1,3-cyclopentanediol, 16326-98-0; Ph_3P, 603-35-0.

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Asymmetric Synthesis of γ-Lactones. A Facile Synthesis of the Sex Pheromone of the Japanese Beetle

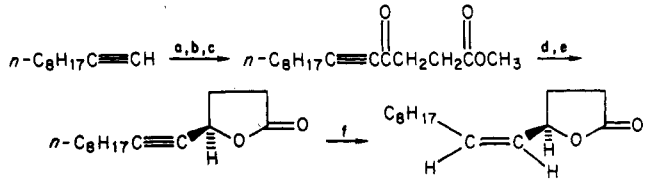
Summary: The sex pheromone of the Japanese beetle, (*R*)-(−)-(*Z*)-5-tetradecen-4-olide, has been prepared in essentially 100% optical purity by using the asymmetric reducing agent *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane to introduce chirality.

Sir: Chirality often plays a critical role in the biological activity of molecules. This phenomenon is particularly important for the sex pheromone produced by the female Japanese beetle, *Popillia japonica*, which has been identified as (*R*)-(−)-(*Z*)-5-tetradecen-4-olide. As little as 1% of the *S,Z* isomer can significantly reduce the response of male beetles to the *R,Z* isomer. The *R* and *S* enantiomers of the pheromone were originally prepared from glutamic acid.[1] Unfortunately, only the more expensive *R*-(−)-glutamic acid leads to the correct enantiomer. More recently the pheromone has been prepared by resolution[2] and by asymmetric reduction[3] of an intermediate. However, these methods do not all give product of high optical purity.[4] Since the pheromone can be used to survey and control this major pest, effective methods for its synthesis would be useful.

We recently reported a route to γ-lactones through the asymmetric reduction of 4-oxo-2-alkynoates.[5] Application of this method to a synthesis of the Japanese beetle pheromone was complicated by the length of the synthesis and the need to manipulate sensitive intermediates. We now report a short synthesis which provides pheromone of essentially 100% optical purity.

The procedure is outlined in Scheme I. The propargyl ketone was prepared in 67% yield from 1-decyne and the acid chloride[6] by using the procedure of Normant.[7] By using the copper(I) bromide–methyl sulfide complex[8] the yield of the propargyl ketone could be increased to 85%. The chiral center was then introduced to asymmetric reduction of the propargyl ketone with *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane (Alpine-borane).[9] The reagent from (+)-α-pinene produced the required *R* enantiomer in

Scheme I[a]



[a] Reagents: (a) *n*-BuLi. (b) CuI/LiI. (c) $ClCOCH_2CH_2CO_2CH_3$, 0 °C, 5 min. (d) Alpine-borane room temperature, 7 days. (e) NaOH/MeOH, reflux, 15 min. Neutralize, 1 N HCl, recrystallize with cyclohexylamine, H^+, distill. (f) $H_2Pd/CaCO_3$ poisoned with lead/quinoline.

70–75% chemical yield. Commercially available (+)-α-pinene (92% optical purity) gave product of 85–90% enantiomeric excess as judged by the use of a chiral NMR shift reagent. Using optically-pure (+)-α-pinene[10] resulted in a product in which none of the minor enantiomer could be detected by NMR (less than 3% *S* probably could not be detected). The crude ester was then saponified[11] and after neutralization the hydroxy acid was distilled [Kugelrohr, 140 °C (pot), 0.01 mm] to give the acetylenic lactone.[12] Reduction of the acetylene gave the pheromone in 80–90% overall yield from the ester. The product was eluted through a short silica gel column with methylene chloride/hexane/ethyl acetate (150/50/5). The α-pinene of 92% optical purity gave a final product of 78–88% optical purity, while optically-pure α-pinene gave product of 97% optical purity.[1]

The limiting factor in obtaining product of high optical purity with the Alpine-borane reagent is usually the optical purity of the α-pinene. High optical purity α-pinene is available.[10] However, the purification of the α-pinene requires extra steps. We therefore sought methods to enrich the desired enantiomer. All intermediates were oils and could not be crystallized. However, we found that the 4-hydroxy acid could be crystallized from acetonitrile as a cyclohexylamine salt[13] (mp 94–95 °C). After two recrystallizations, conversion to the pheromone gave material with a rotation of $[\alpha]^{26}_D$ −69.93° (9.84, $CHCl_3$) [lit. $[\alpha]^{26}_D$ −69.6 (5.0, $CHCl_3$);[1] $[\alpha]^{25}_D$ −70.0 (6.4, $CHCl_3$)[2a]], which was spectroscopically indentical with the natural material.

