 (d, J = 11.7 Hz, 1H), 4.37 (d, J = 6.6 Hz, 1H), 4.41 (d, J = 6.6 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 7.23-7.34 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.9, 29.7, 35.9, 39.0, 42.3, 42.8, 51.2, 67.6, 71.5, 73.0, 73.1, 125.3, 127.2, 127.3, 127.4, 127.6, 127.7 (2×), 128.1, 128.2 (2×), 129.6, 138.5, 173.9; HRMS calcd $C_{24}H_{30}O_4$ 382.2145, found 382.2142.

7-Hydroxymethylperhydrocyclopenta[*c*]oxin-3-one (7)

A solution of ester **6** (0.5 g, 1.3 mmol) in ethanol (15 mL) was stirred under hydrogen at 25 °C with palladium in charcoal (15 mg) as catalyst for 12 h. The mixture was filtered, and the filtrate was evaporated to give crude products. The crude products were purified by chromatography on silica gel (hexane/ethyl acetate = 1/2) to give lactone **7** (210 mg, 95%) as a colorless oil: IR (neat) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.38-2.02 (m, 4H), 2.28-2.35 (m, 2H), 2.59-2.65 (m, 3H), 2.75 (br s, 1H), 3.62-3.76 (m, 2H), 4.20-4.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.7, 32.6, 34.5, 34.9, 37.9, 45.3, 62.3, 67.2, 174.2; HRMS calcd $C_9H_{14}O_3$ 170.0943, found 170.0933.

7-(4-Methylphenylsulfonyloxymethyl)-3-oxoperhydrocyclopenta[*c*]oxine (8)

To a solution of alcohol **7** (85 mg, 0.5 mmol) in pyridine (4 mL) was added *p*-toluenesulphonyl chloride (0.3 g, 1.6 mmol) and a pinch of 4-(dimethylamino)pyridine and the mixture was stirred for overnight at room temperature before being poured into 2 N hydrochloric acid solution (5 mL), and the aqueous layers were extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to afford curde products. The crude products were purified by chromatography on silica gel (hexane/ethyl acetate = 2/1) to give tosylate **8** (0.14 g, 86%) as a colorless oil: IR (neat) 1736, 2859, 2917 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26-1.43 (m, 1H), 1.50-1.59 (m, 1H), 1.64-1.74 (m, 1H), 1.85-1.99 (m, 1H), 2.29 (dd, J = 14.7, 6.6 Hz, 1H), 2.37-2.48 (m, 1H), 2.46 (s, 3H), 2.54-2.73 (m, 3H), 3.97-4.18 (m, 4H), 7.37 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 27.8, 32.6, 34.5, 34.9, 37.7, 42.4, 66.4, 69.9, 127.8 (2×), 130.0 (2×), 132.5, 145.1, 173.1; HRMS calcd $C_{16}H_{20}O_5S$ 324.1032, found 324.1031.

Boschnialactone (1)

A mixture of compound **8** (0.1 g, 0.3 mmol), zinc (0.6 g), and sodium iodide (0.2 g, 1.3 mmol) in 1,4-dioxane (10 mL) was heated at 100 °C for 3 h. The mixture was diluted with ethyl acetate (15 mL) and filtered through a short pad of Celite, and the solid filter was washed with ethyl acetate (15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to afford crude products. The crude products were purified by chromatography on silica gel (hexane/ethyl acetate = 4/1) to give compound (**1**) (45 mg, 95%) as a colorless oil, identified by direct comparison with an authentic sample by its ^{1}H and ^{13}C NMR spectra.[14]

2-[4,5-Di(benzyloxymethyl)-2-cyclopentenylmethyl]-1,3-dioxolane (9)

A mixture of aldehyde **3** (1.0 g, 2.9 mmol), ethylene glycol (0.3 g, 4.8 mmol) and *p*-toluenesulfonic acid monohydrate (20 mg) in benzene (50 mL) were heated at reflux under a Dean-Stark trap for 4 h. The cooled reaction mixture was diluted with ether (30 mL) and washed sucessively with saturated sodium carbonate solution (10 mL) and brine. The aqueous layers were extracted with ether (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. The crude products were purified by chromatography on silica gel (hexane/ethyl acetate = 6/1) to give dibenzyl ketal **9** (1.0 g, 88%) as a colorless oil: IR (neat) 1090, 2860, 3030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ

