Tetrahedron Letters,Vol.24,No.50,pp 5571-5574,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

A NEW GENERAL SYNTHETIC ROUTE TO BRIDGED CARBOXYLIC ORTHO ESTERS

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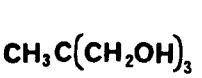
Summary: Acylation of the readily available 3-methyl-3-hydroxymethyl oxetane (2) leads to the corresponding oxetane esters (3) which rearrange smoothly in the presence of boron trifluoride etherate in methylene chloride at -15° to form ortho esters of the 2,6,7-trioxabicyclo[2.2.2]octane series (4).

Protection of the carboxylic acid function as an ortho ester derivative is a valuable tactic of synthetic practice, in part because of the stability of the ortho ester unit toward strongly basic reagents and the ease of carboxylic acid regeneration under mildly acidic conditions. Bridged ortho esters derived from 2,2-bishydroxymethyl-1-propanol (1) are especially useful because of their chromatographic stability as compared to acyclic ortho esters.[1,2] We describe herein a new and practical synthetic route to bridged ortho esters from carboxylic acids. Previously ortho esters have been prepared principally from nitriles or imido esters, or by ortho ester exchange,[1,2,3] but not directly from carboxylic acids.

3-Methyl-3-hydroxymethyloxetane (2) could be prepared in quantity from inexpensive commercial 2,2-bishydroxymethyl-1-propanol (1) by previously described methodology.[4,5] Conversion of 2 to a variety of carboxylic esters 3 was readily effected by reaction with acyl chlorides and pyridine in methylene chloride solution at 0° (for ca. 12 hr.) (75-85% yields). Treatment of the oxetane esters 3 with 0.25 equiv. of boron trifluoride etherate in CH_2Cl_2 (-15°, 4-12 hr. or 0°, 2-3 hr.) gave the isomeric bridged ortho esters 4 in 85-95% analytical and 75-90% isolated yields.



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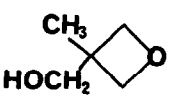

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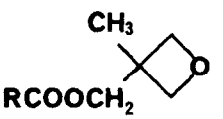

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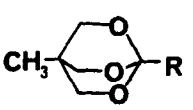

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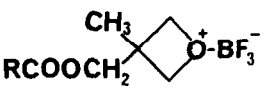
The use of 2 as a reagent for the synthesis of ortho esters in the 2,6,7-trioxabicyclo[2.2.2] octane series (4) was suggested by the surmise that coordination of the oxetane esters 3 with Lewis acid to form 5 could induce heterolysis of the dioxetane C-O bond with ester carbonyl participation to give zwitterion 6, collapse of which produces the desired 4. The thermodynamic driving force for the rearrangement 3⟶4 clearly is the result of the ring angle strain of 3.



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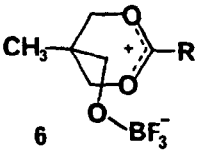

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The generality of this route to the bridged ortho esters 4 was shown by experimental study of the cases listed immediately below.

3	R	Yield (3⟶4) (%, Isolated)	React. Time (hr. at -15°C)
a	$C_6H_5CH_2CH_2CH_2$	75	12
b	n-C_5H_{11}	90	8
c	$BrCH_2CH_2CH_2$	91	4
d	$HC\equiv CCH_2CH_2CH_2$	90	10

The utility of the bridged ortho ester 4c (R=$CH_2CH_2CH_2Br$) can be appreciated from its conversion to the lithio ortho ester 4, R=$CH_2CH_2CH_2Li$, (2 equiv. of t-BuLi, THF at -78° for 15 min.) and then to 4, R=$CH_2CH_2CH_2Si(CH_3)_3$, (1.5 equiv. of $(CH_3)_3SiCl$ at -78°) in an overall yield of 86%.

The ortho ester 4d (R=$CH_2CH_2CH_2C\equiv CH$) was converted into two intermediates of considerable value in eicosanoid total synthesis: 4, R = $(CH_3)_3SiCH_2C\equiv C(CH_2)_3$, (1 equiv. of n-BuLi in THF at -78° followed by reaction with trimethylsilylmethyltriflate[6] in THF-HMPA at -78° to 20° over 8 hr. (95% yield)), and 4, R = $CH_2=C=C(I)CH_2CH_2CH_2$, by subsequent reaction with 1 equiv. of iodine-silver trifluoroacetate reagent (95%).[7]

The procedures which follow provide detail for the methodology outlined above.

3-Methyl-3-hydroxymethyloxetane (2).

