# Pictet-Spengler Reactions in Aprotic Media. Stereospecificity in the Pictet-Spengler Reaction

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Earlier, it was reported that execution of the Pictet-Spengler reaction of tryptophan methyl esters (**1a** or **1b**) (Scheme I) with acid-labile aldehydes in aprotic media (PhH, Δ) permitted the synthesis of a wide variety of *cis*- and *trans*-1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines (**3** and **4**, respectively) in high yield.[1-3] Later, it was demonstrated that condensation of $N_b$-benzyltryptophan methyl ester (**5a**) with aldehydes **2** (R′ = $C_6H_{11}$, $C_6H_5$) led, stereospecifically, to the formation of the trans diastereomers **6a** or **6b**, respectively (Scheme I).[4] Evidence was presented to implicate the $N_b$-benzyl group in the observed stereospecificity of this process especially when aldehydes substituted with bulky groups (R′) were employed in the cyclization. More recently, another modification of the process has been reported which employed the reaction of tryptophan alkyl esters with conjugated alkynoates, followed by in situ cyclization of the intermediate enamines in dichloromethane/trifluoroacetic acid.[5] Both this variation and the original process[1,4] have been used extensively for the synthesis of various optically active tetrahydro-β-carbolines[4,6] including intermediates en route to indole alkaloid natural products such as pyridindolol,[3] the fumitremorgins,[7] and the eudistomin alkaloids.[8]

Ottenheijm et al.[8a] have recently reported on the Pictet-Spengler reaction of $N_b$-hydroxyl- and $N_b$-(benzyloxy)tryptophan ethyl esters (**7a** and **7b**, respectively) with acetals **10a** or **10b** as models for the synthesis of eudistomin alkaloids (Scheme II). However, they observed that the reaction which employed the $N_b$-(benzyloxy)tryptophan ethyl ester **7b** ($PhCH_2ON_b$) did not proceed with the stereospecificity earlier observed in the case of the $N_b$-benzyltryptophan congener **5a** ($PhCH_2N_b$) executed in our laboratory.[4] Instead substantial amounts (50%) of the cis diastereomer **8c** (Table I) were observed in the case of **7b**, although the solvent and reaction conditions were different for the two cases. In regard to both the results of Ottenheijm[8a] and our studies directed toward the synthesis of optically active tetrahydro-β-carbolines,[9] it was of interest to determine if the oxygen substituent ($NOCH_2Ph$) in the Pictet-Spengler reaction of **7b** was responsible for the decreased stereospecificity (50/50) when compared to the $N_b$-benzyl tryptophan **5a** (100% trans, **6b**, R′ = $C_6H_5$) reported earlier.[4] For this reason the variations in solvent and substrate (**2**) between the two reaction processes[4,8a] were eliminated. Ongoing investigations in this laboratory,[4,9] and others,[10] have explored the limits of the stereospecificity of the Pictet-Spengler reaction, and many of the reasons for variations in the cis/trans ratios have been cited. Cis stereoselectivity has been reported[10] in the reaction of tryptophan methyl ester and a variety of aldehydes by performing the cyclization at low temperature. The generation, stereospecifically, of the trans isomer originally utilized the reaction between bulky aldehydes **2** (Scheme I), such as cyclohexanecarboxaldehyde (**2a**) or benzaldehyde **2b**, with $N_b$-benzyltryptophan methyl ester (**5a**) or with $N_a$-methyl-$N_b$-benzyltryptophan methyl ester (**5b**).[4] More recent work has shown that aldehydes which occupy a smaller molecular volume than *tert*-butyl carboxaldehyde[11] or cyclohexanecarboxaldehyde **2a** yield both the cis and trans tetrahydro-β-carbolines, although the cis diastereomer represents a minor product in this process. For example, butyraldehyde on reaction with **5a** in refluxing benzene gave the trans (**4**) and cis (**3**) diastereomers in a ratio of 77:23,[11] while **5a** on heating with isobutyraldehyde gave the two diastereomers in a ratio of trans (95):cis (5).[11] It is, therefore, not surprising that the reaction of $N_b$-(benzyloxy)tryptophan ethyl ester (**7b**) with the small acetaldehyde equivalent **10a** (acetaldehyde dimethyl acetal) in $CH_2Cl_2$/TFA observed by Ottenheijm[8a] furnished substantial amounts of the cis isomer **8c**, as illustrated in Table I. As mentioned above, however, the oxygen functionality (see **7a**, **7b**) substantially alters the electronic properties of the starting amine as well as intermediates which result and may facilitate the additional loss of stereoselectivity.

