olsilane product on deprotonation in the kinetic manner with lithium hexamethyldisilazane and trapping of the resulting enolate with trimethylsilyl chloride.[15] The structure of this substance was not forthcoming however, until it was treated with palladium acetate (trimeric) in anhydrous acetonitrile—whereupon the enone **10** (oil, 73%) was isolated.[16]

Basic hydrogen peroxide treatment of **10** and subsequent reduction of the α-epoxy ketone with triisobutylaluminum gave the *trans*-epoxy alcohol **11**.[17] This material, without purification, was submitted to epoxide ring opening using an excess of dilithioacetate in hexamethylphosphoramide and DME. Acid workup of the reaction served both to secure formation of the cis lactone and to hydrolyze the THP residue—this product was treated with trimethylsilyl chloride and then purified to give the tricyclic lactone derivative **12** (mp 121-122 °C, 55% from **10**).[18]

Methylenation of the lactone by treatment with methoxymagnesium carbonate (20 equiv, 140 °C, 2 h), followed by reaction of the resultant lactone acid **13** with 30% formalin solution containing diethylamine, afforded crystalline dihydrohelenalin, **14** (mp 156.5-157.5 °C) in 76% yield from **12**.[19] Lastly, oxidation of **14** with manganese dioxide gave crystalline racemic helenalin, mp 224-226 °C, in 6.6% overall yield from **3**. This material was found identical with a sample of synthetic helenalin kindly provided by Professor P. Grieco—further, the substance was found identical except for optical rotation to natural helenalin generously provided by Professor W. Herz.[20]

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(2) Y. Ohfune, P. A. Grieco, D. L. J. Wang, and G. Majetich, *J. Am. Chem. Soc.*, **100**, 5946 (1978).

(3) (a) J. A. Marshall and R. H. Ellison, *J. Am. Chem. Soc.*, **98**, 4312 (1976); (b) M. F. Semmelhack, A. Yamashita, J. C. Tomesch, and J. Hirotsu, *ibid.*, **100**, 5565 (1978); (c) P. A. Wender, M. A. Eissenstat, and M. P. Filosa, *ibid.*, **101**, 2196 (1979).

(4) (a) R. Kretchmer and W. J. Thompson, *J. Am. Chem. Soc.*, **98**, 3379 (1976); (b) P. De Clercq and M. Vanderwalle, *J. Org. Chem.*, **42**, 3447 (1977); (c) P. A. Grieco, Y. Ohfune, and G. Majetich, *J. Am. Chem. Soc.*, **99**, 7397 (1977); (d) ref 3c.

(5) We thank Dr. P. Wehrli of the Roche Corporation for a very generous sample of this material as well as detailed instruction for its preparation.

(6) D. H. R. Barton, M. J. Day, R. H. Hesse, and M. M. Pechet, *J. Chem. Soc., Perkin Trans. 1*, 1764 (1975).

(7) C. A. Henrick, E. Böhme, J. A. Edwards, and J. H. Fried, *J. Am. Chem. Soc.*, **90**, 5926 (1968).

(8) Compound **5** must be formed in the following manner: lithio dimethyl methylphosphonate adds to the carbonyl group of lactam **4**—either under the reaction conditions or under workup conditions this adduct rearranges, by ring opening, into the *N*-methyl imine analogue of **5**. Although normally not isolated, this imine has been fully characterized as have all other compounds reported herein.

(9) Compound **1** arises from **5** by base-induced retro-aldol ring opening of the latter followed by protonation of the resultant aldehyde enolate and subsequent intramolecular condensation between the β-ketophosphonate enolate and the aldehyde residue. We assumed that the critical trans geometry required for **1** would result via stereoselective protonation of the aldehyde enolate from the side opposite that occupied by the adjacent methyl group. Implicit in this stereochemical outcome is the assumption that both the oxy-*tert*-butyl residue and the side chain bearing the phosphonate moiety would occupy equatorial positions while the methyl group would reside in an axial environment. The stereochemistry of **1** was demonstrated to be trans with respect to $C_1 \rightarrow C_5$ ring fusion by reduction of it into its C_9–C_{10} dihydro analogue. Compound **1** also was treated with DBU to give the C_1–C_{10} β,γ-unsaturated ketone. The latter material was then reduced to give a 4:1 mixture of trans and cis saturated ketones, respectively—a result anticipated from previous work carried out by Marshall and co-workers.[3a] The 270-MHz NMR spectra of trans and cis ketones are clearly different and consistent with the structures assigned them.

