Side Reactions in Peptide Synthesis. 11.[1] Possible Removal of the 9-Fluorenylmethyloxycarbonyl Group by the Amino Components during Coupling

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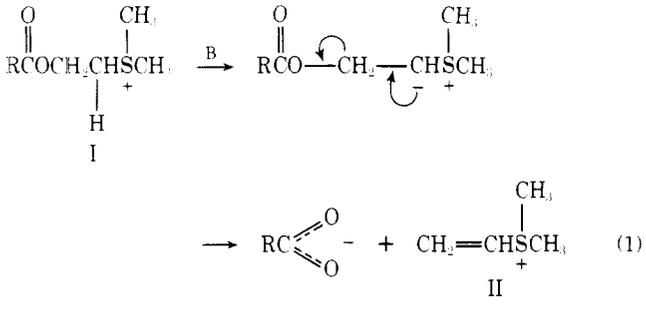
Aminolysis of the 9-fluorenylmethyloxycarbonyl (FMOC) group from protected amino acids is not limited to liquid ammonia or piperidine, which were recommended for this purpose. It occurs, although at a lower rate, by the action of the primary or secondary amines, which are the nucleophilic components of coupling reactions. Tertiary amines added for the liberation of the free amines from their salts also cleave the FMOC group, the hindered diisopropylethylamine only at a low rate. The undesired removal of the FMOC protecting group is somewhat inhibited by the addition of 2,4-dinitrophenol or pentachlorophenol to the reaction mixture.

Protection of carboxyl groups and also of amino functions can be accomplished by the application of esters. In the case of amino groups, these have to be present in the form of carbamoic acids which decarboxylate after ester cleavage. The classical method of deprotection by hydrogenolysis could be replaced by acidolysis[3] when the relative stability of the benzyl cation was put to good use. The same principle led to further developments with the utilization of stable carbocations such as the *tert*-butyl[4] or the biphenylisopropyl[5] carbenium ions. A significant broadening of tactical possibilities was provided by the introduction of protecting groups which can be removed with nucleophiles. A β-substituted ethyl ester that can be cleaved by treatment with bases was proposed by Crane and Rydon.[6] Abstraction of a proton from the β carbon of the ethyl group (cf. compound I in eq 1) is facilitated by the adjacent electron-withdrawing sulfonium function. The resulting carbanion eliminates the carboxylate with the formation of a vinylsulfonium salt (II). In the case of urethanes, decarboxylation follows. An analogous mechanism is operative in the removal of the protecting group proposed by Kader and Stirling[7] (eq 2). Here the *p*-toluenesulfonyl group provides the negative inductive effect which renders the hydrogen on the β carbon acidic and hence abstractable by bases. The principle of ethyl esters with an electron-withdrawing β substituent is the foundation of several other more recently recommended protecting groups such as the 2-(methylthio)-ethyl esters,[8] the 2-(*p*-nitrophenylthio)ethyl esters,[9] which have an acidic proton on the β carbon of ethanol after oxidation or alkylation, and also the 2-(methylsulfonyl)ethyloxycarbonyl (MSC) group,[10] already applied in practical syntheses.[11,12] In the perhaps most sophisticated implementation of this principle, the 9-fluorenylmethyloxycarbonyl (FMOC) group of Carpino and Han,[13] the β carbon of ethyl carbamoates is incorporated in the fluorene ring system (eq 3). The electron-withdrawing forces of the aromatic system render the remaining hydrogen atom on the β carbon quite acidic, and its ready abstraction even by weak bases allows the removal of the FMOC group in liquid ammonia or neat piperidine.[14,15] This led to the systematic application of the FMOC group in solid-phase synthesis.[16,17]



