Stereoselective Synthesis of *syn*-1,3-Diol Acetonides by Reductive Decyanation of Cyanohydrins

Scott D. Rychnovsky,* Sam Zeller, Donald J. Skalitzky, and George Griesgraber

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Received August 16, 1990

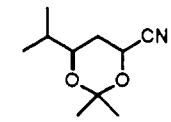
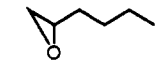
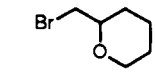
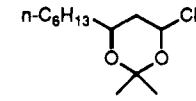
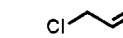
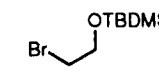
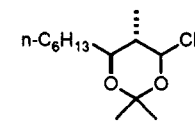
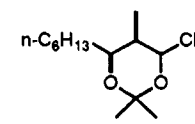
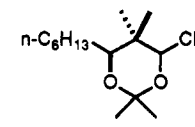
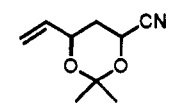
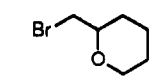
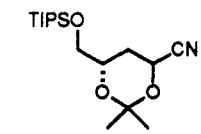
Summary: *syn*-1,3-Diol acetonides are produced with >99:1 selectivity by reductive decyanation of the corresponding cyanohydrin acetonides. Cyanohydrin acetonides (4,6-dialkyl-4-cyano-2,2-dimethyl-1,3-dioxanes) are available from 3-hydroxy aldehydes by cyanohydrin formation and alkylation, or directly from β-hydroxy ketones. The former method is particularly well suited to the *convergent* synthesis of alternating (1,3,5,...) polyol chains which are found in the polyene macrolide antibiotics.[1]

We have been exploring new methods for assembling alternating polyol chains and recently reported a convergent synthesis of polyol chains based on the generation and alkylation of *cis*- or *trans*-6-alkyl-2,2-dimethyl-4-lithio-1,3-dioxanes.[2,3] The *trans*-alkyllithium reagent is available in 75–80% yield and can be alkylated to give protected *anti*-1,3-diols. The *cis*-alkyllithium reagent gives protected *syn*-1,3-diols, but it is produced in an unsatisfying 50–55% yield. We sought to develop a more effective convergent synthesis of protected *syn*-1,3-diols.

Our new approach to protected *syn*-1,3-diols is described in Scheme I. 3-((Trimethylsilyl)oxy) aldehyde **1** is converted into 6-alkyl-4-cyano-2,2-dimethyl-1,3-dioxane (**2**) in excellent yield by reaction with trimethylsilyl cyanide (TMSCN) and potassium cyanide–18-crown-6 complex[4] followed by treatment with acetone, 2,2-dimethoxypropane, and an acid catalyst. The protected cyanohydrin **2** is produced as a 1:1 mixture of syn and anti isomers which were used without separation. Deprotonation of protected cyanohydrin **2** with lithium diethylamide and alkylation[5] gives cyanohydrin acetonide **3** as a single stereoisomer with the nitrile substituent axial.[6] Finally reductive decyanation of cyanohydrin acetonide **3** by treatment with sodium in ammonia at −78 °C gives *syn*-1,3-diol acetonide **4** as a single isomer in excellent yield.[7,8]

This procedure has been applied to a variety of 3-((trimethylsilyl)oxy) aldehydes **1** and a variety of alkylating agents; the results are presented in Table I. Protected cyanohydrin anions are very good nucleophiles and can be alkylated with reactive (entry 4) and unreactive (entries 2, 3) alkylating agents in good yield. The secondary methyl groups found in polypropionate chains can be directly incorporated into cyanohdyrin acetonides; subsequent alkylation and reductive decyanation proceed as expected

Table I. Synthesis, Alkylation, and Reductive Decyanation of Cyanohydrin Acetonides (Structures Are Given in Scheme I)[a]

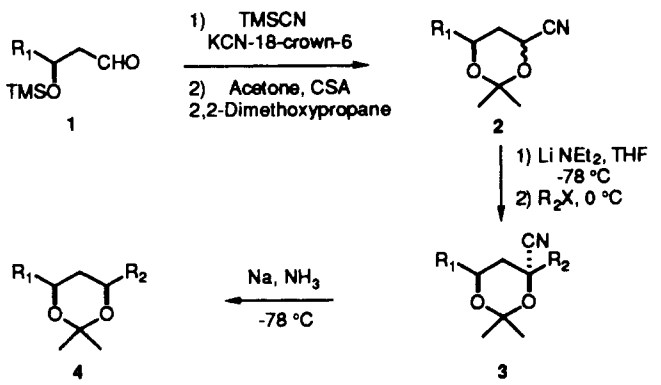
entry	structure **2**[b]	yield **2**, %	R_2X	**3**, %	**4**, %
1		91	n-C_5H_{11}Br	90[c]	95
2	II			—	63[d,g]
3	II			76	94[g]
4		94		68	87
5	II			65	92
6		91	n-C_4H_9Br	66	87
7		99	n-C_4H_9Br	74	73
8		87	n-C_4H_9Br	76	77[e]
9		88		75	83[f,g]
10		84	n-C_5H_{11}Br	77	90

[a] All new compounds were characterized by ^1H and ^{13}C NMR, IR, analysis, and/or MS. [b] Aldehydes **1** were prepared according to the literature[2] or by standard methods. [c] LDA was used. [d] The alkylation product was reduced directly. [e] Reduced with Li/$EtNH_2$ at 0 °C. [f] Reduced with LiDBB in THF at −78 °C and protonated with methanol. [g] A ~1:1 mixture of diastereomeric products are produced from racemic starting materials.

