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STUDIES ON TERPENES—7†

A SHORT ROUTE TO A PENTALENOLACTONE E PRECURSOR

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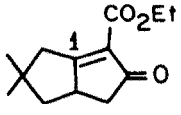
Abstract—The bicyclic enone **6** was converted into the adduct **13** by photochemical addition of allene, and then elaborated through a fragmentation sequence into the α-methylene ketone **17**.

As part of our general interest in the use of photochemical reactions for the synthesis of terpenes,[1] the series of sesquiterpenes pentalenolactone **1**,[2] pentalenolactone H (**2**; X=H, OH), pentalenolactone G (**2**; X = O),[3] pentalenolactone E (**3**),[4] quadrone (**4**),[5] and pentalenic acid **5**[3] has been undertaken. These compounds have common structural features that might enable a general synthetic route to these terpenes to be established. The simpler members of this series, pentalenolactone G, H, pentalenic acid and the bridged derivative quadrone provide interesting targets, and we speculated that in order to design a short route to these cytotoxic sesquiterpenes, pentalenolactone E could be effectively considered a representative of these compounds.

The bicyclo[3.3.0]octenone **6** should provide a versatile synthon since it can be elaborated, in principle, in a number of ways into these sequiterpenes, and what is more, possibly provide simpler versions of these molecules **1–5** with comparable or improved biological properties.

4,4-Dimethylcyclopentenone **7**[6] was subjected to the reductive silylation conditions described by Ojima,[7] namely triethylsilane-rhodium tris(triphenylphosphine)chloride, to give the triethylsilylenol ether **8** in 88% yield after purification by distillation (b.p. 69–70°/0.5 mm Hg).



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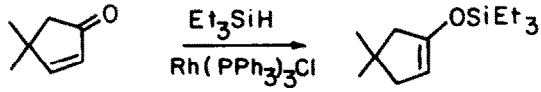

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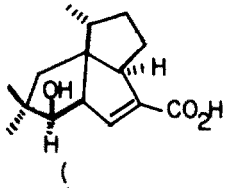
The triethylsilylenol ether **8** was treated with lithium amide in liquid ammonia to generate the lithium enolate which was quenched with the alkylating agent **9**[8] to give



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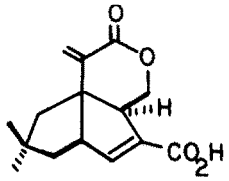

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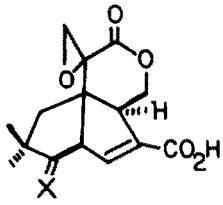
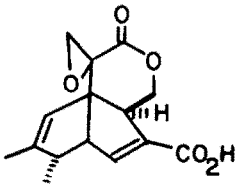


(2; X=H, OH; or X=O)



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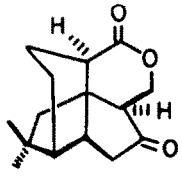

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Scheme A.

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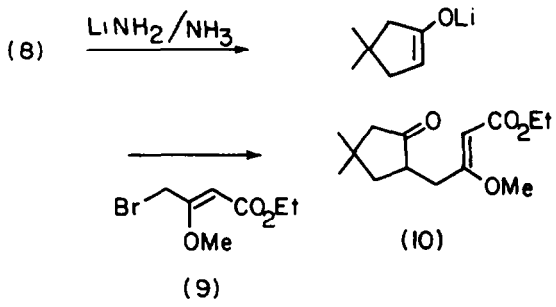
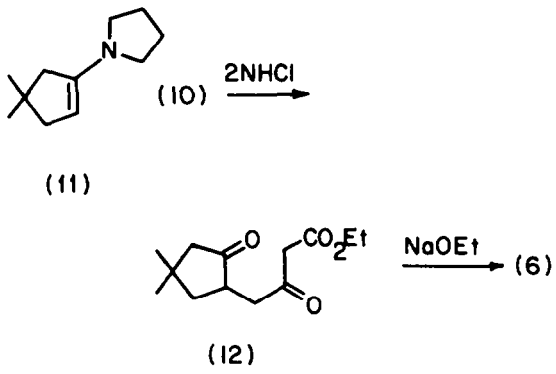
†For Part 6: see A. Gopalan and P. Magnus, *J. Am. Chem. Soc.* **102**, 1756 (1980).

the desired precursor to **6**, namely **10**, in high yield (58% to **12**). This procedure was consistently superior to the alternative (see below), and most importantly gave no problems with enolate exchange, resulting in loss of regiospecificity and diminished yields.



