Fluorous Linker-Facilitated Chemical Synthesis

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Contents

1. Introduction

Linkers have bifunctional moieties; one side is permanently bound to a support and the other side is temporarily attached to a reaction substrate so it can be cleaved to release the product from the support at the end of synthesis. A spacer between the support and the linker is used to minimize the stereoelectronic effect of the support and to give the attached substrate more mobility for better reaction kinetics. A wide

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Dr. Wei Zhang is an Associate Professor in the Department of Chemistry, University of Massachusetts Boston. He received his B.S. degree from Nanjing University and Ph.D. degree from the University of Pittsburgh in 1993 under the supervision of the late Professor Paul Dowd. After a two-year appointment at the same university as a Research Assistant Professor, he joined DuPont Agricultural Products in 1995. In 2001 he joined the newly founded Fluorous Technologies, Inc. and later became the Director of Discovery Chemistry. Dr. Wei Zhang has published around 100 peer-reviewed articles on the topics of fluorous reactions and separations, synthesis of drug-like molecules and natural product analogs, parallel and high-throughput synthesis, free radical chemistry, and microwave-assisted reactions. This is his third article in *Chemical Reviews*. He received Global Technology Accomplishment Award from DuPont Agricultural Products in 1998 and HIV Drug Discovery and Development Research Award from GlaxoSmithKline in 2003. He is currently a Visiting Professor of Nanjing University of Science & Technology and an Associate Editor of *Molecular Diversity* (Springer).

rang of polymer-supported linkers are now commercially available for solid-phase organic synthesis.[1−7]

Perfluoroalkyl (fluorous) tags are lipophobic and hydrophobic.[8] The solvophobicity repulses the fluorous compounds away from organic or aqueous phases and makes them self-assembled in the fluorous phase. The unique solvophobicity and fluorophilicity[9] characteristics have been exploited in the development of fluorous linkers for solution-phase synthesis.[10−12] A fluorous linker has a perfluorocarbon tag (Rf) attached to the reactive functional group through a hydrocarbon spacer to minimize the electronic effect generated from the strong electron-withdrawing Rf group. In literature, fluorous linkers are also known as "fluorous protecting groups" or "fluorous tags".[13,14]

For a comparison, the structures of normal *p*-methoxybenzyl (PMB) group, the polymer-supported, and fluorous-supported versions of PMB are show in Scheme 1. The bifunctional fluorous PMB is similar to the polymer-supported PMB (Wang resin), except the phase tag is a perfluorinated alkyl group. Fluorous PMB also has a monofunctional version; the functional group is attached to the fluorous tag through a carbon−carbon bond.

The utility of fluorous linkers is to anchor substrates for solution-phase reactions, similar to that of polymer-linkers used in solid-phase synthesis. Fluorous linkers are real molecules and have defined structures and molecular weights. In contrast, polymer linkers are functional materials, which have batch-dependent loading and relatively short shelf life. In addition, fluorous linkers have the following advantages for the solution-phase synthesis: (1) reasonable solubility in common organic solvents at room or elevated temperatures; (2) favorable homogeneous solution-phase reaction kinetics;[15] (3) no residue functional groups that usually exist in the polymer-supported linkers; (4) easy intermediate analysis by conventional tools such as TLC, NMR, MS, and HPLC; (5) quick adaptation of literature synthetic procedures; and (6) capability for linker recycle.

This Review covers the utilities of fluorous linkers for the synthesis and separation of small molecules and biomolecules such as peptides, oligosaccharides, and oligonucleotides.[16] The use of fluorous permanent linkers for microarray screening, enzymatic reactions, and making fluorous polymers and nanomaterials are not the focal points of this article.

1.2. Fluorous Protective, Displaceable, and Safety-Catch Linkers

Fluorous linkers can be used for protection of functional groups and as the "phase tags" for fluorous separations. This "kill two birds with one stone" strategy increases the efficiency of fluorous synthesis. Depending on the way of linker cleavage, fluorous linkers can be classified into following three categories: (1) protective linkers, (2) displaceable linkers, and (3) safety-catch linkers.

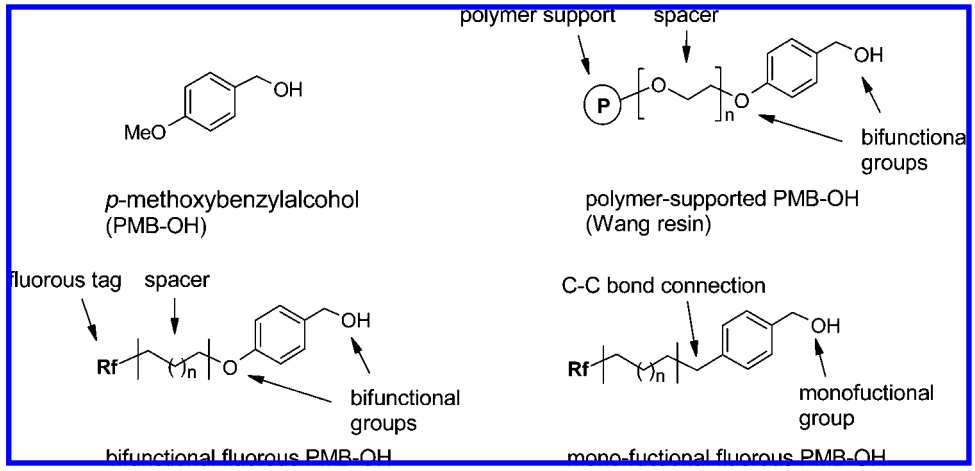
Fluorous protective linkers structurally resemble the common protecting groups such as TIPS, Boc, Fmoc, PMB, and Cbz. They are employed to protect amino, hydroxyl, carboxyl and other functional groups. The protected functional group X−Y can be regenerated after the linker cleavage (Scheme 2). Fluorous protective linkers are suitable for multistep syntheses that require the protection of functional groups. In most cases, reaction conditions developed for the attachment and cleavage of normal protecting groups can be readily applied to reactions involving fluorous protective linkers.

Fluorous displaceable linkers are able to convert the original functional group X−Y to a new group X−Z after the linker cleavage (Scheme 3).[7] The fluorous sulfonyl linker, for example, can convert phenols to biaryl groups after the cleavage by Suzuki coupling reactions (Section 3.2). Displaceable linkers are useful for diversity-oriented synthesis (DOS) to introduce new functional groups. If the fluorous displaceable linkers are cleaved *via* cyclization, they can build a new ring to increase the structure complexity of the final product. Fluorous alcohol-attached carboxylic esters can be cleaved by cyclization to generate *N*-heterocyclic compounds (Section 3.7). In literature many displaceable linkers are mistakenly called as traceless linkers. According to IUPAC "Glossary of terms used in combinatorial chemistry",[17] traceless linkers only produce the C−H bonds and leave no other functional residue after cleavage.

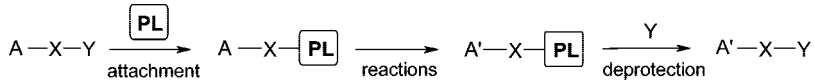
Safety-catch linkers are stable under a wide range of reaction conditions and can only be cleaved after activation (Scheme 4).[18] The linker cleavage requires two steps to secure the safety of attached functional groups in the multistep reaction sequence. The alkylthio and arylgemanyl linkers described in Section 4 belong to this class. The former one is activated by oxidation, and the later one is activated by photolysis.

Some fluorous linkers have multiple utilities. The benzaldehyde linker, for example, can attach to an amine group through reductive amination (Section 2.1.7) or attach to a diol through acetalization (Section 2.2.9). In some cases, a protective linker can also be used as a displaceable linker. The silyl linker for protection of hydoxy groups (Section 2.2.1) can be used to attach aryl halide groups and cleaved in a traceless fashion (Section 3.9). The PMB-OH linker for the protection of carboxylic acids (Section 2.3.3) can lead

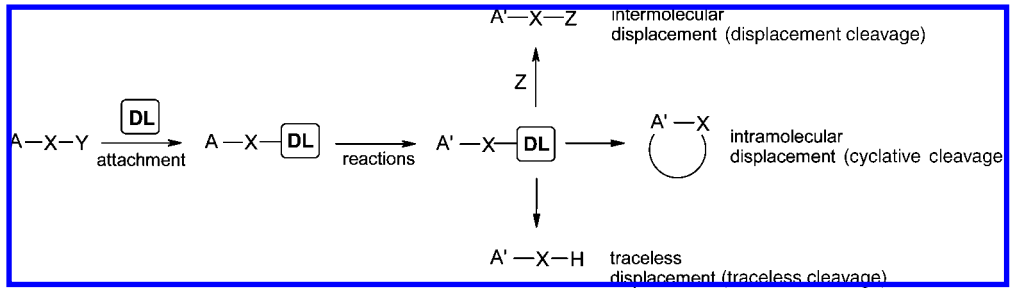
Scheme 1. PMB-OH, Polymer- and Fluorous-Supported PMB-OH Linkers



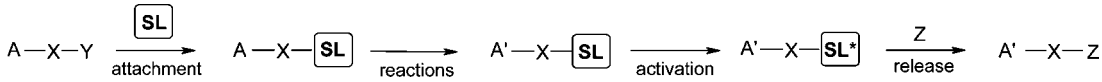
Scheme 2. Fluorous Protective Linker (PL)



Scheme 3. Fluorous Displaceable Linker (DL)



Scheme 4. Fluorous Safety-Catch Linker (SL)



to the formation of lactams, uraciles, or other *N*-heterocyclic compounds through cyclative cleavage (Section 3.7).

1.3. Linkers with Heavy and Light Fluorous Tags

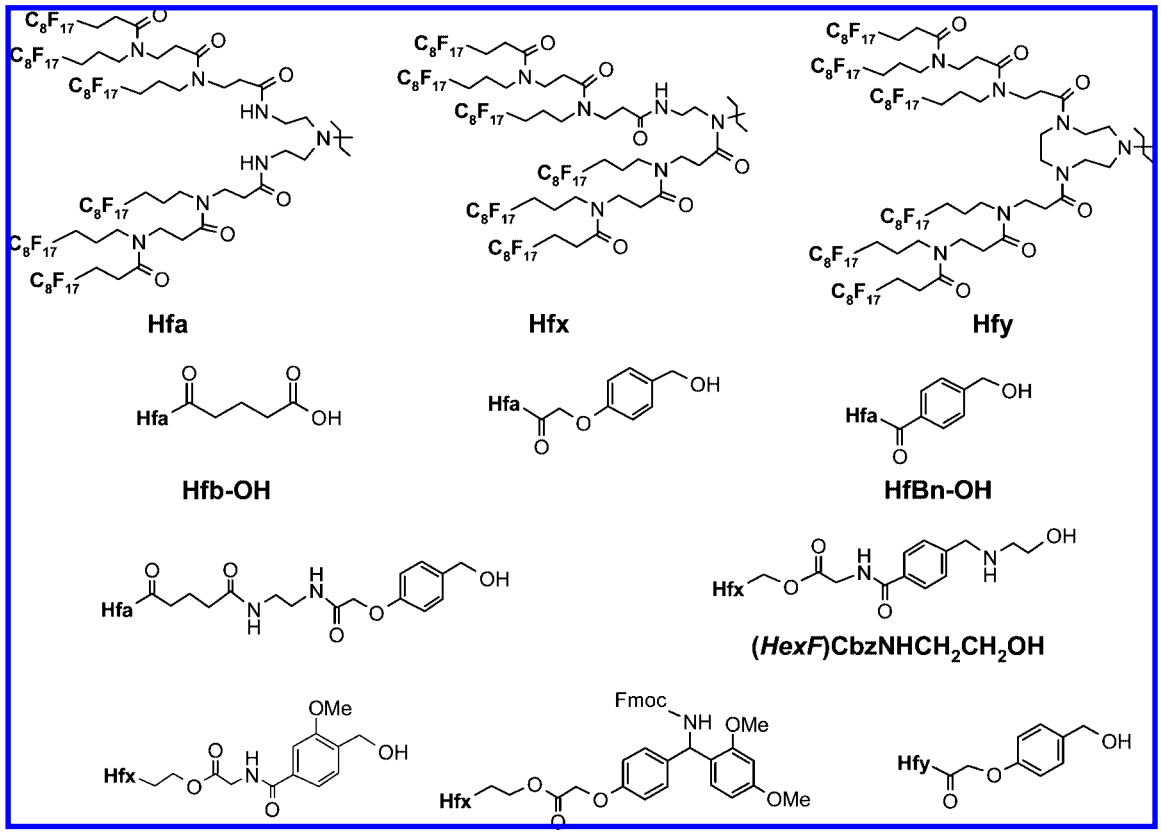
Heavy fluorous tags possess multiple perfluoralkyl chains. More than 60% molecular weight of heavy fluorous molecules come from the fluorine atoms.[19,20] The reaction and purification of heavy fluorous molecules usually requires fluorous solvents. At the step of fluorous liquid−liquid extraction (F-LLE), heavy fluorous molecules have good partition coefficiency in a fluorous solvent. However, at the homogeneous solution-phase reaction step, heavy fluorous molecules may have low miscibility with nonfluorous reactants and solvents. Using a fluorous cosolvent and heating up the reaction system are two ways to achieve a homogeneous reaction environment. In the synthesis of oligomers such as peptides and oligosaccharides, with the progress of iterated coupling reactions, molecular weights of the oligmers are increased and the fluorine content of the oligomers as well as their partition coefficiencies in the fluorous phase are decreased. A series of linkers with very heavy fluorous tags have been developed for the F-LLE-based synthesis of biomolecules (Scheme 5).[21]

The haircut of the heavy fluorous ponytails produces light fluorous tags that only have one or two perfluoroalkyl chains. Since light fluorous substrates have better solubilities in common organic solvents, their reactions can be carried out in MeOH, CH_2Cl_2, THF, DMF, toluene and other common organic solvents. Light fluorous molecules have low partition coefficiencies for F-LLE, but they can be well retained on fluorous silica gels by solid-phase extraction (SPE) when eluted with a fluorophobic solvent such as 80:20 MeOH-H_2O. In light fluorous synthesis, neither the reaction nor the separation steps require fluorous solvents. Compared to heavy fluorous linkers, light fluorous linkers are easier to make and more cost-effective to use. Their reactions can be conducted under a wide range of solution-phase conditions. The heavy and light fluorous PMB-OH linkers are shown in Scheme 6. The heavy fluorous PMB-OH linker containing 102 fluorine atoms has been used for F-LLE-based peptide synthesis. The light fluorous PMB-OH linker containing 17 fluorine atoms has been used for F-SPE-based peptide synthesis.

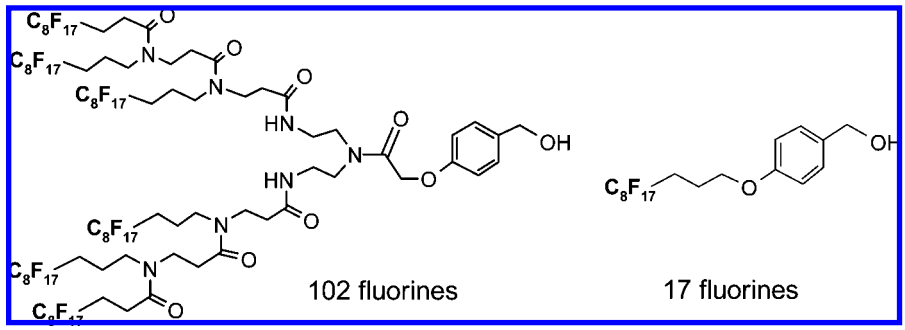
1.4. Fluorous Liquid−Liquid Extraction (F-LLE)

The fluorous phase is orthogonal to organic and aqueous phases. The temperature-dependent miscibility of fluorous solvents with organic solvents has been utilized in homogeneous reactions and organic-fluorous biphasic liquid−liquid extractions. If water-soluble inorganic salts are involved, an organic-aqueous-fluorous triphasic extraction system can be

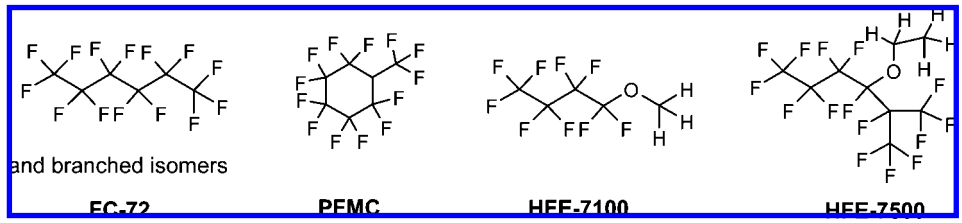
Scheme 5. Heavy Fluorous Tags (Hfa, Hfx, and Hfy) and Attached Linkers



Scheme 6. Heavy (left) and Light (right) Fluorous PMB Linkers



Scheme 7. Common Fluorous Solvents

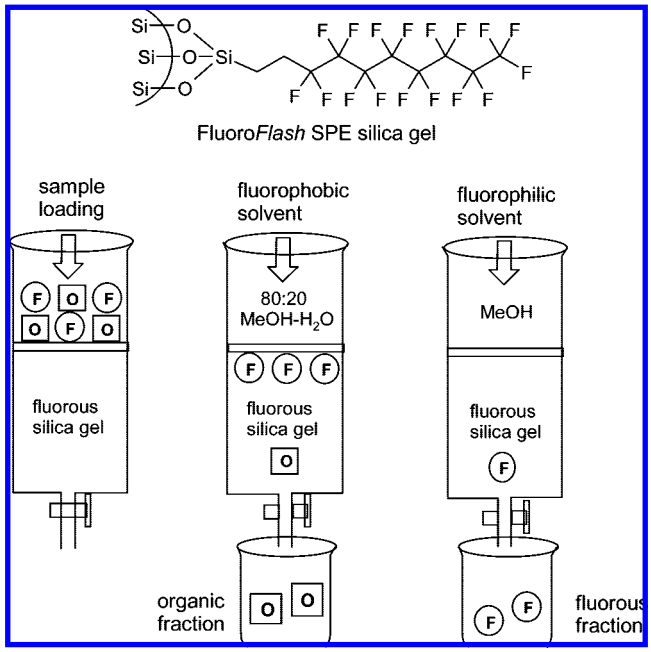


used for the product purification. F-LLE relies on heavy fluorous molecules to ensure good partition coefficiency in fluorous solvents. Perfluorohexanes (FC-72), perfluoromethylcyclohexane (PFMC), perfluorobutylmethylether (HFE-7100), perfluorobutylethylether, and $C_3F_7CF(OC_2H_5)CF(CF_3)_2$ (HFE-7500) are the common fluorous solvents for F-LLE (Scheme 7).[22]

1.5. Fluorous Solid-Phase Extraction (F-SPE)

Fluorous silica gels are commercially available from Fluorous Technologies, Inc. (FTI), Silicycle, and Fluka. The Fluoro*Flash* silica gels from FTI have been applied to both F-SPE and F-HPLC applications. Fluoro*Flash* silica gel for F-SPE has a $C_8F_{17}CH_2CH_2Si$- stationary phase, which is derived from $C_8F_{17}CH_2CH_2SiCl_3$. F-SPE separates light fluorous molecules from nonfluorous molecules.[23] The crude reaction mixture as a slurry or a solution in minimal amount of solvent is loaded onto the SPE cartridge. The cartridge is first eluted with a fluorophobic solvent such as 80:20 MeOH/H_2O for the nonfluorous compounds. It is then eluted with a more fluorophilic solvent such as MeOH, acetone, acetonitrile, or THF for fluorous compounds. The suggested

Scheme 8. Schematic Diagram of F-SPE



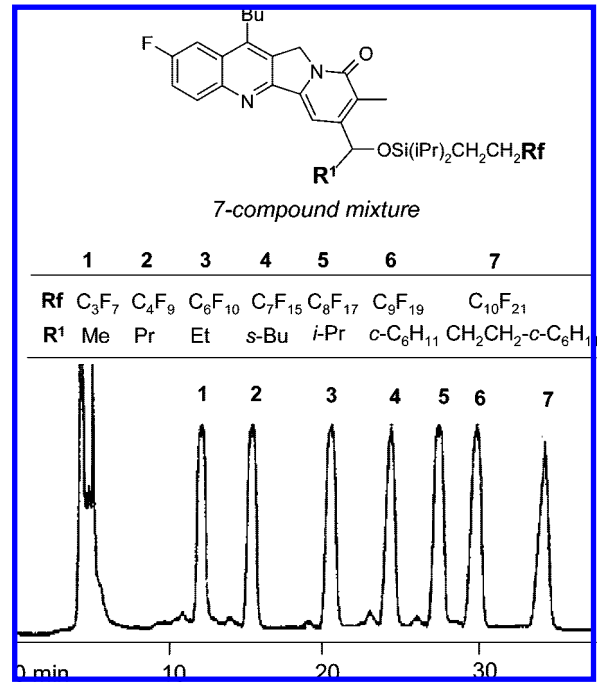
loading for F-SPE separation is around 5%. The cartridge can be conditioned by washing with the fluorophilic solvents for reuse. In addition to single cartridge F-SPE, 24- and 96-well plate-to-plate F-SPE, and automated F-SPE have been developed for parallel and high-throughput syntheses.[24−26] Large scale F-SPE on commercial available flash chromatography systems (such as Isco and Biotage) has also been used for purification of fluorous intermediates. Scheme 8 shows the F-SPE separation of a mixture containing organic and fluorous components. The nonfluorous component is washed out by 80:20 MeOH/H_2O (middle tube). The fluorous component is retained until washed with 100% MeOH (right tube).

F-SPE has another version called reverse F-SPE.[27] It uses normal-phase silica gel as the packing material and fluorous solvents as the mobile phase. The fluorous compounds are eluted with a highly fluorinated solvent and collected as the first fraction. The nonfluorous compounds are retained on the cartridge until washed with a polar organic solvent. The elution order of fluorous and nonfluorous compounds is reversed from that in normal F-SPE. The reverse F-SPE is good for the separation of mixtures containing fluorous molecules with low polarity. If the fluorous compounds are relatively polar, the retention on the normal-phase silica gel will compete with the elution with the fluorinated solvent.

1.6. Fluorous High Performance Liquid Chromatography (F-HPLC)

Fluoro*Flash* HPLC grade silica gel has a $C_8F_{17}CH_2CH_2Si$- stationary phase. F-HPLC has much better resolution than F-SPE so it is capable of separating a mixture containing different fluorinated compounds.[28,29] Molecules with a higher fluorine content have a longer retention time on the column. A typical F-HPLC mobile phase is a MeOH-H_2O gradient. Other solvents such as MeCN or THF can be used to replace MeOH for gradient elution. In addition to the analysis of fluorous compound mixtures, F-HPLC has been used in fluorous mixture synthesis (FMS) for the separation of small molecules and oligomers (Section 5). Scheme 9 shows a semipreparative scale F-HPLC to separate a seven-component mixture of mappicine analogs with different R^1 paired with different fluorous Rf tags.[30]

Scheme 9. Semi-Preparative HPLC Separation of a Seven-Component Fluorous Mixture[a]



[a] Fluophase-RP column (20 × 250 mm, 5 μm), flow rate 12 mL/min; gradient 88:12 MeOH−H_2O to 100% MeOH in 28 min, then to 100% THF. From ref 30.

2. Synthetic Applications of Fluorous Protective Linkers

Fluorous protective linkers are primarily used to protect amino, hydroxyl, and carboxyl functional groups (Table 1). These functional groups can be regenerated after the linker cleavage. Fluorous protective linkers are particularly suitable for multistep syntheses requiring functional group protections. Because the fluorous linkers are the analogs of the normal protecting groups, common attachment and cleavage reaction conditions can be applied to reactions of fluorous protective linkers.

2.1. Amino Group Protections

Normal amino group protecting agents and related polymer-supported linkers are popular in solution-phase and solid-phase syntheses. A series of fluorous linkers related to Boc, Cbz, Fmoc, Msc, benzaldehyde, and sulfonyl groups have been developed for solution-phase parallel synthesis and fluorous mixture synthesis (Section 5).

2.1.1. t-Butyloxycarbonyl (Boc)-Type Linkers

The Curran group introduced the F-BocON and demonstrated its utility in the parallel synthesis of a small library of isonipecotic acid derivatives **4** (Scheme 10).[31] The amino group of the isonipecotic acid was first protected with the F-Boc under conventional solution-phase reaction conditions. The fluorous intermediate **1** was coupled with eight amines (R^1NHR^2) to give **2**. After F-Boc deprotection with TFA,

Table 1. Protective Linkers

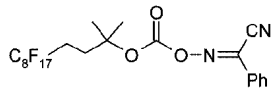
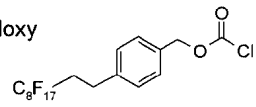
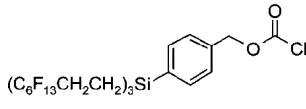
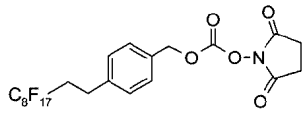
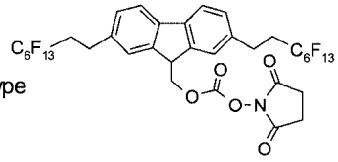
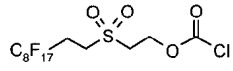
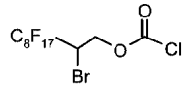
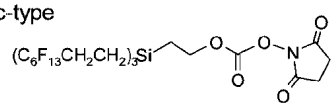
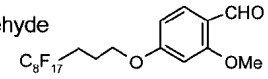
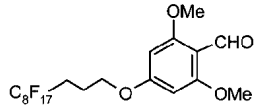
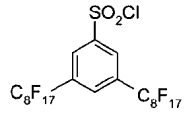
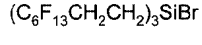
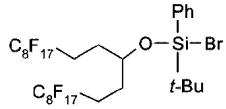
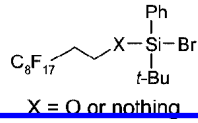
Fluorous linker	Structure	Separation method	Attach to	Conditions for attachment	Conditions for cleavage	Ref
Boc-type		F-SPE	Amines Amino acids	THF	TFA, CH_2Cl_2	31-34
Carbobenzyloxy (Cbz-type)		F-HPLC	Amines Amino acids	DIPEA	98:2 TFA-H_2O	35
		F-LLE	Amines Amino acids	DIEPA or Et_3N THF	Et_3N, DMF	36,37
		F-SPE	Amines Amino acids	Et_3N THF-H_2O	H_2, Pd-C MeOH	38,39
Fmoc-type		F-SPE	Amines Amino acids	Et_3N 90% aq. MeCN		40
Msc-type		F-SPE F-HPLC	Amines Amino acids	aq.$NaHCO_3$	Zn, Ac_2O Et_3N	41
Froc		F-SPE	Amines Amino acids	$NaHCO_3$, H_2O	Zn, Ac_2O/Et_3N	42
Teoc-type		F-LLE	Amines Amino acids	Et_3N,THF-H_2O	TBAF, THF	43
Benzaldehyde		F-SPE	Amines	$NaBH(OAc)_3$ CH_2Cl_2	TFA, TES, H_2O	44
		F-SPE	Amines	$NaBH(OAc)_3$ CH_2Cl_2	90:5:5 TFA-H_2O-DMS	45
Arylsulfonyl		F-SPE	Amines	DMAP, Et_3N, CH_2Cl_2	Mg, NH_4Cl 1:1 THF-MeOH	47,48
Silyl		F-LLE	Alcohols	Et_3N, THF	HF-pyridine	49
		F-LLE	Alcohols Saccharides	NEt_3, DMAP CH_2CH_2, rt	TBAF, THF	50
	 X = O or nothing	F-SPE	Alcohols	Et_3N, DMAP CH_2CH_2	TBAF, THF	51-54

Table 1. Continued

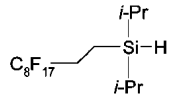
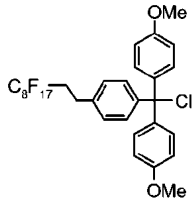
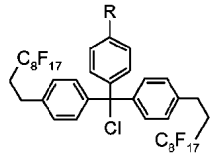
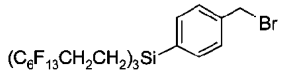
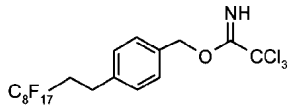
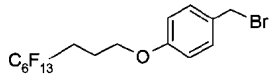
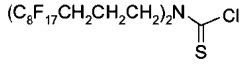
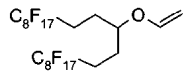
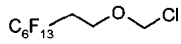
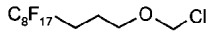
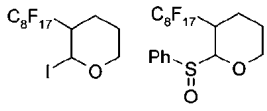
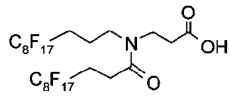
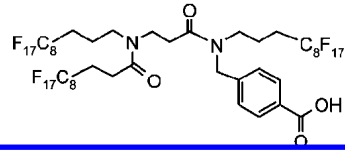
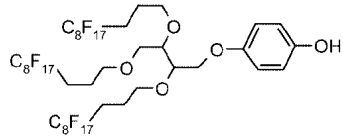
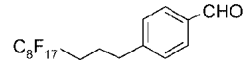
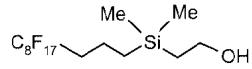
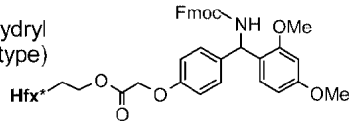
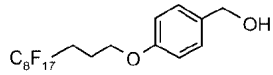
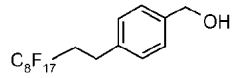
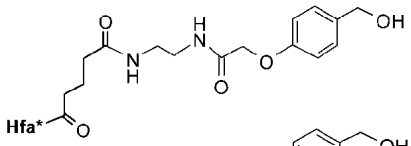
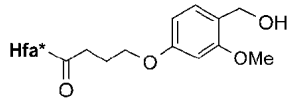
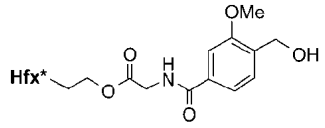
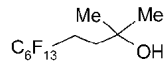
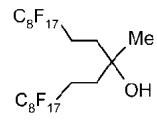
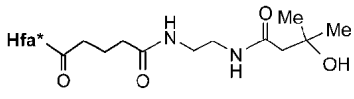
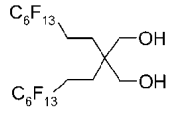
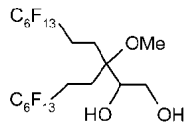
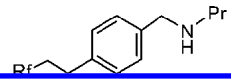
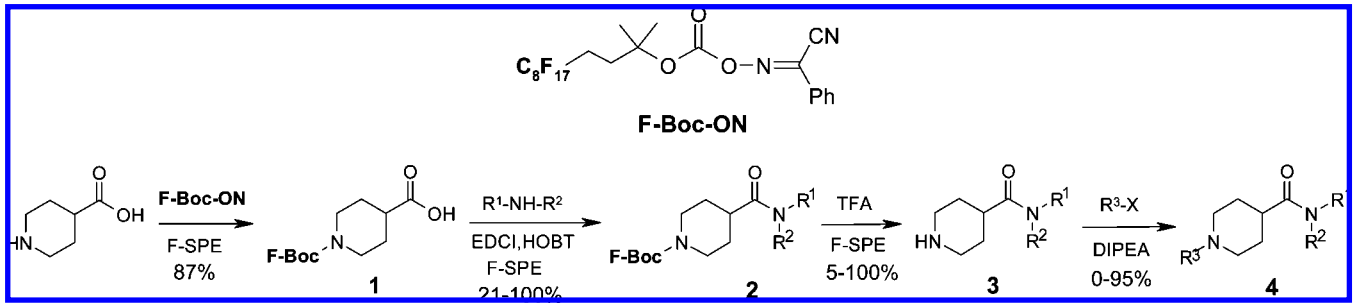
Fluorous linker	Structure	Separation method	Attach to	Conditions for attachment	Conditions for cleavage	Ref
TIPS-type		F-SPE	Alcohols	TfOH, 2,6-lutidine CH_2Cl_2	HF-pyridine THF	30,55,56 116,140
Trityl-type		F-SPE	Alcohols Saccharides	pyridine	3% TFA	57
		F-LLE	Alcohols Saccharides	pyridine	acidic	58
Benzyl		F-LLE	Alcohols Saccharides	NaH, TBAI DMF, BTF	$H_2/Pd(OH)_2$ FC-72	59
		F-SPE	Alcohols	cat. CSA CH_2CH_2	DDQ 2:1 CH_2Cl_2/H_2O	60
PMB-type		F-HPLC	Alcohols	*t*-BuOK, THF	DDQ	124,133
DMTC-type		F-SPE	Alcohols Saccharides	NaH, THF	*m*CPBA CH_2Cl_2 $KHCO_3$	61
Alkoxyethyl		F-LLE	Alcohols Amines	cat. CSA Et_2O or THF	cat. CSA Et_2O, MeOH	62
MOM-type		F-SPE	Alcohols	DIPEA, DMF	TMSBr, CH_2Cl_2	63
		F-SPE	Alcohols	DIPEA, CH_2Cl_2	$ZnBr_2$-BuSH CH_2Cl_2	64
THP-type		F-SPE	Alcohols	Cp_2ZrCl_2, $AgClO_4$ CH_2Cl_2, 4 A MS	TsOH, MeOH, THF	65
Carbonyl		F-LLE	Alcohols Saccharides	DCC, DMAP CH_2CH_2	NaOMe, Et_2O MeOH	21i 21b 21f
		F-LLE	Alcohols	DCC, DMAP CH_2CH_2	NaOMe, Et_2O MeOH	66

Table 1. Continued

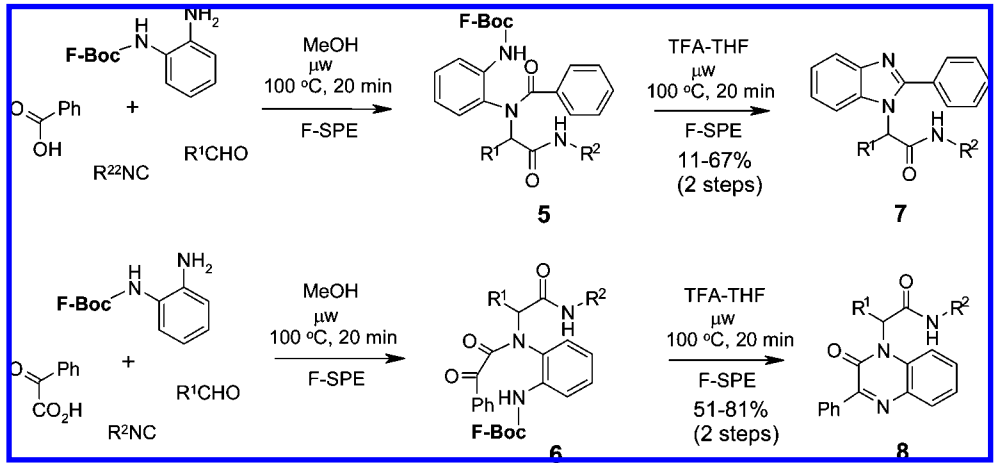
Fluorous linker	Structure	Separation method	Attach to	Conditions for attachment	Conditions for cleavage	Ref
Phenole		F-LLE	Acetylated alchol	BF_3.OEt_2 CH_2Cl_2-$MeOC_4F_9$	$ZnBr_2$, CH_2Cl_2	67
Benzaldehyde		F-SPE	Diols Saccharides	$CH(OMe)_3$ *p*-TsOH-H_2O Na_2SO_4, MeCN	aq AcOH or 10% Pd/C, H_2	68 128 129
TMSE-type		F-SPE	Carboxylic acids	DIC, HOBt DMAP, CH_2CH_2	TBAF, BnBr 4 Å MS, THF	69
Benzhydryl (Rink-type)		F-LLE	Carboxylic acids	PyBOP, DIPEA C_4F_9OEt, CH_2CH_2	95% TFA, 2.5% H_2O, 2.5% 1,4-butanedithiol	70 21f 21h
PMB-type		F-SPE	Carboxylic acids	EDCI, DMAP CH_2CH_2	$Pd(OH)_2$, H_2 *t*-BuOH	71
Benzyl		F-SPE	Amino acids			72
		F-LLE	Amino acids			70
		F-LLE	Amino acids	DCC, DMAP C_4F_9OEt-CH_2CH_2	95% TFA	73
		F-LLE	Amino acids	DIC, DIPEA DMAP CH_2CH_2-$EtOC_4F_9$	95% TFA	21f 21h
t-Butyl-type		F-SPE	Carboxylic acids	DCC, DMAP CH_2CH_2	TFA	74
		F-LLE	Caboxylic acids	DCC, DMAP CH_2CH_2	TFA	74
		F-LLE	Carboxylic acids			70
Diol		F-LLE	Ketones Aldehydes	*p*-TsOH Me_3Ph	2N HCl acetone	75
		F-LLE	Ketones Aldehydes	*p*-TsOH CF_3Ph	aq. HOAc	76
Benzylamine		F-HPLC	Diazonium salts	K_2CO_3, MeCN	HBF_4-OMe_2	136

* Hfa and Hfx are heavy fluorous tags shown in Scheme 5.

