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A NOVEL SYNTHESIS OF α-METHYLENE-γ-BUTYROLACTONES FROM 1-(N,N-DIMETHYLAMINOMETHYL)CYCLOPROPANECARBOXYLATE ESTERS

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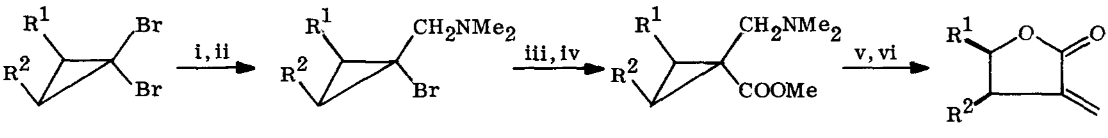
A new method is reported for constructing α-methylene-γ-butyrolactone moiety under neutral, anhydrous conditions. Olefin-dibromocarbene adducts are transformed to methyl 1-(N,N-dimethylaminomethyl)cyclopropanecarboxylates which in turn are treated with trimethylsilyl iodide and the crude products distilled to give the title compounds with high regio- and stereoselectivity.

Several kinds of terpenes possess α-methylene-γ-butyrolactone moiety in common. Due mainly to interest in its physiological activity efforts for synthesizing such structural unit have been made extensively,[1,2] but a highly selective method seems still awaited. We wish to report here a novel method for constructing the structure under neutral, anhydrous conditions. The process involves ring reorganization of methyl 1-(N,N-dimethylaminomethyl)cyclopropanecarboxylate (III) with concomitant elimination of the amino group,[3] and is characterized by its high stereo- and regioselectivity. The transformation is accomplished by treatment of III with trimethylsilyl iodide[4] followed by distillative thermolysis.

The starting amino ester III is prepared by means of the corresponding carbenoid as illustrated in Scheme 1. gem-Dibromocyclopropane I was exposed to butyllithium at -95° to undergo bromine-lithium exchange reaction[5] The resulting carbenoid was then treated with dimethyl(methylene)ammonium iodide[6]

Scheme 1



I II III IV

a: R^1 = Ph, R^2 = H; b: R^1 = n-C_6H_{13}, R^2 = H; c: R^1,R^2 = $-(CH_2)_4-$

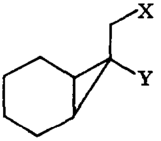
(i) n-BuLi, -95°, THF; (ii) $CH_2{=}\overset{+}{N}Me_2I^-$; (iii) n-BuLi or t-BuLi, -78°, THF
(iv) $(MeO)_2C{=}O$; (v) Me_3SiI; (vi) distil

at -95° to give an amino bromide II stereochemically homogeneous on PMR analysis except IIb which contained 12% of the stereo isomer.[7] The configuration of the dimethylaminomethyl group was inferred to be cis or endo relative to the substituents R^1 and R^2 on the analogy of our previous observation.[5] Successively, II was converted to cyclopropyllithium by the action of butyllithium or t-butyllithium at -78°. The bromine-lithium exchange is particularly facilitated by the dimethylamino group which coordinates lithium ion.[8] The cyclopropyllithium thus produced was quenched with dimethyl carbonate to give rise to III.

The ester III was treated with 3 mol of trimethylsilyl iodide in benzene or 1,2-dichloroethane at 50-95° for several hours. After the starting material was all consumed (TLC),[9] the solvent and the remaining silicon reagent were evaporated in vacuo. At first, we have dissolved the residue in high boiling solvents and heated as high as 200°, but no trace of the desired product was formed. The thermal reaction was, however, readily attained simply by distilling the residue under reduced pressure with bath temperature of 170° or above by use of Kugel-rohr, thermally unstable product being immediately removed from the hot reaction pot The distillate was purified by preparative TLC to afford α-methylene-γ-butyrolactone IV. The results (dibromocyclopropane, product[10a] (% yield)) are as follows: Ia, IIa (59), IIIa (73)[10b], IVa (62); Ib, IIb (71), IIIb[10c] (60), IVb[10d] (58); Ic, IIc (61), IIIc (61), IVc (64).

