trogen was added pulverized potassium cyanide (78 mg, 1.20 mmol) and the mixture was refluxed gently for 3 h. After removal of the solvent in vacuo, the residue was treated with saturated $NaHCO_3$ and extracted with methylene chloride. The extract was washed with saturated NaCl, dried over anhydrous K_2CO_3, and concentrated in vacuo to afford a dark red oil (153 mg). Preparative thin-layer chromatography on silica gel developed with 5% methanol–chloroform gave (±)-16-cyano-14,15-didehydroquebrachamine (**36**; 20 mg, 27.4%) as a clear viscous oil: IR (neat) 3320, 2225; NMR ($CDCl_3$) δ 0.83 (3 H, t, J = 6.0 Hz), 3.52 (1 H, dd, J = 7.0 Hz and 4.0 Hz), 5.30–6.2 (2 H, m), 6.90–7.70 (4 H, m), 8.20 (1 H, br s, disapp. with D_2O); MS *m/e* 305 (M^+), 278, 249, 223, 210, 208, 205, 194, 181, 168, 123, 121, 119, 117, 108. The mass spectrum of this material was identical with the reported data.[6]

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Lactone Annulation of β-Keto Esters with β-Vinylbutenolide and the Total Synthesis of Racemic Frullanolide[1]

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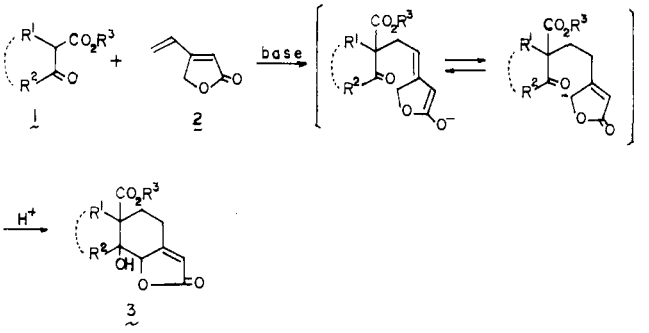
Abstract: A new annulation reaction, in which sodium enolates of β-keto esters **6–11** and β-vinylbutenolide (**2**) yield lactone annulated products **12–17** in one step, is described. Racemic frullanolide (**30**) has been synthesized from one of these annulation products, **14a.**

In the preliminary communication we reported the reactions of 2-methylcyclohexane-1,3-dione and 2-ethoxycarbonylcyclohexanone with β-vinylbutenolide (**2**) affording lactone annulated products.[1a,2] Recently we have extended this annulation reaction to some β-keto esters for the exploration of a new synthetic approach to eudesmanolides.

The reaction is shown by the following general equation, i.e., 1,6-conjugate addition of keto esters **1** to **2** and concomitant intramolecular cyclization yielding lactone annulated products **3.**



The reagent, β-vinylbutenolide (**2**), was expediently prepared from β-vinylbutyrolactone (**4**), easily accessible from (*E*)-2-butene-1,4-diol and ethyl orthoacetate in good yield,[3] as follows: the lithium enolate of the latter lactone was sulfenylated with diphenyl disulfide[4] yielding thiophenoxylactone **5** (Chart I). The product was oxidized with *m*-chloroperbenzoic acid to the corresponding sulfoxide, which was then heated, without purification, in refluxing toluene to afford **2.**[5] This compound is unstable, slowly changing into a polymeric substance even on refrigeration, while **5** is much more stable in storage. In the reaction we usually employed **2** freshly prepared from **5.**

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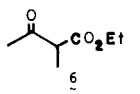
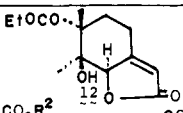
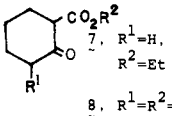
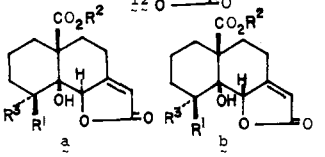
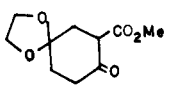
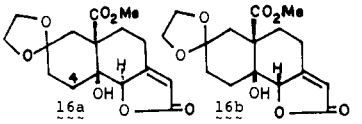
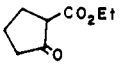
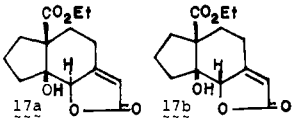
Table I. Lactone Annulation of β-Keto Esters with γ-Vinylbutenolide

