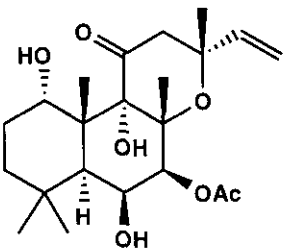
SYNTHETIC STUDIES OF FORSKOLIN. A FORMAL SYNTHESIS *VIA* A NICOLAOU'S ADVANCED INTERMEDIATE[1]

Hsing-Jang Liu and Xiao Shang*

Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

Abstract – A formal synthesis of (±)-forskolin (**1**) has been effected making use of enone (**2**) as a relay compound.

Since its first isolation from *Coleus forskohlii* Briq. independently by two Indian research groups in 1977,[2,3] the highly oxygenated labdane diterpene forskolin (**1**) has spurred a copiousness of synthetic activities[4] due to its interesting structural architecture and the broad spectrum of useful physiological properties associated with it.[5] Over the past decade, there have been a number of elegant solutions emerged[4] to meet the synthetic challenge presented by this natural product. One such solution was reported by Nicolaou *et al.*[6] who



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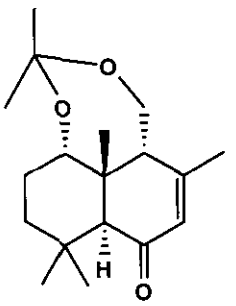

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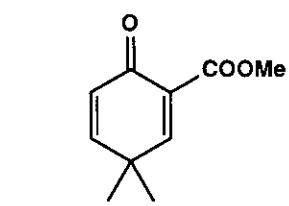
prepared enone (**2**) *via* the cyclization of *E,E*-farnesol. Enone (**2**) served as an intermediate leading to the total synthesis of forskolin (**1**) which was effected in conjunction, in part, with Ziegler's approach[7] to the natural product. We wish to report herein an alternative preparation of this synthetic intermediate (**2**).

The synthesis began with the zinc chloride catalyzed Diels-Alder reaction of dienone ester (**3**) with diene alcohol (**4**). Towards the synthesis of the target compound (**2**), the Diels-Alder adduct (**5**) thus obtained was converted to hydroxy ketal (**6**) *via* a six-step synthetic sequence as described in the previous report of this series.[8] In an attempt to deoxygenate the hydroxy group, the corresponding mesylate (**7**) was prepared and was subsequently treated with Zn dust and sodium iodide. Interestingly, a totally unexpected product (**8**) was formed exclusively in high yield. This serendipitous discovery resulted eventually in the development of an alternative synthesis[8] of Corey's endoperoxide intermediate (**9**)[9] leading to foskolin (**1**).



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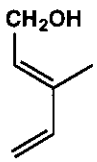

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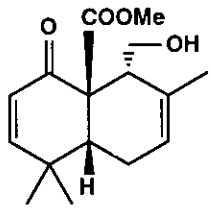

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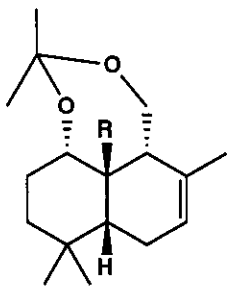
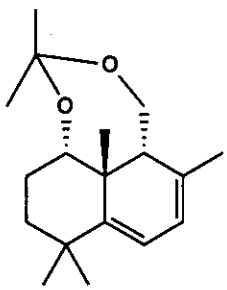


6 R=CH_2OH

7 R=CH_2OMs



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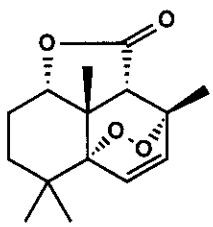

