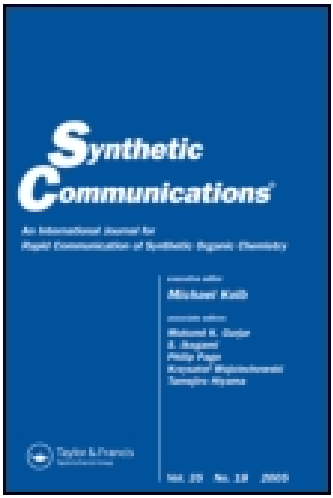

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A Convenient Synthesis of 2,2,4-Trimethylcyclohexane-1,3-Dione: A Useful Precursor for The Taxoid a Ring

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A CONVENIENT SYNTHESIS OF 2,2,4-TRIMETHYLCYCLOHEXANE-1,3-DIONE: A USEFUL PRECURSOR FOR THE TAXOID A RING

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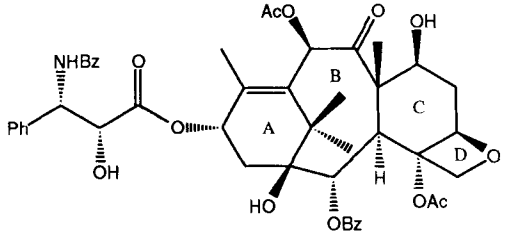
Abstract: A simple and inexpensive route to the title compound is described which should be readily amenable to large scale synthesis. Thus, reaction of 3-pentanone with methyl acrylate in the presence of sodium methoxide provided 2,4-dimethylcyclohexane-1,3-dione. Methylation with iodomethane gave the title compound in 63% overall yield.

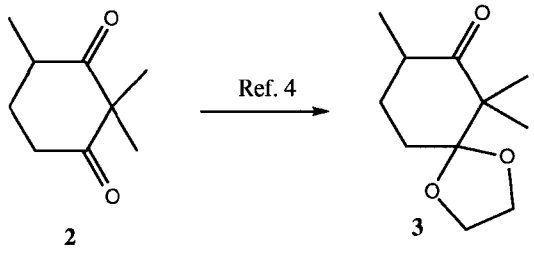
Taxol (**1**), a naturally occurring tetracyclic diterpenoid isolated from the pacific yew tree, has emerged as a very promising antitumor agent. [1] Its complex structure, natural scarcity, and unique mode of action (inhibition of cell growth by accelerating the polymerization of tublin and inhibiting the required depolymerization) has resulted in a tremendous amount of interest in the synthesis of this natural product [2] and its structurally related derivatives. [3]



1: Taxol (Paclitaxel)

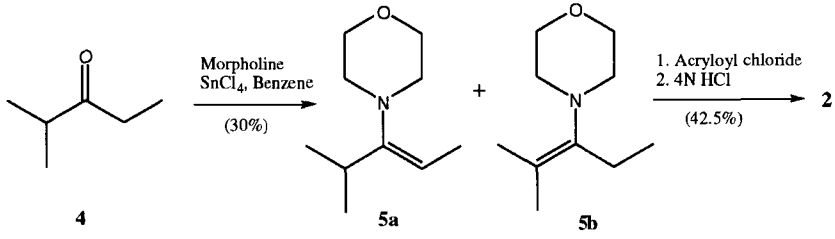
*To whome correspondence should be addressed

2,2,4-Trimethylcyclohexane-1,3-dione (**2**) is an important intermediate for the construction of the A-ring of the taxoid skeleton. It is typically converted to the monoacetal (**3**) [4] before further transformation into the taxoid system. [5]



Scheme 1

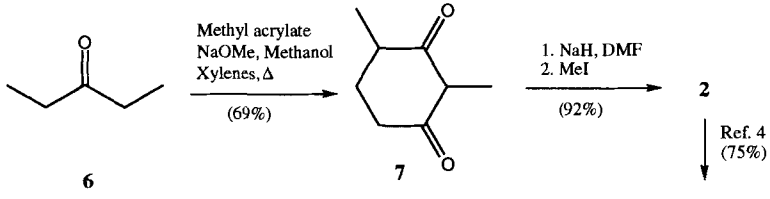
All references for the synthesis of dione **2** lead to the work reported by Hargreaves et al. [6] This involves the reaction of, the expensive, 2-methyl-3-pentanone (**4**) with morpholine in the presence of tin(IV)chloride to give, after distillation, a 3:7 mixture of the enamines **5a** and **5b** respectively in 30% yield. This mixture is then treated with acryloyl chloride in dry benzene to give 2,2,4-trimethyl-3-morpholinocyclohex-3-enone which is hydrolyzed with 4N-hydrochloric acid to give **2** in 42.5% yield after distillation (13% yield from 2-methyl-3-pentanone). This is an inefficient and rather expensive way to make large quantities of this useful intermediate.