Noteworthy is the regio- and stereochemistry of the lactone formation. The transformation of IIIa afforded 4-hydroxy-2-methylene-4-phenylbutanoic lactone (IVa) as the sole product. Thus, the bond between the substituted carbons of cyclopropane ring is preferentially cleaved. The same preference was observed in the reaction of IIIb[7] which gave IVb as the major product (88%) accompanied by the regioisomer, 3-hydroxymethyl-2-methylenenonanoic lactone (12%).[11] The carbon-carbon bond cleavage and carbon-oxygen bond formation proceeded with retention of configuration as observed in the reaction of IIIc which afforded only cis isomer of IVc [12,13]

Of special interest in the present transformation is the intermediary species leading to IV. Treatment of IIIc with trimethylsilyl iodide followed by evaporation of all volatile material as above gave an oil which exhibited a singlet peak at δ 3.69 ($CDCl_3$) without reasonably intense peaks due to trimethylsilyl groups. The IR spectrum revealed the presence of carboxylic acid (3650-2200, 1710 cm^{-1}) and/or carboxylate anion (1620, 1400 cm^{-1}, neat film) functional group(s). Thus, the most likely intermediate seems to be V which is derived from trimethylsilyl iodide mediated ester hydrolysis and quarternization.[14] Indeed, when V was produced alternatively by the following methods and subjected to thermolysis, IVc was produced albeit in somewhat lower yields. Conditions and the yield of IVc were: A, (1) MeI, (2) Me_3SiI (2 eq),

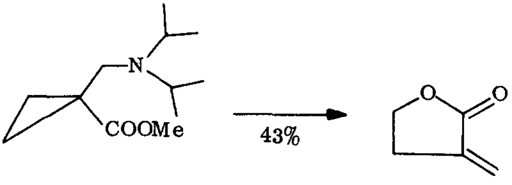


V: X = $\overset{+}{N}Me_3$, Y = COO^- and/or COOH
VI: X = $\overset{+}{N}HMe_2$, Y = COO^-
VII: X = NMe_2, Y = $COOCH_2C_6H_5$

(3) distil, 49%, B, (1) MeI, (2) aq KOH, (3) distil, 43%, C, (1) aq KOH, (2) MeI, (3) distil, 34%. Another possible intermediate VI could clearly be eliminated as following two procedures failed to give IVc: D, (1) hydrolysis of IIIc with 1.2 eq KOH, (2) neutralization with 1.2 eq HCl, (3) distil, or E, (1) hydrogenolysis of VII[15] (Pd/C, H_2), (2) distil. Of course, the benzyl ester VII was transformed to IVc by the standard procedure (60-61%) or by hydrogenolysis followed by quarternization (MeI) and distillation (51% yield).

In these respects the α-methylene-γ-butyrolactone synthesis described herein has a remarkable feature involving anhydrous, neutral conditions in sharp contrast to the related system which employs aqueous strong acidic conditions.[16] Furthermore, the present method has wide applicability as the starting gem-dibromocyclopropanes are readily available from olefins and dibromocarbene.

Finally, the sequence was successfully applied to the synthesis of tulipalin (IX), a hemiterpene lactone isolated from tulip bulb[17] and also from Adder's Tongue (Erythronium americanum),[18] starting with VIII[19]. In this reaction diisopropylamino group is especially pertinent as the dimethylamino derivative gave only trace amount of the desired product. Bulky amino leaving group seems essential for the isolation of the remarkably unstable product [20]



VIII IX

References and Notes

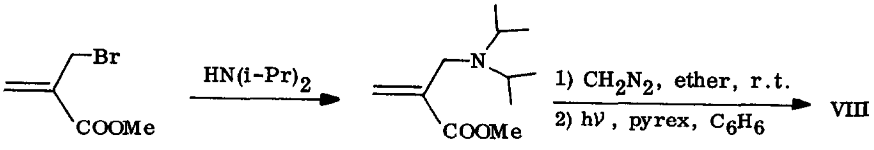
1. P. A. Grieco, Synthesis, 67 (1975).
2 (a) R. B. Gammill, C. A. Wilson, and T. A. Bryson, Synth. Commun., 5, 245 (1975).
   (b) S. S. Newaz, Aldrichimica Acta, 10, 64 (1977).
3. *Dimethylamino group is often utilized for protection of α-methylene moiety of α-methylene-γ-butyrolactones.* See S Danishefsky, P. F. Schuda, T. Kitahara, and S. J. Etheredge, J. Am. Chem. Soc., 99, 6066 (1977). S. Danishefsky, T. Kitahara, R. McKee, and P. F. Schuda, ibid., 98, 6715 (1976)
4 (a) M E. Jung and M. A. Lyster, J. Am. Chem. Soc., 99, 968 (1977); J. Org. Chem., 42, 3761 (1977). (b) T.-L. Ho and G. A. Olah, Angew. Chem., 88, 847 (1976)
5. K. Kitatani, T. Hiyama, and H. Nozaki, Bull. Chem. Soc. Jpn., 50, 3288 (1977).
6. J. Schreiber, H. Maag, N. Hashimoto, and A. Eschenmoser, Angew. Chem. Int. Ed., 10, 330 (1971)
7. The isomer is 1-*r*-bromo-1-(N,N-dimethylaminomethyl)-2-*c*-hexylcyclopropane. The observed stereoselectivity is consistent with the results obtained in thermodynamically controlled generation of the lithium carbenoid. See ref. 5.
8. Bromine-lithium exchange of 7-substituted 7-bromonorcarane system proceeds often sluggishly by means of butyllithium or t-butyllithium. See H. Yamamoto, K. Kitatani, T. Hiyama, and H. Nozaki, J. Am. Chem. Soc., 99, 5816 (1977).
9. In some cases IV was produced to some extent (less than 40% yield as estimated by PMR) during trimethylsilyl iodide treatment. However, transformation to the desired product was effectively executed by the subsequent thermolysis.