In order to make comparisons, the reactions originally reported in refluxing benzene[3] were carried out under the conditions of Ottenheijm[8a] in dichloromethane/trifluoroacetic acid ($CH_2Cl_2$/TFA). In addition, the (±)-$N_b$-methyl- and (±)-$N_b$-phenethyltryptophan methyl esters, **11b** and **11d**, respectively, were prepared to be employed as carbon analogues of the corresponding $N_b$-hydroxy- and $N_b$-(benzyloxy)tryptophan (**7a** and **7b**) derivatives. This permits a direct comparison between the effects of size and electronegativity (O vs C) on the stereoselectivity of the condensation. Due to the small size of acetaldehyde dimethyl acetal **10a**, substantial amounts of the cis diastereomer were observed, as expected when the $N_b$-tryptophans **11a**/**11b** were reacted with acetal **10a** (see Table II). However, significant trends were observed when the size of the substituent on the $N_b$-nitrogen atom was increased as discovered earlier in our laboratory.[4] For example, the condensation of tryptophan methyl ester **11a** (R = R′ = H) with **10a** yielded predominantly the cis diastereomer **12a** in a ratio of 75:25, while the corresponding reaction of the $N_b$-benzyl derivative **11c** with **10a** gave the trans diastereomer **14b** with high stereoselectivity [cis (16)/trans (84)] in agreement with earlier work.[9,12] As the bulk of

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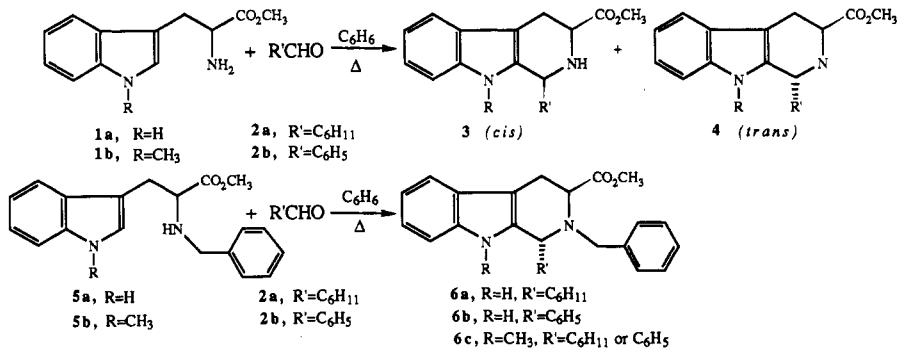
0022-3263/89/1954-5636$01.50/0 

**Scheme I**




**Scheme II**

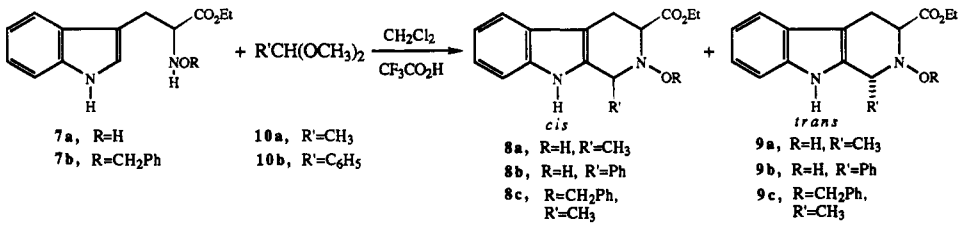
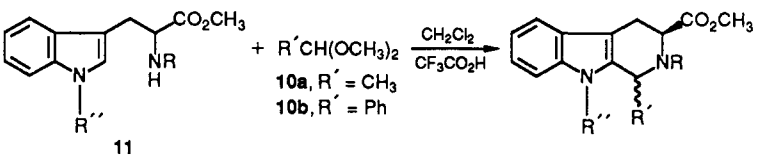



**Table I**

| reactants | R | R′ | products: cis | products: trans | time, h | yield, % |
|---|---|---|---|---|---|---|
| **7a + 10a** | H | $CH_3$ | **8a**, 2 (67) | **9a**, 1 (33) | 72 | 95 |
| **7a + 10b** | H | $C_6H_5$ | **8b**, 2 (40) | **9b**, 3 (60) | 6 | 77 |
| **7b + 10a** | $CH_2Ph$ | $CH_3$ | **8c**, 1 (50) | **9c**, 1 (50) | 3 | 96 |

**Table II**




| | R″ | R | R′ | product ratios[a]: cis (%) | product ratios[a]: trans (%) | time, h |
|---|---|---|---|---|---|---|
| **11a** | H | H | $CH_3$ | **12a** (75) | **12b** (25) | 48 |
| **11b** | H | $CH_3$ | $CH_3$ | **13a** (66) | **13b** (34) | 24 |
| **11c** | H | $CH_2Ph$ | $CH_3$ | **14a** (16) | **14b** (84) | 72 |
| **11d** | H | $CH_2CH_2Ph$ | $CH_3$ | **15a** (16) | **15b** (84) | 168 |
| **11e** | H | $CH_2Ph$ | $C_6H_5$ | **16a** (0) | **16b** (100) | 48 |
| **17** | $CH_3$ | $CH_3$ | $CH_3$ | **18a** (16) | **18b** (84) | 288 |

