Rearrangement of Cyclobutenones to 2,5- and 2,6-Dialkylated 1,4-Benzoquinones. Synthesis of *O*-Methylperezone and *O*-Methylisoperezone

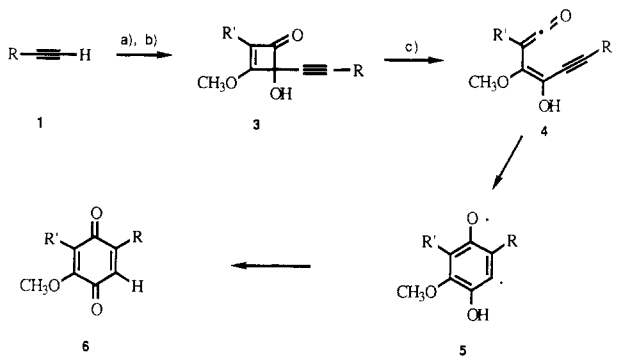
Summary: 2,5-Dialkylated benzoquinones have been prepared from 4-alkenyl-4-hydroxycyclobutenones by thermolysis followed by oxidation, while 2,6-dialkylated benzoquinones are available by thermolysis of 4-alkynyl-4-hydroxycyclobutenones. The complementarity of these procedures is illustrated by the preparation of pairs of regioisomeric benzoquinones, including the natural product *O*-methylperezone and its unnatural regioisomer *O*-methylisoperezone.

Sir: In previous publications we reported the ring expansion of 4-alkynyl-4-hydroxycyclobutenones to 1,4-benzoquinones, a transformation outlined in Scheme I.[1,2] The overall sequence starts with the conversion of the alkyne **1** into the corresponding lithium acetylide, which is then treated with a cyclobutenedione. When the dione used is unsymmetrical, the resulting cyclobutenone **3** is formed regiospecifically by addition of the alkyne anion to the more electrophilic carbonyl group. Thermolysis of **3** in refluxing *p*-xylene then leads to the benzoquinone **6**. This synthetically useful and mechanistically interesting rearrangement proceeds by stereospecific electrocyclic ring opening of **3** to the conjugated ketene **4**, which undergoes ring closure to the diradical **5**. Upon intramolecular migration of the hydroxyl hydrogen atom, the quinone **6** is formed.

Reported here is a complementary reaction (Scheme II) allowing the synthesis of the regioisomeric benzoquinones **10**. This involves generation of the vinyllithium reagent **2**, which can be accomplished from a variety of precursors, including the alkyne **1**.[3,4] Conversion of **2** into the cyclobutenone **7** takes place in THF at −78 °C. Thermolysis of **7** results in a four-electron electrocyclic ring opening to the ketene **8**, which gives the hydroquinone **9** upon a six-electron electrocyclic ring closure. Oxidative workup then provides the benzoquinone **10**.

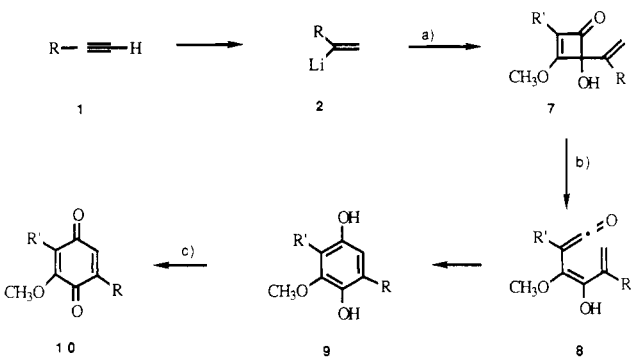
As illustrations of the scope of this methodology, the regioisomeric pairs of benzoquinones **11**/**12** and **13**/**14** as well as the individual quinone **15** were prepared from, respectively, 3-methoxy-4-methylcyclobutenedione and 3-ethoxy-4-phenylcyclobutenedione and a suitable lithium reagent.[5] For each pair, the first member was prepared from the appropriate lithioalkyne and the second from the corresponding 2-lithioalkenyl reagent. For both pairs, the vinyllithium reagent was prepared from the corresponding alkyne. The former case involved treatment of the alkyne with (trimethylstannyl)copper–dimethyl sulfide followed by reaction of the resulting vinylstannane with methyllithium according to the method of Piers.[3] The latter used a method reported by Cousseau and involves treatment of 3-phenyl-1-propyne with tetraethylammonium bromide hydrobromide to give the 2-bromoalkene.[4] Generation of the lithium reagent was then accomplished by treatment of the bromoalkene with butyllithium.