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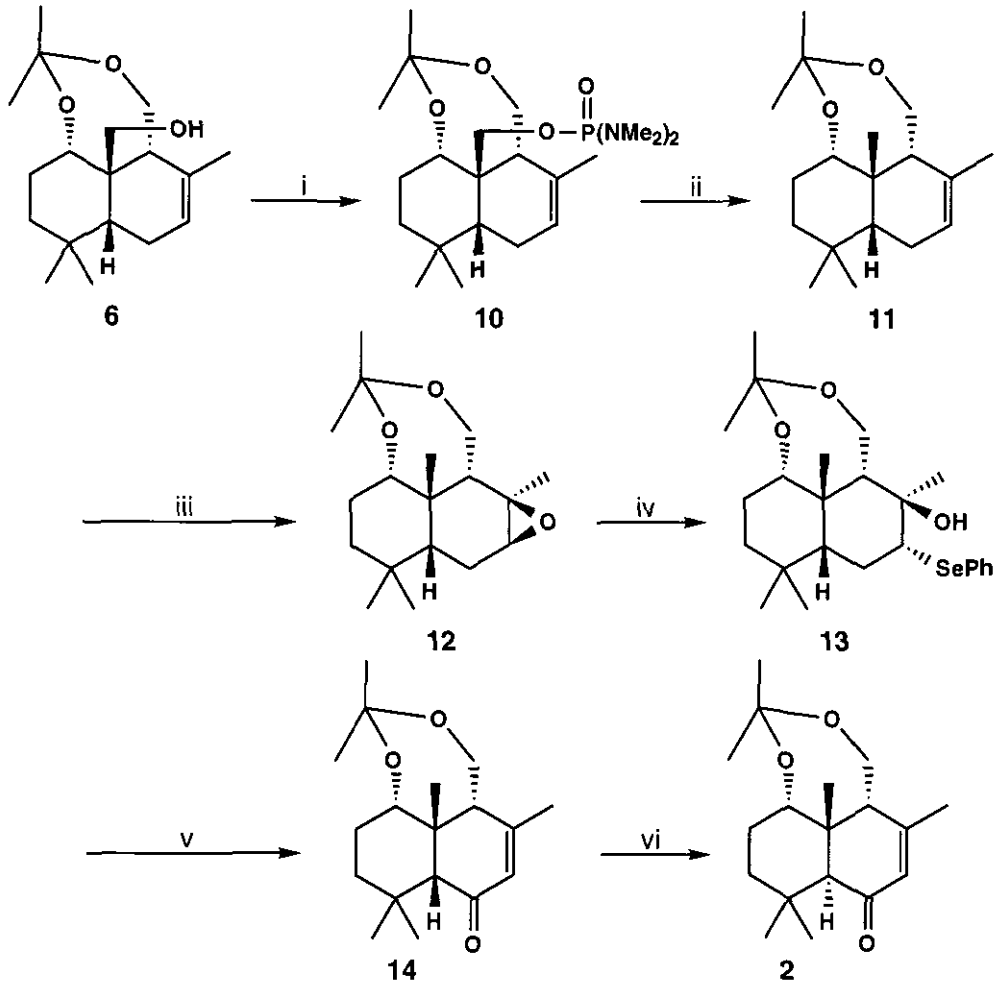
In further pursuance of the original synthetic plan aimed at Nicolaou's enone (**2**), hydroxy ketal (**6**) was subjected to sequential treatment with *n*-butyllithium, *N,N*-dimethylamidophosphorodichloridate and dimethylamine[10] to give the corresponding *N,N,N',N'*-tetramethylphosphorodiamidate (**10**) in quantitative yield (Scheme 1). Subsequent reduction of **10** either with lithium in ethylamine at 0°C or with lithium naphthalenide in tetrahydrofuran[11] at room temperature gave the expected product (**11**) in good yield (~80% yield).

The conversion of olefin (**11**) to enone (**2**) requires the introduction of an oxygen to the allylic carbon. Our original synthetic plan called for allylic oxidation. Unfortunately, attempts to

implement this direct approach were fruitless. Treatment of **11** with chromium pentacarbonyl and *tert*-butyl hydroperoxide in refluxing acetonitrile[12,13] resulted in complete recovery of the

Scheme 1



(i) *n*-BuLi, $Me_2NCH_2CH_2NMe_2$, DME, 0°C, 15 min; then Me_2NPOCl_2, rt, 10 h; then Me_2NH, 0°C, 20 min; 100% yield; (ii) Li, $EtNH_2$, 0°C, 10 min; 85% yield; or lithium *naphthalenide*, *THF*, *rt*, *30 min*; *80% yield*; *(iii)* *m*-$ClC_6H_4CO_3H$, aq. $NaHCO_3$, CH_2Cl_2, rt, 1 h; 89% yield; (iv) PhSeNa, EtOH, reflux, 60 h; 83% yield; (v) CrO_3, Py, rt, 20 h; (vi) aq. NaOH, MeOH, rt, 4 h; 49% yield from **13**.

starting material, while the use of chromium trioxide in combination with *tert*-butyl hydroperoxide[14] or 3,5-dimethylpyrazole[15] under a variety of conditions gave invariably complex mixtures. Consequently, an indirect route was conceived and successfully carried out as follows.

