Notes

Chemically Modified Potassium Hydride. Significant Improvement in Yields in Some Oxy-Cope Rearrangements

Timothy L. Macdonald,* Kenneth J. Natalie, Jr., Girija Prasad, and J. Scott Sawyer

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

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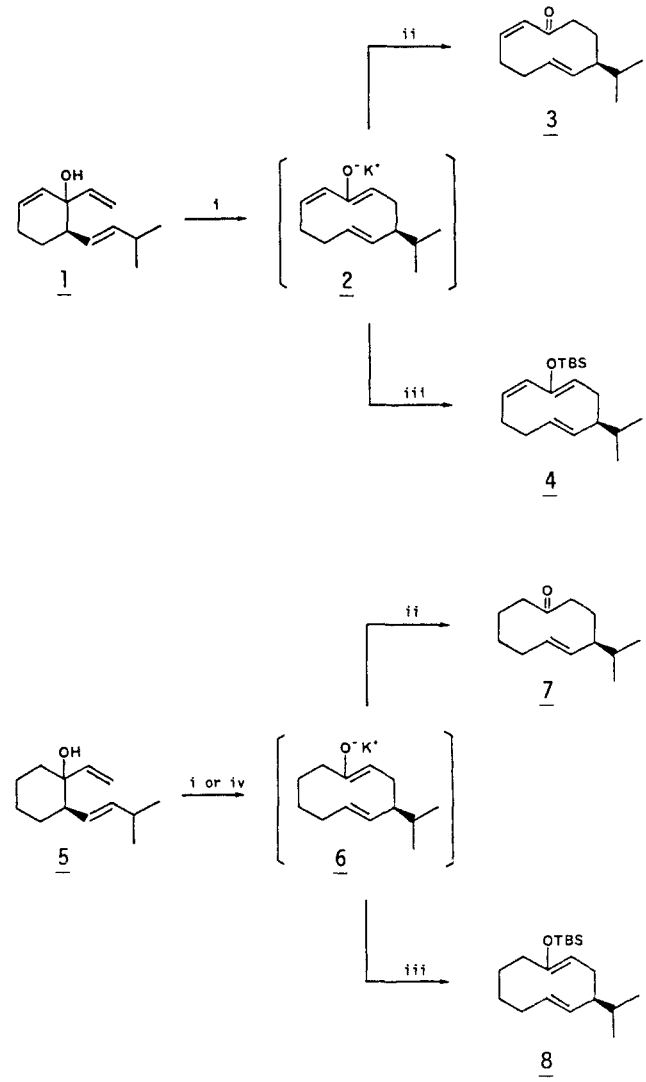
Potassium hydride is a valuable synthetic reagent in both organic and inorganic chemistry. However, we have found, as have others,[1,2] that the commercial reagent can be variably contaminated with impurities that can exhibit a pronounced effect upon the efficiencies of many synthetic processes.[3] For example, in our studies of the anionic oxy-Cope rearrangement leading to germacranadienone species discussed below, we have obtained yields of rearrangement products varying from 0% to 76% under ostensibly identical reaction conditions, with the only variable being the potassium hydride commericial lot number (although yields were highly reproducible with a given potassium hydride lot). Since potassium hydride is prepared commercially through reduction of a paraffin oil suspension of finely divided metallic potassium with hydrogen at 230–400 °C,[4] the variable presence of unreacted elemental potassium or its subsequent oxidation product, potassium superoxide, appeared possible. Previous methods directed at the regeneration of "poisoned" potassium hydride described by Brown[1] failed to stabilize the variable yields we observed in sensitive anion accelerated oxy-Cope rearrangements. We report here a method involving iodine treatment of commercial potassium hydride which serves to remove this contaminant and presumably generates potassium iodide in situ. Utilizing this technique with commercial potassium hydride from the same container, we have reproducibly improved the yields of the described oxy-Cope rearrangement from 0% to ~75% and of a literature example of "potassium hydride sensitivity"[2] from 0% to 78% (literature yield: ~65%[5]).

