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A KEY INTERMEDIATE FOR THE SYNTHESIS OF MAYTANSINE AND RELATED ANTITUMOR AGENTS

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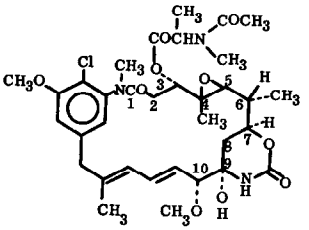
The dienal 1 is a strategic intermediate for the synthesis of antitumor agents in the maytansine[1,2] series by a variety of approaches, and has, in fact, been applied in these laboratories to the first successful synthesis of one of the members of this family. We describe herein an effective route to 1 which allows the preparation of this crucial substance simply and with complete stereochemical control.



Maytansine

Reaction of either the amide-ester 2 or the amino ester 3[3] in tetrahydrofuran (THF) (ca. 7 ml/g ester) with an excess of a 0.9 M solution of lithium aluminum hydride (Ventron Corp.) at 0-5° for 30 min and 45 hr at 23° afforded after standard workup and distillation 88% yield of the amine 4 (bp 145-150° at 0.1 mm).[4] Reaction of the amino alcohol 4 in acetone (15 ml/g of 4) with 4 equiv of methyl chloroformate and 6 equiv of anhydrous potassium carbonate at reflux for 12 hr, and subsequent isolation and treatment of the crude product with 4% methanolic sodium hydroxide at 25° for 2 hr afforded upon workup the urethane 5 (90%). From this intermediate the iodide 6, mp 92°, was obtained in 94% yield by reaction with 1.35 equiv of methanesulfonyl chloride and 1.5 equiv of triethylamine in THF (at -78° then at -25° for 30 min) and treatment of the resulting mesylate (without isolation) with sodium iodide (2 equiv) in DME (28 ml/g of NaI) at -25° for 15 min and 23° for 2.5 hr, with the usual isolation. The iodide 6 was transformed efficiently and selectively into the E-trisubstituted olefinic derivative 7 through a cross coupling reaction[5] with a specially designed mixed[6] Gilman reagent (cuprate) which was obtained as follows.

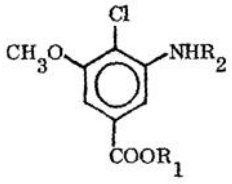
Addition of erythro-2,3-dibromobutane-1-ol (mp 36°, bp 119° at 18 mm, prepared from trans crotyl alcohol and bromine in CCl_4 at -10 to -20°) in THF (8 ml/g) to 2.3 equiv of lithium diisopropylamide and 0.5 equiv of hexamethylphosphoric amide (HMPA) in THF (15 ml/g of dibromide) at -78° over a 1.3 hr period and additional stirring at that temperature for 2 hr produced after addition of water, extraction and

distillation E-3-bromo-2-buten-1-ol,[7] 10, (ca. 50%, bp 92-93° at 16 mm). Reaction of the alcohol 10 in THF (5 ml/g of 10) at 0° with a small excess of dihydropyran and p-toluenesulfonic acid (0.4 mg/g of 10) for 3 hr cleanly afforded the tetrahydropyranyl (THP) derivative 11 (89%, bp 105° at 2 mm). The bromo THP derivative 11 was converted to the mixed Gilman reagent 12 by treatment in THF (dry, under argon, 10 ml/g of 12) first with 1 equiv of n-butyllithium at -105° for 0.5 hr (liquid nitrogen pentane bath) and subsequent reaction with a THF solution of 1 equiv of the cuprous acetylide 13 at -78° for 15 min. The acetylide 13 was formed in THF solution at 0° by reaction of 3-methoxy-2-methyl-1-butyne[8] with 1 equiv of n-butyllithium and then 1 equiv of cuprous iodide. A solution of the benzylic iodide 6 (ca. 20% in dry THF) was added to a solution of the mixed Gilman reagent 12 in THF at -78° with stirring under argon. After 30 min at -78° and 4 hr at -25° the coupling product 7 was isolated by quenching with aqueous ammonium chloride and extraction with ether. The yield of 7 after chromatographic purification on silica gel was 90%.

