Synthesis and Properties of Ring-Deactivated Deuterated (Hydroxymethyl)pyrroles

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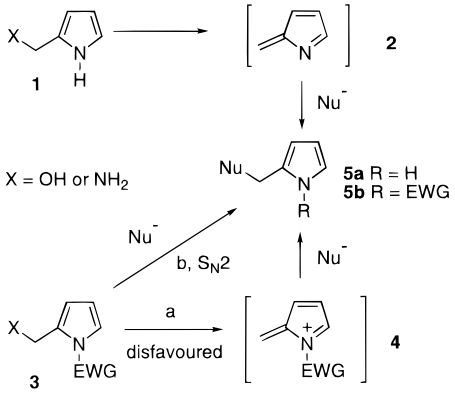
Abstract: A sequence, based on a Mitsunobu displacement at the hydroxymethyl position of deuterium-labeled, *N*-substituted 2-(hydroxymethyl)pyrroles, is reported as a general procedure to determine the ability of the *N*-substituent to deactivate the heterocycle. An S_N2 mechanism, in this reaction, has been shown to be favored over reaction via an azafulvenium intermediate, by employing *N*-(trifluoromethyl)sulfonyl as the deactivating group. Deuterium-labeling studies have demonstrated that suppression of contributions to the reaction from an azafulvenium intermediate is less effective with other deactivating groups, and the order for deactivation is triflyl > mesyl > BOC ≈ acetyl. The attachment of an electron-withdrawing group onto the nitrogen of a 2-formyl[*formyl-d*]pyrrole has also been shown to allow reduction to give a 2-(hydroxymethyl[*methylene-*d_1])pyrrole of high configurational purity. The utility of the *N*-triflyl group to deactivate a pyrrole was demonstrated with the preparation of deuterium-labeled porphobilinogen precursor.

Introduction

The introduction of an electron-withdrawing group (EWG) on the nitrogen atom of a pyrrole results in a decrease in aromaticity of the pyrrole ring.[1−11] The resulting deactivated pyrroles react with dienophiles in Diels−Alder reactions,[2] are readily reduced under Birch conditions,[3] allow the synthesis of 2-substituted pyrroles via α-lithiation,[4] and also undergo regiocontrolled acylation.[4,5] An electron-withdrawing group on the nitrogen atom of a pyrrole has also been observed to stabilize intermediates in photocyclization reactions.[6] As a result, the deactivation of a pyrrole has attracted considerable interest as a means of preparing pyrrole oligomers, terpyrroles, tropane alkaloids, and numerous other synthetic targets.[2−9]

Scheme 1



The presence of an electron-withdrawing group on the pyrrole nitrogen in compounds of type **3** is thought to suppress the formation of highly reactive azafulvenium species **4** (Scheme 1). In the absence of such deactivation, (hydroxymethyl)-pyrroles and (aminomethyl)pyrroles of type **1** readily react with a nucleophile, via the postulated azafulvene intermediate **2**, to give products of type **5**.[1,10] A mechanism of this type has been invoked to explain the increased susceptibility of these pyrroles to nucleophilic substitution. Such a sequence involving azafulvenes is thought to play a key role in the biosynthesis of (hydroxymethyl)bilane (**9**) and uroporphyrinogen III (uro'gen III) (**10**), important intermediates in the biosynthesis of porphyrins and corrins (Scheme 22).[11] Here, porphobilinogen (PBG) (**6**), the substrate for (hydroxymethyl)bilane synthase (PBG deaminase), gives rise to the azafulvene **7** which becomes covalently bound to the enzyme via a dipyrromethane cofactor. This sets up the ES_1 complex **8**, and three further pyrrole units are added to **8**, again involving **7**, to generate an enzyme bound tetrapyrrole which is released as (hydroxymethyl)bilane (**9**). The current view is that the azafulvene **11** is the intermediate which reacts with water to afford **9**. (Hydroxymethyl)bilane (**9**) then

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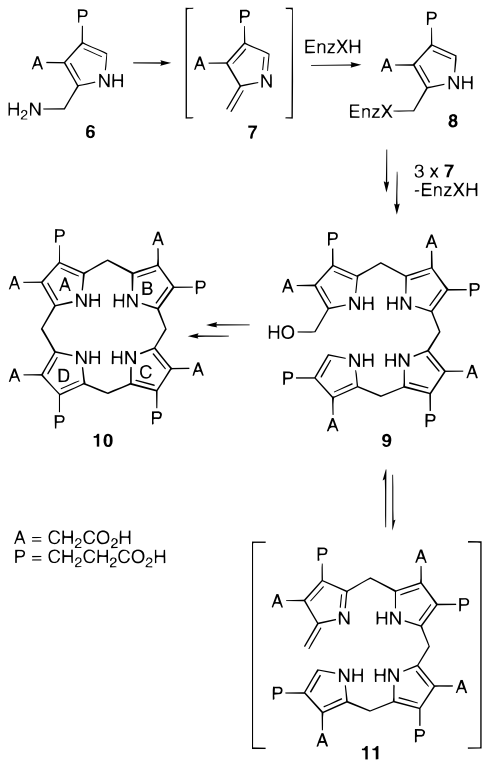
Scheme 2



acts as the substrate for a second enzyme, cosynthetase, which brings about cyclization with inversion of ring-D to yield uro'gen III (**10**). Again, the mechanism of this cyclization probably involves the azafulvene **11**.

