(1962)). In analogous, separate incubations of mevalonate with *d*-1 and *l*-1 the yields of squalene 2,3-oxide were 16 and 14% and the yields of squalene 2,3:22,23-dioxide were 14 and 11%.

(14) Both squalene 2,3-oxide and squalene 2,3:22,23-dioxide are reported by E. J. Corey, P. R. Ortiz de Montellano, K. Lin, and P. D. G. Dean, *J. Am. Chem. Soc.*, **89**, 2797 (1967), to accumulate when 2,3-iminosqualene is used as an inhibitor.

(15) CHO cells possess intact cholesterol biosynthetic capacity: (a) T. Y. Chang and P. R. Vagelos, *Proc. Natl. Acad. Sci. U.S.A.*, **73**, 24 (1976); (b) T. Y. Chang, C. Telakowski, W. Vanden Heuvel, A. W. Alberts, and P. R. Vagelos, *ibid.*, **74**, 832 (1977).

(16) A. S. Kandutsch and H. W. Chen, *J. Biol. Chem.*, **249**, 6057 (1974).

(17) TLC of the product obtained from this [^{14}C]acetate incorporation experiment yielded bands corresponding to [^{14}C]squalene 2,3-oxide and [^{14}C]squalene 2,3:22,23-dioxide which contained 30 and 10%, respectively, of the total radioactivity in the nonsaponifiable fraction.

(18) Pertinent reviews: (a) W. L. Bencze, "Handbook of Experimental Pharmacology", Vol. 41, D. Kritchevsky, Ed., Springer-Verlag, Berlin, 1975, p 349; (b) R. Howe, *Adv. Drug Res.*, **9**, 7 (1974); (c) W. Bencze, R. Hess, and G. de Stevens, *Prog. Drug Res.*, **13**, 217 (1969).

(19) Compound 3, reported as an oil by M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956), was isolated as a solid, mp 47–50 °C (characterized by IR, NMR, and combustion analysis), from NaBH$_4$ reduction of 4α,10β-dimethyl-*trans*-decal-3-one, obtained via Li/NH$_3$ reduction of 4,10-dimethyl-Δ^4-decal-3-one, prepared by the method of N. C. Ross and R. Levine, *ibid.*, **29**, 2341 (1964).

(20) E. E. van Tamelen, A. D. Pedlar, E. Li, and D. R. James, *J. Am. Chem. Soc.*, **99**, 6778 (1977).

James A. Nelson,* Michael R. Czarny
Thomas A. Spencer*

Department of Chemistry, Dartmouth College
*Hanover, New Hampshire 03755*

James S. Limanek, Keith R. McCrae, Ta Yuan Chang*

Department of Biochemistry, Dartmouth Medical School
Hanover, New Hampshire 03755
Received April 17, 1978

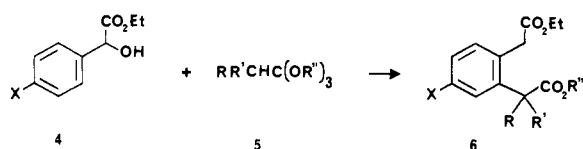# Regiospecific Synthesis of Substituted Arenes. [3,3] Sigmatropic Rearrangement of Benzyl Vinyl Ethers[1]

Sir:

The [3,3] sigmatropic rearrangement of allyl vinyl ethers provides a versatile method for the construction of new carbon to carbon bonds with high regio- and stereospecificity under mild reaction conditions.[2] Although the [3,3] sigmatropic rearrangement of *allyl phenyl ethers* is well exampled in the classic Claisen rearrangement,[3] the [3,3] sigmatropic rearrangement of *benzyl vinyl ethers* **1** (W = H) is not generally
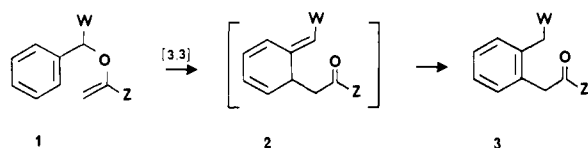
possible.[4] Inspection of the putative intermediate **2** suggested to us that the [3,3] sigmatropic rearrangement of **1** should be facilitated by an appropriately selected and suitably positioned substituent W.[5,6]

