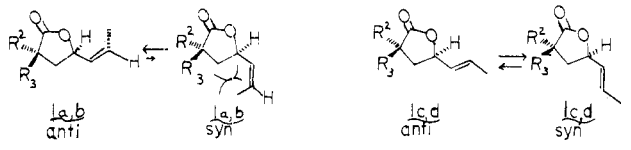
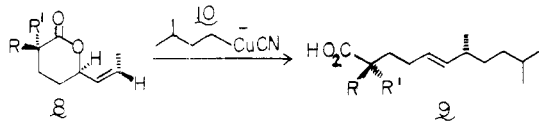
6b which was confirmed by the ratio of **4a***[8] to **4b**. Similar analysis of **7** (**7a**, δ 139.68, 124.50, 37.80, 25.05, 20.82; **7b**, δ 139.00, 124.26, 37.36, 25.20, 21.16) revealed a ratio of **7a** to **7b** of 84:16 which was confirmed after hydrogenation to **4b***[8] and **4a**, respectively.

These results are consistent with a net S_N2' alkylation with inversion in all cases but with selective ionization from one conformer in the *Z* series and from both conformers in the *E* series (in contrast to the palladium results which showed only one isomer in both olefin series). Consideration of the nonbonded interactions in the anti and syn conformers required for ionization reveals that only in the



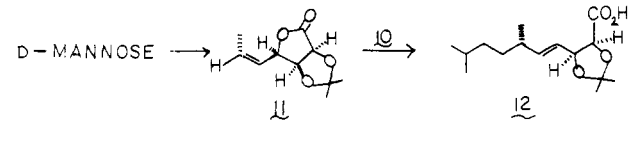
1a,b syn conformer does a substantial nonbonded interaction exist to destabilize this conformer. Thus, in the *Z* olefin isomers, ionization occurs only from the anti form. On the other hand, the difference between *anti*-**1c,d** and *syn*-**1c,d** is much less, although some preference still exists for products from the anti form. The difference between copper and palladium presumably reflects the ability of the increased bulk of the palladium catalyst to accentuate the steric differences in the transition state of ionization from the anti form (which produces the more stable syn–syn complex) and the syn form (which produces the less stable syn–anti complex).

By varying ring size, the relationship of new chiral centers can be manipulated. For example, the six-membered-ring lactones **8a**[5a,6,9] (R = CH_3, R′ = H) and **8b**[5a,6,9] (R = H, R′ = CH_3) each led to a single alkylation product,



9a[5a,6] (R = CH_3, R′ = H) and **9b**[5a,6] (R = H, R′ = CH_3), respectively, with no crossover upon treatment with cuprate **10**. With the *E* olefin series related to **8**, substantial crossover occurred again.

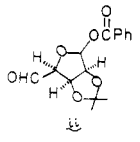
An advantage of this approach is the ready availability of chiral substrates from carbohydrates. Thus, the lactone **11** [mp 107–108 °C; $[\alpha]^{25}_D$ +62.14° (*c* 0.985 $CHCl_3$)] is



available in 10–15% overall yield from D-mannose.[10]

(9) Available in a manner similar to that reported[2] for the five-membered lactones. The details will be published in the full account of this work.

(10) The known aldehyde ii was prepared by reported methods: Ohrui, H.; Emoti, S. *Tetrahedron Lett.* **1975**, 2765. This aldehyde was converted to **11** by a Wittig reaction ($Ph_3P^+CH_2CH_3Br^-$, KOC_4H_9-*t*, THF, −78 °C to room temperature), hydrolysis to the lactol (KOH, CH_3OH, room temperature), and Moffatt oxidation (ClCOCOCl, Me_2SO, $(C_2H_5)_3N$). The Wittig reaction gave an 85:15 mixture of the *Z* and *E* olefins from which the pure *Z* isomer was isolated by recrystallization from hexane.



Coupling of **11** with cuprate **10** gave a single product **12**, characterized as its methyl ester ($[\alpha]^{25}_D$ +57.52° (*c* 1.01, $CHCl_3$)) in 90–91% yield.

Thus vinyl lactones represent excellent substrates for chirality transfer via organometallic intermediates. As illustrated, variation of the distance between the chiral centers can be controlled by ring size of the lactone as well as by positioning of the substituents on the substrate. Furthermore, net S_N2' reaction with either retention or inversion is available by choosing either palladium or copper chemistry, respectively. The more limited selectivity in the copper chemistry compared to that of palladium is noteworthy.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for their generous support of our programs. Dr. Noal Cohen provided generous samples of comparison compounds for which were are grateful. We thank Messrs. Patrick McDougal and Norman Schmuff for helpful suggestions during this work.