The anionic modification of the oxy-Cope rearrangement as described by Evans and co-workers[6] has proven highly useful in the synthesis of natural products, including notably the germacrane sesquiterpenes.[7] In connection with recent studies directed toward the cyclodecadienone ring system of many natural products, we noted a striking

Scheme I[a]



[a] (i) KH (I_2 pretreated), 18-crown-6, THF (reflux), 2 h; or KH (I_2 pretreated), 18-crown-6, THF (20 °C), 8 h; (ii) EtOH, −78 °C; (iii) TBSCl, −78 °C; then EtOH; (iv) KH, 18-crown-6, THF (reflux), 2 h; or KH, 18-crown-6, THF (20 °C), 8 h.

dependence of the anion accelerated oxy-Cope rearrangement of certain divinyl cyclohexenols (e.g., 1) to the corresponding 10-membered ring system on the precise source of the potassium hydride employed (e.g., commercial supplier, reagent lot number). In contrast, divinyl cyclohexanols (e.g., 5) displayed substantial tolerance to all potassium hydride samples tested, smoothly rearranging to the expected products in good to excellent yields.

In specific cases, carbinols 1 and 5 (readily available as 1:1 diasteromeric mixtures from the corresponding ketones in 65% and 73% isolated yields, respectively, via known procedures[7a,b]) were subjected to anionic oxy-Cope rearrangements with different lots of potassium hydride obtained from commercial sources (see Scheme I). Invariably, carbinols 5 rearranged smoothly to give intermediate enolate 6, which could be protonated at low temperature to provide ketone 7 (85%) or trapped with *tert*-butyldi-

(1) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913.
(2) For a well-studied example of sensitivity to different "lots" of commercial potassium hydride, see: Newcomb, M.; Smith, M. G. *J. Organomet. Chem.* **1982**, *228*, 61.
(3) Other reagents used to alleviate synthetic problems associated with potassium hydride variability. (a) Potassium diisopropyl amide/lithium *t*-butoxide: see ref 2. (b) Potassium *tert*-butoxide: Snowden, R. L.; Muller, B. L.; Schulte-Elte, K. H. *Tetrahedron Lett.* **1982**, 335. (c) Potassium hexamethyldisilazane: Sreekumar, C.; Darst, K. P.; Still, W. C. *J. Org. Chem.* **1980**, *45*, 4260.
(4) Wiberg, E.; Amberger, E. In "Hydrides of the Elements of Main Groups I–IV"; Elsevier: New York, 1971; pp 34–35.
(5) Corriu, R. J. P.; Guerin, C. *J. Organomet. Chem.* **1980**, *197*, C19.
(6) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765.
(7) For references to the synthesis of the germacrane skeleton employing this strategy, see: (a) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4168. (b) Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493. (c) Schreiber, S. L.; Santini, C. *J. Am. Chem. Soc.* **1984**, *106*, 4038. For a closely related system, see: Wender, P. A.; Sieburth, S. M. *Tetrahedron Lett.* **1981**, 2471.

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methylsilyl chloride to provide the unstable *tert*-[(butyldimethylsilyl)oxy]cyclodecadiene **8** (81%, of undetermined enol silyl ether geometry). Alternatively, carbinols **1** provided highly erratic yields of the desired cyclodecadienone **3** or *tert*-butyldimethylsilyl enol ether **4** by using the identical potassium hydride samples applied to carbinols **5**. In rearrangements in which low yields (<10%) of the desired product was isolated, the primary product appeared to consist after reaction workup of "polymerized" cyclodecenone units by NMR spectral analysis [with the major species having multiple cyclodecenone units by mass spectral analysis], suggesting destruction of the rearranged dienolate intermediate **2** in situ. Although the mechanism(s) underlying this putative polymerization process is unclear, dienolate polymerization could be anticipated to be induced through either the corresponding radical, obtained via oxidation of the dienolate (possibly by potassium superoxide), though the corresponding radical anion, obtained via dienolate reduction possibly by elemental potassium), or a KH-unreactive proton source. The sensitivity of dienolate **2**, in comparison with its saturated counterpart (**6**), would then be ascribed to differences in the relative facility of dienolate single-electron oxidation and reduction. Whatever the nature of the impurity and the mechanism by which it executes its deleterious effects, iodine treatment of commercial potassium hydride appears to resolve the synthetic difficulties associated with it.[8] Thus, under the standard conditions for the anionic oxy-Cope rearrangement [potassium hydride (5 mol equiv); 18-crown-6 (5 mol equiv); THF], treatment of potassium hydride with iodine (10 mol %) prior to substrate (1 mol equiv) introduction improved the yields of both cyclodecadienone **3** and (silyloxy)cyclodecatriene **4** from often 0% to a consistent and reproducible 70–80%.