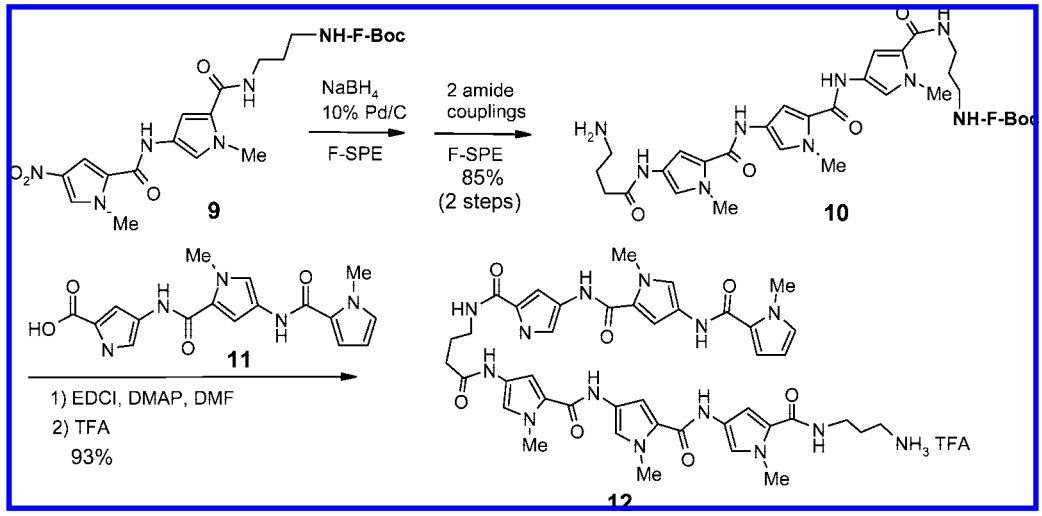
Scheme 10. F-Boc-Facilitated Synthesis of Amides



Scheme 11. Fluorous-Facilitated Synthesis of Benzimidazoles and Quinoxalinones



Scheme 12. F-Boc-Facilitated Synthesis of Hairpin Polyamide

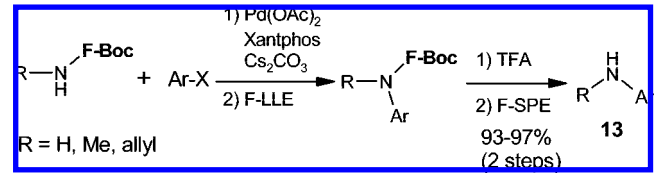


resulting compounds **3** were further reacted with twelve electrophiles (R^3X) to give 96 isonipecotic acid derivatives **4**.

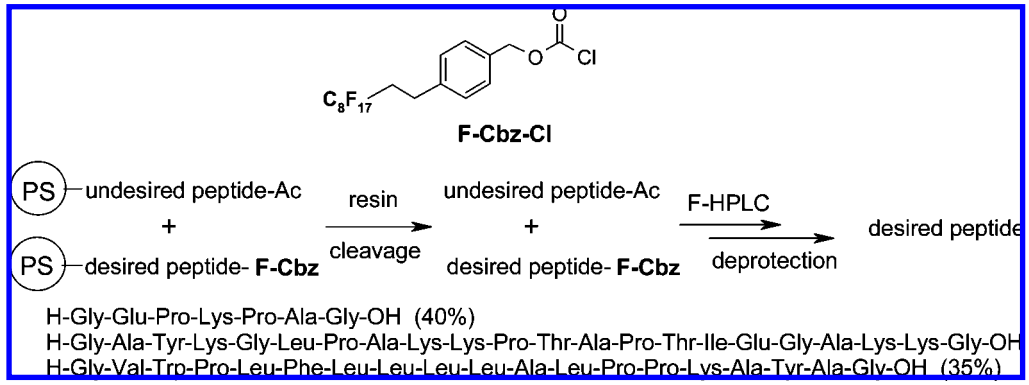
Using microwave-assisted fluorous synthesis, Zhang and Tempest improved the efficiency of the Ugi/de-Boc/cyclization method in the synthesis of benzimidazoles **7** and quinoxalinones **8** (Scheme 11).[32] Ugi reactions involving the F-Boc protected-aniline were completed in 20 min under microwave conditions. F-SPE isolated the condensation products **5** and **6** from the reaction mixture containing excess aldehydes and unreacted acids. The deprotection of F-Boc group with TFA and final product purification also benefited from the microwave-assisted fluorous synthesis.

The Firestine group applied F-Boc in the synthesis of a polyamide that is a minor groove binding agent related to biologically active distamycin. The target hairpin-kind product has a unique heterocycle-joined polyamide structure (Scheme 12).[33] The fluorous synthesis started from the reduction of the nitro group of F-Boc protected dipeptide **9** followed by the sequential amide coupling reactions to afford polyamide **10**. Hairpin polyamide **12** was prepared by coupling fluorous fragment **10** with nonfluorous fragment **11** followed by the cleavage of F-Boc.

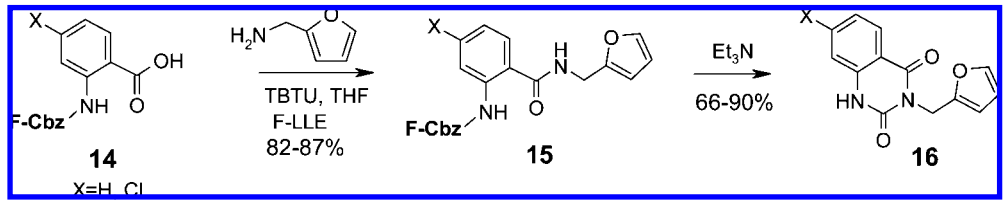
Scheme 13. F-Boc Facilitated Synthesis of Amides



Scheme 14. F-Cbz-Facilitated Synthesis of Peptides



Scheme 15. F-Cbz-Facilitated Synthesis of Quinazoline-2,4-diones



Trabanco and co-workers reported the F-Boc-assisted synthesis of anilines and *N*-substituted anilines (Scheme 13).[34] F-Boc-protected amines underwent Buchwald-Hartwig palladium-catalyzed amination-hydrolysis with arylhalides followed by the de-Boc to afford desired products **13**. The intermediates were purified by F-LLE with 4:1 MeOH/H_2O and HFE-7100. The final products were purified by F-SPE.

2.1.2. Benzyloxycarbonyl (Cbz)-Type Linkers

The utility of F-Cbz-type linkers was first reported by the van Boom group in the development of Fmoc-based solid-phase peptide synthesis (Scheme 14).[35] After each amide coupling step the unreacted free amine was capped with the acetyl group. Once the whole coupling sequence was completed, deprotection of the final Fmoc group followed by the attachment of the F-CbzCl gave the fluorous desired sequence. Resin cleavage gave a mixture containing desired fluorous product and acetyl-capped byproducts. The mixture was separated by F-HPLC. Peptides up to 22 amino acids were synthesized and purified using this method.

The Bannwarth group employed F-Cbz-protected analines in the synthesis of quinazoline-2,4-diones **16** (Scheme 15).[36] Amide coupling of fluorous protected acid **14** followed by cyclative deprotection of **15** led to the formation of the desired heterocyclic ring. Products were purified by F-LLE. The Bannwarth group also reported the improved purification procedure using a fluorous silica gel to absorb the fluorous molecules and to eliminate the use of fluorous solvents in the reaction and separation processes.[37]

The Curran group reported the synthesis of eighteen F-Cbz-attached natural L-amino and eighteen synthetic D-amino acids (Scheme 16).[38] The L-amino acids were attached to the C_8F_{17} tag and the D-amino acids were attached to the C_6F_{13} tag. These protected amino acids are useful building blocks for fluorous synthesis of small molecules and peptides.

Microfluidic devices have the advantages of favorable reaction kinetics, easy automation, and high-throughput for a parallel process. Li and his co-workers designed a microfluidic chip device for F-SPE of fluorous Cbz-tagged amino acids.[39] A mixture of F-Cbz tagged and nontagged amino acids was carried into the F-SPE chamber through an electrokinetic pump and successfully separated by F-SPE. The F-SPE microchips showed good reproducibility and efficiency. This work demonstrates that fluorous techniques can be utilized in microfluidic devices and opens a new avenue for fluorous applications.

Application of Cbz-type linkers for fluorous mixture synthesis of tecomanine-like and fused-tricyclic hydantoin-type compound libraries are descried in Section 5.2.1.

2.1.3. Fluorenylmethoxycarbonyl (Fmoc)-Type Linkers

Fmoc is an important amino group protecting agent. The Matsugi and Curran groups introduced the double fluorous chain-attached Fmoc-OSu for protection of amino acids **17** (Scheme 17).[40] Those fluorous amino acids have potential utility in the synthesis of bioconjugates such as peptides and glycopeptides.

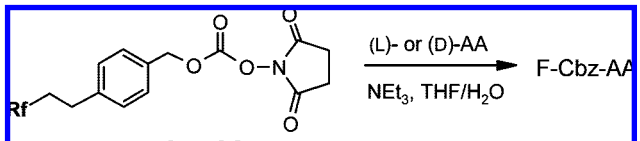
2.1.4. Methylsulfonylethoxycarbonyl (Msc)-Type Linkers

In the development of F-Cbz described above,[35] the van Boom group found that F-Cbz was partially deprotected during acidic resin cleavage. To address this issue, Overkleeft and co-workers developed a base-labile fluorous methylsulfonylethoxycarbonyl (F-Msc) as an alternative amine protecting group.[41] Separations of resin cleaved mixtures were conducted by F-HPLC or F-SPE (Scheme 18). F-SPE gave good results for peptides **18** and **19**, whereas F-HPLC succeeded in all three cases of **18**−**20**.

2.1.5. Trichloethoxycarbonyl (Froc) Linkers

Manzoni and Castelli modified the structure of 2,2,2-trichloroethoxycarbonyl (Troc) and developed a Froc linker for amino group protection in peptide and carbohydrate synthesis (Scheme 19).[42] In the synthesis of a disaccharide, Froc-protected glucosamine **21** was peracetylated with Ac_2O. The acetyl group in the anomeric position was removed by hydrazinium acetate and protected with

Scheme 16. Synthesis of F-Cbc-Attached Amino Acids



F-Cbz-AA	yield (%)*	F-Cbz-AA	yield (%)*
(L)-Ala	81 (58)	(D)-Ala	92
(L)-Val	89 (46)	(D)-Val	95
(L)-Leu	84 (52)	(D)-Leu	85
(L)-Ile	89 (66)	(D)-Ile	89
(L)-Ser	100 (69)	(D)-Ser	80 (69)
(L)-Phe	97	(D)-Phe	95
(L)-Asn	92	(D)-Asn	92
(L)-Gln	97	(D)-Gln	97
(L)-Thr	82 (65)	(D)-Thr	88 (72)
(L)-Met	84 (70)	(D)-Met	95
(L)-Asp	61 (38)	(D)-Asp	97
(L)-Gle	92 (39)	(D)-Gle	85 (83)
(L)-Trp	83 (67)	(D)-Trp	72 (64)
(L)-Tyr	92 (69)	(D)-Tyr	92 (66)
(L)-Pro	87	(D)-Pro	81

*crude (recrystalized)

texyldimethylsilyl group to afford **22**. Removal of the remaining acetyl groups followed by the treatment of the crude product with benzaldehyde dimethylacetal afforded the fluorous glycosyl acceptor **23**. This compound was glycosylated with tetraacetylatylgalactose trichloroacetimidate, followed by the cleavage of the Froc group, to afford the final disaccharide **24**.

2.1.6. 2-(Trimethylsilyl)ethoxycarbonyl (Teoc)-Type Linkers

Takeuchi and co-workers developed a heavy fluorous 2-[tri(perfluorodecyl)silyl]-ethoxycarbonyl (F-Teoc)-type linker and used it in the synthesis of bistratamide H, a unique macrolactam its analogs have moderate cytotoxic activity and antimicrobial properties. The F-Teoc has three $C_8F_{17}CH_2CH_2$ chains to ensure a good partition coefficiency of Teoc-attached substrates for F-LLE (Scheme 20).[43] Fluorous synthesis started from the coupling of F-Teoc-attached thiazole amino acid **25** with unprotected thiazole amino acid **26**. The resulting thiazole dipeptide ester **27** was hydrolyzed and then coupled with the oxazole amino acid methyl ester **28** to give tripeptide acid **29**. Cleavage of the F-Teoc group with TBAF, followed by the intramilecular coupling reaction and preparative TLC gave bistratamide H.

2.1.7. Benzaldehyde Linkers

Ladlow and co-workers developed an acid-labile fluorous benzaldehyde linker **30** for the parallel synthesis of sulfonamides **34** (Scheme 21).[44] The fluorous linker was attached to aryl bromides by reductive amination to form **31**. The Suzuki coupling reaction of **31** afforded **32**. Sulfonamidation products **33** were subjected to linker cleavage to yield biaryl sulfonamides **34** which has three points of diversity.

The Zhang group employed a fluorous benzaldehyde linker in the synthesis of sclerotigenin-type natural product analogs (Scheme 22).[45] Sclerotigenin is the simplest member of the benzodiazepine-quinazolinone natural alkaloid family. Other members in this family, such as circumdatins A-G and benzomalvins A-C, possess interesting biological activities. In the synthesis of sclerotigenin-type analogs, the fluorous benzaldehyde **35** was attached to amino esters by reductive aminations to form **36**. Amide coupling afforded **37** which then underwent a base-promoted cyclization to afford the benzodiazepinedinon ring system **38**. Sequential *N*-acylation, nitro group reduction, and cyclization yielded **39**. Linker cleavage of produced the benzodiazepine-quinazolinone scaffold **40**.

2.1.8. Arylsulfonyl Linkers

Bisindole natural alkaloids such as rebeccamycin and asteeriquinone B1 have antitumor activity and are the insulin receptor activators.[46] They have a unique structure, in that two indole units are linked through a central heterocyclic ring. To make synthetic bisindole analogs for a biological test, Kasahara and Kondo developed a concise fluorous route involving consecutive cross-coupling reactions of fluorous indolylborons with dichloro- or dibromosubstituted heterocyclic compounds (Scheme 23).[47] Fluorous sulfonyl linker-attached boronate **41** underwent consecutive Pd-catalyzed cross-coupling reactions with **42** and then with **44** to afforded **43** and **45**, respectively. Methylation and sequential Mg-promoted linker cleavage afforded bisindole **46**. This double cross-coupling protocol has been used to make symmetrical and asymmetrical bisindolyl-substituted heterocycle analogs by reactions of indolylborons with different kinds of dihalo central rings.

Since fluorous sulfonyl linkers have no acidic protons, it does not eliminate "HF" and thus is stable for the lithiation reaction. In the fluorous synthesis of yuehchukene reported by the Kondo group, the attached indole **47** was treated with mesityllithium and then reacted with the monoterpenoid aldehyde to give alcohol **48** (Scheme 24).[48] Oxidation of **48** with 2-iodoxybenzoic acid (IBX) followed by $BF_3 \cdot OEt_2$-catalyzed cyclization gave *cis*-hexahydroindeno[2,1-*b*]indol-6-one derivative **49**. The ketone was stereoselectivly reduced to alcohol using DIBAH and then condensed with indole to afford attached fluorous yuehchukene **50**. The fluorous linker was removed by treatment with TBAF.

2.2. Hydroxyl Group Protections

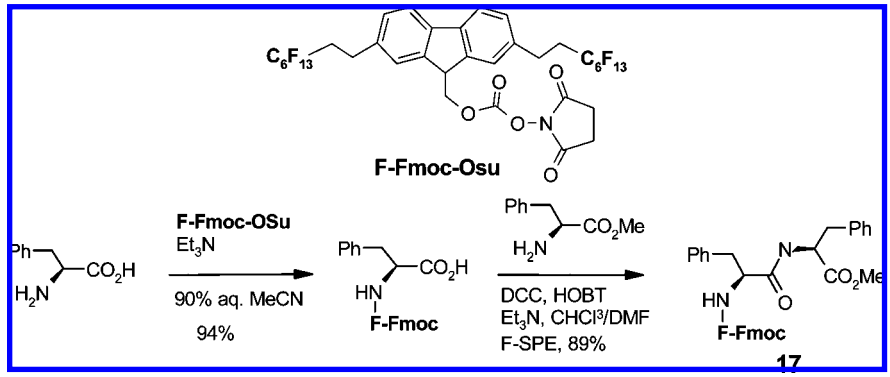
2.2.1. Silyl Linkers

Studer and Curran reported the synthesis of isoxazolines **51** and isoxazoles **52** by cycloadditions of nitrile oxides with fluorous silyl-protected allyl- and propargyl alcohols (Scheme 25).[49] An excess amount of nitrile oxides were used to drive the cycloaddition reaction to completion. Unreacted nitrile oxides were isolated by F-LLE with FC-72/benzene/H_2O. After HF-pyridine desilylation, the final products were purified by another F-LLE with FC-72/CH_2Cl_2/aq. NH_4Cl.

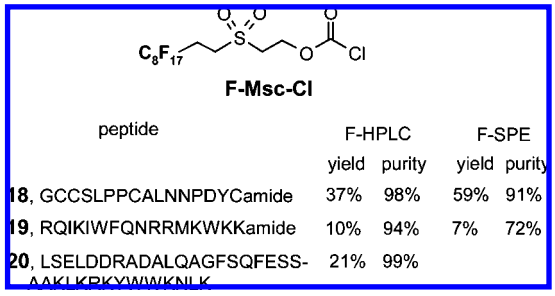
The normal fluorous silyl linkers are acid sensitive. Rover and Wipf developed more acid-stable fluorous alkyoxysilyl linkers with single or double fluorous chains (Scheme 26).[50] The alcohol protection and deprotection were evaluated and the linkers were found stable under acidic conditions and could be purified by F-LLE with FC-72/CH_3CN or by F-SPE.

The Wipf group employed fluorous silyl linkers in solid-phase synthesis of oxazoles and thioazoles analogs of curacin **56** (Scheme 27).[51] Resin-bound intermediates **53** prepared

Scheme 17. Synthesis of F-Fmoc-Attached Amino Acids



Scheme 18. F-Msc-Facilitated Synthesis of Peptides



peptide	F-HPLC yield	F-HPLC purity	F-SPE yield	F-SPE purity
18, GCCSLPPCALNNPDYCamide	37%	98%	59%	91%
19, RQIKIWFQNRRMKWKKamide	10%	94%	7%	72%
20, LSELDDRADALQAGFSQFESS-AAKLKRKYWWKNLK	21%	99%		

by multistep solid-phase synthesis were attached to the BPFOS linker. Resulting fluorous molecule **54** and unattached byproducts accumulated from the previous steps were cleaved from the polymer support. Fluorous product **55** was isolated by F-SPE and carried on for additional reactions to afford desired products **56**.

Tripathi and co-workers employed fluorous silyl-protected phosphoramidite **57** in the synthesis of oligonucleotides (Scheme 28).[52] The fluorous monomer was incorporated in the last synthesis cycle. The enhanced hydrophobicity of fluorous oligonucleotide sequences made them precipitate when suspended in water. Fluorous linker cleavage was achieved by treatment with tetrabutylammonium fluoride (TBAF) in THF, and the cleaved linker was isolated by F-LLE with FC-72 and H_2O. The products were further purified by HPLC. The same F-silyl linker has been used in the synthesis of oligodeoxyribonucleotides.

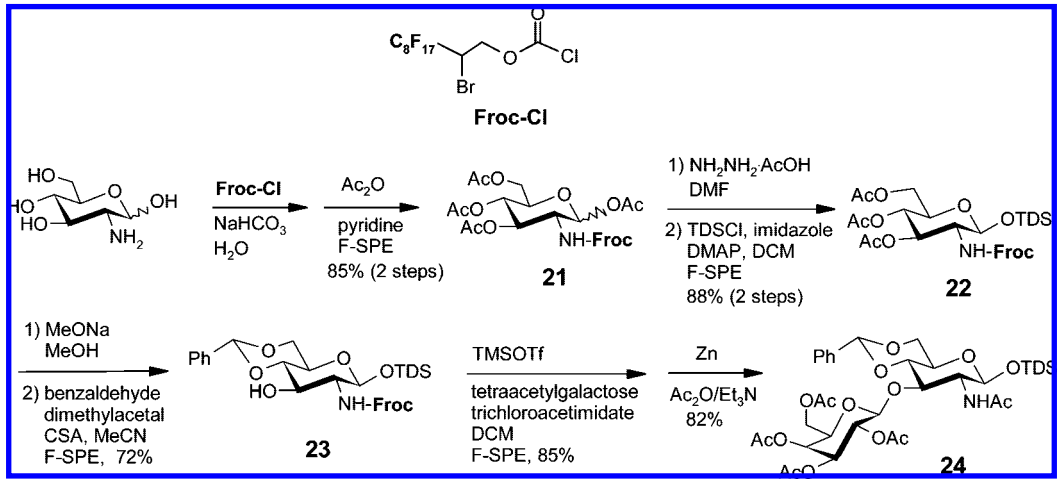
Manzoni utilized a fluorous silyl linker to synthesize trisaccharide Lewis a (Scheme 29).[53,54] The fluorous linker was attached to the anomeric hydroxyl group to form **58**. Removal of the acetyl groups from **58** followed by the treatment of the crude product with benzaldehyde dimethylacetal yielded the fluorous glycosyl acceptor **59**. This compound was subjected to glycosylation to form **60** followed by the second glycosylation and linker cleavage with TBAF to afford trisaccharide Lewis a.

Seeberger and co-workers employed fluorous TIPS-type reagent to cap the hydroxyl group of the deletion sequences in automated solid-phase synthesis of oligosaccharides (Scheme 30).[55] After resin cleavage, the desired sequence was separated from fluorous byproducts by HPLC. A much cleaner trisaccharide **61** was prepared by the fluorous capping strategy as compared to a similar synthesis without fluorous capping, where a significant amount of deletion sequences (*n*-1 and *n*-2) was observed.

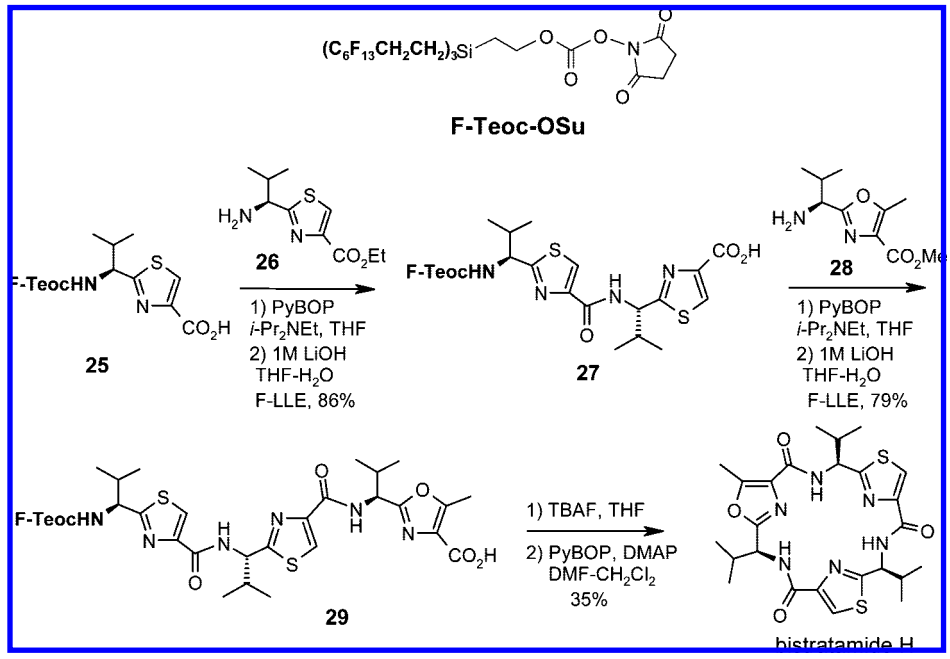
The Seeberger group also applied the fluorous TIPS-type linker to attach the desired sequence in solid-phase synthesis of oligosaccharides (Scheme 31).[56] After each glycosylation reaction, the deletion sequences were capped by a treatment of acetyl anhydride. The final desired sequence was attached with the fluorous TIPS. The mixture cleaved from the resin was subject to F-SPE to separate the fluorous desired sequence from the capped-nonfluorous deletion sequences. The cleavage of F-TIPS afforded the trisaccharide product **62**.

Applications of fluorous silyl linkers for qusiracemic mixture synthesis of enantiomers of pyridovericin and mappcine are described in Section 5.1.1; for the syntheses of diastereomers of dictyostatin, passifloricin A, and lagunapyrone B are described in Section 5.1.2.

