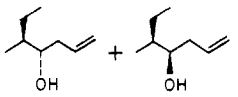
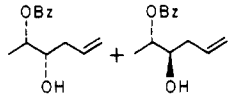
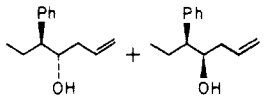
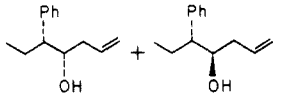
Table I. Reaction of Chiral Aldehydes 10-13 with the Reagents 8 and 9[a,b]

aldehydes[c]	reagents (yield, %)[d]	diastereomeric ratio[e,f]
10	(81) →	
	8	96:4
	9	5:95
11	(80) →	
	8	94:6
	9	4:96
12	(74) →	
	8	97:3
	9	26:74
13	(72) →	
	8	67:33
	9	2:98

[a] All of the reactions were carried out at −78 °C under a nitrogen atmosphere.[11] [b] Reactions were carried out with a 1:1 molar ratio of reagent to chiral aldehyde. [c] Chiral aldehydes (**10**, 95% ee; **11**, 98% ee; **12** and **13**, 80–85% ee) were prepared, stored, and used in solution. The optical purity of all aldehydes were routinely checked by comparing the optical rotations of the corresponding alcohols produced by BMS reduction of the aldehydes. [d] Isolated yield. [e] The ratios of diastereomers were determined by capillary GC analysis of the MTPA esters of the product alcohols using a column, methyl silicone, 50 M × 0.25 mm, except in the reaction of **11** with **8** and **9**. In addition to the presence of the desired two diastereomers, the capillary GC analysis revealed the presence of 2–9% of the other two diastereomers, presumably arising from the presence of small amounts of the other enantiomeric aldehyde. Hence, the diastereomeric ratios were calculated from the two most prominent products postulated to arise from the enantiomerically pure aldehyde present in major amounts. In the reaction of **11** with **8** and **9**, the diastereomeric ratios were obtained by direct capillary GC analysis of the product alcohols using a column, methyl silicone, 50 M × 0.25 mm. [f] Configurations of the newly formed stereocenter at the aldehydic carbonyl position are predicted by analogy to the configuration realized in the products obtained in the reaction of the allyldiisopinocampheylborane derivatives with achiral aldehydes.[8f]

The results are summarized in Table I.

The reagent **8** adds to chiral aldehyde **10** with very high diastereofacial selectivity (96:4). In the reaction of the antipodal reagent **9** with aldehyde **10**, the facial selectivity is completely reversed (5:95). Similar selectivities are exhibited by the reagents **8** and **9** with chiral aldehyde **11** (the reagent **8** furnished 94:6 and **9** furnished 4:96). Even the aldehyde **12** with a more bulky α-substituent exhibited excellent facial selectivity (97:3) with reagent **8** and a moderately lower facial selectivity (26:74) with reagent **9**. Similar selectivities are observed for the antipodal aldehyde **13** with reagents **8** and **9** (the reagent **8** providing 67:33 and **9** providing 2:98).

It is clear from these results that the allyldiisopinocampheylboranes **8** and **9** are highly diastereoselective reagents with α-substituted chiral aldehydes **10–13**. The stereochemistry at the carbonyl carbon of the aldehyde is controlled simply by selecting the appropriate enantiomeric reagent, either **8** or **9**; thus, the chirality of the reagent controls the overall diastereofacial selectivity achieved in the reaction. This synthesis is operationally very simple, providing access to all four possible syn and anti stereoisomers in high optical purity merely by selecting the proper antipode of α-pinene in the preparation of the reagent and either *R* or *S* α-substituted chiral aldehyde. These results further demonstrate the superior chiral-directing properties of the 3-pinanyl group in asymmetric synthesis. Thus the results presently available reveal that the Ipc_2B allyl derivatives, such as **8** and **9**, are not only the most enantioselective[8] but also the most diastereoselective derivatives available for allylborations.