Scheme I[a]



[a] Reagents: (a) nBuLi, THF, −78 °C; (b) a cyclobutenedione (c) *p*-xylene, 138 °C.

Scheme II[a]



[a] Reagents: (a) a cyclobutenedione; (b) *p*-xylene, 138 °C; (c) oxidation.

The synthesis of the quinones **11** and **12** is of interest since it illustrates that the method is applicable to the construction of relatively complex molecules.[5] The required alkyne employed in these syntheses was prepared from erythorbic acid. Specifically, this was converted to 3,4-*O*-isopropylidene-D-erythronolactone as described in *Organic Syntheses*.[6] Treatment of this lactone with 1-(trimethylsilyl)-3-lithiopropyne followed by methylation with methanol/TsOH in dimethoxypropane and deprotection gave the terminal alkyne needed for the synthesis of **11** as well as for the preparation of the vinylstannane precursor required for the synthesis of **12**. Analysis (^{1}H NMR and ^{13}C NMR) of **11** and **12** showed them each to be single diastereomers. The respective absolute configurations were not established but are considered to be as drawn.[5]

Compound **15** was prepared by using 2-lithio-2-phenylethene, and this particular example is worthy of further note since it portrays an advantage of the ring expansion of 4-alkenyl- over 4-alkynylcyclobutenones as a synthetic route to arylquinones. Specifically, it has been shown previously that the ring expansion of 4-(2-arylethynyl)cyclobutenones results in the formation of both

(1) Karlsson, J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 3392.
(2) Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975.
(3) Piers, E.; Chong, M. *J. Chem. Soc., Chem. Commun.* **1983**, 934.
(4) Cousseau, J. *Synthesis* **1980**, 805.
(5) The yields of the quinones **11** and **12** were 43% and 28%, respectively, from the cyclobutenedione. Quinone **12** is contaminated by about 10% of the quinone **11** since the addition of the vinyllithium reagent to the dione is not regiospecific. Both of these quinones were optically active: **11**, $[\alpha]_D = -111°$, $c = 1.365$ in CH_2Cl_2, $T = 26$ °C; **12**, $[\alpha]_D = -97°$, $c = 0.205$ in CH_2Cl_2, $T = 26$ °C. The relative stereochemistry shown is consistent with NOE data. Quinones **13**, **14**, and **15** were produced in 46%, 76%, and 71% yields, respectively, from the corresponding 4-hydroxycyclobutenone, and all of these are previously unknown compounds.
(6) The lithium reagents utilized for the synthesis of **11** and **12** were prepared by propargylation of the protected (actonide) lactone, which, in turn, was prepared as described by Cohen et al.: Cohen, N.; Banner, B. L.; Laurenzano, J.; Carozza, L. *Org. Synth.* **1986**, *63*, 127.

