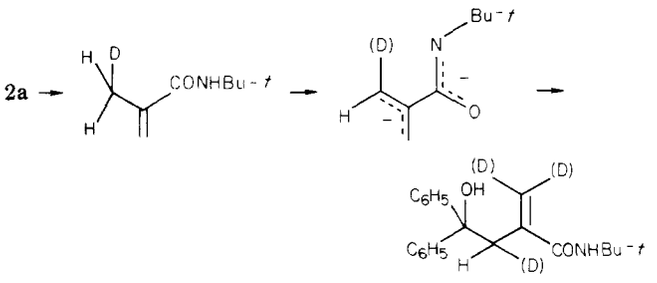
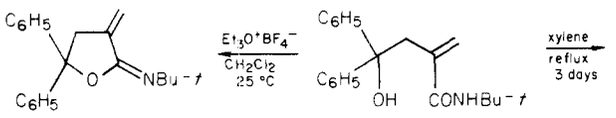
Scheme II

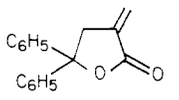


Scheme III



77%, mp 134 °C

4a



87%, mp 101 °C

of HMPA prior to the alkylating agent produces the α-substituted acrylamide. The presence of the other isomer could not be detected under these experimental conditions. Thus, through a judicious selection of the reaction conditions, either of the two possible isomers can be obtained.

Not unexpectedly the deprotonated species **3** exhibits the behavior of an allylic carbanion. This is exemplified by deprotonating the monodeuterated amide **2a**[7] followed by addition to benzophenone. The deuterium label in the product **4a** is scrambled as expected to both the sp^2 and the allylic carbon atoms (Scheme II).

Selection of the *tert*-butyl amide **2a** brought about the sought for advantages in the formation of the dianion **3a**; however, further elaboration of the carbinols **4–8** was rendered somewhat more difficult because of the relative inertness of the bulky amide group. Hydrolysis under a variety of acidic and basic conditions proved to be unsuccessful. The mildest method of amide activation, namely, O-alkylation with triethyloxonium tetrafluoroborate in methylene chloride, leads to instant internal nucleophilic attack by the carbinol oxygen and formation of the corresponding crystalline α-methylene iminolactones. While these species serve as effective Michael acceptors toward good nucleophiles (e.g., thiophenol), their stability toward aqueous acids is remarkable.[8] In no instance was it possible to obtain the corresponding lactones. These, however, are accessible by prolonged heating of the carbinol amides in xylene (Scheme III).

Similarly obtained were the respective iminolactone from **8** (42% overall from **2a**, mp 94 °C) and the lactone from **7** (60%, mp 47 °C).

In synopsis, we have illustrated the feasibility of dilithiation of secondary methacrylamides[9] and the reaction of the resulting dianions with various electrophiles. *N-tert*-Butylmethacrylamide in particular is perceived as a useful reagent for an efficient elaboration of γ-disubstituted α-methylene butyrolactones and, quite generally, for the direct introduction of the methacrylamide fragment.

(7) Obtained by quenching **3a** with D_2O. Deuterium content >90% by mass spectrum and NMR.

(8) A similar stability of spiro-α-methylene iminolactones has been reported in the case of a steroid: Riediker, M.; Graf, W. *Helv. Chim. Acta* **1979**, *62*, 1586.

(9) (a) The feasibility of dimetalation of cyclic and more highly substituted acrylamides has independently been observed by P. Beak, University of Illinois. We thank Dr. Beak for informing us of his observations. (b) Beak, P.; Kempf, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 4550.

Registry No. 2a, 6554-73-0; **2b**, 3887-02-3; **4a**, 74844-20-5; **4a** iminolactone, 74844-21-6; **4a** lactone, 29043-99-0; **4b**, 74844-32-9; **5**, 74844-22-7; **6**, 74844-23-8; **7**, 74844-24-9; **7** lactone, 74844-25-0; **8**, 74844-26-1; **8** iminolactone, 74844-27-2; **9**, 74844-28-3; **10**, 74844-29-4; **11**, 74844-30-7; **12**, 74844-31-8; diphenylmethanone, 119-61-9; adamantanone, 700-58-3; 1-phenylethanone, 98-86-2; 4-methoxybenzaldehyde, 123-11-5; (*E*)-3-phenyl-2-propenal, 14371-10-9; (bromomethyl)benzene, 100-39-0; 1-iodopropane, 107-08-4; ethylene oxide, 75-21-8.

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A Chiral Total Synthesis of (−)- and (+)-Nonactic Acids from Carbohydrate Precursors and the Definition of the Transition for the Enolate Claisen Rearrangement in Heterocyclic Systems[1]

Summary: A total synthesis of the (−)- and (+)-nonactic acids (**7R**) and (**8S**) from D-mannose and D-gulono-γ-lactone, respectively, which utilizes the enolate Claisen rearrangement and serves to define the boat-like transition state for the rearrangement in these heterocyclic systems is described.