Entry	Ketoester	Reaction conditions: Solvent	Temp. °C	Time h	Annulation product	Isolated yield[a] %	Ratio of epimers[b] (a : b)	δ value of butenolide γ-proton: a	b
1	 6	THF	55	15	 12	42	–	5.38	
2	 7, R^1=H, R^2=Et	DME	room temp.	16	 a b	13, R^1=R^3=H, R^2=Et	57	5:2	5.17	5.56
3	8, R^1=R^2=Me	THF	room temp.	14		14, R^1=R^2=Me, R^3=H	51[c]	2:1[d]	5.27	5.72
4	8	THF	50-60[e]	40			43	0:1		
5	9, R^1=CO_2Me, R^2=Me	DME	70-73[e]	15		15, R^1=CO_2Me, R^2=Me, R^3=H	62	0:1	-	5.54
6	 10	THF	55	14	 16a 16b		47	3:10	5.35	5.68
7	 11	THF	room temp.	17	 17a 17b		30[f]	12:1	4.73	5.36
8		THF	50-55	15			58	0:1		

a Based on β-vinylbutenolide used. b Based on separated epimers. c Based on a mixture of 14a and 14b (see Experimental Section). d Determined by PMR. e After stirring for 15 h at room temperature, the mixture was heated at this temperature. f The adduct 22 was also formed in 21% yield.

Chart I

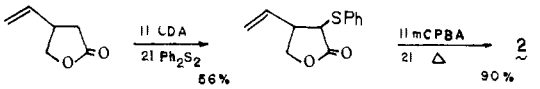
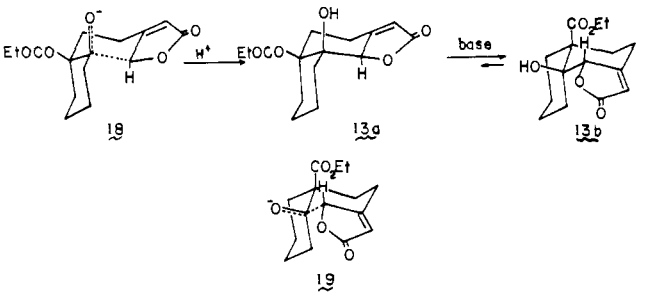


Chart II



Sodium enolates of some β-keto esters **6–11** listed in Table I reacted with **2** in THF or DME giving annulated products **12–17.** In the reaction of ethyl α-methylacetoacetate (**6**), only one product, **12,** was isolated (entry 1). In the ^{1}H NMR spectra of this compound, a large nuclear Overhauser effect (17%) was observed between a methyl singlet at δ 1.52 (Me-C-OH) and the γ proton of the butenolide ring, whereas another methyl singlet at δ 1.33 (Me-C-CO_2Et) showed no such observable effect with the γ proton. These results suggest that this compound has the stereochemistry as depicted.

Since stereochemical situations are more complicated in annulated products from cyclic keto esters, we first worked in detail on the stereochemistry of products from 2-ethoxycarbonylcyclohexanone (**7**) (entry 2). In this case we obtained a mixture of two diastereomers, **13a** and **13b,**[6] which was separable by preparative TLC. Their spectral data are well consistent with the structures proposed. *cis*-Decalol stereostructures of the products are based on the well-documented stereochemical outcome of Robinson annulation products from α-substituted cyclohexanones and vinyl ketones.[7] Europium-induced shifts of ^{1}H NMR signals of the products revealed relative disposition of angular hydroxyl groups and γ hydrogens of the butenolide rings; e.g., tris(dipivalomethanato)-europium added to a solution of the major product **13a** caused only slight low-field shifts of the γ-proton signal, whereas under the same conditions the γ-proton signal of the minor product **13b** considerably shifted to lower field. These observations indicate that the hydroxyl group and γ hydrogen are in a trans or cis relationship in the major or minor product, respectively. The difference in stereochemical environment mentioned above also reflects on chemical shifts of the butenolide γ protons in the standard ^{1}H NMR spectra, resulting in a distinct difference between those of the epimers (Table I). As summarized in Table I, the chemical shifts of the γ protons of related annulation products can be divided into two categories, i.e., ranges of 5.1–5.4 and 5.5–5.8 ppm, which are useful for diagnosis of their stereochemistry.[8]

Since butenolide rings in these annulation products distort the cyclohexane rings flanking them, it is presumable from molecular models that the nonsteroid conformation **13a** (Chart II) is preferable for the major product to a steroid one, whereas the minor product most likely takes the steroid conformation **13b.** Upon base treatment (*t*-BuOK) the major product almost completely isomerized into the minor one, the result indicating that the former compound is the kinetic product via the transition state **18** which would be sterically preferable to the alternative congested transition state **19.** Presumably the minor product **13b** would be an epimerization product of the major one **13a** during the reaction.