We have additionally applied this technique to the in situ generation of tri-*n*-butylstannyl potassium from potassium hydride and tri-*n*-butyltin hydride. Newcomb and Smith[2] have reported "potassium hydride supplier" dependent yields of alkyl tri-*n*-butylstannanes utilizing an *in situ* KH-mediated $(n\text{-Bu})_3\text{SnK}$ generation/alkyl halide alkylation procedure,[5] which produced variable yields for the several alkyl halides examined.[2,5] In instances in which low yields of the desired tetraalkylstannanes were obtained (<10%), hexa-*n*-butylditin was produced as the major or exclusive tin-containing product.[2] We have confirmed these results and find that for a potassium hydride lot which produces a 0% yield of benzyl tri-*n*-butylstannane under the standard conditions, iodine pretreatment improves the isolated yield of the desired product to 78%. Thus, we have established truly significant improvements in yields for select synthetic processes that are sensitive to potassium hydride source utilizing potassium hydride chemically modified with iodine. We anticipate that this simple procedure may have wide applicability in synthesis.

Experimental Section

Materials and General Techniques. Infrared spectra were recorded on a Perkin-Elmer Model 1430 ratio recording infrared spectrophotometer. Proton nuclear magnetic resonance spectra were obtained on a Varian Model EM 390 spectrometer at 90 MHz or a Nicolet NT-360 spectrometer with 1280-293B data system at 360 MHz. Carbon nuclear magnetic resonance spectra were determined on a Nicolet 360 spectrometer at 90 MHz. Chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane (^{1}H NMR) or referenced from the central peak of deuterochloroform at 77.0 ppm (^{13}C NMR). All ^{13}C NMR spectra are proton decoupled. Mass spectra were determined on a Finnegan MAT 4615 GC/MS/DS instrument utilizing chemical ionization with butane. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Column chromatographic separations were undertaken on Woelm Silica 32–63 mesh using a modified short/flash column technique or on Florisil using a short column technique. Thin-layer chromatography was undertaken with E. Merck glass plates precoated with silica gel 60 F-254 and visualized with either chromic acid or vanillin/sulfuric acid spray. Tetrahydrofuran (THF) and diethyl ether were distilled under argon from sodium benzophenone ketyl prior to use. Mineral oil suspensions of potassium hydride were purchased from Aldrich and Alfa Ventron. All reactions were conducted under an argon atmosphere. The syntheses and spectral data for the precursor divinylcyclohexenols **1** and divinylcyclohexanols **5** employed in these investigations of the anion-accelerated oxy-Cope rearrangement are detailed in the supplementary material.

General Method for the Treatment of Potassium Hydride with Iodine. Commercial potassium hydride (35% suspension in mineral oil) was washed with petroleum ether (~4 mL/10 mmol KH; 3×) and then resuspended in the desired solvent (THF, DME, ether) at 0.1–1.0 M. The resulting KH suspension can either be "titrated" with a solution of iodine in the desired solvent (0.1–0.5 M) until the purple-orange iodine color persists for at least 5 min[8] or treated dropwise with a standard quantity of iodine (10 mol %) in the desired solvent, since in no instance that we have examined has more than this percentage been required. The suspenion of potassium hydride/potassium iodide thus generated can be employed to generate tri-*n*-butyltin hydride,[5] which can be utilized in alkyl halide displacements without competing undesired reactions.[2] Further examples of the employment of this chemically modified potassium hydride follow.