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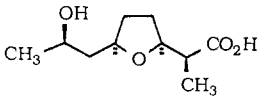
Stereoselective Synthesis of (±)-Methyl Nonactate[1]

Summary: Racemic methyl nonactate has been prepared in 11 steps from 2,2-dimethyl-3(2*H*)-furanone with the diastereoisomeric relationships between C-2 and C-3, C-3 and C-6, and C-6 and C-8 established with stereoselectivities of 32:1, 50:1, and 24:1, respectively.

Sir: Nonactic acid (**1**) is the monomeric subunit of the macrotetrolide nonactin, a meso [(+), (−), (+), (−)] ionophoric antibiotic isolated from a variety of *Streptomyces* cultures.[2] Synthetic effort in this area has been brisk, with eleven reported syntheses of the nonactic acid subunit,[3] four in optically active form[3h,j,k,o] and three of which have also resulted in syntheses of nonactin itself.[3b,e,h] In most cases the levels of relative stereochemical control have not been outstanding at all stages.



1

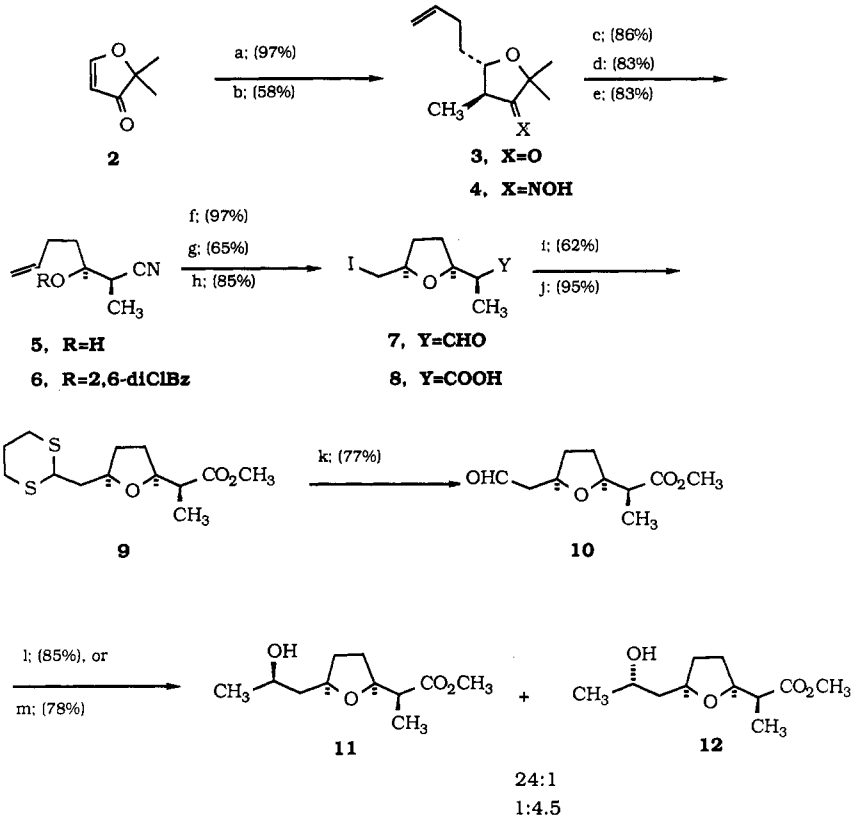
(1) (a) Presented in part at the 189th National Meeting of The American Chemical Society, Miami Beach, FL, April 28–May 5, 1985; paper ORGN 0032. (b) Taken in part from the Ph.D. Dissertation of J.M.M. (Duke University, 1985). (c) All new stable compounds gave satisfactory elemental analyses and spectral data (IR, ^1H NMR, ^{13}C NMR) consistent with the assigned structures.