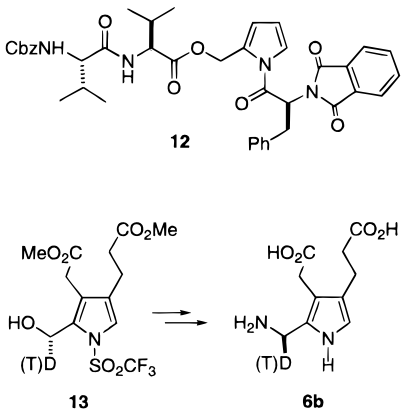


Figure 1.

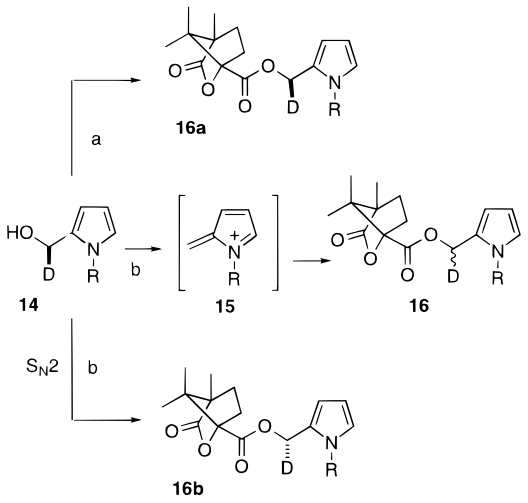
The idea of suppressing azafulvene formation by the introduction of an EWG has also been used to develop latent reactive inhibitors of serine proteases.[12] Here, a (hydroxymethyl)pyrrole derivative (e.g., **12**) is stabilized by *N*-acylation with an amino acid—chosen to be recognized by the target enzyme. Enzyme-catalyzed deacylation yields a reactive azafulvene, **2**, which is then thought to lead to covalent inactivation of the enzyme (see Scheme 1 where Nu^- is an amino acid in the enzyme's active site). Despite their implication in numerous examples of pyrrole-based chemistry, simple 1-azafulvenes such as **2**, have not been characterized; however, some more complex examples have been isolated.[1,10,13]

A number of different substituents have been used to deactivate and/or protect pyrroles. Examples of these groups include phenylsulfonyl, *tert*-butoxycarbonyl (BOC), *tert*-butylcarbamoyl, dimethylamino, trialkylsilyl, [2-(trimethylsilyl)ethoxy]methyl (SEM), trityl, and alkoxycarbonyl. In this paper we present a general method to assess the ability of an EWG to deactivate a pyrrole. The information gained in these studies was then used to develop a synthesis of the deuterium-labeled (hydroxymethyl)pyrrole **13**. Compound **13** is a key synthetic intermediate en route to labeled porphobilinogen (**6b**), which is a very useful tool for studying the biosynthesis of naturally occurring porphyrins and corrins.[14] We suggest that an *N*-triflyl group should be employed whenever deactivation of a pyrrole is required.

Results and Discussion

We chose to study the conversion of deuterium-labeled (hydroxymethyl)pyrroles of type **14** into the corresponding camphanates **16** (for specific examples see Schemes 5 and 8), under both Mitsunobu[15] conditions (Scheme 3, conditions b) and via reaction with (1*S*)−(−)-camphanic chloride (Scheme 3, conditions a), as a means of assessing the deactivating ability of an *N*-protecting group (R substituent in **14**). The camphanate group was chosen to provide a chiral handle to discriminate between the hydrogens on the pyrrolic methylene group of **16**. Reaction of **14** with the acid chloride provided reference camphanate samples for ^{1}H NMR analysis where the configurational purity at the deuterium-labeled center of **14** was maintained and indeed measurable (Scheme 3, pathway a). However, reaction of **14** with (1*S*)−(−)-camphanic acid, under Mitsunobu conditions, can occur via either an azafulvene, **15**, resulting in scrambling of the deuterium label, or an S_N2 mechanism to give inversion of configuration at the labeled center, yielding **16b** (Scheme 3, pathway b). The Mitsunobu conditions were chosen since they are known to promote substitution with inversion of configuration.[15]

Scheme 3



(a) DMAP, diisopropylethylamine, (1S)-(-)-camphanic chloride;
(b) Ph_3P, DEAD, (1S)-(-)-camphanic acid (Mitsunobu conditions)

It was considered that the greater the deactivating ability of the R group on the pyrrolic nitrogen the less would be the contribution from the azafulvene mechanism. A comparison of the stereochemical integrity at the deuterium-labeled center

