Communications

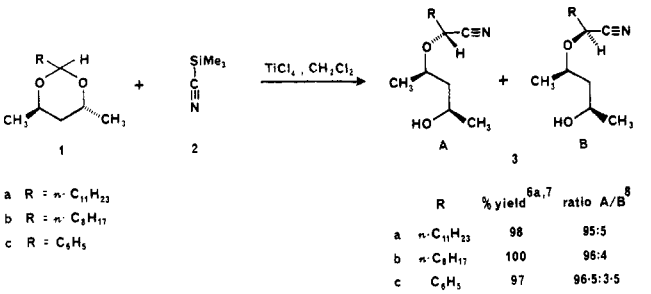
Asymmetric Synthesis via Acetal Templates. 5.[1] Reactions with Cyanotrimethylsilane. Enantioselective Preparation of Cyanohydrins and Derivatives

Summary: The titanium tetrachloride catalyzed reaction of the 2(*R*),4(*R*)-pentanediol acetals **1a–c** with cyanotrimethylsilane proceeds in excellent yield and high diastereoselectivity to give cyanohydrin ethers **3a–c**, and conditions have been developed for conversion of these ethers into cyanohydrins, β-amino alcohols and α-hydroxy esters with optical purities of greater than 90%.

Sir: Recent studies, inspired by Bartlett's[2] theoretical considerations, have led to the discovery of the highly diastereoselective reaction of acetals (e.g., **1b**) derived from (*R,R*)-[3] and (*S,S*)-pentane-2,4-diol with allyltrimethylsilane[2] as well as with some silylacetylenes.[1] As part of a program designed to extend this reaction to other nucleophiles, we disclose herewith the results of a study on the use of cyanotrimethylsilane in this context,[4] which has led to the production of cyanohydrin ethers and derivatives thereof in very high optical and chemical yields.

When the chiral acetals **1a-c**[5] were treated with titanium tetrachloride[3] and cyanotrimethylsilane[3] (**2**), the cyanohydrin ethers **3a–c**[6a,7] were formed in excellent yield and with very high diastereoselectivity[8] (see Scheme I). The reaction conditions for acetals **1a** and **1b** were as follows: Titanium tetrachloride (0.42 mL, 3.82 mmol) was added rapidly to a stirred solution of 0.67 g (2.43 mmol) of acetal **1a** and 1.17 mL (8.77 mmol) of cyanotrimethylsilane (**2**) in dry dichloromethane (60 mL) at −40 °C under argon. After 1 h at −40 °C, and then 1 h at −20 °C, the mixture was treated with methanol (1 mL) and warmed to room temperature, and finally excess 1 M hydrochloric acid was added. The product **3a** amounted to 0.71 g (96% yield),[6a,7] and the GC of the corresponding *tert*-butyldimethylsilyl ether showed two distinctly separate peaks in the ratio of 95:5.

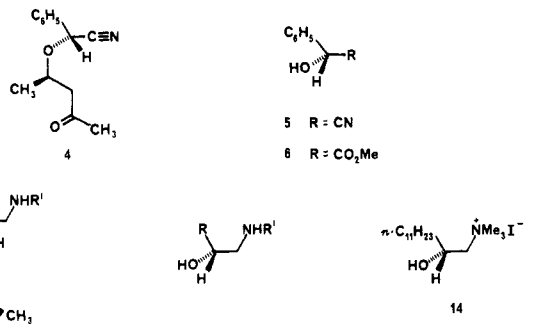
Scheme I



a R = n-C11H23
b R = n-C8H17
c R = C6H5

	R	% yield[6a,7]	ratio A/B[8]
a	n-C11H23	98	95:5
b	n-C8H17	100	96:4
c	C6H5	97	96·5:3·5

Chart I



7 R = n-C11H23, R' = H
8 R = C6H5, R' = H
9 R = n-C11H23, R' = CHO
10 R = C6H5, R' = CO2t-Bu
11 R = n-C11H23, R' = CHO
12 R = C6H5, R' = CO2t-Bu
13 R = C6H5, R' = H