[a] The stereochemistry and ratios of the cis and trans diastereomers were determined by $^1H$ and $^{13}C$ NMR spectroscopy.[12,13]

the $N_b$-alkyl substituent increases, H < $CH_3$ < $CH_2Ph$ < $CH_2CH_2Ph$, the amount of trans diastereomer increases, as illustrated in Table II. Similarly, the formation of the trans product increases in the case of the oxygenated analogues (Table I) in going from H < OH < $OCH_2Ph$ [(% trans) 25:33:50], although not as dramatically as observed for the $N_b$-alkyl analogues (Table II). Comparison of the data from Tables I and II indicates that the oxygen atom of **7b** ($N_bOCH_2Ph$) clearly decreases the stereoselectivity [(%) **8c** cis (50), **9c** trans (50)] of the condensation in comparison to the $N_b$-benzyltryptophan **11c** [(%) **14a** cis (16), **14b** trans (84)] and $N_b$-phenethyltryptophan **11d** [(%), **15a** cis (16), **15b** trans (84)] methyl ester derivatives. The large differences in the cis/trans ratios for the isosteric benzoloxy- and phenethyl-substituted tryptophans (**7b** and **11d**) must result from the electronic contributions of the oxygen atom during the Pictet–Spengler reaction.

The comparison of the ratios obtained on reaction of the $N_b$-hydroxyl- and $N_b$-methyltryptophan derivatives, **7a** and **11b**, respectively, with acetal **10a** is misleading. Condensation of both these amines provided the cis diastereomer in a ratio of 2:1 (cis/trans), and the similar size (OH vs $CH_3$) of the substituents would support the influence, predominantly, of steric effects on the stereoselectivity. However, the intermediate imine from hydroxylamine **7a** can tautomerize to a nitrone, which alters the reaction kinetics. The significance of this observation will be discussed in a later section.

The lesser p$K_a$ of tryptophan methyl ester (**11a**) (7.98)[14] in comparison to tryptamine (10.2) was employed previously to rationalize why **11a** underwent the Pictet–Spen-

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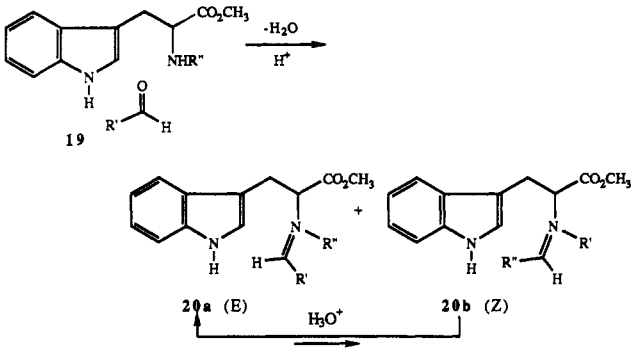
**Table III**

| amine | $pK_a$[14] | amine | $pK_a$[14] |
|---|---|---|---|
| $CH_3NH_2$ | 10.62 | $(CH_3)_2NOH$ | 5.20 |
| $(CH_3)_2NH$ | 10.73 | $(CH_3)NHOCH_3$ | 4.75 |
| $CH_3NHOH$ | 5.96 | $(CH_3)_2NOCH_3$ | 3.65 |

**Scheme III**



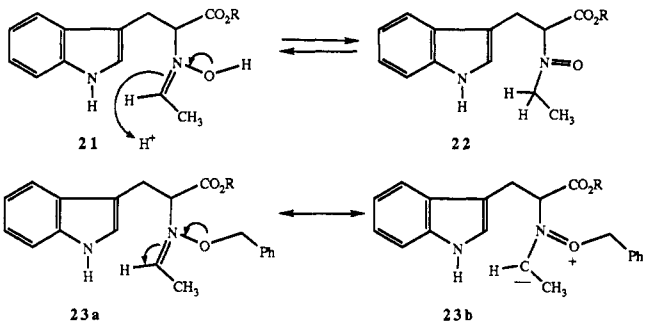

gler reaction more rapidly in refluxing benzene.[3,4] The smaller value of the $pK_a$ is indicative of the lower electron density on the $N_b$-nitrogen atom, the result of which is to provide a more electrophilic, reactive imine intermediate in the rate-determining step of the Pictet–Spengler reaction.[15] This increases the rate at which the cyclization takes place.[3,4] By analogy, other amines of lower $pK_a$ would be expected to react faster in the Pictet–Spengler reaction than **11a**. The $pK_a$'s of hydroxy- and methoxyamines are significantly lower than the corresponding methylamines (Table III), the former ($R_2NOR'$) of which would be expected to be more reactive, as observed in the cyclization (compare hours, Table I vs Table II).

The increased reactivity of the intermediate imine can be employed to explain the loss in trans stereoselectivity during reaction of the $N_b$-OR derivatives (**7a**, **7b**) in comparison to their $N_b$-alkyl counterparts (**11c**, **11d**). The intermediate imine can exist in both the *E* (**20a**) and *Z* (**20b**) forms, as illustrated in Scheme III. If the Pictet–Spengler reaction is rapid both stereoisomers of the imine will cyclize to provide a mixture of the cis and trans diastereomers. If, however, the cyclization is slower, then the *Z* imine **20b** can isomerize to the more stable *E* isomer **20a**, which may then undergo attack by the indole double bond ($C_1$–$C_2$) from the face opposite the methoxycarbonyl group, as previously described.[4] This would provide the trans diastereomer. Consequently, the more reactive (less selective) $N_b$-benzyloxy derivative **7b** yields (with **10a**) more of the cis diasteromer **8c** (50:50) than does the $N_b$-phenethyltryptophan methyl ester **11d** (c/t, 16:84) under the same conditions.