Epoxidation of olefin (**11**) with *m*-chloroperbenzoic acid in methylene chloride in the presence of sodium bicarbonate at room temperature gave, as expected on steric grounds, epoxide (**12**) exclusively in 89% yield. This compound was then subjected to treatment with sodium phenylselenide[16,17] in refluxing ethanol to give a 83% yield of alcohol (**13**) resulting from the preferential attack of phenylselenide on the sterically less hindered carbon center of the epoxy ring. Subsequent treatment of alcohol (**13**) with Sarett reagent[18] at room temperature resulted in concomitant oxidative-elimination of the phenylselenenyl group and oxidative [1,3] sigmatropic rearrangement of the resulting allylic alcohol to give *cis*-enone (**14**), which was readily epimerized to the *trans*-isomer (**2**) (49% yield from **13**) upon exposure to aqueous sodium hydroxide. Enone (**2**) thus obtained in 18% overall yield from dienone ester (**3**) *via* an eleven-step synthetic sequence was found to be identical spectroscopically with that prepared from farnesol by Nicolaou *et al.*[6] Since enone (**2**) has been converted previously to forskolin (**1**),[6,7] the current work constitutes a formal synthesis, in racemic form, of this interesting diterpenoid.

EXPERIMENTAL

General and Material

Fourier transform IR spectra were recorded on a Nicolet 7199 or Nicolet MX-1 FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AM-300, Bruker AMR-360 or Bruker AM-400 NMR spectrometer. Coupling constants are reported to within ±0.5 Hz. ^{13}C NMR spectra were recorded on a Bruker WH-300 (75 MHz) NMR spectrometer. Carbon-13 multiplicities were derived from Carr-Purcell-Meiboon-Gill spin echo *J*-modulated experiments (Attached Proton Test). Methyl and methine groups are shown as singlets antiphase (a) with respect to the deuteriochloroform signal, whereas methylene groups, quaternary carbons, and carbonyl groups appear in phase (p) with it. HRMS were recorded using an A.E.I. model MS-50 mass spectrometer. CIMS were recorded on an A.E.I. model MS-12 mass spectrometer, using ammonia as the reagent gas. The following solvents were distilled under argon from appropriate drying agents befor use: 1,2-dimethoxyethane (DME) from a blue or purple solution of sodium benzophenone ketyl; pyridine, *N,N,N',N'*-tetramethylethylenediamine

(TMEDA) from calcium hydride; ethanol from magnesium. Flash chromatography was used routinely for purification and separation of product mixtures, using silica gel (Merck) of 230-400 mesh. All solvents were distilled prior to use for chromatography, and concentrations of solvent systems are given by volumes. Skelly B refers to Skelly Oil Company light petroleum, bp 62-70°C. Anhydrous magnesium sulfate was used for drying organic solutions.

(1R,5R*,9S*,14S*)-2,6,6,11,11-Pentamethyl-14-tetramethyldiamidophosphoroxymethyl-10,12-dioxatricyclo[7.4.1.0^{5,14}]tetradec-2-ene (**10**)*

