Communications

Hydroxymercuration—Reductive Coupling Route to δ-Lactones. Synthesis of Malyngolide, an Antibiotic from a Marine Blue-Green Alga

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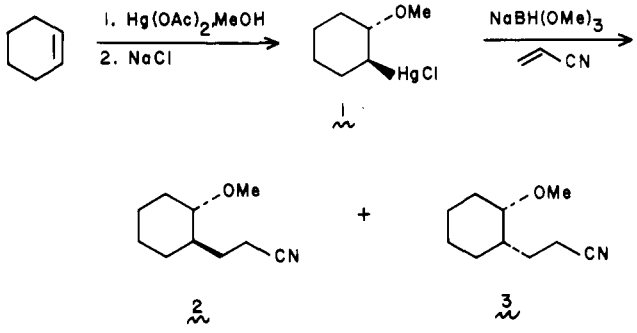
Summary: Radical intermediates can be generated from the hydroxymercuration products of alkenes by reduction with sodium trimethoxyborohydride. These β-hydroxyalkyl radicals react with electron-deficient olefins (methyl acrylate and acrylonitrile to provide δ-hydroxy esters and nitriles which can in turn be cyclized to 5-substituted δ-lactones. Such lactones comprise important part structures of numerous naturally occurring products. The utility of this new hydroxymercuration–reductive coupling route to δ-lactones has been demonstrated through a simple synthesis of malyngolide, an antibiotic isolated from a marine blue-green alga.

Giese and co-workers have reported over the past several years in a number of articles that the radicals formed on reduction of organomercurials can be trapped with electron-deficient olefins to produce coupled products.[1] Of these reports, the most exciting was Giese's demonstration that even the mercurial produced by methoxymercuration of an olefin could be employed in this reduction–radical coupling scheme.[2] Thus, the methoxymercuration product of cyclohexene 1 on reduction with sodium trimethoxy-



borohydride in the presence of a large excess of acrylonitrile produced a 65:35 *trans/cis* stereoisomeric mixture of the substituted cyclohexanes **2** and **3** in 77% yield. An extensive investigation of the effect of variation in the nature of the olefin used to trap the radical intermediate has been made. Reactivities and selectivities have been explained in terms of frontier molecular orbital theory.[3]

Since the process does represent a tremendously versatile new method for producing vicinally functionalized molecular systems, we felt that additional studies were warranted. Specifically, we were concerned with the question of whether the organomercurial generated from *hydroxymercuration* of an olefin could be used in this coupling scheme. We believed that if the coupling step still proceeded in good yield with the hydroxyl group unprotected, then a very useful route to 5-substituted δ-lactones would be at hand, for the product of the coupling process would merely have to be exposed to acid (or base and then acid) to effect lactonization. The 5-substituted δ-lactones do, of course, represent fairly ubiquitous structure types in nature (e.g., malyngolide, compactin lactone, pestalotin, and massoilactone).[4]

Table I. Preparation of δ-Lactones from Alkenes via Their Hydroxymercurials

starting alkene	coupling yield,[a] %	lactone yield, %/ method[a,b]
1-octene	50[c]	70/b
2-methyl-2-pentene	43[c]	88/b
cyclohexene	78[c]	95/b
allyl benzyl ether	50[c]	65/b
styrene	37[c]	100/a
1-octene	60[d]	50/a
2-methyl-2-pentene	70[d]	97/a
cyclohexene	74[d]	62/a
allyl benzyl ether	94[d]	60/b
styrene	72[d]	65/b

[a] The products were purified by silica gel chromatography and characterized by ^{1}H NMR, IR, and mass spectral analysis. [b] a = refluxing with *p*-TSA; b = hydrolysis with 10% aqueous sodium hydroxide and then acidification with 3 N HCl. [c] With methyl acrylate. [d] With acrylonitrile.

A number of different olefins (1-octene, 2-methyl-2-pentene, cyclohexene, allyl benzyl ether, and styrene) were thus hydroxymercurated [$Hg(OAc)_2$, H_2O][5] and converted to their generally crystalline chloromercuri derivatives by ligand exchange with chloride ion.

Reduction of these mercurials was carried out in methylene chloride by using 3 equiv of sodium trimethoxyborohydride as the reducing agent.[3] Both acrylonitrile and methyl acrylate were examined as trapping agents. In general, both of these acceptors did, in fact, give fair to good yields of coupled products. In the majority of cases, however, acrylonitrile proved to be the more efficient trapping agent (Table I).

Having substantiated the first stage of the alkene to lactone conversion, the final stage required that we now cyclize the δ-hydroxy esters or δ-hydroxy nitriles. This was accomplished easily by use of one of two general procedures: (a) refluxing the nitrile or ester with *p*-TSA in DME or (b) hydrolysis with 10% aqueous NaOH at room temperature and then acidification with 3 N HCl.