(2) (a) Corbaz, R.; Ettlinger, L.; Gaumann, E.; Keller-Schielein, W.; Kradolfer, F.; Neipp, L.; Prelog, V.; Zahner, H. *Helv. Chim. Acta* **1955**, *38*, 1445. (b) Keller-Schierlein, W. *Fortschr. Chem. Org. Naturst.* **1968**, *26*, 161. (c) Keller-Schierlein, W. *Ibid.* **1973**, *30*, 313. (d) Dominquez, J.; Dunitz, J. D.; Gerlach, H.; Prelog, V. *Helv. Chim. Acta* **1962**, *45*, 129. (e) Gerlach, H.; Prelog, V. *Justus Liebigs Ann. Chem.* **1963**, *669*, 121. (f) Prestegard, J. H.; Chan, S. I. *J. Am. Chem. Soc.* **1970**, *92*, 4440.

(3) (a) Beck, G.; Henseleit, E. *Chem. Ber.* **1971**, *21*, 104. (b) Gerlach, H.; Wetter, H. *Helv. Chim. Acta* **1974**, *57*, 2306. (c) Gombos, J.; Haslinger, E.; Zak, H.; Schmidt, U. *Montash Chem.* **1975**, *106*, 219. (d) Zak, H.; Schmidt, U. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 432. (e) Schmidt, U.; Gombos, J.; Hastinger, E.; Zak, H. *Chem. Ber.* **1976**, *109*, 2628. (f) Arco, M. J.; Trammell, M. H.; White, J. D. *J. Org. Chem.* **1976**, *41*, 2075. (g) Bartlett, P. A.; Jernstedt, K. K. *Tetrahedron Lett.* **1980**, *21*, 1607. (h) Bartlett, P. A.; Meadows, J. D.; Ottow, W. *J. Am. Chem. Soc.* **1984**, *106*, 5304. (i) Ireland, R. E.; Vevert, J. P. *J. Org. Chem.* **1980**, *45*, 4259. (j) Ireland, R. E.; Vevert, J. P. *Can. J. Chem.* **1981**, *59*, 572. (k) Sun, K. M.; Fraser-Reid, B. *Can. J. Chem.* **1980**, *58*, 2732. (l) Barrett, A. G. M.; Sheth, H. G. *J. Chem. Soc., Chem. Commun.* **1982**, 170. (m) Barrett, A. G. M.; Sheth, H. G. *J. Org. Chem.* **1983**, *48*, 5017. (n) Still, W. C.; MacPherson, L. J.; Harada, T.; Callahan, J. F.; Rheingold, A. L. *Tetrahedron* **1984**, *40*, 2275. (o) Batmangherlich, S.; Davidson, A. H. *J. Chem. Soc., Chem. Commun.* **1985**, 1399.

0022-3263/87/1952-0320$01.50/0

Scheme I[a]



[a] (a) 3-butenyl-MgBr/CuBr·$(CH_3)_2S$/THF/−78 °C; (b) LDA/THF/NH_3/CH_3I; (c) NH_2OH, pyridine, EtOH; (d) $SOCl_2$, CCl_4, −10 °C; (e) NaH, THF, 2,6-Cl_2BzBr; (f) DiBALH, CH_2Cl_2, H_3O^+; (g) I_2, CH_3CN; (h) CrO_3, H_2SO_4, H_2O, acetone; (i) Li-1,3-dithiane, THF, HMPA; (j) CH_2N_2, Et_2O; (k) HgO, BF_3·Et_2O, THF, H_2O; (l) $TiCl_4$, $(CH_3)_2Zn$, CH_2Cl_2, −78 °C; (m) $Li(CH_3)_2Cu$, Et_2O, −78 °C.

We have recently shown that application of a conjugate addition/alkylation reaction sequence to 2,2-dimethyl-3-(2*H*)-furanone (**2**), followed by oxidative excission of C-2, is a convenient entry to anti β-hydroxypropanoic acid derivatives (threo aldol products).[4] Reported here is an highly stereoselective synthesis of methyl nonactate which makes effective use of this process.