Scheme 2: Preparation of **2** by the procedure of Hargreaves et al. (ref. 6)

In this paper we report a simple and inexpensive two step procedure to **2**. Thus, 3-pentanone (**6**) was treated with methyl acrylate in the presence of sodium methoxide in xylenes in a manner similar to that reported by Baumann and

Hoffmann [7] to give 2,4-dimethylcyclohexane-1,3-dione (**7**) [8] in 69% yield. Further purification of this intermediate was unnecessary. The dione (**7**) was treated with one equivalent of sodium hydride in DMF followed by the addition of iodomethane to give the desired intermediate (**2**) in 92% yield. The material obtained from this procedure may be used without further purification. For example, reaction with ethylene glycol, triethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid gave the acetal (**3**) in 75% yield as reported by Detering and Martin. [4]



Scheme 3

In conclusion, we report the synthesis of **2** in 63% overall yield using cheap starting materials. The reactions are simple, the products do not require further purification, and should be easy to scale up.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Varian VXR-300 spectrometer. Chemical shifts are reported in ppm downfield from internal standard TMS.

2,4-Dimethylcyclohexane-1,3-dione (7). [8] To a freshly prepared solution of sodium methoxide, obtained from anhydrous methanol (100 mL) and sodium (11.75 g, 0.511 mol), was added anhydrous xylenes (250 mL). To this vigorously stirred mixture, maintained at 35 °C was added dropwise a mixture of 3-pentanone (46.9 mL, 0.4644 mol) and methyl acrylate (41.82 mL, 0.4644 mol) under nitrogen. The addition funnel was replaced with a distillation head fitted with a cold finger condenser apparatus. The mixture was heated at 120 °C (sand

bath temperature) until all the methanol was removed by distillation (1-2 h). After cooling to room temperature, the yellow-orange solid was collected by filtration at the pump and washed with hexane (2 X 100 mL). The solid was dissolved in water (150 mL) and acidified to pH 2 with conc. hydrochloric acid. The mixture was extracted with methylene chloride (4 X 100 mL). The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, and the solvent was removed in vacuo. The residue was triturated with hexane, and the colorless solid was filtered at the pump and dried in vacou (45.3 g, 69%), mp 114-117 °C (lit. [6] mp 117-118 °C). The ^{1}H nmr data was similar to that reported by Piers et al. [8(c)] This material was used without further purification.

2,2,4-Trimethylcyclohexane-1,3-dione (2). [6] Sodium hydride (60% dispersion in oil; 6.864 g, 0.172 mol) was washed with hexane, which was decanted to remove the oil. Anhydrous DMF (50 mL) was added, followed by the dropwise addition of 2,4-dimethylcyclohexane-1,3-dione (20 g, 0.143 mol) in DMF (100 mL). The reaction mixture was heated for 0.5 h in a sand bath at 50 °C, and then cooled to 20 °C, and iodomethane (9.79 mL, 0.157 mol) was added dropwise. The mixture was reheated to 50 °C for 2.5 h and cooled to 20 °C. Water (150 mL) was added and the mixture was extracted with ethyl acetate (4 X 100 mL). The organic layers were combined and washed with water (2 X 100 mL), dried over anhydrous magnesium sulfate, filtered, and the solvent and residual DMF were removed in vacou to give a colorless oil (21.83 g, 92%). Further purification of this material was unnecessary. Bp 79-80 °C/3 mm Hg; ^{1}H NMR ($CDCl_3$) δ 1.16 (d, 3H, J = 6.55 Hz), 1.23 (s, 3H), 1.38 (s, 3H), 1.49 (dq, 1H, J = 4.92, 13.38 Hz), 2.13 (m, 1H), 2.62 (m, 1H), 2.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.71, 18.95, 25.86, 26.33, 37.07, 40.70, 61.00, 210.79, 211.40.