Similar annulation products, **16a** and **16b**, were obtained

Chart III

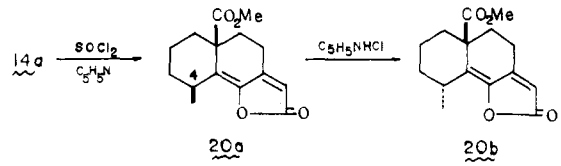
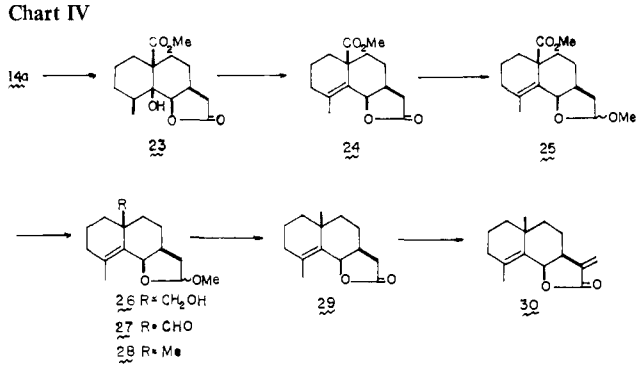


Chart IV

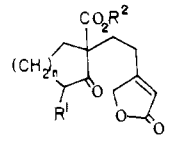


from keto ester **10**[9] (entry 6). Since introduction of a methyl group into the C(4) positions of these products would be possible by a sequence of reactions, i.e., hydrolysis of the ketal blocking group, introduction of unsaturation giving a conjugate enone, and conjugative methylation of the enone, the annulation products may be expected as potential precursors for eudesmanolides.

In the reaction with 2-methoxycarbonyl-6-methylcyclohexanone (**8**)[10] or 2,6-dimethoxycarbonylcyclohexanone (**9**),[11] the stereochemical situation of their annulation products becomes more complicated than that in the case of **7**, owing to an additional substituent (methyl or methoxycarbonyl). A pair of epimers, **14a** and **14b**, was obtained from **8** at room temperature (entry 3). The disposition of their butenolide γ hydrogens relative to hydroxyl groups was analogously assigned on the basis of their chemical shifts (Table I). Almost complete epimerization of the major product **14a** to its epimer **14b** was effected by the sodium enolate of **8** in warm THF. Actually **14b** was obtained as the sole product in the reaction of **8** and **2** at elevated temperature (entry 4). Dehydration of **14a** ($SOCl_2$–C_5H_5N, 0 °C) gave $\alpha,\beta,\gamma,\delta$-unsaturated lactone **20a** in good yield (Chart III). In its ^1H NMR spectrum the allylic C(4) proton was observed as a broad singlet with a half-height width of 7 Hz on irradiation of the C(4)-methyl doublet. These evidently demonstrate an axial configuration of the C(4)-methyl group in **14a**, and this assignment also rationalizes the complete epimerization to the epimer **14b**. When dehydration of **14a** was conducted with the same reagent at room temperature for a longer time, it was found that the product consisted mainly of an epimer of **20a**, viz., **20b**. This was apparently due to the epimerization of the quasi-axial C(4) methyl of **20a**, initially formed, by pyridinium chloride, and the presumption was verified by treatment of **20a** with the pyridinium salt in pyridine.

Although the conjugate addition of **9** to **2** occurred smoothly to give the adduct **21** (54%), the subsequent intramolecular cyclization of the adduct was sluggish probably owing to the enolic nature of the ketone carbonyl. When higher temperature was applied to promote the cyclization, the isolable product was only one of the anticipated diastereomers, **15b**, which had a cis stereochemistry with respect to the butenolide γ hydrogen and hydroxyl (entry 5). The secondary methoxycarbonyl group was assigned as equatorial from the coupling pattern of its α proton (a quartet) at δ 3.42. Thus the whole stereostructure can be depicted as **15b** and demonstrates this compound to be the thermodynamic product caused by high reaction temperature.

A similar situation was observed in the reaction of 2-ethoxycarbonylcyclopentanone (**11**). At room temperature, the reaction gave a mixture of **17a**, **17b**, and the Michael adduct **22** (54:4:42), while **17b** was the sole isolable product at elevated temperature (entry 7). It is noteworthy that the butenolide γ protons of these hydrindan derivatives show higher chemical shift values than those of the corresponding decalin derivatives (Table I).[12]



21 n=2, R^1=CO_2Me, R^2=Me
22 n=1, R^1=H, R^2=Et

Thus we found that the annulation reaction of β-keto esters with β-vinylbutanolide provided a facile and efficient entry toward eudesmanolides. To illustrate the efficiency of this reaction in eudesmanolide synthesis, we then focused our attention to the synthesis of frullanolide[13] (**30**), a typical and allergenic eudesmanolide.[14] We selected the annulation product **14a** as starting material, because it possesses 14 carbons of the eudesmanolide framework and was in an oxidation stage close to that of the target.