n-Butyllithium (1.6 M in hexane, 0.18 mL, 0.28 mmol) was added to a solution of compound (**6**) (57.85 mg, 0.196 mmol) in DME-TMEDA (4:1, 1mL) at 0°C under argon. After 15 min at rt, *N,N*-dimethylphosphoramidic dichloride (0.12 mL, 1.0 mmol) was added and the reaction mixture was stirred at rt under argon for 10 h. Dimethylamine (1 mL) was added at 0°C and stirring was contiuned at this tepmperature for another 20 min. The reaction mixture was poured into ice water and extracted with ether (3 x 10 mL). The extracts were washed with brine, dried, filtered and concentrated. The residue was subjected to flash chromatography on silica gel pre-treated with Et_3N. Elution with acetone and Skelly B (1:5) afforded **10** (73.7 mg, 100%) as a coloress oil: IR (acetone-d_6, cast): 1220 (P=O), 1075 cm^{-1} (C-O); ^{1}H NMR (360 MHz, $CDCl_3$): δ 5.73 (m, 1H, C**H**=C), 4.27 (d, *J* = 7 Hz, 1H, OC**H**), 3.70 (dd, *J* = 12, 10.5 Hz, 1H, OC**H**$_2$CH), 3.61 (dd, *J* = 10, 5 Hz, 1H, POC**H**$_2$), 3.33 (dd, *J* = 12, 4 Hz, 1H, OC**H**$_2$CH), 3.30 (dd, *J* = 10, 5 Hz, 1H, POC**H**$_2$), 2.63 (d, *J* = 10 Hz, 6H, PNC**H**$_3$), 2.61 (d, *J* = 10 Hz, 6H, PNC**H**$_3$), 2.59 (dd, *J* = 10.5, 4 Hz, 1H, OCH$_2$C**H**), 2.12 (dddd, *J* = 15, 9, 7, 3 Hz, 1H, OCHC**H**$_2$CH$_2$, ax), 1.98 (m, 2H, CHC**H**$_2$CH=C), 1.74 (d, *J* = 1 Hz, 3H, CH=CC**H**$_3$), 1.69 (dddd, *J* = 15, 9, 9, 1 Hz, 1H, OCHC**H**$_2$CH$_2$, eq), 1.53 (ddd, *J* = 14, 9, 3 Hz, 1H, OCHCH$_2$C**H**$_2$, eq), 1.41 (ddd, *J* = 14, 9, 9 Hz, 1H, OCHCH$_2$C**H**$_2$, ax), 1.28 (s, 3H, C**H**$_3$), 1.24 (s, 3H, C**H**$_3$), 1.16 (s, 3H, C**H**$_3$), 0.96 (s, 3H, C**H**$_3$), 0.80 (dd, *J* = 9.5, 7.5 Hz, 1H, C**H**CH$_2$CH=C); ^{13}C NMR (acetone-d_6): δ 136.1 (p), 125.9 (a), 101.0 (p), 71.2 (d, *J* = 5 Hz, p), 68.2 (a), 62.0 (p), 50.0 (a), 48.3 (a), 44.8 (p), 36.8 (d, *J* = 3.5 Hz, a), 36.7 (d, J = 3.5 Hz, a), 34.7 (a), 34.6 (p), 32.5 (p), 25.8 (a), 25.6 (p), 25.0 (a), 23.9 (a) 23.0 (a); HRMS 428.2800 (M$^+$, cacld for $C_{22}H_{41}N_2O_4P$: 428.2804). Anal. Calcd for $C_{22}H_{41}N_2O_4P$: C 61.66, H 9.64; Found: C 61.83, H 9.75.

(1R,5R*,9S*,14S*)-2,6,6,11,11,14-Hexamethyl-10,12-dioxatricyclo[7.4.1.0^{5,14}]tetradec-2-ene (**11**)*

Compound (**10**) (0.158 g, 0.40 mmol) in THF (0.5 mL) was slowly added to a blue solution of lithium (about 15 mg, 2.1 mmol) in ethylamine (5 mL) at 0°C under argon. After 10 min, water was added and the resulting mixture was extracted with ether (3 x 10 mL). The extracts were washed with brine (2 x 10 mL), dried, filtered and concentrated. Flash chromatography with Skelly B afford **11** (9.45 mg, 85%) as a colorless oil. Further elution with ethyl acetate-Skelly B (15:85) afforded **6** (4.7 mg, 4%) as a colorless oil. Compound (**11**): IR (acetone-d_6, cast): 1220 cm^{-1} (C-O); ^{1}H NMR (300 MHz, acetone-d_6): δ 5.68 (m, 1H, C**H**=CCH$_3$), 3.93 (d, *J* = 6 Hz, 1H, OC**H**CH$_2$CH$_2$), 3.70 (dd, *J* = 13, 9 Hz, 1H, OC**H**$_2$CH), 3.44 (dd, *J* = 13, 3.5 Hz, 1H, OC**H**$_2$CH), 2.00 (m, 5H, OCHC**H**$_2$CH$_2$, OCH$_2$C**H**, C**H**C**H**$_2$CH=C), 1.70 (pseudo t, *J* = 2 Hz, 3H, CH=CC**H**$_3$), 1.62 (dddd, *J* = 14.5, 7, 7, 2 Hz, 1H, OCHC**H**$_2$CH$_2$, eq), 1.52 (ddd, *J* = 13, 7.5, 5.5 Hz, 1H, OCHCH$_2$C**H**$_2$, eq), 1,.35 (ddd, *J* = 13, 7, 7 Hz, 1H, OCHCH$_2$C**H**$_2$, ax), 1.28 (s, 3H, C**H**$_3$), 1.20 (d, *J* = 1 Hz, 3H, C**H**$_3$), 1.13 (s, 3H, C**H**$_3$), 0.99 (s, 3H, C**H**$_3$), 0.98 (s, 3H, C**H**$_3$); ^{13}C NMR (acetone-d_6): δ 135.6 (p), 125.7 (a), 100.7 (p), 73.1 (a), 62.1 (p), 57.4 (a), 51.4 (a), 41.1 (p), 34.0 (a), 33.9 (a), 33.2 (p), 27.1 (p), 27.1 (a), 26.9 (a), 26.4 (p), 23.2 (a), 23.1 (a); HRMS: 278.2240 (M$^+$, calcd for $C_{18}H_{30}O_2$: 278.2246), 248.2131 (M$^+$-CH_2O, calcd for $C_{17}H_{28}O$: 248.2140). Anal. Calcd for $C_{18}H_{30}O_2$: C 77.65, H 10.86; Found: C 77.92, H 10.71.