References and Notes

1. Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.*, **1971**, *93*, 2325. Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M., Eds.; ACS Symposium Series 583, "Taxane Anticancer Agents: Basic Science and Current Status," American Chemical Society, Washington D.C., 1995. Suffness, M., Ed.; "Taxol: Science and Applications," CRC Press, New York, 1995. Guenard, D.; Gueritte-

Voegelein, F.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160, and references cited therein.

2. For total syntheses of taxol: (a) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630. (b) Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599. (c) Masters, J. J.; Link, J. T.; Synder, L. B.; Young, W. B.; Danishefsky, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1723. (d) Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. *J. Am. Chem. Soc.* **1997**, *119*, 2757.

3. For reviews on synthetic approaches to taxol systems: (a) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15. (b) Boa, A. N.; Jenkins, P. R.; Nawrence, N. J. *Contemp. Org. Synth.* **1994**, *1*, 47. (c) Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. *Prog. Chem. Org. Nat. Prod.* **1993**, *61*, 1. (d) Swindell, C. S. Stud. *Nat. Prod. Chem.* **1993**, *12*, 179. (e) Paquette, L. A. Stud. *Nat. Prod. Chem.* **1992**, *11*, 3. (f) Kingston, D. G. I. *Pharmac. Ther.* **1991**, *52*, 1. (f) Swindell, C. S. *Org. Prep. Proced. Int.* **1991**, *23*, 465.

4. Detering, J.; Martin, H.-D. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 695.

5. (a) Queneau, Y.; Krol, W. J.; Bornmann, W. G.; Danishefsky, J. *J. Org. Chem.* **1992**, *57*, 4043. (b) De Grandi, M. J.; Jung, D. K.; Krol, W. J.; Danishefksy, S. J. *J. Org. Chem.* **1993**, *58*, 4989. (c) Young, W. B.; Masters, J. J.; Danishefsky, S. *J. Am. Chem. Soc.* **1995**, *117*, 5228. (d) Masters, J. J.; Jung, D. K.; Danishefsky, S. J.; Synder, L. B.; Park, T. K.; Isaacs, R. C. A.; Alaimo, C. A.; Young, W. B. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 452. (e) Montalbetti, C.; Savignac, M.; Bonnefis, F.; Genet, J. P. *Tetrahedron Letts.* **1995**, *36*, 5891. (f) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Synder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843. (g) Swindell, C. S.; Fan, W. *Tetrahedron Letts.* **1996**, *37*, 2321. (h) Swindell, C. S.;

Chander, M. C.; Heerding, J. M.; Klimko, P. G.; Rahman, L. T.; Raman, J. V.; Venkataraman, H. *J. Org. Chem.* **1996**, *61*, 1101. (i) Swindell, C. S.; Fan, W. *J. Org. Chem.* **1996**, *61*, 1109. (j) Delaloge, F.; Prunet, J.; Pancrazi, A.; Lallemand, J-Y. *Tetrahedron Letts.* **1997**, *38*, 237.

6. Hargreaves, J. R.; Hickmott, P. W.; Hopkins, B. J. *J. Chem. Soc. (C)* **1968**, 2599.

7. Baumann, M.; Hoffmann, W. *Ger. Offen.* DE 3,112,056; *Chem. Abstr.* **1983**, *98*: 34307u.

8. For other methods to **7**: (a) Via reaction of 3-morpholinopent-2-ene with acryloyl chloride see ref. 6. (b) Methylation of enolate derived from 2-methyl-3-(1-pyrrolidyl)-2-cyclohexen-1-one: Telschow, J. E,; Reusch, W. *J. Org. Chem.* **1975**, **40**, 862. (c) Methylation of 3-*iso*-butoxy-2-methyl-2-cyclohexene-1-one: Piers, E.; Grierson, J. R.; Lau, C. K.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 210; Muskopf, J. W.; Coates, R. M. *J. Org. Chem.* **1985**, *50*, 69. (d) Via cyclization: Vakulova, L. A.; Fokina, L. N.; Mishchenko, V. V.; Filippova, T. M.; Dzhiembaev, B. Zh.; Starostina, A. K.; Yakovieva, I. M.; Samokhvalov, G. I. *Zhurnal Obshchei Khimii* **1975**, *45*, 2499; Schaafsma, S. E.; Claassens, J. E. L.; Verheijen, E. J. M. *Ger. Offen.* **1974**, 2,412,313; *Chem. Abstr.* **1975**, 82, 3861k; Mueller, W. H.; Hey, H.; Meidert, H. *Ger. Offen.* **1976**, 2,448,677; *Chem. Abstr.* **1976**, *85*, 32524v.

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