The butenolide **14a** was reduced ($NaBH_4$, $NiCl_2$[15]) quantitatively to **23** (Chart IV). When the product was treated with thionyl chloride in pyridine, in contrast to the case of **14a**, dehydration took place regioselectively to give **24**. This reversed regioselectivity of dehydration seems to demonstrate that the fixed nonsteroid conformation of **14a** inverts to a steroid conformation in **23** on saturation of the double bond. Prior to reduction of the methoxycarbonyl group in **24** to methyl, the γ-lactone moiety was protected as an acetal on treatment with diisobutylaluminum hydride followed by triethyl orthoformate and pyridinium *p*-toluenesulfonate catalyst,[16] affording a mixture of **25** and its epimer regarding the acetal methoxyl group (72:28). To avoid spectral and chromatographic complexity in further steps, we proceeded with the major acetal and the minor one was oxidized with Jones reagent to γ-lactone **24** in good yield. Reduction of the ester group in **25** to methyl was conducted by successive treatment with lithium aluminum hydride and Collins reagent and then by Huang-Minlon reduction, via **26** and **27**. The resulting acetal **28** was oxidized with Jones reagent leading to lactone **29**. Methylenation of **29** was performed according to the procedure described by Grieco and Hiroi[17] (lithium diisopropylamide, formaldehyde; methanesulfonyl chloride, pyridine; DBU), affording racemic frullanolide (**30**) as identified by spectral comparison with the natural product.

Experimental Section

IR spectra were recorded on a Hitachi EPI-S 32 or a JASCO A-3 spectrophotometer in $CHCl_3$ solutions, and ^1H NMR spectra were taken on a JEOL C-60HL (60 MHz) or a JEOL PS-100 (100 MHz) spectrometer using Me_4Si (δ 0) as an internal standard and $CDCl_3$ as the solvent. Coupling constants are given in hertz.

2,3,4,5-Tetrahydro-2-oxo-3-phenylthio-4-vinylfuran (5). A solution of β-vinylbutyrolactone **4**[3] (50 g, 0.45 mol) in THF (300 mL) was added to a stirred solution of LDA, prepared from diisopropylamine (54.2 g, 0.54 mol) in THF (300 mL) and *n*-BuLi (0.54 mol) in hexane, over 2 h at −70 °C under N_2. After the temperature had been allowed to rise to −30 °C, the mixture was cooled to −40 °C, and a solution of diphenyl disulfide (146 g, 0.67 mol) and HMPA (136 g) in THF (250 mL) was added to the above enolate solution. The mixture was gradually warmed to room temperature with stirring. After acidification with dilute HCl, the product was extracted with ether and the extract was washed and dried. Removal of the solvent left an oil, which was chromatographed on a silica gel column. Petroleum ether eluted

diphenyl disulfide, and then **5** was obtained by eluting with ether. Distillation of the latter fraction (bp 150–152 °C (1 mmHg)) gave **5** (54.8 g, 56%): IR 1776, 1015, and 925 cm^{-1}; ^1H NMR δ 3.06 (q, 1 H, $J_{\beta\alpha} = J_{\beta\gamma} = J_{\beta\gamma'} = 8$ Hz), 3.60 (d, 1 H, $J_{\alpha\beta} = 8$ Hz), 3.98 (t, 1 H, $J_{\gamma\beta'} = J_{\gamma\gamma'} = 8$ Hz), 4.26 (t, 1 H, $J_{\gamma\beta} = J_{\gamma\gamma'} = 8$ Hz), 5.16–5.90 (m, 3 H, an ABX pattern), and 7.40 (m, 5 H).

Anal. ($C_{12}H_{12}SO_2$) C, H.

2,5-Dihydro-2-oxo-4-vinylfuran (2). A solution of *m*-chloroperbenzoic acid (173 mg, 1 mmol) in CH_2Cl_2 was added to a solution of **5** (220 mg, 1 mmol) in the same solvent (5 mL). After stirring for 30 min at 0 °C, the mixture was filtered, and the filtrate was washed with aqueous $NaHCO_3$, water, and then brine. The crude product (230 mg) obtained by evaporation was dissolved in toluene (10 mL) and refluxed for 2 h. After removal of the solvent, the residue was purified by preparative silica gel TLC using CH_2Cl_2 as the solvent, giving **2** (102 mg, 93%): IR 1783, 1745, 1643, and 990 cm^{-1}; ^1H NMR δ 5.05 (m, 2 H), 6.02 (m, 1 H), 5.55–6.83 (m, 3 H, an ABX pattern).

No analytically pure specimen was obtained owing to its instability.

General Procedure for the Reaction of β-Keto Esters and 2. A solution of a keto ester (4 mmol) in THF or DME (2 mL) was added to a suspension of Na powder (46 mg, 2 mmol) in the same solvent (2 mL). To complete enol formation, the mixture was heated at 50–55 °C for ca. 1 h under N_2 with stirring. A solution of **2** (220 mg, 2 mmol) in the same solvent (1 mL) was added dropwise to the enolate solution at room temperature, and the mixture was stirred at the same temperature for 14–17 h, and, if necessary, heated further at elevated temperature until no unreacted **2** was detected in TLC. The mixture was poured into ice water, acidified with dilute HCl, and then extracted with CH_2Cl_2. The extract was washed with water and dried over $MgSO_4$, and the crude product was separated by preparative silica gel TLC using a mixture of CH_2Cl_2 and ether as the solvent.