Hydrogenation of **7** over 10% palladium/C in ethyl acetate gave 3,3 - dimethyl - cyclopentanone (81%) which was converted directly into the pyrrolidine enamine **11**. Treatment of this enamine with **9** in dry dioxane heated at reflux for 18 hr gave **10**, which was directly hydrolyzed (2N aqueous HCl is acetone) to give, after chromatography and distillation to remove impurities, the β-keto ester **12** in 34% overall yield. This procedure is not nearly so convenient as the first described method.

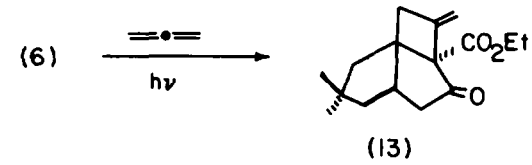
When **12** was treated with sodium ethoxide in ethanol at −25° for 2 hr the required enone **6** was formed in 86% yield, m.p. 73–73.5°. This complete sequence from 4,4-



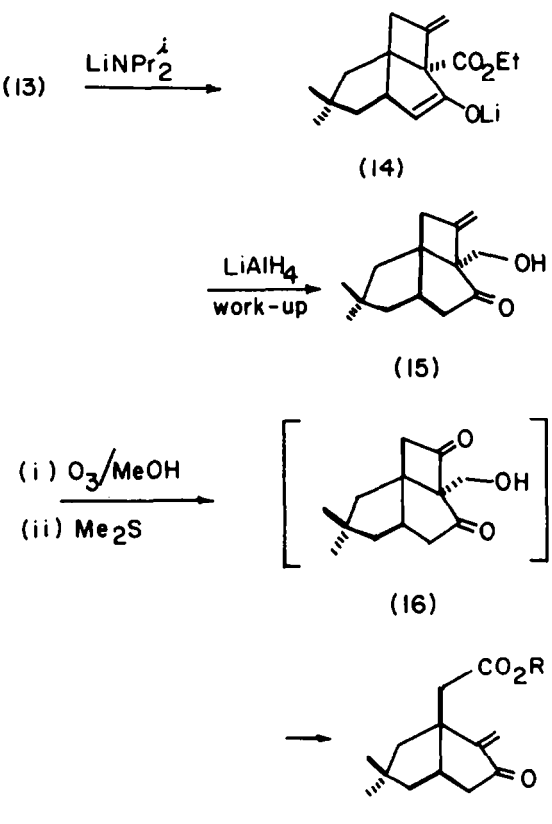
dimethylcyclopentenone **7** to the bicyclo[3.3.0]enone **6** proceeds in 39% overall yield on a multigram scale.

At this stage we required a method for introducing an acetic acid side-chain unit into **6** at the C1 position, and to be able to convert the ester at C-2 into a methylene group (Scheme B), thereby requiring a distinction to be made between the two carboxyl functionalities.

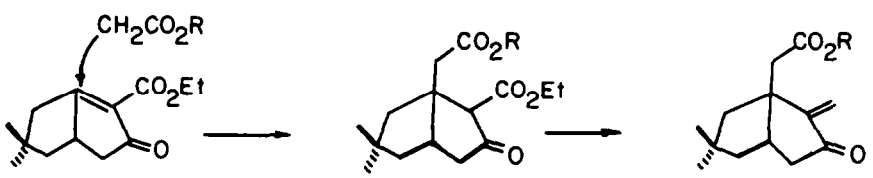
Irradiation (450W Hanova lamp–Pyrex filter) of **6** in hexane–tetrahydrofuran at −80° in the presence of allene for 2 hr, gave after distillation the photo-adduct **13** (83%; b.p. 110°C/0.2 mm Hg). The stereochemical and regiochemical result observed is in keeping with the extensive literature on this photochemical cyclo-addition, most notable being the pioneering work of Wiesner.[9]