(10) We had originally intended to use the reagent lithium dimethylcuprate to carry out this reaction; in this instance, however, a 4:1 ratio of **6** and its β-methyl analogue was obtained. These isomeric substances proved difficult to separate, and, thus, we resorted to the magnesium derived reagent. Our development of this reagent was guided by literature reports from P. R. McGuirk, A. Marfat, and P. Helquist, *Tetrahedron Lett.*, 2973 (1978), and G. L. van Mourik and H. J. Pabon, *ibid.*, 2705 (1978).

(11) Reaction sequences for which an overall yield is reported normally were carried out using crude intermediates—only the final product of the sequence was chromatographically purified.

(12) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).

(13) For an excellent leading reference on this methodology, see B. M. Trost, T. N. Salzmann, and K. Hivoi, *J. Am. Chem. Soc.*, **98**, 4887 (1976).

(14) Removal of the α proton at C_7 appeared to be the most likely experimental result given that **9** would occupy a minimal energy configuration at −78 °C and that carbon–hydrogen bond rupture would yield a filled p orbital (anion) maximally oriented for interaction with the carbonyl residue.

(15) Several alkylation reactions in addition to that described have been carried out with this anion—all of these products are regioselectively formed. Deprotonation of **9** with lithium hexamethyldisilazane in the thermodynamic mode followed by various enolate trapping reactions affords regioindiscriminate products.

(16) This methodology is described in detail by Y. Ito, T. Hirao, and T. Saegusa, *J. Org. Chem.*, **43**, 1011 (1978). The structure of **10** logically follows from its IR and NMR spectrum. NMR spectra of crude reaction mixtures indicate **10** to be the only product formed in this reaction. Sulfide alkylation of the kinetic enolate of **9**, followed by oxidative elimination[13] also affords **10**, but in lower yield.

(17) For an example of this methodology, see M. R. Roberts, W. H. Parsons, and R. H. Schlessinger, *J. Org. Chem.*, **43**, 3970 (1978).

(18) Very similar reaction sequences which appeared during the course of our work have been reported by Grieco[2] and by P. Kok, P. De Clercq, M. Vanderwalle, J. P. De Clercq, G. Germain, and M. Van Meerssche, *Tetrahedron Lett.*, 2063 (1979). For other examples of α-oxy epoxide ring-opening reactions, see S. Danishefsky, M. Y. Tsai, and T. Kitahara, *J. Org. Chem.*, **42**, 394 (1977); G. R. Kieczykowski, M. R. Roberts, and R. H. Schlessinger, *ibid.*, **43**, 788 (1978).

(19) For a detailed description of this methodology see W. H. Parker and F. J. Johnson, *J. Org. Chem.*, **38**, 2489 (1973).

(20) Comparisons were based on the IR, 270-HMz NMR, mass spectra, TLC, and melting points of these materials.

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Total Syntheses of *dl*-Confertin and *dl*-Damsin

Sir:

In the preceeding manuscript we described the stereoselective conversion of the perhydroazulenone **1** into the sesquiterpene helenalin; herein, we report the transformation of **1** into the pseudoguaianolides confertin (**2**)[1] and damsin (**3**).[2] Introduction of a β-oriented methyl group at C_{10} and attachment of an acetic acid residue at C_7 are required for the elaboration of **1** into confertin, whereas a 1,3 transposition of oxygen from C_8 to C_6 together with the previously stipulated manipulations at C_{10} and C_7 are demanded for obtaining damsin from **1**.

The synthesis of **2** and **3** commences by addition of lithium dimethylcuprate to **1** followed by trapping of the resulting enolate with chlorotrimethylsilane.[3] Reaction of this enolsilane with palladium acetate (trimeric) in anhydrous acetonitrile[4] smoothly affords the enone **4** (mp 59-60 °C) in 83% overall yield from **1**.[5] Establishment of the β-configured C_{10} methyl group was then secured by reduction of the enone with rhodium on alumina in ethanol—a reaction which gives essentially pure **5** (mp 98-98.5 °C) in 95% yield.[6] By this route, quantities of **5** were readily available, and the conversion of this substance into confertin and damsin is outlined below.