Although the $N_b$-hydroxyl analogue **7a** would be anticipated to have a lower $pK_a$ as compared with tryptophan methyl ester (see trend in Table III), the reaction of **7a** with **10a** is slow due to the tautomeric equilibrium between imine **21** and nitrone **22** (Scheme IV). Although tautomer **21** may readily undergo cyclization, the nitrone **22** cannot, and the cis isomer **8a** is provided in a ratio (67:33) almost identical with that of the corresponding $N_b$-methyl analogue **11b** (Table II). The influence of the nitrone **22** has been to retard the rate of cyclization and permit equilibration to the *E* isomer (Scheme III). Cyclization via the *E* isomer from the face opposite the ester function[4] would provide the trans diastereomer, although this process does not compete effectively with the cyclization, and the cis

(15) Ungemach, F.; Cook, J. M. *Heterocycles* **1978**, *9*, 1089 and references cited therein.

**Scheme IV**




isomer **8a** is still the major product by a 2:1 ratio. There is no corresponding tautomeric equilibrium available for the $N_bOCH_2Ph$ analogue **7b**, and the dipolar resonance form **23b** would not be expected to make a major contribution to the resonance hybrid. In this example, the influence of the oxygen atom (the $N_bOCH_2Ph$ series) is to increase the reaction rate (has a lower $pK_a$ as compared to $N_b$-alkyl) and result in the formation of more of the cis isomer in relation to **11d** ($N_bCH_2CH_2Ph$). The influence of the $pK_a$'s, the mechanism of the Pictet–Spengler reaction,[15] and the influence of nitrone **22** on the reaction rate all contribute to the stereoselectivity observed both within the class of $N_b$-oxygenated compounds (**7a**, **7b**) themselves, as well as to the loss of stereoselectivity observed by Ottenheijm (compare **7b** vs **11c**).[8a] The influence of the oxygen atom on this cyclization is to decrease the stereoselectivity at the expense of the trans diastereomer.

The sensitivity of the Pictet–Spengler reaction to steric factors can be demonstrated by comparison (Table II) of the cis/trans ratios of the $N_a$-methyl-substituted tetrahydro-β-carbolines [compare **13a** cis (66):**13b** trans (34) to **18a** cis (16):**18b** trans (84)] to those of their unsubstituted counterparts. The condensation of **11b** (R" = H, R = $CH_3$) with **10a** gave predominantly the cis diastereomer **13a**, while the stereoselectivity of **10a** with **17** (R" = $CH_3$, R = $CH_3$) was reversed to provide the trans isomer **18b** preferentially (84%).[4,12] The reaction of the $N_b$-hydroxyl derivative **7a** with benzaldehyde dimethyl acetal (**10b**) in $CH_2Cl_2$/TFA gave predominantly the trans diastereomer [**8b** (cis) 40:**9b** (trans) 60]; moreover, the corresponding reaction of the $N_b$-benzyl derivative **11e** with **10b** gave exclusively the trans diastereomer **16b**. The ratio of the cis and trans isomers **8b** (40) and **9b** (60) from **7a** and **10b** (R' = $C_6H_5$) is entirely consistent with the result provided here for the reaction of **7a** with **10a** (R' = $CH_3$), described above.

In summary, the electronic effect of the $N_b$-oxygen substituent (see **7a**/**7b**) on the Pictet–Spengler reaction is to increase the rate of cyclization and decrease the trans stereoselectivity. The cis/trans ratio is dependent then on the reactivity and electronic character of the intermediate imine unless the nitrone tautomer **22** intervenes in the equilibrium. While the stereospecificity previously observed with bulky aldehydes **10** R = $C_6H_{11}$, $C_6H_5$, $(CH_3)_3C$] in the Pictet–Spengler reaction is decreased when aldehydes with smaller substituents such as **10a** are employed, the stereoselectivity is still very high [**14a** (cis) 16%:**14b** (trans) 84%]. Further work is under way to thoroughly define the factors that affect the cis/trans ratios of the Pictet–Spengler reaction in aprotic media.

## Experimental Section

Microanalysis was performed on an F and M Scientific Corp. Model 185 carbon, hydrogen, and nitrogen analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus

and are uncorrected. Proton NMR spectra were recorded on a Varian EM-360 or a Bruker 250-MHz NMR spectrometer, and $^{13}C$ NMR spectra were recorded on a Varian CFT-20 or a Bruker 250-MHz NMR spectrometer. Infrared spectra were taken on a Beckmann Acculab-1 instrument or a Mattson Polaris IR-10400, while mass spectral data were obtained on a Hewlett-Packard 5855 GC–mass spectrometer.