1.58 (ddd, J = 13.2, 11.4, 4.8 Hz, 1H), 1.92 (ddd, J = 13.2, 5.1, 4.2 Hz, 1H), 2.51-2.81 (m, 1H), 2.88-3.01 (m, 2H), 3.35-3.66 (m, 4H), 3.82-3.90 (m, 2H), 3.93-3.99 (m, 2H), 4.41-4.51 (m, 4H), 4.92 (t, J = 4.8 Hz, 1H), 5.78-5.82 (m, 1H), 5.97-6.02 (m, 1H), 7.27-7.35 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.1, 42.0, 42.6, 46.8, 64.6, 64.8, 68.2, 71.3, 73.1, 73.2, 104.1, 127.4 (2×), 127.6 (2×), 127.7 (2×), 128.2 (4×), 131.8, 135.6, 138.3, 138.4; HRMS calcd $C_{25}H_{30}O_4$ 394.2145, found 394.2150. Anal. Calcd for $C_{25}H_{30}O_4$: C, 76.11; H, 7.66. Found: C, 76.14; H, 7.72.

4-(1,3-Dioxolan-2-ylmethyl)-5-hydroxymethyl-2-cyclopentenylmethanol (10)

To a solution of naphthalene (3.3 g, 25.8 mmol) in tetrahydrofuran (50 mL), was added lithium metal (106 mg, 15.2 mmol) in small pieces. The reaction mixture was stirred at room temperature under a nitrogen atmosphere until the lithium metal was completely dissolved (*ca.* 3 h). The resulting dark green solution of lithium naphthalenide was then cooled to 0 °C, followed by addition of a solution of dibenzyl ketal **9** (1.0 g, 2.5 mmol) in tetrahydrofuran (10 mL) dropwise over 5 min. The resulting mixture was stirred at 0 °C for 2 h. Saturated aqueous ammonium chloride solution (10 mL) and water (10 mL) were then added. The resulting solution was extracted with ether (3 × 30 mL). The combined extracts were washed with water and brine, dried ($MgSO_4$), filtered and evaporated. The crude products were purified by chromatography on silica gel (hexane/ethyl acetate = 1/1) to give diol ketal **10** (480 mg, 88%) as a colorless solid: mp = 38-40 °C; IR ($CHCl_3$) 1025, 2910, 3380 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.54 (ddd, J = 13.5, 4.5, 3.9 Hz, 1H), 1.83 (dt, J = 13.5, 5.1 Hz, 1H), 2.08 (br s, 1H), 2.64-2.70 (m, 1H), 2.82-2.90 (m, 1H), 2.95-3.01 (m, 1H), 3.39 (br s, 1H), 3.55-3.63 (m, 2H), 3.80-3.99 (m, 6H), 4.87 (t, J = 4.5 Hz, 1H), 5.60-5.63 (m, 1H), 5.92-5.95 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.2, 41.8, 44.9, 49.5, 60.4, 63.2, 64.7, 64.9, 103.8, 130.3, 136.5; HRMS calcd $C_{11}H_{16}O_3$ [(M-H_2O)$^+$] 196.1100, found 196.1093. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.67; H, 8.47. Found: C, 61.42; H, 8.64.

2,6-Dimethoxy-2a,4a,5,6,7a,7b-hexahydro-2*H*-1,7-dioxafuro[1,2,3,*cd*]isobenzofuran (11)

To a solution of oxalyl chloride (0.57 mL, 6.5 mmol) in dichloromathane (30 mL) at -78 °C was added carefully dimethyl sulfoxide (0.76 mL, 10.7 mmol). The solution was warmed to -40 °C for 15 min and recooled to -78 °C, and then a solution of diol ketal **10** (300 mg, 1.4 mmol) in dichloromathane (5 mL) was added dropwise followed by excess triethylamine. The reaction mixture was warmed to room temperature and poured into saturated aqueous sodium bicarbonate solution (10 mL). The organic layers were washed with aqueous sodium bicarbonate solution (2 × 5 mL) and then dried ($MgSO_4$), filtered and evaporated. The crude products (250 mg) were dissolved in methanol (10 mL) and *p*-toluenesulfonic acid (10 mg) was added. The reaction mixture was refluxed for 3 h. It was cooled and neutralized with a cool solution of sodium bicarbonate (1 mL). The products were isolated with ethyl acetate extracts (3 × 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated. The crude products were purified by chromatography on silica gel (hexane/ethyl acetate = 5/1) to give tricyclic hemiacetal **11** (180 mg, 60%) as a colorless oil: IR ($CHCl_3$) 1644 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.70-1.90 (m, 2H), 2.80-2.87 (m, 1H), 3.18-3.22 (m, 1H), 3.34-3.50 (m, 2H), 3.39 (s, 3H), 3.47 (s, 3H), 4.64 (dd, J = 8.7, 2.7 Hz, 1H), 4.77 (s, 1H), 5.63-5.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.0, 36.9, 41.3, 54.7, 55.9, 58.3, 95.6, 101.8, 105.0, 130.0, 137.0.