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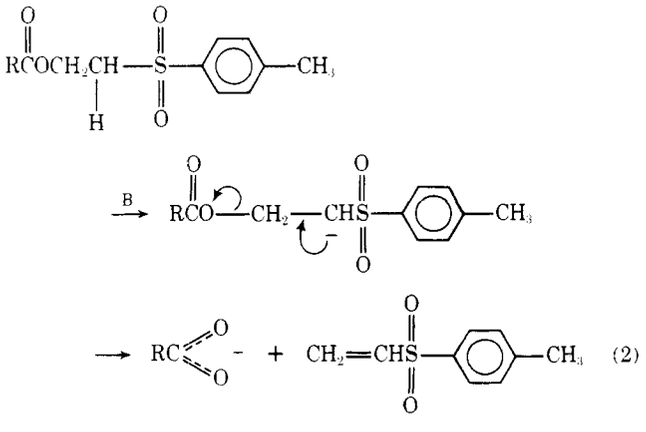

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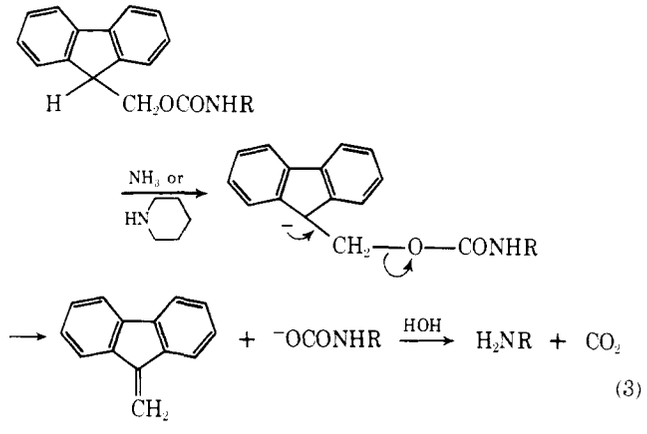

(3)

While considering the adaptation of the FMOC group for the protection of the α-amino function in syntheses carried out in solution, we felt some concern about the stability of this group against the attack by the amino groups of the components to be acylated. The ability of such basic groups to abstract a proton from the β carbon of negatively substituted ethyl esters is not necessarily negligible. Should, however, the free amino group of a C-terminal segment deblock the protected amino component or the part of the product which has already been formed in the coupling, then side reactions such as double incorporation of the carboxyl component could occur. These side reactions could be negligible in some instances, e.g., when the FMOC group applied is in solid-phase peptide synthesis, where the physical separation between blocked and free amino groups might be sufficient to decrease the extent of unwanted deblocking to a negligible minimum. Yet, in solution, where no such separation exists, the side re-

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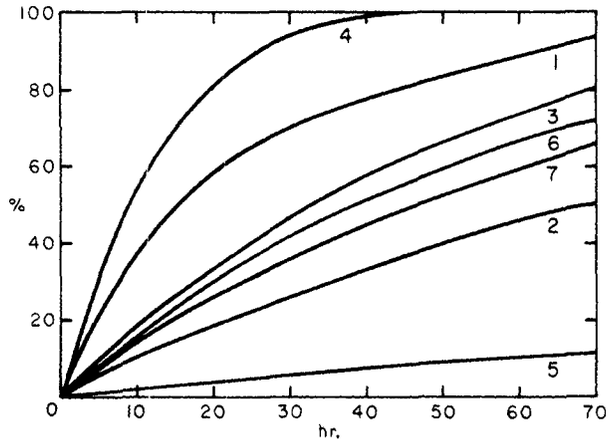

Figure 1. The amount of L-alanine (expressed as percent of the total present in the protected amino acid) released from FMOC-L-Ala by the action of: 1, Gly-OEt·HCl + DIEA; 2, L-Val-O-*t*-Bu·HCl + DIEA; 3, L-Val-O-*t*-Bu; 4, L-Pro-O-*t*-Bu; 5, DIEA; 6, L-Pro-L-Lys(*p*-NO_2Z)Gly-OEt·TFA + DIEA; 7, L-Val-L-Leu-L-Thr-NH_2 (DIEA, diisopropylethylamine; TFA, trifluoroacetic acid).