The photo-adduct **13** was treated with lithium diisopropylamide in tetrahydrofuran at −25°, and the resulting enolate anion **14** exposed to lithium aluminum hydride. Work-up, by quenching with ethyl acetate to avoid over-reduction to diols gave the keto-alcohol **15**, 77%, b.p. 130°/0.2 mm Hg. To complete the sequence, **15** was exposed to ozone in dichloromethane containing methanol, and the resulting ozonide or hydroperoxy



species reduced with dimethylsulfide to give the intermediate cyclobutanone **16**. In the presence of methanol



Scheme B.

the cyclobutanone is cleaved to give (17; R=Me), 86%, b.p. 120°/0.1 mm Hg. If methanol is excluded in the ozonolysis procedure, and the reaction mixture worked up with water, the acid (17, R=H), 85%, b.p. 180°/0.2 mm Hg is produced. The overall sequence from 7 to (17, R=Me or H) proceeds in 21% yield.

The enone (17, R=H) proved remarkably inert to intramolecular lactonization to give the δ-lactone 18; a result that should be contrasted with seco-quadrone 19[5] which on heating in the absence of solvent (190–195°) gave quadrone 4. Exposure of (17; R=H) to p-toluenesulfonic acid monohydrate in benzene or toluene, heated at reflux, gave only the γ-lactone 20,[5] paralleling Danishefsky's observations made during the synthesis of quadrone. Interestingly, the ester (17; R=Me) on treatment with ammonia gave the δ-lactam 21 in high yield. Presumably 21 arises by conjugate addition of ammonia to the enone followed by reaction (intramolecular) with the ester. All efforts to add water to the enone (17; R=Me) followed by lactonization to give 18 failed.

Since seco-quadrone 19 is presumed to be the intermediate responsible for the biological activity of quadrone[5] (by analogy with α-methylene lactones), we have submitted (17; R=H) for screening, and are examining the conversion of (17; R=Me) into naturally occurring pentalenolactones.

In summary, the route described here provides a very short (6 steps) sequence to an analog of *seco*-quadrone utilizing a key photochemical allene addition, and the fragmentation of a cyclobutanone into an α-methylene ketone.

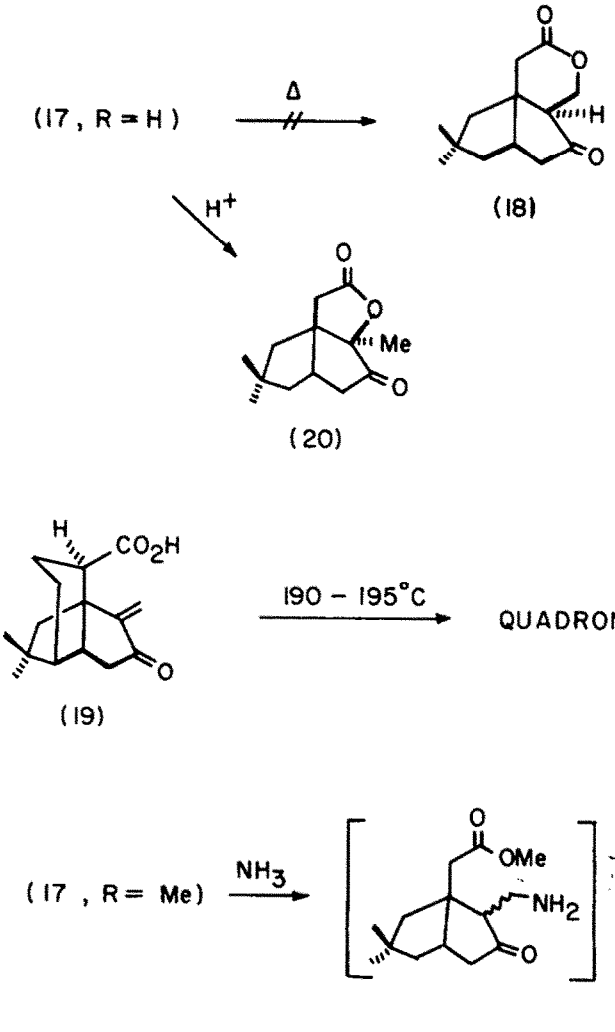
EXPERIMENTAL

4,4 - Dimethyl - 1 - triethylsilyloxycyclopentene (8)

To a solution of 4,4 - dimethylcyclopent - 2 - ene - 1 - one 7[6] (11.0 g, 100 mmol) and triethylsilane (12.0 g, 113 mmol) in dry benzene (100 ml), previously purged with dry argon for 1 hr at 0°, was added rhodium tris(triphenylphosphine)chloride (0.1 g.) and the mixture was stirred (magnetically) at 50° for 2 hr. The mixture was evaporated and the residue distilled to give the silylenol ether 8 (19.8 g; 88%), b.p. 69–70°/0.5 mm Hg ν_{max} (CCl_4) 1643 cm^{-1} NMR (CCl_4) δ0.53 – 1.20 (21H,m), 2.03 (4H, s) and 4.38 (1H, bs). MS. *m/e* 226.176 (calc. for $C_{13}H_{26}OSi$, 226.175).