2,4,5,6,7,7aα-Hexahydro-6β,7α-dimethyl-7β-hydroxy-6α-methoxycarbonyl-2-oxo-1-benzofuran (12): mp 128–131 °C (recrystallized from CH_2Cl_2–petroleum ether); IR 3450, 1790–1720, and 1650 cm^{-1}; ^1H NMR 1.30 (t, 3 H, $J = 7$ Hz), 1.33 (s, 3 H), 1.52 (s, 3 H), 4.19 (q, 2 H, $J = 7$ Hz), 5.38 (m, 1 H), and 5.73 (m, 1 H).

Anal. ($C_{13}H_{18}O_5$) C, H.

2,4,5,5a,6,7,8,9,9a,9bα-Decahydro-5aβ-ethoxycarbonyl-9aβ-hydroxy-2-oxonaphtho[1,2-*b*]furan (13a) and Its 9b Epimer (13b). These diastereomers **13a** and **13b** were obtained as crystals of mp 128 and 171 °C (recrystallized from CH_2Cl_2–petroleum ether) from polar and less polar fractions in TLC, respectively: IR (**13a**) 3450, 1780, 1745, 1705, and 1655 cm^{-1}, (**13b**) 3400, 1770, 1745, 1715, and 1640 cm^{-1}; ^1H NMR (**13a**) δ 1.30 (t, 3 H, $J = 7$ Hz), 4.20 (q, 2 H, $J = 7$ Hz), 5.17 (m, 1 H), and 5.75 (m, 1 H), (**13b**) 1.30 (t, 3 H, $J = 7$ Hz), 4.20 (q, 2 H, $J = 7$ Hz), 5.56 (m, 1 H), and 5.70 (m, 1 H).

Anal. ($C_{15}H_{20}O_5$) C, H (for **13a** and **13b**).

Epimerization of 13a to 13b. Butenolide **13a** (70 mg) was heated in THF (5 mL) containing *t*-BuOK (28 mg) at 50 °C for 3 h. The crude product obtained on usual workup was purified by TLC (CH_2Cl_2–ether), giving crystals of **13b** (58 mg, 82%), whose spectra were indistinguishable from those of an authentic sample.

2,4,5,5a,6,7,8,9,9a,9bα-Decahydro-9aβ-hydroxy-5aβ-methoxycarbonyl-9β-methyl-2-oxonaphtho[1,2-*b*]furan (14a) and Its 9b Epimer (14b). Since these diastereomers were not cleanly separable in TLC, the following modified procedure was employed. The crude product obtained from 260 mg of **2** was submitted to preparative TLC using CH_2Cl_2–ether (20:7) to separate a mixture of **14a** and **14b** (337 mg, 51% yield) from the excess keto ester. The crystalline mixture was triturated with ether and filtered. Crystals obtained were recrystallized from CH_2Cl_2–petroleum ether to give pure **14a** (221 mg): mp 168–169 °C; IR 3450, 1780, 1745, 1700, and 1655 cm^{-1}; ^1H NMR δ 0.89 (d, 3 H, $J = 7$ Hz), 3.77 (s, 3 H), 5.27 (m, 1 H), and 5.77 (m, 1 H).

The minor isomer **14b** in the filtrate was separated by TLC using CH_2Cl_2 and obtained from less polar fractions as crystals (89 mg): mp 141–142 °C (recrystallized from ether–petroleum ether); IR 3450, 1780, 1740, 1720, and 1650 cm^{-1}; ^1H NMR δ 1.05 (d, 3 H, $J = 7$ Hz), 3.74 (s, 3 H), and 5.72 (br s, 2 H).

Anal. ($C_{15}H_{20}O_5$) C, H (for **14a** and **14b**).

The minor isomer **14b** was the sole product at elevated temperature and separated by the standard procedure (Table I, entry 4).

2,4,5,5a,6,7,8,9,9a,9bβ-Decahydro-5aβ,9β-dimethoxycarbonyl-9aβ-hydroxy-2-oxonaphtho[1,2-*b*]furan (15b) and 2-(2,5-Dihydro-2-oxo-4-furyl)ethyl-2,5-dimethoxycarbonylcyclohexan-1-one (21). For **15b**: mp 147–149 °C (recrystallized from MeOH); IR 1780, 1745, 1715, and 1650 cm^{-1}; ^1H NMR δ 3.42 (q, 1 H, $J = 6$ and 12 Hz), 3.78 (s, 3 H), 3.80 (s, 3 H), 5.54 (m, 1 H), and 5.70 (m, 1 H).

Anal. ($C_{16}H_{20}O_7$) C, H.

In the reaction at room temperature for ca. 15 h, the isolable product was only **21**: mp 103–105 °C (recrystallized from CCl_4); IR 1780, 1750, 1740, 1660, and 1620 cm^{-1}; ^1H NMR[18] δ 3.76 (s, 3 H), 3.82 (s, 3 H), 4.78 (br s, 2 H), and 6.86 (br s, 1 H).

Anal. ($C_{16}H_{20}O_7$) C, H.

