× 0.06 × 0.16 mm was used for intensity measurements with Cu Kα radiation and a graphite monochromator. The step-scan technique was used with a scan speed of 2°/min, a scan width of 3.4°, and a $2\theta_{max}$ of 138°. Of the 1518 unique reflections measured, 721 had intensities greater than 3σ. A partial trial solution, 27 atoms, was obtained by direct methods by using MULTAN80.[17] The remaining atoms were found by successive Fourier syntheses. The structure was refined by least squares; parameters varied were coordinates of all non-hydrogen atoms, anisotropic thermal parameters for non-hydrogen atoms, isotropic thermal parameters for solvent atoms, and a site occupancy factor for the solvent. The enantiomer determination, using the method Bijvoet,[18] was carried out by calculating structure factors for both enantiomers and computer searching for the reflections most significantly affected by anomalous dispersion. Found were 34 reflections, which were scanned very accurately over each of their four positions with 23 showing an enantiomeric preference. Of these 23 reflections, 22 favored the enantiomer with its quaternary carbon in the *R* configuration and its methine carbon in the *S* configuration (Figure 1). Further details of the X-ray determination including fractional coordinates and bond lengths and angles are readily available.[18]

Conversion of 5 to 8. Repeating the mild methanolic NH_4OH hydrolysis of **4** under slightly modified conditions proved interesting. Slightly less water was present since the 5 mM NH_4OH was prepared by diluting concentrated NH_4OH with MeOH instead of diluting aqueous 1 N NH_4OH with MeOH as before. Unlike the previous hydrolysis, TLCD after 22, 42, and 72 h indicated the presence of a minor component of intermediate mobility between **4** and **5**, subsequently found to be **8**.[19] After 6 days, only **5** and a small amount of **3** were evident, and the solution was evaporated to dryness, reconstituted in acetone, and stored in the freezer for 16 days. After storage, TLCD indicated that **8** was the major component with **5** as a minor component along with a small amount of **3**. A sample of homogeneous **8** was isolated by CCC with the solvent phases from hexane–ethyl ether–MeOH–Water (1:2:2:1). **8**: HRMS $(M + H)^+$ 375.0639 ($C_{19}H_{17}Cl_2N_2O_2$ requires 375.0667). Treating **8** with dilute methanolic NH_4OH afforded **5**. Acylating **8** with 4-chlorobenzoyl chloride and triethylamine afforded **4**. TLCD indicated that an acetone solution of pure **5** was rapidly converted into homogeneous **8** by HCl or pyridine hydrochloride.

Competitive Acylation of a Mixture of 3, 5, and 8. The previously described mixture of **3**, **5**, and **8** was treated with the same conditions used to acylate **3**, and the acylation to **4** was monitored at intervals by TLCD. Under these conditions, **3** was essentially all reacted in the first 2 min, half of **8** remained after 20 min, and one-third after 2 h, and 78% of **5** remained after 20 h.

(17) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. MULTAN80. A system of computer programs for the automatic solution of crystal structures from X-ray diffraction data; Universities of York, England, and Louvain, Belgium, 1980.

(18) Watt, W.; Martin, D. G.; Duchamp, D. J.; Mizsak, S. A.; Nielsen, J. W.; Prairie, M. D. *Acta Crystallogr.*, in press.

(19) TLCD (3:1 MeOH–H_2O, 280 nm): **4**, R_f 0.05; **8**, R_f 0.24; **5**, R_f 0.44; **3**, R_f 0.63.

Tetraphenylbutadienes via (1,1-Diphenylallyl)lithium

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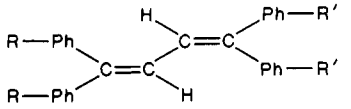
Tetraphenylbutadienes[3] (TPBs) exhibit interesting fluorescence features. The spectral and physical properties of TPBs can be controlled to some extent by the introduction of substituents on the aromatic rings, and methods to synthesize substituted TPBs are therefore of interest. The parent TPB has been prepared by the addition of excess PhMgBr to diethyl succinate, followed by dehydration of the resulting diol. This method, introduced many years ago by Wittig and von Lupin,[4] is suitable for the preparation of TPBs such as **1** in which R = R′ but would be inappropriate for the synthesis of unsymmetrical derivatives. Similar symmetry considerations are inherent in most other TPB preparative methods,[5] and examination of these procedures failed to provide an attractive solution to the problem of preparing unsymmetrical TPBs of the general structure **1** (R ≠ R′). This substitution pattern is of particular interest since it avoids the complications of *E,Z* isomerism.