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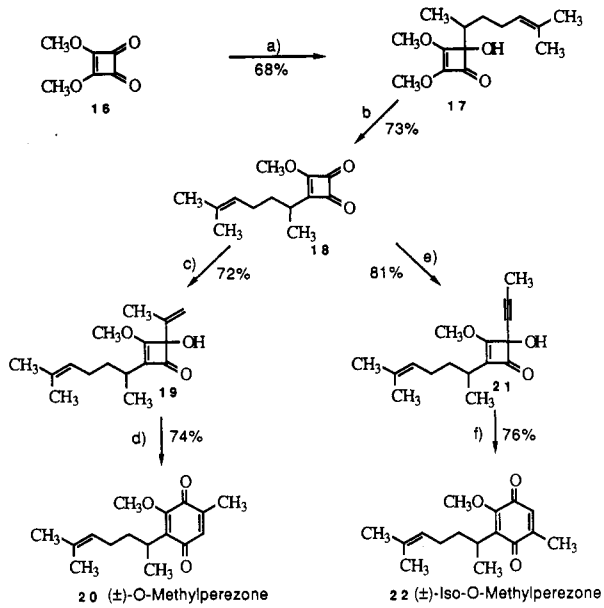
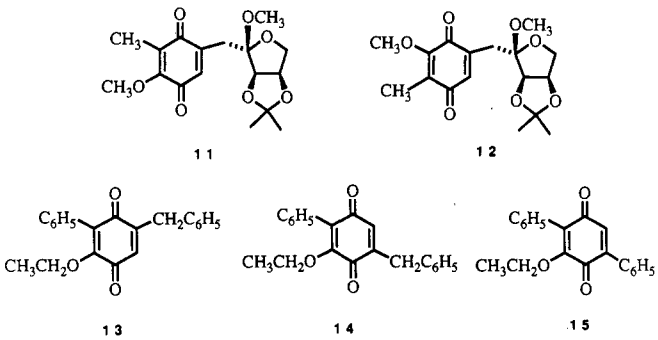
Scheme III[a]



[a] Reagents: (a) $CH_3CHCl(CH_2)_2CH{=}C(CH_3)_2$, Li/Na (98:2) sonication/hexane;[9] (b) trifluoroacetic anhydride, pyridine, ether; (c) 2-lithiopropene, ether/THF; (d) (i) benzene, reflux, 2 h; (ii) Ce(IV), CH_2Cl_2; (e) 1-lithiopropyne, THF; (f) acetonitrile, reflux.

benzoquinones and cyclopentenediones, i.e., the ketene intermediate **4** undergoes ring closure to give both six- and five-membered rings.[1,2] *In contrast, only six-membered-ring formation is observed for the analogous 4-(2-arylethenyl)cyclobutenone series.*



As an illustration of the synthetic utility of the 4-alkenyl-4-hydroxycyclobutenone/benzoquinone rearrangement, an efficient synthesis of the naturally occurring sesquiterpene quinone *O*-methylperezone (**20**) is described herein (Scheme III). This quinone has been reported to occur in the aerial parts of *Coreopsis fasciculata*, and its synthesis was previously reported in 1985.[7,8] The synthesis described in this paper involves treatment of dimethyl squarate (**16**) with 6-lithio-2-methyl-2-heptene to furnish the cyclobutenone **17** in 68% purified yield.[9] Hydrolysis

Table I. Carbon-13 and Proton NMR Data

(±)-*O*-methylperezone		(±)-*O*-methylisoperezone	
^{1}H NMR[a]	^{13}C NMR[b]	^{1}H NMR[a]	^{13}C NMR[b]
1.18 (d)	188.25	1.18 (d)	188.42
1.54 (br s)	184.39	1.54 (br s)	184.23
1.65 (d)	156.50	1.65 (d)	156.16
1.60, 1.74 (m, m)	143.51	1.60, 1.75 (m, m)	146.35
1.89 (m)	136.98	1.87, 1.93 (m, m)	137.09
2.02 (d)	133.89	2.02 (d)	131.73
3.08 (sext)	131.67	3.12 (sext)	131.51
3.94 (s)	124.60	3.96 (s)	124.72
5.05 (qq)	61.04	5.05 (qq)	61.16
6.47 (q)	34.89	6.43 (q)	34.89
	29.94		30.24
	26.97		27.04
	25.87		25.92
	19.11		19.12
	17.83		17.87
	15.36		16.21

[a] In parts per million measured from internal standard TMS in $CDCl_3$ used as the solvent. [b] In parts per million measured from the central $CDCl_3$ peak used as the solvent.

of **17** upon treatment with trifluoroacetic anhydride and pyridine gave the cyclobutenedione **18** in 73% yield.[10] Addition of 2-lithiopropene to **18** then provided the cyclobutenone **19** in 72% yield. Thermolysis of **19** followed by oxidation provided (±)-*O*-methylperezone (**20**) in 74% yield. Comparison of the ^{13}C NMR and ^{1}H NMR spectral data obtained for this synthetic product with those reported for the natural product showed them to be identical.[8] This synthesis constitutes a 27% overall yield of the racemic natural product from dimethyl squarate in four steps as compared to the previously reported synthesis which provided a slightly lower overall yield (21%) from 2,3-dimethoxytoluene in eight steps.