4,4 - Dimethyl - 2 - (3' - carbethoxy - 2' - methoxyprop - 2' - enyl)cyclopentanone (10)

To a solution of lithium amide [from 140 mg of lithium/trace of $Fe(NO_3)_3$] in dry liquid ammonia (100 ml) at −33° under argon was added dropwise a solution of the silylenol ether 8 (4.2 g) in dry tetrahydrofuran (50 ml). After stirring at −33° for 0.5 hr a solution of ethyl 4 - bromo - 3 - methoxycrotonate 9 (4.56 g) in dry tetrahydrofuran (25 ml) was added, and the reaction mixture was stirred at −33° for 4 hr. Solid NH_4Cl (1.07 g) was added and the ammonia allowed to evaporate. The residue was partitioned



between water (50 ml) and ether (100 ml). The aqueous phase was separated and extracted with ether (2 × 100 ml). The combined extracts were washed with saturated aqueous sodium chloride solution (50 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product **10** (8.6 g). ν_{max} (CCl_4) 1745, 1715 and 1627 cm^{-1}. NMR ($CDCl_3$) δ1.09 (3H, s), 1.20 (3H, s), 1.26 (3H, t J = 7Hz), 1.57 (1H, d j = 11 Hz), 1.77 (1H, d J = 8 Hz), 2.04 (2H, s), 2.45–2.80 (1H, m), 2.97 (2H, q J's = 6.5 and 2.0 Hz), 3.66 (3H, s), 4.06 (2H, q J = 7 Hz), 4.99 (1H, s). MS *m/e* 254.153 (calc. for $C_{14}H_{22}O_4$ 254.152).

The crude product **10** in acetone (50 ml.) was treated with 2N HCl (25 ml) at 50° for 1 hr. After cooling to 25° the mixture was saturated with solid sodium chloride and extracted with ether (3 × 50 ml). The combined extracts were washed with saturated aqueous sodium chloride solution (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over silica gel (25.3 cm column) eluting with 33% ethyl acetate in light petroleum to give the β-keto ester (3.1 g; 70%). Distillation gave the pure adduct **12** (2.6 g; 58%).

3,3 - *Dimethylcyclopentanone*

4,4 - Dimethylcyclopentenone **7** (14.06 g) in ethyl acetate (80 ml) was hydrogenated over 10% palladium on carbon (0.7 g) at 25° until complete by glc (5% FFAP). After filtration the mixture was evaporated at atmospheric pressure and the residue distilled to give 3,3 - dimethylcyclopentanone (11.55 g; 81%), b.p. 153–155°/760 mm Hg.

4,4 - *Dimethyl* - 1 - *pyrrolidinocyclopentene* (**11**)

3,3-Dimethylcyclopentanone (11.5 g) in dry benzene (150 ml) containing pyrrolidine (15 g) and ρ-toluenesulfonic acid monohydrate (10 mg) was heated under reflux with provision (Dean and Stark apparatus) for the removal of water. After 18 hr the mixture was concentrated by evaporation of benzene (ca. 120 ml.) and the residue further concentrated to a dark red oil **11** under vacuum. Purification of **11** was not attempted, it was used directly in the next stage.