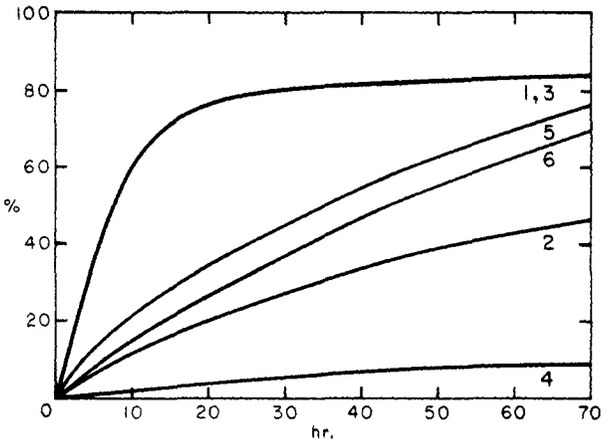

Figure 2. The amount of glycine (expressed as percent of the total present in the protected amino acid) released by the action of: 1, Gly-OEt·HCl + DIEA; 2, L-Val-O-*t*-Bu·HCl + DIEA; 3, L-Pro-O-*t*-Bu; 4, DIEA; 5, L-Pro-L-Lys(*p*-NO_2Z)Gly-OEt + DIEA; 6, L-Val-L-Leu-L-Thr-NH_2.

actions could be significant. This possibility was explored in the experiments here reported.

The protected amino acids FMOC-L-alanine and FMOC-glycine were selected as substrates for our model experiments. The former, with an uncomplicated side chain, was chosen as the representative of amino acids in general, although the individuality of amino acids with respect to reactivities has not been overlooked. In FMOC-glycine the absence of a side chain could produce increased sensitivity to the attack by bases. The effects of tertiary amines, that of the commonly used triethylamine and of the hindered diisopropylethylamine, were also investigated. Already, the first experiments revealed that our concern was not unwarranted. A slow, but definite cleavage of the FMOC group was observed when FMOC-glycine or FMOC-L-alanine was exposed, in dimethylformamide at room temperature, to the effect of L-valine *tert*-butyl ester, glycine ethyl ester, L-proline *tert*-butyl ester, triethylamine, and diisopropylethylamine. The appearance of dibenzofulvene and of the free amino acids on TLC demonstrated the lability of the FMOC group toward these bases.[18] Our investigations were extended also to the effects of L-valyl-L-leucyl-L-threonine amide and L-prolyl-N^{ϵ}-*p*-nitrobenzyloxycarbonyl-L-lysylglycine ethyl ester.[19] A quantitation of the effect was achieved through the determination of the amount of free amino acid released from the FMOC derivatives.

In the experiments where the primary or secondary amines were applied in the form of their hydrochlorides or trifluoroacetates, a tertiary amine was added to liberate the free amino group. As tertiary amine, diisopropylethylamine was used because this hindered amine in itself had little effect on FMOC-amino acids (cf. Figures 1 and 2). This can be best explained by the steric hindrance in the protecting group combined with the bulkiness in the structure of the amine. Under the same conditions, triethylamine caused significant cleavage in FMOC-L-alanine within 1 h, and almost complete decomposition of the protected amino acid occurred within a day.

The results of the experiments carried out with FMOC-L-alanine are summarized in Figure 1. From the primary amines tested, glycine ethyl ester was the most harmful, with 16 h as half-reaction time ($t_{1/2}$). The more hindered L-valine *tert*-butyl ester reacted with FMOC-L-alanine less rapidly ($t_{1/2}$ = 70 h). Interestingly, when this latter amine was applied, not as an equimolar mixture of L-valine *tert*-butyl ester hydrochloride and diisopropylethylamine but as the free amine, the cleavage was noticeably faster ($t_{1/2}$ = 25 h). Obviously, the addition of the tertiary amine to the ester hydrochloride can set free only a fraction of the primary amine; hence its active concentration cannot reach that of the free amine applied as such.[20] The protecting group in FMOC-L-alanine was cleaved more rapidly by L-proline *tert*-butyl ester than by L-valine *tert*-butyl ester. This might be due to the absence of steric hindrance in proline or to the fact that it is a secondary amine.[13,14] The two tripeptide derivatives also cleaved the FMOC group from L-alanine, as shown in Figure 1. Once again the compound with N-terminal L-proline seemed to be more reactive ($t_{1/2}$ = 40 h) than the one with N-terminal L-valine ($t_{1/2}$ = 60 h), even though the former was applied as a hydrochloride while the latter as the free amine. Still, the observed difference might be due in part also to steric hindrance in the valine side chain.