We are now pleased to report that the reaction of ethyl mandelate derivatives **4** in the Claisen ortho ester rearrangement[7,8] with **5** provides an extremely convenient method for

the regiospecific synthesis of substituted arenes **6**.[9] The results of these studies are summarized in Table I.[10]

Several noteworthy features of the above transformation follow: (1) a large assortment of substituted ethyl mandelates

Table I. Claisen Ortho Ester Rearrangement of Ethyl Mandelates (**4**)

entry	mandelate (**4**), X	ortho ester (**5**) R	R′	R″	reaction[a] conditions	% yield[b] of 6
a	H	H	H	Et	A	84
b	H	Me	H	Et	B	50
c	H	Me	Me	Et	A	41
d	Me	H	H	Et	B	65
e	Me	Me	H	Et	B	47
f	MeO	H	H	Et	C	50
g	Cl	H	H	Et	A	30
h	Cl	Me	H	Et	B	21
i	EtO$_2$C	H	H	Et	A	33
j	EtO$_2$C	Me	H	Et	B	18

[a] All reactions use 6 to 8 equiv of **5** and 0.1 equiv of hexanoic acid/equiv of **4**. The reaction flask is fitted with a 15-cm Vigreux column during the first time period and a short-path distillation head during the second time period (see sample experimental procedure). Reaction conditions: A, 12 h at 220 °C, 8 h at 185 °C; B, 12 h at 220 °C, 12 h at 185 °C; C, 5 h at 220 °C, 7 h at 185 °C. [b] See ref 10.

Table II. Claisen Ortho Ester Rearrangement with 3-Indoleglycolates

entry	indole 7, W	ortho ester 5[a] R	R′	R″	% yield[b] of 8
a	CO$_2$Et	H	H	Et	79
b	CO$_2$Et	H	H	Me	48[c]
c	CO$_2$Et	Me	H	Et	40
d	CONMe$_2$	H	H	Me	59
e	H	H	H	Me	*d*

[a] All reactions use 30 equiv of **5** and 0.1 equiv of hexanoic acid/equiv of **4**. The reaction flask was filtered with a 15-cm Vigreux column topped with a short-path distillation head and was heated at reflux for 12 h, the Vigreux column was removed, and heating was continued at 185 °C for 8 h. [b] See ref 10. [c] No ester exchange was detected. [d] The corresponding mixed ortho ester was isolated (90%).[18]

4[11] and ortho esters **5**[12] are readily available; (2) the reaction occurs for ethyl mandelates with either electron-donating or electron-withdrawing groups; (3) the reaction conditions are compatible with a wide array of functionality;[13] (4) the reaction provides a method for the regiospecific synthesis of substituted arenes[14] that would be difficulty accessible by alternative methods; and (5) the carboethoxy groups are convenient handles for subsequent synthetic transformations.

We have also extended this procedure to the Claisen ortho ester rearrangement of **5** with the 3-indoleglycolic acid derivatives **7** (W = CO$_2$Et or CONMe$_2$)[15,16] to give 2,3-disubstituted indoles **8**[17] (Table II).[10] The crucial influence of the
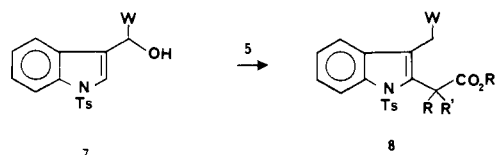
carboxy derivative at the benzylic position in facilitating the [3,3] sigmatropic rearrangement is again illustrated by experiments in which 1-tosyl-3-indolemethanol (**7**, W = H) failed to undergo any detectable rearrangement with trimethyl orthoacetate under comparable reaction conditions, but led only to the corresponding mixed ortho ester.[18]

It is notable that the 2,3-disubstituted indoles **8** contain both a two-carbon functionalized chain at the 3 position and an α-substituted carboxy group at the 2 position. These features are present in a number of indole alkaloids such as vincadine, vindoline, carbomethoxyvelbanamine, and catharanthine. We are currently investigating the application of the [3,3] sig-

matropic rearrangement of 3-indoleglycolic acid derivatives as the key step in a general scheme for the total synthesis of indole alkaloids; further investigations concerning the use of the [3,3] sigmatropic rearrangement for the regiospecific synthesis of other substituted arenes are also in progress.