Registry No. (±)-**1a**, 74911-64-1; (±)-**1b**, 74911-65-2; (±)-**1c**, 74911-66-3; (±)-**1d**, 74911-67-4; **2**, 74924-87-1; (±)-**3a**, 74911-68-5; (±)-**3b**, 74911-69-6; (±)-**4a**, 74957-65-6; (±)-**4b**, 42763-78-0; (±)-**5a**, 74911-70-9; (±)-**5b**, 74911-71-0; (±)-**6b**, 74911-72-1; (±)-**7b**, 74911-73-2; (±)-(*Z*)-**8a**, 74911-74-3; (±)-(*E*)-**8a**, 74911-75-4; (±)-(*Z*)-**8b**, 74911-76-5; (±)-(*E*)-**8b**, 74911-77-6; (±)-(*E*)-**9a**, 74911-78-7; (±)-(*Z*)-**9a**, 74911-79-8; (±)-(*E*)-**9a** methyl ester, 74911-80-1; (±)-(*E*)-**9b**, 74911-81-2; (±)-(*Z*)-**9b**, 74911-82-3; (±)-(*E*)-**9b** methyl ester, 74911-83-4; **10**, 74924-88-2; (*Z*)-**11**, 74911-84-5; (*E*)-**11**, 74957-66-7; **12**, 74911-85-6; **12** methyl ester, 74911-86-7; D-mannose, 3458-28-4.

Supplementary Material Available: Detailed description of spectral data for **3a,b**, **5a,b**, **6a,b**, **7a,b**, **8a,b**, **9a,b**, **11**, and **12** (4 pages). Ordering information is given on any current masthead page.

Barry M. Trost,* T. P. Klun
McElvain Laboratories of Organic Chemistry
Department of Chemistry
University of Wisconsin
Madison, Wisconsin 53706
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Dimetalation of *N-tert*-Butylmethacrylamide: A New Synthetic Reagent

Summary: Dimetalation of *N-tert*-butylmethacrylamide with *n*-butyllithium gives a reagent equivalent to the dianion of methacrylic acid. Its reaction with various electrophiles and the transformation of certain primary products to α-methylene lactones is exemplified.

Sir: With the possible exception of the zinc reagent derived from α-(bromomethyl)acrylic acid esters,[1] a general synthetic equivalent to the dianion of methacrylic acid has been elusive to date. We here report the successful dilithiation of *N-tert*-butylmethacrylamide, resulting in a useful reagent for the facile preparation of α-methylene lactones and α-substituted acrylamides.

A major reason for the previously reported failures to form mono- or dideprotonated methacrylic acid derivatives has been the marked propensity of these substrates to serve as Michael acceptors toward the bases utilized or to undergo rapid self-addition upon deprotonation. Such

(1) (a) Loeffler, A.; Pratt, R. D.; Pucknat, T.; Geibard, G.; Dreiding, A. S. *Chimia* **1969**, *23*, 413. (b) Oehler, E.; Reininger, D.; Schmidt, U. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 457.

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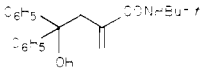
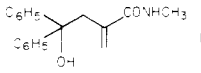
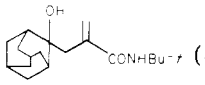
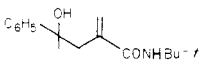
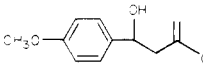
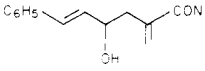
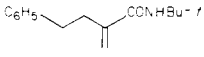
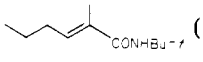
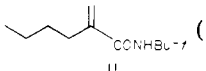
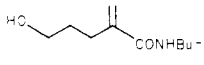
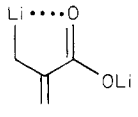
Table I. Reaction of the Dianion of *N-tert*-Butylmethacrylamide with Electrophiles

amide[a]	electrophile	product	isolated yield,[b] %	mp (bp), °C	reaction conditions[c]
2a	$(C_6H_5)_2CO$	 (4a)	88.1	104-106	−20/25 °C, 1 h
2b	$(C_6H_5)_2CO$	 (4b)	52.5	131-133	−20/25 °C, 1 h
2a	adamantanone	 (5)	84.7	121-125	−20/25 °C, 1.5 h
2a	$C_6H_5COCH_3$	 (6)	75.9	98-100	−20/25 °C, 1.5 h
2a	4-$CH_3OC_6H_4CHO$	 (7)	73.4	83-85	−20/25 °C, 1.5 h
2a	*trans*-C_6H_5CH=CHCHO	 (8)	(>70)	(oil)	−70/25 °C, 1.5 h
2a	$C_6H_5CH_2Br$	 (9)	56.5	72-74	−70 °C, 1 equiv of HMPA, 25 °C, 16 h
2a	$CH_3CH_2CH_2I$	 (10)	65.6	100 (0.25 mmHg)	−70/25 °C, 16 h
2a	$CH_3CH_2CH_2I$	 (11)	60	125 (0.5 mmHg)	−70 °C, 1 equiv of HMPA, 25 °C, 16 h
2a	ethylene oxide	 (12)	68.6	128 (0.2 mmHg)	−70 °C, 4 equiv of ethylene oxide, 25 °C, 16 h

[a] Metalation of the amides was performed as described above. [b] Yields indicated are for analytically pure material. All compounds (except 8 which was directly converted to the iminolactone, vide infra) gave satisfactory analytical and spectroscopic data. [c] The conditions indicate: temperature at which electrophile is added, cosolvents, if any, and temperature and reaction time after addition of substrate.