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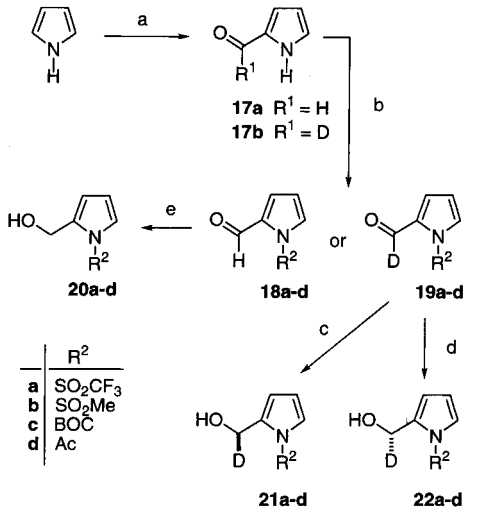
Scheme 4



(a) $POCl_3$, DMF or DMF-d_7, 1,2-dichloroethane; (b) either $(CF_3SO_2)_2O$, CH_2Cl_2, diisopropylethylamine, -78 °C or NaH, THF followed by electrophile; (c) (S)-Alpine borane®, THF, rt; (d) (R)-Alpine borane®, THF, rt; (e) $Zn(BH_4)_2$, ether, 0 °C.

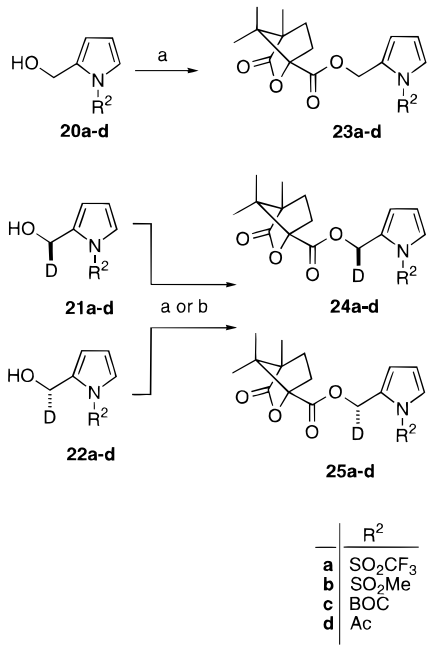
in **16**, derived from the Mitsunobu sequence on a range of substrates **14** (Scheme 3, reaction conditions b), would then provide an assessment of the deactivating ability of R.

Deuterium-Labeling Studies. The key deuterium-labeled formylpyrrole **17b** was readily prepared by Vilsmeier formylation of pyrrole using phosphorus oxychloride and DMF-d_7 (Scheme 4). The *N*-(trifluoromethyl)sulfonyl-protected formylpyrroles **18a** and **19a** were conveniently prepared by reacting **17a** or **17b** with trifluoromethanesulfonic anhydride in the presence of diisopropylethylamine. The remaining *N*-protected formylpyrroles **18b**−**d** and **19b**−**d** were prepared by reacting the pyrrole anion of either **17a** or **17b** (prepared by treatment with sodium hydride) with methanesulfonyl chloride, 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC−ON), or acetyl chloride (Scheme 4). The unlabeled (hydroxymethyl)pyrroles **20a**−**d** were then conveniently prepared by reducing the *N*-protected formylpyrroles **18a**−**d** with zinc borohydride. The corresponding deuterium-labeled analogues, **21a**−**d** and **22a**−**d**, were prepared by reduction of **19a**−**d** with (*S*)-Alpine-Borane (*B*-isopinocampheyl-9-borobicyclo[3.3.1]nonane) and (*R*)-Alpine-Borane,[16] respectively (Scheme 4).

The configurational purities of **21a**−**d** and **22a**−**d** were determined by conversion into the camphanates **24a**−**d** and **25a**−**d** by reaction with (1*S*)−(−)-camphanic chloride (see Table 1 and Scheme 5, reaction conditions a). The unlabeled camphanates **23a**−**d** were similarly prepared as reference compounds for subsequent ^{1}H NMR analysis. The ^{1}H NMR spectra of the unlabeled reference compounds **23a**−**d** revealed that, in each case, the resonance for the (hydroxymethyl)pyrrole methylene group was observed as an AB quartet (Table 1, last row of spectra). The corresponding resonances for the deuterium-labeled analogues **24a**−**d** and **25a**−**d** were observed as singlets with distinguishable chemical shifts (see Table 1, first four rows of spectra). The relative integrals of these signals gave a measure of the stereochemical purity of the camphanate samples, and hence of the precursor (hydroxymethyl)pyrroles **21a**−**d** and **22a**−**d** derived from both the (*S*)-Alpine-Borane and (*R*)-Alpine-Borane routes (Schemes 3 and 4).