References and Notes

(1) Synthesis via Sigmatropic Rearrangements. 1.
(2) For recent reviews, see (a) S. J. Rhoads and N. R. Raulins, *Org. React.*, **22**, 1 (1975); (b) F. E. Ziegler, *Acc. Chem. Res.*, **10**, 227 (1977); (c) G. B. Bennett, *Synthesis*, 589 (1977).
(3) D. S. Tarbell, *Org. React.*, **2**, 1 (1944).
(4) For a discussion of the [3,3] sigmatropic rearrangement of benzyl vinyl ethers, see (a) G. B. Gill, *Q. Rev. (London)*, **22**, 338 (1968). Thermal rearrangements of benzyl vinyl ethers generally occur via radical processes (i → ii): (b) K. B. Wiberg, R. R. Kintner, and E. L. Motell, *J. Am. Chem. Soc.*, **85**, 450 (1963); (c) A. W. Burgstahler, L. K. Gibbons, and I. C. Nordin, *J. Chem. Soc.*, 4986 (1963). Free-radical processes also occur in heterocyclic systems: (d) A. F. Thomas, *Helv. Chim. Acta*, **53**, 605 (1970). The conversion of **1** to **3** where W = H and Z = NMe₂ is a notable exception: (e)
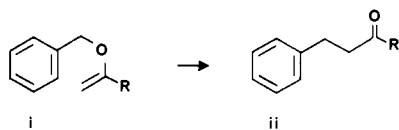
A. E. Wick, D. Felix, K. Steen, and A. Eschenmoser, *ibid.*, **47**, 2425 (1964); (f) D. Felix, K. Gschwend-Steen, A. E. Wick and A. Eschenmoser, *ibid.*, **52**, 1030 (1969). Benzyl *o*-methylphenylacetate was obtained from ketene dibenzyl acetal, generated in situ by dehydrohalogenation of bromoacetaldehyde dibenzyl acetal: (g) S. M. McElvain, H. I. Anthes, and S. H. Shapiro, *J. Am. Chem. Soc.*, **64**, 2525 (1942). For another exception, see (h) W. J. LeNoble, P. J. Crean, and B. Gabrielson, *ibid.*, **86**, 1649 (1964).
(5) It is noteworthy that, when W = carbonyl, **2** is vinylogously related to the cyclohexadienone which is initially formed in the [3,3] sigmatropic rearrangement of allyl phenyl ethers.
(6) For a recent example of the dramatic influence on a [3,3] sigmatropic rearrangement caused by an effective change in substituents (i.e., –OH → –O⁻K⁺), see D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, **97**, 4765 (1975).
(7) (a) W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T.-T. Li, D. J. Faulkner, and M. R. Peterson, *J. Am. Chem. Soc.*, **92**, 741 (1970). (b) As usual in the Claisen ortho ester rearrangement, we made no attempts to isolate the intermediate benzyl vinyl ether.
(8) We have also effected Claisen rearrangement of ethyl mandelate with 1-methoxycyclohexene to give iii.
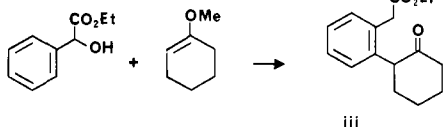
(9) In marked contrast, reaction of benzyl alcohol with triethyl orthoacetate, under the same conditions used for ethyl mandelate, gave predominantly benzyl diethyl orthoacetate accompanied by small amounts of ethyl 3-phenylpropionate and ethyl *o*-methylphenylacetate (presumably via radical processes; cf. ref 4b–d).
(10) (a) A typical experimental procedure follows. A solution of ethyl mandelate (2.00 mmol), triethyl orthoacetate (16 mmol), and hexanoic acid (0.20 mmol) in a 50-mL flask fitted with a 15-cm Vigreux column topped with a short-path distillation head was heated at 220 °C for 12 h in an argon atmosphere; ethanol was allowed to distil out of the reaction solution as it was formed. The Vigreux column was removed, the short-path distillation head was placed on the reaction flask, and heating was continued at 185 °C for 8 h. Excess ortho ester was removed (35 °C, 1 mm) and the residue was purified by chromatography on silica gel (30 g, hexane–ether eluent), followed by evaporative distillation (120 °C, 0.002 mm) to give diethyl *o*-benzenediacetate (**6a**) as a colorless liquid (210 mg, 84%): ¹H NMR (CCl₄) δ 1.15 (t, *J* = 7 Hz, 6 H), 3.60 (s, 4 H, ArCH₂–), 4.08 (q, *J* = 7 Hz, 4 H), 7.13 (s, 4 H); IR (neat) ν 1740 cm⁻¹. Anal. (C₁₄H₁₈O₄) C, H, O. Found *m/e* 250.1196. (b) All new compounds were fully characterized by spectroscopic methods. Yields are given for isolated products purified by column chromatography (silica gel) followed by evaporative distillation and are not optimized. The unrearranged mixed ortho ester of **4** and **5** (10–20%) and tarry polymers comprise the remainder of the mass balance; no other characterizable products were isolated. (c) Additional ¹H NMR data (CCl₄): **6b**, δ 1.15 (t, *J* = 7 Hz), 1.23 (t, *J* = 7 Hz), and 1.46 (d, *J* = 7 Hz, CH₃CH) (total 9 H), 3.71 (AB, *J* = 16 Hz, Δν = 0.40 ppm, ArCH₂CO₂Et) and 3.95–4.40 (m) (total 7 H), 7.20–7.40 (m, 4 H); **6c**, 1.08–1.36 (two overlapping t) and 1.28 (s) (total 12 H), 3.90–4.32 (m, 6 H), 7.38 (s, 4 H). ¹H NMR data (CDCl₃): **8a**, δ 1.16 (t, *J* = 7 Hz) and 1.27 (t, *J* = 7 Hz) (total 6 H), 2.33 (s, 3 H, *p*-CH₃Ar), 3.67 (s, 2 H, 3-indolyl-CH₂CO₂Et), 3.9–4.4 (two overlapping q), and 4.20 (s, 2-indolyl-CH₂CO₂Et) (total 6 H), 7.0–8.2 (m, 8 H);

