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A FACILE, STEREOSELECTIVE PREPARATION OF (Z)-2,4-PENTADIENOATES BY FAVORSKII REARRANGEMENT

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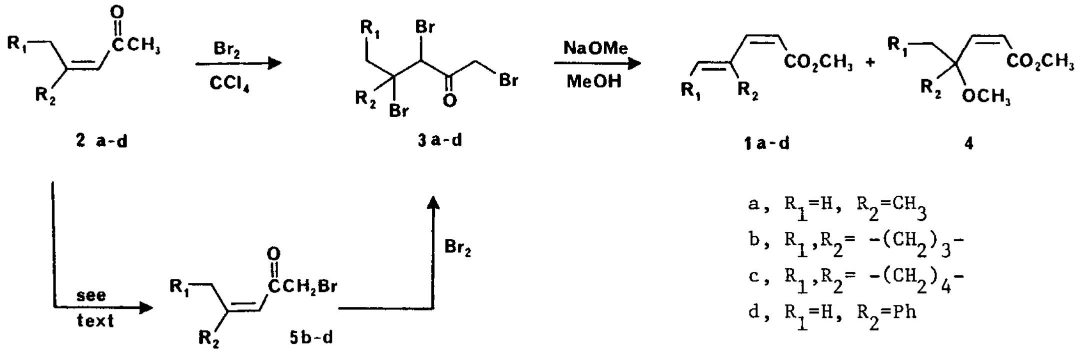
Abstract: Reaction of 1,3,4-tribromo-2-alkanones, efficiently prepared by direct bromination of the parent enone, with methanolic sodium methoxide gives methyl (Z)-2,4-pentadienoates with high (Z) selectivity about the α,β-double bond.

We report a simple, highly stereoselective and efficient procedure for the preparation of (Z)-2,4-pentadienoate esters **1** from readily available enones **2**. Few useful methods exist for the stereoselective preparation of these systems.[1] Our method relies on a Favorskii rearrangement and double elimination of hydrogen bromide from 1,3,4-tribromo-2-alkanones **3** which are synthesized by direct bromination of the parent enones **2** (Scheme I).

Scheme I

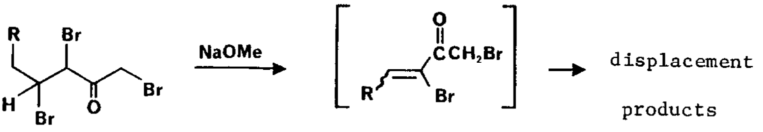


a, R_1=H, R_2=CH_3
b, R_1,R_2= $-(CH_2)_3-$
c, R_1,R_2= $-(CH_2)_4-$
d, R_1=H, R_2=Ph

Thus, addition of bromine (2.05 equiv) to a solution of mesityl oxide, **2a**, in carbon tetrachloride at -20°C resulted in vigorous evolution of hydrogen bromide over the last one-third of the addition and produced tribromide **3a** in quantitative yield by PMR. The crude tribromide **3a** was transferred directly[2] to a solution of sodium methoxide (4 equiv) in methanol at 0°C to afford, after standard workup[3] and fractional distillation, **1a** in 66% yield (bp 78-83°C/35 mm) and **4a** in 17% yield (bp 53-57°C/6 mm). A 97:3 ratio of (Z):(E) isomers of **1a** was obtained.[4,6] In a similar manner, enones **2b-d**[5] gave **1b-d** in good yield and with high (Z) selectivity and **4b-d**.[6] As an alternate bromination method, the α-methyl group in **2b-d** was brominated regiospecifically with dibromo-Meldrum's acid[7] or by the sequence: kinetic deprotonation (LDA), silylation (TMSCl) and bromination (1 equiv NBS). The resulting 1-bromoenones **5b-d** were treated with bromine (1 equiv) in carbon tetrachloride to yield **3b-d** followed by reaction with sodium methoxide (3 equiv) in methanol as outlined above to give **1b-d** in comparable yields and (Z):(E) selectivity. These results are summarized in Table I.

The conditions for the transformation of **3a** to **1a** are noteworthy. Best results were obtained with sodium methoxide in methanol. With methanolic sodium bicarbonate or potassium carbonate, higher temperatures (23°C) and longer reaction times were required to effect complete reaction and lower yields of **1a** (26% and 50%, respectively) were found. Larger amounts of the by-product **4a** (31% and 33%, respectively) were also produced under these conditions. Of particular note, reaction of **3a** with triethylamine in methanol at room temperature gave mainly (E)-**1a** [91:9 (E):(Z)] in 78% yield.