Sir: As an extension of the methodology and synthetic strategy that has led to the total synthesis of the ionophore antibiotic lasalocid A (X537A) from chiral carbohydrate precursors,[2] the component nonactic acids **7S** and **8R** of the macrotetrolide nonactin[3] loom as appropriate targets. While nonactin[4] and its component acids[5] have been synthesized several times with more or less stereochemical control, the enolate Claisen rearrangement as applied to carbohydrate-derived furanoid glycals[6] for the control of side-chain stereochemistry seemed ideally suited for the efficient construction of these molecules. In addition, since the absolute configurations of the nonactic acids **7S** and **8R** are known,[3] the introduction of the C2 and C3 chiral centers of the propionic acid side chain via the enolate Claisen rearrangement provides an opportunity to check the character of the transition state (chair or boat?) for this reaction in these heterocyclic systems. We earlier showed[7] that the *E*/*Z* ratio of the enolate generated by the action of lithium diisopropylamide (LDA) on propionate esters is solvent dependent and that the geometrical isomer of choice can be made to predominate to the extent of

(1) Contribution no. 6222. Grateful acknowledgement is made to the National Science Foundation for a Grant (CHE 7821066) in support of this work.

(2) Ireland, R. E.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 1155–1157.

(3) Dominguez, J.; Dumitz, J. D.; Gerlach, H.; Prelog, V. *Helv. Chim. Acta* **1962**, *45*, 129–138. Keller-Schierlein, W.; Gerlach, H. *Fortschr. Chem. Org. Naturst.* **1968**, *26*, 161–189.

(4) Gerlach, H.; Oertle, K.; Thalmann, A.; Servi, S. *Helv. Chim. Acta* **1975**, *58*, 2036–2043. Schmidt, U.; Gombos, J.; Haslinger, E.; Zak, H. *Chem. Ber.* **1976**, *109*, 2628–2644.

(5) For a review, see: Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2–72.

(6) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48–61.

(7) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877.

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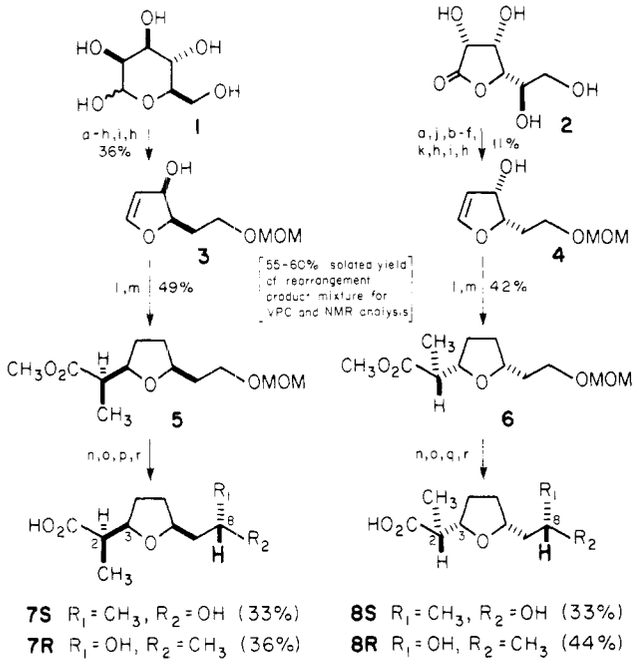
Scheme I. Synthesis[8] of (−)- and (+)-Nonactic Acids[a]

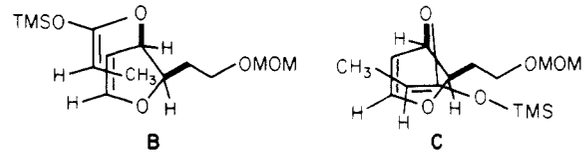


[a] a, CH_3COCH_3, H^+; b, NaH, $C_6H_5CH_2Cl$, DMF; c, concentrated HCl, CH_3OH; d, $(CH_3)_2NCH(OCH_3)_2$, CH_2Cl_2; e, $(CH_3CO)_2O$, 130 °C; f, 9-BBN, THF; H_2O_2, aqueous NaOH; g, KH, $ClCH_2OCH_3$; h, Li, NH_3; i, $(C_6H_5)_3P$, CCl_4; j, *i*-Bu_2AlH, Et_2O; k, $CH_2(OCH_3)_2$, P_2O_5; l, *n*-BuLi; C_2H_5COCl; LDA, THF; Me_4SiCl, room temp; H_2O, OH^-; CH_2N_2; m, H_2, Rh/C, THF; n, 2% HCl, CH_3OH; o, $(COCl)_2$, Me_2SO; Et_3N; p, $LiCu(CH_3)_2$, pentane; q, CH_3MgBr, Et_2O, −78 to −10 °C; r, 2 N KOH, H_2O.