The results obtained for the lactonization methods are displayed in Table I. While no special efforts were taken to optimize these reactions, the yields range from fair to excellent.

(1) Giese, B.; Meister, J. *Chem. Ber.* **1977**, *110*, 2588.
(2) Giese, B.; Heuck, K.; Lüning, U. *Tetrahedron Lett.* **1981**, *22*, 2155. Giese, B.; Heuck, K. *Ibid.* **1980**, *21*, 1829. Giese, B.; Heuck, K. *Chem. Ber.* **1979**, *112*, 3759.
(3) Giese, B.; Kretzschmar, G.; Meisner, J. *Chem. Ber.* **1980**, *113*, 2787.
(4) Chmielewski, M.; Jurczak, J. *J. Org. Chem.* **1981**, *46*, 2230 and references cited therein.
(5) Brown, H. C.; Lynch, G. J. *J. Org. Chem.* **1981**, *46*, 531 and references cited therein.

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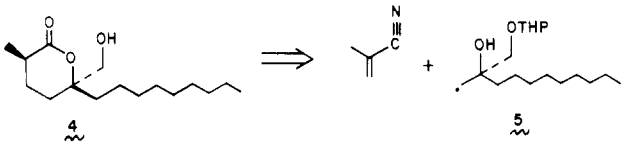
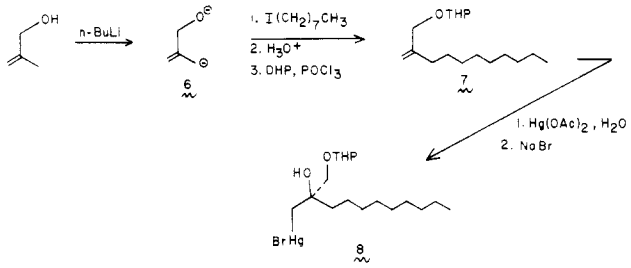
The operational simplicity of this new method for δ-lactone construction was further demonstrated through a synthesis of malyngolide (4), the major antibiotic found



in the lipid extract of *L. majuscula* Gomont from Kahala Beach, Oahu.[6a] Malyngolide has been shown to be active against *M. Smegmatis* and *Streptococcus pyogenes* and somewhat less active against *Staphylococcus aureus* and *Bacillus subtilis*.[6b]

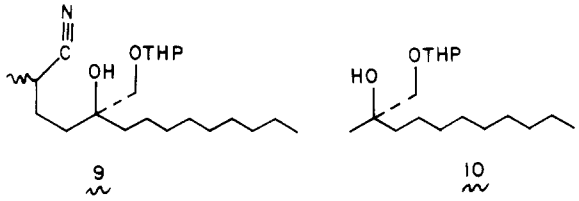
As can be seen from the retrosynthetic analysis of this substance, the radical **5** must be generated from the corresponding organomercurial and coupled with methacrylonitrile.

The olefin required for the initial hydroxymercuration reaction was assembled from the dianion **6** of methallyl



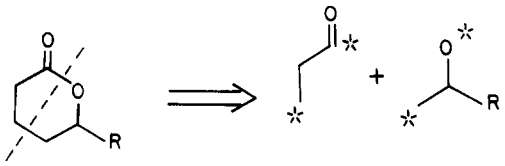
alcohol.[7] Protection of the hydroxyl group as its tetrahydropyranyl ether, and hydroxymercuration of the olefin delivered **8** after ligand exchange with sodium bromide (45% overall yield). The mercurial **8** proved to be a fairly unstable substance. When left standing for several hours, it turned from a clear to an opaque oil.

For the coupling step, the freshly prepared mercurial **8** was dissolved in methylene chloride containing a large excess (30 equiv) of methacrylonitrile. To this mixture was added a 1 M solution (5 equiv) of sodium trimethoxyborohydride in tetrahydrofuran. The reaction mixture was stirred for 14 h and then quenched with water. An easily separable 4:1 mixture of the desired δ-hydroxy nitrile **9** plus



the reduction product **10** was isolated. While the yield of coupled product was modest (49%) the synthesis was completed merely by refluxing the δ-hydroxy nitrile with *p*-toluenesulfonic acid in THF for 17 h. As in previously reported syntheses of **1**,[8] a 1:1 mixture of diastereoisomeric lactones was obtained which could be separated readily by gravity chromatography. The spectral properties of the synthetic compound were identical with those reported for the natural product.[6a,9]

The hydroxymercuration–reductive coupling sequence does thus expand greatly the importance of mercurials in organic chemistry. The use of this "3 + 3" technology for the preparation of other δ-lactone systems is currently being investigated.