Table I. Substituted Tetraphenylbutadienes (1)[a]

R =	R′	mp, °C
H	*p*-*n*-Pr	100–101
H	*m*-Br	136–138
H	*p*-Br	172–173
H	*p*-Ph	200–201
H	*o*-(bond)[b]	189–190
H	*o*-(–O–)[c]	167–169
H	*o*-(–S–)[d]	214–216
p-*n*-Pr	*p*-Br[e]	179–181
p-*n*-Br	*p*-Ph[f]	200–202

[a] These products were formed by the stiochiometric ratio procedure described in the Experimental Section, in yields (after recrystallization from HOAc or ethanol) that ranged from 15 to 35%; they were characterized by MS and ^1H NMR spectra. All products where R = H were prepared from 3,3-diphenylpropene and the appropriate substituted benzophenone. Other starting materials were [b] fluorenone; [c] xanthone; [d] thioxanthone; [e] 3,3-bis(4-propylphenyl)propene and 4,4′-dibromobenzophenone; [f] 4,4′-diphenylbenzophenone.



1

Indirect acid-enhancing methods such as Wittig ylide chemistry are widely employed to prepare olefins, and the parent TPB has been made by coupling of the 3,3-diphenyl-2-propenyl ylide to benzophenone.[5g] However, a more direct approach, which capitalizes on the inherent acidity[6] of 1,1-diphenylpropene (**2**), appeared to be feasible and is the subject of the present study. The sequence is illustrated in eq 1–3 for TPB itself (**1**, R = R′ = H).

(1) Recipient of President's Undergraduate, Faculty Women's, and College of Creative Studies Fellowships.

(2) On leave from The Hebrew University, Jerusalem.

(3) The *Chemical Abstracts* name for tetraphenylbutadiene is 1,1′,1″,1‴-(1,3-butadiene-1,4-diylidene)tetrakisbenzene.

(4) Wittig, G.; von Lupin, F. *Chem. Ber.* **1928**, *61*, 1627.

(5) (a) Brand, K.; Krucke-Amelung, D. *Chem. Ber.* **1939**, *72*, 1029. (b) Kuhn, R.; Plotzer, B. *Ibid.* **1940**, *73*, 1410. (c) Tadros, W.; Sakla, A. B.; Akhookh, Y. *J. Chem. Soc.* **1956**, 2701. (d) Wirth, H. O.; Koenigstein, O.; Kern, W. *Justus Liebigs Ann. Chem.* **1960**, *634*, 84. (e) Huttel, R.; Kratzer, J.; Bechter, M. *Chem. Ber.* **1961**, *94*, 766. (f) Sket, B.; Zupan, M. *Synth. Commun.* **1976**, *6*, 309. (g) Schweizer, E. E.; Kim, C. S. *J. Org. Chem.* **1971**, *36*, 4033.

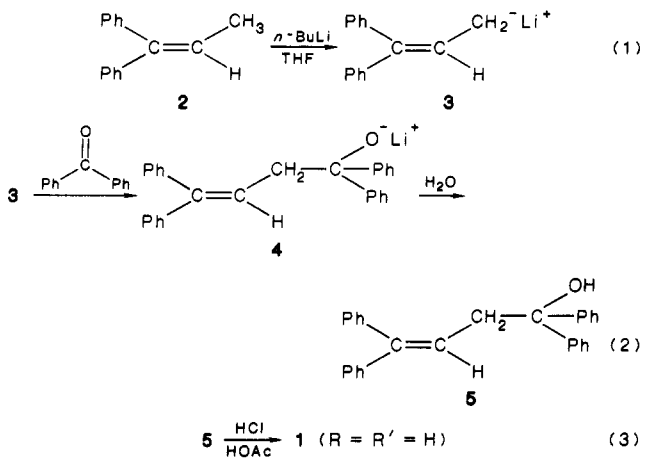
(6) 1,1-Diphenylpropene was examined very early in work aimed at establishing acidity scales for hydrocarbons, where "pK_a" values of 30[7] and 36[8] were found (different scales). It appears not to have been reexamined in this context subsequently.[9]

(7) Conant, J. B.; Wheland, G. W. *J. Am. Chem. Soc.* **1932**, *54*, 1212.