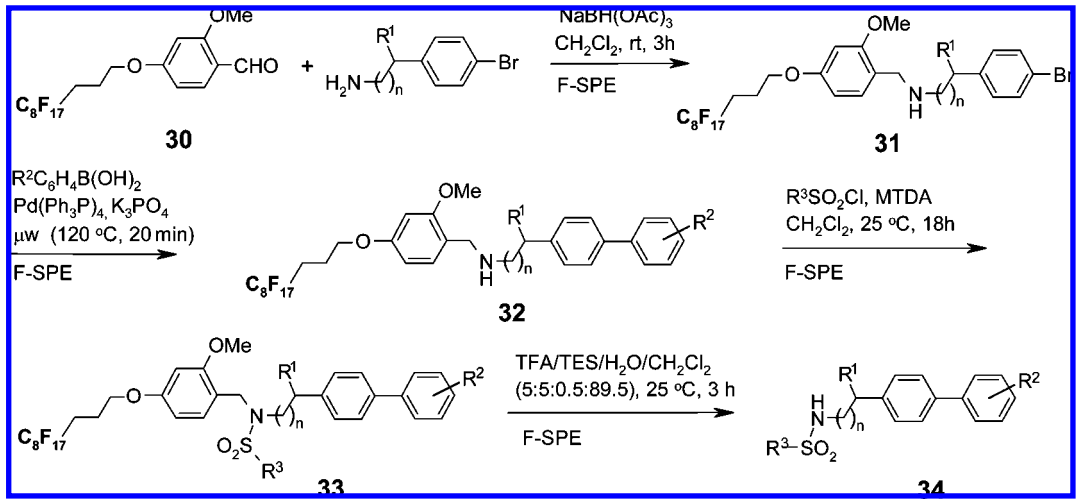
Scheme 19. Froc-Facilitated Synthesis of Trisaccharine



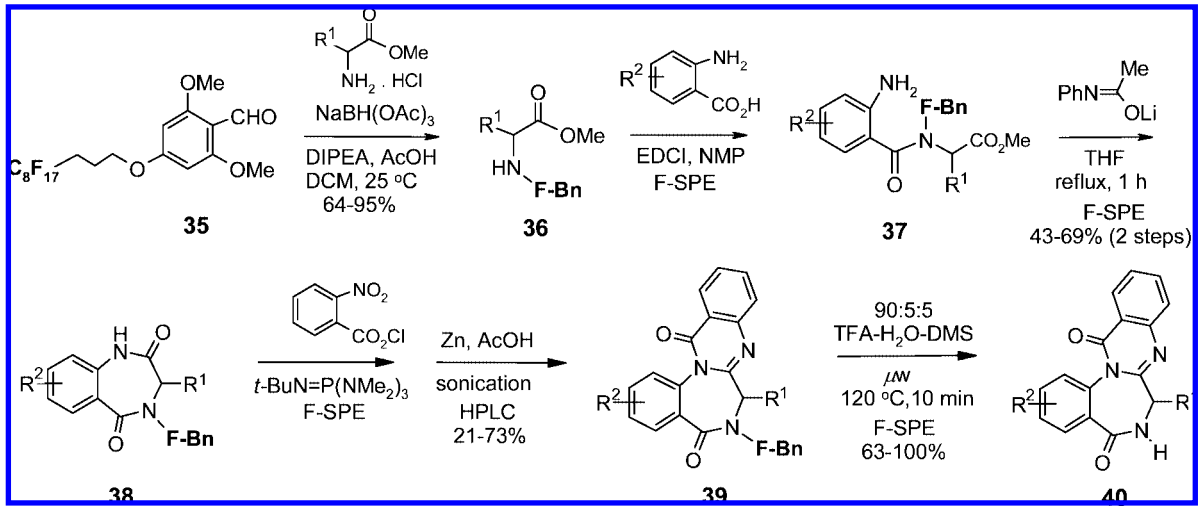
Scheme 20. F-Teoc-Facilitated Synthesis of Bistratamide H



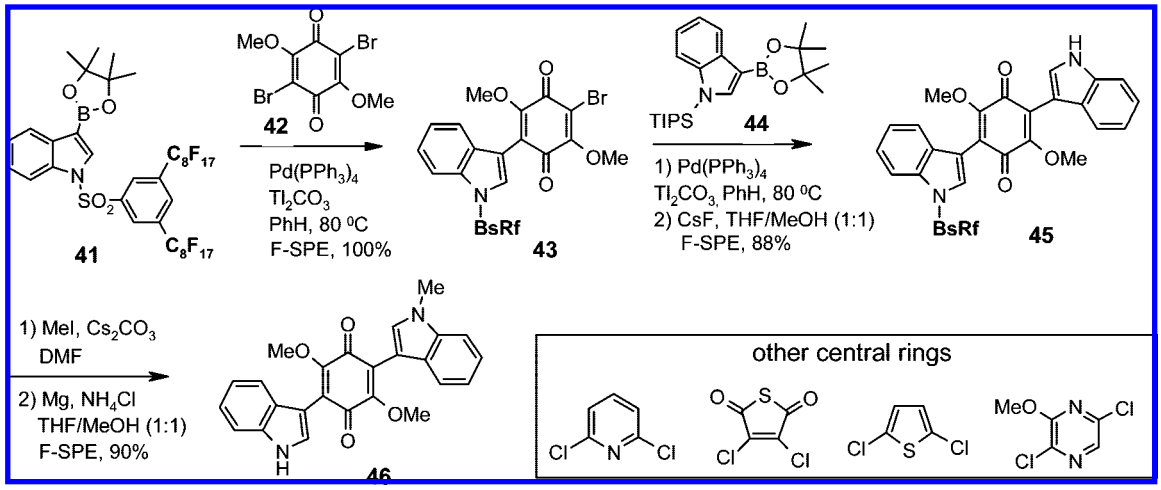
Scheme 21. F-PMB-Facilitated Synthesis of Sulfonamides



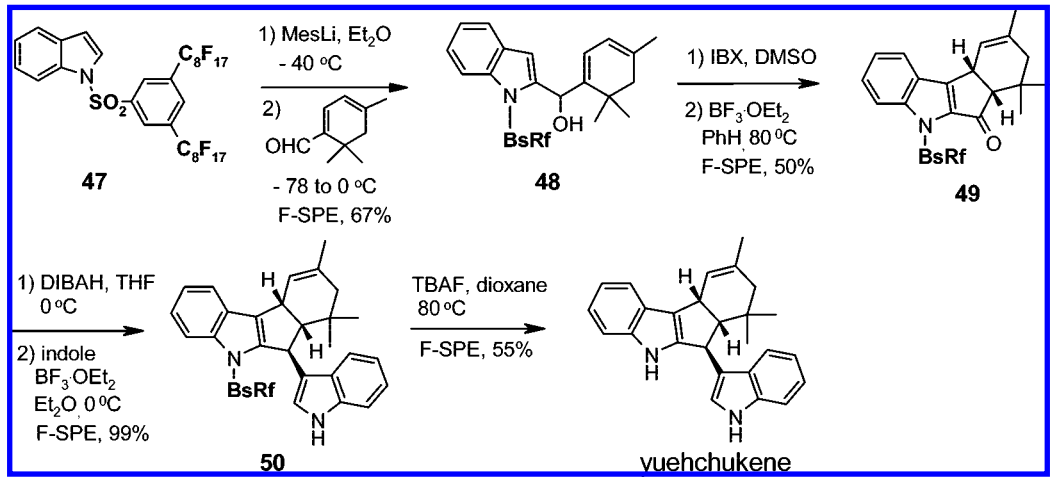
Scheme 22. F-PMB-Assisted Synthesis of Benzodiazepine-Quinazolinones



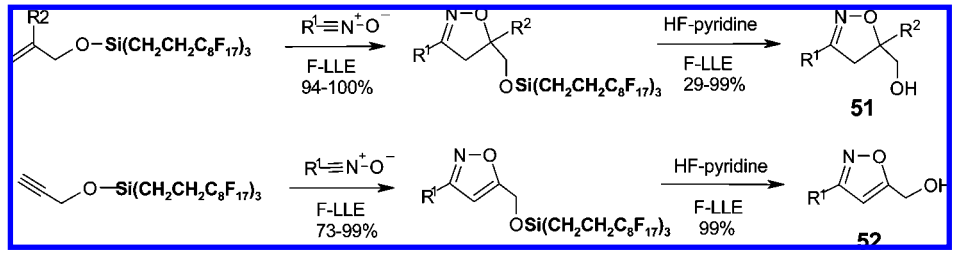
Scheme 23. Fluorous Sulfonyl Linker-Assisted Synthesis of Bisindole Analogs



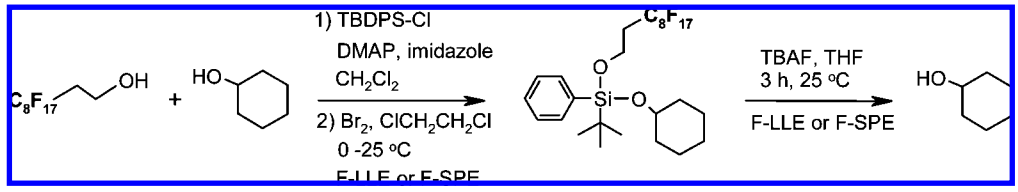
Scheme 24. Fluorous Sulfonyl Linker-Facilitated Synthesis of Yuehchukene



Scheme 25. Fluorous Silyl Linker-Facilitated Synthesis of Isoxazolines and Isoxazoles



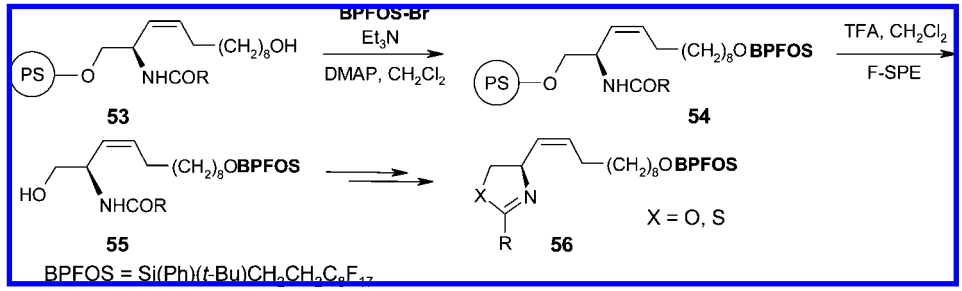
Scheme 26. Alkyoxysilyl Linker for Alcohol Protection



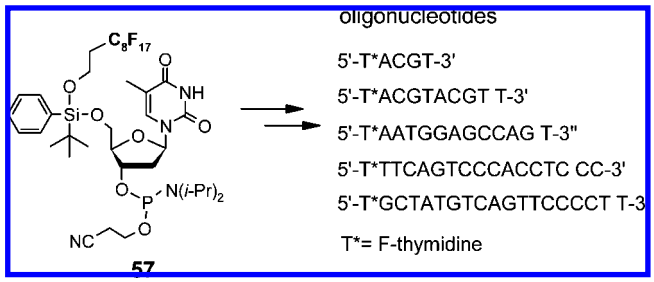
2.2.2. Trityl-Type Linkers

Pearson and co-workers employed fluorous dimethoxytrityl (FDMT)-attached nucleoside phosphoramidites **63** for solid-phase synthesis of oligonucleotides (Scheme 32).[57] The mixture generated from the resin cleavage and containing the fluorous desired sequence was subjected to F-SPE with a high pH-stable fluorinated sorbent. It efficiently retained the fluorous component and removed the nonfluorous failure sequences by washing with 10% MeCN in 0.1 M aqueous Et_3NHOAc and water. This step was followed by on-column detritylation with 3% aqueous trifluoroacetic acid. FDMT-off oligonucleotide product was eluted with 10% aqueous MeCN, and the cleaved FDMT linker was retained on the cartridge. This fluorous purification technique combines the linker cleavage and separation steps in a one-pass loading process without ammonia removal. It has high selectivity, good recovery (70−100%), and capability to purify oligonucleotides up to 100-mers.

Scheme 27. Silyl Linker-Assisted Synthesis of Oxazoles and Thioazoles



Scheme 28. Fluorous Silyl Linker-Assisted Synthesis of Oligonucleotides



Beller and Bannwarth developed two fluorous trityl linkers and used them to make 5′-*O*-attached thymidine-3′-phosphoramidites **64** in the synthesis of DNA (Scheme 33).[58] Fluorous trityl-on purification (F-TOP) on a fluorous silica gel cartridge followed by linker cleavage provided 9- to 30-mer DNA sequences.

2.2.3. Benzyl and p-Methoxybenzyl (PMB)-Type Linkers

The Curran group introduced fluorous benzylbromide (F-Bn-Br) linker for the synthesis of disaccharides (Scheme 34).[59] Tribenzyl-attached D-glucal was coupled with excess diacetone galactose under standard reaction conditions using benzotrifluoride (BTF) as the solvent. The resulting fluorous compound was debenzylated by catalytic hydrogenation. After F-LLE, the product in the organic phase was isolated and then acylated to give disaccharide **65**.

Applications of F-PMB linkers for the synthesis of truncated discodermolide analogs are described in Section 5.2.1; for the syntheses of stereoisomers of murisolin are described in Section 5.1.2.

Winssinger and co-workers developed a benzyl trichloroacetimidate linker and applied it in the total synthesis of Radicicol A, a biologically interesting compound belonging to the resorcylic acid lactone family. In this work, cross-metathesis of the linker with the vinyl borolane afforded the *trans*-vinyl borolane **66** in excellent yield (Scheme 35).[60] This compound was stereospecifically converted to the *cis*-vinyl bromide. Treatment with *t*-BuLi and the addition of a TBDPS-protected aldehyde followed by EOM protection led to the formation of **67** and then **68** after iodo exchange of the silyloxy group. Sequential alkylation of **68** with an aromatic fragment, oxidation, and then removal of the selenide group afforded **69**. Removal of F-Bn and acrocyclisation under fluorous Mitsunobu conditions afforded **70.** Cleavage of methyloxy and acetonide groups followed by selective oxidation led to formation of radicicol A.

2.2.4. Dimethylthiocarbamate (DMTC)-Type Linkers

N,*N*-Bis(perfluoroalkyl)thiocarbamoyl chloride (F-DMTC-Cl) was developed by Takeuchi and co-workers. It has been used to protect the hydroxyl group of carbohydrates (Scheme 36).[61] The linker can be readily removed by oxidation with *m*-chloroperbenzoic acid (*m*-CPBA) and subsequent hydrolysis with $KHCO_3$

2.2.5. Alkoxyethyl and Methyloxymetyl (MOM)-Type Linkers

Hydroxyl group protection with fluorous vinyl ethers has been reported by Wipf and Reeves (Scheme 37).[62] The protection was carried out under a mild acidic condition in the presence of a catalytic amount of camphorsulfonic acid (CSA). The deprotection of fluorous acetals also proceeded under a mild condition. Treatment of the protected substrates in a 1:1 solution of Et_2O and MeOH with a catalytic amount of CSA gave excellent yields of deprotected substrates. Fluorous alcohol was recovered in a quantitative yield by F-LLE with FC-72.

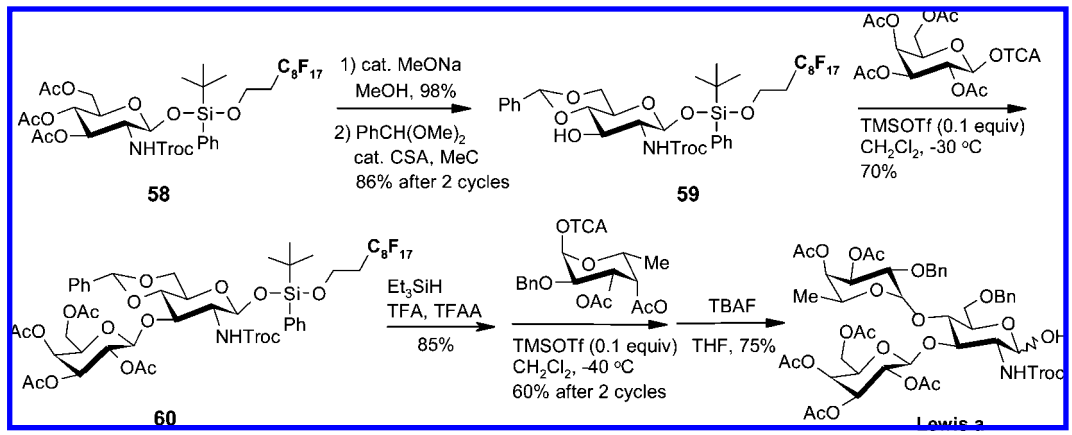
Ikeda and co-workers developed a fluorous methyloxymetyl (MOM)-type protecting group and applied it in chemoenzymatic synthesis of 2-deoxy-2,3-didehydrosialic acid (Scheme 38).[63] After removal of acetyl and the glycosidic benzyl groups, F-MOM-attached *N*-acetyl-D-mannosamine **71** was employed for Neu5Ac aldolase-catalyzed chemoenzymatic transformation to form **72**. Sequential esterification of **72** followed by AcCl treatment afforded **73**. Deprotection of the fluorous acetal group of **73** with trimethylsilyl bromide (TMSBr) under mild acidic conditions gave desired product **74.** The F-MOM protecting group was found to have minimal effect on the reactivity of the attached molecules for the enzyme reaction, and very effective for F-SPE purification.

Curran and Ogoe developed a similar F-MOM **75** that has a propylene spacer (Scheme 39).[64] The protection reaction was carried out with DIPEA, and the deprotection was carried out with $ZnBr_2$−BuSH or CSA.

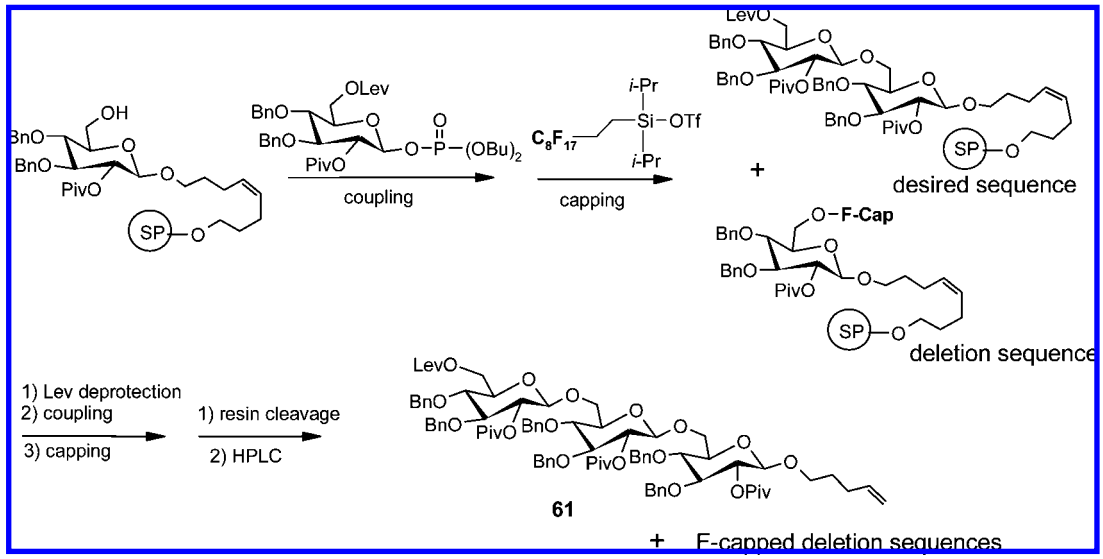
2.2.6. Tetrahydropyran (THP)-Type Linkers

Fluorous tetrahydropyran (THP)-type linkers with iodo or sulfoxide leaving groups were introduced by Wipf and Reeves.[65] A new glycosylation method using Cp_2ZrCl_2−$AgClO_4$ to activate an anomeric sulfoxide has also been developed. Scheme 40 shows the application of F-THP-sulfoxide for the protection and deprotection of cholesterol **76**.

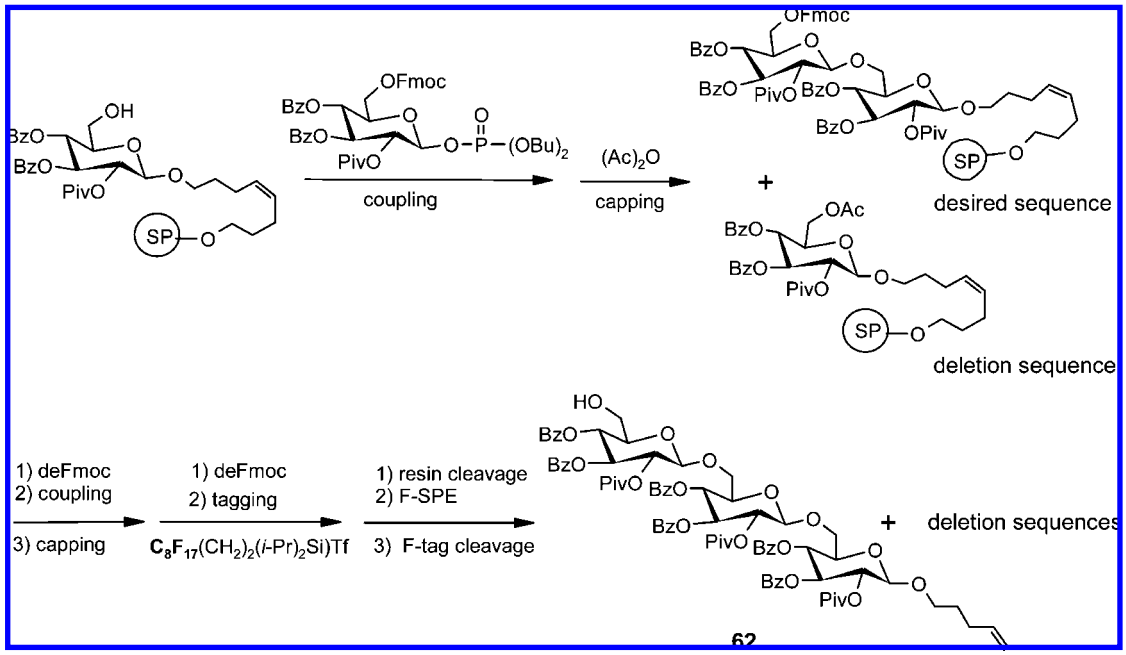
Scheme 29. Fluorous Silyl Linker-Facilitated Synthesis of Lewis a



Scheme 30. Fluorous Silyl Capping Agent-Facilitated Synthesis of Trisaccharide



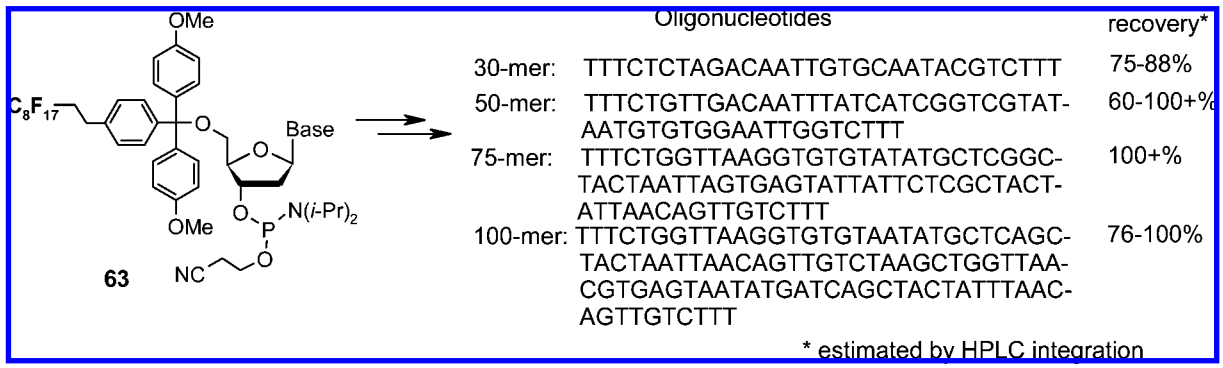
Scheme 31. Fluorous Silyl Linker-Facilitated Synthesis of Trisaccharide



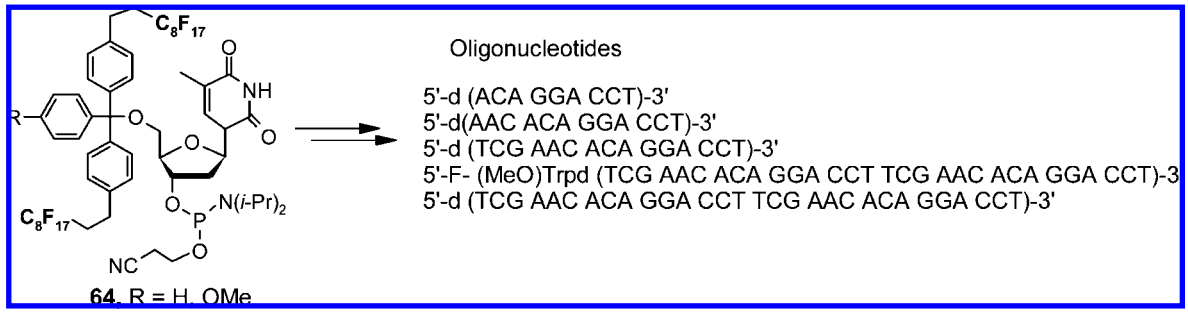
2.2.7. Carbonyl Linkers

Mizuno, Inazu, and their co-workers have developed a series of heavy fluorous carbonyl linkers for F-LLE-based peptide and oligosaccharide syntheses (Scheme 5).[21] Linkers bearing Hfa, Hfb, Bfp, and TfBz groups have 34 to 102 fluorine atoms. Scheme 41 highlights the synthesis of

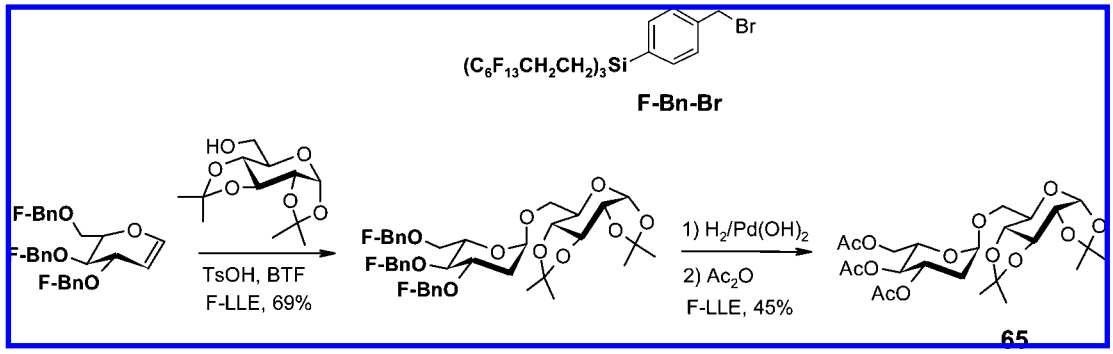
Scheme 32. F-Trityl-Facilitated Synthesis of Oligonucleotides



Scheme 33. F-Trityl-Facilitated Synthesis of Oligonucleotides



Scheme 34. F-Bn-Facilitated Synthesis of Disaccharide



disaccharide **79** using three Bfp-protected mannose derivatives.[21b] The triphenylmethyl (Trt) group of **77** was selectively removed by treatment of 10-camphorsulfonic acid (CSA). The deprotected hydroxyl group was coupled with a galactose derivative to give disaccharide **78**. The removal of both the acetyl and Bfp groups followed by FC-72/MeOH extraction gave disaccharide **79**.

The Bfp linker has also been employed in the synthesis trisacchride Gb3 (Scheme 42).[21e] The Bfp group was introduced to four hydroxyl groups of lactose derivative **80**. After the deprotection of benzylidene and trityl (Tr) groups of **81**, the benzoyl (Bz) group was selectively introduced to two primary hydroxyl groups to afford glycosyl acceptor **82**. This compound was reacted with the glycosyl donor to afford α-linked fluorous trisaccharide **83**. Removal of Bfp group with sodium methoxide followed by acetylation afforded desired product Gb3. The synthesis of a pentasaccharide shown in Scheme 42 also involved the use of Bfp linker.[21b]

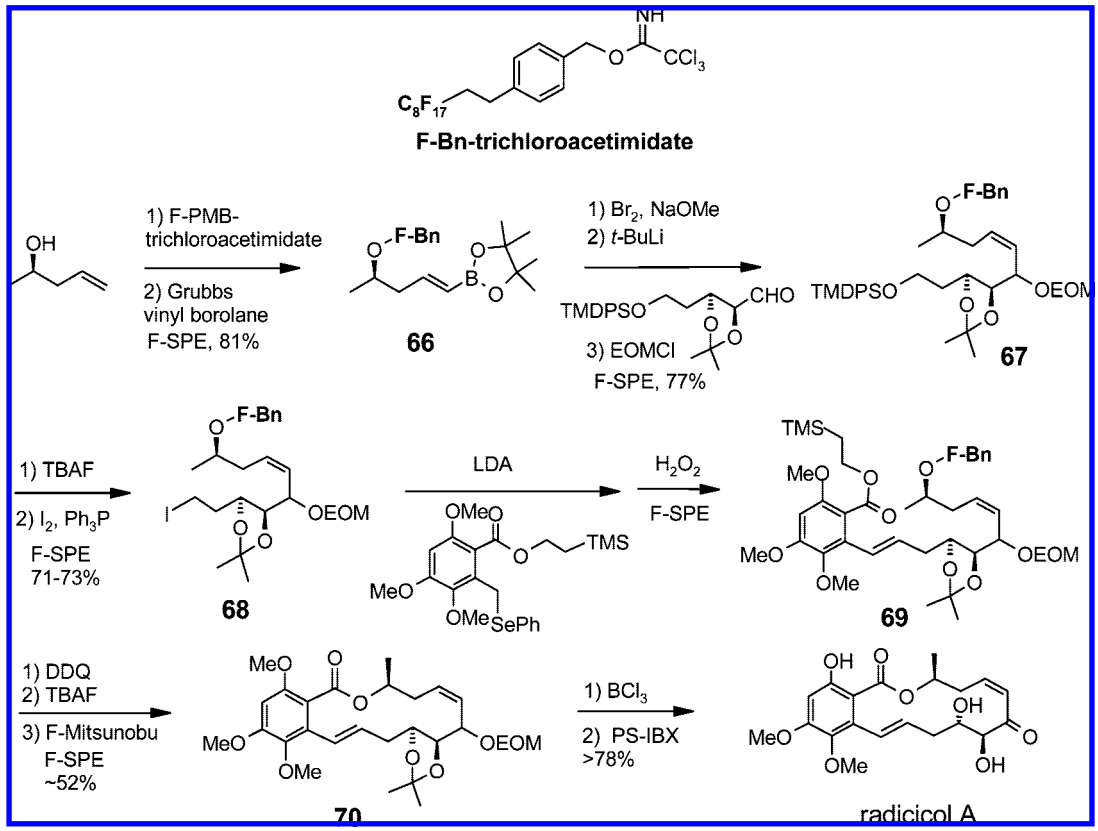
In the synthesis of disaccharide **87**, the Mizuno and Inazu group used TfBz linkers to attach three hydroxyl functions of a galactose derivative **84** (Scheme 43).[66] Each TfBz has three C_8F_{17} tags and a total of 51 fluorine atoms. They have a higher fluorine content than the Bfp (34 fluorine atoms) described above. TfBz-attached intermediates **85** and **86**were purified by F-LLE with FC-72. The final disaccharide product **87** was purified by silica gel column chromatography.

The Hfb linker (Scheme 5) contains a total of 102 fluorine atoms, which is much heavier than the Bfp and TfBz groups described above. A single Hfb was found fluorophilic enough for F-LLE in the synthesis of trisaccharide **88** (Scheme 44).[21d]

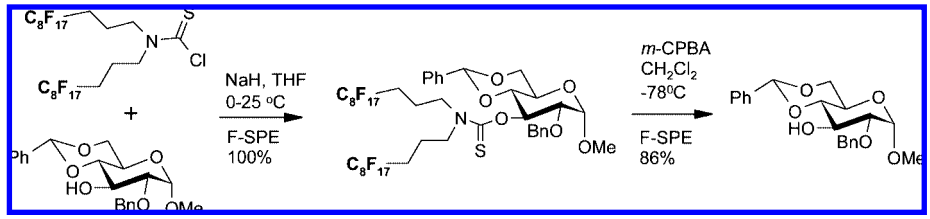
2.2.8. Phenol Linkers

Goto and Mizuno reported the synthesis of a glycosyl donor using a heavy fluorous phenol linker containing three C_8F_{17} chains (Scheme 45).[67] $BF_3 \cdot OEt_2$-promoted coupling of the linker and per-*O*-acetyl-β-D-galactopyranose **89** followed by the deacetylation with NaOMe in MeOH-$MeOC_4F_9$ gave **90**. Selective benzylation using Bu_2SnO followed by acetylation gave **91**. Hydrogenation product **92** underwent monochloroacetylation to give **93**. The final linker cleavage afforded glycosyl donor **94**. In this sequence, all the fluorous intermediates were purified by F-LLE with FC-72 or hybrid fluorous solvents, no further purifications were conducted after the F-LLE.