8b, δ 1.18 (t, *J* = 7 Hz, 3 H), 2.30 (s, 3 H, *p*-CH₃Ar), 3.66 (s, 3-indolyl-CH₂CO₂Et) and 3.72 (s, CO₂CH₃) (total 5 H), 4.10 (q, *J* = 7 Hz, CO₂CH₂) and 4.20 (s, 2-indolyl-CH₂CO₂Me) (total 4 H), 7.1–8.2 (m, 8 H); **8c**, δ 1.17 (t, *J* = 7 Hz) and 1.20 (t, *J* = 7 Hz) (total 6 H), 1.60 (d, *J* = 7 Hz, 2 H, CH₃CH<), 2.34 (s, 3 H, *p*-CH₃Ar), 3.68 (s, 2 H, 3-indolyl-CH₂CO₂Et), 3.8–4.3 (two overlapping q, 4 H), 4.95 (q, *J* = 7 Hz, 1 H, 2-indolyl-CH(CH₃)CO₂Et), 7.1–8.2 (m, 8 H); **8d**, δ 2.35 (s, 3 H, *p*-CH₃Ar), 2.95 (br s, 6 H, N(CH₃)₂), 3.73 (two overlapping s, 5 H, 3-indolyl-CH₂CONMe₂ and CO₂CH₃), 4.20 (s, 2 H, 2-indolyl-CH₂CO₂Me), 7.1–8.2 (m, 8 H). Additional data: Anal. (C₁₅H₂₀O₄, **6b**) C, H, O. Found *m/e* 264.1328. Anal. (C₁₆H₂₂O₄, **6c**) C, H, O. Found *m/e* 278.1516.
(11) Substituted ethyl mandelates may be prepared either from the corresponding cyanohydrins, which are, in turn, readily available from aromatic aldehydes, or by NaBH₄ reduction of ethyl phenylglyoxylates prepared from arenes by Friedel–Crafts acylation with ethyl oxalyl chloride.
(12) R. H. DeWolfe, "Carboxylic Ortho Acid Derivatives", Academic Press, New York, N.Y., 1970.
(13) The majority of methods available for the formation of new carbon to carbon bonds in aromatic systems involve reaction conditions which are either acidic (e.g., Friedel–Crafts) or basic–nucleophilic (e.g., organometallic), and, therefore, incompatible with some functional groups.
(14) For recent examples of procedures which allow the formation of a new carbon to aromatic carbon bond ortho to a heteroatom, see (a) P. G. Gassman and G. D. Gruetzmacher, *J. Am. Chem. Soc.*, **96**, 5487 (1974); (b) P. G. Gassman, T. J. van Bergen, D. P. Gilbert, and B. W. Cue, Jr., *ibid.*, **96**, 5495 (1974); (c) P. G. Gassman and T. J. van Bergen, *ibid.*, **96**, 5508 (1974); (d) P. G. Gassman, G. Gruetzmacher, and T. J. van Bergen, *ibid.*, **96**, 5512 (1974); (e) P. G. Gassman and D. R. Amick, *Tetrahedron Lett.*, 889 (1974); (f) P. G. Gassman and D. R. Amick, *ibid.*, 3463 (1974); (g) R. M. Coates and I. M. Said, *J. Am. Chem. Soc.*, **99**, 2355 (1977). For examples of directed ortho metalation, see (h) D. W. Slocum and W. Acherman, *J. Chem. Soc., Chem. Commun.*, 968 (1974); (i) H. W. Gschwend and A. Hamdan, *J. Org. Chem.*, **40**, 2008 (1975).