Molecular models suggested that deprotonation of **5** in the kinetic manner would occur at C_7 thereby generating an eno-

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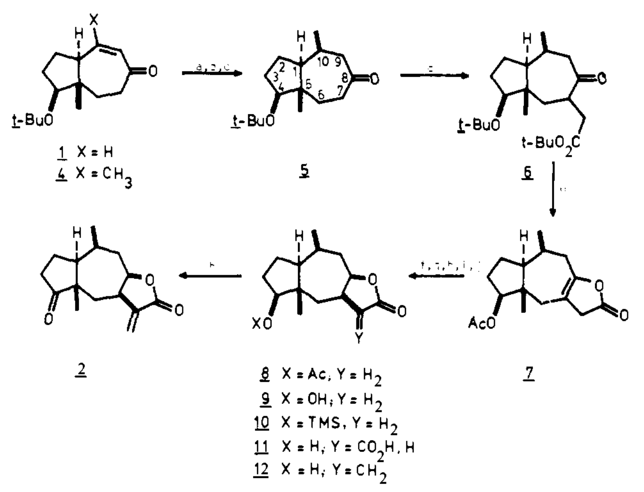
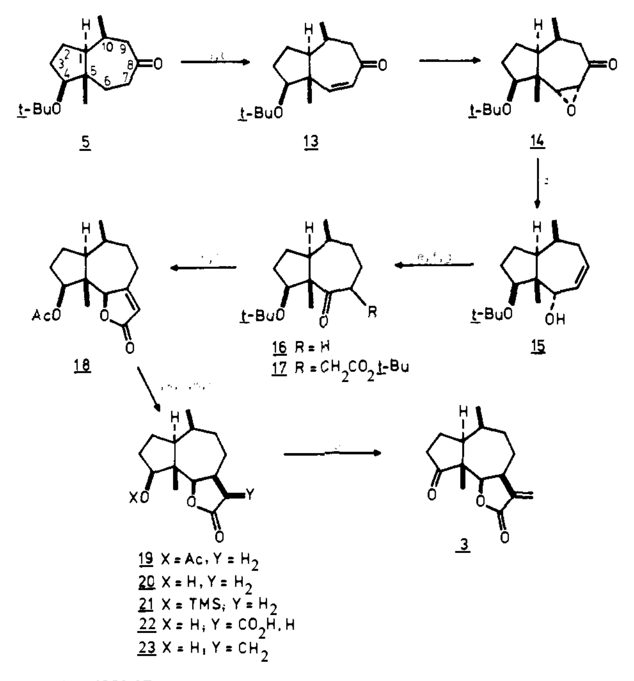
Scheme I[a]



[a] (a) $(CH_3)_2CuLi$, THF, 0 °C, TMSCl, Et_3N. (b) $Pd(OAc)_2$, CH_3CN, 22 °C. (c) H_2, Rh·Al_2O_3, EtOH, 22 °C. (d) LiHMDS, ICH_2CO_2-*t*-Bu, TMEDA, THF, −78 °C. (e) Ac_2O, $HClO_4$, EtOAc, 0 °C. (f) Rh·Al_2O_3, EtOH, H_2, 500 psi. (g) MeOH, KOH, H_2O, 22 °C. (h) TMSCl, C_5H_5N, 22 °C. (i) MMC, 140 °C. (j) 30% CH_2O, Et_2NH, 22 °C. (k) Jones.

Scheme II[a]



[a] (a) LiHMDS, THF, TMSCl, Et_3N, −78 °C. (b) $Pd(OAc)_2$, CH_3CN, 22 °C. (c) MeOH, NaOH, H_2O_2, H_2O, 22 °C. (d) HOAc, N_2H_4, MeOH, Et_2O, 0 °C. (e) Rh·Al_2O_3, EtOH, H_2, 22 °C. (f) Jones, 22 °C. (g) LiHMDS, THF, HMPA, ICH_2CO_2-*t*-Bu, −78 °C. (h) EtOAc, Ac_2O, $HClO_4$, 0 °C. (i) Ac_2O, NaOAc, 140 °C. (j) Rh·Al_2O_3, EtOH, H_2, 22 °C. (k) KOH, H_2O, MeOH. (l) TMSCl, C_5H_5N, 22 °C. (m) MMC, 140 °C. (n) 30% CH_2O, Et_2NH, 22 °C. (o) Jones, −10 °C.

late species critical to the attachment of an acetic acid residue at this site.[7] This surmise was proven valid by experiment, for, when **5** was added to lithium hexamethyldisilazane in THF solution with the resulting enolate reaction with *tert*-butyl iodoacetate, a single product, **6** (mp 81-82 °C), was obtained. Without purification, this material was converted into its corresponding enol lactone **7** employing a mixture of acetic anhydride and perchloric acid in ethyl acetate.[8] In turn, **7** was reduced with rhodium on alumina in ethyl acetate to give **8** (mp 110-111 °C) in 63% yield from **5** (Scheme I).