All chemicals were purchased from Aldrich Chemical Co. unless otherwise stated. Analytical TLC plates used were E. Merck Brinkmann UV active silica gel or alumina on plastic. Silica gel 60 and aluminum oxide for column chromatography were purchased from E. M. Laboratories and J. T. Baker, respectively. The TLC plates were visualized under UV light or developed with spray reagents. Alkaloids were visualized utilizing Dragendorf's reagent, which was prepared by adding a solution of bismuth subnitrate (8 g) in $HNO_3$ (70 mL, 30%) and an aqueous solution of potassium iodide (27.2 g, 50 mL) to water (100 mL), followed by filtration.

Methanol was dried over magnesium metal, and DMF was distilled from $MgSO_4$, under reduced pressure. Tetrahydrofuran (THF) and dioxane were distilled after drying over sodium with benzophenone added as an oxygen and water scavenger. *tert*-Butyl alcohol was distilled from $CaH_2$, and anhydrous ethanol was obtained from U.S. Industrial Chemicals.

The stereochemistry of the mixture of 1,3-disubstituted tetrahydro-$\beta$-carbolines were assigned routinely by the $^{13}C$ NMR method devised by Cook et al.;[12] the corresponding 1,2,3-trisubstituted tetrahydro-$\beta$-carbolines were assigned by the modification of Bailey and Hollinshead.[13]

**$N_b$-(2-Phenethyl)tryptophan Methyl Ester (11d).** (±)-Tryptophan methyl ester (2.97 g, 13 mmol) and phenylacetaldehyde (1.82 g, 15 mmol) were stirred in dry methanol (50 mL). After 30 min sodium cyanoborohydride (1.0 g) was added, and the mixture was stirred for 18 h. Aqueous hydrochloric acid (6 N, 50 mL) was added, and the solution was stirred an additional 30 min. The mixture was then brought to pH 10 with aqueous ammonia and extracted with ether (3 × 100 mL). The ether extracts were combined, washed with brine, and dried ($K_2CO_3$). The solvent was removed under reduced pressure to provide a yellow oil (4.059 g). The oil was flash chromatographed on silica gel (EtOAc/hexane, 1:4) to provide the $N_b$-phenethyl derivative **11d** (1.044 g, 24%) accompanied by two additional compounds (0.278 g, 7%), which were identified as the cyclized Pictet–Spengler products, *cis*- and *trans*-3-(methoxycarbonyl)-1-benzyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole. These two diastereomers were not separated. $N_b$-(2-Phenethyl)tryptophan methyl ester (**11d**): mp (HCl salt) 152–4 °C; IR (NaCl, neat, free base) 3400 (NH), 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, free base) $\delta$ 2.65–2.92 (4 H, m), 3.15 (2 H, *ABX*, $J_{AB}$ = 14.4, $J_{AX}$ = 7.1, and $J_{BX}$ = 6.2 Hz), 3.35 (3 H, s), 3.40 (1 H, m), 7.18 (1 H, s), 7.30–7.61 (8 H, m), 7.95 (1 H, d, $J$ = 7.6 Hz), 8.62 (1 H, br s); $^{13}C$ NMR ($CDCl_3$, 62.5 MHz) $\delta$ 29.07, 36.20, 49.39, 51.69, 62.00, 111.02, 111.14, 118.67, 119.40, 122.02, 122.80, 126.05, 127.37, 128.32, 128.61, 136.18, 139.58, 175.07; mass spectrum (CI, $CH_4$) $m/e$ 323 (M + 1, 100); high-resolution mass spectrum, $m/e$ 322.1679 ($C_{20}H_{22}N_2O_2$ requires 322.1681).

***cis*/*trans*-3-(Methoxycarbonyl)-1-benzyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole:** IR (NaCl) neat 3440, 1730 $cm^{-1}$; $^{13}C$ NMR (62.5 MHz, $CDCl_3$) $\delta$ (cis/trans peaks not differentiated) 28.79, 29.14, 39.41, 39.91, 50.30, 51.04, 52.10, 59.42, 60.56, 63.62, 110.84, 111.24, 118.74, 119.60, 122.19, 122.31, 122.75, 122.99, 127.43, 128.67, 129.40, 135.13, 136.19, 173.62, 173.90; $^1H$ NMR (250 MHz $CDCl_3$) $\delta$ 2.85–3.30 (4 H, m), 3.45–3.70 (2 H, m), 3.72 (3 H, s), 6.90–7.60 (9 H, m), 7.95–8.10 (1 H, overlapping broad singlets).

**Pictet–Spengler Reaction: General Method.** The appropriately substituted (±)-tryptophan methyl ester, acetaldehyde dimethyl acetal, and trifluoroacetic acid[8,10] were stirred in methylene chloride until the starting ester was no longer observed by TLC. The reaction mixture was then basified with aqueous ammonia (14%, 50 mL) and extracted with methylene chloride. The organic layer was then washed with brine and dried ($K_2CO_3$). The solvent was removed under reduced pressure to produce an oil. The oil was then dissolved completely in $CDCl_3$, and the cis/trans ratio was determined by integration of the 250-MHz $^1H$ NMR spectrum. The NMR spectrum was obtained on the crude reaction mixture without any attempt at separation of the diastereomers to avoid loss of the minor isomers on the column support, which would result in an incorrect cis/trans ratio.