Extention of the above method to 1,3,4-tribromo-2-alkanones with a secondary carbon-bromine bond at C-4 have thus far failed to yield dienoic esters. For these systems, products are obtained resulting from initial α,β-elimination of HBr to an intermediate 1,3-dibromoenone **7** (eq 1), an event which thwarts the Favorskii process. We reason, therefore, that the likely first step[8] of the mechanism leading to **1** from **3** involves kinetic deprotonation of **3** to afford enolate **8** which gives cis-cyclopropanone **10** perhaps via electrocyclic ring closure of zwitterion **9** (Scheme II). Addition of methoxide to **10** then affords cyclopropyloxide **11** which undergoes an oxyanion-promoted disrotatory electrocyclic ring opening with concerted expulsion of bromide to give **12**.[9,14] Dehydrobromination of **12** gives **1**. Alternately, the immediate precursor to **1** may be **14** formed from elimination of HBr from **11** or **13**. Indeed, it is not clear when, or how, elimination of HBr to give the γ,δ-double bond in **1** occurs in the mechanism. However, the following paper demonstrates that the presence of unsaturation at C-4 of a 1,3-dibromoketone does not affect the cis selectivity of the Favorskii rearrangement. By-product **4** may arise from solvolytic displacement of the 3° bromide in **13** via a cyclopropylcarbinyl cation.



(1)

6 R= H, CH$_3$ or (CH$_3$)$_2$

7

Of further note, simple aliphatic α,β-dibromoketones yield β,γ-unsaturated esters when treated with sodium methoxide.[10] The reactions described in the present report apparently follow a different course raising interesting mechanistic implications. We are continuing to investigate the mechanism and synthetic applications of this process.

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Table I: Preparation of Methyl (Z)-2,4-Pentadienoates from 3-Buten-2-ones

					Isolated Yields [(Z):(E)]	
Compound	R_1	R_2	Method[a]	**5**	**1**	**4**
2a	H	CH_3	A		66 (97:3)[c]	17
2b	$-(CH_2)_3-$		A		67 (97:3)[c]	<5
			B	60	73 (98.5:1.5)[c]	n.d.[d]
2c	$-(CH_2)_4-$		A		52 (95:5)[b]	21
			B	88	64 (96:4)[c]	13
2d	H	Ph	A		46 (>95:5)[b]	n.d.
			C	59	64 (>95:5)[b]	n.d.

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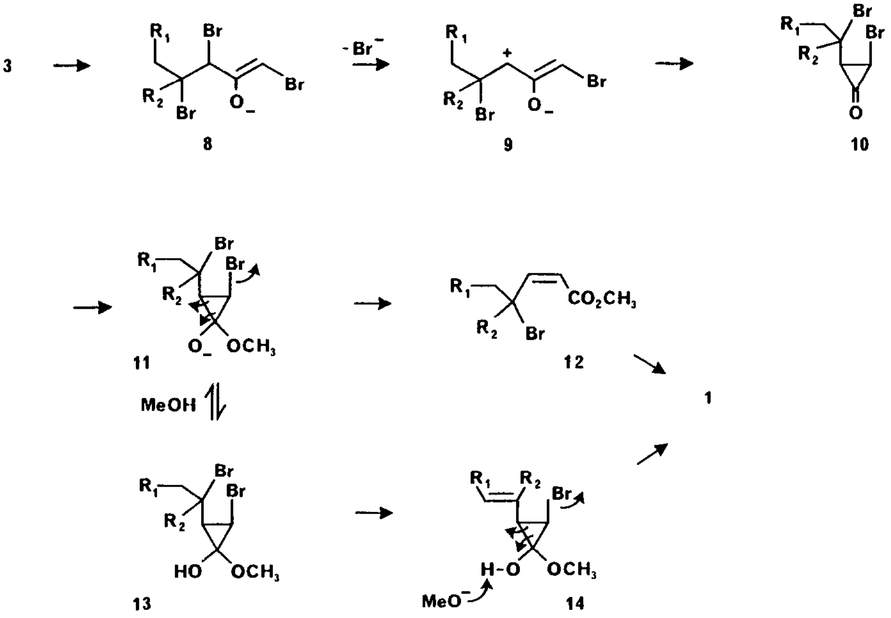
a) Method A: Generation of 3 *in situ* by direct bromination of 2 followed by treatement with NaOMe.
Method B: Monobromination of 2 with dibromo-Meldrum's acid to give 5 and then bromination to yield 3 and *in situ* treatment with NaOMe.
Method C: Formation and isolation of 5 by the sequence: i) LDA, ii) TMSCl and iii) NBS (1 equiv) and then generation of 3 followed by *in situ* reaction with NaOMe.

b) Ratio determined by 300 MHz ^{1}H NMR.

c) Ratio determined by vpc.

d) n.d. = not determined.