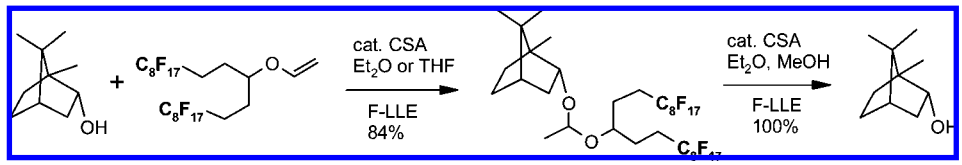
Scheme 35. F-Bn-Facilitated Synthesis of Radicicol A



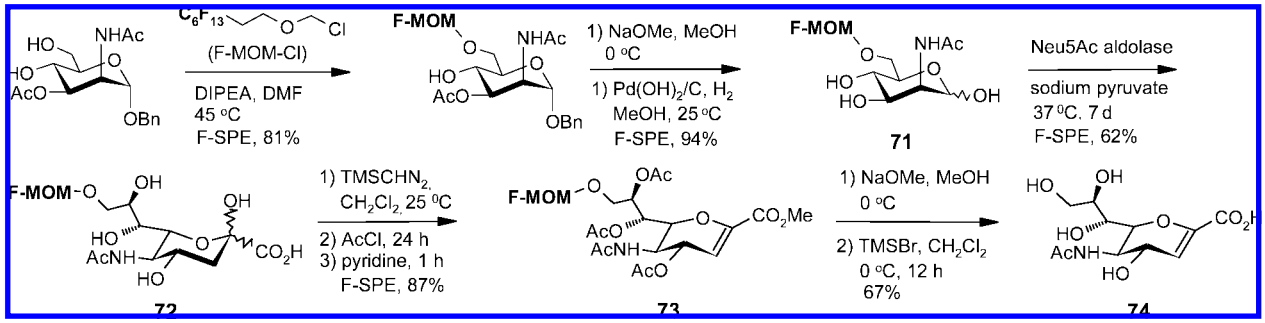
Scheme 36. F-DMTC for Hydroxyl Group Protection



Scheme 37. Fluorous Vinyl Ether for Hydroxyl Protection



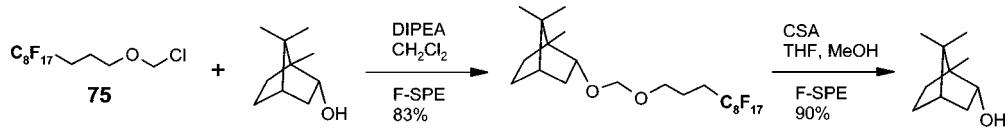
Scheme 38. F-MOM-Facilitated Chemoenzymatic Transformations



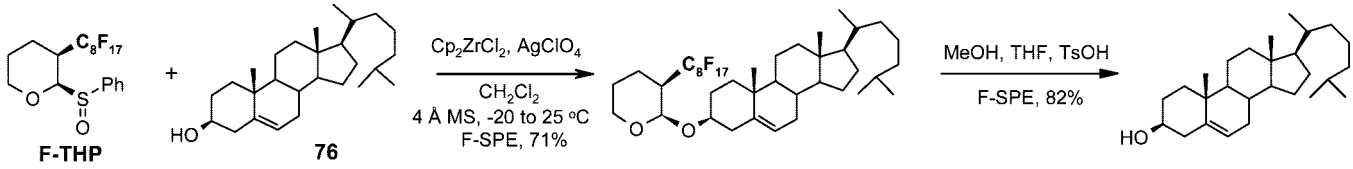
2.2.9. Benzaldehyde Linkers for Diol Protections

The Takeuchi group employed the fluorous benzaldehyde as an acetal protecting group for regioselective carbohydrate synthesis (Scheme 46).[68] The benzaldehyde was first converted to dimethyl acetal through reacting with trimethylorthoformate in the presence of *p*-TsOH·H_2O. The methyl α-D-glucopyranoside was added to the reaction mixture to form benzylidene acetal **95**. Acylation of **95** gave **96** which was then treated with Et_3SiH-TFA for selective acetal ring-opening to afford compound **97**. The glycosidation and

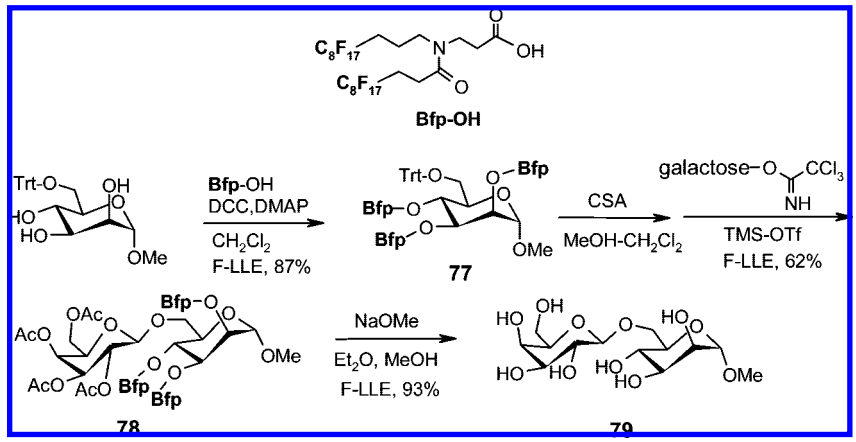
Scheme 39. Protection of Hydroxyl Group with F-MOM



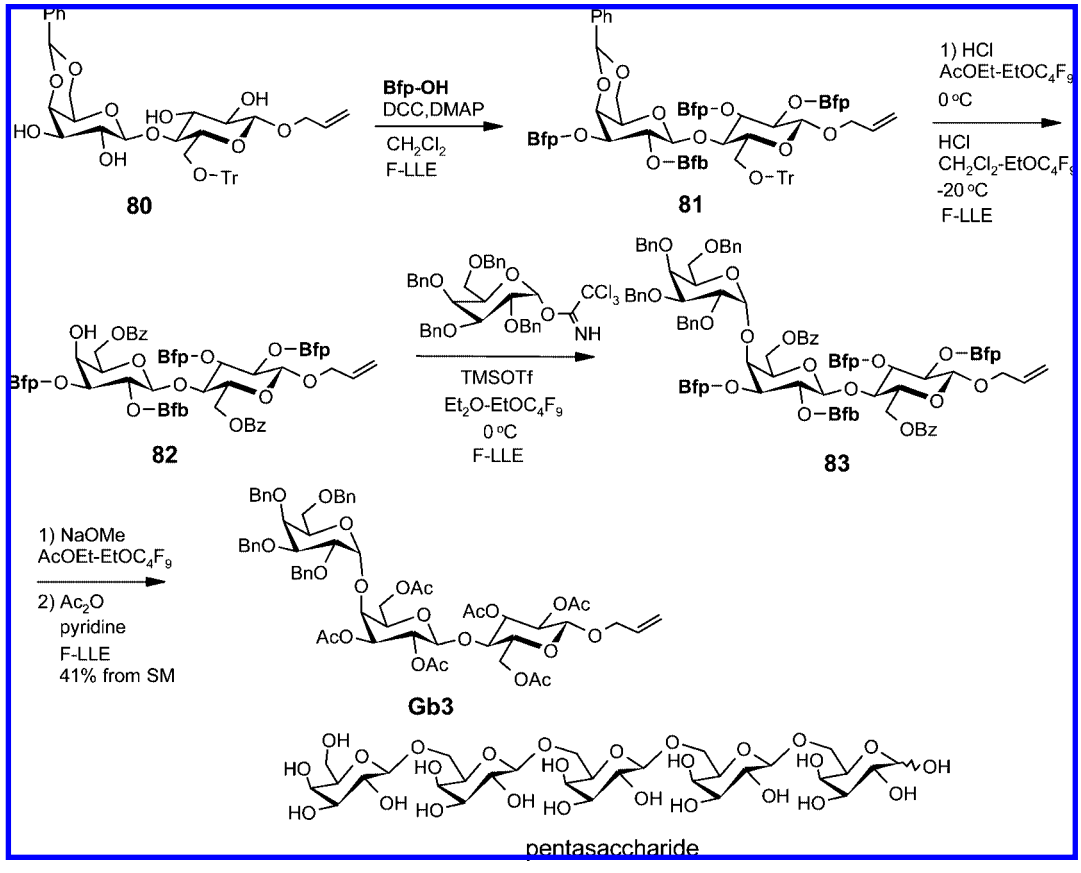
Scheme 40. F-THP Linker for Hydroxyl Group Protection



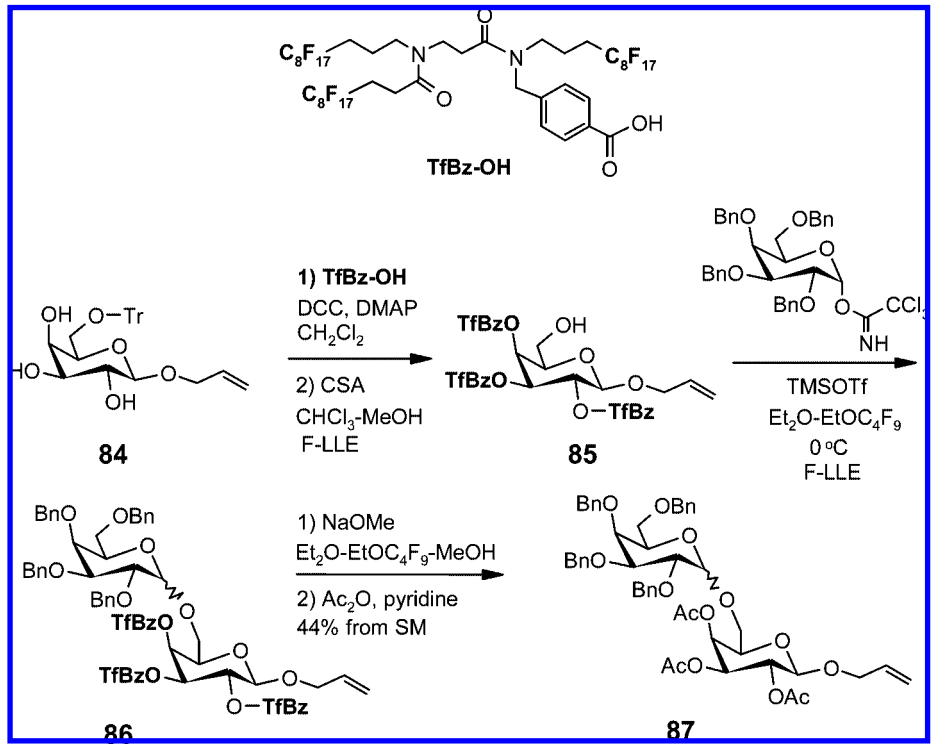
Scheme 41. Bfp-Facilitated Synthesis of Disaccharide



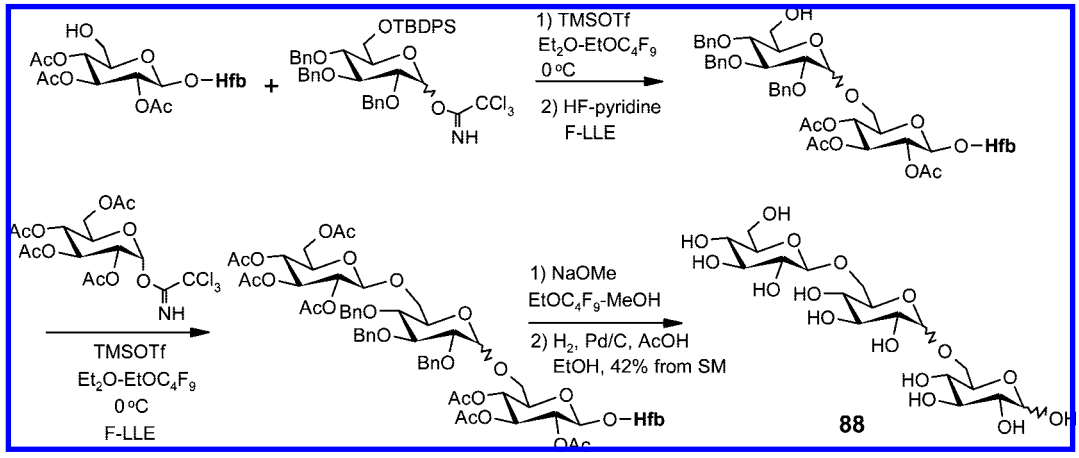
Scheme 42. Bfp-Facilitated Synthesis of Gb3 and Pentasaccharide



Scheme 43. TfBz-Facilitated Synthesis of Disaccharide



Scheme 44. Hfb-Facilitated Synthesis of a Trisaccharide



removal of the fluorous linker from **98** afforded the final disaccharide **99**.

The application of fluorous benzaldehyde linkers for FMS of stereoisomers of pinesaw fly sex heromone is described in Section 5.1.2.

2.3. Carboxyl Group Protections

2.3.1. Trimetylsilylethyl (TMSE)-Type Linkers

To make the fluorous alcohol linker easily cleavable from an ester, the Fustero group developed F-TMSE and demonstrated in the synthesis of tripeptide **100**.[69] The fluorous linker was attached under a standard esterification condition with DIC and HOBt. The linker was easily cleaved by treatment with TBAF (Scheme 47).

2.3.2. Benzhydryl (Rink)-Type Linkers

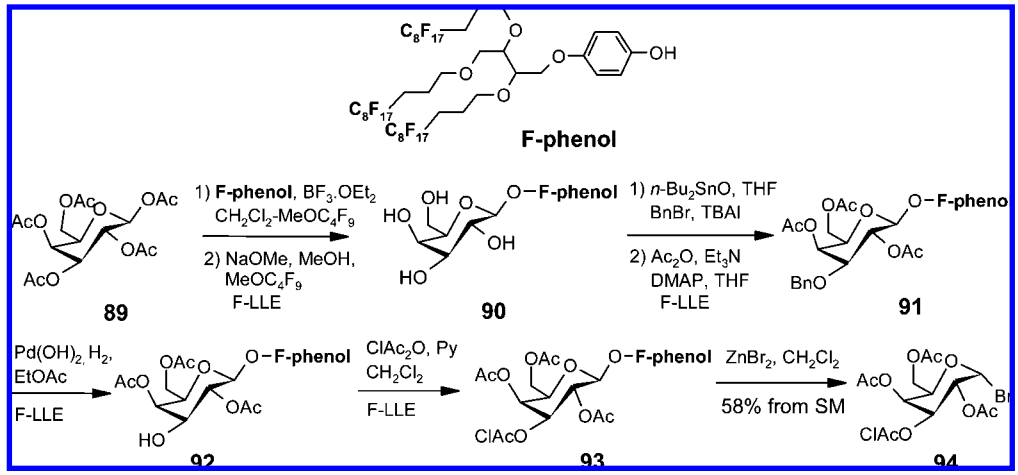
The Inazu group developed a Hfb-attached a Rink-type linker and applied it in the synthesis of a bioactive tripeptide thyrotropin-releasing hormone (TRH) (Scheme 48).[70] The Fmoc group from the linker was cleaved by 5% piperidine/FC-72-DMF solution. The amide coupling reaction was promoted by PyBOP. A 4-fold excess of the amino acid derivative was used in each coupling reaction. The attached TRH tripeptide **101** and the side-chain protecting group were cleaved with TFA containing 2.5% H_2O and 1,4-butanedithiol.

Mizuno and co-workers introduced a new Rink-type linker bearing a hexakisfluorous (Hfx) tag (Scheme 5) for F-LLE-based peptide synthesis. It has been utilized in the synthesis of a C-terminal amide-type dipeptide and a pentapeptide (H-Gly-Pro-Gly-Ala-Lys-NH_2).[21h]

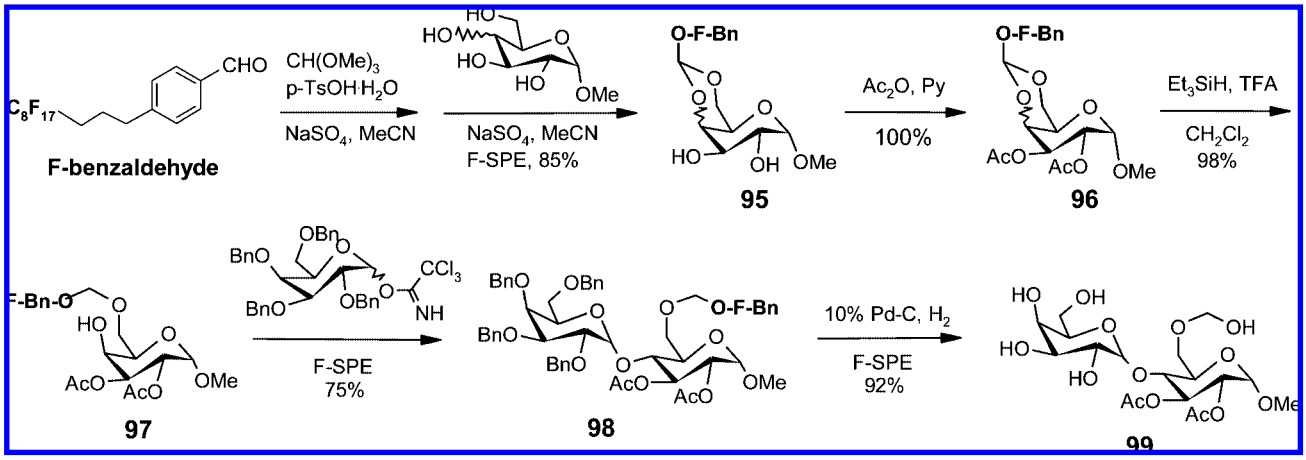
2.3.3. PMB-OH-Type Linkers

β-Peptides have different structures, folding patterns, and potential biological activities from α-peptides. Instead of using the traditional approach of coupling of *N*-protected β-peptides, the Nelson group introduced a new approach that starts from β-azido acids and involves an iterative sequence

Scheme 45. F-Phenol Linker for Hydroxyl Group Protection



Scheme 46. F-Benzylaldehyde-Facilitated Synthesis of Disaccharide

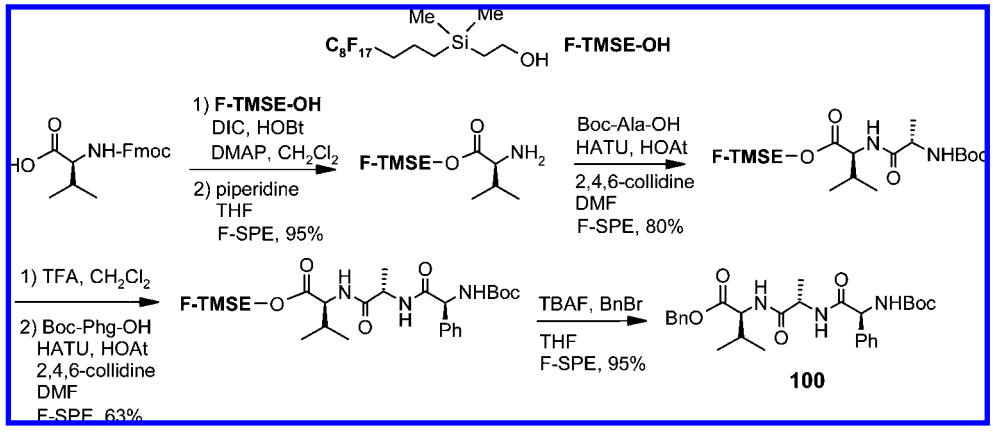


of reduction of the azide to an amine followed by amide coupling with the next β-azido acid (Scheme 49).[71] β-Azido acids **102** were prepared by the NaN_3 reaction of β-lactones. The acidic group was attached to fluorous PMB-OH to form azido-esters **103** that were used as the starting material for fluorous β-peptide synthesis. Using this protocol, the Nelson and Curran groups synthesized numbers of tri-β-peptide analogs **104**. The intermediate purification was facilitated by F-SPE.

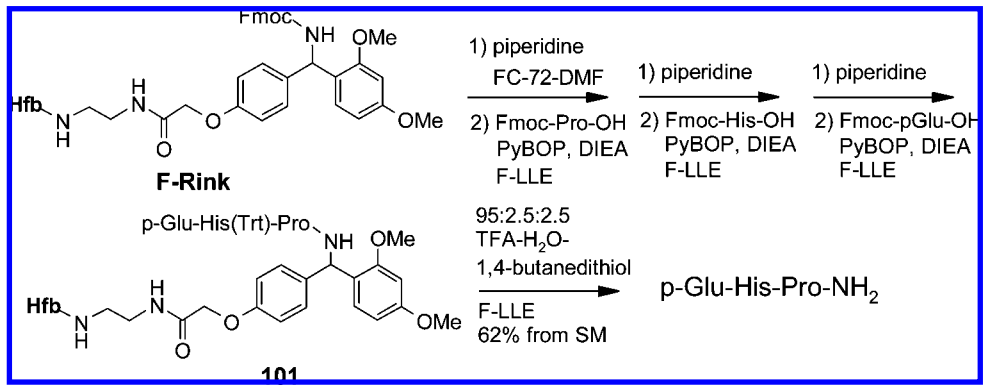
In another case of F-PMB-assisted synthesis *of* β-peptides, the Seebach and Seeberger groups employed traditional Boc- or Fmoc-amide coupling protocol and conducted the reactions in a microreaction device (Scheme 50).[72] The synthesis of β-peptides on traditional solid supports has been a challenge to chemists due to easy formation of secondary structures. The authors addressed these issues in the synthesis of a β-peptides tetramer **105** by conducting the solution phase reaction in a silicon continuous flow microreactor at high temperature (90−120 °C). The F-PMB liker proved to be particularly useful for the F-SPE purification of poorly soluble products.

Mizuno, Inazu and their co-workers employed Hfa-attached heavy fluorous PMB-type linkers (Scheme 51) for F-LLE-based synthesis of α-peptides.[70a] A bioactive

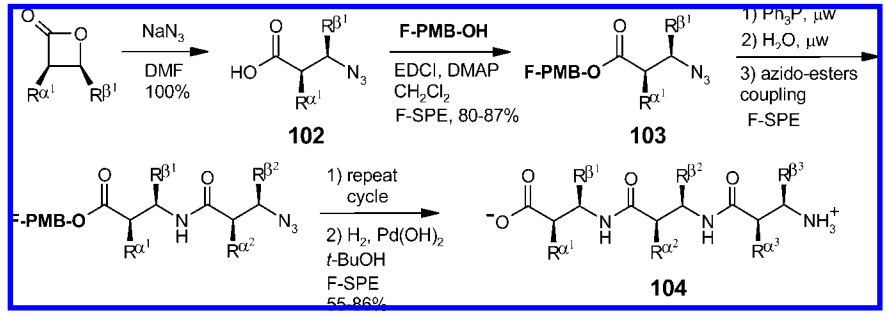
Scheme 47. F-TMSE-Facilitated Peptide Synthesis



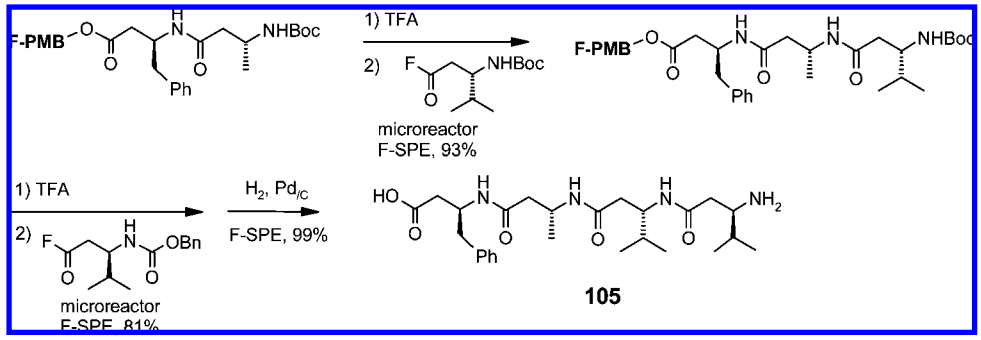
Scheme 48. F-Rink-Facilitated Synthesis of Tripeptide



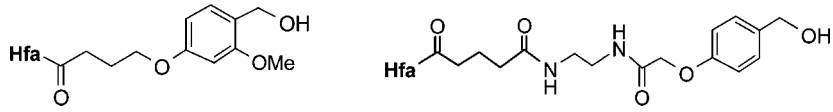
Scheme 49. F-PMB-Facilitated Synthesis of *β*-Peptides



Scheme 50. F-PMB-Facilitated Synthesis of *β*-Peptide Tetramer



Scheme 51. Hfa-Attached Heavy Fluorous PMB-Type Linkers



pentapeptide, Leu-enkephalin (H-Tyr-Gly-Gly-Phe-Leu-OH) was successfully prepared by the Fmoc-strategy.[70b]

The Mizuno group extended the utility of heavy fluorous PMB-type linkers for glycopeptide synthesis (Scheme 52).[73] A C-terminal protected fluorous leucine was used for the synthesis of a tripeptide **106**. This compound was then coupled with Fmoc-Asn(GlcNAc)-OMpt, followed by de-Fmoc, coupling with Boc-Ile-Ompt, and linker cleavage to afford glycopeptide **108**. Intermediates **106** and **107** were isolated by F-LLE with FC-72. The final product **108** was purified by reverse-phase HPLC.

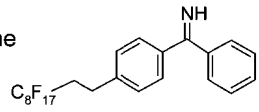
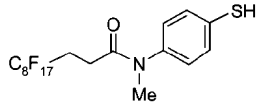
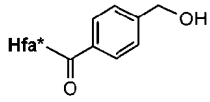
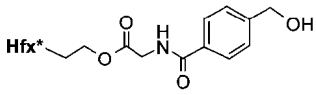
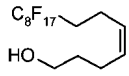
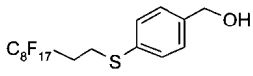
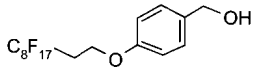
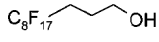
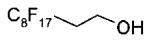
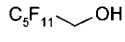
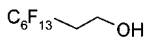
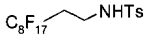
2.3.4. t-Butyl-Type Linkers

The Cobas group introduced several single and double fluorous tag-attached *t*-butyl-type linkers for carboxylic acid protections (Scheme 53).[74] The esterification of carboxylic acids with fluorous *t*-butyl-type linkers were carried out under standard conditions using DCC and DMAP in CH_2Cl_2, and the deprotection was conducted with the treatment of TFA. The esters with the double fluorous-tagged *t*-butyl linker have a good partition coefficiency in fluorous solvents such as FC-72 and perfluoromethylcyclohexane. The single-tagged substrates could be separated by F-SPE as well. The Inazu group introduced an Hfa-attached *t*-butyl-type linker for C-terminal protection in peptide synthesis.[70]

2.4. Diol Linkers for Carbonyl Group Protections

Read and Zhang demonstrated the utility of fluorous diol **109** as the carbonyl group protecting agent in the synthesis of a pyridine derivative **110** (Scheme 54).[75] One of the carbonyl groups of the dialdehyde was protected with fluorous diol. The protected compound underwent condensation, cycloaddition, oxidation and linker deprotection reactions to afford substituted pyridine **110**.

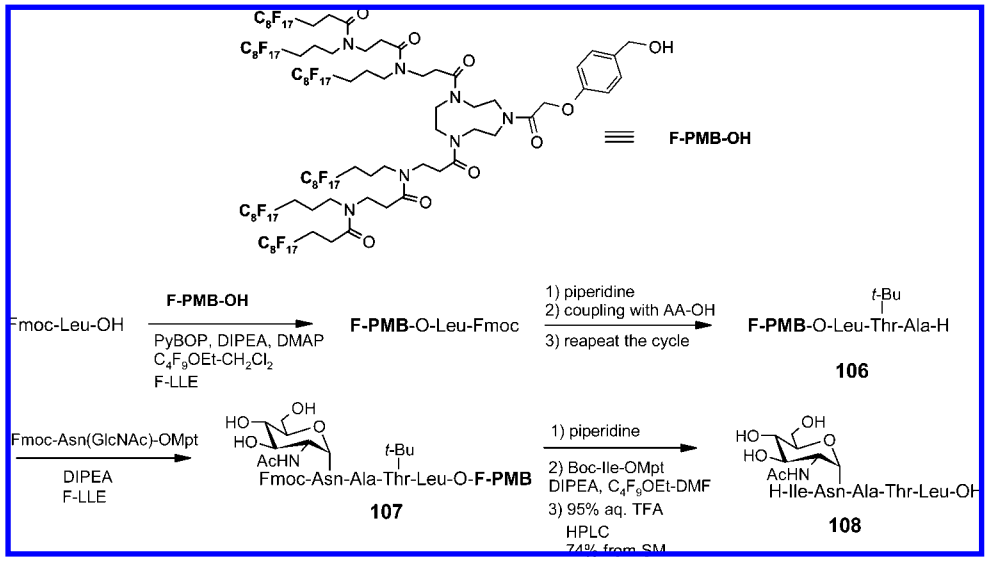
Table 2. Displaceable Linkers

Fluorous linker	Structure	Separation method	Functional group convertion	Conditions for attachment	Conditions for displacement	Ref
Benzophenone amino		F-SPE	Halides to amines	Pd_2dba_3 BINAP *t*-BuONa MePH	2 N HCl, THF MP-carbonate	77
Sulfonyl	$C_8F_{17}O_2SOF$	F-SPE	Phenoles to biaryls, arylamines, arylthiols, aromatics	K_2CO_3, DMF	Pd-cat. coupling	79-84
Thiophenol		F-SPE	Sacchride halides to ethers	aq. $NaCO_3$ EtOAc	NIS/AgOTf or NIS/TfOH or *p*-TolSCl/AgOTf	85
Alcohol		F-LLE	Sacchride sulfides to ethers	TfOH, NIS $EtOC_4F_9$-CH_2Cl_2	$Pd(OH)_2$, H_2 $EtOC_4F_9$-EtOH	21c
		F-LLE	Sacchride sulfides to ethers	TfOH, NIS CH_2Cl_2	NaOMe $EtOC_4F_9$-MeOH	86
		F-SPE	Glycosyl phosphate to diverse groups	TMSOTf, CH_2Cl_2	diverse conditions	87,88
		F-SPE	Carboxylic acids to amides	DIC,DMAP	Amines, THF	89
		F-SPE	Carboxylic acids to uracils	Ac_2O, Et_3N DMAP,THF	Isocyanates NaH, DMP	91
		F-SPE	Carboxylic acids to amides	DIC, HOBT, DMAP, DMF	cyclative deprotection	93-97
		F-SPE	Carboxylic acids to hydrazine derivatives	DCC, DMAP	NH_2NH_2 AcOH	90,92,98
		F-SPE	Carboxylic acids to lactones	NaH, THF	K_2CO_3, ether	99
		F-SPE	Diazoacetic acid to acetyl derivatives			100
Sulfonamide		F-SPE	Alcohols to cyclic alkenes	Ph_3P, DEAD, THF	Ru-cat, CH_2Cl_2	101
Silyl	$(C_{10}F_{21}CH_2CH_2)_3SiBr$	F-LLE	Arylhalides to aromatics	*t*-BuLi, Et_2O	TBAF	102,103
Alkylstannyl	$(C_8F_{17}CH_2CH_2)_3Sn$-Br	F-LLE	Stille reaction			
			Arylzinc iodides to aryliodides	THF	radio active NaI iodogen, AcOH	104

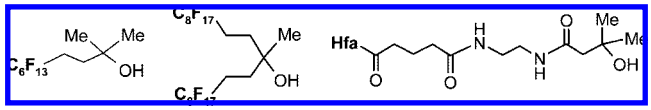
* Hfa and Hfx are heavy fluorous tags shown in Scheme 5.

Huang and Qing introduced a different double-chain diol **111** for carbonyl protection (Scheme 55).[76] Acetal **112** generated from the diol and bromobenzaldehyde was separated by F-LLE. This compound was subjected to the Suzuki

Scheme 52. F-PMB-Facilitated Synthesis of Glycopeptide



Scheme 53. *t*-Butyl-Type Fluorous Linkers



coupling reaction and linker cleavage to afford biaryl aldehyde **113**.

3. Synthetic Applications of Fluorous Displaceable Linkers

A fluorous displaceable linker is capable of converting the original protected functional group to a new group at the end of a multistep reaction sequence. It is a useful strategy to incorporate new substitution groups in DOS via displacement reactions or to construct new ring skeletons via cyclization reactions (Table 2).

3.1. Benzophenone Imine Linkers for Converting Halides To Amines

Herr and co-workers employed fluorous benzophenone imine linker **114** to attach aryl halides and triflates. *N*-aryl benzophenone imines **115** were then converted to corresponding amines by hydrolysis (Scheme 56).[77] The fluorous benzophenone was recovered by F-SPE for regeneration of **114**.

3.2. Alkylsulfonyl Linkers for Converting Phenols to Diverse Functional Groups

The perfluorooctylsulfonyl is a versatile linker for phenols. Attached fluorous sulfonates have similar reactivity as the triflate and can be cleaved by cross-coupling reactions to form aryl C−C (biaryl), C−S, C−N, and C−H bonds (Scheme 57).[78] The cross-coupling reactions are usually carried out under microwave conditions. In the multistep synthesis, the fluorous sulfonyl linker facilitates the intermediate purification, serves as a hydroxy protecting group at the early steps, and activates the hydroxyl group for the coupling reaction at the last step.

Two examples shown in Scheme 58 demonstrate the utility of fluorous sulfonyl-attached benzaldehydes. Reductive amination of benzaldehyde **116** afforded **117**. This compound was then reacted with an isocyanate to form substituted hydantoin **118** or with a benzoyl chloride to form amide **119**. F-SPE purified **118** and **119** were used for palladium-catalyzed cross-couplings to form biaryl **120** and aryl sulfide **121**, respectively.[79−81]

In another multistep synthesis, fluorous benzaldehyde **122** was condensed with a ketone to form α, *β*-unsatuated ketone **123**.[82] It was converted to a triaryl-substituted pyrimidine **124** by cycloaddition with benzamidine. This compound was reacted with HCO_2H under Pd-catalyzed conditions to give traceless linker cleavage product **125** (Scheme 59).

Perfluorosulfonyl-attached benzaldehydes are a valuable synthon for multicomponent reactions.[78] In a three-component reaction, fluorous benzaldehyde **126** was reacted with isonitriles and 2-aminopyridines to form imidazo[1,2-*a*]pyridine **127** (Scheme 60).[83] The condensation product was employed for a Suzuki-type reaction to form compounds **128**. This protocol has been used for parallel synthesis of an 80-membered compound library.

Fluorous benzaldehyde **129** has been used in one-pot, three-component 1,3-dipolar cycloaddition reaction shown in Scheme 61.[84] Condensed product **130** was used for Suzuki coupling reaction to remove the linker and form compound **131**. A demonstration library of biaryl-substituted proline derivatives was prepared by this protocol.

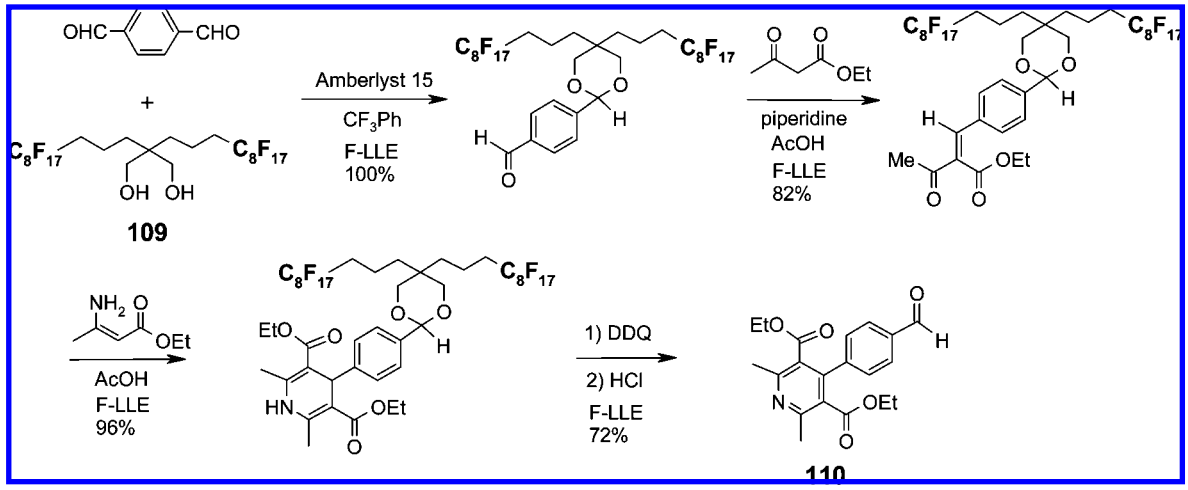
3.3. Thiophenol Linkers for Converting Glycol Halides to Ethers

The Huang group employed fluorous thiol linker **132** to displace the bromo group of tetraacetyl-α-glucosyl bromide **133** (Scheme 62).[85] After removal of the acetate, thiolglucoside **134** was subjected to benzoylation, glycosylation, and linker cleavage to form disaccharide **136**. Up to 75% of the fluorous thiol linker was recovered as a disulfide by F-SPE.