2,4,5,5a,6,7,8,9,9a,9bα-Decahydro-2,7-dioxo-9aβ-hydroxy-5aβ-methoxycarbonylnaphtho[1,2-*b*]furan 7-Ethylene Acetal (16a) and Its 9b Epimer (16b). These diastereomers **16a** and **16b** were obtained as crystals (mp 181 and 216 °C, recrystallized from CH_2Cl_2–ether) from polar and less polar fractions in TLC, respectively: IR (**16a**) 3500, 1785, 1750, 1720, and 1650 cm^{-1}; (**16b**) 3400, 1780, 1755, 1730, and 1645 cm^{-1}; ^1H NMR (**16a**) δ 3.77 (s, 3 H), 3.90 (br s, 4 H), 5.35 (m, 1 H), and 5.70 (m, 1 H); (**16b**) 3.70 (s, 3 H), 3.87 (m, 4 H), and 5.68 (br s, 2 H).

Anal. ($C_{16}H_{20}O_7$) C, H (for **16a** and **16b**).

2,4,5,5a,6,7,8a,8bα-Octahydro-5aβ-ethoxycarbonyl-8aβ-hydroxyindeno[4,5-*b*]furan (17a) and Its 8b Epimer (17b) and 2-(2,5-Dihydro-2-oxo-4-furyl)ethyl-2-ethoxycarbonylcyclopentan-1-one (22). These butenolides **17a, 17b,** and **22** were obtained from middle, most polar, and least polar fractions in TLC, respectively. Recrystallization from CCl_4 gave pure products: (**17a**) mp 146–147 °C; IR 3450, 1780, 1750, and 1650 cm^{-1}; ^1H NMR δ 1.28 (t, 3 H, $J = 7$ Hz), 4.20 (q, 2 H, $J = 7$ Hz), 4.73 (br s, 1 H), and 5.80 (br s, 1 H); (**17b**) mp 54–56 °C; IR 3450, 1775, 1740, 1700, and 1650 cm^{-1}; ^1H NMR δ 1.30 (t, 3 H, $J = 7$ Hz), 4.25 (q, 2 H, $J = 7$ Hz), 5.36 (m, 1 H), and 5.78 (m, 1 H); (**22**) mp 58–59 °C; IR 1780, 1750, 1720, and 1640 cm^{-1}; ^1H NMR δ 1.27 (t, 3 H, $J = 7$ Hz), 4.18 (q, 2 H, $J = 7$ Hz), 4.75 (d, 2 H, $J = 7$ Hz), and 5.83 (m, 1 H).

Anal. ($C_{14}H_{18}O_5$) C, H (for **17a, 17b,** and **22**).

The isomer **17b** was the sole isolable product at elevated temperature.

Epimerization of 14a to 14b. A sodium enolate solution was prepared from **8** (68 mg) and Na powder (9 mg) in THF under the standard conditions. Butenolide **14a** (90 mg) was added to the above solution, and the mixture was heated at 55–60 °C for 56 h. TLC showed almost no detectable **14a** in the product. After workup, **14b** (73 mg, 81%) was separated by TLC using CH_2Cl_2–ether (10:1). Its melting point and spectra were identical with those of an authentic sample. *t*-BuOK did not effect this epimerization.

2,4,5,5a,6,7,8,9-Octahydro-5aβ-methoxycarbonyl-9β-methyl-2-oxonaphtho[1,2-*b*]furan (20a). Thionyl chloride (80 mg, 0.67 mmol) was added to a stirred solution of **14a** (60 mg, 0.21 mmol) in pyridine (1 mL) in an ice bath. After stirring for 15 min, the mixture was washed with dilute HCl and water and dried. Separation by TLC using CH_2Cl_2 gave **20a** (49 mg, 87%): mp 83–84 °C (recrystallized from petroleum ether–CH_2Cl_2); IR 1780, 1770, 1750, 1730, 1670, and 1610 cm^{-1}; ^1H NMR δ 1.02 (d, 3 H, $J = 8$ Hz), 3.28 (m, 1 H, changed to a singlet of $W/2 = 7$ Hz on irradiation at δ 1.02), and 3.66 (s, 3 H).

Anal. ($C_{15}H_{18}O_4$) C, H.

2,4,5,5a,6,7,8,9-Octahydro-5aβ-methoxycarbonyl-9α-methyl-2-oxonaphtho[1,2-*b*]furan (20b) from 14a. Thionyl chloride (89 mg, 0.75 mmol) was added to a solution of **14a** (70 mg, 0.25 mmol) in pyridine (3 mL) and the mixture was stirred at room temperature for 18 h. The crude product obtained on usual workup was shown by ^1H NMR to be almost pure **20b.** TLC purification gave pure **20b** (52 mg, 79%): mp 125–126 °C (recrystallized from petroleum ether–CH_2Cl_2); IR 1780, 1770, 1750, 1730, 1650, and 1610 cm^{-1}; ^1H NMR δ 1.46 (d, 3 H, $J = 8$ Hz), 3.73 (s, 3 H), and 5.71 (m, 1 H).