Conjugate addition of the magnesium bromide cuprate derived from 4-bromo-1-butene to furanone **2** followed by alkylation with methyl iodide afforded **3** as a 10/1 mixture of trans/cis isomers (Scheme I). Treatment of **3** with hydroxylamine and fragmentation of the derived oxime then yielded β-hydroxy nitrile **4**, which was shown to be a 32/1 mixture of anti/syn isomers by 250-MHz ^1H NMR and capillary gas chromatographic analyses. The isomeric enrichment had apparently occurred during the oximation step as was seen in earlier model studies.[4]

Of the several possible techniques for cyclizing **4** to the cis 2,5-disubstituted tetrahydrofuran ring present in the nonactins, the method of Bartlett involving treatment of an 3-alkenyl ether with iodine was chosen.[5] Thus, conversion of the 2,6-dichlorobenzyl ether **5** to the corresponding aldehyde **6** (DIBALH: H_3O^+) followed by exposure to iodine/acetonitrile yielded the cyclized iodo aldehyde **7** as a 50/1 mixture of cis/trans isomers about the tetrahydrofuran ring.[5,6] Oxidation of **7** to the carboxylic acid **8** followed by treatment with an excess of the lithium anion of 1,3-dithiane then yielded **9** in good yield. Liberation of the masked aldehyde **10** was accomplished according to the method of Vedejs.[7]

It was our intention to employ **10** as a precursor to both methyl nonactate **11** and its 8-epi isomer **12** by a judicious choice of organometallic reagent even though the existing literature on this point was not encouraging. For instance, Ireland had shown that the addition of lithium dimethylcopper to **10** in pentane afforded a 1/1 mixture of isomers at C-8,[3h,i] the same result as observed by White for the addition of ethereal methyl magnesium bromide to **10** at −78 °C.[3f] However, the related report by White[3f] that reduction of the corresponding methyl ketone with L-Selectride (Aldrich) gives a 9/1 mixture favoring the 8-epi isomer suggested that selective approach of a nucleophile to a C-8 carbonyl could be achieved in some instances, a suggestion that has been borne out in model studies.[8]

In the event, precomplexation of a CH_2Cl_2 solution of **10** with $TiCl_4$ followed by the addition of $(CH_3)_2Zn$ afforded a 24/1 mixture methyl nonactate (**11**) and 8-*epi*-methyl nonactate (**12**) in 85% yield. The 250-MHz ^1H NMR spectrum of **11** was identical in all respects with a spectrum authentic methyl nonactate.[9] Although the presumed reactive species under these reaction conditions is CH_3TiCl_3,[10] use of preformed CH_3TiCl_3 led only to recovered starting material.

(4) Baldwin, S. W.; McIver, J. M. manuscript submitted for publication in *Tetrahedron Lett.*

(5) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963.

(6) In complete accord with the results of Bartlett,[5] iodocyclization of the benzyl, *tert*-butyldimethylsilyl, *p*-bromobenzyl, and 2,6-dichlorobenzyl ethers of hydroxy nitrile **6** afforded cis/trans product ratios of 1:1, 4:1, 7:1, and 50:1, respectively.

(7) Vedejs, E.; Fuchs, P. L. *J. Org. Chem.* **1971**, *36*, 366.

(8) Baldwin, S. W.; McIver, J. M., manuscript in preparation.

(9) We thank Professor P. A. Bartlett for spectra of authentic methyl nonactate and 8-*epi*-methyl nonactate.

(10) (a) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

Alternatively, addition of lithium dimethylcopper to **10** in ether afforded **11** and **12** in a 1/4.5 mixture, this time favoring 8-*epi*-methyl nonactate (**12**), the ^{1}H NMR spectrum of which was identical with one of an authentic sample.[9] This result is in contrast to the 1/1 mixture previously obtained for the same reaction carried out in pentane.[3ij] The exact nature of this interesting solvent effect is not clear at the present time.