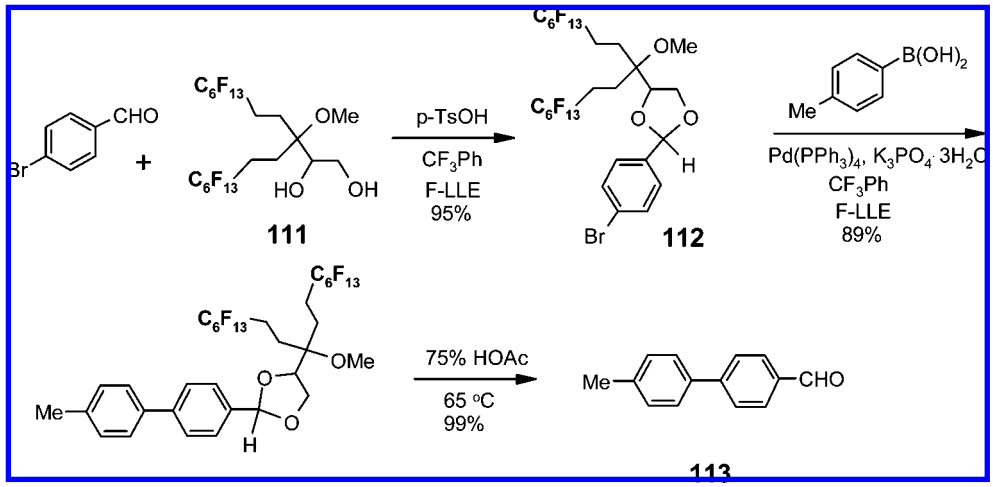
3.4. Alcohol Linkers for Converting Glycosyl Thioaryl Groups to Ethers

Miura, Inazu and their co-workers introduced a PMB-type HfBn linker (shown in Scheme 5) for attachment of glucose derivative **137** through an arylthio displacement glycosylation (Scheme 63).[21c] Removal of the TBDPS group of **138** afforded fluorous glycosyl acceptor which was reacted with

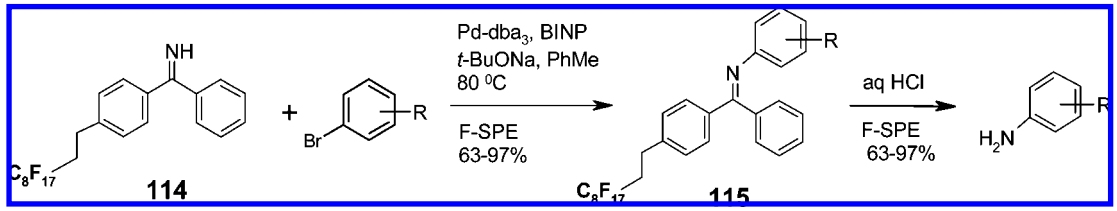
Scheme 54. Fluorous Diol for Carbonyl Protection



Scheme 55. Fluorous Diol for Carbonyl Protection



Scheme 56. Fluorous Benzophenone Imine for Halide Attachment



a glycosyl donor to give a fluorous disaccharide **139**. Debenzylation followed by HfBn cleavage afforded disaccharide **140**.

The Mizuno group developed a heavy fluorous HexF-attached Cbz -type linker (shown in Scheme 5) and applied it in the synthesis of aminoglycoside derivatives containing 2,6-diamino-2,6-dideoxy-D-glucopyranose disaccharide such as compounds **141** and **142** following the similar synthetic sequence described above (Scheme 64).[86]

3.5. Alcohol Linkers for Reaction with Glycosyl Donors

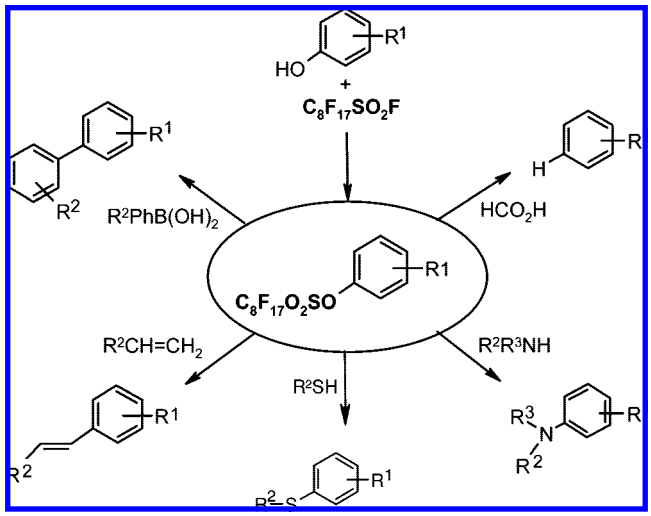
The Pohl group reported a general protocol to attach fluorous alcohol linker **143** to a series of trichloroacetimidated donors (Scheme 65).[87] Resulting fluorous carbohydrates **144** were used for microarry on fluorous slides for screening.

Seeberger and co-workers used fluorous alcohol **146** for the attachment of Fmoc-protected glucosyl phosphate **145** (Scheme 66).[88] The attached building block was used for oligosaccharide assembling to form tetrasaccharide **148** in a microreactor setting. The purification of the intermediates was facilitated by F-SPE. Tetrasaccharide **148** was further functionalized to pentenyl glycoside **150** by olefin cross-metathesis, to aldehyde **151** by ozonolysis of **149**, and to glycosyl trichloroacetimidate **152** by hydrolysis and sequential transformation of **149**.

3.6. Marshall-Type (FluoMar) Linkers for Converting Carboxylic Acids to Amides

As a fluorous version of Marshall resin, FluoMar has been developed as a catch and release linker for converting carboxylic acids to amides (Scheme 67).[89] FluoMar was attached to carboxylic acids under general coupling conditions with

Scheme 57. Pd-Catalyzed Displacement of Fluorous Sulfonyl Linkers



diisopropylcarbodiimide (DIC) and dimethylaminopyridine (DMAP). Tagged compound **153** underwent Boc deprotection and sequential acylation to give amide **154.** The linker was then displaced with a set of amines to give diamides **155**.

3.7. Alcohol Linkers for Carboxylic Acids

Wipf and Methot employed fluorous alcohol protected carboxylic acid **156** for synthesis of dihydropyridazinones **161** (Scheme 68).[90] A standard esterification converted the **156** to fluorous ester **157**. Cationic zirconocene reaction with 1-hexyne afforded **158** followed by conjugate addition with Me_2CuLi and acid hydrolysis to yield **159**. Keto ester was treated with hydrazine to form dihydropyridazinone **160**. The fluorous alcohol was cleaved during the cyclization.

Fustero and co-workers introduced fluorous acetates **162** by the reaction of fluorous alcohols with acetic anhydride (Scheme 69). The fluorous acetates were enolated with bis(trimentylsilyl)amide and then reacted with fluorinated allyl- or arylnitrile to afford fluorous enamino esters **163**. The treatment of fluorous enamino esters with isocyanates or isothiocanates generated ureas/thioureas **164** which spontaneously cyclized to form corresponding uraciles/thioureaciles **165**. It was found that two kinds of fluorous linkers had no significant influence on product yields and reaction conditions.

Eames and Khanom prepared fluorous acetate **166** by reacting fluorous alcohol with acetyl chloride (Scheme 70).[92] The fluorous acetate was used as an enolizable component for the aldol reaction with a benzaldehyde. Resulting β-hydroxy ester **167** was purified by F-LLE and then subjected to $LiHBEt_3$-promoted reductive linker cleavage to afford diol product **168**. It was isolated from the reaction mixture by FC-72 extraction for nine times.

The Zhang group employed fluorous alcohol-attached amino acids in the parallel synthesis of a hydantoin/thiohydantoin library (Scheme 71).[93] Fluorous amino esters **169** underwent reductive amination with aldehydes. Intermediates **170** were reacted with aryl isocyanates/aryl isothiocyanates. The resulting ureas/thioureas **171** were spontaneously cyclized to form heterocyclic products **172**.

The Zhang group employed fluorous amino esters in the synthesis of a library containing *N*-alkylated dihydropteridinone analogs **177** (Scheme 72).[94] The 4,6-dichloro-5-nitropyrimidine was first displaced with fluorous amino esters to form **173**, then with secondary amines to form **174**. Reduction of the nitro group of **174** gave **175**, which then underwent microwave-promoted cyclization. Compounds **176** were *N*-alkylated to give product **177**.

The Zhang group employed fluorous amino ester as the limiting agent for one-pot, three-component cycloaddition reactions. Reactions were conducted under conventional or microwave heating to afford highly stereoselective bicyclic pyrrolidines **178** (Scheme 73).[95] The cycloaddition products were used for diversity-oriented synthesis (DOS) and led to the formation of hydantoin-, piperazinedione-, and benzodiazepine-fused heterocyclic systems **180, 182,** and **184**, respectively (Scheme 74). Each of these three scaffolds has four stereocenters on the central pyrrolidine ring and up to four points of diversity (R^1 to R^4).

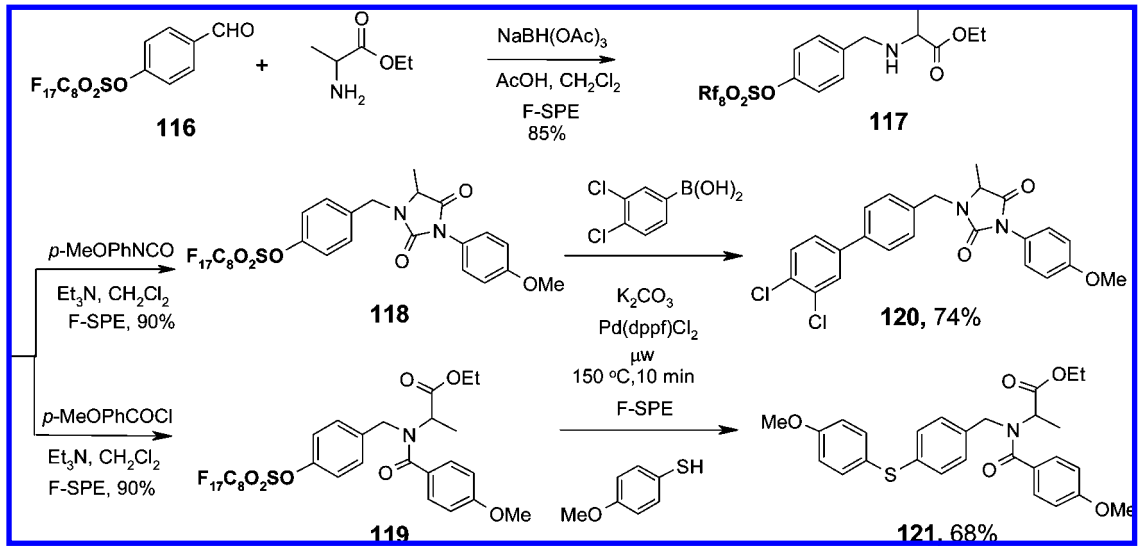
The synthesis of scaffold **180** was accomplished by the reaction of **178** with phenylisocyanate in the presence of catalytic amounts of *N*,*N*-4-dimethylaminopyridine (DMAP) followed by microwave-promoted linker cleavage and cyclization of **179** to form hydantoin-fused compounds **180**. Piperazinedione-fused tricyclic scaffold **182** was synthesized by acylation of **178** with chloroacetyl chloride followed by chlorine displacement of chlorine with $BuNH_2$ to form **181**. 1,8-diazabicyclo[4.3.0]non-5-ene (DBU) promoted cyclization gave **182.** Synthesis of benzodiazepine-fused scaffold **184** was accomplished by a three-step post-MCR modification. *N*-acylation of **178** with 2-nitrobenzoyl chloride followed by zinc-acetic acid reduction under sonication gave compound **183**. Cleavage of the fluorous linker by DBU produced **184**. The chemistry developed for synthesis of **180** and **184** has been applied to the fluorous mixture synthesis of libraries (Section 5.2).

The Zhang group discovered an unprecedented reaction sequence that led to formation of a novel hexacyclic ring system (Scheme 75).[96] The one-pot, double [3 + 2] cycloaddition reaction of the fluorous amino ester **185** with excess amount of *O*-allyl salicyladehyde yielded novel polycyclic system **187** in a stereoselective fashion. The major diastereomer was isolated and its structure was confirmed by X-ray crystal analysis. This is a highly efficient reaction that generates four new rings, six bonds, and seven diastereocenters from a one-pot reaction.

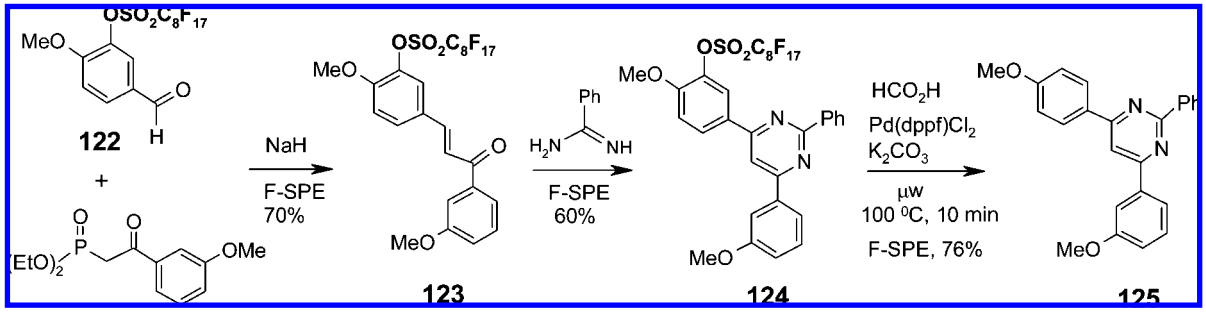
The Sun and Zhang groups employed the fluorous alcohol in the synthesis of a hydantion-fused tetrahydro-β-carboline library (Scheme 76).[97] The fluorous alcohol was attached to Boc-L-tryptpohan using DCC and DMAP as the coupling agents. After Boc deprotection with TFA, fluorous amino ester **188** was subjected to the Pictect-Spengler reaction with aldehydes to form tetrahydro-β-carboline derivatives **189**. The treatment of **189** with isocyanates led to formation of ureas **190** that spontaneously cyclized to afford tetrahydro-β-carboline hydantoins **191**.

The α-methylene-γ-lactone moiety exists in a wide range of natural products. The Gouault group developed a fluorous protocol for parallel synthesis of α-methylene-γ-lactone derivatives (Scheme 77).[98] Fluorous intermediates **193** were prepared by the Baylis-Hillman (BH) reaction of fluorous acrylate **192** with aldehydes and separated by F-SPE. Palladium catalyzed carbonyl allylation of **193** led to the formation of mono- or disubstituted α-methylene-γ-lactones **194**. Twenty-five analogs generated by this two-step reaction sequence were screened against human melanoma cell line.

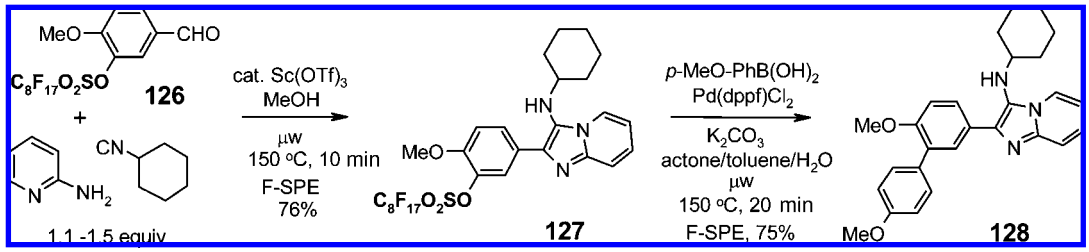
Scheme 58. Application of Fluorous Sulfonyl-Attached Benzaldehyde



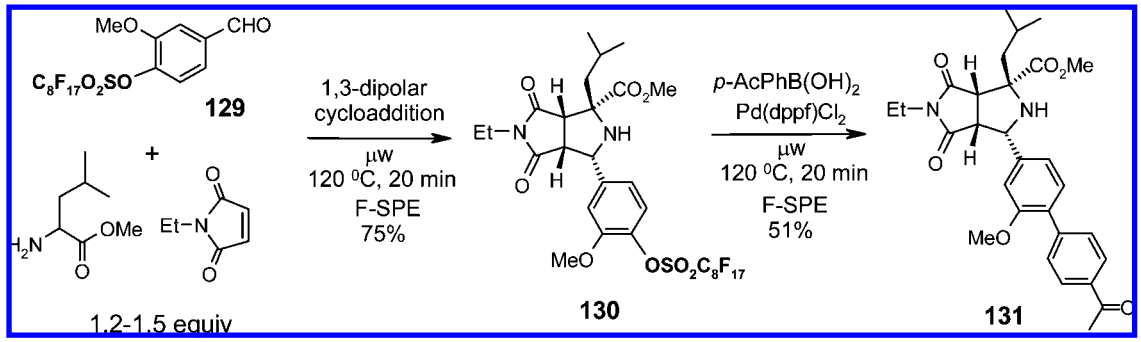
Scheme 59. Fluorous Sulfonyl Traceless Linker for Synthesis of Benzamidine



Scheme 60. Fluorous Benzaldehyde for Synthesis of Imidazo[1,2-*a*]pyridine



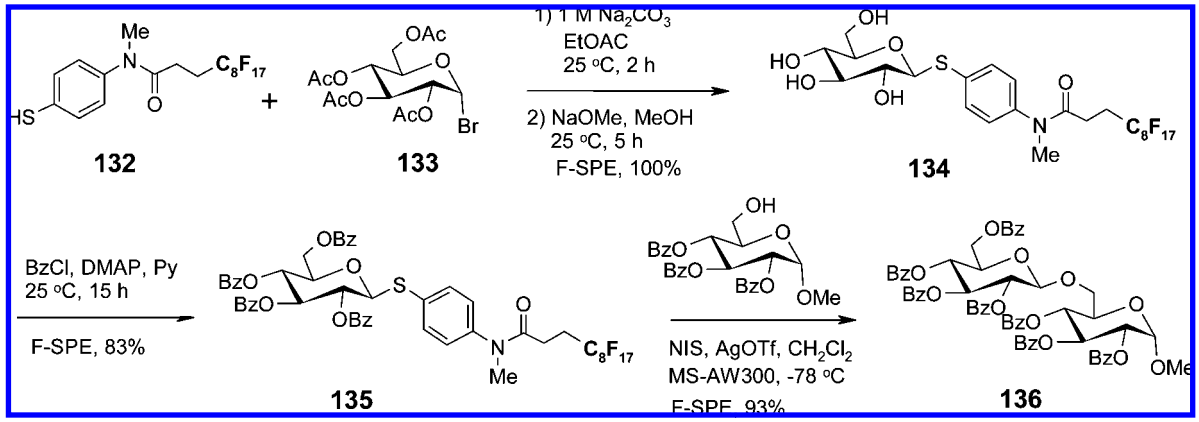
Scheme 61. Fluorous Benzaldehyde for Biaryl-Substituted Proline Derivative



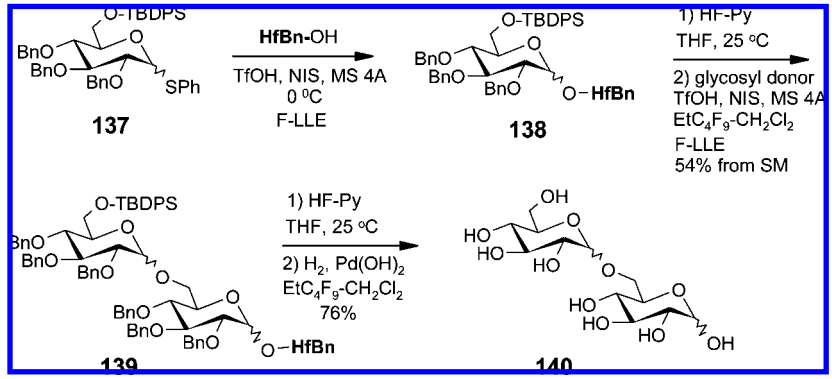
Conducting reactions in water is considered by many people as a green chemistry approach. However, aqueous reactions have the following limitations: (1) reaction mixtures still need organic solvents for extraction; (2) removing water is a time-consuming and energy-intensive process. The Li group introduced the fluorous linker strategy to address those issues.[99] They have demonstrated that by using a light fluorous tag (C_5F_{11}), the indium-mediated allylation reaction could be conducted in hot water to afford **195** (Scheme 78). The reaction mixture was directly purified by F-SPE. A higher water content solvent (up to 50%) was used as a fluorophobic wash to increase the retention of the fluorous molecule on the SPE cartridge. The combined reaction in water and F-SPE has increased the value of this green chemistry approach.

The Spring group made use of a fluorous diazoacetate **196** as a versatile synthon in the synthesis of diverse ring

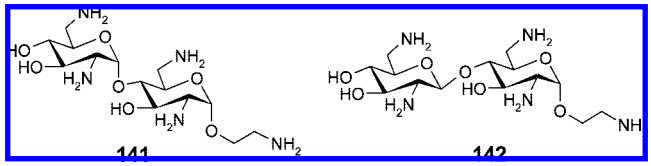
Scheme 62. Fluorous Thiol Linker-Facilitated Synthesis of Disaccharide



Scheme 63. HfBn-Facilitated Synthesis of Disaccharide



Scheme 64. F-Cbz-Facilitated Synthesis of Disaccharides



skeletons (Scheme 79).[100] The diazoacetate was converted to 1,3-keto esters **197** through condensation with ketones. The β-dicarbonyl compounds were subject to different kind of cycloadditions to generate heterocyclic rings including **198**, coumarine **199** and amino pyrimidinone **200**.

3.8. Toluenesulfonamide Linkers for Alcohols

The Nelson group employed Fukuyamma-Mitsunobu reactions to anchor toluenesulfonamide linker **201** to an alcohol (Scheme 80).[101] The resulting intermediate **202** was converted to **203** for fluorous Grubbs-Hoveyda-type catalyst-promoted ring-close metathesis to facilitate the separation of **204**. The product was isolated by F-SPE and collected in the organic fraction. The catalyst and the cleaved linker were in the fluorous fraction. This protocol has been applied to the parallel synthesis of small, medium, and marocyclic heterocyclic ring systems.

3.9. Silyl Linkers for Traceless Cleavage

The Wipf and Curran groups employed heavy fluorous silyl-attached benzoic acid **205** as a limiting agent for the Ugi reaction (Scheme 81).[102] The Ugi condensation product **206** was isolated from excess nonfluorous starting materials by F-LLE. The fluorous silyl group was removed in a traceless fashion through treatment with TBAF.

In another example of multicomponent reactions, Biginelli reactions were conducted using fluorous silyl-attached urea **207**, β-ketone ester, and aldehyde to form fluorous dihydropyrimidines (Scheme 82).[102] F-LLE with FC-84 followed by desilylation with TBAF afforded the desired products **208**.

3.10. Alkylstannyl Linkers For Stille Reactions and Halide Exchanges

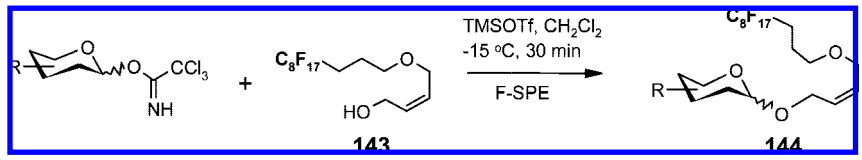
Stille reactions are powerful for formation of carbon−carbon bonds. However, the removal of alkyltannyl fragments from the reaction mixture is not an easy task. The Curran and Hallberg groups employed fluorous alkylstannyl linkers to facilitate the purification. Under microwave conditions, the fluorous Stille couplings can be done in less than 2 min, and products **209** and **210** were separated by F-LLE (Scheme 83).[103]

The Valliant group utilized fluorous alkylstannyl linkers to convert arylzinc iodides to radioactive aryliodides (Scheme 84).[104] Reaction and purification of ^{125}I labeled benzamides under "precursor-free" conditions facilitated the radiopharmaceutical studies. Fluorous alkylstannyl-attached benzoate **211** was converted to activated esters and reacted with amines to provide fluorous benzamide **212**. The ^{125}I was introduced in the final iododestannylation step. Intermediates were readily purified by F-LLE, while the displaced fluorous tin species was removed by F-SPE to give the desired radiolabeled compound **213** in 85% radiochemical yield and 98% radiochemical purity.

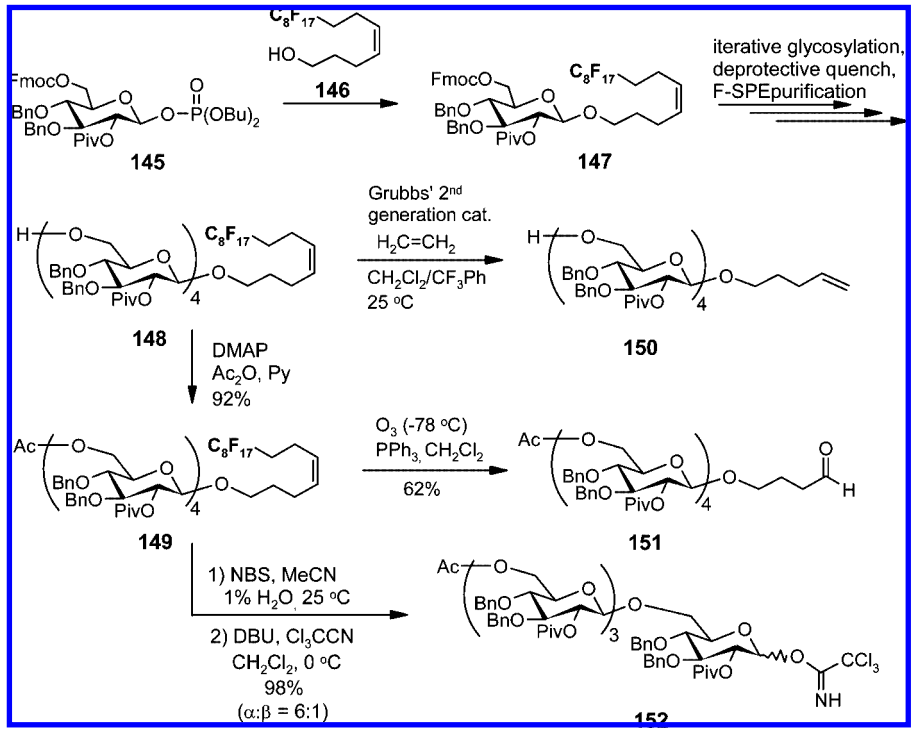
4. Synthetic Applications of Fluorous Safety-Catch Linkers

Safety-catch linkers are stable under common reaction conditions and can be cleaved after activation, which provides

Scheme 65. Fluorous Alcohol-Attached Carbohydrates



Scheme 66. Fluorous Alcohol-Facilitated Synthesis of Oligosaccharides



extra safety and selectivity for functional group protections. So far, only alkylthio and arylgemanyl linkers have been developed as fluorous safety-catch linkers (Table 3).

4.1. Alkylthio Linkers

Fluorous thiols have a broad range of applications in fluorous synthesis. They have been used as scavengers to catch activated halides and other electrophiles from the reaction mixtures,[105] as linkers for selective attachment of desired peptide sequences in proteomics studies,[106] as safety-catch linkers for arylhalides,[107] for Pummerer cyclization products,[108] and for natural product purifications.[109]

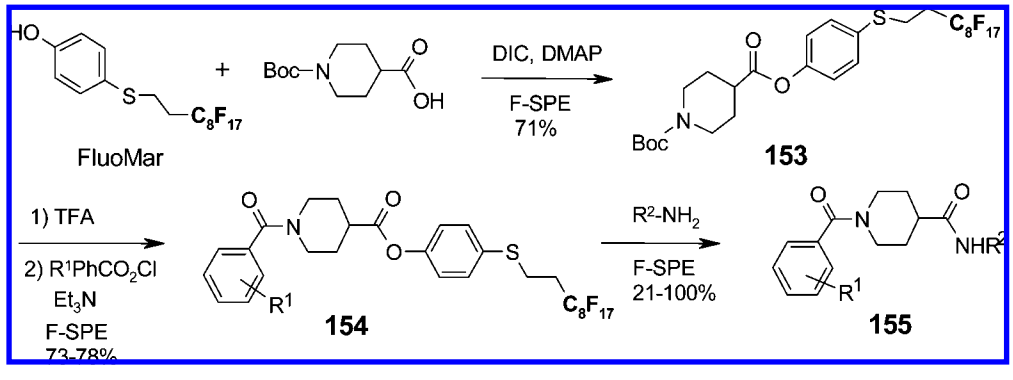
4.1.1. Catch and Release of Arylhalides

The Zhang group reported the utility of fluorous thiol as a nucleophilic linker to anchor 2,4-dichloropyrimidine (Scheme 85).[107] The attached substrate **214** was further displaced with 3-(trifluoromethyl)pyrazole to form **215.** The thio group was then activated by oxidation to sulfone **216** and then displaced by nucleophiles to afford disubstituted pyrimidines **217**.