(8) McEwen, W. K. *J. Am. Chem. Soc.* **1936**, *58*, 1124.

(9) Streitwieser, A., Jr.; Juaristi, E.; Nebenzahl, L. L. In *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: New York, 1980; Part A, Chapter 10.

0022-3263/88/1953-4613$01.50/0



This approach is indeed successful and has been used to prepare a number of substituted TPBs (see Table I). Although the yields from reactions involving stoichiometric (1:1:1) quantities of diarylpropene, *n*-butyllithium, and substituted benzophenone are low, typically 25–35%, the procedure is so straightforward that it is the method of choice for the facile preparation of TPBs of the type described here.

Efforts aimed at identifying the yield-limiting feature(s) of this sequence, while not providing a definitive answer, have given some insights into the unexpectedly complex chemistry involved.

A sample of the alcohol **5** was isolated by chromatography and subjected to the elimination conditions of eq 3 (refluxing HOAc containing concentrated HCl). TPB was formed in essentially quantitative yield, showing that this step is not responsible for the losses.

Single-electron transfer (SET) reactions between **3** and the benzophenones may occur,[10] and could interfere to some extent with the coupling shown in eq 2, but yields did not appear to be influenced by changes in the benzophenone substituents. Furthermore, the starting materials (i.e. **2** and the benzophenone) were invariably present in crude product mixtures from stoichiometric ratio reactions, suggesting that there was insufficient base available for consumption of these substrates and pointing to eq 1 as the major problem step.[11]

Treatment of **2** in THF solvent with *n*-butyllithium (in hexane) rapidly generates a blood-red solution. The color is attributed[12] to the anion (organolithium reagent) **3** depicted in eq 1. Somewhat erratically, the red color was observed to fade. For example, slow dropwise addition of *n*-butyllithium caused the fleeting formation of a reddish color, which rapidly faded, and the maintenance of a red color for several minutes was not observed until a significant amount (even up to 1 equiv) of the base had been added. Less *n*-butyllithium was needed to form red solutions if added rapidly, but this effect was difficult to quantify. The red solutions also faded to pale yellow, typically over a period of 0.5–1 h (ice bath). The addition of another equivalent of *n*-butyllithium at this stage regenerated a red color, but anion formation was not a fully reversible process, i.e. some decomposition of **2** occurs upon anion formation followed by color fading. This was shown by the increasing complexity of the ^1H NMR spectra of aliquots taken at several stages of a repeated cycle of *n*-BuLi additions after each loss of red color. Examination of the ^{13}C NMR spectra of red (unquenched) THF solutions indicated that some decomposition of the solvent THF[13] may have occurred, but it was not possible to assign all of the absorptions observed, and the spectra of these solutions also became increasingly complex on standing. Efforts to isolate individual decomposition products by chromatography were unsuccessful, but examination of fractions by NMR (complex aromatic region) and MS showed that **2** was partially converted to a mixture of higher molecular weight materials.

The reaction of **2** with *n*-butyllithium/hexane in diethyl ether solvent is too slow to be useful and is not visibly improved by the addition of a small amount of lithium diisopropylamide; the pale pink solutions obtained in this solvent gave no measurable deuterium incorporation upon quenching with D_2O. Some of the benzophenones of interest in this work have slight solubility even in THF, and exploration of other solvents was therefore not pursued. MeMgBr added to a THF solution of **2** did not develop a color, and no deuterium was found in the **2** recovered after D_2O quenching. The addition of $MgBr_2$ (in ether) to a red THF solution of **3** had no obvious effect on the yield of TPB. Methyllithium was not a suitable alternative to *n*-butyllithium for anion generation in THF; very little color developed, and the addition of benzophenone gave 1,1-diphenylethanol as the major product.

Because base was being consumed by unknown side reactions at the stage of eq 1, the simple expedient of using "excess" *n*-butyllithium was examined, even though it was recognized that residual *n*-butyllithium could compete with the anion **3** for reaction with the benzophenone. This approach led to a significant improvement in yield of TPB (to a maximum of 60–65%) and an additional interesting observation. When 2.2 equiv of *n*-butyllithium was employed, the red coloration persisted even after the addition of benzophenone (1 equiv). In this instance the red color[15] is attributed to the dianion **6**, formed by proton abstraction from the initial adduct **4** as shown in eq 4.