In the case of acetal **1c** the following modification was preferred: Titanium tetrachloride (0.13 mL, 1.2 mmol) was added to a stirred solution of 0.2 g (1.04 mmol) of **1c** in dry dichloromethane (20 mL) at −78 °C under argon. After 25 min, 0.28 mL (2.08 mmol) of cyanotrimethylsilane (**2**) was added dropwise (2 min), the mixture was stirred for 45 min at −78 °C, and then 3 mL of methanol/dichloromethane (1:1) was added dropwise (10 min). After warming to 25 °C, the mixture was treated with water. The GC of the product **3c**[6a,7] (0.221 g, 97% yield) showed two peaks in the ratio 96.5:3.5.

The predominant diastereomer of the reaction products **3** may be presumed to have the configuration A (Scheme I) on the basis of previous studies.[1,2] Confirmation of this conclusion has been obtained in the case of **3a** and **3b** by the following transformations, which serve also to demonstrate the potential of compounds **3** as precursors to a variety of optically active products.

The feasibility of converting the ether **3** into the cyanohydrins and thence into the α-hydroxy esters without noticeable racemization was demonstrated in the mandelonitrile series. Thus ether **3c** was oxidized[9] to the corresponding ketone **4**[6a,7] (98% yield, Chart I). Since the base-catalyzed procedure[2,10] for effecting β-elimination of

(1) Paper 4.: Johnson, W. S.; Elliott, R.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2904.
(2) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088. See also: McNamara, J. M.; Kishi, Y. *Ibid.* **1982**, *104*, 7371–7372.
(3) Available from Aldrich Chemical Co.
(4) The zinc iodide catalyzed reaction of aldehydes and ketones with cyanotrimethylsilane to give *O*-(trimethylsilyl)cyanohydrins is well-known. See inter alia: Groutas, W. C.; Felker, D. *Synthesis* **1980**, 861–868. Evans, D. A.; Truesdale, L. K.; Carroll, G. L. *J. Chem. Soc., Chem. Commun.* **1973**, 55–56. More recently the preparation of cyanohydrin *O*-alkyl ethers has been described by means of the Lewis acid catalyzed coupling of achiral dialkyl acetals with cyanotrimethylsilane: Utimoto, K.; Wakabayashi, Y.; Shishiyama, Y.; Inoue, M.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4279–4280. Utimoto, K.; Wakabayashi, Y.; Horiie, T.; Inoue, M.; Shishiyama, Y.; Obayashi, M.; Nozaki, H. *Tetrahedron* **1983**, *39*, 967–973.
(5) Prepared according to the conditions given in ref 2.
(6) (a) The crude product was homogeneous with respect to GC and TLC; substances **3c**, **4**, **6**, and **10** were evaporatively distilled (0.05 mm). (b) The product was purified by low-pressure column chromatography using "Merck silica gel 60 H for thin layer chromatography".
(7) (a) The NMR, IR, and mass spectra were consistent with the assigned structure. The identities of **5**, **6**, and **13** were confirmed by comparison (above spectra and GC coinjection) with authentic *dl* specimens. (b) A satisfactory combustion analysis was obtained for an appropriately purified specimen of this compound.
(8) The diastereomeric ratio was determined by GC on a 12-m SE-54 capillary column, which showed a base-line separation of the two peaks. In the case of **3a** it was necessary to prepare the *tert*-butyldimethylsilyl ether to obtain a base-line separation.
(9) Pyridinium chlorochromate (1.5 molar equiv), CH_2Cl_2, 25 °C, 18 h. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647–2650.
(10) THF/MeOH/2.5 M aqueous KOH (4:2:1), 5 h, 25 °C.