***cis*/*trans*-3-(Methoxycarbonyl)-1-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (12a and 12b).** Tryptophan methyl ester **11a** (0.270 g, 1.2 mmol), acetaldehyde dimethyl acetal **10a** (0.330 g, 3.7 mmol), and trifluoroacetic acid (0.420 g, 3.7 mmol) were stirred for 48 h to provide a dark yellow oil (0.282 g, 1.16 mmol, 97%), which comprised a mixture of two diastereoisomeric tetrahydro-$\beta$-carbolines **12a** and **12b**. The cis/trans ratio was determined by 250-MHz $^1H$ NMR spectroscopy to be 75:25 (c/t): IR (KBr) 3420, 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.44 (0.8 H, d, $J$ = 6.7 Hz, $CHCH_3$ trans), 1.49 (2.2 H, d, $J$ = 6.7 Hz, $CHCH_3$ cis), 2.20 (1 H, br s, N*H*), 2.72–3.22 (2 H, m), 3.75 (0.6 H, s, $OCH_3$ trans), 3.85 (2.4 H, s, $OCH_3$ cis), 3.91–4.16 (1 H, m), 4.22–4.48 (1 H, m), 7.00–7.51 (4 H, m), 7.85 (1 H, br s, indole N*H*); $^{13}C$ NMR ($CDCl_3$) 20.20, 21.39, 24.95, 25.85, 45.65, 48.27, 52.01, 52.07, 52.30, 56.47, 106.20, 107.17, 110.70, 110.77, 117.87, 119.23, 119.41, 121.49, 121.58, 126.90, 127.02, 135.81, 136.20, 136.37, 173.57, 174.10; mass spectrum (CI, $CH_4$), $m/e$ 245 (M + 1, 100%); high-resolution mass spectrum, $m/e$ 244.1202 ($C_{14}H_{16}N_2O_2$ requires 244.1212).

***cis*/*trans*-2-Benzyl-3-(methoxycarbonyl)-1-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (14a, 14b).** $N_b$-Benzyltryptophan methyl ester **11c** (0.308 g, 1.0 mmol), acetaldehyde dimethyl acetal **10a** (0.200 g, 2.2 mmol), and trifluoroacetic acid (0.253 g, 2.2 mmol) were stirred for 72 h to provide **14a** and **14b** as a dark yellow oil (0.320 g, 0.96 mmol, 96%). The cis/trans ratio was measured by $^1H$ NMR spectroscopy to be 16:84 (c/t): IR (KBr) 3420, 1725 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.36 (0.6 H, d, $J$ = 6.7 Hz, $CHCH_3$ cis), 1.45 (2.4 H, d, $J$ = 6.8 Hz, $CHCH_3$ trans), 2.95–3.33 (m), 3.65 (s, $OCH_3$ cis), 3.70 (s, $OCH_3$, trans), 3.75–4.30 (m), 7.00–7.55 (9 H, m), 7.68 (1 H, s, N*H*); $^{13}C$ NMR ($CDCl_3$) 21.15, 22.26, 22.39, 51.07, 51.66, 52.79, 53.99, 57.05, 59.86, 106.41, 110.77, 118.13, 119.48, 121.61, 127.01, 127.21, 128.37, 128.45, 136.26, 140.05, 173.71; mass spectrum (CI, $CH_4$), $m/e$ 335 (M + 1, 100%); high-resolution mass spectrum, $m/e$ 334.1675 ($C_{21}H_{22}N_2O_2$ requires 334.1681).