The mixed Gilman reagent 12 is superior to various other mixed reagents (e.g., the n-pentynyl mixed cuprate[6]) in this application because of its high solubility which allows the whole process to be conducted under homogeneous conditions in THF solution and leads to considerably higher yield of coupling product. The utility of other mixed Gilman reagents derived from 13 will be discussed elsewhere.[9]

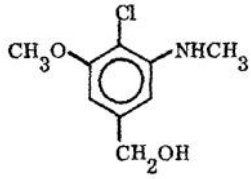
The tetrahydropyranyl group in 7 was cleaved using p-toluenesulfonic acid (3 mg/g of 7) in methanol (ca. 50 ml/g of 7) at 23° for 12 hr to afford the corresponding alcohol 8 (93%), mp 86-87°. Oxidation of 8 with active manganese dioxide in methylene chloride with vigorous stirring at 0° produced the corresponding aldehyde 9 (97%) which could be utilized directly in the next step without purification after drying azeotropically with toluene under reduced pressure. The elaboration of the enal 9 to the dienal 1 was carried out using recently described[10] methodology which was developed specifically for use in maytansine synthesis. The α-trimethylsilyl derivative of acetaldehyde N-t-butylimine[10] was converted to the α-lithio derivative by reaction with sec-butyllithium in dry ether under argon at -78° (30 min) and then allowed to react with the aldehyde 9 at -78° for 1 hr. After quenching with a 1:1 mixture of acetic acid-sodium acetate (1 M aqueous solution) the mixture was allowed to warm to 23° and kept at that temperature for 3 hr after the addition of sufficient acetone to effect homogeneity. The product was isolated by vacuum concentration (to remove a large part of acetone and ether), dilution with saturated sodium chloride solution and extraction with ether. Purification by chromatography on silica gel (ether-pentane for elution) afforded the pure dienal 1 in 80% yield.[11]

The utilization of intermediate 1 in the synthesis of maytansines will be described in due course.[12]



2, $R_1 = CH_3$, $R_2 = CHO$

3, $R_1 = C_2H_5$, $R_2 = CH_3$



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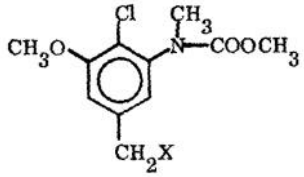
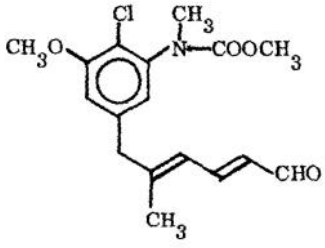


5, X=OH

6, X=I



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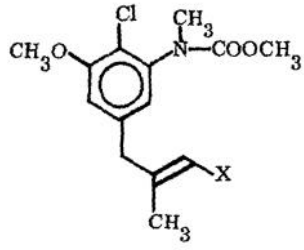
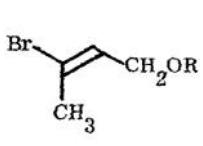


7, $X = CH_2OTHP$

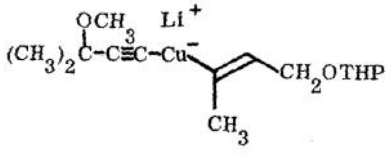
8, $X = CH_2OH$

9, X=CHO



10, R=H

11, R=THP



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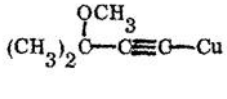

13

References and Notes

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3. E. J. Corey, H. F. Wetter, A. P. Kozikowski and A. V. Rama Rao, Tetrahedron Lett., 777 (1977); see also J. E. Foy and B. Ganem, ibid., 775 (1977) and J. M. Kane and A. I. Meyers, ibid., 771 (1977).
4. Satisfactory infrared, proton magnetic resonance and mass spectra were obtained for chromatographically homogeneous samples of each intermediate.
5. E. J. Corey and G. H. Posner, J. Am. Chem. Soc., 89, 3911 (1967); 90, 5615 (1968); G. H. Posner, Org. React., 22, 1 (1974).
6. E. J. Corey and D. J. Beames, J. Am. Chem. Soc., 94, 7210 (1972).
7. See, M. Schlosser and E. Hammer, Helv. Chim. Acta, 57, 2547 (1974).
8. 3-Methoxy-3-methyl-1-butyne, bp 78°, was prepared conveniently from commercially available 3-hydroxy-3-methyl-1-butyne by deprotonation with 1.5 equiv of sodium hydride in dimethylformamide at 0° with stirring (ca. 30 min) and subsequent reaction with 1.5 equiv of dimethyl sulfate at 0 to 25° for ca. 1.5 hr.
9. E. J. Corey, D. Floyd and B. Lipshutz, manuscript in preparation.
10. E. J. Corey, D. Enders and M. G. Bock, Tetrahedron Lett., 7 (1976).
11. Some R_f values for intermediates in this synthesis on silica gel plates with ether as solvent are as follows: 7, 0.63; 8, 0.22; 9, 0.33; 1, 0.42.
12. This work was assisted financially by a grant from the National Institutes of Health.