Improved Asymmetric Total Synthesis of Corticoids via Biomimetic Polyene Cyclization Methodology[1]

Summary: Addition of lithium (trimethylsilyl)acetylide (**8**), complexed with the Mukaiyama chiral ligand, to the aldehyde **3** at −120 °C gave, in 70% yield and 90% ee, the alcohol **9** which is an intermediate for producing the cyclization substrate **1** leading (via **2**) to corticoids. A more practical approach which affords higher optical yields involves the use of a new reagent **12** for producing an acetylenic ketone, i.e., **12** → **14** → **15**. Reduction of **15** by the Midland method with (+)-α-pinene–9-BBN gave **9a** in 71–75% yield and 96–97% ee. Thus the asymmetric total synthesis of corticoids via biomimetic polyene cyclization methodology has been improved with respect to convergency and optical yield.

Sir: The biomimetic cyclization of the substrate **1** has been shown to give **2** which is convertible (in 7 steps) into hydrocortisone acetate.[2] The cyclization is enantiospecific; i.e., the percent enantiomeric excess of the product **2** was the same as that of the substrate **1**. Thus the optical yield of **2** is determined by the optical yield for that stage at which the chiral center at pro-C-11 is introduced. In the previous work this was accomplished by the following steps: reaction of the lithium salt of **4** with the aldehyde **3** to give the racemic adduct **6**, oxidation of this propargylic alcohol to the ketone **7**, and then enantioselective reduction of **7** with lithium aluminum hydride–Darvon alcohol complex[3,4] at −78 °C.[5] The best optical yield obtained in this way was 84% (i.e., **6a**:**6b** = 92:8), and the result could be duplicated only by working under very carefully controlled conditions.[6] The present communication discloses some successful experiments aimed at improving the process for enantioselective generation of the chiral center at pro-C-11.

Scheme I

Scheme II

An alternative approach[2] to the key propargylic alcohol **6** involves the steps shown in Scheme I, i.e., addition of lithium (trimethylsilyl)acetylide (**8**) to aldehyde **3**, giving **9**, desilylation (KOH–MeOH) to give **10**, and then alkylation of its *tert*-butyldimethylsilyl ether with the diketal bromide **5**. Mukaiyama et al.[7] have reported unusually high optical yields for the addition of **8** to aldehydes in the presence of the chiral ligand (2*S*,2′*S*)-2-(hydroxymethyl)-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine.[7c] Using his procedure we examined the condensation of **8** with 0.5 mmol of the aldehyde **3** at two different reaction temperatures. At −78 °C, the yield of **9**[8a] was 70%, and at −120 °C it was 75%. These products were desilylated (5% KOH in MeOH, 1.75 h, 23 °C) to give samples of **10**[8a,d] in >80%, showing $[\alpha]^{20}_{D}$ +51.9° and +69.2° (*c* 2.0, $CHCl_3$) for the products derived from the −78 and −120 °C reactions, respectively. The ratios of the diastereomeric MTPA esters[9] **11a** to **11b** produced from these two samples were accurately determined by GC analysis[10] to be 85:15 and 95:5, respectively. Thus the optical yield for the Mukaiyama reaction with **3** at −120 °C was 90% which is high compared with those (68–80%) that have been obtained with simple aliphatic aldehydes.[7b] The method suffers only from the necessity of achieving the very low reaction tem-

(1) For a recent paper in this series on biomimetic polyene cyclizations, see: Schmid, R.; Huesmann, P. L.; Johnson, W. S. *J. Am. Chem. Soc.* **1980**, *102*, 5122.

(2) Johnson, W. S.; Brinkmeyer, R. S.; Kapoor, V. M.; Yarnell, T. M. *J. Am. Chem. Soc.* **1977**, *99*, 8341.

(3) Brinkmeyer, R. S.; Kapoor, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339.

(4) Yamaguchi, S.; Mosher, H. S.; Pohland, A. *J. Am. Chem. Soc.* **1972**, *94*, 9254; Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870.

(5) The succeeding steps to give **1**, i.e., reduction of **6** to the allylic alcohol, hydrolysis of the ketal functions, cyclodehydration of the resulting dione, and addition of methyllithium to the cyclopentenone, all proceed without detectable racemization of the pro-C-11 chiral center.