(15) Prepared from ethyl 3-indoleglyoxylate or *N,N*-dimethyl-3-indoleglyoxamide by reaction with NaH–TsCl, followed by reduction with NaBH₄.
(16) (a) The protection of the indole nitrogen with the electron-withdrawing tosyl group was found to be essential. Reaction of either ethyl 3-indoleglycolate (iv, W = CO₂Et) or 3-indolemethanol (iv, W = H) with triethyl orthoacetate
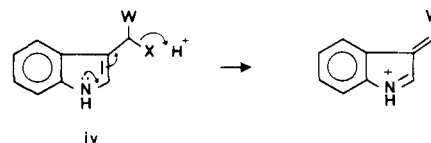
(30 equiv) and hexanoic acid (0.1 equiv) at 120 °C led to rapid and extensive decomposition, possibly by the pathway involving the unshared electrons on nitrogen which is depicted below (X = –OC(OEt)₂CH₃ or –OH). (b) For related pathways, see E. Leete, *J. Am. Chem. Soc.*, **81**, 6023 (1959), and references therein.
(17) For other approaches to functionalized 2,3-disubstituted indoles, see, inter alia, (a) H. Plieninger, W. Muller, and K. Weinerth, *Chem. Ber.*, **97**, 667 (1964); (b) E. Wenkert, K. G. Dave, C. T. Gnewuch, and P. W. Sprague, *J. Am. Chem. Soc.*, **90**, 5251 (1968); (c) A. R. Battersby and A. K. Bhatnagar, *Chem. Commun.*, 193 (1970).
(18) ¹H NMR (CDCl₃): δ 1.53 (s, 3 H, CH₃C(OMe)₂OR), 2.28 (s, 3 H, *p*-CH₃Ar), 3.30 (s, 6 H, C(OCH₃)₂), 4.72 (s, 2 H, –CH₂O–), 7.0–8.2 (m, 8 H).
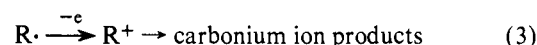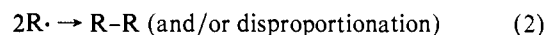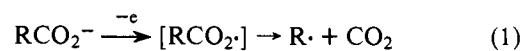
Stanley Raucher,* Alfred S.-T. Lui
Department of Chemistry, University of Washington
Seattle, Washington 98195

Direct Observation of Radical Intermediates in the Photo-Kolbe Reaction—Heterogeneous Photocatalytic Radical Formation by Electron Spin Resonance

Sir:

Many electroinitiated chemical reactions are thought to proceed via radical intermediates. For example, the widely studied Kolbe reaction of carboxylates[1] is believed to follow the mechanism

$$RCO_2^- \xrightarrow{-e} [RCO_2\cdot] \rightarrow R\cdot + CO_2 \qquad (1)$$

$$2R\cdot \rightarrow R{-}R \text{ (and/or disproportionation)} \qquad (2)$$

$$R\cdot \xrightarrow{-e} R^+ \rightarrow \text{carbonium ion products} \qquad (3)$$

The mechanistic details of this electrooxidative decarboxylation are still a matter of controversy.[2] Not only does the hypothetical primary product of electron transfer, the acyloxy radical ($RCO_2\cdot$), rapidly split into CO_2 and a hydrocarbon