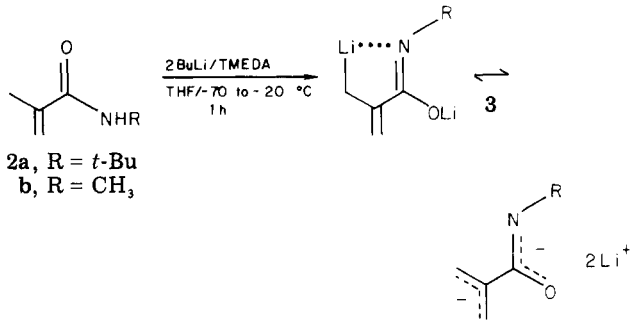
observations have been made in the case of methacrylic acid itself,[2] the diisopropyl amide,[3] and the corresponding oxazoline.[4] Accordingly, the successful generation of a reagent such as **1** had to be based on the ability of a



1

modified carboxyl function to suppress or ideally avoid both 1,2- and 1,4-addition of the metalating agent as well as to stabilize the resulting carbanion through internal chelation. The secondary amide group has successfully been employed to facilitate and direct ortho metalation in carbocyclic and heterocyclic aromatic systems, and it enabled the efficient deprotonation of the nuclear methyl group in *o*-toluamide.[5] An investigation of the lithiation of amides of methacrylic acid revealed that the secondary amide group indeed meets the desired criteria (Scheme I). Although the methyl amide **2b** can be utilized, the *tert*-butyl amide **2a** is clearly superior, as it is a considerably more stable crystalline compound with little tendency to polymerize.

Scheme I



2a, R = *t*-Bu
b, R = CH_3

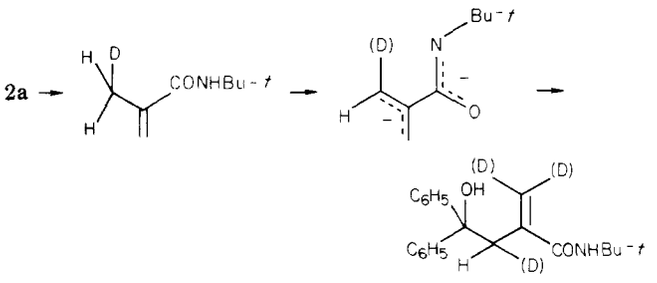
Treatment of a solution of amide **2a** (1.41 g, 10 mmol) and TMEDA (tetramethylethylenediamine, 3 mL, 20 mmol) in THF (30 mL) at −70 °C with 20 mmol of *n*-butyllithium (9.1 mL of a 2.4 M solution in hexane) followed by warming to −20 °C produces after 1 h at −20 °C a nearly optimal amount of the desired anion **3**.[6] Reaction with benzophenone (1.52 g, 8.3 mmol in 5 mL of THF, −20 to +25 °C, 1 h) followed by aqueous workup (ether, brine) leads to the isolation of 2.36 g of amide **4a** (88.1%, mp 104–106 °C, from ether/hexane). As is evident from Table I, the reaction of the dianion **3a** with ketones, aldehydes, halides, and epoxides proceeds fairly well and is optimal in the case of nonenolizable ketones (entries **4a** and **5**).

An interesting facet in the alkylation of the dianion **3a** with alkyl halides is the location of the double bond in the product. In the absence of hexamethylphosphoramide (HMPA), the alkylation product is exclusively the one with the trisubstituted double bond, whereas addition of 1 equiv

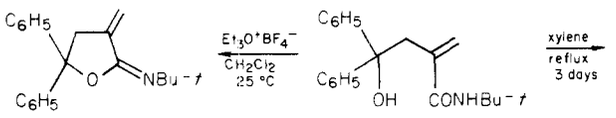
(2) Cf. Carlson, R. M. *Tetrahedron Lett.* **1978**, 111.
(3) Bannwarth, W.; Eidenschink, R.; Kauffmann, Th. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 468.
(4) (a) Meyers, A. I.; Smith, R. K.; Whitten, C. E. *J. Org. Chem.* **1979**, *44*, 2250 and references cited therein. (b) The oxazoline derived from α-methylacrylic acid, a distillable but readily polymerizable compound, could not be deprotonated in the classical sense with either *n*-BuLi or lithium tetramethylpiperidide due to the exceedingly facile 1,4-addition of both bases.
(5) Vaulx, R. H.; Puterbaugh, W. H.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 3514. (b) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1.

(6) The presence of TMEDA markedly increases the ease of deprotonation.

Scheme II

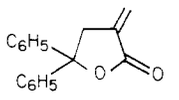


Scheme III



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.

John J. Fitt, Heinz W. Gschwend*
CIBA-GEIGY Corporation
Pharmaceuticals Division
Research Department
Summit, New Jersey 07901
Received June 11, 1980

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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