4,4 - *Dimethyl* - 2 - (3' - *carboethoxy* - 2' - *oxo* - *propyl*) - *cyclopentanone* (**12**)

To the above crude enamine **11** in freshly dried dioxane (100 ml) was added ethyl 4 - bromo - 3 - methoxycrotonate **9** (16.0 g) and the mixture stirred at room temp. for 4 hr under argon. The mixture was heated at reflux for 18 hr cooled, and acetic acid (20 ml) and water (80 ml) added. After stirring this mixture for 1 h at 25°C, ether (350 ml) was added and the solution washed with water (50 ml), saturated aqueous sodium hydrogen carbonate (50 ml) and again with water (50 ml). The organic phase was dried ($MgSO_4$) and concentrated to give a brown oil (15.0 g) which was dissolved in acetone (200 ml) and 2N hydrochloric acid (50 ml) added. The resulting mixture was stirred for 1 hr at 50°. The mixture was evaporated and the residue dissolved in ether (300 ml), washed with water (40 ml), saturated $NaHCO_3$ (40 ml) and water (40 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give a brown oil (10 g). This oil was chromatographed over silica gel (400 g), eluting with 20% ethyl acetate in light petroleum ether to remove impurities, followed by 40% ethyl acetate in light petroleum ether to give the β-keto ester **12** (5.75 g; 34%) b.p. 145–155°/0.4 mm Hg. NMR ($CDCl_3$) δ1.08 (3H, s), 1.17 (3H, s), 1.23 (3H, t J = 7.0 Hz), 2.13 (2H, s), 2.10–2.40 (2H, m), 2.6–3.1 (3H, m), 3.45 (2H, s), 4.17 (2H, q J = 7.0 Hz). ν_{max} (CCl_4) 1720 and 1740 cm^{-1}. MS: *m/e* 240.137 (calc. for $C_{13}H_{20}O_4$: 240.136).

2 - *Ethoxycarbonyl* - 7,7 - *dimethylbicyclo*[3.3.0]*oct* - 1 - *en* - 3 - *one* (**6**)

To a solution of sodium ethoxide (from 140 mg of sodium) in dry ethanol (10 ml) at −25° was added dropwise over 30 min, a solution of **12** (1.22 g) in dry ethanol (20 ml). The mixture was stirred at −25 for 2 hr and warmed to 20° over 30 min. Solid NH_4Cl (1.3 g) was added to the above mixture, and the mixture evaporated *in vacuo*. The residue was dissolved in ether (120 ml) and washed with saturated NaCl (3 × 20 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. Distillation of the residue gave the bicyclic enone **6** (976 mg. 86%) b.p. 140–150/0.2 mm Hg; m.p. 73–73.5° (from petroleum ether). ν_{max} ($CHCl_3$) 1710, 1740, 1620 cm^{-1}. NMR ($CDCl_3$) δ1.20 (3H, s), 1.24 (3H, s), 1.30 (3H, t J = 7.0 Hz), 1.8–3.3 (7H, m), 4.15 (2H, q J = 7.0 Hz). Found; C, 69.95; H, 8.13: $C_{13}H_{18}O_3$ requires C, 70.25; H, 8.17% MS: *m/e* 222.126 (calc. for $C_{13}H_{18}O_3$; 222.126).

Photo-adduct **13**

A solution of **6** (2.00 g. 9 mmol) in dry olefin-free hexane (250 ml) and tetrahydrofuran (10 ml) was cooled to −80°C and purged with nitrogen for 1 hr. Allene (10 g, 25 equiv) was distilled into the reaction mixture and the solution irradiated (450 W Hanova lamp–Pyrex filter) for 2 hr with N_2 passing through the solution. Evaporation of the solvent in vacuo and bulb to bulb distillation gave the photo-adduct **13** (1.95 g. 83%) b.p. 110°/0.2 mm Hg. NMR ($CDCl_3$) δ1.01 (3H, s), 1.07 (3H, s), 1.27 (3H, t J = 7.0 Hz), 1.20–3.20 (9H, m), 4.15 (2H, q J = 7.0 Hz), 4.97 and 5.16 (2H, m). ν_{max} ($CHCl_3$) 1720 and 1680 cm^{-1}. MS: *m/e* 262.158 (calc. for $C_{16}H_{22}O_3$: 262.157).