The experimental procedures for the preparation of **8** and **9** are representative.

Hydroxymercuration. To a stirred solution of olefin **7** (0.25 g, 0.93 mmol) in 6 mL of THF was added 0.30 g (0.93 mmol) of mercuric acetate and 2 mL of water. After 3 h the reaction mixture was diluted with aqueous sodium bromide and extracted with dichloromethane. The organic layer was dried and concentrated to yield 0.48 g (91%) of the mercurial **8** as an oil: IR (thin film) 3430, 2950, 2870, 1470, 1210, 1130, 1080, 1040, 980, 920 cm^{-1}; NMR ($CDCl_3$) δ 4.57 (two dd, 1 H), 4.01–3.34 (m, 4 H), 2.15–1.33 (m, 9 H), 1.24 (br s, 16 H), 0.85 (t, 3 H); mass spectrum (15 eV), *m/e* 467, 465 ($^{202}Hg^{81}Br$, $^{202}Hg^{79}Br$).

Reductive Coupling. To a solution of 0.95 g (1.68 mmol) of mercurial **8** and 3.8 g (50 mmol) of methacrylonitrile in 25 mL of dichloromethane was added by syringe pump (flow rate = 0.15 mL/min) 1.1 g (8.4 mmol) of sodium trimethoxyborohydride (1 M in THF). The reaction mixture darkened, and a thick gray precipitate formed. After 14 h at room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated, and the resultant oil was chromatographed on silica gel with 14% ethyl acetate–hexanes as eluent to furnish 0.08 g (18%) of the reduction product **10** and 0.29 g (49%) of coupled product **9**: IR (thin film) 3480, 2950, 2890, 2280, 1465, 1215, 1135, 1080, 1040, 990, 925 cm^{-1}; NMR ($CDCl_3$) δ 4.52 (br s, 1 H), 3.82 (m, 1 H), 3.55 (m, 2 H), 2.77 (m, 1 H), 2.57 (q, 1 H, J = 6.9 Hz), 1.90–1.38 (m, 12 H), 1.29 (d, 3 H, J = 6.9 Hz), 1.23 (br s, 14 H), 0.84 (t, 3 H); mass spectrum (15 eV) *m/e* 323.

Acknowledgment. This work was supported in part by the National Institutes of Health (Grant No. AI 16138-03. The 300-MHz Brücker NMR instrument used in the studies was purchased through funds provided by the National Science Foundation (Grant No. CHE-79-05-185).

Registry No. **1**, 5274-83-9; **2**, 72887-19-5; **3**, 72886-98-7; **4**, 71582-80-4; **7**, 80697-28-5; **8**, 80697-29-6; **9**, 80719-00-2; **10**, 80697-30-9; 1-octene, 111-66-0; 2-methyl-2-pentene, 625-27-4; cyclohexene, 110-83-8; allyl benzyl ether, 14593-43-2; styrene, 100-42-5; methyl acrylate, 96-33-3; acrylonitrile, 107-13-1; 1-octene δ-hydroxynitrile, 80697-31-0; 2-methyl-2-pentene δ-hydroxynitrile, 80697-32-1; cyclohexene δ-hydroxynitrile, 63714-95-4; allyl benzyl ether δ-hydroxynitrile, 80697-33-2; styrene δ-hydroxynitrile, 80697-34-3; 1-octene δ-hydroxyester, 80697-35-4; 2-methyl-2-pentene δ-hydroxyester, 80697-36-5; cyclohexene δ-hydroxyester, 21197-34-2; allyl benzyl ether δ-hydroxyester, 80697-37-6; styrene δ-hydroxyester, 80697-38-7; 1-octene δ-lactone, 710-04-3; 2-methyl-2-pentene δ-lactone, 80697-39-8; cyclohexene δ-lactone, 4430-31-3; allyl benzyl ether δ-lactone, 80697-40-1; styrene δ-lactone, 80697-41-2.

Supplementary Material Available: Spectral data for organic compounds (2 pages). Ordering information is given on any current masthead page.

(6) (a) Structure: Cardllina, J. H.; Moore, R. E.; Arnold, E. V.; Clardy, J. *J. Org. Chem.* **1979**, *44*, 4039. (b) Biological activity: Starr, T. J.; Dieg, E. F.; Church, K. K.; Allen, M. B. *Tex. Rep. Biol. Med.* **1962**, *20*, 271. Burkholder, P. R.; Burkholder, L. M.; Almodovar, L. R. *Bot. Mar.* **1960**, *2*, 149.

(7) Carlson, R. M. *Tetrahedron Lett.* **1978**, 111.

(8) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1981**, *46*, 2439.

(9) Satisfactory NMR, IR, and mass spectral data were obtained for all new compounds.