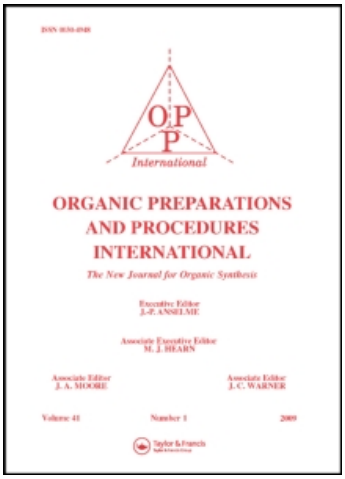

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2,2-DIMETHYL-6-[(TRIPHENYLPHOSPHORANYLIDENE)METHYL]-4H-1,3-DIOXIN-4-ONE. A FOUR-CARBON HOMOLOGATING AGENT REQUIRING NO ACTIVATION

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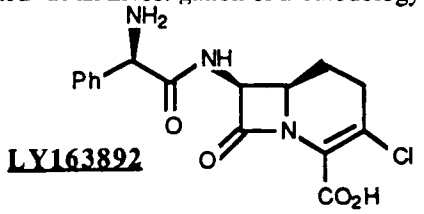
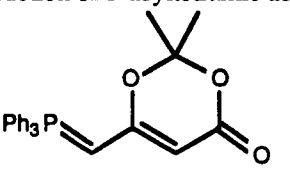
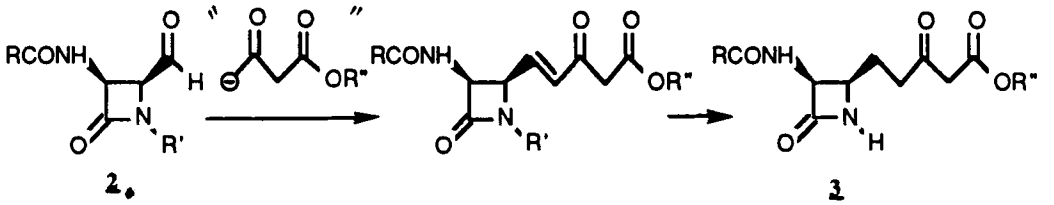
In connection with the development of a refined synthesis of antibiotic LY163892,[1] we required substantial amounts of compound 1 for the conversion of β-lactam 2 into 3. Phosphorane 1 is doubly attractive as it needs no activation with base to undergo the coupling reaction and the β-keto ester group is masked as a dioxinone system. Although 1 has been reported[2] in an investigation of methodology for the construction of 3-acyltetramic acids, a detail



LY163892



synthesis has not appeared in the literature. We would like to report a simple, large-scale synthesis of this versatile reagent.

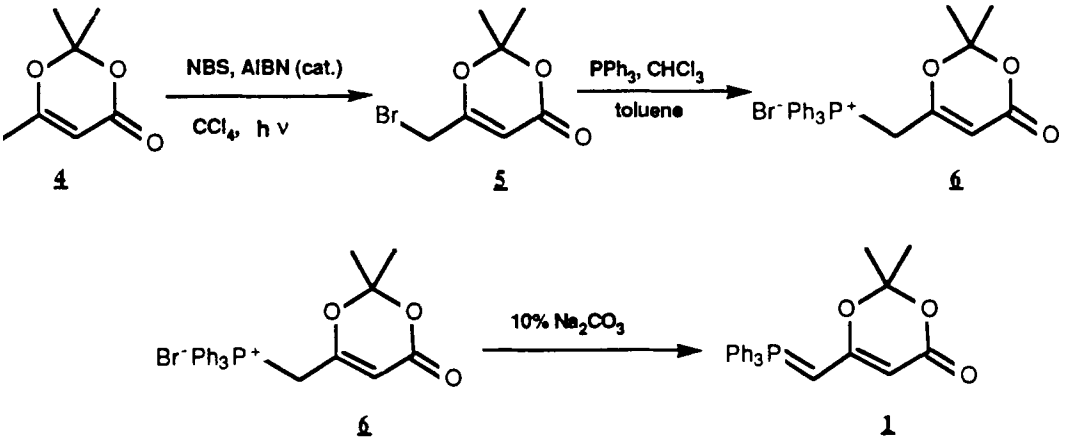


2 3

The sequence used to prepare compound 1 is shown below. The final product (1) is obtained pure in three steps with no formal isolations.

The starting material, 2,3,6-trimethyl-3-dioxen-4-one (4), may be purchased or prepared by combining acetone and diketene in the presence of a catalytic amount of p-toluenesulfonic acid and distilling the product.[3] The photochemical bromination[2] reaction was optimally efficient when run to 75% conversion of 4 to 5. Longer reaction times resulted in the formation of the dibromo (7,7') analog of 5 and severe degradation. Accordingly, a mixture of 5 and 4 (typically 75:25 as determined by 300 MHz ^{1}H-NMR) was carried into the phosphonium salt reaction. Since 4 does not react with triphenylphosphine, the phosphonium salt 6 could be isolated by simple filtration of the reaction mixture. The phosphonium salt was dissolved in water, added to a 10% aqueous solution of sodium carbonate and the final product collected by filtration. After

thorough drying, the product was found to have co-crystallized with one equivalent of water, affording the monohydrate of 1. The water did not appear to interfere with the subsequent Wittig reaction. This sequence was performed several times on a 0.3 mole scale beginning with bromination in a 1-liter photochemical apparatus. On this scale, one obtains 77 g of the pure phosphonium salt 6 (53% yield from dioxinone 4) which is converted in 92% yield to the phosphorane 1 (59 g), thus 1 is obtained in three steps in an overall yield of 49% from 4.