7-(2-Propyl)-2(*Z*),6(*E*)-cyclodecadienone (3). Potassium hydride (2.61 mmol) in a mineral oil suspension was washed with pentane (1.0 mL; 3×) and suspended in THF (2.0 mL). The resulting suspension was treated with iodine (0.25 mmol) in THF (0.5 mL) as described in the general procedure. 18-Crown-6 (690 mg, 2.61 mmol) and divinylcyclohexenol **1** (101 mg, 0.522 mmol) dissolved in a minimum volume of THF (~0.5 mL) were added in a single portion, and the resulting mixture was either refluxed for 2 h or stirred at room temperature for 8 h. The reaction was then cooled to −78 °C and quenched with absolute ethanol (1.5 mL) via rapid injection. The resulting slurry was immediately poured into a mixture of petroleum ether (5 mL) and a solution of saturated ammonium chloride (5 mL) and thoroughly shaken. The organic layer was washed with brine (5 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to give an orange oil. Chromatography [silica gel; ether (5%)/petroleum ether (95%)] affored pure cyclodecadienone **3** (75.2 mg, 75%) as a low melting, waxy solid (mp ~35 °C).

3: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.31 (1 H, d, J = 11.6 Hz), 5.72 (1 H, dt, J = 11.6, 8.5 Hz), 4.99 (1 H, m), 4.82 (1 H, m), 2.33–2.55 (2 H, m), 2.29 (2 H, ddd, J = 14.9, 7.7, 7.7 Hz), 2.16 (1 H, m), 1.65–1.90 (4 H, m), 1.53 (1 H, sextet, J = 6.3 Hz), 0.88 (3 H, d, J = 6.8 Hz), 0.85 (3 H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 206.08, 136.68, 135.52, 133.47, 127.66, 52.09, 43.49, 31.72, 30.64, 25.64, 20.76, 19.51. IR (NaCl, cm^{-1}) 2940, 2860, 1680, 1610, 1451, 1397, 1202, 1073, 970, 829, 735; MS (CI), m/e (relative intensity) 193 (M + 1, 28), 175 (100), 149 (5), 133 (6), 119 (37); TLC [ethyl acetate (5%), petroleum ether (95%)] R_f 0.31. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.15; H, 10.50.

2-[(*tert*-Butyldimethylsilyl)oxy]-9-(2-propyl)-1(*Z*),3(*Z*),7(*E*)-cyclodecatriene (4). Potassium hydride pretreatment and divinylcyclohexenol rearrangement were undertaken in an identical manner as for cyclodecadienone **3**, except that after cooling to −78 °C, *tert*-butyldimethylsilyl chloride (156 mg, 1.04 mmol) dissolved in THF (0.75 mL) was introduced via syringe instead of ethanol. After an adequate reaction period to ensure complete silyl halide trapping (as monitored by TLC; typically 0.5 h at −78 °C), the excess potassium hydride was rapidly quenched with ethanol (1.0 mL) and processed as described for

(8) Iodine (1 mole equiv) would oxidize elemental potassium (2 mol equiv) to potassium iodide and potassium superoxide (2 mole equiv) to potassium iodide and oxygen. In this chemical treatment method, initial iodine (1–3 mol % of potassium hydride, depending on the commercial lot) is rapidly consumed (essentially a titration), whereas the remaining iodine (4–8 mol %) is consumed at a much slower rate (~5–15 min). We attribute this behavior to an initial rapid reaction phase, in which the major portion of the impurity is consumed, and a slower phase, in which the principal reaction is with potassium hydride.

3. Solvent removal in vacuo provided a light yellow oil [R_f 0.67; ethyl acetate (5%)/petroleum ether (95%)], which proved to be unstable toward further purification. Formation of silyl enol ether **4** was verified by treatment of the crude material with tetra-*n*-butylammonium fluoride as the trihydrate (631 mg, 2.0 mmol) in THF (2 mL) to provide after purification cyclodecadienone **3** (71% from divinylcyclohexenol **1**).