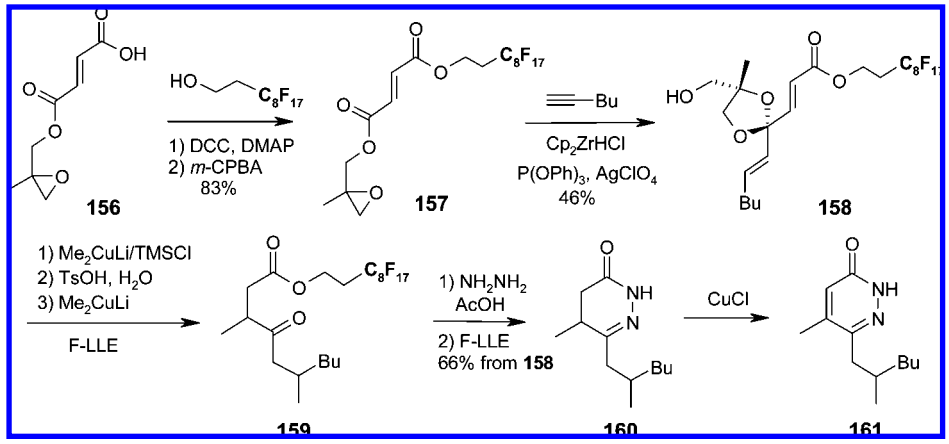
4.1.2. Catch and Release of Pummerer Cyclization Products

The Procter group developed a fluorous Pummerer cyclative-capture strategy for synthesis of nitrogen-containing heterocycles.[108a,b] This work was intended to improve on earlier experiments using a solid-phase strategy that was frustrated by difficulties in monitoring intermediate transformations. Use of a fluorous thiol as a solution-phase safety catch linker allows in-process analysis and also enables simple and effective F-SPE purification after each reaction step. Scheme 86 highlights an example using

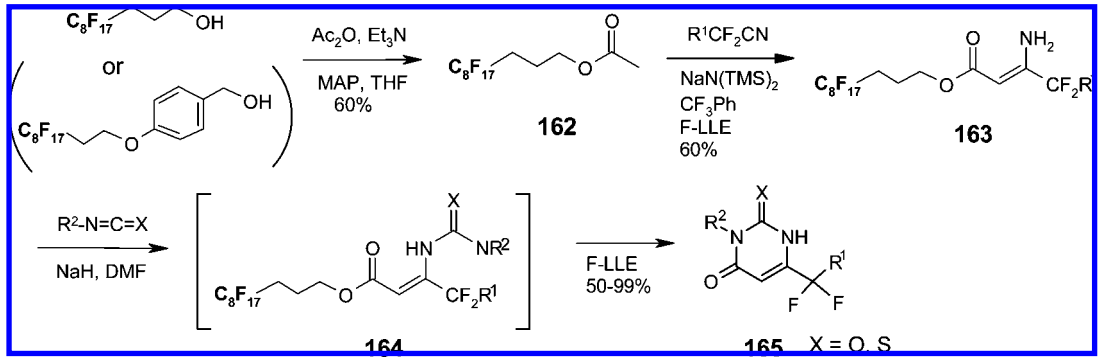
Scheme 67. FluoMar-Facilitated Synthesis of Amides



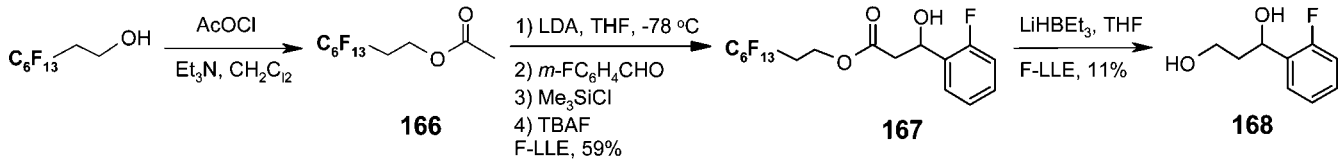
Scheme 68. Fluorous Alcohol-Facilitated Synthesis of Dihydropyridazinones



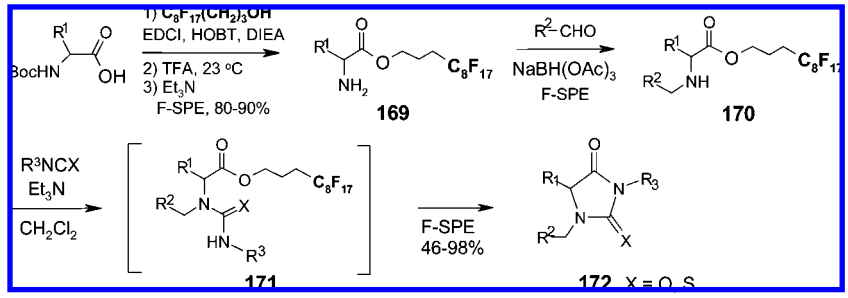
Scheme 69. Fluorous Alcohol-Facilitated Synthesis of Uraciles and Thioureaciles



Scheme 70. Fluorous Alcohol-Facilitated Synthesis of Diol



Scheme 71. Fluorous Alcohol-Facilitated Synthesis of Hydantoins and Thiohydantoins



fluorous thiol to catch Pummerer cyclization product to form **218**. This compound was activated by oxidation and then removed in a traceless fashion to afford **219**. The Procter group has extended the utility of fluorous Pummerer cyclization products for DOS of biaryl, spirosulfone, spirolactame, and fused-heterocyclic compounds. [108c−e]

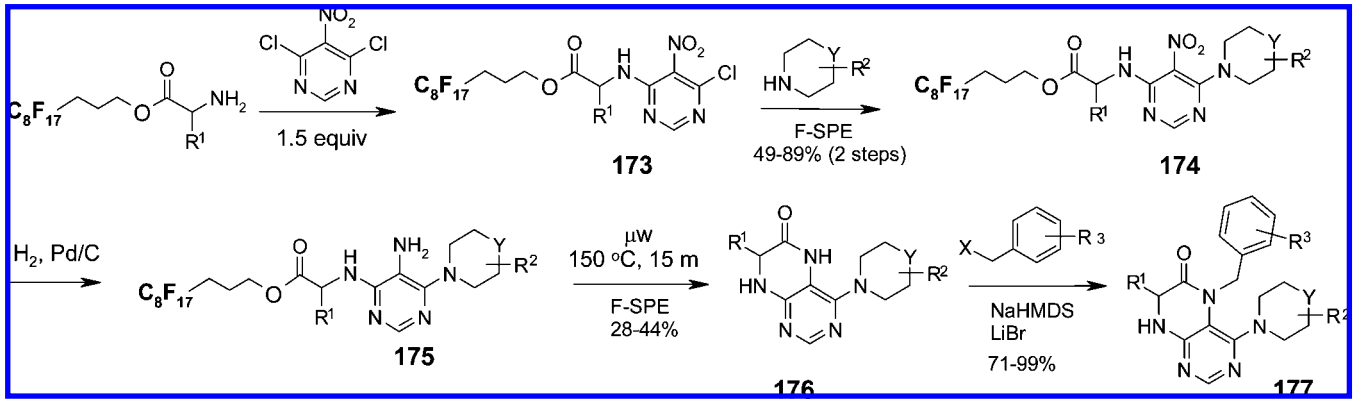
4.1.3. Isolation of Natural Products

The Gouault group reported the first example of using fluorous linkers for natural product isolations (Scheme 87).[109] A mixture of three paraconic acids extracted from the Island moss (*Cetraria islandica* (L.) Ach.) was treated with a fluorous thiol. (+)-Protolichesterinic acid **220** was caught by the thiol via the Michael addition to form **223** and it was separated from the other two components by F-SPE. (+)-Protolichesterinic acid was then released via a retro-Michael addition. The fluorous catch and release protocol gave (+)-protolichesterinic acid in 42% yield which is higher than that obtained by classic preparative TLC. The mixture having the other two components was separated by preparative TLC to afford (+)-lichesterinic acid **221** and (+)-roccellaric acid **222**.

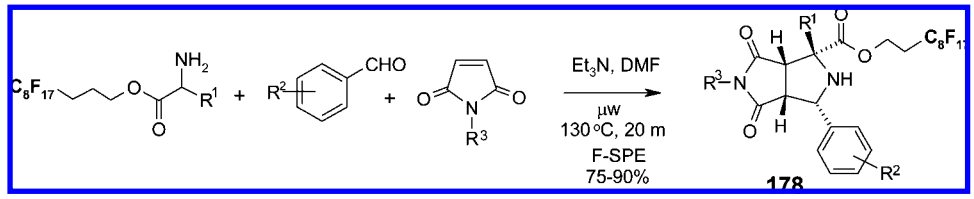
4.2. Arylgermanyl Linkers for Catch and Release of Arylhalides

The Spivey group employed arylgermanyl linkers for the catch and release of arylhalides to form biaryl compounds

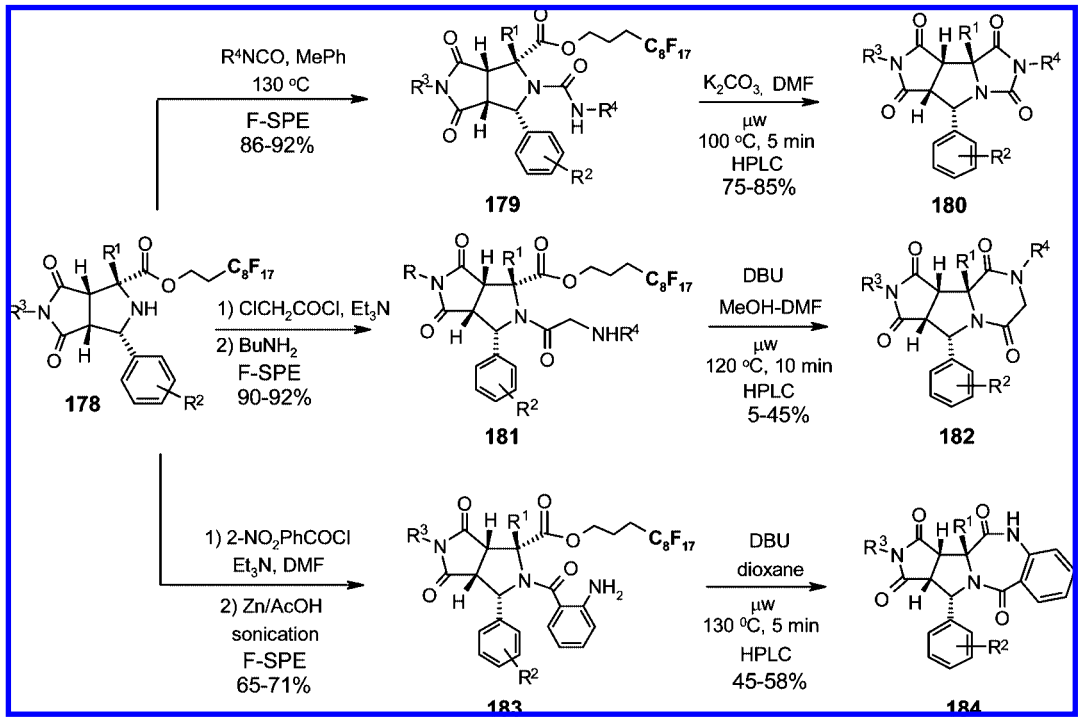
Scheme 72. Fluorous Alcohol-Facilitated Synthesis of *N*-Alkylated Dihydropteridinones



Scheme 73. Fluorous Amino Ester Involved [3 + 2] Cycloaddition

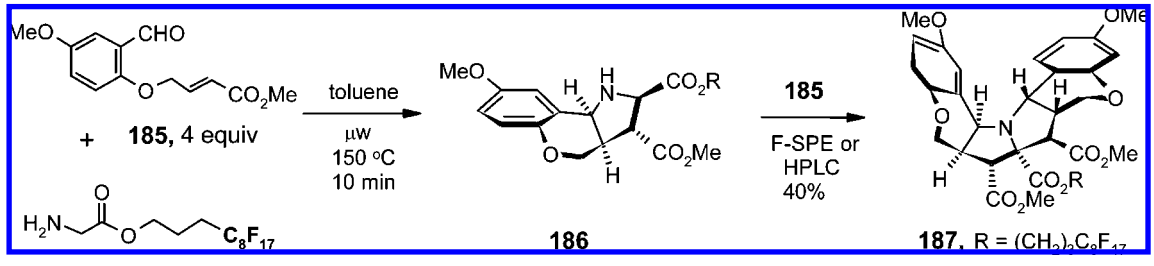


Scheme 74. Fluorous Alcohol-Facilitated DOS of Heterocyclic Systems

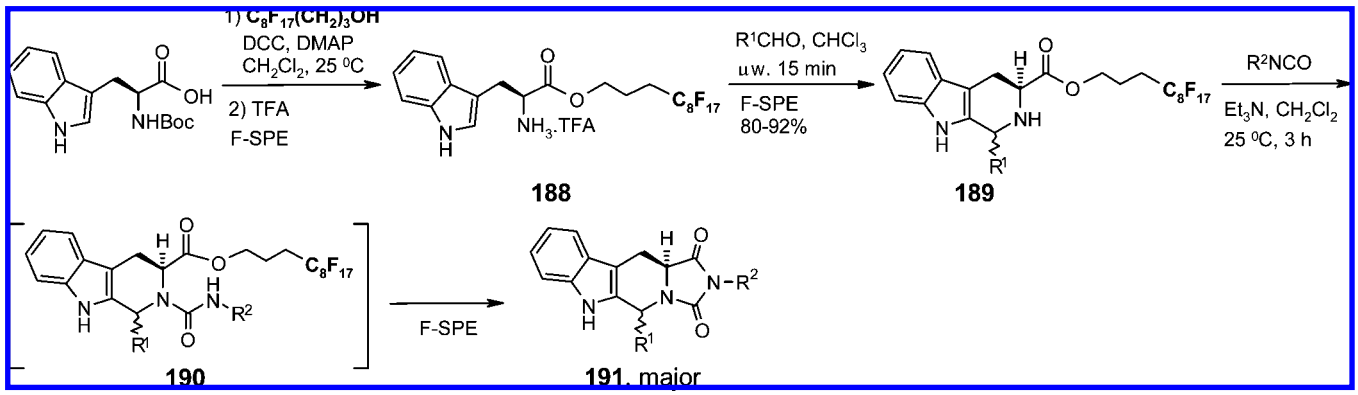


(Scheme 88).[110] The reactions of a fluorous iodide and germanium(II) chloride led to the formation of bis(2-naphthylmethyl)germyl bromide **224** in four steps. This compound was then reacted with aryllithium or Grignard reagents to form the fluorous arylgermanyl-attached aryl compound **225**. These attached compounds were activated

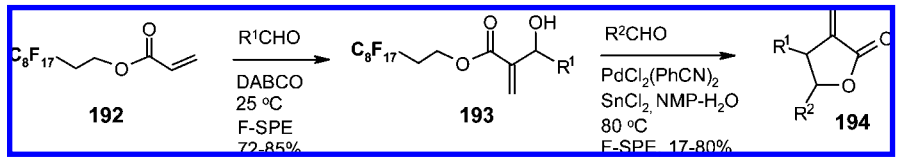
Scheme 75. Fluorous Amino Ester Involved Double [3 + 2] Cycloaddition



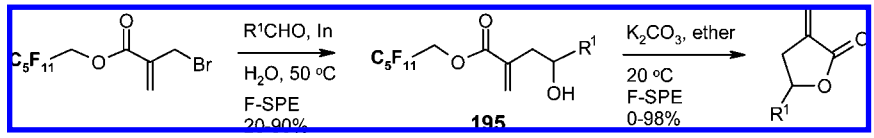
Scheme 76. Fluorous Alcohol-Facilitated Synthesis of Tetrahydro-β-carboline Hydantoins



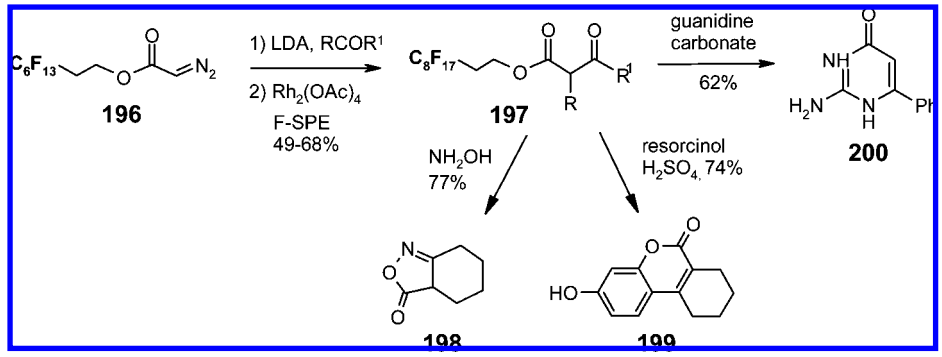
Scheme 77. Fluorous Alcohol-Facilitated Synthesis of α-Methylene-γ-lactones



Scheme 78. Fluorous Alcohol-Facilitated Synthesis of α-Methylene-γ-lactones



Scheme 79. Fluorous Alcohol for DOS of Heterocyclic Systems



by photolysis and coupled with aryl bromides to form biaryl products **226**. In the example shown in Scheme 88, attached compound **225** (R = 4-Cl) was coupled with nitrobiaryl, followed by an $SnCl_2$ reduction and then DCC-mediated amidation with 2-chloronicotinic acid to afford fungicide Boscalid **226** (R = 4-Cl).

5. Linkers for Fluorous Mixture Synthesis (FMS)

Fluorous mixture synthesis (FMS) is a solution-phase technology for making individual pure compounds without performing the deconvolution. Since this technology was introduced by the Curran group in 2001,[111] it has been applied to the synthesis of enantiomers and diastereomers of complex natural products as well as novel drug-like compound libraries and oligomers.[112] A wide range of fluorous protective linkers such as TIPS, Boc, Fmoc, PMB, Cbz as well as displaceable linkers such as alcohol and alkylsulfonyl have been used in FMS.

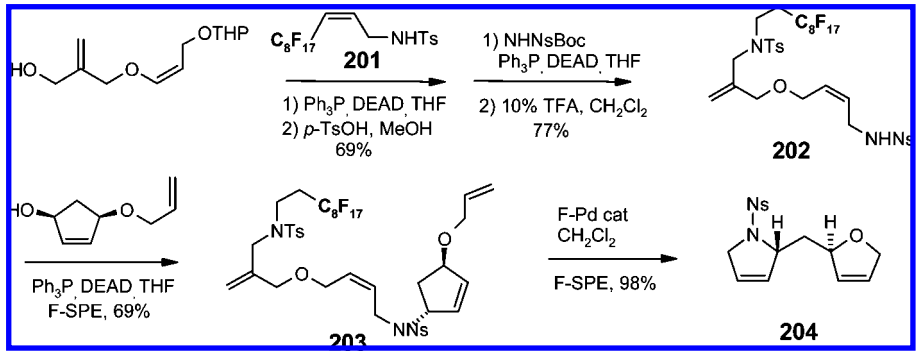
5.1. Quasiracemic Synthesis

Quasiracemic FMS provides a new approach for making enantiomeric compounds (Scheme 89).[113] Quasiracemic synthesis starts with two individual *R*- and *S*-enantimers attached to two fluorous linkers with different fluorine contents. After multisteps of mixture synthesis followed by F-HPLC demixing and linker cleavage, it yields two individual products as enantiomers. The separation and identification of the quasienantiomers are ensured by the phase tag-based F-HPLC. In a more complicated quasiracemic FMS, additional enantiomeric pure building blocks and fluorous linkers can be used to generate multiple chiral centers and more than two stereoiomers.

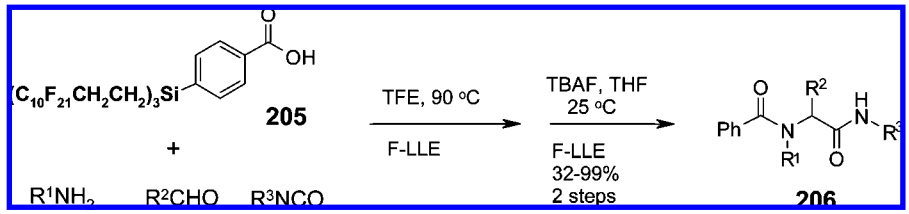
5.1.1. Enantiomers of Natural Products

Natural product (*S*)-mappicine was isolated from *mappia fetida* and it is active against the herpes viruses (HSV).[114] Its ketone analog nothapodytine B is active against human cytomegalovirus (HCMV).[115] Quasiracemic FMS of map-

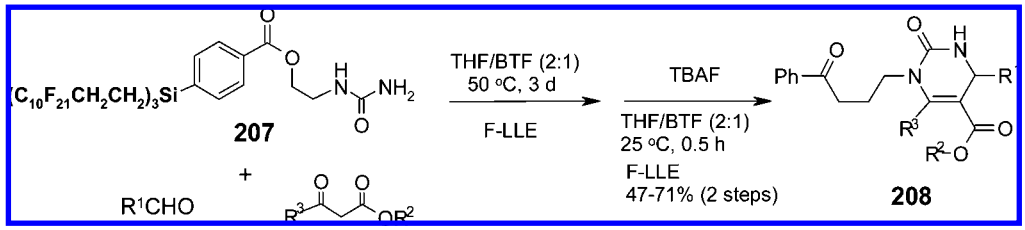
Scheme 80. Toluenesulfonamide Linker-Facilitated ROM Reaction



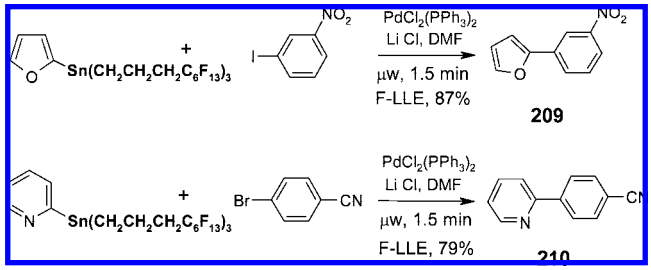
Scheme 81. Traceless Silyl Linker for Ugi Reactions



Scheme 82. Traceless Silyl Linker for Biginelli Reaction



Scheme 83. Alkylstannyl Linker-Facilitated Stille Reactions



picines has been accomplished by the Curran group (Scheme 90).[116] Enantiomeric (*R*)- and (*S*)-alcohols were individually attached to silanes containing C_6F_{13} and C_8F_{17} tags to form quasienantiomers (*R*)-**227a** and (*S*)-**227b**. The equimolar mixture of these two compounds was subjected to TMS group exchange with ICl followed by demethylation with BBr_3 to form pyridine M-**228**. *N*-Propargylation and subsequent radical cyclization with phenyl isonitrile provided quasiracemic mixture M-**229**. The separation of this mixture by F-PHLC yielded two quasienantiomers of **229**. Both (+)-**230a** and (−)-**230b** mappicines were then obtained in enantiopure forms after deprotection with TBAF in THF. The Zhang and Curran groups extend this protocol for a seven-component FMS to prepare 560 mappicine analogs (Section 5.2.1).

Natural product pyridovericin is an inhibitor of the protein tyrosine kinase.[117] The Curran group developed a quasiracemic FMS protocol for the synthesis the enantiomers of pyridovericin (Scheme 91).[116] Two fluorous TIPS-type linkers with C_6F_{13} and C_8F_{17} groups were individually attached to form (*S*)-**231a** and (*R*)-**231b** alcohols. A mixture of these two attached alcohols was taken through a sequential reactions to form aldehydes M-**232**, β-ketoesters M-**233,** and then M-**234**. M-**234** was thermally agitated to close the ring and then separated by F-HPLC to give two quasienantiomers, (*S*)-**235a** and (*R*)-**235b**. The fluorous linkers were cleaved to form enantiomers of pyridovericin (*S*)-**236a** and (*R*)-**236b.**

5.1.2. Stereoisomers of Natural Products

Marine macrolactone (−)-dictyostatin has potent anticancer activity.[118] The Curran group accomplished the FMS of (−)-dictyostatin and three diastereomers (Scheme 92).[119] A set of four enantiopure alcohols with chiral centers at C6 and C7 were individually attached to a set of four fluorous TIPS-type linkers bearing C_3F_7, C_4F_9, C_6F_{13}, and C_8F_{17} groups. The attached alcohols were converted to fluorous esters **237a-d**. The mixture of the four esters was converted to M-**238** in three steps and then coupled with an alkynyllithium followed by the reduction with (*S*,*S*)-Noyori's catalyst to give M-**239**. The alkyne group in M-**239** was reduced to the *cis*-alkene, the hydroxy group was protected with the TBS, and the TES was cleaved to give M-**240**. Sequential Dess-Martin oxidation, coupling with **241,** reduction of the alkene with Stryker's reagent, and another reduction of the ketone with $LiAl(Ot\text{-}Bu)_3H$ gave β-alcohols M-**242** as the major product. Additional reactions involving TBS protection, removal of the trityl group with $ZnBr_2$, oxidation with the Dess-Martin reagent, and Still-Gennari reaction provided (*E*),(*Z*)-dienes M-**243**. Removal of PMB, hydrolysis of the conjugated esters, followed by macrolactonization gave (2*Z*),(4*E*)-macrolactone **244** as a major product and (2*E*),(4*E*)-macrolactone as a minor product. The mixture was separated by

Scheme 84. Alkylstannyl Linker-Facilitated Synthesis of Radioactive Aryliodide

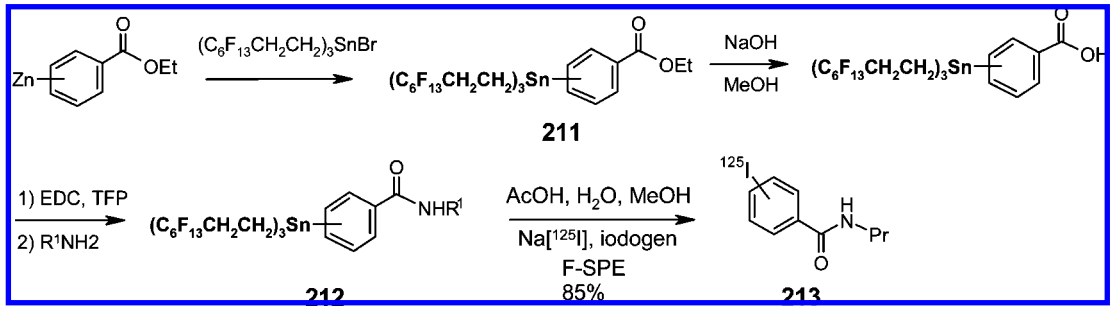
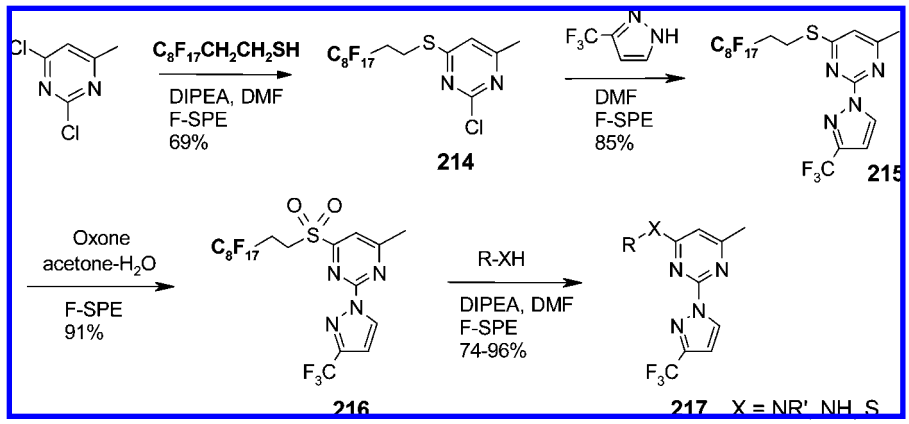


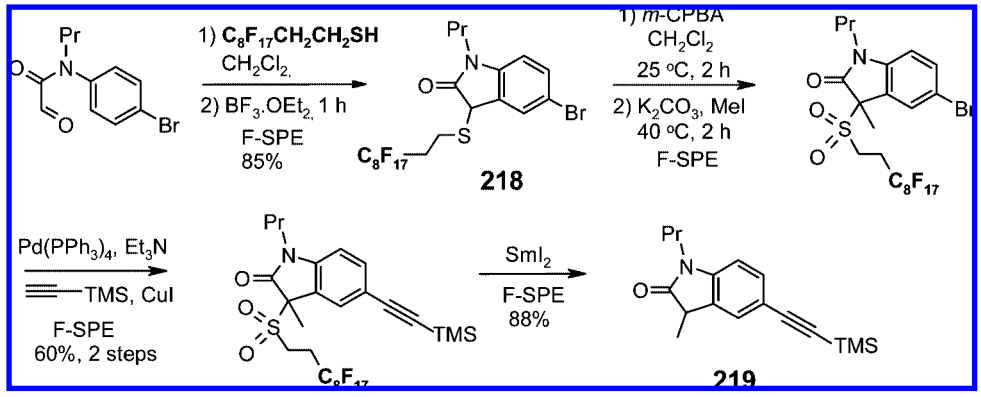
Table 3. Safety-Catch Linkers

Fluorous linker	Structure	Separation method	Attach to	Conditions for attachment	Conditions for release	Ref
Alkylthio	C_8F_{17}–SH	F-SPE	Arylhalides	DIPEA, HF,DMF	1) Oxozon 2) amines or thiols	107
		F-SPE	Pummerer cyclization products	quench Pummerer cyclizations	1) oxidation 2) diverse transfermations	108
		F-SPE	(+)-Protoliches-terinic acid	Et_3N, DMF	1) *m*CPBA, THF 2) MePhH, reflux	109
Arylgermyl	2-Nap, 2-Nap, Ge, C_8F_{17}, Br	F-SPE	Aryllithiums or Grignard reagents		1) *hν* in Pyrex tube $Cu(BF_4)_2$-nH_2O 2) Pd-catalized coupling	110

Scheme 85. Thio Linker-Facilitated Synthesis of Disubstituted Pyrimidines



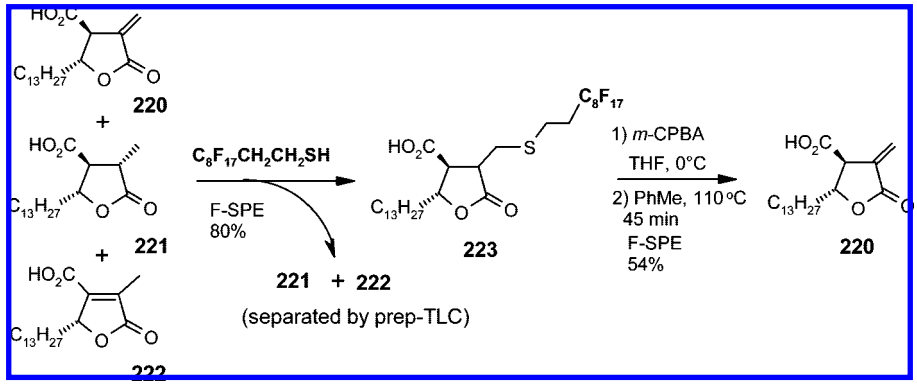
Scheme 86. Thiol Linker for Catch and Release of Pummerer Cyclization Products



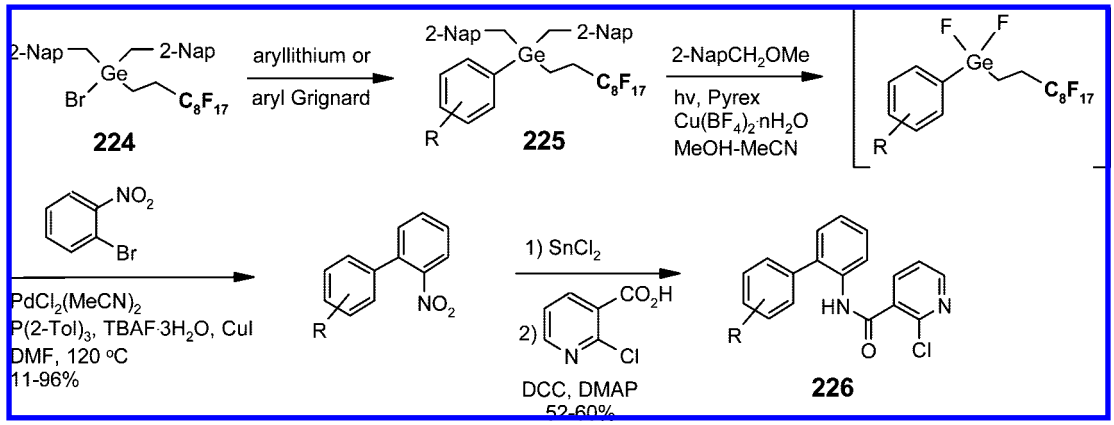
F-HPLC followed by linker cleavage to afford dictyostatin (6*R*,7*S*)-**244a** and three C6,C7-*epi*-dictyostatin diastereomers.