85–90% of the mixture. This observation, coupled with the appropriate choice of a chiral carbohydrate precursor for the allylic alcohol portion of the diene system, uniquely defines the geometrical and stereochemical parameters of the rearrangement substrate. As a result, the stereochemistry of the single bond that is formed in the rearrangement will depend only on whether a chair-like or boat-like transition state is followed.

For the synthesis of (−)-nonactic acid (**7S**) (Scheme I) the furanoid glycal **3**, available[6] in 36% overall yield in ten steps from D-mannose (**1**), is the appropriate chiral precursor for definition of the allylic alcohol portion. Correspondingly, the glycal **4**, derived[6] from D-gulono-γ-lactone (**2**) in 11% overall yield in 11 stages, is required for the (+)-nonactic acid (**8R**) synthesis. When the labile[6] intermediate propionates of these enantiomeric glycals **3** and **4** are enolized with LDA in pure THF, previous work[7] shows that the *Z* enolate is the predominate geometrical isomer formed, and thereby the rearrangement substrate is defined. After the enolate is trapped with Me_3SiCl, rearrangement is allowed to occur, and the subsequent product mixture is further processed by esterification and then hydrogenation. Analysis (VPC and NMR) of the product mixtures[8] obtained in moderate yield from each of the glycals **3** and **4** showed that in each case one diastereomer of the esters **5** and **6** predominated in an 86–89/14–11 ratio. After separation by column chromatography, each of the major ester constituents was converted to the nonactic acid structure as shown (Scheme I). No stereochemical control was possible in the organometallic addition step of this sequence, and thus both epimers about C8 were obtained in approximately equal amounts. Comparison of the optical, physical, and spectral data[8] of these products with those published[4] for the nonactic acids and their C8 epimers established that the D-mannose derived glycal **3** had led to (−)-nonactic acid (**7S**) and its C8 epimer **7R**, while the D-gulano-γ-lactone glycal **4** had generated (+)-nonactic acid (**8R**) and its C8 epimer **8S**.

In addition to the completion of a new, chiral synthesis of the nonactic acids, these results serve to establish that in these heterocyclic systems (like in the cycloalkyl systems[9]) the Claisen rearrangement takes place through a boat-like transition state that probably resembles diagram B for the silyl ketene acetal from the glycal **3**, for instance. Rearrangement of this *E* silyl ketene acetal through a transition state like B will lead to the 2*R*,3*R* ester enantiomer **5** and thence to the (−)-nonactic acids (**7R**) and (**7S**).



Rearrangement of this *E* silyl ketene acetal through the alternate chair-like transition state C would have generated the 2*S*,3*R* diastereomer of the ester **5** and thence the 2-epinonactic acids. This definition of the pathway for these types of Claisen rearrangements is important to the scope of this useful reaction sequence.

Supplementary Material Available: Infrared and proton magnetic resonance spectra, optical rotations, physical constants, thin-layer chromatographic mobility, and elemental combustion analyses of compounds 3–8 and isolated intermediates (9 pages). Ordering information is given on any current masthead page.

(8) All isolated intermediates and synthetic (−)- and (+)-nonactic acids were characterized by appropriate physical, optical, and spectral (IR, NMR) data, thin-layer and vapor-phase chromatographic behavior and combustion analysis. For details, see the supplementary material.

(9) Lythgoe, B.; Cave, R. J.; Metcalfe, D. A.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1218–1228.

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A Direct Synthesis of *Z*-Trisubstituted Allylic Alcohols via the Wittig Reaction

Summary: The lithium-free modification of the Wittig reaction of unstabilized ylides and acyclic α-alkoxy ketones leads to protected trisubstituted allylic alcohols with high stereoselectivity for the *Z* isomer.

Sir: In the 25 or so years since its discovery, the Wittig reaction has served as a most powerful method for the regiocontrolled and, more recently, the stereocontrolled construction of carbon–carbon double bonds.[1] The latter aspect is of special significance and it is largely through publications of Schlosser and co-workers that highly ster-

(1) Reviews: A. W. Johnson, "Ylid Chemistry", Academic Press, New York, 1966; M. Schlosser, *Top. Stereochem.*, 5, 1 (1970); H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, Menlo Park, CA, 1972, pp 682–709; M. Schlosser in "Methodicum Chimicum", Vol. 7, F. Korte, H. Zimmer, and K. Niedenzu, Eds., Thieme, Stuttgart, 1976, pp 529–552.

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