***cis*/*trans*-2-(2-Phenylethyl)-3-(methoxycarbonyl)-1-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (15a, 15b).** $N_b$-(2-Phenylethyl)tryptophan methyl ester **11d** (0.285 g, 0.89 mmol), acetaldehyde dimethyl acetal **10a** (0.155 g, 1.72 mmol), and trifluoroacetic acid (0.196 g, 1.72 mmol) were stirred for 7 days to provide a dark yellow oil (0.302 g, 0.87 mmol, 97%). Two diastereomers were present as evidenced by TLC; the cis/trans ratio was measured by $^1H$ NMR analysis to be 16:84 (c/t). **15a,b**: IR (neat) 3430, 1725 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.40 (2.4 H, d, $J$ = 6.9 Hz, $CHCH_3$ trans), 1.58 (0.6 H, d, $J$ = 6.9 Hz, $CHCH_3$ cis), 2.70–3.21 (m), 3.65 (2.4 H, s, $OCH_3$ trans), 3.78 (0.6 H, s, $OCH_3$ cis), 3.98 (1 H, m), 4.24 (1 H, m), 7.02–7.53 (9 H, m), 7.93 (0.8 H, br s, N*H* trans) 8.05 (0.2 H, br s, N*H* cis). $^{13}C$ NMR ($CDCl_3$) 18.17, 21.09, 22.61, 22.99, 34.99, 36.38, 51.57, 51.86, 52.87, 52.98, 57.90, 61.25, 106.18, 106.56, 110.74, 118.04, 119.37, 119.50, 121.49, 121.59, 126.01, 127.11, 128.25, 128.43, 128.69, 128.93, 136.24, 136.38, 140.25, 140.40, 173.83, 173.94; mass spectrum (CI, $CH_4$), $m/e$ 349 (M + 1, 100%); IR (neat) 3430, 1725 $cm^{-1}$. Data for **15b** (trans): $^1H$ NMR ($CDCl_3$) $\delta$ 1.45 (3 H, d, $J$ = 6.9 Hz), 2.71–3.15 (6 H, m), 3.61 (3 H, s), 3.98 (1 H, t, $J$ = 6.3 Hz), 4.32 (1 H, q, $J$ = 6.2 Hz), 7.01–7.52 (9 H, m), 7.80 (1 H, br s); $^{13}C$ NMR ($CDCl_3$) $\delta$ 21.17, 22.63, 36.42, 51.65, 51.89, 53.04, 57.93, 106.30, 110.77, 118.10, 119.45, 121.57, 126.06, 127.16, 128.31, 128.97, 136.25, 136.38, 140.43, 173.83; mass spectrum (CI, $CH_4$), $m/e$ 349 (M + 1, 100%); high-resolution mass spectrum, $m/e$ 348.1841 ($C_{22}H_{24}N_2O_2$ requires 348.1841).

***cis*/*trans*-2-Methyl-3-(methoxycarbonyl)-1-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (13a, 13b).** $N_b$-Methyltryptophan methyl ester **11b** (0.291 g, 1.25 mmol), acetaldehyde dimethyl acetal **10a** (0.250 g, 2.78 mmol), and trifluoroacetic acid (0.316 g, 2.78 mmol) were stirred for 24 h to provide a dark oil (0.320 g, 1.24 mmol, 99%). Two diastereomers were present as evidenced by TLC; the cis/trans ratio was measured by $^1H$ NMR spectroscopy to be 67:33 (c/t). **13a,b**: IR (KBr) 3420, 1725 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.45 (2 H, d, $J$ = 6.8 Hz, $CHCH_3$ cis), 1.52 (1 H, d, $J$ = 6.7 Hz, $CHCH_3$ trans), 2.33 (1 H, s, $NCH_3$ trans), 2.58 (2 H, s, $NCH_3$ cis), 2.92–3.21 (2 H, m), 3.68 (2 H, s, $OCH_3$ cis), 3.82 (1 H, s, $OCH_3$ trans), 3.93 (1 H, t, $J$ = 6.3 Hz), 4.16 (1 H, q, $J$ = 6.3 Hz), 7.05–7.51 (9 H, m), 7.83–7.92 (1 H, br, N*H*); $^{13}C$ NMR ($CDCl_3$) 17.63, 20.16, 22.17, 22.36, 35.23, 39.06, 51.63, 52.15, 53.30, 55.30, 59.47, 110.70, 110.79, 117.98, 119.32,

119.53, 121.44, 121.58, 126.99, 134.46, 135.79, 136.17, 173.25; mass spectrum (CI, $CH_4$), $m/e$ 259 (M + 1, 100%); high-resolution mass spectrum, $m/e$ 258.1369 ($C_{15}H_{18}N_2O_2$ requires 258.1368).

**2-Methyl-3-(methoxycarbonyl)-1,9-dimethyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (18a, 18b).** $N_a$,$N_b$-Dimethyltryptophan methyl ester **17** (0.014 g, 0.057 mmol), acetaldehyde dimethyl acetal **10a** (0.010 g, 0.11 mmol), and trifluoroacetic acid (0.012 g, 0.11 mmol) were stirred for 12 days to provide **18a,b** as a dark oil (0.0155 g, 0.057 mmol, 100%); the cis/trans ratio was measured by $^1H$ NMR analysis to be 14:86 (c/t): $^1H$ NMR ($CDCl_3$) $\delta$ 1.52 (3 H, d, $J$ = 6.9 Hz, $CHCH_3$ cis and trans), 2.47 (2.6 H, s, $NCH_3$ trans), 2.57 (0.4 H, s, $NCH_3$ cis), 2.90-3.18 (2 H, m), 3.62 (3 H, s), 3.63-4.04 (2 H, m including a singlet (3 H) at 3.72), 7.01-7.50 (4 H, m); mass spectrum (CI, $CH_4$), $m/e$ 273 (M + 1, 100%).