The Curran group developed an "*en route*" strategy for the synthesis of eight stereoisomers of passifloricin A at C5, C7, and C9 (Scheme 93).[120] For a four-component FMS, the fluorine content of each attached-molecule is defined by two fluorous linkers. Enantiopure allyl silyl ether (*R*)-**245** was subjected to hydroboration and oxidation to form

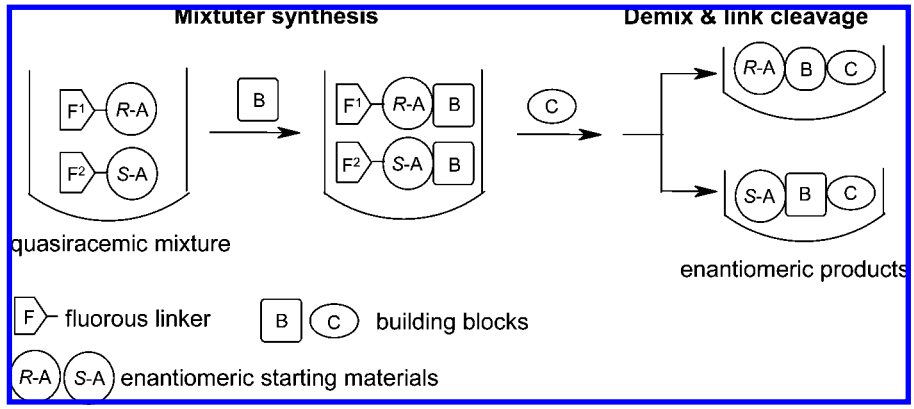
Scheme 87. Thio Linker-Facilitated Separation of (+)-Protolichesterinic Acid



Scheme 88. Arylgermanyl Linker-Facilitated Synthesis



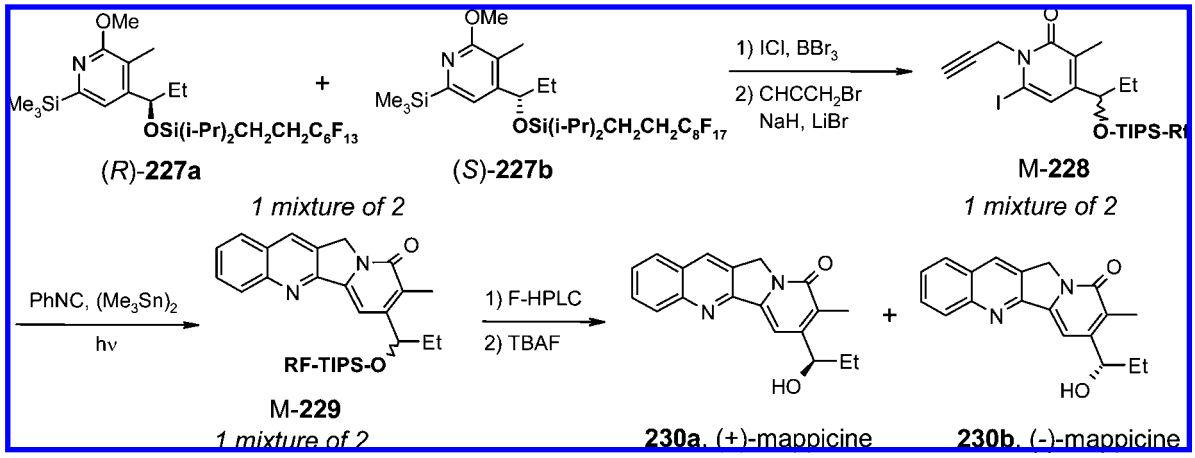
Scheme 89. Schematic Diagram of Quasiracemic FMS



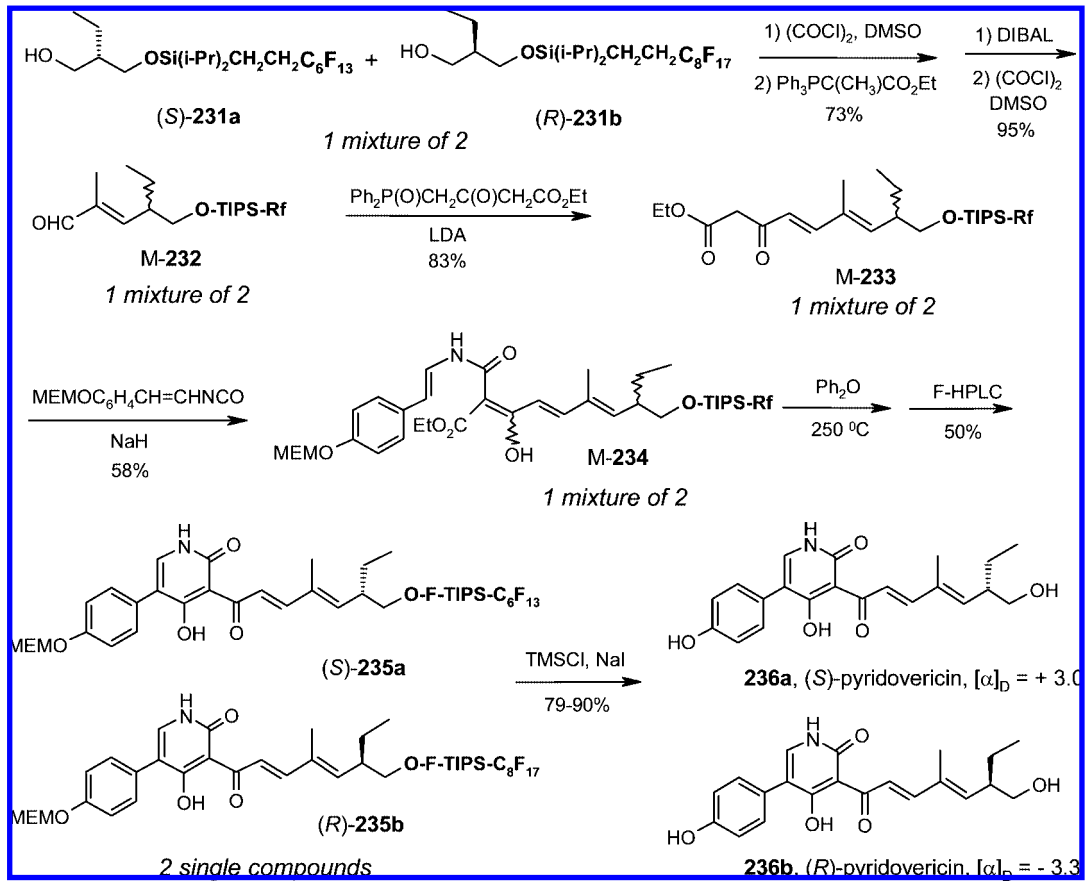
aldehyde. Half of the aldehyde was treated with the (*R*,*R*)-Duthaler-Hafner (DH) reagent, and the resulting alcohol was attached with fluorous triisopropylsilyl trifluoromethanesulfonate (F-TIPSOTf) bearing a C_4F_9 group. The other half was treated with the (*S*,*S*)-DH reagent, and the alcohol was attached to F-TIPS group bearing C_3F_7. The quasiracemic mixture M-**246** was split to two portions and subjected to oxidation, allylation, and then linker-attachment reactions. The product from the (*R*,*R*)-DH reagent got a new nonfluorous TIPS, and the product from the (*S*,*S*)-DH reagent got the repeat C_3F_7 group. A pair of two-compound mixtures was mixed to make a four-compound mixture M-**247**. Repeated split, oxidation, and allylation of M-**247** gave two four-component mixtures M-**248.** The mixtures were acylated followed by ring-closing metathesis to provide the eight stereoisomers of protected passifloricins as two mixtures of four compounds M-**249**. Each of these two mixtures has four components with C_3F_7, C_4F_9, two C_3F_7, and two C_4F_9 group. Because of the number of fluorine atoms on each component in the mixture is different, they were easily demixed by F-HPLC. All eight isomers of **249** were deprotected individually to provide eight compounds **250** including an enantiomer of passifloricin A (*5S*,*7R*,*9R*,*12R*) and seven diastereomers with R configurations at C12 and all the possible configurations at C5, C7, and C9.

Lagunapyrones A, B, and C were isolated from the secondary metabolites of estuarine actinomycetes.[121] Lagunapyrone B is active against a human colon cancer cell line. This class of compounds features a 24-carbon chain consisting of an α-pyrone ring with two adjacent stereocenters (C6,7) and a second group of three stereocenters (C19−21). No synthetic efforts toward the lagunapyrones have been reported before the Curran group accomplished the FMS (Scheme 94).[122] Two components of the left fragment (*R*,*S*)-**252** and (*S*,*R*)-**252** each containing two stereocenters were prepared by quasiracemic FMS starting

Scheme 90. Quasiracemic FMS of (+)- and (−)-Mappicines



Scheme 91. Quasiracemic FMS of (*S*)- and (*R*)-Pyridovericins

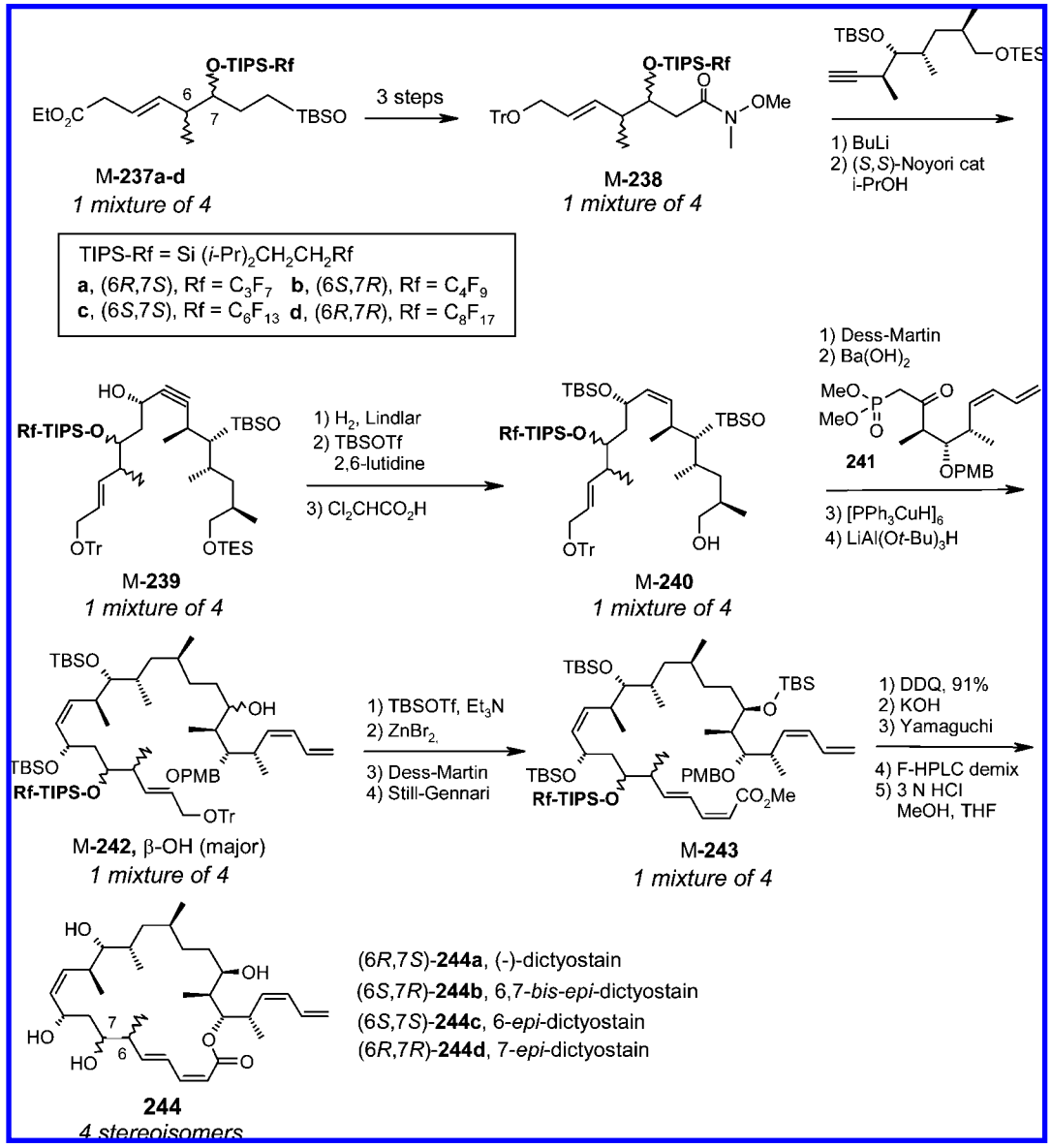


from M-**251**. The right fragment M-**254** containing C19−21 stereocenters was prepared by quasiracemic FMS from (*R*,*R*)-**253** and (*S*,*S*)-**253**. The mixture of M-**254** was reacted with (*R*,*S*)-**252** and (*S*,*R*)-**252** through the Stille coupling reaction to give two quasiracemic mixtures of attached products. These two mixtures were separated by F-HPLC followed by linker cleavage to afford lagunapyrone B **255** and three stereoisomers.

The murisolin class of monotetrahydrofuran acetogenins has six stereocenters at C4, C15, C16, C19, C20, and C34 positions. Among the known murisolin diastereomers, the most active one has extremely high cytotoxicity (IC_{50}) at 1 femptomolar range, while the potency of other diastereomers may differ by factors of up to 1 billion.[123] The Curran group reported the FMS of 16 diastereomers of murisolin (Scheme 95).[124] Sixteen stereoisomers are derivatives of four stereocenters at C15, C16, C19, and C20 positions of dihydroxytetrahydrofuran fragment with fixed 4(*R*) and 34(*S*) centers. The FMS started from M-**256,** a mixture of four enantiomerically pure compounds each tagged by a PMB with different Rf groups (C_2F_5, C_4F_9, C_6F_{13}, and C_8F_{17}). M-**256** was then taken through a sequence of organic reactions to form M-**257**, M-**258**, M-**259**, M-**260**, M-**261**, and finally M-**262.** Two split and parallel syntheses were conducted for M-**258** to M-**259**. Fluorous HPLC separation of 4 mixtures of M-**262** followed by linker cleavage provided 16 desired diastereomers of murisolin **263**.

The development of a double linker strategy further improved the synthetic efficiency for preparation of murisolin stereoisomers.[125,126] A mixture of four stere-

Scheme 92. FMS of (−)-Dictyostatin and Three Stereoisomers



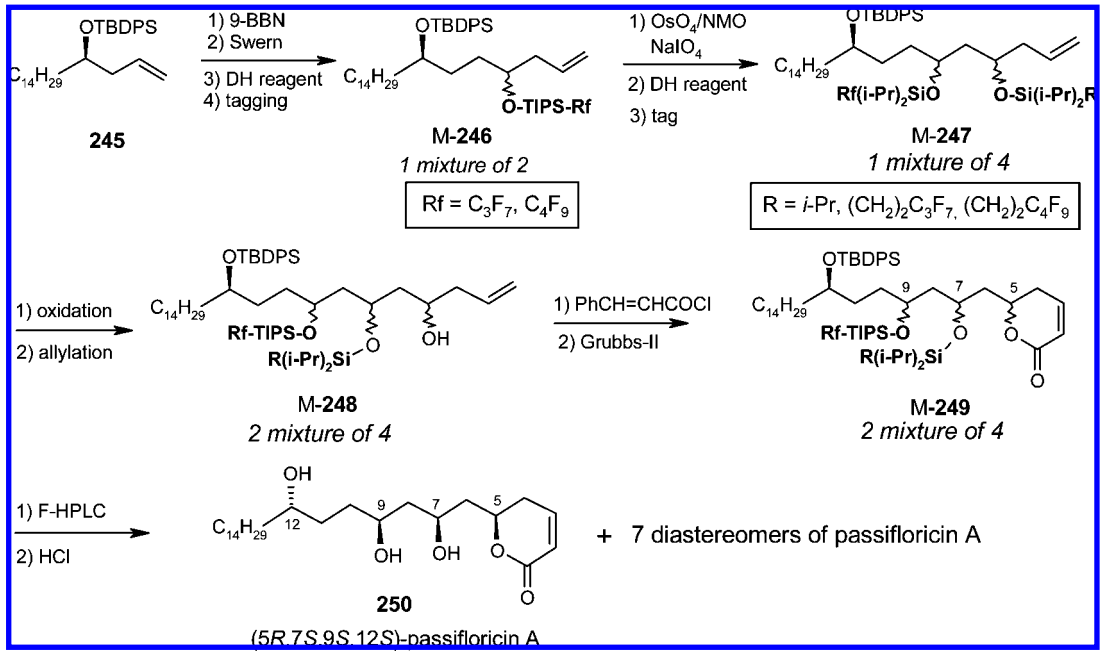
oisomers of dihydroxytetrahydrofuran encoded with four fluorous linkers at C19 and C20 was coupled to a mixture of four stereoisomers of hydroxybutenolide fragments encoded with four oligoethylene glycol (OEG, $[OCH_2CH_2O]_n$) tags at C4 and C34. The mixture containing 16 double-linked murisolin diastereomers was first demixed by flash chromatography on normal silica gel to give four fractions according to the length (polarity) of the OEG tags. The second F-HPLC demixing gave 16 individual double-attached compounds 264 (Scheme 96). Both fluorous and OEG supports were cleaved by the treatment with DDQ. Sixteen murisolin diastereomers were produced in a single solution-phase synthesis without splitting.

The propionate ester of 3,7,11-trimethyl-2-tridecanol is a female sex pheromone of the minor sawfly *Microdiprion pallipes*.[127] This molecule has four chiral centers and 16 possible stereoisomers. The Curran group developed prepare all 16 steroisomers of pinesaw fly sex pheromones using F-PMB-attached enantomerically pure aldehydes as the starting materials for a four-component FMS.[128,129] Four F-PMB-attached aldehydes **265** were individually prepared by reaction of F-PMB aldehyde with a diol followed by reduction with DIBAL and DMP oxidation (Scheme 97). These four attached aldehydes were mixed to form M-**265** and then split to two portions to react with sulfone (*R*)-**266** and (*S*)-**266** to form aldehyde (*R*)-M-**267** and (*S*)-M-**267**, respectively (Scheme 98). Each of these two mixtures was subjected to reduction, coupling with (*R*)-**266** and (*S*)-**266**, TBS deprotection, oxidation, and Wittig reaction to give four mixtures of triene M-**269**. Hydrogenation of alkene followed by F-HPLC demixing of M-**269** afforded sixteen individual F-PMB-attached tridecanols **270**. They were then converted to sixteen pinesaw fly sex pheromone diastereomers **271** by parallel linker cleavage and acylation reactions.

5.2. Analog Synthesis

FMS has been applied to synthesize compound libraries using a set of analogous starting materials individually attached to a set of analogs fluorous linkers with different length of fluorous tags (Scheme 99).[111,112] The mixture of attached substrates is treated as a single compound and subjected to one-pot and split-parallel reactions. The attached product mixtures are demixed by F-HPLC followed by linker cleavages to release final products. The efficiency of FMS

Scheme 93. FMS of Passifloricin A and its Stereoisomers

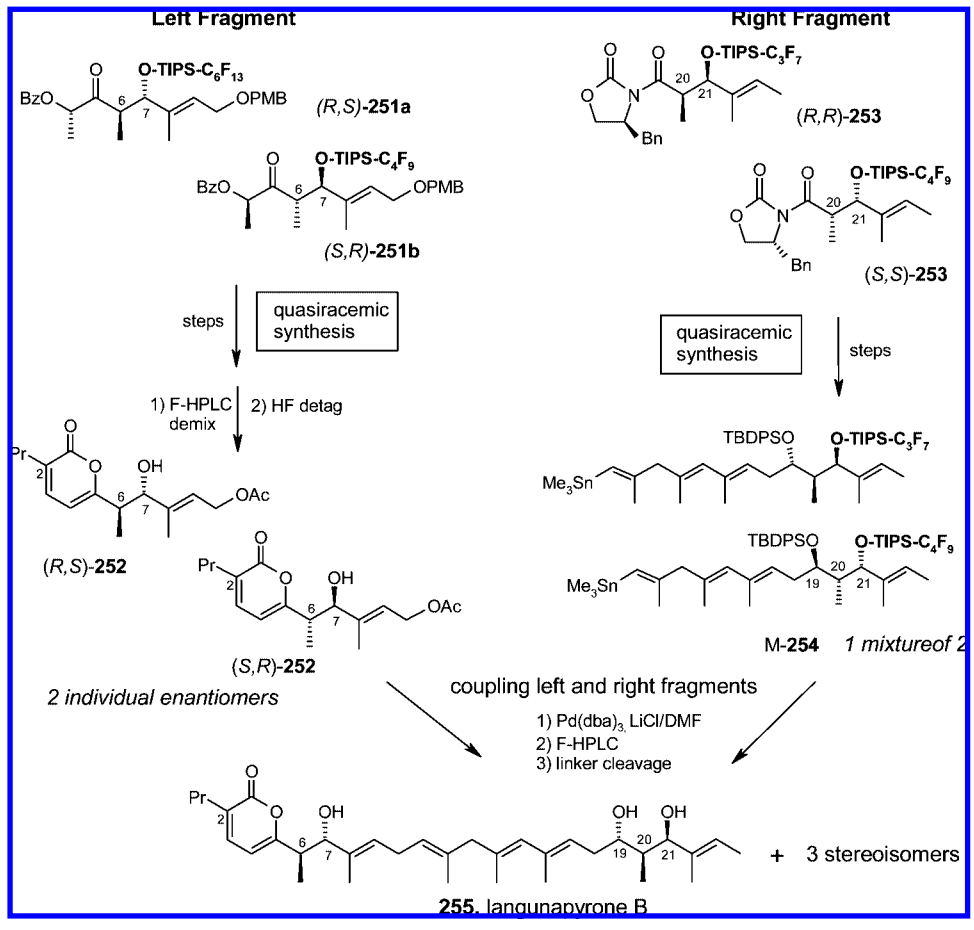


is directly proportional to the number of components mixed (step 2), the length of mixture synthesis (step 3), and the number of splits (step 3).

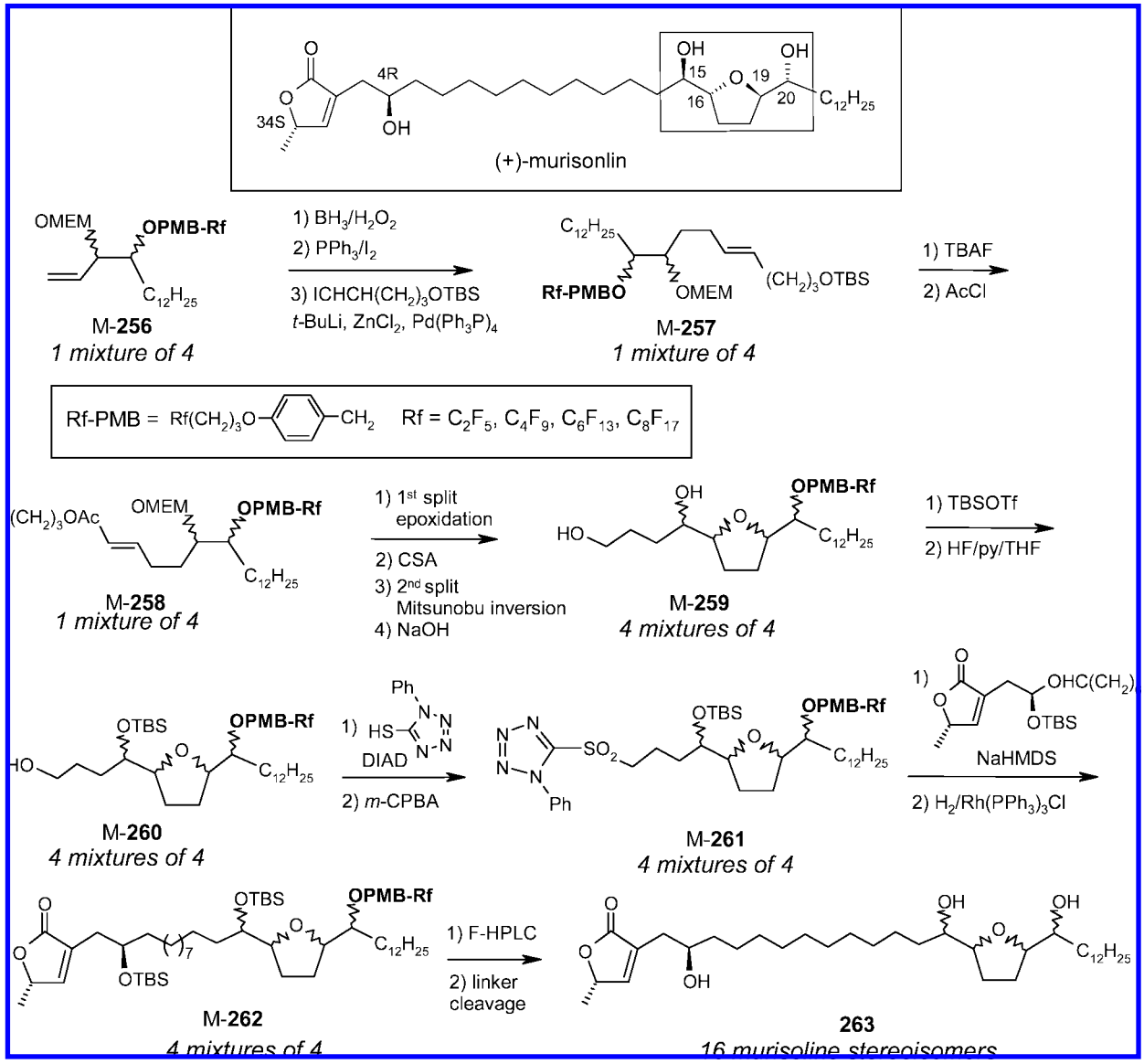
5.2.1. Natural Product and Natural Product-Like Libraries

Tecomanine is an alkaloid and has good hypoglycemic activity.[130] The Curran groups produced a 16-compound library of 4-alkylidine cyclopentenones by a 4-component FMS (Scheme 100).[131] The 4-alkylidne cyclopentenone ring skeleton of tecomanine is a bicyclic α-amino acid derivative that can be useful in the synthesis of peptidomimetics. Four fluorous CBzs bearing C_4F_7, C_6F_{13}, C_8F_{17}, and C_9F_{19} groups were individually attached to a set of amino acids with different R^1. Equimolar F-CBz protected amino acids were

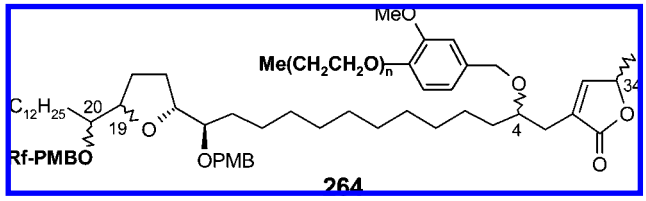
Scheme 94. FMS of Lagunapyrone B and Three Stereoisomers



Scheme 95. FMS of Murisolin and Stereoisomers



Scheme 96. Double-Linker-Attached Murisoline Diastereomers

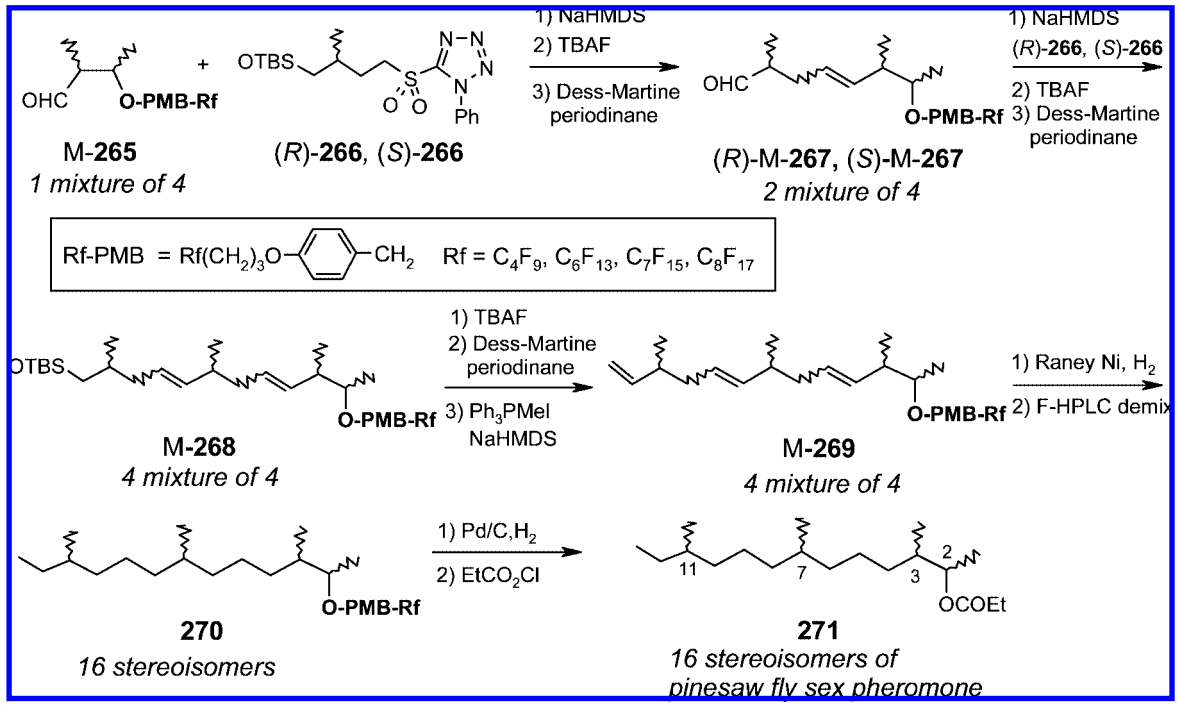


mixed and reacted with a propargyl alcohol to form a 4-component mixture of esters M-**272**. Claisen rearrangement of propargyl esters M-**273** afforded allenic amino acid M-**274**. The mixture was split into four portions and reacted with one of four different propargyl bromides to afford four mixtures of alkynyl allenes M-**275**. The [2 + 2+1] cycloaddition of allenes M-**275** followed by F-HPLC demix afforded 16 individual 4-alkylidene cyclopentenones **276**. Removal of fluorous Cbz by treatment with dimethyl sulfide and BF_3-Et_2O afforded 16 final products **277**.

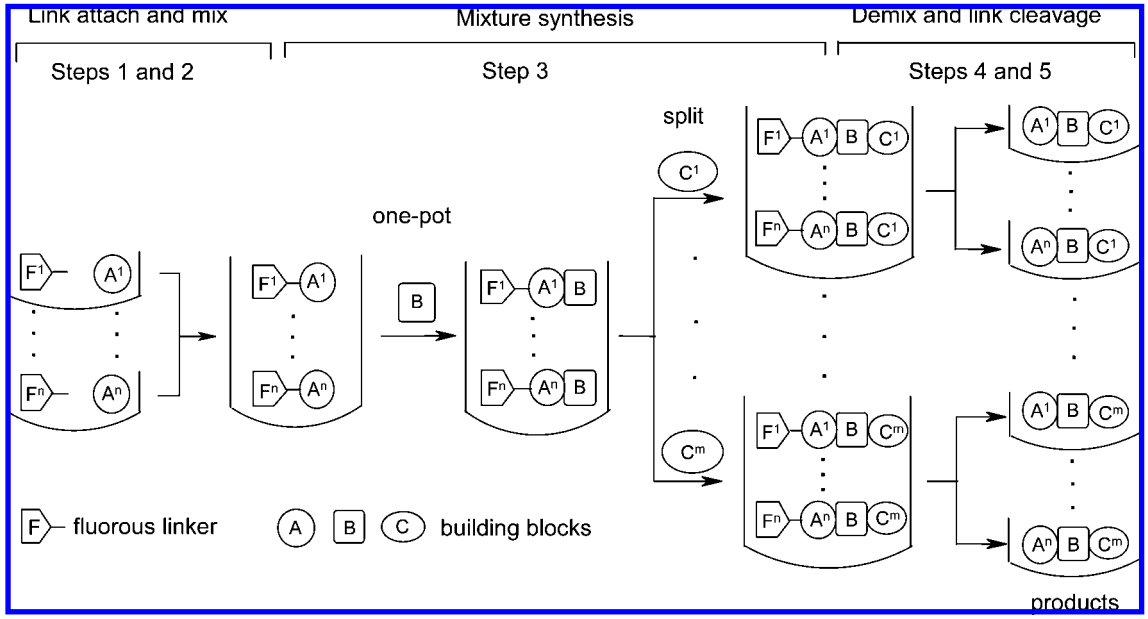
A "redundant tag" strategy for F-Cbz-based FMS of fused-tricyclic hydantoins has been developed by the Curran group.[132] Since both substrates and linkers containing fluorine atoms, the right combination can make each component in the mixture has different fluorine content despite the tag redundancy. The six F-Cbz-attached carbobenzyloxy amino acids were prepared individually and then mixed to give M-**278** (Scheme 101). The mixture underwent esterification, Claisen rearrangement, *tert*-butyl esterification, and removal of Me_3Si group to yield M-**280**. *N*-propargylation of M-**280** followed by allenic Pauson-Khand reaction of alkynyl allenes M-**281** afforded three products; R-alkylidenecyclopentenone stereoisomers M-**282**-*syn* and M-**283**-*anti* along with 4-alkylidenecyclopentanone regioisomer M-**283**. This complex mixture showed only three main spots in a standard silica TLC analysis, and it was purified by flash chromatography over regular silica gel. The single mixture of M-**282**-*syn*, M-**282**-*anti*, and M-**283** was treated with TFA to cleave the *tert*-butyl group, and the resulting acid mixture was coupled with phenethylamine. The mixture was separated by normal silica gel flash chromatography to give three submixtures containing predominately M-**284**-*syn*, M−**284**-*anti*, and M-**285**. These mixtures were then demixed by F-HPLC to give 17 crude individual products **284**-*syn/anti* and **285**. These crude products were not isomerically pure. Removal of the fluorous tag and hydantoin formation was achieved by treatment of the

Scheme 97. F-PMB-Attached Chiral Aldehydes

Scheme 98. FMS of 16 Steroisomers of Pinesaw Fly Sex Pheromone



Scheme 99. Schematic Diagram of FMS

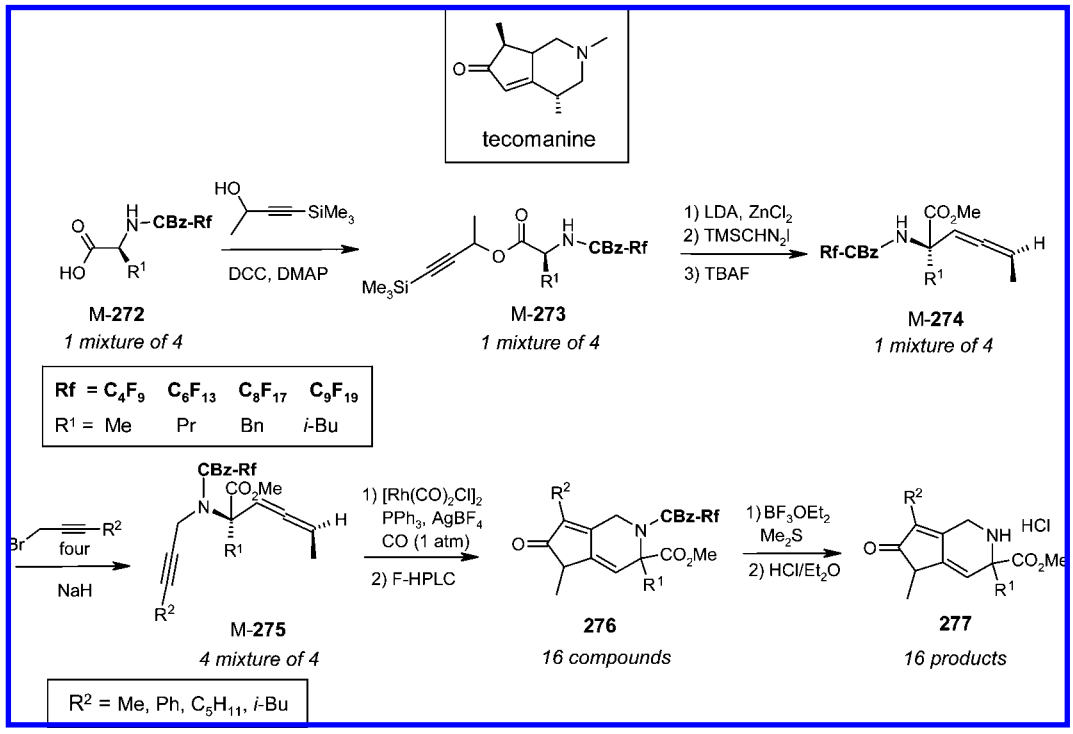


individual amides **284**-*syn/anti* and **285** with diisopropylethylamine (DIPEA) under microwave conditions. The cyclative cleavage reactions of **284**-*syn* and **284**-*anti* provided the same products **286**. Normal phase HPLC purification gave 11 of possible 12 final products **286** and **287**.