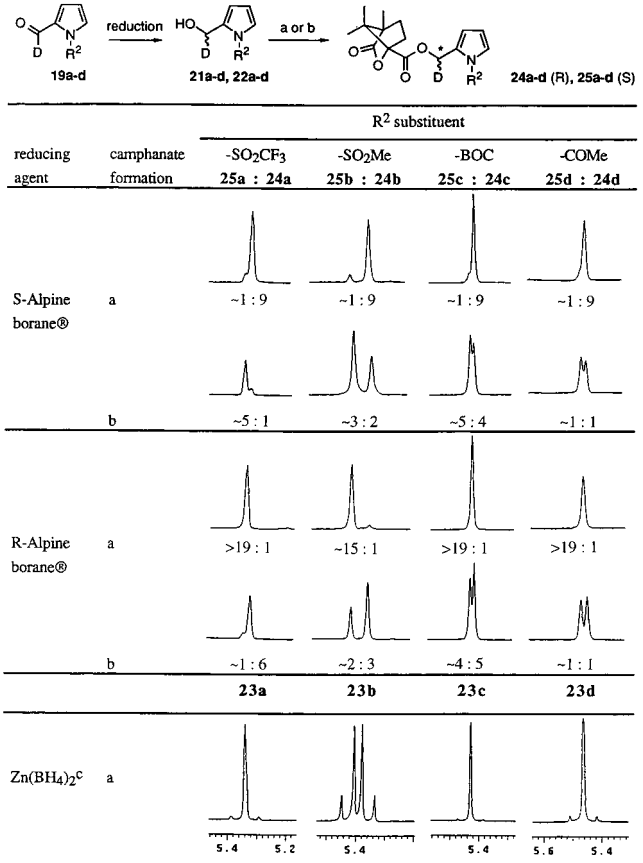
(16) Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352.

Scheme 5



(a) DMAP, diisopropylethylamine, (1S)-(-)-camphanic chloride; (b) Ph_3P, DEAD, (1S)-(-)-camphanic acid (Mitsunobu conditions)

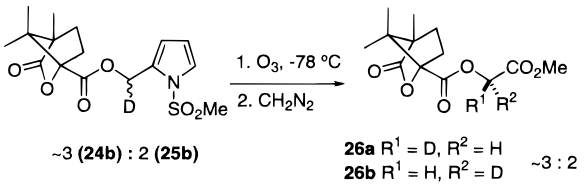
Table 1. ^{1}H NMR Analysis of the Methylene (*) of **23**, **24**, and **25**



[a] DMAP, diisopropylethylamine, (1*S*)-(−)-camphanic chloride. [b] Ph_3P, DEAD, (1*S*)-(−)-camphanic acid (Mitsunobu conditions). [c] Reaction sequence was performed using unlabeled **18a**−**d** to give **23a**−**d.**

An analysis of the data obtained for the sequence using (*S*)-Alpine-Borane, followed by camphanate formation according to method a in Table 1 (first row of spectra), revealed

Scheme 6



comparable ratios of **25** to **24** for the triflyl, mesyl, BOC, and acetyl series (∼1:9 for **25a**/**24a**, **25b**/**24b**, **25c**/**24c**, and **25d**/**24d**). Importantly, the series derived from reduction of **19a**−**d** with and (*R*)-Alpine-Borane gave the opposite isomers **25a**−**d** as the major products (Table 1, third row of spectra). The series derived from the (*R*)-Alpine-Borane reductions gave a slightly higher excess of the major isomers **22a**−**d** and hence **25a**−**d**.

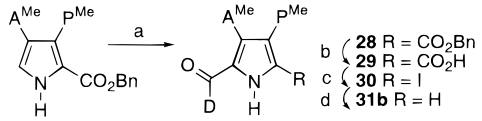
In the crucial experiments, separate samples of **21a**−**d**, of known configurational purity, were treated with (1*S*)−(−)-camphanic acid under Mitsunobu conditions (Scheme 5, reaction conditions b). The results of an ^{1}H NMR analysis of the camphanates from these reactions, **24a**−**d** and **25a**−**d**, are given in Table 1, second row of spectra. The ratio of **25** to **24**, observed on reaction of the *N*-(trifluoromethyl)sulfonyl (triflyl), *N*-methylsulfonyl (mesyl), *N*-*tert*-butoxycarbonyl (BOC), and *N*-acetyl series, were ∼5:1, ∼3:2, ∼5:4, and ∼1:1, respectively (the initial ratios of **22a**−**d** to **21a**−**d**, used in their preparation, were ∼1:9). The major isomers formed in these reactions, the camphanates **25a**−**c**, are the products of an inversion of configuration due to an S_N2 displacement on **21a**−**c** under the Mitsunobu conditions (Scheme 3). The higher the proportion of configuration **25** relative to configuration **24** in these products, the greater has been the effectiveness of the EWG used in disfavoring involvement of the azafulvenium **15**. The *N*-triflyl group of **21a** promotes substitution via an S_N2 mechanism almost exclusively to give **25a**. At the other extreme, the *N*-acetyl and *N*-BOC systems, **21c** and **21d**, allow substantial substitution via an azafulvenium mechanism. The equivalent Mitsunobu reactions of (1*S*)−(−)-camphanic acid with **22a**−**d** gave complementary results to those obtained for the reactions of **21a**−**d** as discussed above (Table 1, fourth row of spectra).