4: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.03 (1 H, d, J = 11.1 Hz), 5.33 (1 H, dt, J = 7.1, 10.3 Hz), 4.87 (1 H, ddd, J = 15.3, 10.3, 4.6 Hz), 4.63 (1 H, dd, J = 15.8, 9.1 Hz), 4.59 (1 H, t, J = 8.5 Hz), 2.35 (1 H, m), 2.08 (2 H, m), 1.98 (1 H, m), 1.44–1.64 (3 H, m), 1.35 (1 H, d, J = 10.3 Hz), 0.92 (6 H, d, J = 6.1 Hz), 0.90 (9 H, s), 0.11 (6 H, s), 0.08 (6 H, s); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 150.18, 132.98, 132.33, 130.33, 127.45, 107.29, 53.80, 32.71, 32.03, 31.70, 28.61, 25.75, 21.30, 20.33, 18.15, -4.31; IR (NaCl, cm^{-1}) 2945, 2846, 1679, 1608, 1466, 1458, 1248, 965, 831, 774; MS (CI), m/e (relative intensity) 309 (6), 308 (23), 307 (M + 1, 89), 291 (36), 279 (24), 249 (15), 175 (100), 119 (26); TLC [ethyl acetate (5%)/petroleum ether (95%)] R_f 0.67.

4-(2-Propyl)-5(*E*)-cyclodecenone (7). Potassium hydride (2.61 mmol) in a mineral oil suspension was washed with pentane (1.0 mL; 3x) and suspended in THF (2.0 mL). The resulting THF suspension could either be employed directly without iodine chemical modification or with iodine pretreatment as described above; yields of the desired rearrangement products **7** and **8** were essentially identical. 18-Crown-6 (690 mg, 2.61 mmol) and divinylcyclohexanol **5** (102 mg, 0.522 mmol) dissolved in a minimum volume of THF (~1.5 mL) were added in a single portion, and the resulting mixture was refluxed for 2 h or stirred at room temperature for 8 h. The reaction was then cooled to -78 °C and quenched with absolute ethanol (1.5 mL) via rapid injection. The resulting slurry was immediately poured into a mixture of petroleum ether (5 mL) and a solution of saturated ammonium chloride (5 mL) and thoroughly shaken. The organic layer was washed with brine (5 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to provide an orange semisolid. Chromatography [silica gel; ether (5%)/petroleum ether (95%)] afforded cyclodecenone **7** (85.5 mg, 85%) as a waxy solid (mp ~28 °C).

7: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 5.30 (1 H, ddd, J = 14.7, 11.0, 3.7 Hz), 4.94 (1 H, dd, J = 14.7, 10.6 Hz), 2.50 (1 H, dd, J = 16.1, 9.9 Hz), 2.12–2.43 (4 H, m), 2.04 (1 H, q, J = 12.6 Hz), 1.93 (2 H, m), 1.77 (2 H, m), 1.63 (2 H, m), 1.48 (1 H, hextet, J = 6.7 Hz), 1.32 (1 H, q, J = 13.4 Hz), 0.86 (3 H, d, J = 6.7 Hz), 0.82 (3 H, d, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 212.52, 137.07, 130.26, 53.16, 45.39, 42.56, 33.07, 31.39, 28.62, 22.15, 20.70, 20.24; IR (NaCl, cm^{-1}) 2913, 2847, 1700, 1428, 1353, 1095, 977; MS (CI), m/e (relative intensity) 195 (M + 1, 33), 177 (100), 121 (47), 95 (12), 81 (7); TLC [ethyl acetate (10%)/petroleum ether (90%)] R_f 0.47. anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.20; H, 11.44.