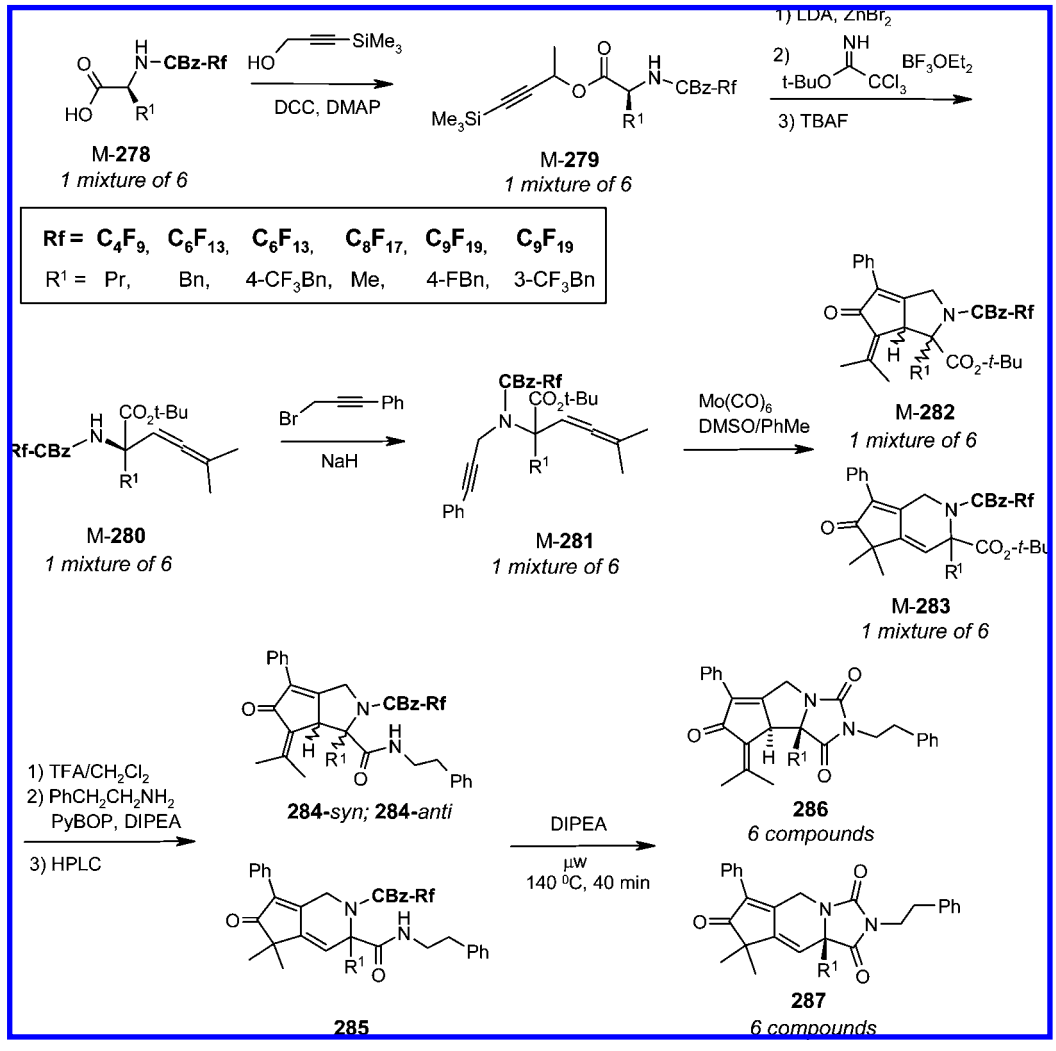
The Curran group employed fluorous benzylbromide linkers for FMS of truncated analogs of (+)-discodermolide at the C22 position.[133] Four starting materials with different R group (H, CH=CH_2, Et, Ph) were protected with the corresponding fluorous PMB (Rf = C_4F_9, C_6F_{13}, C_8F_{17}, $C_{10}F_{21}$) (Scheme 102) and mixed to form M-**288**. 4-Component FMS converted M-**288** sequentially to phosphonium salt M-**289**, Wittig reaction product M-**290**, carbamate M-**291**, and then product M−**292**. Four truncated discodermolide analogs **293** were produced after demix and linker cleavage.

Other than quasiracemic FMS of mappicine enantiomers (Scheme 90), a library containing 560 mappicine analogs has been prepared by a seven-component FMS (Scheme 103).[30] In this case, fluorous linkers encoded the analogous

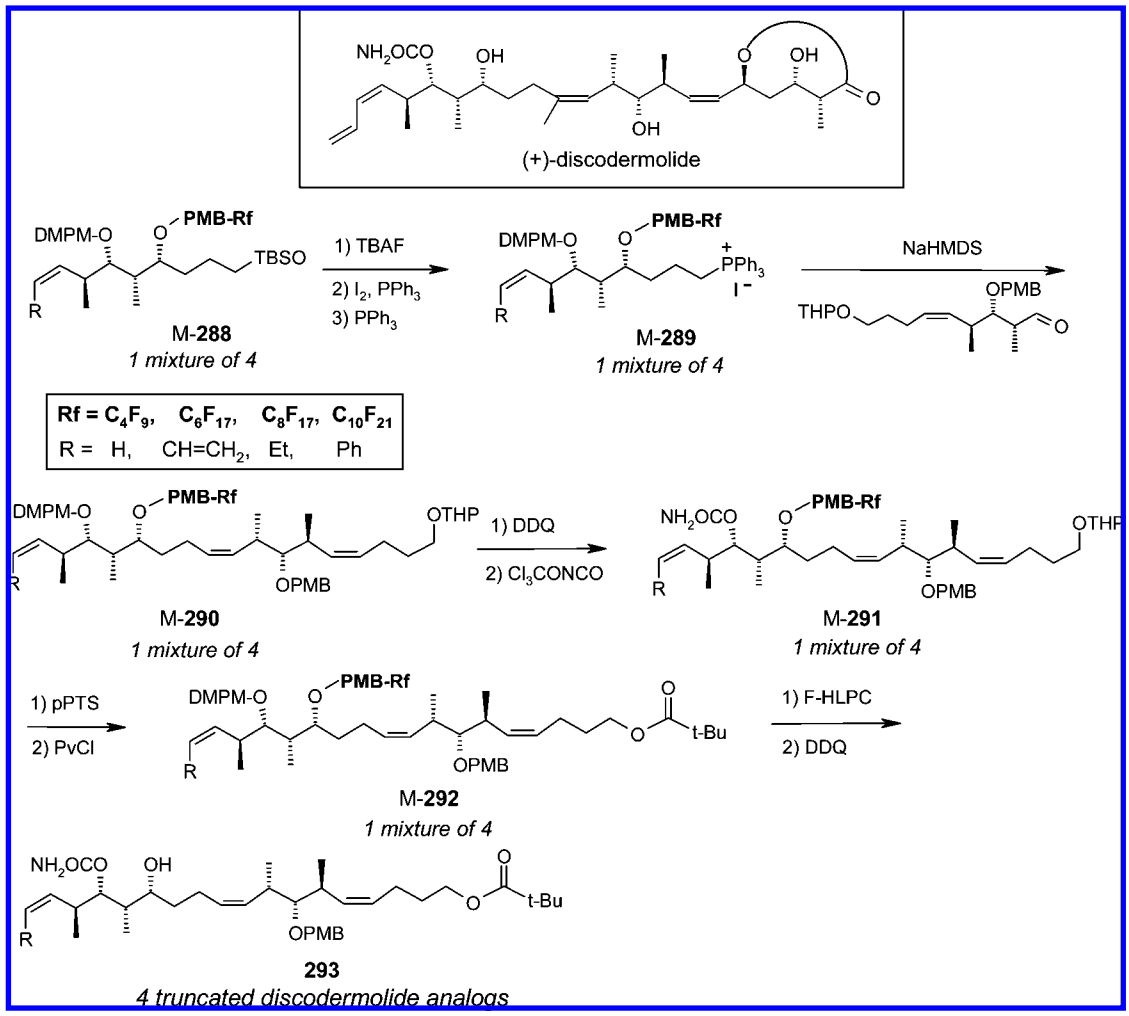
Scheme 100. FMS of 16 Tecomanine-Like Compounds



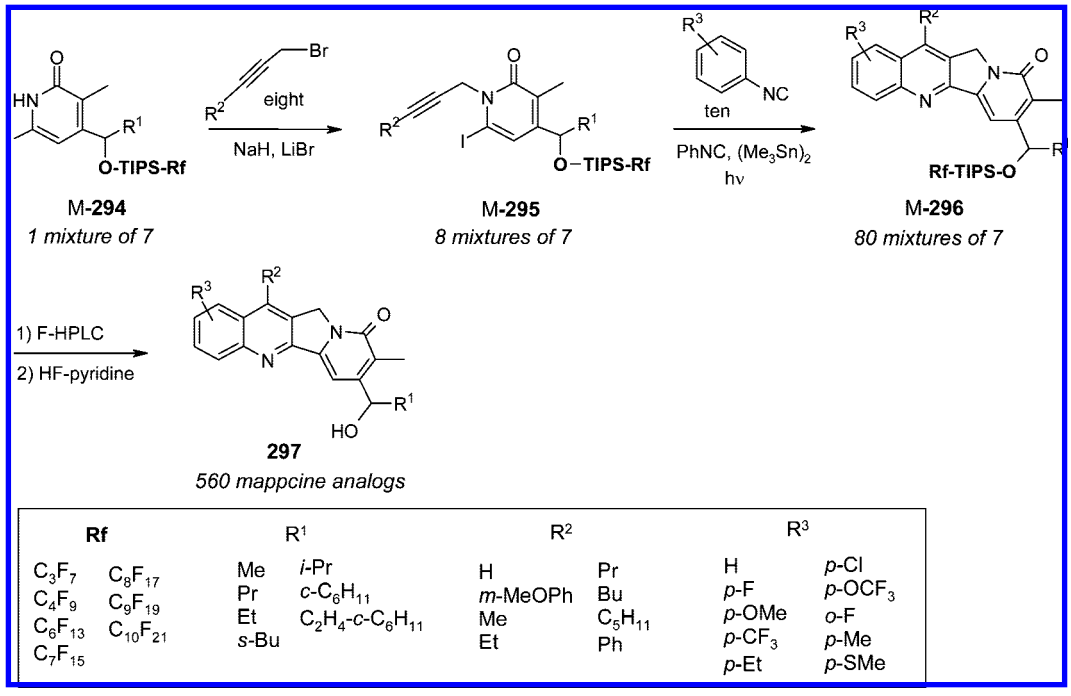
Scheme 101. FMS of Two Fused-Tricyclic Hydantoin Scaffolds



Scheme 102. FMS of Truncated Analogs of Discodermolide

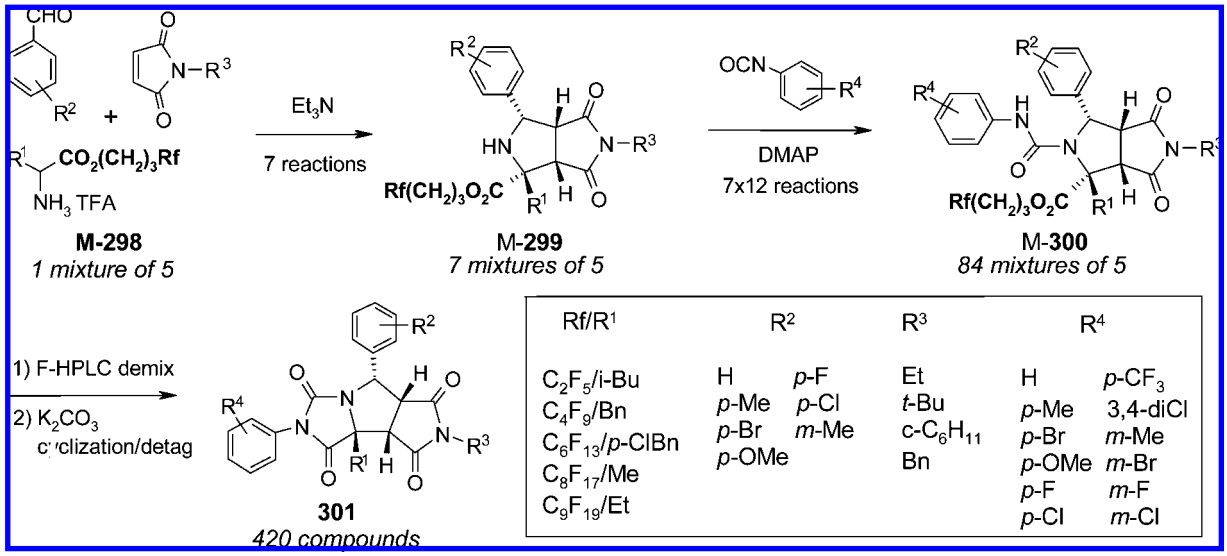


Scheme 103. 7-Component FMS of a 560-Member Mappicine Library

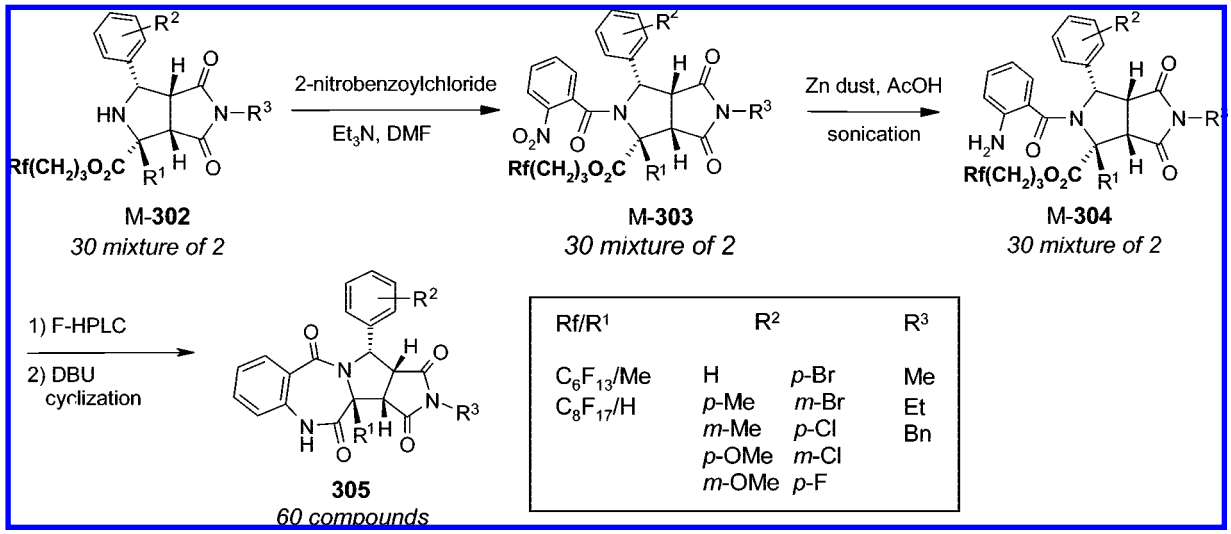


substrates instead of enantiomers. The seven-component mixture M-**294** was split into 8 portions and subjected to *N*-propargylations with 8 different bromides to give 8 mixtures of M-**295**. Each of the 8 mixtures of M-**295** was further split into 10 portions for radical annulation reaction with isonitriles. The resulting 80 mixtures of M-**296** were

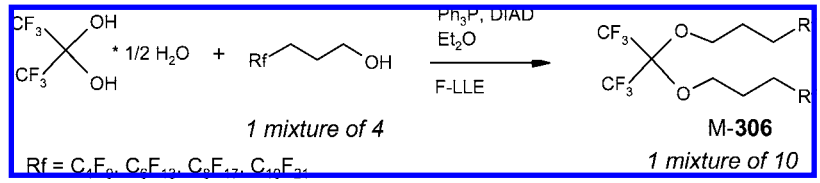
Scheme 104. Five-Component FMS of a 420-Membered Fused-Hydantoin Library



Scheme 105. Two-Component FMS of Fused-Benzodiazapindione Library



Scheme 106. Fluorous Alcohols for FMS of Ketals



demixed by F-HPLC (Scheme 9) and then treated with HF-pyridine to give a 560-member mappicine library **297**.

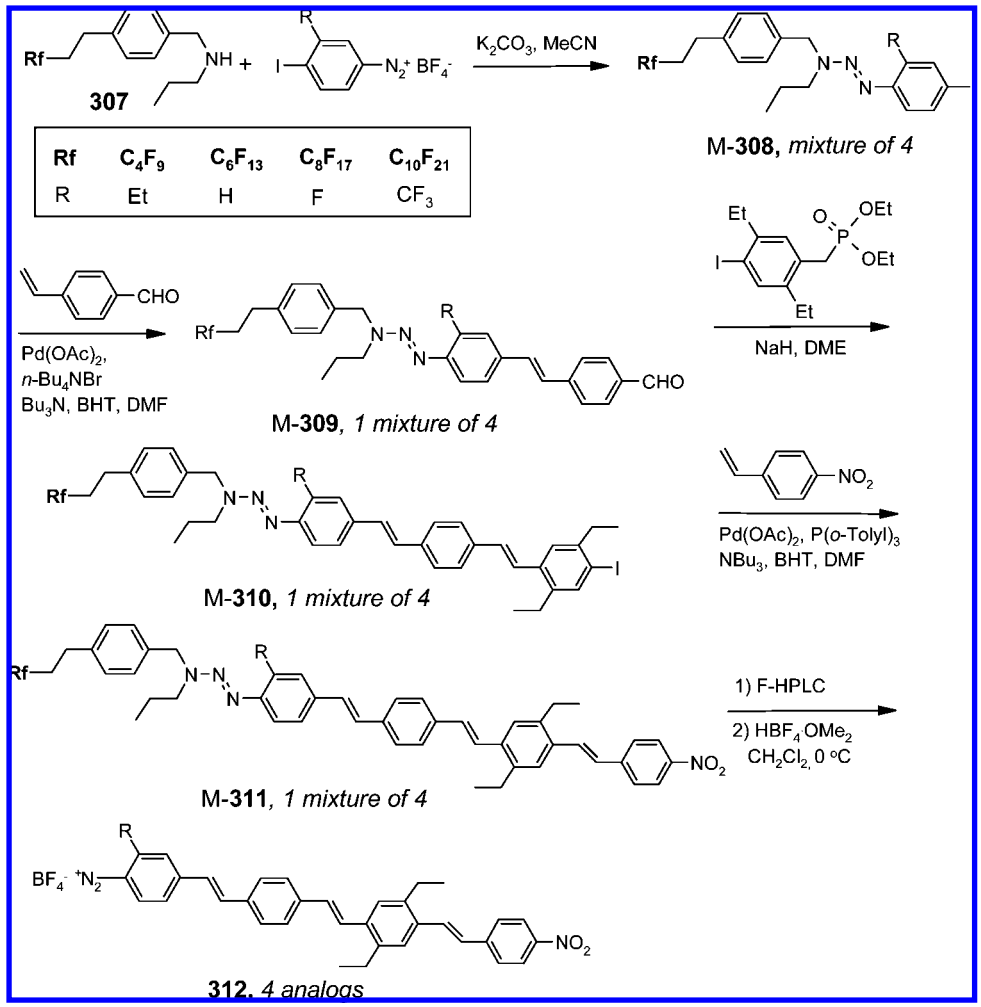
5.2.2. Novel Heterocyclic Compound Libraries

A five-component FMS method for preparation of a 420-membered hydantoin-fused tricyclic compound library has been developed (Scheme 104).[134] Five α-amino acids bearing different R^1 groups were paired with five perfluoroalkyl alcohols in such: C_2F_5/*i*-Bu, C_4F_9/Bn, C_6F_{13}/*p*-ClBn, C_8F_{17}/Me, C_9F_{19}/Et. An equal molar mixture of five fluorous amino ester M-**298** was split to seven portions for 1,3-dipolar cycloaddition reactions with one of the seven benzaldehydes and one of the four maleimides. The resulting seven mixtures of M-**299**were each split to twelve portions and reacted with one of the twelve phenylisocyanates to form 84 mixtures of M-**300**. F-HPLC demixing followed by parallel cyclative linker cleavage produced a 420-member library of **301.**

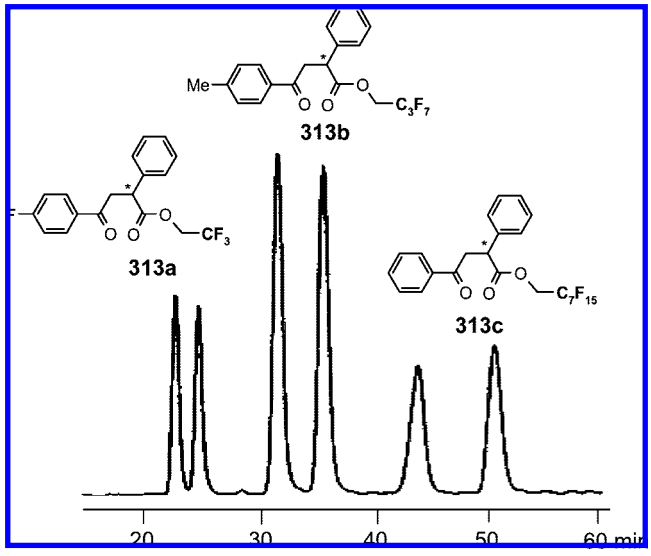
Incorporation of 4-column parallel F-HPLC coupled with multichannel MS interface increased the speed for both sample analysis as well as sample demixing.[134] A 5 min analysis method for baseline separation of five components of M-**302** has been developed for four-channel parallel LC-MS analysis. Four mixture samples containing a total of 20 compounds could be separated in 5 min, which dramatically improves the efficiency of FMS.

Synthesis of a 60-member benzodiazepine-fused tetracyclic proline library **305** has also been accomplished.[134] A mixture of two fluorous amino acids was reacted with ten aldehydes and three maleimides to give thirty mixtures of M-**302**

Scheme 107. FMS of of Oligo(Phenylene Vinylene)s

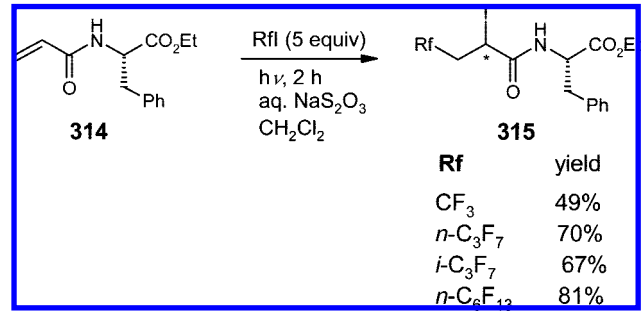


Scheme 108. Chiral HPLC Separation of Three Racemic Mixtures[a]



[a] β-CD column (OA-7500), gradient MeOH-H_2O 75:25 to 85:15 in 60 min, flow rate 0.5 mL/min. From ref 138a.

Scheme 109. Racemic Mixture Synthesis of Iodopeptides



(Scheme 105). *N*-acylation followed by the nitro group reduction of M-**303** with zinc dust under sonication conditions gave 30 mixtures of M-**304** that were demixed by F-HPLC to give 60 individual compounds. These compounds underwent cyclative linker cleavage with DBU to form corresponding benzodiazepine-fused tetracyclic compounds **305**.

In addition to the synthesis of heterocyclic compounds, fluorous alcohols have been used by the Rabai group for FMS of ketals (Scheme 106).[135] The Rabai group reported a one-pot Mistunobu reaction of four homologous 3-perfluoroalkypropanols with hexafluoroacetones to produce ten fluorous ketals M-**306**. The reaction mixture was analyzed by GC for a fluorophilicity study.

5.3. Synthesis of Oligomers

Jian and Tour used four fluorous secondary benzylamines linkers for the attachment of a diazo group in FMS of oligo(phenylene vinylene)s (OPVs) and hybrid oligomers

(Scheme 107).[136] These compounds can be used as surface grafting moieties in hybrid silicon/molecule assemblies. The fluorous linkers **307** and the diazonium substrates were anchored together to form a four-component mixture of triazine M-**308**. The mixture was subjected to alternating Heck coupling to form M-**309** and M-**310** followed by Horner-Wadswoth-Emmons (HWE) reactions to form M-**311**. The mixture synthesis was monitored by analytical F-HPLC, and isolations of final OPV and hybrid oligomer tetramers M-**311** were achieved by preparative F-HPLC. The demixed products were cleaved from the fluorous linkers to afford a series of aryl diazonium compounds **312**. The cleaved fluorous linkers could be recovered for reuse.

5.4. Racemic Mixture Synthesis

Different from the quasiracemic synthesis in which a pair of enantiomers is attached to two fluorous linkers and the separation of fluorous quasiracemic products is achieved by F-HPLC,[113] fluorous racemic mixture synthesis has been developed by Mikami and the co-workers using racemic or prochiral mixtures as the starting materials.[137] The resolution of the fluorous racemic products is achieved by chiral HPLC on the stationary phases such as β-cyclodextrin (β-CD).[138] The fluorous racemic mixture synthesis have following unique features: (1) they use only one fluorous linker for a pair of racemates; (2) racemization of attached compounds during the reactions is not a issue since the enantiomers are separated by the chiral HPLC; (3) not only are the racemates bearing the same linker separatable, the analogs bearing the different length of fluorous tags can also be isolated. Because the separation on the β-CD column is related to the carbon number of the analysts, and not reliant on the fluorine−fluorine interaction between the analysts and the stationary phase, the β-CD column cannot guarantee good separation of two compounds in which one has a fluorous chain and the other has a similar, but not fluorous, chain. In other words, on the β-CD column the separation of fluorous compounds from the nonfluorous analogs is not as predictable as that on the fluorous column since F-HPLC is a fluorine content-based separation.

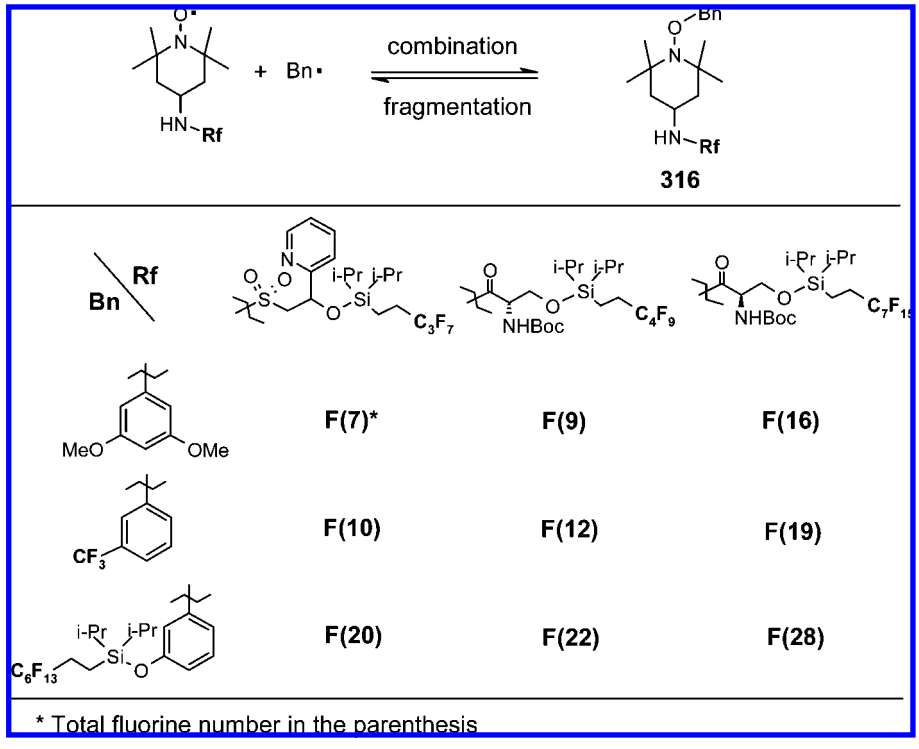
5.4.1. Separation by Chiral β-Cyclodextrin HPLC

In a proof-of-principle experiment, Mikami and co-workers made a mixture of three racemic *O*-benzoylmandelates **313a**−**c** bearing different length of fluorous alcohols (Scheme 108).[138a] The mixture was separated and gave three pairs (a total of six peaks) on a β-CD column. The racemic compounds were separated from each other according to fluorine content, and each racemic compound was further separated to two enantiomers.

5.4.2. Separation by Fluorous HPLC Followed by Chiral HPLC

Because the β-CD column may not always have enough resolution to spontaneously separate analogs and the racemates of each analog, Mikami and co-workers developed a more practical approach by orthogonal use of fluorous and chiral HPLC columns. A multicomponent fluorous racemic mixture was first separated by a F-HPLC to single racemic compound according to fluorine content, and each racemic compound was then further resolved to two enantiomers by a chiral HPLC. A set of four perfluoroalkyliodides **314** was reacted with an acrylamide derivative in one-pot to produce a four-component mixture of iodopeptides **315,** each of them bearing a different fluorous chain (Scheme 109).[139] Separation of this mixture by F-HPLC gave three peaks since the *n*-C_3F_7 and *i*-C_3F_7 have the same fluorine content and could not be separated by F-HPLC. Each CF_3 and *n*-C_6F_{13}-attached racemic compounds was separated to two enantiomers by the chiral column. Interestingly, the mixture of two racemic compounds bearing *n*-C_3F_7 and *i*-C_3F_7 groups were separated by the chiral HPLC to give two pairs of peaks.

Scheme 110. Fluorous Double Linker-Facilitated Synthesis of Heterobivalent Compounds



5.5. Double Fluorous Linker Shuffling for Making Heterobivalent Compounds

Crich and co-workers employed dimerization-type reactions for FMS of heterobivalent compounds **316** (Scheme 110).[140] Living radical fragmentation of a 3 × 3 array of *N*-functionalized TEMPOL benzyl ethers produced a total of 9 new products after recombination. The benzyl and the amino groups on the TEMPOL moiety each have a fluorous chain. The fluorous chains were selected as such that after the heterobivalent recombination, each of the nine new products has a different fluorine atom count from 7 to 28 fluorines. The mixture could be separated to nine peaks by analytical F-HPLC. Since the resolution was not high enough for preparative-scale HPLC to separate the reaction mixture, a two-step separation protocol was then developed; first using a normal phase chromatography to fractionate the mixture into 3 mixtures based on their polarity, and then using F-HPLC to separate each of those mixtures to three compounds based on the fluorine content.

6. Summary

Fluorous linker-facilitated synthesis integrates the characteristics of solution-phase reactions and phase-tag-based separation. It has advantages of favorable homogeneous reaction kinetics, broad synthetic scope, easy monitoring of the reaction process, and compatibility with other synthetic and separation technologies. Complementary to the polymer linkers for solid-phase synthesis, the fluorous linkers have significantly enabled high-throughput synthesis and solution-phase chemistry. In addition to organic, medicinal, analytical, and separation applications, fluorous linker-based chemistry also has great potential in other areas such as biocatalysis, microarray, nanomaterial, green chemistry, and microfluidic technologies.

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