The sensitivity of FMOC-glycine toward various primary and secondary amines was similar (Figure 2) to that of FMOC-L-alanine (Figure 1), with the notable exception of the reaction between FMOC-glycine and glycine ethyl ester. Here the half-reaction time ($t_{1/2}$ = 10 h) was definitely less than in the reaction of FMOC-L-alanine and glycine ethyl ester ($t_{1/2}$ = 16 h). With FMOC-glycine as substrate, L-proline *tert*-butyl ester and glycine ethyl ester (applied as the hydrochloride together with diisopropylethylamine) were about equally reactive (Figure 2).

At this point it should be noted that the experiments summarized in Figures 1 and 2 were carried out under conditions which are more harmful to the FMOC group than the conditions usually encountered in practical syntheses. In actual coupling reactions, the basicity of the reaction mixture decreases with time, rapidly at an early stage of acylation, and practically disappears on completion of the coupling. In the model experiments of the present study, however, the concentration of base remained constant and therefore decomposition of the FMOC derivatives is exaggerated. In a coupling of FMOC-L-alanine *p*-nitrophenyl ester with L-proline *tert*-butyl ester 1.3% of the FMOC groups was eliminated in the form of dibenzofulvene. With glycine ethyl ester hydrochloride–diisopropylethylamine mixture as the amino component the decomposition of the protecting group was only 0.4%. It might be possible to further decrease the unwanted cleavage by the addition of weak acids which lower the basicity of the mixture but do not prevent the acylation reaction by complete protonation. In couplings with dicyclohexylcarbodiimide the carboxyl component itself is a proton donor; in acylation with

Table I. Effects of Additives on the Removal of the FMOC Group by Val-O-*t*-Bu[a]

no. of equiv				% of Ala[b,e]		
FMOC-Ala[c]	Val-O-*t*-Bu-HCl[d]	DIEA	additives	18 h	24 h	48 h
1	2	2	none	19	21	38
1	2	2	HOBt (1)	13	15	33
1	2	3	HOBt (1)[f]	19	22	45
1	2	2	2,4-dinitrophenol (1)[g]	9	11	18
1	2	2	pentachlorophenol (1)[h]	10	12	20
1	2	3	HOBt (1) + 2,4-dinitrophenol (1)	11	12	24
1	2	3	HOBt (1) + pentachlorophenol (1)	11	13	26
1	2	3	HOBt (1) + 2,4-dinitrophenol (2)	2.5	3	5

[a] The solutions (in DMF) were 0.1 M with respect to FMOC-L-Ala. [b] Determined by amino acid analysis. Samples, after dilution with citrate buffer, of pH 2.2 were extracted twice with EtOAc. Aspartic acid was added as an internal standard. [c] Registry no.: 35661-39-3. [d] Registry no.: 13518-40-6. [e] Registry no.: 56-41-7. [f] Registry no.: 2592-95-2. [g] Registry no.: 51-28-5. [h] Registry no.: 87-86-5.

symmetrical or mixed anhydrides the gradually released acid can play that role.