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the chiral side chain promised to result in decomposition of the cyanohydrin,[11] an acid-catalyzed method was developed (0.6% p-TsOH·H_2O in 2:1 dioxane/H_2O, reflux, 16 h), which effected conversion of **4** into (*R*)-mandelonitrile (**5**, 93% yield),[6a,7a] $[\alpha]^{25}_D$ +43.5° (*c* 5, $CHCl_3$).[12] The optical purity of **5** was confirmed to be 92.5% by conversion to the MTPA ester[13] (1.5 molar equiv MTPACl, pyridine, 3.5 h, 25 °C). Treatment of **4** with methanolic hydrogen chloride (3:1 Et_2O/MeOH saturated with HCl, 4 °C, 16 h) afforded (*R*)-methyl mandelate (**6**)[6a] mp 52.5–54 °C (97% yield from **4**), $[\alpha]^{25}_D$ −168° (*c* 0.8, C_6H_6).[14]

The reduction of cyanohydrins and derivatives to provide β-amino alcohols is well documented.[15] We decided therefore to explore the possibility of converting the chiral ethers **3** into β-amino alcohols while retaining the stereochemical integrity of the carbinol group. In the event, treatment of ethers **3a** and **3c** with borane (1.5 molar equiv BH_3·THF,[3] reflux 4 h) led respectively to the amino ethers **7** and **8**.[7a] Substance **7** was formylated[16] to give **9** in 85% overall yield,[6b,7] and the GC of the corresponding *tert*-butyldimethylsilyl ether showed two peaks in the ratio 96:4, confirming that no detectable epimerization had occurred during reduction.[17] The chiral auxilliary was removed[2] by oxidation to the ketone (Jones reagent), followed by base-catalyzed β-elimination[10] to produce **11**[6b,7] (89% yield from **9**). The configuration of **11** was shown to be *R* by its transformation[18] into the known quarternary iodide **14**.[19]

Ether **3c** was also reduced as described above, and the product **8** was converted[20] into the *tert*-butoxycarbonyl derivative **10**[6,7a] in 90% yield. Removal of the chiral auxilliary[2,9,10] afforded **12**,[6,7a] the optical purity of which was shown to be 91.5% by conversion to the MTPA ester,[13] thus confirming that little, if any, racemization occurred during the reduction step. Deprotection of **12** (TFA/H_2O (3:1), 25 °C, 0.5 h) afforded the known 2(*R*)-hydroxy-2-phenylethylamine (**13**), monohydrate[6,7a] in 80% yield (from **10**), $[\alpha]^{25}_D$ −60° (*c* 2, $CHCl_3$).[21]

The study described above illustrates the suitability of chiral cyanohydrin ethers of type **3** as precursors to optically active cyanohydrins, β-amino secondary alcohols, and α-hydroxy esters. A particularly noteworthy aspect of our methodology for the preparation of ethers **3** is that it permits the easy access to either antipodal form at the newly generated chiral center (Scheme I) dependent, in a reliable manner, upon the choice of an acetal **1** derived from (2*R*,4*R*)- or (2*S*,4*S*)-pentane-2,4-diol.[22-24]

Acknowledgment. We are indebted to the National Institutes of Health and the National Science Foundation for support of this research.