Finally, the absolute configurations of **24a**−**d** and **25a**−**d**, although being consistent with literature reports for Alpine-Borane reductions,[16] were confirmed by ozonizing a sample containing a ∼3:2 mixture of **24b** and **25b** and trapping the resulting acid with an excess of diazomethane to give a ∼3:2 mixture of **26a** and **26b** (Scheme 6). An ^{1}H NMR spectrum of this mixture was consistent with data from authentic samples of **26** and the unlabeled analogue **35**.[14,17]

The conclusion from the labeling experiments is that the order for the deactivating ability of the pyrrole *N*-protecting groups considered in this study is triflyl > mesyl > BOC ≈ acetyl. The deactivating ability of the *N*-triflyl group was then used in the synthesis of the deuterium-labeled (hydroxymethyl)pyrroles **13** (Scheme 8). This compound is a key synthetic intermediate to labeled porphobilinogen (**6b**) (Figure 1), a very useful tool for studying the biosynthesis of naturally occurring porphyrins and corrins.[14]

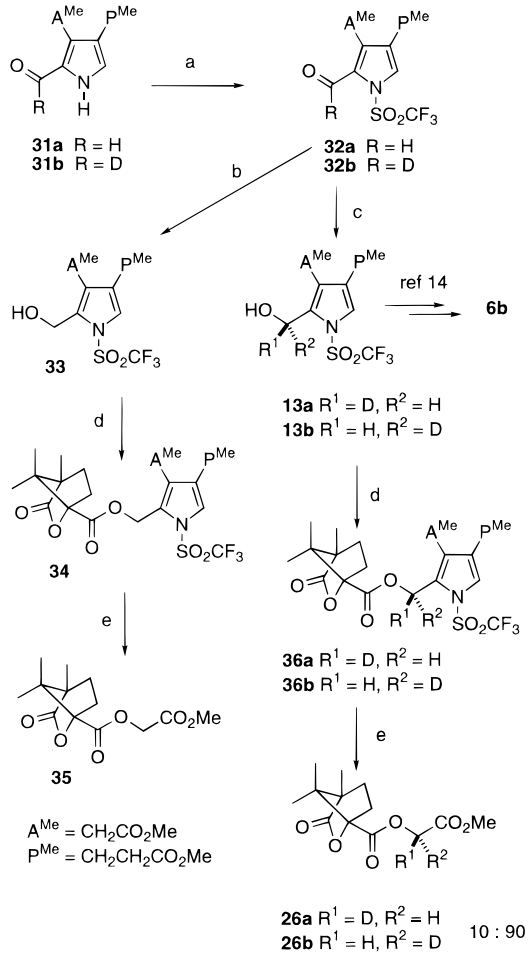
Synthesis of Deuterium-Labeled Porphobilinogen Precursor. The α-free pyrrole benzyl ester **27**[18] was formylated under Vilsmeier conditions using DMF-d_7 to give the labeled formylpyrrole **28** (Scheme 7). TFA-catalyzed hydrolysis of the benzyl ester, followed by reaction with iodine and potassium iodide

Scheme 7



(a) $POCl_3$, DMF-d_7, CH_3CN; (b) H_2SO_4, TFA, rt; (c) $NaHCO_3$, H_2O, KI, I_2, reflux; (d) PtO_2, MeOH, H_2.

Scheme 8



(a) $(CF_3SO_2)_2O$, CH_2Cl_2, diisopropylethylamine, -78 °C; (b) $NaBH_4$, CH_2Cl_2, MeOH, 0 °C; (c) (R)-Alpine borane®, THF, rt; (d) DMAP, diisopropylethylamine, (1S)-(-)-camphanic chloride; (e) O_3, silica, -78 °C then CH_2N_2.

and finally hydrogenolysis in the presence of platinum(IV) oxide, gave **31b**.

The subsequent synthesis of the deuterium-labeled (hydroxymethyl)pyrroles **13** is detailed in Scheme 8. The unlabeled and deuterium-labeled formylpyrroles **31a**[18] and **31b** were converted into the corresponding *N*-triflyl derivatives **32a** and **32b** using trifluoromethanesulfonic anhydride.[9] Reduction of **32a** with sodium borohydride gave the (hydroxymethyl)pyrrole[9] **33** which was converted into its camphanate **34** by reaction with (1*S*)−(−)-camphanic chloride. Reduction of the deuterium-labeled analogue **32b** with (*R*)-Alpine-Borane gave a mixture of **13a** and **13b** (∼1:9). The configurational purity of the mixture of **13a** and **13b** was determined by a sequence involving reaction with (1*S*)−(−)-camphanic chloride, to give **36a** and

(17) Arigoni, D.; Besmer, P. (see Besmer, P. Diss. ETH, No. 4435, 1970).

(18) Battersby, A. R.; Ihara, M.; McDonald, E.; Saunders: J.; Wells, R. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 283.

36b, followed by ozonolysis and methylation to give the known reference compounds[14,17] **26a** and **26b** (∼1:9 by ^{1}H NMR). The observed excess of **13b** over **13a** is consistent with the (*R*)-Alpine-Borane reductions of **21** and **22**, Table 1. The unlabeled analogues **34** and **35** were also prepared for comparison. (Hydroxymethyl)pyrroles of type **13** have been converted into the corresponding PBG analogues **6b** by a sequence involving conversion of the alcohol into an azide under Mitsunobu conditions (inversion of configuration) followed by reduction and *N*-deprotection.[14]

Conclusion. S_N2 displacements at the hydroxymethyl group of compounds of type **3**, Scheme 1, are favored by use of *N*-triflyl as the deactivating group and Mitsunobu reaction conditions. The suppression of contributions to the reaction from azafulvenium intermediates **4** is less effective with other deactivating groups, and the order for deactivation is triflyl > mesyl > BOC ≈ acetyl. An *N*-triflyl group should, therefore, be employed when maximum deactivation of a pyrrole ring is desired. Attachment of an *N*-triflyl group onto a 2-formyl-[*formyl-d*]pyrrole also allows it to be converted into a 2-(hydroxymethyl[*methylene-d*$_1$])pyrrole of high configurational purity. It has been assumed that the introduction of an electron-withdrawing group onto a pyrrole nitrogen, as in **3**, suppresses the formation of highly reactive azafulvenium intermediates **4**, but until now little direct evidence for this has been available.