EXPERIMENTAL SECTION

Melting points were determined in open glass capillaries on a Thomas Hoover melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a General Electric QE 300 Spectrometer. IR spectra were obtained on a Nicolet DX-10 F. T. I. R. Spectrophotometer. Mass spectra were taken on a Varian-MAT model 731 mass spectrometer. Elemental analyses were determined by the Physical Chemistry Department of the Lilly Research Laboratories on a Perkin-Elmer Elemental Analyzer 240. The photochemical operations were performed in a 1-liter Ace Glass Photochemical reaction vessel (supermixing, complete with immersion well) using a quartz glass sleeve as filter. A Hanovia 200-watt immersion lamp was used as the photochemical source and it was powered by an Ace-Glass 7830-32 power supply.

4-Triphenyphosphonium-2,2,6-trimethyl-4H-1,3-dioxin-4-one Bromide (6).- To a 1000 mL photochemical apparatus was added 2,2,6-trimethyl-4H-1,3-dioxin-4-one (4, 44.8 g, 41.4 ml, 0.3 mol), N-bromosuccinimide (64.1 g, 0.36 mol), 2,2'-azobis(2-methylpropionitrile) (0.2 g, 0.001 mol), and carbon tetrachloride (0.7 L). The mixture was exposed to the light source with stirring and heating for 4 hrs. The internal temperature was held at 79°. The reaction mixture was cooled and the solids filtered and washed with cold carbon tetrachloride. The filtrate (composed of a ca. 75:25 mixture of bromide 5 and starting material 4 as determined by integration of the proton on C-5 in the 300 MHz ^{1}H-NMR) was concentrated to 50% of its original volume and treated with carbon. The carbon was filtered and the remainder of the solvent removed. The resulting oil was redissolved in 284 mL of a 1:1 mixture of chloroform and toluene. Triphenylphosphine (78.6 g, 0.3 mol in 284 mL of a 1:1 mixture of chloroform

and toluene) was added over 45 min and the reaction stirred at room temperature for 16 hrs. The solid was collected and the filter cake washed with a 1:1 solution of chloroform and toluene. The material was dried in vacuo at 40° for 18 hrs to give 77.0 g (53%) of phosphonium salt 6 as colorless crystals, mp. 169-171°. ^{1}H NMR (DMSO-d_6): δ 1.3 (s, 6H), 5.4 (d, J = 16.8 Hz, 2H), 5.8 (m, 1H), 7.7-8.0 (m, 15H). MS (FD): 404 (M-79). IR (mull): 2900 (s), 2850 (s), 1730 (m), 1635 (w), 1450 (m), 1370 (m), 1100 (w) cm^{-1}.

Anal. Calcd. for $C_{25}H_{24}BrO_3P$: C, 62.12; H, 5.01; Br, 16.53; O, 9.93

Found: C, 62.34; H, 5.28; Br, 16.33; O, 9.85

2,2-Dimethyl-6-[(triphenylphosphoranylidene)methyl]-4H-1,3-dioxin-4-one (1).- The phosphonium salt 6 (77.0 g, 0.16 mol) was dissolved in water (3.2 L) with gentle warming (40°), filtered and the resulting solution added in a slow stream over 25 min to an aqueous solution of sodium carbonate (10.1 g in 100 mL of water). The resulting slurry was stirred at 25° for 3 hrs. The solid was collected, washed with water and dried for 18 hrs at 45° to afford 59 g (92%) of 1 as colorless needles, mp. 142-144°. ^{1}H NMR (DMSO-d_6): δ 1.0 (s, 6H), 3.4 (d, J = 20 Hz, 1H), 4.4 (s, 1H), 7.5-7.9 (m, 15H). MS (FD): 402 (M^+). IR (KBr): 1650 (s), 1540 (s), 1430 (m), 1350 (m), 1258 (m) cm^{-1}.

Anal. Calcd. for $C_{25}H_{23}O_3P \cdot H_2O$: C, 71.41; H, 5.99. Found: C, 71.23; H, 5.94

REFERENCES

1. C. C. Bodurow and M. A. Carr, Tetrahedron Lett., 30, 4081 (1989); C. C. Bodurow et al., ibid., 30, 2321 (1989).

2. R. K. Boeckman, Jr. and A. J. Thomas, J. Org. Chem., 47, 2823 (1982).

3. M. F. Carroll and A. R. Bader, J. Am. Chem. Soc., 75, 5400 (1953); 74, 6305 (1952).

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