In summary, racemic methyl nonactate and 8-*epi*-methyl nonactate have each been prepared with good efficiency and high stereospecificity. The three diastereoisomeric relationships of methyl nonactate were introduced with stereoselectivities of 32:1, 50:1, and 24:1.

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Supplementary Material Available: A complete experimental section with synthetic procedures for all compounds in this work (9 pages). Ordering information is given on any current masthead page.

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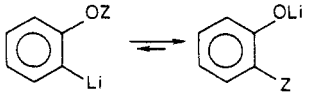
The Metal-Promoted Fries Rearrangement†

Summary: Upon reaction with *sec*-butyllithium at low temperature, *o*-bromophenyl esters **3** undergo an intramolecular acyl migration to produce, after hydrolysis, the corresponding *o*-hydroxy ketones **4**.

Sir: The O→C migration of silicon in **1** (Z = R_3Si) to form the corresponding lithum phenoxide **2** is a well-documented process.[1] This migration occurs when group Z (as

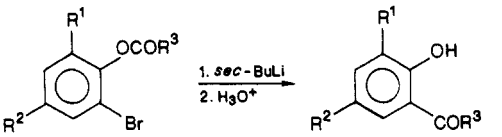


1 **2**

with R_3Si) is an electrophilic center with the capacity to serve as a bridge to effectively transport the negative charge from the aromatic carbon to the phenolic oxygen. Such a requirement is met when Z = acyl, and this has prompted our examination of the corresponding aryl ester → *o*-hydroxy ketone transformation, which can formally be viewed as a metal-promoted Fries rearrangement.[2,3]

We now wish to report that the Fries reaction can indeed be metal-promoted to afford, under the proper reaction conditions, good yields of *ortho-specific* acyl migration products (Table I).[4,5] For example, *o*-bromophenyl pivaloate (**3c**) was treated at −95 °C with *sec*-butyllithium (1.1 equiv, 4:1:1 THF/ether/hexane, 0.25 M) and stirred for 30 min. After an additional 30 min at −78 °C, the mixture was hydrolyzed with saturated NH_4Cl. GC analysis showed the formation of *o*-hydroxypivalophenone (**4c**)[6] in 76% yield.[7] The only other products detected were phenyl pivaloate and the starting aryl ester **3c**, each present in ca. 5% yield. It is significant that none of the regioisomeric *p*-hydroxypivalophenone is found in this reaction, since ortho/para mixtures are known to be commonplace with the Fries rearrangement.[8] In fact, treatment of phenyl pivaloate with $AlCl_3$ (1.2 equiv, $ClCH_2CH_2Cl$, reflux, 18 h) afforded, besides phenol (65%), *p*-*tert*-butylphenol (25%) as the only product derived from electrophilic aromatic substitution.[9,10] None of the *o*- or *p*-hydroxypivalophenones were found by GC examination. Thus, a distinct advantage of the metal-promoted Fries

Table I. Yields of *o*-Hydroxy Ketones 4 Derived from *o*-Bromophenyl Esters 3



3 **4**

entry	R^1	R^2	R^3	yield (%) of 4[d] GC (isolated)
a[a]	H	H	Et	17
b[a]	H	H	*i*-Pr	62 (54)
c	H	H	*t*-Bu	76 (68)
d[a,b]	H	H	Ph	7
e	H	H	1-adamantyl	(81)
f	H	H	*tert*-pentyl	91 (85)
g	H	Me	*t*-Bu	71 (62)
h	H	Me	*tert*-pentyl	84 (76)
i	H	H	$C(Me)_2CH_2Cl$	(49)
j[a]	Me	Me	Et	31 (17)
k[a]	Me	Me	*i*-Pr	72 (61)
l[a,c]	*t*-Bu	*t*-Bu	Me	52 (43)

[a] Yield (GC) of residual starting ester: **3a** (39%); **3b** (30%); **3d** (31%); **3j** (39%); **3k** (24%); **3l** (9%). [b] Major byproduct was di-*sec*-butylphenylcarbinol (30%). [c] 2.0 equiv of *sec*-butyllithium was used. [d] The IR and ^{1}H and ^{13}C NMR data of the isolated compounds were consistent with the assigned structure. In addition, all new compounds have yielded satisfactory high-resolution mass spectra.