Anal. ($C_{15}H_{18}O_4$) C, H.

Epimerization of 20a to 20b by Pyridinium Chloride. A solution of **20a** (48 mg) and pyridinium chloride (62 mg) in pyridine (2 mL) was allowed to stand at room temperature for 17 h. The crude product was purified by TLC to give **20b** (11 mg, 23%), which was identified spectroscopically.

2,3,3aα,4,5,5a,6,7,8,9,9a,9bα-Dodecahydro-9aβ-hydroxy-5aβ-methoxycarbonyl-9β-methyl-2-oxonaphtho[1,2-*b*]furan (23). $NaBH_4$ (114 mg, 3 mmol) was added portionwise to a stirred solution of **14a** (211 mg, 0.75 mmol) and $NiCl_2 \cdot 6H_2O$ (45 mg, 0.19 mmol) in MeOH (11 mL) at 0 °C. The mixture was further stirred at the same temperature for an additional 4.5 h and diluted with CH_2Cl_2. After acidification with 6 N HCl, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts

were washed with aqueous $NaHCO_3$ and water and then dried. Removal of the solvent gave almost pure **23** as crystals (210 mg). An analytical sample, mp 99–100 °C, was obtained by recrystallization from CH_2Cl_2–petroleum ether: IR 3450, 1780, 1730, and 1700 cm^{-1}; ^1H NMR δ 0.97 (d, 3 H, J = 6 Hz), 3.72 (s, 3 H), 4.52 (d, 1 H, J = 3 Hz), and 5.17 (s, 1 H, OH).

Anal. ($C_{15}H_{22}O_5$) C, H.

2,3,3aα,4,5,5a,6,7,8,9bα-Decahydro-5aβ-methoxycarbonyl-9-methyl-2-oxonaphtho[1,2-*b*]furan (24). Thionyl chloride (0.08 mL) was added dropwise to a stirred solution of **23** (115 mg, 0.41 mmol) in dry pyridine (2 mL) at 0 °C. The mixture was then stirred at the same temperature for an additional 30 min and diluted with CH_2Cl_2. The solution was washed with cold 6 N HCl and then water and dried. Removal of the solvent left an oil, which was purified by preparative silica gel TLC using ether–petroleum ether (3:1) as the solvent, affording **24** (80 mg, 74%). An analytical sample, mp 92–93 °C, was obtained by recrystallization from ether–petroleum ether: IR 1770, 1740, 1720, and 1650 cm^{-1}; ^1H NMR δ 1.85 (s, 3 H), and 5.28 (d, 1 H, J = 4 Hz).

Anal. ($C_{15}H_{20}O_4$) C, H.

2,3,3aα,4,5,5a,6,7,8,9bα-Decahydro-2-methoxy-5aβ-methoxycarbonyl-9-methylnaphtho[1,2-*b*]furan (25). After diisobutylaluminum hydride solution in hexane (18%, 1.3 mL) had been added dropwise to a stirred solution of **24** (217 mg, 0.82 mmol) in a mixture of toluene (4 mL) and THF (0.8 mL) at −78 °C, the mixture was further stirred at the same temperature for an additional 80 min. To quench the reaction, saturated aqueous NH_4Cl (3 mL) was added, and then the mixture was acidified with AcOH and extracted with CH_2Cl_2. The extract was washed with aqueous K_2CO_3 and then water and dried. Evaporation gave a mixture of lactols as crystals (217 mg). A solution of the crude lactol mixture (222 mg), trimethyl orthoformate (0.4 mL), and pyridinium *p*-toluenesulfonate[16] (45 mg) in CH_2Cl_2 (7 mL) was stirred at 0 °C for 35 min and then diluted with CH_2Cl_2. The mixture was washed with aqueous K_2CO_3 and then water and dried. Evaporation gave a mixture of **25** and its epimer, which were separated by preparative silica gel TLC using CH_2Cl_2–ether (10:1) as the solvent, giving **25** (126 mg, 54%) and its epimer (49 mg, 21%) from polar and less polar fractions, respectively. Recrystallization from petroleum ether gave the analytically pure major acetal (**25**), mp 71–72 °C, and the minor acetal, mp 108–110 °C. Major acetal **25**: IR 1715 and 1655 cm^{-1}; ^1H NMR δ 1.80 (s, 3 H), 3.33 (s, 3 H), 3.65 (s, 3 H), 4.83 (d, 1 H, J = 4 Hz), and 4.95 (t, 1 H, J = 5 Hz). Minor acetal: IR 1720 and 1655 cm^{-1}; ^1H NMR δ 1.80 (s, 3 H), 3.28 (s, 3 H), 3.67 (s, 3 H), 4.70 (m, 1 H), and 4.87 (d, 1 H, J = 7 Hz).

Anal. ($C_{16}H_{24}O_4$) C, H (for both acetals).