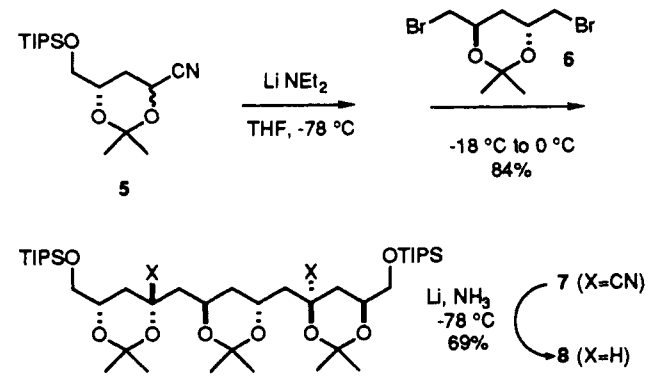
(1) Omura, S.; Tanaka, H. In *Macrolide Antibiotics: Chemistry, Biology and Practice*; Omura, S., Ed.; Academic Press: 1984; pp 351–404.
(2) Rychnovsky, S. D. *J. Org. Chem.* **1989**, *54*, 4982–4984.
(3) Other convergent polyol methods: (a) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419–5422. (b) Mori, Y.; Takeuchi, A.; Kageyama, H.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5423–5426. (c) Mori, Y.; Suzuki, M. *Tetrahedron Lett.* **1989**, *30*, 4383–4386. (d) Mori, Y.; Suzuki, M. *Tetrahedron Lett.* **1989**, *30*, 4387–4388. (e) Mori, Y.; Kohchi, Y.; Ota, T.; Suzuki, M. *Tetrahedron Lett.* **1990**, *31*, 2915–2916. (f) Nakata, T.; Suenaga, T.; Oishi, T. *Tetrahedron Lett.* **1989**, *30*, 6525–6528. (g) Nakata, T.; Suenaga, T.; Nakashima, K.; Oishi, T. *Tetrahedron Lett.* **1989**, *30*, 6529–6532.
(4) Evans, D. A.; Truesdale, L. K.; Carroll, G. L. *J. Chem. Soc., Chem. Commun.* **1973**, 55.
(5) Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1971**, *93*, 5286–5287. For a review of cyanohydrins as acyl anion equivalents, see: Albright, J. D. *Tetrahedron* **1983**, *39*, 3207–3233.
(6) The small *A* value of a nitrile means that it behaves like a hydrogen in a ^{13}C acetonide analysis. Based on the observed ^{13}C acetonide chemical shifts [30.8, 21.5 ppm], the alkyl substituents are syn. Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945–948.
(7) Stereochemical assignments were consistant with ^{13}C acetonide analysis (ref 6).
(8) The product ratios for entry 1 were determined by GC using authentic standards: **3** is produced in a ratio of 99.6:0.4 and **4** is produced in a ratio of 99.8:0.2. Only for entry 8 was the anti isomer of **4** formed in significant quantities (94:6 syn to anti by GC).

0022-3263/90/1955-5550$02.50/0

Scheme I



Scheme II



without any loss of stereochemistry at the secondary methyl centers (entries 6, 7).[9] Isolated olefins are not affected by this procedure (entry 4), and allylic ethers are tolerated if lithium di-*tert*-butylbiphenylide in THF is used in the reductive decyanation (entry 9). Even compounds with an intervening quaternary centers give good results (entry 8). The example presented in Scheme II illustrates the potential of this procedure in polyene macrolide antibiotics synthesis. Reaction of scalemic dibromide **6**[10] with 2.8 equiv of the cyanohydrin anion derived from scalemic **5** gives the dialkylated product **7** in 84% yield. Reductive decyanation with lithium in ammonia gives a 69% yield of **8**, which has the correct relative stereochemistry for C15 to C27 of roxaticin.[11] This new method will dramatically simplify the synthesis of complex polyol chains.