(6) In order to realize good optical yields freshly prepared reducing agent must be submitted to a critical, short incubation period at 0 °C (see ref 3 and 4) and the reduction temperature must not exceed −78 °C (see footnote 7 of ref 3).

(7) (a) Mukaiyama, T.; Suzuki, K.; Soai, K.; Sato, T. *Chem. Lett.* **1979**, 447. (b) Mukaiyama, T.; Suzuki, K. *Ibid.* **1980**, 255. (c) Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455.

(8) The product was purified by (a) chromatography on Florisil, (b) chromatography on alumina, (c) chromatography on silical gel, (d) distillation at reduced pressure through a short-path apparatus, or a short Vigreux column, or (for high-boiling compounds and/or small amounts of material) a Kugelrohr with a Büchi Kugelrohrofen.

(9) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(10) Base-line separation was observed with a 7.5-m, WCOT OV-101 glass column at 155 °C.

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perature which renders the procedure impractical except for small-scale runs.

An alternative approach to the syntheses of **6a** via **10a** employs a new reagent, the [(trimethylsilyl)ethynyl]dithiane **12**, for synthesizing an acetylenic ketone as suggested in Scheme II. The thioacetal **12**[11] was readily prepared in 59% overall yield[8c,d] by condensation (BF_3·Et_2O in HOAc, 15 min, 15 °C) of 1,3-propanedithiol with 3-(trimethylsilyl)propynal[11a] which was formed,[8d] in turn, by pyridinium chlorochromate oxidation[12] of the corresponding alcohol.[13]

The thioacetal (0.99 mmol) **12** was converted (1.05 mmol of *n*-BuLi, 5 mL of THF, 1 h, −40 to −20 °C) into its lithium salt, which was alkylated with the known[14] allylic chloride **13** (0.92 mmol, 1 mL of THF, −20 to −15 °C, 4 h) to give the thioketal **14**[8c,d,11] in 84% yield. A variety of known methods were tried for the hydrolysis of **14**, but the only satisfactory procedure[15] was the treatment of **14** (0.279 mmol in 2 mL of THF) with thallium(III) nitrate trihydrate (0.443 mmol in 5 mL of MeOH) for 5 min at 23 °C, followed by further treatment (5 min, 23 °C) with 2 mL of 5% HCl. Thus the known ketone **15**[2] was obtained[8c,d] in 86% yield. Reduction of **15** (0.13 mmol) was effected by the method of Midland,[16] using the complex from (+)-α-pinene[17] (0.617 mmol) and 9-BBN (0.5 mmol) in THF (43 h, ~20 °C). The product **9**[8c] (75% yield) was desilylated (see above) and purified,[8a,c] giving **10**, $[\alpha]^{20}_D$ +72.4° (*c* 0.71, $CHCl_3$). The composition of the diastereomeric MTPA esters[9] derived from this +72.4° specimen of **10** was shown by GC[10] to be 98.5:1.5 **11a**/**11b**, corresponding to an optical yield of 97%. The Midland reduction of **15** has been repeated successfully several times; thus on a 2.74-mmol scale a 71% yield of **9**, having 96% ee of **9a**, was obtained.

The new approach to the cyclization substrate **1** via the sequence described in Scheme II has the following novel features: (1) the overall process is more convergent than the original scheme; (2) the process gives very high optical yields; (3) a new reagent, namely, **12**, for producing the acetylenic ketone **15** has been developed; (4) finally, the process (as in Scheme II) involving alkylation of the reagent **12**, followed by deketalization, asymmetric reduction, and then further alkylation should be useful for synthesizing a variety of optically pure alcohols.