Experimental Section

General Methods. Melting points were obtained using a hot stage microscope and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 300 spectrometer, a Varian XL-300 spectrometer, or a Bruker AM400 spectrometer in the specified solvent and at a probe temperature of 23 °C unless otherwise specified. Infrared spectra were obtained using a Perkin-Elmer 1600 FTIR spectrophotometer. Mass spectra were obtained on a Kratos MS80RFA magnetic sector double focusing mass spectrometer. Petroleum ether refers to a hydrocarbon fraction of bp 60−70 °C.

General Procedure A: *N*-Acylation of Pyrrole-2-carboxaldehyde. To a stirred suspension of sodium hydride (typically 1.26 mmol, 80% suspension in oil washed twice with dry petroleum ether) in THF (6 mL) was added the pyrrole aldehyde **17a** or **17b** (typically 1.09 mmol) dissolved in dry THF (2 mL). After the mixture was stirred at room temperature (rt) for 15 min, the electrophile (typically 1.2−1.4 equiv) in dry THF (2 mL) was slowly added, and stirring was continued for 60 min at rt. Water (10 mL) was added, the THF was removed under reduced pressure, and the aqueous residue was extracted with dichloromethane (4 × 15 mL). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate (10 mL), water (10 mL), and brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on silica. See the Supporting Information for details.

General Procedure B: Zinc Borohydride Reductions. The *N*-substituted pyrrole-2-carboxaldehyde (typically 0.16 mmol) was dissolved in ether (10 mL) at 0 °C under N_2. $Zn(BH_4)_2$ (1 equiv of a 0.14 M solution in ether) was added, and the resultant solution was stirred at 0 °C for 30 min. Water (2 mL) and glacial acetic acid (2 mL, 10% solution in water) were carefully added to quench the reaction. The separated aqueous phase was extracted with dichloromethane (2 × 10 mL), and the combined organic phases were washed with water (2 × 10 mL) and brine (10 mL), dried, and concentrated under reduced pressure. The residue was purified by chromatography on silica. See the Supporting Information for details.

General Procedure C: Alpine-Borane Reductions. The *N*-substituted pyrrole-2-carboxaldehyde (typically 0.49 mmol) was dissolved in THF (10 mL) at rt under N_2. (*R*)- or (*S*)-Alpine-borane (1.1 equiv of 0.5 M solution in THF) was added, and the resultant solution was stirred at rt for 4 h. The volatiles were removed under reduced pressure, and the resultant oil was purified by chromatography on silica. See the Supporting Information for details.

General Procedure D: Camphanate Preparation Using (−)-Camphanic Chloride. The (hydroxymethyl)pyrrole (typically 0.12 mmol), DMAP (1 equiv), and diisopropylethylamine (1.2 equiv) were dissolved in dichloromethane (8 mL) at rt. (1*S*)−(−)-Camphanic chloride (1.2 equiv), dissolved in dichloromethane (2 mL), was added, and the resultant solution was stirred for 24 h. The solution was extracted with ethyl acetate (10 mL), and the organic phase was washed with 10% aqueous citric acid (10 mL) and water (2 × 10 mL), dried, and evaporated under reduced pressure. The resultant oil was purified by silica chromatography. See the Supporting Information for details.

General Procedure E: Camphanate Preparation Using Mitsunobu Conditions. The (hydroxymethyl)pyrrole (typically 0.11 mmol), triphenylphosphine (1.3 equiv), and (1*S*)−(−)-camphanic acid (1.5 equiv) were dissolved in THF (2 mL), and the solution was stirred under N_2, at rt, for 5 min. Diethyl azodicarboxylate (1.5 equiv) was added, and the resultant solution was stirred for 3 h. The solvent was evaporated under reduced pressure, and the resultant oil was purified by silica chromatography. See the Supporting Information for details.

[*formyl-d*$_1$]-2-formyl-4-((methoxycarbonyl)ethyl)-3-((methoxycarbonyl)methyl)pyrrole 31b. DMF-d_7 (99 atoms %, 2.38 g) was stirred at 0 °C under nitrogen, and freshly distilled phosphorus oxychloride (4.92 g) was added dropwise. Dry acetonitrile (16 mL) was added followed by the α-free pyrrole **27**[18] (7.91 g, 0.02 mmol) and more acetonitrile (16 mL). After being stirred at rt for 45 h, the solution was transferred under nitrogen into a mixture of methanol-d_1/deuterium oxide (90 mL, 2:1). This solution was warmed to 40 °C over 30 min, aqueous potassium carbonate (300 mL, 2%) was added, and the product was extracted into dichloromethane (4 × 50 mL). The combined organic phases were dried and evaporated under reduced pressure. Recrystallization of the residue from dichloromethane/ether/hexane gave **28** (8.49 g, 99%), mp 78−81 °C (unlabeled analog[22] mp 77−81 °C).