(10) A good deal of evidence has accumulated to support SET processes between organometallics and carbonyl compounds, although it is often unclear if these steps are important in the major coupling processes. For some recent examples, see: (a) Ashby, E. C.; Argyropoulos, J. N. *J. Org. Chem.* **1986**, *51*, 472 (enolates with diaryl ketones). (b) Ashby, E. C.; Argyropoulos, J. N. *Ibid.* **1986**, *51*, 3593 (lithium alkoxides and benzophenone). (c) Yamataka, H.; Fujimura, N.; Kawafuji, Y.; Hanafusa, T. *J. Am. Chem. Soc.* **1987**, *109*, 4305 (methyllithium with benzophenone). (d) Stamm, H.; Sommer, A.; Onistschenko, A.; Woderer, A. *J. Org. Chem.* **1986**, *51*, 4979 (chalcone with "anthracene hydride").

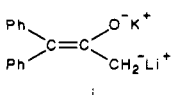
(11) The possibility that the reaction of **3** with benzophenone to give **4** might be readily reversible with a small equilibrium constant was discounted because the red coloration due to **3** disappeared as the ketone was added (typically when ca. half had been added); see also discussion in the text.

(12) Deuterium incorporation in recovered **2** was observed only when red solutions were quenched with D_2O; aliquots examined after the color had faded did not take up the electrophile. This organolithium reagent (λ_{max} 486 nM) and its reactions with *tert*-alkyl bromides have recently been described: Tanaka, J.; Nojima, M.; Kusabayashi, S. *J. Am. Chem. Soc.* **1987**, *109*, 3391.

(13) The reaction of THF with *n*-butyllithium, to form ethylene and acetaldehyde enolate, is known to be concentration dependent and quite rapid at 25 °C. For example, Holm[14] found that over the range 10^{-4}–10^{-2} M the initial reaction of *n*-butyllithium with THF is first order, with a half-life of less than a minute. At higher concentrations, the rate continues to increase, but the kinetic order falls below unity, i.e., from the standpoint of percentage decomposition the more concentrated solutions are more stable.

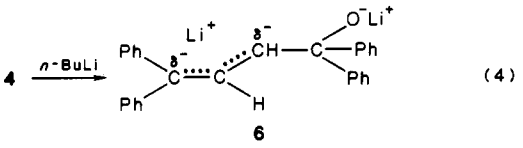
(14) Holm, T. *Acta Chem. Scand., Ser. B* **1978**, *B32*, 162.

(15) The dianion **6** is expected to be red in solution, by analogy with **3** and also the dianion **i**, which Adam and coworkers[16] have described as "deep red".



i

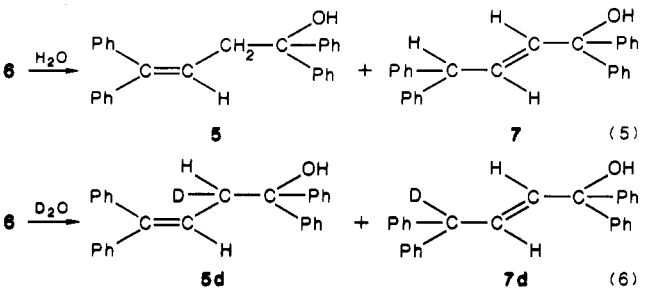
(16) Adam, W.; Berkessel, A.; Peters, E.; Peters, K.; von Schnering, H. G. *J. Org. Chem.* **1985**, *50*, 2811.



(4)

Reaction of the adduct **4** with the anion **3** could in principle lead to the formation of **6** and account for diminished TPB yields. However, this possibility was discounted by D_2O quenching of a reaction mixture (typically pale green/yellow) from a stoichiometric ratio reaction; no evidence for formation of **6** was obtained under these circumstances. This suggests that *n*-BuLi is the base responsible for the formation of **6**, from which it follows that both the reaction of **3** with benzophenone and the subsequent deprotonation of **4** by *n*-BuLi must be more rapid than the addition of *n*-BuLi to benzophenone.

The presence of dianion **6** in runs utilizing 2 equiv of *n*-BuLi was demonstrated by quenching (red) solutions with H_2O and D_2O, respectively. Column chromatography gave mixtures (not separated) of the alcohols **5** and **7** (eq 5), and **5d** and **7d** (eq 6).