The finishing stages of the synthesis of confertin were accomplished starting with hydrolysis of the acetate residue of **8** into its corresponding alcohol **9** using potassium hydroxide in methanol. The secondary alcohol was then protected as its trimethylsilyl derivative **10** (chlorotrimethylsilane in pyridine). Methylenation of the lactone was initiated by reaction of **10** with methoxymagnesium carbonate (20 equiv, 140 °C, 30 min), followed by conversion of the resulting carboxylic acid **11** into the α-methylene lactone **12** with 30% formalin solution containing diethylamine.[9] Jones oxidation of **12** provided confertin (**2**) in 62% yield from **8**: mp 119-120.5 °C. Racemic confertin obtained by the method outlined above proved identical with a synthetic sample of **2** kindly provided by Professor M. Semmelhack.[10] The overall yield of confertin from the perhydroazulenone **1** is 30% over 12 steps.

Conversion of the cycloheptanone **5** into damsin required a 1,3 transposition of its C_8 carbonyl residue to the C_6 position. A reaction sequence designed to accomplish this end was devised, taking advantage both of the well-known Wharton methodology as well as tactics learned in the confertin synthesis.[11] Thus, deprotonation of **5** with lithium hexamethyldisilazane (THF solution) in the kinetic manner, followed by enolate trapping with chlorotrimethylsilane, afforded a single enolsilane which without purification was reacted with palladium acetate (trimeric) in anhydrous acetonitrile to give the cycloheptenone **13** (mp 43-44 °C) in 89% yield (Scheme II).[7,4] The unsaturated ketone was epoxidized in the usual manner with basic hydrogen peroxide, whereby the α-epoxy ketone **14** (mp 85-86 °C) was obtained. Crude **14** was submitted to reaction with 100% hydrazine hydrate in a mixture of acetic acid, ether, and methanol to afford the allylic alcohol **15** (mp 92-93 °C) in 73% overall yield from **13**.[12] Reduction of this system with rhodium on alumina in ethanol, followed by Jones oxidation, gave the desired cycloheptanone **16** (mp 43-44 °C) in 80% yield from **15**.

Securing an efficient means for obtaining **16** enabled us to commence the terminating phase of this synthesis. In spite of the experience of previous workers in this area, alkylation of **16** with *tert*-butyl iodoacetate (lithium hexamethyldisilizane in THF-HMPA) proceeded smoothly to yield the keto ester **17**.[13] Without purification this substance was treated first with a mixture of ethyl acetate, acetic anhydride, and perchloric acid and then with acetic anhydride and sodium acetate[8,14]—a sequence which transformed the keto ester into the unsaturated lactone **18** (mp 91-92 °C). Rhodium-on-alumina reduction of the crude lactone afforded the saturated lactone **19** (mp 96-97 °C) in 64% overall yield from **16**.[15]

Methylenation of this lactone was initiated by hydrolysis of the acetate residue (potassium hydroxide, methanol, water). The resulting secondary alcohol **20** was then treated with chlorotrimethylsilane to yield compound **21**. Reaction of the latter material with methoxymagnesium carbonate (20 equiv, 140 °C, 30 min) gave the lactone acid **22** which on admixture with 30% formalin solution containing diethylamine gave rise to the α-methylene lactone **23**.[9] Jones oxidation of the secondary alcohol portion of **23** afforded synthetic damsin (**3**, mp 124.5-125.5 °C) in 61% overall yield from **18**. The conversion of cycloheptanone **5** into damsin requires 15 steps and proceeds in 20% overall yield. Synthetic damsin obtained in this manner proved identical in all respects with a racemic sample of the natural product supplied by Professor P. Grieco.[16]

On the basis of the above work and that described in the preceding communication, it is clear that the readily available cycloheptenone **1** is a versatile synthon for the elaboration of pseudoguaianolide systems.