(11) Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1971**, *93*, 5286–5287.
(12) Lit. $[\alpha]^{20}_D$ +39° (*c* 5, $CHCl_3$), ref 15b.
(13) Determined by GC analysis (base-line separation) of (*R*)-(+)-MTPA esters. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.
(14) Lit. mp 54–55 °C, $[\alpha^{20}_D$ −176° (*c* 0.83, C_6H_6). Noe, C. R. *Chem. Ber.* **1982**, *115*, 1591–1606.
(15) See inter alia: (a) Anhoury, M. L.; Crooy, P.; De Neys, R.; Eliaers, J. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1015–1017, and references therein. (b) Becker, W.; Freund, *H.*; Pfeil, E. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1079. (c) Evans, D. A.; Carroll, G. L; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914–917.
(16) The substrate was heated to 60 °C with excess HCO_2H/Ac_2O (1:1) for 1 h, and then the crude formate ester was isolated and saponified by stirring with K_2CO_3, MeOH, H_2O.
(17) Epimerization of **3a**, A/B 95:5 (LDA, THF, −78 °C;[11] H_2O) gave a sample of **3a**, A/B 51:49 (GC coinjection and ^1H NMR spectroscopy). This sample was transformed into the *tert*-butyldimethylsilyl ether of **9**, which showed two GC peaks, ratio 49:51, of identical retention times (coinjection) with the sample mentioned above (ratio 95:5).
(18) Amide **11** was converted (37% aqueous $HCHO/HCO_2H$ (1:1), reflux 12 h) into the tertiary amine,[7a] which was further methylated (MeI, MeOH, reflux 16 h) to give **14**; mp 178–180 °C, $[\alpha]^{25}_D$ −10.9° (*c* 1, EtOH), [reported[19] mp 170–172 °C, $[\alpha]^{25}_D$ −12.23° (*c* 1, EtOH)].
(19) Coke, J. L.; Richon, A. B. *J. Org. Chem.* **1976**, *41*, 3516–3517.
(20) Di-*tert*-butyl dicarbonate,[3] THF, reflux, 45 min. Cf. Tarbell, D. S.; Yamamoto, Y.; Pope, B. M. *Proc. Natl. Acad. Sci. U.S.A.* **1972**, *69*, 730–732.
(21) Lit. $[\alpha]^{20}_D$ −71° (*c* 5, $CHCl_3$), ref 15b.
(22) For a theoretical discussion of the origins of diastereoselectivity in these processes, see ref 2.
(23) For the preparation of both (2*R*,4*R*)- and (2*S*,4*S*)-pentane-2,4-diol, via asymmetric hydrogenation of acetylacetone, see: Ito, K.; Harada, T.; Tai, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3367–3368.
(24) During the course of this work, Ito et al. [Ito, Y.; Kato, H.; Imai, H.; Saegusa, T. *J. Am. Chem. Soc.* **1982**, *104*, 6449–6450] reported the reaction of a dimethyl acetal with *tert*-butyl isocyanide in the presence of $TiCl_4$ to give a cyanohydrin *O*-methyl ether. When chiral acetal **1b** was treated with *t*-BuNC under conditions otherwise identical with those employed for Me_3SiCN, **3b** was formed, quantitatively, with a diastereomeric ratio A/B 96:4 (GC coinjection and ^1H NMR spectroscopy).

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Peptide Decomposition in the Neutral pH Region via the Formation of Diketopiperazines

Summary: In the neutral pH region, the decomposition of the tripeptides Leu-Gly-Gly and Gly-Leu-Gly at 130 °C and the hexapeptide Phe-Gly-Leu-Gly-Val-Gly at 100 °C has been found to involve the formation of diketopiperazines from the N-terminal position of the peptides.

Sir: Although the decomposition of peptides in strongly acidic and basic solutions has been extensively investigated,[1] there have been few studies of peptide decomposition at neutral pH. Peptide hydrolytic mechanisms in the neutral pH region would be important to establish since they could be used to elucidate the pathways of protein decomposition in fossils and sediments.[2] Previous results from this laboratory have shown that in the range pH 5–8 dipeptides undergo extensive reversible cyclization to their diketopiperazines.[3] This transformation is accompanied by extensive racemization due to the rapid rate of racemization of amino acid residues in diketopiperazines.[3] In earlier investigations with dipeptide methyl esters and amides, it was demonstrated that internal aminolysis to form the diketopiperazine was much faster than the hydrolysis of the ester or amide functionality.[4] We were thus interested in the possiblity that decomposition of larger peptides would proceed via formation of diketopiperazines at the N-terminal position according to reaction mechanism 1.[5] To test this possiblity, the decomposition of the tripeptides Leu-Gly-Gly,

(1) Hill, R. L. *Adv. Protein Chem.* **1965**, *20*, 37.
(2) Bada, J. L.; Man, E. H. *Earth-Sci. Rev.* **1980**, *16*, 21. Ho, M.-S.; Bada, J. L.; Yan, Z.; Liu, D. In "Aquatic and Terrestrial Humic Materials"; Christman, R. F., Gjessing, E. T., Eds.; Ann Arbor Sci.: Ann Arbor, MI 1983; p 429.
(3) Steinberg, S.; Bada, J. L. *Science (Washington, D.C.)* **1981**, *213*, 544.
(4) Purdie, J. E.; Benoiton, N. L. *J. Chem. Soc., Perkin Trans. 2* **1973**, *13*, 1845.
(5) The continuation of the peptide chain is denoted by ~.

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