As final documentation of the regiocontrol available from the ring expansions of 4-alkenyl- vs 4-alkynyl-4-hydroxycyclobutenones, (±)-*O*-methylisoperezone (**22**) was also prepared. Treatment of the cyclobutenedione **18** with 1-lithiopropyne furnished the cyclobutenone **21** in 81% yield. Thermolysis of **21** in refluxing acetonitrile then provided (±)-*O*-methylisoperezone (**22**) in 76% yield.[11] A comparison of the ^{13}C NMR and ^{1}H NMR data for (±)-*O*-methylperezone with those obtained for (±)-*O*-methylisoperezone is given in Table I, and these data show the compounds to be regioisomeric.

In conclusion, it is shown that 4-alkenyl-4-hydroxycyclobutenones undergo ring expansion to benzohydroquinones upon thermolysis. This ring expansion is complementary to the previously reported rearrangement of the 4-aryl analogues to annelated hydroquinones and the ring expansion of 4-alkynyl-4-hydroxycyclobutenones to benzoquinones.[1,2,12] Comparison of the methodology reported here with the ring expansion of 4-alkynyl-4-hydroxycyclobutenones is of particular note since together these rearrangements provide a powerful method for

(7) Bohlmann, F.; Ahmed, M.; Grenz, M.; King, R. M.; Robinson, H. *Phytochemistry* **1983**, *22*, 2858.

(8) Sanchez, I. H.; Larraza, M. I.; Basurto, F.; Yanez, R.; Avila, S.; Tovar, R.; Joseph-Nathan, P. *Tetrahedron* **1985**, *41*, 2355.

(9) Yields reported are for purified products. Spectral and analytical data are in agreement with the assigned structures. The lithium reagent was prepared according to Oppolzer et al.: Oppolzer, W.; Zutterman, F.; Battig, K. *Helv. Chim. Acta* **1983**, *66*, 522. Preparation of the lithium reagent requires specific conditions. It was necessary to use lithium sand containing 2% sodium (lithium containing 1% sodium did not work) and to employ sonication conditions.

(10) This is a standard method for the preparation of substituted cyclobutenones. For details, see: (a) Reed, M.; Perri, S.; Pollart, D.; Foland, L.; Moore, H. W. *J. Org. Chem.* **1988**, *53*, 2477. (b) Liebeskind, L. S.; Fengl, R. W.; Wirtz, K. R.; Shawe, T. T. *Ibid.* **1988**, *53*, 2482.

(11) This synthesis also illustrates a potentially general route to a variety of analogues which will be of interest in a forthcoming study of the scope of the perezone/pipitzol rearrangement. For results on this rearrangement, see: (a) Walls, F.; Padilla, J.; Joseph-Nathan, P.; Giral, F.; Escobar, M.; Romo, J. *Tetrahedron* **1966**, *22*, 2387. (b) Sanchez, I. H.; Basurto, F.; Joseph-Nathan, P. *J. Nat. Prod.* **1984**, *47*, 382. (c) Joseph-Nathan, P.; Mendoza, V.; Garcia, E. *Tetrahedron* **1977**, *33*, 1573.

(12) (a) Moore, H. W.; Perri, S. T. *J. Org. Chem.* **1988**, *53*, 996. (b) Leibeskind, L. S.; Jewell, C. F.; Iyer, S. *Ibid.* **1986**, *51*, 3065. (c) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *Ibid.* **1986**, *51*, 3067.

controlling the regiochemistry in the synthesis of highly substituted quinones. A more detailed study of this chemistry will be forthcoming.