Our recent studies[23] on the suppression of ring closure of aspartyl peptide and the formation of aminosuccinyl derivatives with additives that can compete with –NH– protons for bases in the reaction mixture led to the recommendation of the application of 2,4-dinitrophenol and pentachlorophenol as additives. The same additives were shown[24] to prevent O-acylation by active esters in peptides with unprotected hydroxyl groups. Since in both cases the abstraction of weakly acidic protons was the initial step in the process, it seemed to be worthwhile to attempt the application of these additives for the prevention of the premature cleavage of FMOC groups. The experiments summarized in Table I revealed that 2,4-dinitrophenol or pentachlorophenol added in an amount equimolar to the FMOC-amino acid substrates slowed down their decomposition, but could not completely prevent the loss of the protecting group. The situation remained about the same when 1-hydroxybenzotriazole[25] was also present in equimolar amount. A twofold excess of 2,4-dinitrophenol had a more substantial effect, but also reduced the rate of acylation.

From the studies presented in this paper it seems to us that the FMOC group is not only an interesting, but probably also an important, addition to the methodology of peptide synthesis. Some loss of protection, however, can occur during coupling and should be taken into consideration.

Experimental Section

For thin-layer chromatography, precoated plates of silica gel (Brinkman 60 F6, 254) were used with the following solvent systems: A, $CHCl_3$–MeOH, 8:2; B, $CHCl_3$–CH_3OH, 9:1; C, *n*-BuOH–AcOH–H_2O, 4:1:1.

Decomposition of FMOC-amino Acids. The protected amino acid (0.1 mmol) was dissolved in DMF (~0.5 mL) and the amine (0.2 mmol of amino acid or peptide ester or amide or their salts) was added. In the case of salt, DIEA (0.2 mmol) was also used. The volume of the solution was adjusted with DMF to 1.0 mL, and the solution was divided into aliquots (0.20 mL each). These aliquots were diluted to 10 mL with a citrate buffer of pH 2.2 at the time intervals indicated in Figures 1 and 2. After further 1:10 dilution with the same buffer, 1.0 mL of the solution was submitted for amino acid analysis on a Beckman-Spinco 120C amino acid analyzer.

Model Compounds. FMOC-L-alanine and FMOC-glycine were purchased from Chemical Dynamics Corp.; proline *tert*-butyl ester, glycine ethyl ester hydrochloride, and valine *tert*-butyl ester and its hydrochloride were obtained from Bachem.

The tripeptide derivative L-valyl-L-leucyl-L-threonine amide (with the C-terminal sequence of hen VIP[26]) was prepared by aminolysis, followed by deprotection of benzyloxycarbonyl-L-valyl-L-leucyl-L-threonine methyl ester. The ester (mp 217–218 °C; $[\alpha]^{25}_D$ −12° (*c* 1.5, DMF); TLC R_fB 0.57, R_fC 0.75. Anal. Calcd for $C_{24}H_{37}N_3O_7$: C, 60.1; H, 7.8; N, 8.8. Found: C, 59.9; H, 7.7; N, 8.8) was obtained similarly to the corresponding *tert*-butyloxycarbonyl derivative.[26] It was ammonolyzed with NH_3 in methanol and the protected tripeptide amide (mp 241–242 °C, R_fC 0.24) was hydrogenated[27] in DMF in the presence of 5% DIEA and a Pd-black catalyst (Strem Chemical). The free amine was isolated by evaporation of most of the solvent in vacuo and precipitation with ether. According to TLC, it contained no starting protected peptide. This material was used without purification for testing the stability of FMOC-amino acids.

For the preparation of L-prolyl-N^{ϵ}-*p*-nitrobenzyloxycarbonyl-L-lysylglycine ethyl ester (trifluoroacetate salt), a sample of N^{α}-*tert*-butyloxycarbonyl-N^{ϵ}-*p*-nitrobenzyloxycarbonly-L-lysine *p*-nitrophenyl ester (Fox Chemical Co.) was allowed to react with ethyl glycinate in DMF. The protected dipeptide ester (mp 94–98 °C, $[\alpha]^{25}_D$ −10° (*c* 2, $CHCl_3$), TLC R_fB 0.68) was isolated by evaporation of the solvent and trituration with ether. It was deblocked with trifluoroacetic acid and coupled with *tert*-butyloxycarbonyl-L-proline *o*-nitrophenyl ester[28] in DMF in the presence of DIEA and 1-hydroxybenzotriazole.[25] The protected tripeptide ester was secured by evaporation of the solvent, dissolution of the residue in EtOAc, and washing with $KHCO_3$, H_2O, citric acid solution, and H_2O. It was crystallized from EtOAc–hexane: mp 124–125 °C, TLC R_fA 0.80. Deblocking with TFA produced a solid trifluoroacetate that was used without purification, with an equimolar amount of DIEA, in the experiments shown in Figures 1 and 2.