Reduction of the photo-adduct (**13**)

To a solution of lithium diisopropylamide (prepared from diisopropylamine 413 mg. and 1.5 M soln of n-butyllithium 2.7 ml) in dry tetrahydrofuran (10 ml) at −25° was added dropwise under argon to a solution of **13** (715 mg.) in dry tetrahydrofuran (2 ml). The mixture was stirred at −25° for 0.5 hr and lithium aluminum hydride (207 mg) was added. The resulting suspension was stirred at −25° for 1 hr. Ethyl acetate (2 ml) was added to quench the excess reducing agent and the reaction mixture warmed to room temperature over 1 hr. Aqueous ammonium chloride solution was added and the mixture partitioned between ether (50 ml) and water (10 ml). The organic phase was washed with saturated NaCl solution (5 ml), dried ($MgSO_4$), and evaporated *in vacuo*. Distillation of the residue gave **15** (465 mg; 77%), b.p. 130°/0.2 mm Hg. NMR ($CDCl_3$) δ1.01 (3H, s), 1.05(3H, s), 1.20–3.10(10H, m), 3.74(2H, ABq, J's = 12 and 16 Hz), 4.83(2H, m). ν_{max} ($CHCl_3$) 3450 and 1725 cm^{-1}. MS: *m/e* 220.147 (calc. for $C_{14}H_{20}O_2$. 220.146).

7,7 - *Dimethyl* - 1 - (*carbomethoxymethyl*) - 2 - *methylene-bicyclo*[3.3.0]*octan* - 3 - *one* (**17**, *R=Me*)

A solution of freshly purified **15** (62.4 mg; 0.28 mmol) in dry dichloromethane (5 ml) containing methanol (0.5 ml) at −78° was treated with ozone/oxygen until the solution turned pale blue. The resulting solution was purged with oxygen for 15 min to remove excess ozone, and dimethylsulfide (1 ml) added. After warming the reaction mixture to 25°, ether (40 ml) was added and the solution washed with water (4 × 10 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by bulb to bulb distillation to give (**17**, R=Me) (57.5 mg. 86%), b.p. 120°C/0.1 mg Hg. NMR ($CDCl_3$) δ0.98(3H, s), 1.05(3H, s), 1.50–2.80(7H, m), 2.53(2H, s), 3.57(3H, s), 5.20(1H, s) 5.95(1H, s), ν_{max} ($CHCl_3$) 1740, 1725 and 1630 cm^{-1}. MS: *m/e* 236.142 (calc. for $C_{14}H_{20}O_3$. 236.141).

7,7 - *Dimethyl* - 1 - (*carboxymethyl*) - 2 - *methylenebicyclo*[3.3.0]*oct* - 3 - *one* (**17**, *R=H*)

The substrate **15** (400 mg) in dry dichloromethane (15 ml) at −78° was ozonized as above, and worked up as above. Distillation gave (**17**; R=H) (344 mg. 85%), bp 180°/0.2 mm Hg. NMR ($CDCl_3$) δ0.98(3H, s), 1.07(3H, s), 1.50–290(7H, m), 2.66(2H, s), 5.36(1H, s), 6.10(1H, s), 8.30(1H, bs). ν_{max} (CCl_4) 3000–3500(b), 1720 and 1630 cm^{-1}. MS: *m/e* 222.125 (calc. for $C_{13}H_{18}O_3$: 222.126).

Lactone **20**

The enone (**17**, R=H) (19.4 mg) ρ-toluenesulfonic acid (1.2 mg) in benzene (2 ml) was heated at reflux for 18 hr. The mixture was evaporated and the residue purified by thick layer chromatography on alumina, followed by bulb to bulb distillation to give **20** (15.0 mg. 78%), b.p. 120°C/0.2 mm Hg. ν_{max} (CCl_4) 1795 and 1758 cm^{-1}. NMR ($CDCl_3$) 1.04(6H, s), 1.33(3H, s), 1.57(2H, s), 1.70–2.20(3H, m), 2.20–2.75(1H, m), 2.81(2H, s), 2.85, 3.10(1H, m). MS: *m/e* 222.125 (calc. for $C_{13}H_{18}O_3$. 222.126).

Amide (21)

The enone (17, R=Me) (99.3 mg) in methanol (2 ml) and ammonia (1 ml) was stirred at −33° for 1 hr. Evaporation of the mixture and crystallization of the residue from ethyl acetate gave the amide (21) (58.2 mg. 64%), m.p. 140–142°. ν_{max} 1735 and 1670 cm^{-1}. NMR ($CDCl_3$) δ1.10(6H, s), 1.2–2.7 (6H, m), 1.8(2H, s), 2.4(2H, s), 3.3–3.5(2H, m), 7.0(1H, bs). MS: *m/e* 221.141 (calc. for $C_{13}H_{19}NO_2$: 221.142).

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