We have previously shown that Alpine-borane is an effective asymmetric reducing agent for a variety of propargyl ketones.[9] Thus by using different acetylenes it should be possible to produce a variety of optically-active γ-lactones by this route. The generality of recrystallizing the 4-hydroxy acids to optically pure products remains to be explored. These vinyl γ-lactones are of considerable interest in synthetic chemistry because they may be used to introduce chirality in acyclic systems through alkylations with organocopper or palladium reagents.[14]

(1) Tumlinson, J. H.; Klein, M. G.; Doolittle, R. E.; Ladd, T. L.; Proveaux, A. T. *Science* **1977**, *197*, 789. Doolittle, R. E.; Tumlinson, J. H.; Proveaux, A. T.; Heath, R. R. *J. Chem. Ecol.* *1980*, *6*, 473.
(2) (a) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1979**, *44*, 2169. (b) Sato, K.; Nakayama, T.; Mori, K. *Agric. Biol. Chem.* **1979**, *43*, 1571.
(3) Nishizawa, M.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 247.
(4) For example, Mori obtained approximately 90% optically-pure material (ref 2b) and Noyori obtained 75% optically-pure material.
(5) Midland, M. M.; Tramontano, A. *Tetrahedron Lett.* **1980**, *21*, 3549.
(6) Cason, J. "Organic Syntheses", Collect. Vol. 3; Wiley: New York, 1955; p 169.
(7) Normant, J. F.; Bourgain, M. *Tetrahedron Lett.* **1970**, 2659.
(8) House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460.
(9) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867. The procedure was modified by adding 1 equiv (to ketone) of methanol to insure that no boron hydride was present. The reaction mixture was stirred at room temperature for 7 days before workup.
(10) Optically-pure α-pinene is available by a resolution process, Brown, H. C.; Yoon, N. M. *Isr. J. Chem.* **1976/1977**, *15*, 12, or by isomerization of β-pinene, Cocker, W.; Shannon, P. V. R.; Staniland, P. A. *J. Chem. Soc. C* **1966**, 41. However, in our hands commercial β-pinene gives α-pinene of only 92% optical purity, research in progress with R. Graham. We are indebted to Professor Harry Mosher for a gift of optically-pure α-pinene.
(11) The purification of the product is greatly simplified at this point by extracting the neutral impurities with ether.
(12) Rotation $[\alpha]^{25}_D$ −3.99 (2.2, $CHCl_3$), [lit.[2b] $[\alpha]^{22}_D$ −4.1 (1.658, $CHCl_3$)].
(13) A β-hydroxy acid has been enriched in 100% optically activity by recrystallization as a dicyclohexylamine salt. Tai, A.; Nakahata, M.; Harada, T.; Izumi, Y.; Kusumoto, S.; Inage, M.; Shiba, T. *Chem. Lett.* **1980**, 1125.
(14) For examples, see Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 2485. Trost, B. M.; Klun, T. P. *Ibid.* **1981**, *103*, 1864; **1979**, *101*, 6756. Trost, B. M.; Klun, T. P. *J. Org. Chem.* **1980**, *45*, 4256.
(15) A. P. Sloan Foundation Fellow, 1978–1982.

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Registry No. Methyl 4-oxo-5-tetradecynoate, 77889-02-2; 1-decyne, 764-93-2; methyl 4-chloro-4-oxobutanoate, 1490-25-1; (*R*)-(−)-5-tetradecyn-4-olide, 72151-69-0; (*R*)-(−)-*Z*-5-tetradecen-4-olide, 64726-91-6; methyl 4-hydroxy-5-tetradecynoate cyclohexylamine salt, 78685-95-7; *B*-3-pinanyl-9-BBN, 64106-79-2.