Scheme II



References and Notes

1. For recent representative examples, see, a) Gais, H.J. Angew. Chem. Int. Ed. **1984**, 23, 143. b) Still, W.C. and Gennari, C. Tetrahedron Lett. **1983**, 24, 4405. c) Normant, J.F. and Alexakis, A. Tetrahedron Lett. **1982**, 23, 5151.
2. Attempted isolation of **3** by chromatography or distillation resulted in evolution of HBr and polymerization.
3. The reaction mixtures were poured onto ice, the resulting mixture extracted with pentanes and the pentanes washed with saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate and dried over magnesium sulfate.
4. It has been reported that a similar sequence of reactions gives only the (E) isomer of **1**; a) Kover, W.B. and de Souza, N.A. J. Org. Chem. **1980**, 45, 4225. We have prepared both (E) and (Z)-**1a** by alternate routes (see reference 13) and have verified that the (Z) isomer is formed. b) Care must be taken to avoid (Z) to (E) isomerization during workup or upon isolation of the product, a problem noted by several researchers: Schamp, N.; De Kimpe, N. and Coppens, W. Tetrahedron **1975**, 31, 2081 and references cited therein.
5. a) Enones **2b** and **2c** were prepared in 67% and 72% yield, respectively, by condensation of diethyl (2-oxopropyl)phosphonate[11] with cyclopentanone and cyclohexanone in heterogeneous media: see Villieras, J. and Rambaud, M. Synthesis **1983**, 300; b) Enone **2d** was prepared by displacement of acetate from 4-acetoxy-3-penten-2-one[12] with lithium diphenylcuprate.
6. Compounds **1a-d** were characterized by 300 MHz ^{1}H and 75.3 MHz ^{13}C NMR, IR, UV and mass spectroscopy including exact mass. All other compounds exhibited proper ^{1}H NMR and IR spectral characteristics. The (Z):(E) ratios of **1a-c** were determined by capillary VPC analysis of the crude reaction mixture prior to isolation of the (Z)/(E) mixtures[13b] by flash chromatography on silica gel or fractional distillation. Compound **1d** decomposed on attempted analysis by VPC, therefore, the (Z):(E) ratio was estimated from 300 MHz ^{1}H NMR spectra. In each case, signals attributed to the minor isomer (E)-**1a-d** were identified by co-injection and/or comparison of the NMR spectra of the crude reaction mixtures with spectra of authentic samples of **1a-d.**[13a]
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8. For excellent reviews and discussions of the mechanism of the Favorskii rearrangement, see a) Baretta, A. and Waegell, B. In "Reactive Intermediates;" Abramovitch, R.A., Ed.; Plenum: New York, 1982, Vol. 2, Chapter 6. b) Hunter, D.H.; Stothers, J.B. and Warnhoff, E.W. In "Rearrangements in Ground and Excited States;" de Mayo, P., Ed.; Academic: New York, 1980; Vol. 1, Chapter 6. c) Rappe, C. In "The Chemistry of the Carbon Halogen Bond, Part 2;" Patai, S., Ed.; John Wiley and Sons: New York, 1973; Chapter 17. d) Akhrem, A.A.; Ustynyuk, T.K. and Titov, Y.A. Russian Chem. Rev. **1970**, 39, 732 and references cited in the above.
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12. Jones, R.A.; Nokkeo, S. and Singh, S. Synth. Commun. **1977**, 7, 195.
13. a) Compounds (E)-**1a** and (Z)-**1a** were independently synthesized by condensation of methacrolein with trimethyl phosphonoacetate [26:1 (E):(Z)] or methyl bis(trifluoroethyl) phosphonoacetate[1b] [78%, 7:1 (Z):(E)] respectively. Isomer (E)-**1b** was prepared by photolytic isomerization of (Z)-**1b**; (E)-**1c** and (E)-**1d** were formed by iodine catalyzed isomerization of (Z)-**1c** and (Z)-**1d**, respectively. b) No attempts were made to separate (E)-**1a,c,d** from (Z)-**1a,c,d**; (E)-**1b** and (Z)-**1b** were chromatographically separable. Compounds (E)-**1b,c** have been previously reported: Trost, B.M.; Weber, L.; Strege, P.; Fullerton, T.J. and Dietsche, T.J. J. Am. Chem. Soc. **1978**, 100, 3426.
14. It has been recently demonstrated that halocyclopropanols analogous to **13/14** collapse to α,β-unsaturated carbonyl compounds in a stereospecific manner: see a) Conia, J.-M. and Blanco, L. Nouv. J. Chim. **1983**, 7, 399. b) Slougui, N. and Rousseau, G. Tetrahedron **1985**, 41, 2643.

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