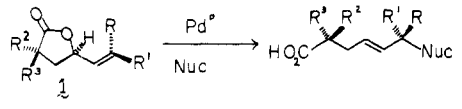
Communications

Chirality Transfer in Acyclic Systems via Organocopper Chemistry

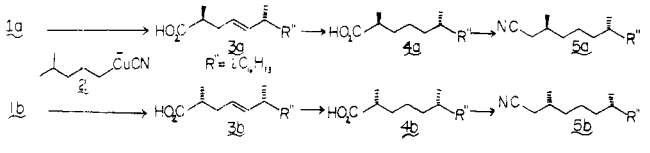
Summary: The reaction of vinyl lactones with alkylcyanocuprates led to a useful approach to chirality transfer.

Sir: Creation of acyclic stereochemistry represents a major synthetic challenge in the total synthesis of complex natural products. Transfer of chirality via highly ordered molecular rearrangements provides a useful approach to this problem.[1] Greater versatility in the structure of the group to be introduced would exist if organometallic derivatives could be used. The regio- and stereochemical instability of main-group alkyl organometallics led us to examine the chemistry of organopalladium intermediates with substrates such as **1**.[2] For chirality transfer to be



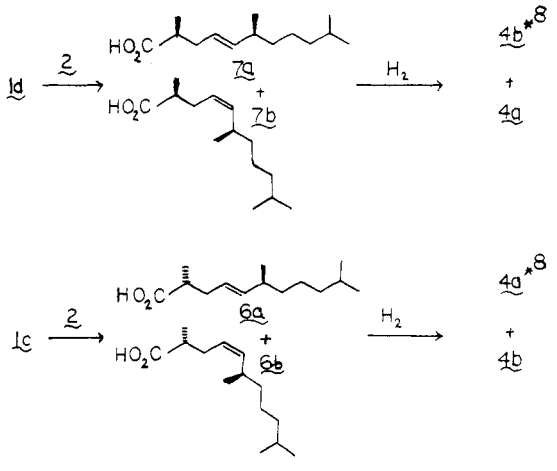
synthetically useful, it must (1) effect ionization of the substrate from a single conformation, (2) form the new C–C bond faster than lose stereochemical information, and (3) react regioselectively. Palladium met all these criteria involving net replacement of a C–O bond with allyl inversion and retention of configuration. The suggestion that organocopper reactions may involve functional equivalents of π-allyl metal species as intermediates[3] (analogous to palladium) led us to explore the reactions of our substrates **1** in the context of creation of the Vitamin E side chain[1a,4] since a stereochemistry complementary to the palladium reaction would be anticipated.

Treatment of the *Z* olefin isomers of **1**[2] (**1a**, R = R² = CH_3, R′ = R³ = H; **1b**, R = R³ = CH_3, R′ = R² = H) with cuprate **2** (ether, −20 to 0 °C) led in each case to a single product **3a** or **3b**, in 94–95% yield, as determined by



67.9-MHz ^{13}C NMR spectroscopy. To confirm the stereohomogeneity and assign stereochemistry, each was reduced (3 atm of H_2, W-2 Raney Ni, C_2H_5OH, and room temperature or 1 atm of H_2, 5% Pd/$BaSO_4$, C_2H_5OAc, and room temperature) to give **4a**[5b] and **4b**,[5b] respectively, and subsequently converted by a three-step operation to nitriles **5a**[5,7] and **5b**[5,7] [(i) BH_3, THF, 0 °C, quench with CH_3OH; (ii) TsCl, C_5H_5N, 0 °C; (iii) NaCN, Me_2SO, 80 °C] in 53% overall yield from starting lactones **1a** and **1b**. For both **4a,b** and **5a,b**, only one set of absorptions was observed in the ^{13}C NMR spectra. Comparison of these spectra to spectra of authentic samples of **5a** and **5b** confirmed their identity and revealed that the cuprate reaction proceeded cleanly by an S_N2' mechanism with inversion of configuration and with no detectable crossover. Admixture of authentic samples of **5a** and **5b** revealed absorptions for each isomer that were easily discernible: δ 37.32, 24.56, 19.62, and 19.45 for **5a** and δ 37.26, 24.49, 19.66, and 19.52 for **5b**. The latter compound has already served as the side-chain portion of vitamin E[7] and could be envisioned as the side-chain portions of phytol, Vitamin K's, etc.