***trans*-2-Benzyl-3-(methoxycarbonyl)-1-phenyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (16b).** $N_b$-Benzyltryptophan methyl ester **11e** (0.308 g, 1.0 mmol), benzaldehyde dimethyl acetal **10b** (0.310 g, 2.0 mmol), and trifluoroacetic acid (0.228 g, 2.0 mmol) were stirred for 48 h to provide a dark yellow oil, which was flash chromatographed on silica gel (hexane/EtOAc, gradient) to provide a light yellow oil (0.375 g, 95%) whose proton NMR and IR spectra were identical with those of the trans diastereomer **16b**[4] obtained from the reaction of $N_b$-benzyltryptophan methyl ester (**11c**) and benzaldehyde in refluxing benzene.[4] No other products were observed in this reaction by TLC or from the NMR spectrum of the crude material.

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**Registry No.** **7a**, 99708-04-0; **7b**, 81095-85-4; **8a**, 123050-53-3; **8b**, 123050-54-4; **8c**, 123050-55-5; **9a**, 123050-56-6; **9b**, 123050-57-7; **9c**, 123050-58-8; **10a**, 534-15-6; **10b**, 1125-88-8; **11a**, 7303-49-3; **11b**, 123003-67-8; **11c**, 73327-10-3; **11d**, 123003-68-9; **12a**, 50302-68-6; **12a** (R′ = $CH_2Ph$), 123003-76-9; **12b**, 75196-51-9; **12b** (R′ = $CH_2Ph$), 123003-77-0; **13a**, 123003-69-0; **13b**, 123003-70-3; **14a**, 93712-65-3; **14b**, 93712-66-4; **15a**, 123003-71-4; **15b**, 123003-72-5; **16b**, 123050-52-2; **17**, 123003-73-6; **18a**, 123003-74-7; **18b**, 123003-75-8; H-DL-Trp-OMe, 7303-49-3; $PhCH_2CHO$, 122-78-1.

## Primary Polyfluoroallylic Alcohols. Preparation and Isomerization into 2-Fluoroacrylic Acid Fluoride and 1-Fluoro Vinyl Ketones

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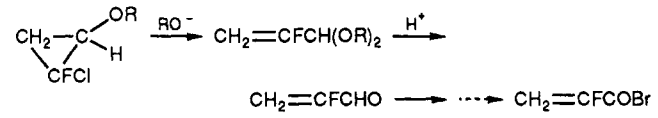
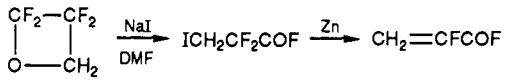
Alkyl and aryl 2-fluoroacrylic acid esters have been used as starting materials for number of coating agents, dental polymers,[1] and special glass.[2] These esters have been commonly prepared from 2-fluoroacrylic acid halides $CH_2$=CFCOX (X = Cl,[3] Br,[4] F[5]). The recent processes for having these intermediates involved the rearrangement

**Scheme I**



**Scheme II**

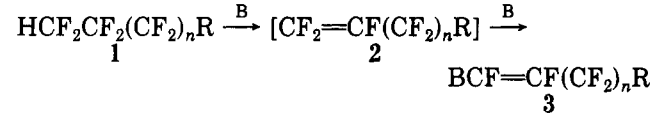


of an alkoxycyclopropane[4] (Scheme I) or the opening of and oxetane by a nucleophile[5] (Scheme II).

These two reactions brought great improvements over the previous method which used as starting material the very toxic 2-fluoroacetic derivatives.[6] The cyclopropane route needs nevertheless several steps, and the oxetane[7] is also toxic. Another possible way of obtaining 2-fluoroacrylic acid halides should be a rearrangement of 2-fluoroacrylic alcohols CXY=CFCH$_2$OH if these alcohols are available. The allylic rearrangements were already performed on secondary and tertiary fluoroallylic alcohols,[8] but not on a primary alcohol. The reason was certainly an absence of a practical method of preparation of these alcohols. Therefore we were searching a convenient method of obtaining primary polyfluoroallylic alcohols.

A few years ago, we showed that 1-H perfluoroalkyl chains are transformed into fluorinated olefins by action of strong bases like lithium dialkylamides[9] or organolithium reagents[10] (Scheme III).

**Scheme III**



This conversion was observed with alcohols $HCF_2CF_2(CF_2)_nCH_2OH$ when $n$ was equal to 2, 4, or 6. The vinylic intermediate **2** was not isolated. This fluorinated olefin, activated by the electron-withdrawing difluoromethylene group, was steadily attacked by the organolithium reagent. However, the case of the alcohol $HCF_2CF_2CH_2OH$ **4** corresponding to $n$ equal to zero, was not examined at that time. Recently we were asking ourselves what could be the reactivity of the intermediate olefin **5** which is not activated by an adjacent electronegative group. Is it possible to stop the condensation at the intermediate step **5** in order to get the allylic alcohol **7** after hydrolysis? (See Scheme IV.)

We report here that this transformation can be performed under controlled conditions of temperature and reaction time. Addition of methyllithium to the alcohol **4** in diethyl ether at 0 °C and stirring during 5 h at room temperature led, after hydrolysis, to a mixture containing 74% of **7**, 16% of **8**, and 10% of the starting material **4** as shown by an NMR analysis. If the condensation is allowed to go to completion when the addition is performed at room temperature the substituted allylic alcohol **8** can

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