Excess Jones reagent was added dropwise to a stirred solution of the minor acetal (10 mg) in acetone (1 mL) at 0 °C, and the mixture was further stirred at the same temperature for 20 min. Workup of the mixture gave crystals (8 mg), which were identified as **24** spectroscopically.

2,3,3aα,4,5,5a,6,7,8,9bα-Decahydro-5aβ,9-dimethyl-2-methoxynaphtho[1,2-*b*]furan (28). A solution of **25** (396 mg, 1.41 mmol) in dry ether (2 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (80 mg, 2.12 mmol) at 0 °C over 10 min. After completion of the addition, the mixture was further stirred for 30 min and then at room temperature for 30 min. The excess reagent was quenched with wet ether and then water. After drying, the organic layer was evaporated to afford crude **26** (356 mg): IR 3420 and 1650 cm^{-1}; ^1H NMR δ 1.78 (s, 3 H), 3.35 (s, 3 H), 3.58 (q, 2 H, J = 11 Hz), 4.83 (d, 1 H, J = 4 Hz), and 5.03 (q, 1 H, J = 4 and 4.5 Hz).

The crude alcohol **26** (356 mg) was treated with a solution of chromic anhydride–dipyridine complex (2.18 g) in CH_2Cl_2 (25 mL) at 0 °C for 10 min and then at room temperature for 30 min. The reaction mixture was passed through a short silica gel column, and the eluate was evaporated to leave **27** (303 mg): IR 2720 and 1710 cm^{-1}; ^1H NMR δ 1.87 (s, 3 H), 3.33 (s, 3 H), 4.88 (d, 1 H, J = 4 Hz), 4.95 (d, 1 H, J = 5.5 Hz), and 9.62 (s, 1 H).

A solution of the crude aldehyde **27** (63 mg), hydrazine hydrate (0.3 mL), and a catalytic amount of hydrazine hydrochloride in ethylene glycol (3.5 mL) was heated at 110–118 °C for 1 h. After the mixture was cooled to room temperature, KOH (160 mg) was added, and the mixture was heated at 200–205 °C for 2 h. The reaction mixture was diluted with water and extracted with ether. The extract was washed with water and then brine and dried. Removal of the solvent gave an oil, which was purified by preparative silica gel TLC using CH_2Cl_2 as the solvent, affording **28** (32 mg, 46% overall yield from **25**): IR 1650 cm^{-1}; ^1H NMR δ 1.15 (s, 3 H), 1.73 (s, 3 H), 3.37 (s, 3 H), 4.79 (d, 1 H, J = 4 Hz), and 5.06 (q, 1 H, J = 4 and 5 Hz).

An exact mass determination of **28** gave *m/e* 236.1748 (calcd for $C_{15}H_{24}O_2$, 236.1774).

2,3,3aα,4,5,5a,6,7,8,9bα-Decahydro-5aβ,9-dimethyl-2-oxonaphtho[1,2-*b*]furan (29). After excess Jones reagent had been added dropwise to a stirred solution of **28** (26 mg, 0.12 mmol) in acetone (1 mL) at 0 °C, stirring was continued for 40 min. The mixture was diluted with water and extracted with CH_2Cl_2, and the extract was washed and dried. Evaporation of the solvent afforded crystals (20 mg), which were recrystallized from ether–petroleum ether to yield an analytical sample of **29**: mp 121–122 °C; IR 1765 and 1645 cm^{-1}; ^1H NMR δ 1.07 (s, 3 H), 1.72 (s, 3 H), and 5.23 (d, 1 H, J = 4 Hz).

Anal. ($C_{14}H_{20}O_2$) C, H.

Racemic Frullanolide (30). A solution of **29** (30 mg, 0.14 mmol) in THF (0.6 mL) was added dropwise to a stirred solution of LDA, prepared from diisopropylamine (41 mg, 0.41 mmol) and *n*-BuLi (0.27 mmol) in THF (0.8 mL), at −78 °C. After the mixture was stirred for an additional 30 min, excess formaldehyde vapor was passed through the mixture at −22 °C with the aid of a nitrogen stream. The mixture was further stirred for 30 min and then quenched by dilute HCl. The product was extracted with $CHCl_3$, and the extract was washed and dried.

The residue (35 mg) obtained from the extract by evaporation was treated with methanesulfonyl chloride (0.03 mL) in pyridine (1 mL) at 0 °C for 2 h. After dilution with water, the product was extracted with CH_2Cl_2. Usual workup gave a crude sulfonate (36 mg). The sulfonate was then dissolved in a solution of DBU (0.03 mL) in benzene (1.5 mL) and stirred for 2 h at room temperature. After dilution with ether, the mixture was successively washed with dilute HCl, water, and brine and then dried. The residue obtained by evaporation was purified by preparative silica gel TLC using CH_2Cl_2 as the solvent, affording crystals of **30** (11 mg, 35% from **29**). An analytical sample, mp 90.5–92 °C (lit.[3a] 92–92.5 °C), was obtained by recrystallization from pentane, being identified by spectral comparison with natural frullanolide.[19]

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