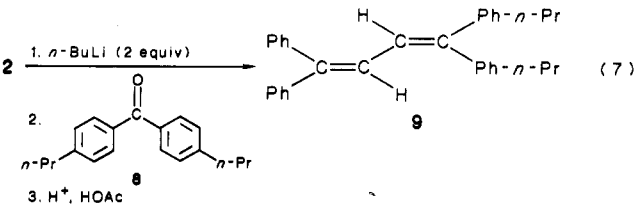
(5)

(6)

The ratio of **5**/**7** (and of **5d**/**7d**) was ca. 1/2. This ratio results from kinetically controlled protonation (deuteration), as demonstrated by NMR analysis. The product mixture of eq 5 exhibited the expected triplet (J = 7 Hz) for the vinylic proton of **5** (this is the only isomer formed in the absence of excess *n*-butyllithium) at 6.03 ppm, coupled with the methylene doublet at 3.14 ppm. The corresponding signals for **5d** were equal-area doublets, with the upfield absorption broadened by geminal deuterium coupling. The vinylic protons of **7** give rise to a pair of doublets (J = 15 Hz), with the downfield (H-3) signals further split by coupling (J = 7 Hz) to the methine (H-4) proton, which in turn is observed at 4.83 ppm. No methine absorption is visible in the spectrum of **7d**, indicating that C-4 is completely deuteriated, and the vinylic proton pattern no longer exhibits the smaller coupling due to interaction with the methine proton in **7**. Comparison of these spectra shows that the products of eq 6 are cleanly monodeuteriated, i.e., both undeuteriated and dideuteriated materials are specifically excluded by the absence of absorptions expected for such products. This proves that both of the isomeric alcohols are formed directly in the quenching step and not by subsequent exchange reactions. The high percentage of C-monodeuteriated products formed upon quenching is taken as strong evidence for the efficient formation of the dianion **6**.

The TPB from the "excess" *n*-butyllithium experiment arises entirely from **6** (as shown by the high level of deuterium incorporation in **5d**/**7d**), and the formation of **6** in turn requires that *n*-butyllithium be present during the addition of benzophenone. Thus (1,1-diphenylpropenyl)lithium (**3**) must add more rapidly than *n*-butyllithium to benzophenone, as noted above. There are reports of benzyl- and allyllithium reacting more rapidly than *n*-butyllithium in, e.g., addition to 1,1-diphenylethene[17] and the deprotonation of triphenylmethane.[18] State-of-aggregation arguments have been advanced to explain this inverse stability/reactivity behavior, and similar factors are presumably involved in the present study. The increased yield from the excess *n*-butyllithium experiment also requires that formation of **4** (see eq 2) be effectively irreversible in the time scale of these experiments, since regeneration of benzophenone would otherwise result in irreversible trapping by *n*-butyllithium. A small amount of the benzophenone/*n*-butyllithium addition product was observed in some of these reactions, but its yield does not increase with time prior to the quench, showing that it is formed in competition with the desired coupling reaction.

The formation of 4,4′-di-*n*-propyl-TPB (**9**) is shown in eq 7 to illustrate an application of this methodology. Through the use of a 2-fold excess of *n*-butyllithium, it was possible to carry this reaction out on a scale for which chromatography is inconvenient and obtain the product (15 g) in 48% yield after purification by repeated recrystallization.



(7)

For most disubstituted TPBs such as **9**, the aromatic ring substituents are most easily introduced on the benzophenone reactant (e.g. **8**), but incorporation on the 1,1-diarylpropene portion is also feasible, and both patterns may be used to prepare tetrasubstituted TPBs such as **1**, R ≠ R′ (neither substituent H).

The improvement caused by the use of a 2-fold excess of *n*-butyllithium was discovered after most of the materials shown in Table I had been prepared, and it is unclear if this approach will prove to be generally useful for increasing yields of substituted TPBs. This work shows that the organolithium species **3** is less stable than anticipated in THF and provides another illustration of the unusual selectivity that is frequently hidden in "rapid" organic reactions.

Experimental Section

All reactions involving organometallics were carried out in oven- or flame-dried glassware under an atmosphere of dry nitrogen or argon, with most transfers by syringe or cannula. Tetrahydrofuran (THF) was distilled from benzophenone sodium ketyl immediately prior to use, and diethyl ether was distilled from $LiAlH_4$. Commercial benzophenone and propiophenone were used as received. The *n*-butyllithium was ca. 1.6 M in hexane solvent; several different containers were employed, with the titre examined periodically. MS data were obtained by Dr. Hugh Webb on a VG 70-250 instrument. NMR spectra were recorded on a NT-300 instrument in $CDCl_3$ solvent, unless otherwise noted.