What factors determine the stereochemistry of these reductive decyanation? The reductive decyanation of protected cyanohydrins has not been reported, but the reductive decyanation of tertiary nitriles is a well-studied reaction which has been known for over 50 years.[12] Reductive decyanation proceeds by fragmentation of a nitrile radical anion to give cyanide anion and an alkyl radical which is subsequently reduced and protonated to give an alkane. In the reduction of axial cyanohydrin **3** the proton is introduced into an axial position, which is due to either stereochemical retention or preferential formation of the axial anion. Cohen and Sinay have shown that reduction of 2-tetrahydropyranyl radicals produces axial anions,[13] which presumably reflects the greater stability of the axial rather than the equatorial radical,[14] whereas Fabre has shown that reductive decyanation of aminonitriles proceeds largely with retention of configuration.[15] To distinguish between preferential formation of an axial anion and stereochemical retention we prepared cyanohydrin acetonide **3** (R_1 = *i*-Pr, R_2 = *n*-C_5H_{11}) and its epimer as a 52:48 mixture from the corresponding ketone.[16] Reduction of this mixture with sodium in liquid ammonia gave *syn*-1,3-diol acetonide **4** (R_1 = *i*-Pr, R_2 = *n*-C_5H_{11}) as a single isomer[17] in 87% yield, demonstrating that the axial anion is formed preferentially from both cyanohydrin epimers. The syn stereochemistry observed in reductive decyanations reflects the configuration preference for axial anomeric radicals and not a retention of configuration.

Acknowledgment. Support has been provided by the Searle Scholars Program, the Petroleum Research Fund, and the National Institutes of Health (GM43854-01).

Supplementary Material Available: Full spectral data for all new compounds and detailed experimental procedures for compounds **2**, **3**, **4** (entry 1), **5**, **7**, and **8** (11 pages). Ordering information is given on any current masthead page.

(9) In entry 6, aldehyde **1** and acetonide **4** are both present as 10:1 mixtures at the methyl center. In entry 7, aldehyde **1** and acetonide **4** are both present as 15–17:1 mixtures at the methyl center.

(10) **6** was prepared in optically pure form by hydrogenating 1,5-dichloro-2,4-pentanedione with $[(S\text{-BINAP})RuCl_2]_2Et_3N$ catalysis and treating the resulting diol sequentially with (i) KOH/Et_2O, (ii) Li_2NIBr_4, and (iii) acetone, 2,2-dimethoxypropane, CSA. Full experimental details will be published separately.

(11) Maehr, R.; Yang, R.; Hong, L.-N.; Liu, C.-M.; Hatada, M. H.; Todaro, L. J. *J. Org. Chem.* **1989**, *54*, 3816–3819.

(12) Walter, L. A.; McElvain, S. M. *J. Am. Chem. Soc.* **1934**, *56*, 1614–1616. Arapakos, P. G. *J. Am. Chem. Soc.* **1967**, *89*, 6794–6796. Arapakos, P. G.; Scott, M. K. *Tetrahedron Lett.* **1968**, 1975–1976. Arapakos, P. G.; Scott, M. K.; Huber, F. E., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 2059–2062. Fabre, C.; Salem, M. H. A.; Welvart, Z. *Bull. Soc. Chim. Fr.* **1975**, 178–182. Bunnelle, W. H.; Shevlin, C. G. *Tetrahedron Lett.* **1989**, *30*, 4203–4206.

(13) Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 6900–6902. Cohen, T.; Lin, M.-T. *J. Am. Chem. Soc.* **1984**, *106*, 1130–1131. Lancelin, J.-M.; Morin-Allory, L.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1984**, 355–356. Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152–161.

(14) Descotes, G. *J. Carbohydr. Chem.* **1988**, *7*, 1–20.

(15) Fabre, C.; Welvart, Z. *C. R. Acad. Sci. Paris* **1970**, *270*, 1887–1889. Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1982**, *23*, 3369–3372.

(16) 2-Hydroxy-3-methyl-5-decanone was converted to **3** (R_1 = *i*-Pr, R_2 = *n*-C_5H_{11}) and its epimer as follows: (i) BSA, CH_3CN; (ii) TMSCN, KCN–18-crown-6; (iii) acetone, 2,2-dimethoxypropane, CSA.

(17) The ratio was 99.0:1.0 syn to anti (see ref 8).

Photocatalytic One-Step Syntheses of Cyclic Imino Acids by Aqueous Semiconductor Suspensions

Bunsho Ohtani,* Shigeto Tsuru, Sei-ichi Nishimoto, and Tsutomu Kagiya
Department of Hydrocarbon Chemistry, Faculty of Engineering, Kyoto University, Kyoto 606, Japan
Kunisuke Izawa
Central Research Laboratories, Ajinomoto Co. Inc. 1-1, Suzuki-cho, Kawasaki-ku, Kawasaki 210, Japan
Received June 14, 1990

Summary: Optically active cyclic imino acids, pipecolinic acid and proline, are readily obtained from α,ω-diamino carboxylic acids and their N_ω-substituted derivatives by the photoirradiation of aqueous suspensions of TiO_2 or CdS loaded with platinum oxides under Ar at room temperature.

0022-3263/90/1955-5551$02.50/0