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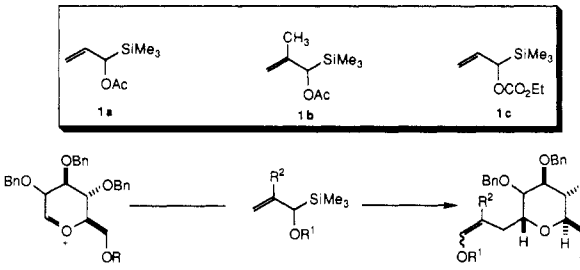
Oxygenated Allylic Silanes: Useful Homoenolate Equivalents for the Stereoselective C-Glycosidation of Pyranoside Derivatives

Summary: Acylated C1-oxygenated allylic silanes, [1-(acetyloxy)-2-propenyl]trimethylsilane (**1a**), [1-(acetyloxy)-2-methyl-2-propenyl]trimethylsilane (**1b**), and ethyl 2-propenyltrimethylsilane-1-carbonate (**1c**), function as homoenolate equivalents in BF_3·OEt_2-catalyzed C-glycosidation reactions of pyranoside derivatives.

Sir: Over the last several years major advances have been made in the evolution of reaction processes that deliver high levels of stereocontrol.[1] An important contribution has been the development of allylic silanes as carbon nucleophiles and their use in stereoselective allylation reactions of carbohydrate derivatives. The variety of carbon nucleophiles known to participate in stereoselective C-glycosidations has spurred efforts toward the chemical synthesis of complex natural products. These include the use of trimethylsilyl enol ethers,[2] allyltrimethylsilane,[3] (*E*)- and (*Z*)-crotyltrialkylsilanes,[4] organoaluminum reagents,[5] allyltrialkylstannanes,[6] and more recently propargylic trialkylstannanes.[7] Among these various derivatives none provide direct access to terminally oxygenated propenyl groups. In the context of efforts applicable to the chemical synthesis of natural products possessing antiviral activity,[8] we required more versatile reagents that could serve as three-carbon alcohol, two-carbon aldehyde, and 2-propanone equivalents. We speculated that C1-oxygenated allylic silanes could fulfill these criteria if they were to function as homoenolate equivalents[9] in Lewis acid catalyzed addition reactions with acetals.[10] Reported in this communication are the results of a study, the aim of which has been to establish the synthetic utility of C1-oxygenated allylic silanes, [1-(acetyloxy)-2-propenyl)trimethylsilane (**1a**),[11a] [1-(acetyloxy)-2-methyl-2-propenyl]trimethylsilane (**1b**),[11b] and ethyl 2-propenyltrimethylsilane-1-carbonate (**1c**)[11c] as effective carbon nucleophiles in C-glycosidation reactions. The equation below serves to illustrate how these reagents can be used to gain access to α-*C*-glycopyranosides.



(1)

The allylic silanes undergo a stereoelectronically controlled axial addition to pyranoside oxonium ions produced through the action of boron trifluoride etherate on D-glucopyranoside and D-mannopyranoside derivatives.[12] The reactions have resulted in the stereoselective C1-functionalization of the pyran ring with incorporation of a 3-(acetyloxy)-2-propenyl, a 3-(acetyloxy)-2-methyl-2-propenyl or an ethoxy-3-(carbonyloxy)-2-propenyl function. The results of this study are detailed in Table I and are complementary to the related C-glycosidation processes for pyranosides and activated glycals. We initiated our study with the readily available 1-acetyl-2,3,4,6-tetrabenzylglucopyranose **2**.[13] Boron trifluoride etherate (BF_3·OEt_2) was found to be the most effective Lewis acid and freshly distilled 1,2-dichloroethane the most suitable