1,1-Diphenylpropene (2). The preferred method is described. It should be noted that the alternative addition of EtMgBr to the benzophenone (which is expedient for the preparation of some substituted 1,1-diarylpropenes) causes appreciable reduction, and separation of the benzhydrol from the desired olefin by distillation may present difficulties.

A solution of commercial PhMgBr (0.283 mol) in 125 mL of ether was cooled in an ice bath, and 34.2 mL (0.25 mol) of pro-

(17) Grovenstein, E., Jr.; Wentworth, G. *J. Am. Chem. Soc.* **1967**, *89*, 1852.
(18) Waack, R.; West, P. *J. Am. Chem. Soc.* **1964**, *86*, 4494.

piophenone in 150 mL of ether was added dropwise with efficient stirring. Shortly after the addition was completed, 200 mL of 5% HCl was added to the still cold solution. The layers were separated, and the aqueous portion was extracted with ether (3 × 50 mL). The combined ether phase was washed with water, bicarbonate, and brine and then dried and evaporated to give 56.9 g (quantitative yield) of crude 1,1-diphenyl-1-propanol. This material was taken up in 400 mL of glacial acetic acid containing 7 mL of concentrated HCl, and the mixture was refluxed for 0.5 h. The green solution was cooled, diluted with 400 mL of water, and extracted with CH_2Cl_2 (3 × 80 mL). The combined organic phase was washed with water, bicarbonate, and brine and then dried (K_2CO_3) and evaporated to give 50.9 g of crude discolored product. Vacuum distillation gave 44.4 g (89%) of pure **2** as a colorless liquid, bp 108 °C (1 Torr), which solidified to a low-melting crystalline mass on standing: NMR (60 MHz) δ 1.75 (d, 3 H, J = 7 Hz), 6.1 (q, 1 H, J = 7 Hz), and 7.0–7.4 (m, 10 H).

Tetraphenylbutadiene (1, R = R′ = H): The Stoichiometric Ratio Reaction. This general procedure was used for all the materials listed in Table I, with the modifications shown in the footnotes. An ice-bath-cooled solution of **2** (1.20 g, 6.19 mmol) in 35 mL of THF was treated with 4.1 mL of 1.6 M *n*-butyllithium in hexane (6.5 mmol) to give a blood red solution. After a few minutes, this was mixed with a solution of 1.13 g (6.22 mmol) of benzophenone in 40 mL of THF. The red color typically changed to yellow-green when about half of the ketone had been added. Dilute HCl was added, at times that ranged from 15 min to 24 h after addition of the ketone with no effect on the yield. The mixture was separated, and the aqueous phase extracted with ether. The combined organic phase was washed with brine and then dried and evaporated to give a viscous oil. Chromatography (silica gel, graded elution, hexanes to CH_2Cl_2) at this stage was used to isolate the alcohol **5**, although this step is not necessary for TPB isolation. The product was taken up in 100 mL of HOAc containing 2 mL of concentrated HCl and refluxed for 1 h to effect dehydration. The crude product in CH_2Cl_2 solvent was washed with KOH solution to remove the acid, dried, and evaporated to give a discolored oil. Column chromatography (silica gel, 10% CH_2Cl_2 in hexanes) gave 0.555 g (25%) of 1,1,4,4-tetraphenyl-1,3-butadiene, identical (NMR, melting point) with authentic commercial material.

Tetraphenylbutadiene: The 2-fold Excess *n*-BuLi Reaction. The procedure was essentially identical with that described above, except that 7.4 mL of *n*-butyllithium (11.9 mmol) was used to prepare **3** from 1.099 g (5.70 mmol) of **2**, and 5.5 mmol of benzophenone was added. The solution remained red after addition of the benzophenone. The solution was divided at this point, with ca. half being quenched by water and the remainder by D_2O. The alcohol mixtures (**5** + **7**) and (**5d** + **7d**), respectively, were isolated by silica gel chromatography and exhibited the NMR characteristics described in the text. The yields of TPB isolated from two analogous experiments with dehydration of the crude alcohols were 60 and 65%.