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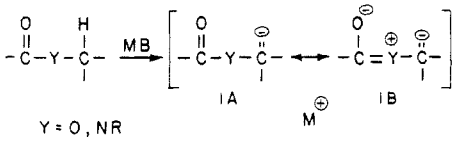
Dipole Stabilization of α-Heteroatom Carbanions: Theory and Experiment

Summary: The results of ab initio SCF calculations verify dipole stabilization in the carbanions formed by loss of a proton from the methyl groups of methyl formate and *N*-methylformamide, but differences between theory for the free anions and experiment is attributed to the effect of lithium ion complexation.

Sir: Carbanions **1** adjacent to the oxygen of an ester (Y = O) or to the nitrogen of an amide (Y = NR) are easily prepared and provide synthetically useful reagents.[1] Such



anions have been termed "dipole stabilized".[1a] While it is intuitively reasonable that carbanionic centers will be favorably influenced by adjacent dipoles, ab initio SCF calculations[2,3] now establish this stabilization to be of substantial magnitude. We also report parallel experimental work which tests the predictions from theory.

A number of conformations of neutral species **2**–**6** and the derived anions **2A**–**6A** were studied theoretically. Energies are summarized in Tables I and II. The preferred geometries are represented in Figure 1; those for **2A** and **4A** have already been discussed.[4] The anionic centers in

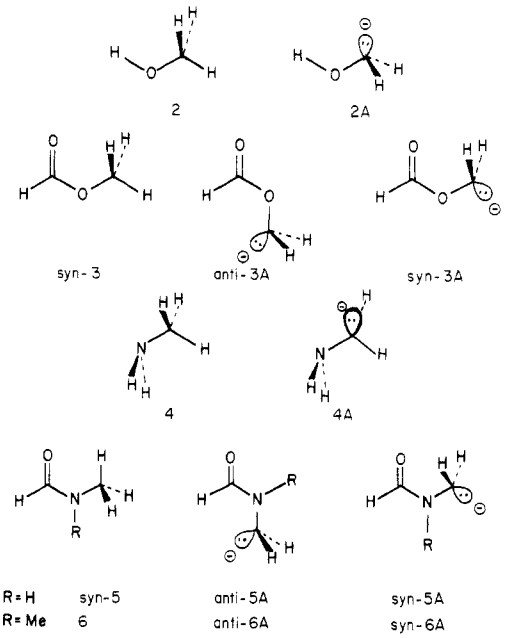
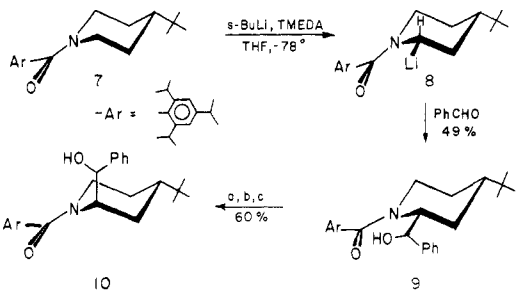


Figure 1. Preferred geometries of species studied theoretically. The anti isomers of **3A**, **5A**, and **6A** are favored over the syn isomers by ~9 kcal/mol (4-31G//STO-3G).

Scheme I. Reagents: a, pyridinium chlorochromate; b, NaOMe; c, $LiAlH_4$



3A, **5A**, and **6A** are distinctly pyramidal with the lone pair in the plane of the molecule oriented as shown.[5] That is, rotations around the O–CH_2 bond in *anti*-**3A** or *syn*-**3A** are unfavorable: 90° rotation of *anti*-**3A** requires 6.6 kcal/mol at the 4-31G//STO-3G level. Furthermore, **3A**, **5A**, and **6A** prefer the anti over the syn geometry by about 9 kcal/mol[6] even though the parent ester **3** and amide **5** favor the syn stereochemistry (by 7.6 and 1.4 kcal/mol, respectively).[7,8] Rotations around the CO–O or CO–N

(1) (a) For a review, see Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 725. (b) For recent related cases, see Lubosch, W.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 102. MacDonald, J. L. *J. Org. Chem.* **1980**, *45*, 193.