(1S,6S*,10R*,12S*,14R*,15S*)-4,4,9,9,14,15-Hexamethyl-3,5,13-trioxatetracyclo[8.4.1.0.^{6,15} 0^{12,14}]pentadecane (**12**)*

Compound (**11**) (8.11 mg, 0.029 mmol) was dissolved in CH_2Cl_2 (1 mL). To this solution were added aqueous saturated $NaHCO_3$ solution (0.5 mL) and *m*-chloroperbenzoic acid (80%, 13 mg, 0.06 mmol). The resulting heterogeneous reaction mixture was stirred at rt for 1 h. Excess MCPBA was destroyed with sodium sulfite and the reaction mixture was extracted with ether. The extracts were washed with brine, dried, filtered and concentrated. Flash chromatography on silica gel pre-treated with triethylamine, eluting with 10% ether in Skelly B, afforded **12** (7.65 mg, 89%) as a colorless oil: IR ($CHCl_3$, cast): 1221 (C-O), 1083 cm^{-1} (C-O); ^{1}H NMR (360 MHz, $CDCl_3$): δ 3.78 (m, 3H, OC**H** and OC**H**$_2$), 3.06 (d, *J* = 4 Hz, 1H, epoxide OC**H**), 2.00 (m, 3H), 1.82 (dd, *J* = 8, 3 Hz, 1H, OCH$_2$C**H**), 1.60-1.40 (m, 4H), 1.40 (s, 3H, C**H**$_3$), 1.33 (s, 3H, C**H**$_3$), 1.29 (s, 3H, C**H**$_3$), 1.07 (s, 3H, C**H**$_3$), 1.06 (s, 3H, C**H**$_3$), 0.97 (s, 3H, C**H**$_3$); ^{13}C NMR

($CDCl_3$): δ 100.1 (p), 72.5 (a), 62.2 (p), 60.1 (a), 58.1 (p), 53.8 (a), 43.3 (a), 40.3 (p), 33.4 (a), 32.6 (a), 32.2 (p), 31.9 (p), 27.1 (a, two carbon signals at 27.2 and 27.1 in a 1:1 mixture of $CDCl_3$-C_6D_6), 26.4 (p), 25.6 (p), 22.7 (a), 22.4 (a); HRMS: 264.2078 (M^+ - CH_2O, calcd for $C_{17}H_{28}O_2$: 264.2089); CIMS: 265.3 (M^+ - CH_2O + 1). Anal. Calcd for $C_{18}H_{30}O_3$: C 73.43, H 10.27; Found: C 73.28, H 10.15.

(1R,2R*,3R*,5R*,9S*,14S*)-2,6,6,11,11,14-Hexamethyl-3-phenylselenyl-10,12-dioxatricyclo-[7.4.1.$0^{5,14}$]tetradecan-2-ol* ***(13)***