† Dedicated to Prof. George Zweifel, an inspiring teacher and scientist, on the occasion of his 60th birthday.

(1) Simchen, G.; Pfletschinger, J. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 428. Habich, D.; Effenberger, F. *Synthesis* **1979**, 841 and references contained therein. Billedeau, R. J.; Sibi, M. P.; Snieckus, V. *Tetrahedron Lett.* **1983**, *24*, 4515.

(2) Although a recent paper has briefly touched on this rearrangement, extremely poor yields of acyl migration products were obtained from the pair of examples described: Hellwinkel, D.; Lammerzahl, F.; Hofmann, G. *Chem. Ber.* **1983**, 3375. The only other precedent to our work using a carbonyl as the migrating unit is the transformation **1** → **2** with Z = $CONR_2$: Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935. Miah, M. A. J.; Snieckus, V. *J. Org. Chem.* **1985**, *50*, 5436.

(3) (a) Interesting analogies to this reaction include the acyl migration occurring from a benzylic carbon to an aromatic carbon atom observed under strenuous reaction conditions,[3b] the Cr(II)-mediated conversion of *o*-*O*-acylbenzylic bromides into ortho-hydroxybenzyl ketones,[3c] and the conversion of phenyl tetrahaloethyl ethers to the corresponding 1-(2-hydroxyphenyl)alkynes.[3d] (b) Dyllick-Brenzinger, R. A.; Strothers, J. B. *J. Chem. Soc., Chem. Commun.* **1979**, 108. (c) Ledoussal, B.; Gorgues, A.; Le Coq, A. *J. Chem. Soc., Chem. Commun.* **1986**, 171. (d) Subramanian, R.; Johnson, F. *J. Org. Chem.* **1985**, *50*, 5430.

(4) The fact that the metal-promoted Fries reaction provides good yields of *o*-hydroxy ketones **4** from esters **3** possessing 2°-substituted acyl moieties (e.g., **3b**,**k**) demonstrates that metal–halogen exchange with subsequent acyl migration occurs in preference to enolization.

(5) No clear advantage in yield or purity of the ketones **4** was gained by substituting bromine in **3** with iodine, or by using alternative organolithium reagents. However, in most cases a 10–20% increase in yield was realized by lowering the reaction temperature from −78 °C to −95 °C.

(6) Basil, B.; Coffee, E. C. J.; Gell, D. L.; Maxwell, D. R.; Sheffield, D. J.; Wooldridge, K. R. H. *J. Med. Chem.* **1970**, *13*, 403.

(7) The attempted direct ortho-metalation of phenyl pivaloate with *sec*-butyllithium/TMEDA (−95 °C) provided the acyl migration product **4c** in only 6% yield.

(8) Blatt, A. H. *Org. React. (N.Y.)* **1942**, *1*, 342. Gerecs, A. in *Friedel-Crafts and Related Reactions*; Olah, G. A., Ed.; J. Wiley & Sons: New York, 1964; Vol. 3, Pt. 1, pp 499–533.

(9) Similar results from the attempted Fries rearrangement of phenyl pivaloate have been observed: Martin, R. *Bull. Soc. Chim. Fr.* **1979**, 373.

(10) Acylium ions which are highly hindered by branching at the α-carbon, such as pivaloyl cation, often furnish only alkylated benzenes in Friedel–Crafts reactions due to the loss of carbon monoxide: Olah, G. A.; Germain, A.; White, A. M. In *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley-Interscience: New York, 1976; Vol. 5, p 2123.

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