A mixture of sulfuric acid (30 drops, 98%) and TFA (4 mL) was added to a stirred solution of **28** (1.05 g). After the mixture was stirred at rt for 30 min, the TFA was removed under reduced pressure, and the residue was partitioned between aqueous sodium carbonate (50 mL, 5%) and ethyl acetate (150 mL). The aqueous layer, together with subsequent aqueous sodium carbonate washings (3 × 20 mL, 5%) of the ethyl acetate layer, was washed with ethyl acetate (50 mL) and acidified to pH 1 using aqueous sulfuric acid (10%). The mixture was extracted into ethyl acetate (3 × 100 mL), washed with brine (50 mL), dried, and evaporated under reduced pressure. The brown solid was chromatographed on silica (methanol/ether, 5:95), and the product **29** was recrystallized from dichloromethane/hexane (615 mg, 76%), mp 129−132 °C.

A mixture of the foregoing carboxylic acid **29** (600 mg) and sodium hydrogen carbonate (480 mg) in chloroform (12 mL) and water (8 mL) was stirred vigorously and heated to reflux. An aqueous solution of iodine and potassium iodide (4.5 mL, 1 M in KI and 0.5 M in I_2) was added, and heating was continued for 5 min. After a further 0.5 h at rt aqueous sodium hydrogen sulfite (10%) was added to neutralize the excess iodine. The organic layer, together with subsequent dichloromethane washings (4 × 15 mL), was dried and evaporated under reduced pressure to give **30** (628 mg, 83%) as a pink oil which crystallized on standing. A solution of the crude **30** (590 mg) in methanol (40 mL) was stirred under a hydrogen atmosphere with sodium acetate (600 mg) and platinum(IV) oxide (90 mg) until uptake ceased (1 h). The catalyst was removed (Celite), and after the addition of sodium hydrogen carbonate (150 mg) the filtrate was evaporated. Water (120 mL) was added, and the mixture was extracted with dichloromethane (5 × 25 mL). The combined organic extracts were dried and evaporated under reduced pressure. The residue was chromatographed on silica (ether) and recrystallization from dichloromethane/ether/hexane gave **31b** (249 mg, 63%), mp 97−99 °C (unlabeled analog[22] mp 97−98 °C).

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[*formyl*-d_1]-2-Formyl- and 2-Formyl-4-((methoxycarbonyl)ethyl)-3-((methoxycarbonyl)methyl)-1-((trifluoromethyl)sulfonyl)pyrrole (32b and 32a). The *d*-formylpyrrole **31b** (400 mg, 1.21 mmol) in dichloromethane (30 mL), containing diisopropylethylamine (550 μL, 2 equiv), was cooled to −78 °C under argon. Trifluoromethanesulfonic anhydride (480 μL, 1.8 equiv) was added dropwise, and after 5 min the resulting brown solution was poured onto saturated aqueous sodium hydrogen carbonate (40 mL). The organic phase, together with subsequent dichloromethane washings (2 × 15 mL), was dried and evaporated under reduced pressure. Purification by preparative TLC (ether/hexane, 2:1) gave **32b** (197 mg, 45%). HRMS *m*/*z* 386.0480 (calcd for $C_{13}H_{13}DF_3NO_7S$ 386.0506).

The unlabeled formyltriflylpyrrole **32a**, similarly prepared from **31a**, was fully characterized: mp 39−41 °C; IR ($CHCl_3$) 2950, 1755, 1660 cm^{-1}; UV λ_{max} 283, 256 nm; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.60 (m, 2H, CH_2CH$_2$CO), 2.77 (m, 2H, CH$_2$CH_2CO), 3.68 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.94 (s, 2H, CH$_2$CO), 7.15 (s, 1H, pyrrole-H), 10.10 (s, 1H, CHO). Anal. Calcd for $C_{13}H_{14}F_3NO_7S$: C, 40.5; H, 3.7; N, 3.6. Found: C, 40.5; H, 3.6; N, 3.6.

[4-((Methoxycarbonyl)ethyl)-3-((methoxycarbonyl)methyl)-1-((trifluoromethyl)sulfonyl)pyrrol-2-yl]methyl Camphanate (34). The formylpyrrole **32a** (600 mg, 1.56 mmol) was dissolved in dichloromethane (20 mL) and methanol (10 mL), and the solution was cooled to 0 °C. Sodium borohydride (90 mg) was added portionwise with stirring, and after 30 min the mixture was partitioned between dichloromethane (20 mL) and aqueous oxalic acid (10 mL, 10%). The organic layer, together with subsequent dichloromethane washings (2 × 10 mL), was washed with water (10 mL), dried, and evaporated under reduced pressure. The residue was purified by preparative TLC (ether) to give **33** (432 mg, 72%) as a colorless oil which was not purified further: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.58 (t, 2H, t, J = 7.5 Hz, CH$_2$CH_2CO), 2.72 (t, 2H, J = 7.5 Hz, CH_2CH$_2$CO), 2.81 (br, 1H, OH), 3.52 (s, 2H, CH$_2$CO), 3.68 (s, 3H, OMe), 3.72 (s, 3H, OMe), 4.68 (d, 2H, J = 4.6 Hz, CH_2OH), 6.90 (s, 1H, pyrrole-H); HRMS *m*/*z* 387.0573 (calcd for $C_{13}H_{16}F_3NO_7S$ 387.0599).