Sodium borohydride (47 mg, 1.2 mmol) was added in batches to a suspension of diphenyl diselenide (270 mg, 0.87 mmol) in EtOH (4 mL) at 0°C until the yellow color of diphenyl diselenide disappeared. The resulting solution was stirred at rt for 20 min so that any remaining $NaBH_4$ would be consumed by the solvent. A solution of **12** (161 mg, 0.55 mmol) in EtOH (4 mL) was added, and the reaction mixture was refluxed under argon for 60 h. After colling with an ice-bath, saturated aqueous NH_4Cl solution was added to quench the reaction. The reaction mixture was extracted with ether (3 x 20 mL). The extracts were washed with brine, dried, filtered and concentrated. The residue was subjected to flash chromatography on silica gel pre-treated with Et_3N. Gradient elution with 10-30% ether in Skelly B afforded **13** (205 mg, 83%) as a colorless oil: IR (CH_2Cl_2, cast): 3445 (br, -OH), 3060 (aromatic C-H), 1265 (C-O), 1221 (C-O), 1121 cm^{-1} (C-O); ^1H NMR (400 MHz, C_6D_6): δ 7.54 (m, 2H, phenyl), 6.97 (m, 3H, phenyl), 4.30 (pseudo t, *J* = 13 Hz, 1H, OC**H**$_2$CH), 3.94 (m, 1H, OC**H**CH$_2$CH$_2$), 3.80 (dd, *J* = 13, 6 Hz 1H, OC**H**$_2$CH), 3.49 (dd, *J* = 12, 8 Hz, 1H, C**H**SePh), 2.38 (m, 2H, CHC**H**$_2$CHSePh), 1.87 (m, 4H), 1.58 (m, 1H), 1.42 (s, 3H, C**H**$_3$), 1.37 (s, 3H, C**H**$_3$), 1.34 (s, 3H, C**H**$_3$), 1.31 (s, 3H, C**H**$_3$), 1.13 (m, 1H), 1.06 (s, 3H, C**H**$_3$), 0.92 (s, 3H, C**H**$_3$); ^{13}C NMR (acetone-d_6): δ 134.1 (a), 132.4 (p), 129.9 (a), 127.8 (a), 100.9 (p), 75.7 (p), 72.8 (a), 64.3 (p), 61.8 (a), 53.6 (a), 47.3 (a), 42.1 (p), 34.8 (a), 34.3 (p), 33.2 (a), 32.9 (p), 31.7 (p), 31.6 (a), 31.0 (a), 26.2 (p), 25.0 (a), 23.6 (a); HRMS: 452.1861 (M^+, calcd for $C_{24}H_{36}O_3{}^{80}Se$: 452.1830), 450.1875 (M^+, calcd for $C_{24}H_{36}O_3{}^{78}Se$: 450.1838). Anal. Calcd for $C_{24}H_{36}O_3Se$: C 63.84, H 8.04; Found: C 63.51, H 8.28.

(1R,5S*,9S*,14R*)-2,6,6,11,11,14-Hexamethyl-10,12-dioxatricyclo[7.4.1.$0^{5,14}$]tetradec-2-en-*

4-one (2)

Chromium trioxide (191 mg, 1.9 mmol) was added to pyridine (1 mL) at 0°C. The reaction mixture was allowed to warm up to rt and stirring was continued under argon for another 10 min. A solution of **13** (51.2 mg, 0.113 mmol) in pyridine (2 mL) was added. The resulting mixture was stirred at rt under argon for 20 h, then filtered through a thin pad of florisil (60-100 mesh) and washed with ether. The filtrate was concentrated with a rotary evaporator equipped with a dry-ice condenser. The residue was dissolved in methanol (3 mL). To this methanolic solution was added aqueous sodium hydroxide solution (1 N, 0.4 mL). The reaction mixture was stirred at rt for 4 h, then extracted with ether (3 x 20 mL). The extracts were washed with brine, dried , filtered and concentrated. The residue was subjected to flash chromatography on silica gel pre-treated with triethylamine. Elution with 5% ethyl acetate in Skelly B gave the desired enone (**2**) (16.1 mg, 49%) as a *colorless oil*: IR (KBr): 1668 cm^{-1} (C=O); ^{1}H NMR (360 MHz, $CDCl_3$): δ 5.71 (d, *J* = 1 Hz, 1H, olefinic), 3.93 (dd, *J* = 13, 10 Hz, 1H, OCH_2CH), 3.73 (d, *J* = 5 Hz, 1H, $OCHCH_2CH_2$), 3.45 (dd, *J* = 13, 3 Hz, 1H, OCH_2CH), 2.71 (s, 1H, CHC=O), 2.03 (dd, *J* = 10, 3 Hz, 1H, OCH_2CH), 1.90 (d, *J* = 1 Hz, 3H, $CH=CCH_3$), 1.87 (m, 2H), 1.42 (m, 2H), 1.37 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.08 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 200.0 (p), 154.4 (p), 128.5 (a), 100.7 (p), 73.2 (a), 59.3 (p), 58.7 (a), 50.9 (a), 43.8 (p), 36.4 (p), 34.4 (a), 31.9 (p), 25.8 (a), 24.7 (p), 23.9 (a), 23.2 (a), 23.0 (a), 22.8 (a); HRMS: 292.2036 (M^+, calcd for $C_{18}H_{28}O_3$: 292.2039), 262.1967 ($M^+ - CH_2O$, calcd for $C_{17}H_{26}O_2$: 262.1933).

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