Perhydro-1,7-dioxafuro[1,2,3-*cd*]isobenzofuran-2,6-dione (12)

To a solution of *m*-chloroperoxybenzoic acid (860 mg, 5.0 mmol) in methylene chloride (10 mL) and diethyl ether (1 mL) at 25 °C was added 1 M boron trifluoride etherate (2.1 mL, 2.1 mmol). The solution was heated to 60 °C for 10 min, and then a solution of tricyclic hemiacetal **11** (150 mg, 0.7 mmol) in dichloromathane (5 mL) was added dropwise for 5 min. The reaction mixture was reacted at reflux for 2 h. And the mixture was allowed to reach 0 °C and poured into saturated aqueous sodium bicarbonate solution (3 mL). The organic layers were washed with aqueous sodium bicarbonate solution (10 mL) and then dried ($MgSO_4$), filtered and evaporated. Without purification, the unstable product (100 mg) in ethyl acetate (10 mL) was stirred under 1 atm of hydrogen at room temperature with 10% palladium in charcoal (10 mg) for 2 h. The mixture was dried ($MgSO_4$), filtered and evaporated. The crude products were purified by chromatography on silica gel (hexane/ethyl acetate = 1/1) to give tricyclic bislactone **12** (92 mg, 72%) as a colorless solid: mp = 99-100 °C; IR ($CHCl_3$) 1130, 1770 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60-1.70 (m, 1H), 1.95-2.10 (m, 1H), 2.21-2.35 (m, 3H), 2.56-2.75 (m, 2H), 3.20-3.40

(m, 2H), 6.25 (d, J = 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.1, 32.4, 32.7, 36.2, 42.3, 45.3, 99.5, 167.8, 176.4; HRMS calcd $C_9H_{11}O_4$ [$(M+H)^+$] 183.0657, found 183.0657. Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.30; H, 5.74.

Tetrahydroanhydrodesoxyaucubigenin (TADA) (2)

To a solution of tricyclic bislactone **12** (80 mg, 0.44 mmol) in dichloromethane (10 mL) was slowly added 1.0 M diisopropylaluminum hydride in hexane (1.1 mL, 1.1 mmol) at -78 °C under a nitrogen system and the mixture was stirred at -78 °C for 2 h. After addition of ethyl acetate (5 mL) and a little amount of water (1 mL) and dilution with ether, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated to give 70 mg of crude products. Without purification, this crude products were dissolved in dichloromethane (10 mL) and cooled to -78 °C under a nitrogen atmosphere. Triethylsilane (87 mg, 0.75 mmol) was added at -78 °C. Then a dichloromethane solution of 1.0 M titalium tetrachloride in hexane (0.4 mL, 0.4 mmol) was added and the resulting solution was stirred for another 30 min at -78 °C. The products were isolated with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated carefully. The crude products were purified by chromatography on silica gel (hexane/ethyl acetate = 20/1) to give tricyclic TADA (**2**) (50 mg, 74%) as a colorless oil: IR (neat) 2870, 2950 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.50-1.72 (m, 4H), 1.87-1.96 (m, 1H), 2.05-2.28 (m, 2H), 2.38 (ddd, J = 14.7, 8.7, 6.0 Hz, 1H), 2.65-2.75 (m, 1H), 3.54 (ddd, J = 11.7, 4.8, 3.0 Hz, 1H), 3.62 (dd, J = 8.7, 3.0 Hz, 1H), 3.86 (t, J = 8.7 Hz, 1H), 3.96 (dt, J = 11.7, 2.7 Hz, 1H), 5.16 (d, J = 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.9, 30.5, 33.5, 34.5, 40.8, 43.0, 56.1, 72.0, 101.8; HRMS calcd for $C_9H_{14}O_2$ 154.0994, found 154.1003.

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Key Words

Boschnialactone; Tetrahydroanhydrodesoxyaucubigenin; Norrish type 1; Bicyclo[2.2.1]heptanone.

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