A mixture of 2,2-bishydroxymethyl-1-propanol (1) (120 g., 1 mole), ethyl carbonate (118 g., 1 mole) and potassium hydroxide (1 g. in 5 ml. of ethanol) was heated at reflux under nitrogen for 15 min. (bath temp. 110°) after which time ethanol was removed by distillation at 1 atm. (still head temp. 80°, bath

temp. gradually raised to 140°) until about 1.8 mole of ethanol had been collected. The pressure was reduced to 50 mm. and the bath temperature was raised to 250° to yield a distillate boiling at 120-140°. Redistillation of this crude product afforded 40 g. of 2,[4] b.p. 80° at 40 mm., as a colorless liquid.

n-Hexanoate Ester of 3-Methyl-3-hydroxymethyloxetane (3, R = n-C_5H_{11}).

To a solution of 2 (500 mg., 5 mmole) and 400 mg. of pyridine in 2 ml. of dichloromethane at 0° was added 670 mg. (5 mmole) of n-hexanoyl chloride and the mixture was stirred for 5 hr. at 0°. Extractive isolation, evaporation of solvent (dichloromethane) and rapid chromatography over silica gel (pretreated with 1% triethylamine in hexane) using 1 : 1 hexane-benzene for elution gave 3, R = n-C_5H_{11}, (840 mg., 84%) as a colorless oil; PMR ($CDCl_3$) (δ): 4.4 (q, J=6Hz, 4H), 3.98 (s, 2H), 2.35 (t, 2H), 1.5 (m, 6H); 1.3 (s, 3H); 0.9 (t, 3H); M/e 200.0.

1-n-Amyl-4-methyl-2, 6, 7-trioxabicyclo[2.2.2]octane (4, R = n-C_5H_{11}).

To a solution of 200 mg. of oxetane ester 3, R = n-C_5H_{11}, (1 mmole) in 1 ml. of dry dichloromethane at -15° was added with stirring 0.25 mmole of distilled boron trifluoride etherate. After stirring at -15° for 8 hr. all starting material had been consumed (tlc analysis) and the reaction mixture was quenched by the addition of 1 mmole of triethylamine, diluted with ether and filtered to remove the amine-BF_3 complex. The filtrate was concentrated and filtered through silica gel (pretreated with triethylamine) using methylene chloride for elution to give 182 mg. (91%) of 4, R = n-C_5H_{11}, as a colorless oil; M/e 200.0; PMR ($CDCl_3$) (δ): 3.9 (s, 6H); 0.9-1.75 (m, 11H), 0.76 (s, 3H); tlc R_f (silica gel - CH_2Cl_2) 0.61.

1-[3-Trimethylsilylpropyl]-4-methyl-2, 6, 7-trioxabicyclo[2.2.2]octane (4, R = $Me_3SiCH_2CH_2CH_2$).

To a solution of t-butyllithium (0.2 mmole) in 0.35 ml. of pentane at -78° under argon was added a precooled solution of 1-[3-bromopropyl]-4-methyl-2, 6, 7-trioxabicyclo[2.2.2]octane (3c) (25 mg., 0.1 mmole) in ether (0.5 ml., -78°) using a stainless steel cannula and argon pressure for the transfer. After stirring for 15 min. at -78°, the reaction mixture was treated with 0.12 mmole of trimethylchlorosilane and allowed to warm gradually to 0°. Addition of aqueous potassium carbonate, extractive isolation using ether and passage of the product in benzene solution through a short column of basic alumina afforded 21 mg. (86%) of the title compound as a colorless oil; M/e 244; PMR ($CDCl_3$) (δ): 3.85 (s, 6H); 1.6, 1.25, 0.9 (m, 6H); 0.75 (s, 3H); 0.05 (s, 9H).

1-[6-Trimethylsilyl-4-hexynyl]-4-methyl-2, 6, 7-trioxabicyclo[2.2.2]octane
(4, R = $Me_3SiCH_2C\equiv CCH_2CH_2CH_2$).

To a solution of ortho ester 4d (prepared from 5-hexynoic acid; 58 mg., 0.3 mmole) in 0.5 ml. of THF at -78° under argon was added 0.3 mmole of n-butyllithium followed by 0.3 mmole of hexamethylphosphorictriamide, and the solution was stirred at -78° for 3 hr. Trimethylsilylmethyl triflate[6] (72 mg.,

0.3 mmole) was added and the mixture was allowed to warm to 23° and stirred at that temperature for 8 hr. Addition of aqueous potassium carbonate, extractive workup and filtration of the crude product in hexane through basic alumina afforded the title compound in pure condition as a colorless oil (78 mg., 95%); M/e 282; PMR ($CDCl_3$) (δ) 3.87 (s, 6H); 2.13 (m, 2H); 1.72 (m, 2H); 1.61 (m, 2H); 1.37 (t, 2H); 0.77 (s, 3H); 0.059 (s, 9H).[8]

References and Notes

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8. This research was assisted financially by a grant from the National Science Foundation.

(Received in USA 26 September 1983)