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(2) Dawe, R. D.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1981**, 1180.
(3) Addition to pyranoside derivatives: (a) Lewis, M. D.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (b) Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1982**, *23*, 2281. (c) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383. (d) Giannis, A.; Sandhoff, K. *Tetrahedron Lett.* **1985**, *26*, 1479. (e) Addition to activated glycals: Danishefsky, S. J.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 3803.
(4) Danishefsky, S. J.; DeNinno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082.
(5) Posner, G. H.; Haines, R. S. *Tetrahedron Lett.* **1985**, *26*, 1823.
(6) (a) Keck, G. E.; Kachensky, D. F.; Enholm, E. J. *J. Org. Chem.* **1984**, *49*, 1462. (b) Keck, G. E.; Kachensky, D. F.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 4317.
(7) Zhai, D.; Zhai, W.; Williams, R. M. *J. Am. Chem. Soc.* **1988**, *110*, 2501.
(8) Exemplified by antiviral agents containing fused pyrano[3,2-*b*]-pyrans such as venustatriol [Sakemi, S.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *Tetrahedron Lett.* **1986**, *27*, 4287] and thyrsiferol [(a) Blunt, J. W.; Hartshorn, M. P.; Munro, M. G. H.; Robinson, W. T.; Yorke, S. C.; *Tetrahedron Lett.* **1978**, 69. (b) Suzuki, T.; Suzuki, M.; Farasaki, A.; Matsumoto, T.; Kato, A.; Imanaka, Y.; Kurosawa, E. *Tetrahedron Lett.* **1985**, *26*, 1329. (d) Suzuki, T.; Takeda, S.; Suzuki, M.; Kurosawa, E.; Kato, A.; Imanaka, Y. *Chem. Lett.* **1987**, 361].
(9) For earlier reports of homoenolate equivalents: (a) Corey, E. J.; Cane, D. E. *J. Org. Chem.* **1970**, *35*, 3405. (b) Corey, E. J.; Erickson, B. W.; Noyori, R. *J. Am. Chem. Soc.* **1971**, *93*, 1724. (c) Hosomi, A.; Hashimoto, H.; Sakurai, H. *J. Org. Chem.* **1978**, *43*, 2551. (d) Still, W. C. *J. Am. Chem. Soc.* **1974**, *96*, 5560. (e) Still, W. C.; Macdonald, T. L. *J. Am. Chem. Soc.* **1974**, *96*, 5561. (f) Evans, D. A.; Andrews, G. C.; Buckwalter, B. *J. Am. Chem. Soc.* **1974**, *96*, 5560. (g) Evans, D. A.; Baillargeon, D. J.; Nelson, J. V. *J. Am. Chem. Soc.* **1978**, *100*, 2242.
(10) Uncertainty arose surrounding the carbon nucleophilicity of these reagents because of the positioning and nature of the heteroatom on the allylic system. The inductive effect of an oxygen atom may reduce the stabilizing hyperconjugative effect of the trimethylsilyl group. The result would lead to the destabilization of the developing β-carbocation, which may be manifested in a decrease in reactivity.
(11) (a) Prepared in 70 to 82% yield by acylation (Ac_2O/cat. DMAP/Et_3N/methylene chloride) of (1-hydroxy-2-propenyl)trimethylsilane. (b) Prepared in 75 to 80% yield by acylation (Ac_2O/cat. DMAP/Et_3N/methylene chloride) of (1-hydroxy-2-methyl-2-propenyl)-trimethylsilane. (c) Prepared in 80% yield by acylation (EtO_2CCl/pyridine/benzene) of (1-hydroxy-2-propenyl)trimethylsilane. (For a detailed preparation of the 1-hydroxy allylic silanes, precursors to **1a-c**: Danheiser, R. L.; Fink, D. M.; Okano, K.; Tsai, Y.-H.; Szczepanski, S. W. *Org. Synth.* **1987**, *66*, 14. Danheiser, R. L.; Fink, D. M.; Okano, K.; Tsai, Y.-H.; Szczepanski, S. W. *J. Org. Chem.* **1985**, *50*, 5393.)
(12) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983; Chapter 2.
(13) (a) Prepared by acylation (Ac_2O/cat. DMAP/triethylamine/methylene chloride) of 2,3,4,6-tetrabenzylglucopyranose: Glaudemans, C. P. J.; Fletcher, H. G., Jr. *Methods Carbohydr. Chem.* **1972**, *6*, 373. This compound may also be purchased from Sigma Chemical Co.

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