On the other hand, reactions of the *E* olefin isomers related to **1**[2] (**1c**, R = R² = H, R′ = R³ = CH_3; **1d** R = R³ = H, R′ = R² = CH_3) under identical cuprate conditions led to a mixture of two isomers (**6a,b**[5b] from **1c** and **7a,b**[5b] from **1d**) which, upon hydrogenation (3 atm of H_2, W-2



Raney Ni, C_2H_5OH, room temperature) still produced two isomers which were identical with **4a***[8] and **4b**. ^{13}C analysis of **6** (**6a**, δ 139.66, 124.55, 37.76, 20.82, 16.19; **6b** δ 138.95, 124.33, 37.78, 21.21, 16.50) revealed a 77:23 ratio of **6a** to

(1) (a) Cohen, N.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1980**, *45*, 582 and earlier references in the series. (b) Hill, R. K; Khatri, H. N. *Tetrahedron Lett.* **1978**, 4337. (c) Bertrand, M.; Dulcere, J.-P.; Gil, G. *Ibid.* **1980** 1945. (d) Ireland, R. E.; Thaisrwongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48 and references therein. (c) Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774. (f) Wilson, S. R.; Myers, R. S. *J. Org. Chem.* **1975**, *40*, 3309. (g) Sucrow, W.; Richter, W. *Chem. Ber.* **1971**, *104*, 3679. (h) Stork, G.; Takahashi, T.; Kawamoto, I.; Suzuki, T. *J. Am. Chem. Soc.* **1978**, *100*, 8272.

(2) Trost, B. M.; Klun, T. P. *J. Am. Chem. Soc.* **1979**, *101*, 6756.

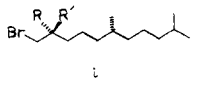
(3) (a) Claesson, A.; Olsson, L.-I. *Chem. Commun.* **1978**, 621. (b) Goering, H. L.; Singleton, V. D. *J. Am. Chem. Soc.* **1976**, *98*, 7854. (c) Both syn and anti S_N2' substitutions have been observed in propargyl systems. Westmijze, H.; Vermeer, P. *Tetrahedron Lett.* **1979**, 4101. Claesson, A.; Olsson, L.-I. *J. Am. Chem. Soc.* **1979**, *101*, 7302.

(4) Fuganti, C.; Grasselli, P. *J. Chem. Soc., Chem. Commun.* **1979**, 995. Zell, R. *Helv. Chim. Acta* **1979**, *62*, 474. Kabbea, H. J.; Heitzer, H. *Synthesis* **1979**, 888. Schmid, M.; Barner, R. *Helv. Chim. Acta* **1979**, *62*, 464.

(5) (a) This compound has been fully characterized by spectral means and elemental composition, by either high-resolution mass spectrometry or combustion analysis. (b) This compound has been characterized only by spectral means.

(6) A detailed description of spectral data for this compound appears in the supplementary material.

(7) These are known compounds prepared by Dr. N. Cohen, Hoffmann-La Roche. Authentic samples were prepared from the bromides i which were generously supplied by Dr. Cohen. For the bromide, see: Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505, 3512.



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(8) From the absolute configurations drawn, hydrogenation of **6a** produces the enantiomer of **4a**, which has been designated **4a***, and of **7b**; the enantiomer of **4b** has been designated **4b***. Since we are operating with racemates, these drawings are only formalisms.

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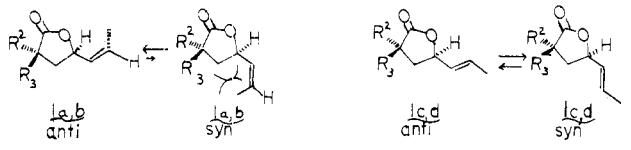
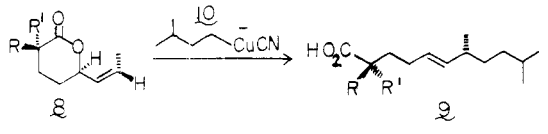
6b which was confirmed by the ratio of **4a***[8] to **4b**. Similar analysis of **7** (**7a**, δ 139.68, 124.50, 37.80, 25.05, 20.82; **7b**, δ 139.00, 124.26, 37.36, 25.20, 21.16) revealed a ratio of **7a** to **7b** of 84:16 which was confirmed after hydrogenation to **4b***[8] and **4a**, respectively.

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



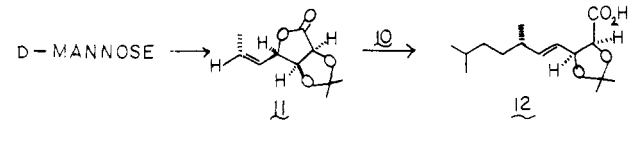
1a,b syn conformer does a substantial nonbonded interaction exist to destabilize this conformer. Thus, in the *Z* olefin isomers, ionization occurs only from the anti form. On the other hand, the difference between *anti*-**1c,d** and *syn*-**1c,d** is much less, although some preference still exists 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.

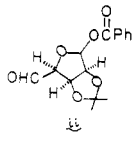
An advantage of this approach is the ready availability of chiral substrates from carbohydrates. Thus, the lactone **11** [mp 107–108 °C; $[\alpha]^{25}_D$ +62.14° (*c* 0.985 $CHCl_3$)] is



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.

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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.

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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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