1-[(*tert*-Butyldimethylsilyl)oxy]-4-(2-propyl)-1,5(*E*)-cyclodecadiene (8). Rearrangement of divinylcyclohexanol **5** was undertaken in an identical manner as detailed for cyclodecenone **7** except that after cooling to -78 °C, *tert*-butyldimethylsilyl chloride (155 mg, 1.04 mmol) dissolved in THF (0.75 mL) was introduced via syringe instead of ethanol. After an adequate reaction period to ensure complete silyl halide trapping (as monitored by TLC; typically 0.5 h at -78 °C), the excess potassium hydride was rapidly quenched with ethanol (1.0 mL) and processed as described for **7**. Solvent removal in vacuo gave a light yellow oil [R_f 0.72; ethyl acetate (5%)/petroleum ether (95%)] which proved highly unstable to further purification on chromatography sorbents or extended handling at room temperature (e.g., acquisition of ^{13}C NMR spectra). Upon treatment of crude silyl enol ether **8** obtained from such a reaction with tetra-*n*-butylammonium fluoride as the trihydrate (630 mg, 2.0 mmol) in THF (2.0 mL), cyclodecenone **7** was obtained in 80% yield from vinyl cyclohexanol **5** after purification on silica gel.

8: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 4.8–5.5 (2 H, m), 4.3 (1 H, m), 1.1–2.6 (12 H, m), 1.0 (6 H, d, J = 6 Hz), 0.9 (9 H, s), 0.1 (6 H, s); IR (NaCl, cm^{-1}) 2951, 2940, 2841, 1660, 1467, 1250, 840, 775.

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Registry No. 1 (isomer 1), 99885-71-9; 1 (isomer 2), 99945-84-3; 3, 99885-72-0; 4, 99885-73-1; 5 (isomer 1), 99885-74-2; 5 (isomer 2), 99945-85-4; 7, 99885-75-3; 8, 99885-76-4; 9, 99885-77-5; 10, 99885-78-6; 11, 99885-79-7; 12, 99885-80-0; 13, 99885-81-1; TBSCl, 18162-48-6; KH, 7693-26-7; I_2, 7553-56-2; $CH_3CH{=}CHCHO$, 4170-30-3; Bu_3SnH, 688-73-3; $CH_2{=}CHBr$, 593-60-2; 2-cyclohexenone, 930-68-7; cyclohexanone, 108-94-1.

Supplementary Material Available: Experimental details for the synthesis of *cis*- and *trans*-**1** (from cyclohexenone) and the synthesis of *cis*- and *trans*-**5** (from cyclohexanone) (8 pages). Ordering information is given on any current masthead page.

Synthesis of Aspartame via Asymmetric Hydrogenation of N-Protected (*Z*)-*N*-α-L-Aspartyl-Δ-phenylalanine Methyl Ester

Claudio Fuganti,* Piero Grasselli, and Luciana Malpezzi

Dipartimento di Chimica del Politecnico, Centro del CNR per la Chimica delle Sostanze Organiche Naturali, 20133 Milano, Italy

Paolo Casati

Sclavo, Divisione Biochimica DE.BI., 20060 Cassina de'Pecchi, Italy

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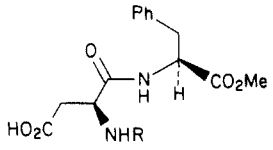
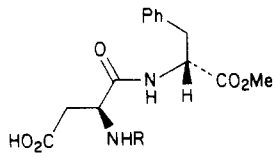
The usefulness of asymmetric hydrogenation of dehydropeptides in the preparation of peptides of high diastereoisomeric purity has been well established.[1] However, this synthetic principle has not been apparently applied to the preparation of the artificial sweetener aspartame (α-L-aspartyl-L-phenylalanine methyl ester)[2] (**1**), whose practical syntheses involve ring opening of N-protected L-aspartic anhydride with L-phenylalanine methyl ester.[3] This convergent approach suffers the drawback of the lack of regiospecificity. Indeed, minor amounts of the β-ring-opening product accompany the desired α-isomer, thus lowering the yield of incorporation of L-phenylalanine into **1**. Furthermore, until recently,[4] there was a considerable



1, R=H
2a, R=CHO
2b, R=COOCH$_2$Ph



3a, R=CHO
3b, R=COOCH$_2$Ph

difference in availability and price between the two amino acids used as starting materials. These circumstances

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