FMOC-L-alanine *p*-Nitrophenyl Ester. To a stirred solution of FMOC-L-alanine (1.37 g, 4.4 mmol, Chemalog) and *p*-nitrophenol (0.67 g, 4.8 mmol) in EtOAc (20 mL), cooled in an ice–water bath, a solution of dicyclohexylcarbodiimide (DCC) (0.82 g, 4 mmol) in EtOAc (20 mL) was added. After 30 min at 0 °C the mixture was allowed to come to room temperature. After 2 h no more DCC could be detected in the IR spectrum. The *N,N'*-dicyclohexylurea was filtered off and washed with EtOAc (150 mL). The combined filtrates were extracted twice with a saturated solution of $NaHCO_3$ (50 mL each) and twice with H_2O (50 mL each), dried over $MgSO_4$, and evaporated to dryness. The residue was triturated with ether (50 mL), filtered, washed with ether, and dried in vacuo: 1.10 g. A second crop, 0.45 g, separated from the filtrate. Both melted at 164–166 °C. The melting point remained unchanged on recrystallization from 95% EtOH containing 0.1% AcOH. On TLC (silica gel, Brinkman) R_f 0.35 in $CHCl_3$ and 0.50 in ether–hexane (8:2); $[\alpha]^{24}_D$ −41.5° (*c* 1.1, $CHCl_3$); active ester CO band at 1762 cm^{-1}.

Elimination of Dibenzofulvene during Coupling. (A) L-Proline *tert*-butyl ester (67 mg, 0.39 mmol, Bachem) and FMOC-L-Ala-ONp[29] (180 mg, 0.42 mmol) were dissolved in DMF[30] (4 mL) and the solution was stored in the dark overnight. The solvent was removed in vacuo and the residue dissolved in a mixture of $CHCl_3$ and hexane (7:18) and chromatographed on a column of silica gel (8 × 1.5 cm, Baker). The same solvent mixture was used for elution and dibenzofulvene was detected (R_f 0.70 in the same system) in the first 50 mL of the eluate. Its amount was determined by absorption at 258 nm. The extent of cleavage was calculated by comparing the absorption with that of dibenzofulvene released from a weighed sample of FMOC-glycine with alkali.

(B) A similar experiment was carried out with glycine ethyl ester hydrochloride (52 mg, 0.37 mmol) and diisopropylethylamine (64 μL, 0.4 mmol) and FMOC-L-Ala-ONp (170 mg, 0.39 mmol) in DMF[30] (3.7 mL).

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Registry No.—L-Valyl-L-leucyl-L-threonine amide, 69462-04-0; benzylcarbonyl-L-valyl-L-leucyl-L-threonine methyl ester, 69462-05-1; L-prolyl-N^{ϵ}-*p*-nitrobenzyloxycarbonyl-L-lysylglycine ethyl ester trifluoroacetate salt, 69470-11-7; N^{α}-*tert*-butoxycarbonyl-N^{ϵ}-*p*-nitrobenzyloxycarbonyl-L-lysine *p*-nitrophenyl ester, 33662-24-7; ethyl glycinate, 459-73-4; *tert*-butyloxycarbonyl-L-proline *o*-nitrophenyl ester, 38605-56-0; *N*-*tert*-butyloxycarboxy-L-prolyl-N^{ϵ}-*p*-nitrobenzyloxycarbonyl-L-lysylglycine ethyl ester, 69462-06-2; FMOC-L-alanine *p*-nitrophenyl ester, 69462-07-3; *p*-nitrophenol, 100-02-7; L-proline *tert*-butyl ester, 2812-46-6.