(2) The Gaussian 70 and Gaussian 76 series of programs were employed: Hehre, W. J.; Lathan, W. A.; Ditchfield, R.; Newton, M. D.; Pople, J. A. *QCPE*, 236 (1973). Binkley, J. S.; Whiteside, R. A.; Hariharan, P. C.; Seeger, R.; Pople, J. A.; Hehre, W. J.; Newton, M. D. *Ibid.* 368 (1978). Geometries, optimized with the minimal STO-3G basis set, were used in single point calculations, employing the split-valence 4-31G basis. Since diffuse basis functions are essential for a reliable estimation of anion proton affinities (PA), additional calculations on the preferred conformations were carried out with the 4-31+G basis set (the 4-31G basis set augmented by a set of diffuse s and p functions on all nonhydrogen atoms).[3] The use of only the STO-3G optimized geometries should not entail any serious error; geometry optimization at the 4-31+G level for a few cases leads only to insignificant changes in the calculated relative PA's (Table I).

(3) Chandrasekhar, J.; Andrade, J. G.; Schleyer, P. v. R. *J. Am. Chem. Soc.*, manuscript submitted for publication. The PA's and stabilization energies relative to CH_3^- are calculated to be lower at the 4-31+G level compared to calculations without diffuse functions.

(4) Clark, T.; Körner, H.; Schleyer, P. v. R. *Tetrahedron Lett.* **1980**, 743. See also, Hinde, A. L.; Pross, A.; Radom, L. *J. Comput. Chem.*, **1980**, *1*, 118. Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1976**, *98*, 7498.

(5) In the anions, ∠HCH = 100–101° and ∠XCH = 99–102°. The energy to planarize *anti*-**3A** is 19.8 kcal/mol, whereas planarization of CH_3^- (∠HCH = 100°) requires +7.6 kcal/mol at the 4-31G//STO-3G level.

(6) Gund, P.; Veber, D. F. *J. Am. Chem. Soc.* **1979**, *101*, 1885, reported that anti DMF anion is favored by 6.7 kcal/mol by CNDO/2. These authors also report that N-methylation enhances the acidity of *N*-methylformamide by 3.6 kcal/mol (*syn*-Me) or 3.1 kcal/mol (*anti*-Me). Our calculations suggest this to be a CNDO/2 artifact; N-methylation has less than a 1 kcal/mol effect on the deprotonation energy of *N*-methylformamide.

(7) Experimental work. Methyl formate: Bock, C. *Can. J. Chem.* **1967**, *45*, 2761. O'Gorman, J. M.; Shank, W.; Shamiker, V. *J. Am. Chem. Soc.* **1950**, *72*, 4222. Wilmshurst, J. K. *J. Mol. Spectrosc.* **1957**, *1*, 201. Curl, R. F., Jr. *J. Chem. Phys.*, **1959**, 30, 1759. *N*-Methylformamide: LaPlanche, L. A.; Rogers, M. T. *J. Am. Chem. Soc.* **1964**, *86*, 337; Drakenberg, T.; Forsén, S. *Chem. Commun.* **1971**, 1404; Allmer, F.; Kriz, J.; Doskocilová, D. *Collect. Czech. Chem. Commun.* **1973**, *38*, 3252.

(8) Theoretical studies. Methylformate: Wennerstrom, H.; Forsén, S.; Roos, B. *J. Phys. Chem.* **1972**, *76*, 2530. John, I. G.; Radom, L. *J. Mol. Struct.* **1977**, *36*, 133. Larson, J. R.; Epiotis, N. D.; Bernardi, F. *J. Am. Chem. Soc.* **1978**, *100*, 5713. *N*-Methylformamide: Tonelli, A. E. *J. Am. Chem. Soc.* **1971**, *93*, 7153.

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