Reaction of **33** according to the general method D gave **34** (80%): IR (film) 3140, 3100, 2950, 1750, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92, 1.02, and 1.08 (each 3H, s, 3 × Me), 1.65, 1.68, 1.92, and 2.38 (each 1H, m), 2.59 (t, 2H, J = 7.5 Hz, CH$_2$CH_2CO), 2 73 (t, 2H, J = 7.5 Hz, CH_2CH$_2$CO), 3.58 (s, 2H, CH$_2$CO), 3.67 (s, 3H, OMe), 3.69 (s, 3H, OMe), 5.29 (s, 2H, CH$_2$O), 6.97 (s, 1H, pyrrole-H). Anal. Calcd for $C_{23}H_{28}F_3NO_{10}S$: C, 48.7; H, 5.0; N, 2.5. Found: C, 48.8; H, 5.1; N, 2.5.

[[11-*methylene*-d_1]-4-((methoxycarbonyl)ethyl)-3-((methoxycarbonyl)methyl)-1-((trifluoromethyl)sulfonyl)pyrrol-2-yl]methyl Camphanates 36a and 36b. The labeled pyrrole **32b** (200 mg, 0.52 mmol) was stirred with (*R*)-Alpine-Borane [prepared from (1*R*)-(+)-α-pinene (103 μL) and 9-BBN (1.17 mL, 0.5 M in THF)] at rt for 2 h. A further sample of (*R*)-Alpine-Borane (0.6 mL, 0.5 M in THF) was added, and the solution was left for 1 h. 2-Aminoethanol was added, and the resulting precipitate was removed by filtration. The filtrate was washed with water, dried, and evaporated under reduced pressure. Purification by silica preparative TLC (ether/hexane, 9:1) gave **13a** and **13b** as a colorless oil (192 mg, 95%, 10:90 from an analysis of the corresponding camphanates): ^{1}H NMR data identical with those described for **33** except for δ_H 4.68 (s, 1H, −C*H*DOH); HRMS *m*/*z* 388.0631 (calcd for $C_{13}H_{15}DF_3NO_7S$ 388.0662).

Reaction of the mixture of **13a** and **13b** according to the general procedure D gave **36a** and **36b** (90%, 10:90): ^{1}H NMR data identical with those described for **34** except for δ_H 5.29 (s, 1H, −CHDO); HRMS *m*/*z* 568.1443 (calcd for $C_{23}H_{27}DF_3NO_{10}$ 568.1449).

Ozonolyses. (1) A mixture of **24b** and **25b** (17.0 mg, 0.05 mmol, ∼3:2) was dissolved in dichloromethane and loaded onto silica (1 g, 50−100 mesh) by evaporation under reduced pressure. The residue was cooled to −78 °C, and ozone was bubbled through the silica until a blue color persisted (approximately 20 min). After warming to rt, the products were eluted from the silica with ethyl acetate. The solvent was removed under reduced pressure, and the residue was dissolved in methanol (10 mL) and treated with an excess of diazomethane. Purification on silica (ethyl acetate/petroleum ether, 1:2) gave a mixture of **26a** and **26b** (5.1 mg, 39%, ∼3:2 by ^{1}H NMR) as a colorless oil:[14,17] IR ($CHCl_3$) 1788, 1727 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.04 (s, 3H, camph-Me), 1.11 (s, 3H, camph-Me), 1.14 (s, 3H, camph-Me), 1.73 (m, 1H, camph-CH$_2$), 1.98 (m, 1H, camph-CH$_2$), 2.10 (m, 1H, camph-CH$_2$), 2.48 (m, 1H, camph-CH$_2$), 3.34 (s, 3H, CO$_2$Me), 4.76 (s, 0.6H, CHDO-camph, **26a**), 4.83 (s, 0.4H, CHDO-camph, **26b**); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.6, 16.6, 16.6, 28.8, 30.8, 41.8, 54.9, 54.9, 62.5 (t, J = 23.0 Hz), 90.8, 165.5, 166.7, 178.0.

(2) A similar treatment of a mixture of **36a** and **36b** (35 mg, ∼1:9) gave **26a** and **26b** (6 mg, 19%, ∼1:9 by ^{1}H NMR).

(3) The reaction was repeated using a sample of **34** to give **35**[17] (21 mg, 41%) as a colorless oil.

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Supporting Information Available: Supplementary data on the preparation of compounds **17b**, **18a**−**d**, **19a**−**d**, **20a**−**d**, **21a**−**d**, **22a**−**d**, **23a**−**d**, **24a**−**d**, and **25a**−**d** and copies of ^{1}H NMR spectra of compounds for which no elemental analysis was obtained (15 pages). See any current masthead page for ordering and Web access instructions.

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