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(18) The free amino acid, glycine or alanine, gradually separated from the solutions in crystalline form.
(19) The 3-peptide with Val as the N-terminal residue was chosen because it allowed comparison with the effect of L-valine *tert*-butyl ester. (Also, this peptide amide was available in our laboratory.) A peptide with proline at its N-terminal seemed to be desirable for the same reasons. The tripeptide ester used was prepared from a dipeptide at hand.
(20) At this point it should be remembered that in syntheses in which the FMOC group is used for the protection of α-amino functions, removal of the protection does not result in a salt of the liberated amine and accordingly no need exists for the addition of a tertiary amine.
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(29) The active ester contained no dibenzofulvene (TLC).
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Highly Stereoselective Synthesis of (±)-α-Multistriatin

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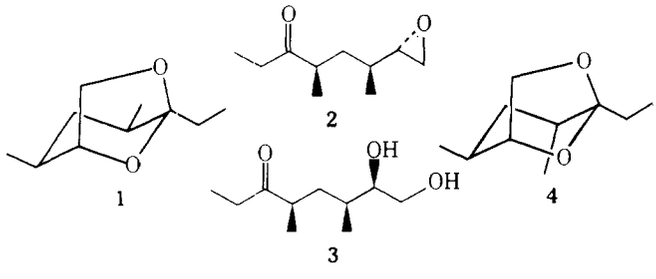
Erythro-2,4-Dimethyl-5-hexenoic acid (**7**), available from *meso*-2,4-dimethylglutaric anhydride, is functionalized in a highly stereoselective manner by iodolactonization. Subsequent methanolysis of the iodo lactone **9** and conversion of the ester to the ethyl ketone provide the desired cyclization substrate **2**. Lewis acid catalyzed cyclization of **2** then affords (±)-α-multistriatin of more than 95% purity in a sequence which necessitates no column or vapor phase chromatography purification steps.

Multistriatin (**1**) has been the target of a number of synthetic endeavors[1] because it is one of the three components of the aggregation pheromone of the European elm bark beetle, *Scolytus multistriatus* Marsham, the primary vector of Dutch elm disease in Europe and North America. With one exception,[1a] all of the reported syntheses entail the construction of the keto epoxide **2**[1c,e] or the keto diol **3**[1b,d] prior to cyclization. None of the syntheses of α-multistriatin is stereospecific in the sense of controlling the relative configurations of the chiral centers, although enantiomerically pure (−)-α-multistriatin has been synthesized from appropriate optically active precursors.[1c-e] In the Diels–Adler approach of Gore, Pearce, and Silverstein[1a] and the route developed by Elliot and Fried,[1b] the relative stereochemistry of carbons 1 and 2 of multistriatin is introduced specifically; however, the natural α isomer is obtained as a mixture with the γ isomer (**4**) after acid-catalyzed equilibration (α/γ = 80:20[1a] or 85:15[1b]). We have completed a synthesis of (±)-α-multistriatin, via the keto epoxide **2**, in which all of the relative stereochemistry is introduced with high selectivity and which provides material of greater than 95% purity without VPC purification at any stage.



1 2 3 4

The addition of dilithiomethyl phenyl sulfone[2] to the readily available *meso*-2,4-dimethylglutaric anhydride (**5**),[3] followed by sodium borohydride reduction and lactonization, gave the sulfonyl lactone **6** as a mixture of isomers. Sodium amalgam reduction[4] of this material then provided the olefinic acid **7** in 66% overall yield from the anhydride **5**. Although this was an efficient process, the acid **7** was occasionally contaminated with varying amounts of the threo isomer, apparently arising from epimerization during the borohydride reduction step, and an alternative stereospecific synthesis was required. The aldehyde ester **8**[5] is available in 80% yield from the anhydride **5** by Rosenmund reduction of the half ester acid chloride. Wittig methylenation of this material and subsequent ester hydrolysis afford the olefinic acid **7** without sig-

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