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Cancer Institute. We also thank the Syntex and Hoffmann-La Roche Corporations for financial support. Lastly, very special thanks to Drs. S. E. Normandin and C. S. Pogonowski for invaluable experiments which initiated this work.

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(1) For syntheses of confertin, see (a) J. A. Marshall and R. H. Ellison, *J. Am. Chem. Soc.*, **98**, 4312 (1976); (b) M. F. Semmelhack, A. Yamashita, J. C. Tomesch, and J. Hirotsu, *ibid.*, **100**, 5545 (1978); (c) P. A. Wender, M. A. Eissenstate, and M. P. Filosa, *ibid.*, **101**, 2196 (1979).

(2) Damsin total syntheses include (a) R. Kretchmer and W. J. Thompson, *J. Am. Chem. Soc.*, **98**, 3379 (1976); (b) P. De Clercq and M. Vandewalle, *J. Org. Chem.*, **42**, 3447 (1977); (c) P. A. Greico, Y. Ohfune, and G. Majetich, *J. Am. Chem. Soc.*, **99**, 7397 (1977).

(3) G. Stork and P. Hudrlik, *J. Am. Chem. Soc.*, **90**, 4462 (1968).

(4) For a detailed description of this highly useful reaction, see Y. Ito, T. Hirao, and T. Saegusa, *J. Org. Chem.*, **43**, 1011 (1978).

(5) All compounds reported herein have been fully characterized.

(6) These hydrogenation conditions proved to be clearly superior, particularly with respect to the stereochemical course of reduction. The α-methyl analogue of **5** is produced in this reaction to the extent of $\sim$5% and was removed by silica gel chromatography.

(7) Removal of the β proton at C_7 appeared to be the most likely experimental result given that **5** would occupy a minimal energy configuration at −78 °C and that carbon–hydrogen bond rupture would yield a filled p orbital anion) maximally oriented for interaction with the carbonyl residue.

(8) J. S. Fritz and G. H. Schenk, *Anal. Chem.*, **31**, 1808 (1959).

(9) For a detailed description of this highly useful methylenation sequence, see W. H. Parker and F. J. Johnson, *J. Org. Chem.*, **38**, 2489 (1973).

(10) We thank Professor Semmelhack for this sample and in addition thank Professor Paul Wender for an 80-MHz spectrum of confertin.

(11) P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, **26**, 3615 (1961).

(12) General conditions for this type of reaction sequence are described by E. Klein and G. Ohloff, *Tetrahedron*, **19**, 1091 (1963).

(13) Grieco and co-workers[2c] have successfully alkylated a very similar ketone enolate with prenyl bromide; however, J. A. Marshall and W. R. Snyder, *J. Org. Chem.*, **40**, 1656 (1975), report that alkylation of a closely related cycloheptanone enolate with methyl bromoacetate was not a synthetically satisfactory reaction. We have found *tert*-butyl iodoacetate generally to be superior with respect to alkylation when compared to methyl bromoacetate.

(14) H. Minato and T. Nagasaki, *Chem. Commun.*, 377 (1965).

(15) Again in our hands, hydrogenation with rhodium on alumina proved considerably superior to other reagent combinations.[1,2,b]

(16) We thank Professor Greico for a sample of synthetic damsin.

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Impregnated Reagents. Characterization of Sodium Cyanide on Alumina[1]

Sir:

Impregnated organic and inorganic reagents are emerging as valuable tools for the synthetic chemist.[2,3] Despite growing interest, however, no serious effort has yet been made to characterize these materials. Several fundamentally important questions need to be answered in order to provide a basis for understanding this chemistry and to define the limitations for practical organic synthesis: specifically, (1) whether the reagent is evenly distributed and is of uniform reactivity, (2) what the primary function of the support is in producing active species, and (3) how reactive the reagent is relative to "naked"[4] analogues in solution need clarification. In the present work one specific impregnated reagent, sodium cyanide on alumina ($NaCN/Al_2O_3$), has been carefully examined. From our results, cyanide ion is shown to be (1) evenly distributed between uniformly active and inactive sites, (2) reactive only at monolayer coverage, and (3) "half-naked".