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Registry No. 3, 58403-88-6; **6a** (R^1 = H; R^2 = OH), 76704-56-8; **6b** (R^1 = H; R^2 = H), 76704-57-9; **8**, 54655-07-1; **9a** (R^1 = H; R^2 = OH), 76649-00-8; **9b** (R^1 = OH; R^2 = H), 76649-01-9; **10a** (R^1 = H; R^2 = OH), 76704-58-0; **10b** (R^1 = OH; R^2 = H), 76704-59-1; **11a** (R^1 = H; R^2 = MTPA-O), 76684-07-6; **11b** (R^1 = MTPA-O; R^2 = H), 76649-02-0; **12**, 76649-03-1; **12** Li, 76665-49-1; **13**, 58403-77-3; **14**, 76649-04-2; **15**, 76649-05-3; 1,3-propanedithiol, 109-80-8; 3-(trimethylsilyl)propynal, 6224-91-5; (2*S*,2′*S*)-2-(hydroxymethyl)-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine, 66283-23-6; (+)-α-pinene-9-BBN, 64106-79-2.

(11) (a) The NMR and IR spectra were consistent with the assigned structures. (b) A satisfactory combustion analysis was obtained for this compound.
(12) Corey, E. J.; Suggs, W. *Tetrahedron Lett.* **1975**, 2647.
(13) Jäger, V. *Methoden Org. Chem. (Houben-Weyl)* **1977**, *V/2a*, 329.
(14) Johnson, W. S.; Escher, S.; Metcalf, B. W. *J. Am. Chem. Soc.* **1976**, *98*, 1039.
(15) Smith, R. A. J.; Hannah, D. J. *Synth. Commun.* **1979**, *9*, 301.
(16) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867.
(17) Optically pure (+)-α-pinene, $[\alpha]^{20}_D$ +51.6° (neat), that had been isolated from a sample of Port Orford cedar oil was used.

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Reaction of Organic Molecules on Solid Surfaces. 1. Facile Deuteration of Active Methylene Compounds with D_2O-Treated Alumina

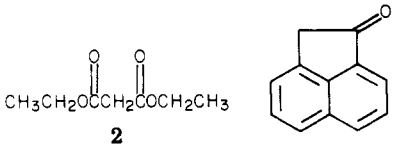
Summary: A procedure has been developed for the preparation of deuterated alumina. Treatment of ketones, active methylene compounds, and acidic hydrocarbons with this solid resulted in the deuteration of the compounds at acidic sites. Deuterated molecular sieves are also effective in these deuterations.

Sir: We report the development of a new, facile, and convenient method by which organic molecules can be deuterated at acidic sites. The procedure involves treatment of acidic organic molecule with deuterated alumina either on a column or as a slurry. The combination of speed, efficiency, convenience, and other factors to be described below should make this method competitive with more traditional methods of deuteration and offers substantial synthetic potential.

Chromatography alumina (Fisher adsorption, 80–200 mesh)[1] has both physisorbed and chemisorbed H_2O, and all such proton sources must be removed and replaced by deuterium before the material can be used for deuteration. Unfortunately, this is not accomplished by simply heating alumina followed by treatment with D_2O.[2] However, we observed that seven to nine sequential heatings (315 °C, 18 h) followed by treatment with D_2O (3 wt %) afforded material which quantitatively deuterated phenylacetylene (**1**) upon passage through a 10-g column (100 mg of **1** in pentane).[3]

$$\underset{\mathbf{1}}{C_6H_5C{\equiv}CH} \xrightarrow{Al_2O_3/D_2O} \underset{\mathbf{1}\text{-}d}{C_6H_5C{\equiv}CD}$$

Several compound types bearing acidic hydrogens were found to be effectively deuterated by deuterated alumina. For example, diethyl malonate (**2**), was >96% deuterated



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at the methylene site when treated as a slurry with the

(1) (a) For a review of the use of alumina in organic synthesis see: Posner, G. H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 487. (b) One group has reported on the tritiation of a keto steroid by chromatography on Al_2O_3/T_2O. See: Klein, P. D.; Knight, J. C. *J. Am. Chem. Soc.* **1965**, *87*, 2657; Klein, P. D.; Erenrich, E. H. *Anal. Chem.* **1966**, *38*, 480.
(2) Peri, J. B. *J. Phys. Chem.* **1960**, *64*, 1526.
(3) The deuterated alumina could be prepared by treating the dehydrated solid with D_2O in dry tetrahydrofuran. It took, however, several additional cycles before a phenylacetylene sample could be completely deuterated.

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