10. (a) All the products are characterized analytically and spectrometrically. (b) Lithiation of IIa with n-BuLi. (c) Contained 12% of the stereoisomer. See note 7. (d) Contained 12% of the regioisomer. See text.
11. When stereochemically pure sample of IIIb was subjected to the reaction conditions, the product ratio was a little improved (91% and 9% respectively).
12. J. A Marshall and N. Cohen, J. Org. Chem., 30, 3475 (1965).
13. Following experimental procedures are typical:

    7-exo-Bromo-7-endo-(N,N-dimethylaminomethyl)norcarane (IIc). At -95° butyllithium in hexane (1.7 M, 3.4 ml, 5.8 mmol) was added under an argon atmosphere to 7,7-dibromonorcarane (1.32 g, 5.2 mmol) dissolved in tetrahydrofuran (THF) (30 ml). After 10 min's stirring dimethyl(methylene)-ammonium iodide (1.40 g, 7.5 mmol) was added portionwise at -95°. The heterogeneous reaction mixture was stirred overnight and warmed gradually to room temperature (10°). Usual work-up followed by chromatography on silica gel column gave IIc (0.73 g, 61% yield). PMR (CCl_4): δ 0.9-2.0 (m, 10H), 2 27 (s, 6H, NMe_2), 2.63 (s, 2H, CH_2N). Exact Mass: obs 231.0641 (M^+) and 233.0613 ($M^+ + 2$).

    7-exo-Methoxycarbonyl-7-endo-(N,N-dimethylaminomethyl)norcarane (IIIc). A pentane solution (2.3 M) of t-butyllithium (1.46 ml, 3.36 mmol) was added to a THF (25 ml) solution of IIc (0.71 g, 3.05 mmol) at -78° under an argon atmosphere, and the mixture was stirred for 1 hr, mixed with dimethyl carbonate (0.5 ml, 6.0 mmol) at -78°, and further stirred overnight. Work-up followed by purification of the product by silica gel column chromatography gave IIIc (0.39 g, 61% yield). Bp 85-100° (bath temp)/0.5 Torr. PMR (CCl_4): δ 1.1-2 0 (m, 10H), 2.17 (s, 6H), 2.67 (s, 2H), 3.57 (s, 3H); IR (neat): 1720 cm^{-1}. Found: C, 68.1; H, 10.3; N, 6.4%. Calcd for $C_{12}H_{21}NO_2$: C, 68.2; H, 10.0; N, 6.6%.

    cis-4-Hydroxy-2-methylene-3,4-tetramethylenebutanoic lactone (IVc). Trimethylsilyl iodide (0.35 ml 2.6 mmol) was mixed with IIIc (0.170 g, 0.80 mmol) in 1,2-dichloroethane (7 ml) under an argon atmosphere, and the reaction mixture was heated at 95° for 14 hr, concentrated and the residue distilled (Kugel-rohr) under reduced pressure. Distillate collected at 160-210° (bath temp) at 0.05 Torr was purified by preparative TLC to give IVc (0.078 g, 64% yield) identical in all respects with the reported data (ref 12).
14. The initial phase of the reaction would be N-trimethylsilyl ammonium formation which is followed by trimethylsilyl-methyl exchange. Similar phenomenon is observed in J. Minamikawa and A. Brossi, Tetrahedron Lett., 3085 (1978).
15. This compound was prepared from IIc and benzyl chloroformate by the standard procedure noted herein, or alternatively from IIIc by ester exchange reaction.
16. P. F. Hudrlik, L. R. Rundnik, and S. H. Korzeniowski, J. Am. Chem. Soc., 95, 6848 (1973).
17. U. W. Brongersma—Oosterhoff, Rec. Trav. Chim., 86, 705 (1967); B. H. H. Bergaman, J. C. M. Beijersbergen, J. C. Overeem, and A. K. Sijpesteijn, ibid., 86, 709 (1967).
18. C. J. Cavallito and T. H. Haskell, J. Am. Chem. Soc., 68, 2332 (1946). Cf. R. Tschesche, F.-J. Kämmerer, and G. Wulff, Chem. Ber., 102, 2057 (1969).
19. The amino ester VIII was prepared according to the following scheme:



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