Neutral alumina chosen for this study was commercially available and used as obtained.[5] It was pure γ-alumina having a surface area of 240 $m^2\ g^{-1}$ (BET, nitrogen adsorption) and possessing a total pore volume of 0.25 $cm^3\ g^{-1}$. Reproducibility of all of the data reported in this work was excellent and independent of the batch of alumina employed. A $NaCN/Al_2O_3$ reagent (**1**) was prepared using 5 mmol of NaCN/g of alumina based on procedures similar to those previously described.[6] The infrared spectrum of **1** (KBr pellet) showed a single and intense cyanide band at 2087 cm^{-1} and was identical with that of sodium cyanide powder. Assuming a tightly packed array of sodium and cyanide ions on the surface, this amount of salt corresponds approximately to that required for monolayer coverage. Reaction of **1** with an excess of 1-bromooctane in toluene at 90 °C revealed that $\sim$60% of the cyanide present was reactive.[7] When the ratio of NaCN (mmol)/alumina (g) was increased by a factor of 2, the amount of reactive cyanide per gram of alumina remained unchanged; when it was decreased by a factor of 2, an approximately twofold reduction was observed. These results provide strong evidence that the salt is uniformly distributed between active and inactive sites and that only monolayer coverage is of practical synthetic value. Additional evidence for a uniform coating of NaCN on alumina comes from adsorption measurements of laurylamine onto **1** and neutral alumina. When 1.0 g of alumina was exposed to 20 mL of a 0.2 M solution of laurylamine in toluene at room temperature for 24 h, 0.35 mmol of the amine was adsorbed (GLC analysis of an aliquot of the liquid phase). In contrast, no detectable amine ($\pm$0.06 mmol) was adsorbed by either 1.0 g of **1** or pulverized NaCN. These data are consistent with a NaCN layer insulating the alumina surface from the bulk organic phase. The average pore diameter of the support is 40 Å (80% being <120 Å) and we tentatively attribute the inactive cyanide to material which is located in small pores, inaccessible to the organic halide.

Kinetic experiments were performed in 50-mL culture tubes (Corning No. 9826, 13 × 100 mm) equipped with a Teflon-lined screw cap and a Teflon-coated stirring bar. In a typical kinetic run, the tube was charged with 1.25 g of **1** plus 2.5 mL of toluene containing 0.5 mmol of 1-bromooctane and 0.5 mmol of *n*-pentadecane (internal standard). The culture tube was placed in an oil bath maintained at 110 ± 0.5 °C and the contents were stirred vigorously. The reaction was followed by withdrawing 1-μL samples and monitoring the disappearance of the organic halide by GLC.[8] Clean pseudo-first-order kinetics was maintained over at least 3 half-lives and material balance (>95%) was good. A second-order specific rate constant, k_0, was calculated by dividing the observed first-order rate constant by the ratio of the number of moles of reactive cyanide to the volume of the organic phase and was equal to 4.2×10^{-4} L mol^{-1} s^{-1}.[9] When a similar reaction was conducted using an excess of organic halide relative to the reagent, pseudo-first-order kinetics was again followed over 3 half-lives.[10] A second-order rate constant obtained under these conditions by dividing the observed first-order rate constant by the concentration of 1-bromooctane in the organic phase was equal to 1.9×10^{-4} L mol^{-1} s^{-1}. Considering the heterogeneity of these systems and the treatment of NaCN on alumina as a "concentration", we regard the agreement between the two rate constants as satisfactory.

In order to put the reactivity of impregnated cyanide ion into perspective, we have also examined an analogous displacement carried out under liquid–liquid phase-transfer conditions. Thus, when 0.75 g of sodium cyanide dissolved in 1 mL of water with 3 mL of toluene containing 0.5 mmol of 1-bromooctane in the presence of 0.12 mmol of dicyclohexyl-18-crown-6 and 0.5 mmol of *n*-pentadecane (internal standard) was stirred, clean pseudo-first-order kinetics yielded a second-order rate constant of 4.0×10^{-2} L mol^{-1} s^{-1} at 110 °C.[11] Based on the $\sim$100-fold lower reactivity of **1** and the fact that pulverized NaCN showed no detectable reaction with 1-bromooctane under similar conditions, we view the impregnated reagent as being "half-naked"; i.e., the alumina exposes only a portion of the cyanide ion to the bulk organic phase.[12] Further studies aimed at establishing the generality of our findings are in progress.

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