Bis(*n*-propyl)-TPB (9). A solution of 14.4 g (0.074 mol) of **2** in 300 mL of THF was cooled in an ice bath and treated with 100 mL of 1.6 M *n*-butyllithium in hexane (0.16 mol), added dropwise over a 20-min period. To the resulting deep red solution was added, over a 2-h period, a solution of 19.4 g (0.073 mol) of 4,4′-di-*n*-propylbenzophenone[19] in THF. The still red solution was quenched shortly after addition by treatment with dilute HCl, which gave a golden orange coloration. The organic layer was separated and combined with 2 × 50-mL ether extractions. It was washed with water and brine and then dried and evaporated to give a dark orange oil, which was subjected to dehydration conditions by refluxing in 300 mL of HOAc containing 4 mL of concentrated HCl. This mixture was treated in the usual way to give 38.5 g of crude product as a brown oil. Recrystallization from ethanol (four times, after decanting from small amounts of less soluble brown oils) gave 15.6 g (48%) of **9**: mp 100–101 °C; NMR δ 0.90 and 0.97 (2 t, 3 H each, J = 7 Hz), 1.5–1.8 (m, 4 H), 2.51 and 2.62 (2 t, 2 H each, J = 7 Hz), 6.77 (AB q, 2 H, vinylic), and 7.0–7.4 (m, 18 H); MS 444 (6.8), 443 (37.1), 442 (M^+, 100), 279 (7.5), 251 (14.1), 191 (7.7), 167 (9).

(19) Muraoka, M.; Itoh, T.; Mizuma, T.; Toyoshima, S. *Chem. Pharm. Bull.* **1960**, *8*, 860.

Acknowledgment. This work was performed under the auspices of the Department of Energy, Contract DE-AC08-83NV10282. We wish to thank Dr. David Tobia for helpful comments.

A Route to Functionalized Branched-Chain Amino Sugars via Nitrous Acid Promoted Spiroaziridine Formation

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The natural occurrence of branched-chain amino and nitro sugars has stimulated extensive research for their synthesis.[1] Methodology for the preparation of isomeric 3-amino-3-deoxy-3-*C*-methyl carbohydrates is well documented.[1] Synthetic schemes involve hydrogenolytic opening of aziridine intermediates generated from cyanhydrines or spirooxiranes. As a continuation of our interest in this area,[2,3] we present in this paper a general method allowing access to functionalized branched-chain amino sugars. Our approach is outlined in Scheme I, its key steps are nitrous acid promoted aziridine formation followed by nucleophilic ring opening of the aziridines.

When methyl 4,6-*O*-benzylidene-3-deoxy-α-D- (**1**) and -β-D-*threo*hexopyranosid-2-ulose (**2**) were separately treated with trimethylsilyl cyanide in a methanolic solution saturated with ammonia, ketone **1** gave stereospecifically an α-amino nitrile with an equatorial amine **3**, while **2** afforded a 2.5:1 mixture of **4a** and **4b**, the former α-amino nitrile having an axial amine being the major compound of the reaction.

Stereochemical proof of the Strecker reaction products was obtained by carbon-13 NMR spectroscopy as described.[2] Chemical shift of the C-4 signal of the α-amino nitriles was diagnostic for the stereochemistry of the C-2 quaternary carbon center of these molecules. In the spectrum of the axial amine **4a** C-4 is shielded by about 2.5 ppm relative to this signal in the spectrum of equatorial amines **3** and **4b**. The same tendency was observed in the carbon-13 NMR spectrum of the corresponding cyanohydrines from which both isomers were available from another study. The axial carbon–oxygen bond at C-2 has greater shielding effect on the C-4 resonance than an axially disposed carbon–carbon linkage.

Direct transformation by metal hydrides [DIBAH, $LiAl(OEt)_3H$, $LiAl(OEt)_2H_2$] of the *N*-acetyl and *N*-tosyl derivatives of the α-amino nitriles into the corresponding protected α-amino aldehydes failed. Therefore the nitrile function of the *N*-tosyl derivatives **5** and **6** were first reduced by lithium aluminium hydride to the corresponding primary amines **7** and **8**, respectively, and the latter deaminated by sodium nitrite in aqueous acetic acid. These reactions furnished respectively *N*-tosyl spiroaziridines **9** and **10** in excellent yield (84–89%). Nucleophilic ring opening of the *N*-tosylaziridines with sodium acetate in *N*,*N*′-dimethylformamide proceeded regiospe-

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