JOC*Article*

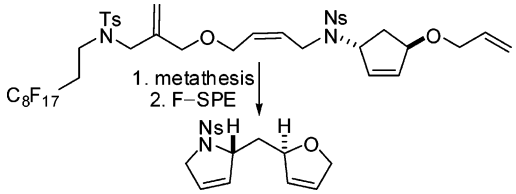
A Fluorous-Tagged Linker from Which Small Molecules Are Released by Ring-Closing Metathesis

Stuart G. Leach, Christopher J. Cordier, Daniel Morton, Gordon J. McKiernan, Stuart Warriner, and Adam Nelson*

School of Chemistry and Astbury Centre for Structural Molecular Biology, University of Leeds, Leeds LS2 9JT, UK

a.s.nelson@leeds.ac.uk

Received December 18, 2007



A fluorous-tagged linker for the parallel synthesis of small- and medium-ring and macrocyclic nitrogen heterocycles using ring-closing metathesis is described. The linker was designed such that "cyclization−release" of the cyclic heterocyclic products was coupled with liberation of the active catalyst. The design of the linker was validated using a non-fluorous-tagged model. A wide range of unsaturated alcohols were used as reagents to functionalize a fluorous-tagged sulfonamide, (*Z*)-{*N*-[4-(2-(*N*′-3,3,4,4,5,5,6,6,7,7,8,8,9,9,-10,10,10-heptadecafluorodecyl)-4-methylsulfonamido)methylallyloxy]but-2-enyl}-2-nitrobenzene-sulfonamide, using Fukuyama−Mitsunobu reactions; in each case, fluorous-solid-phase extraction (F−SPE) was used to purify the functionalized linker from the excess reagents. In general, the "cyclization−release" of cyclic products was triggered using a light-fluorous tagged derivative of the Grubbs−Hoveyda second-generation catalyst. After the metathesis step, F−SPE was used to purify released cyclic compounds from the fluorous-tagged linker and the fluorous-tagged catalyst. The scope and limitations of the approach were determined using a range of substrates which probed different aspects of the functionalization and metathesis steps. In the study as a whole, a wide range of small- and medium-ring and macrocyclic nitrogen heterocycles were prepared using polyene and polyenyne metathesis cascades.

Introduction

Ring-closing metathesis has revolutionalized the synthesis of small- and medium-ring and macrocyclic compounds.[1] Ruthenium and molybdenum complexes have been developed as well-defined catalysts and are widely used to catalyze ring-closing metathesis reactions in organic synthesis.[2] The functional group tolerance of the ruthenium-based catalysts **1**−**3** (Figure 1) is particularly remarkable, and these catalysts have been used widely in the synthesis of highly functionalized products. Ring-closing metathesis has been exploited as a key step in the formation of an exceptional range of small- and medium ring and macrocyclic natural products including callystatin,[3] laurencin,[4] salicylihalamide A,[5] migrastatin,[6] and epothilone A.[7]

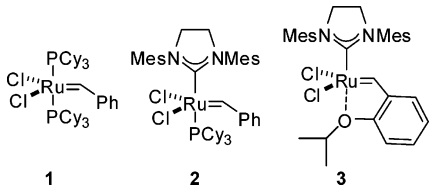


FIGURE 1. Some catalysts for alkene metathesis.

The removal of ruthenium residues from the products of many metathesis reactions can often be problematic. A range of

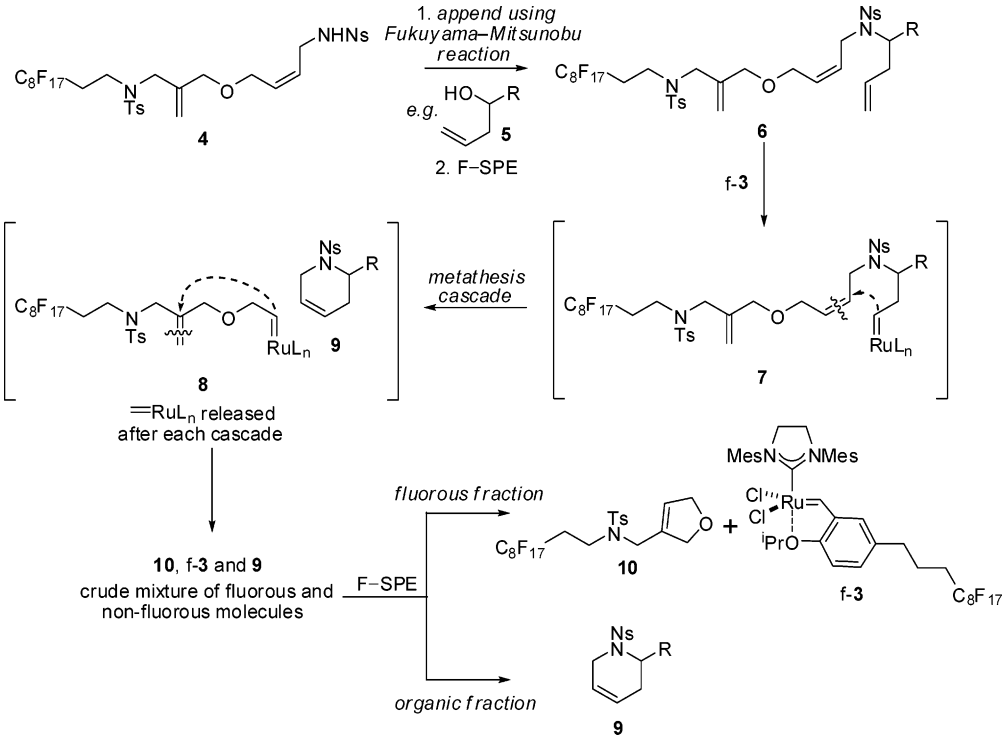
* To whom correspondence should be addressed. Tel: +44 (0)113 343 6502. Fax: +44 (0)113 343 6565.

(1) (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238. (b) Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Rahaman, H.; Roy, B. *Tetrahedron* **2007**, *63*, 3919−3952. (c) Arisawa, M.; Nishida, A.; Nakagawa, M. *J. Organomet. Chem.* **2006**, *691*, 5109−5121. (d) Gradillas, A.; Péres-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086−6101.

(2) (a) Grubbs, R. H. *Handbook of metathesis*; Wiley-VCH: Weinheim, Germany, 2003. (b) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043.(c) Furstner, A. *Alkene metathesis in organic synthesis*; Springer: New York, 1998. (d) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179.

10.1021/jo7026273 CCC: $40.75
Published on Web 03/08/2008

SCHEME 1. Design of a Fluorous-Tagged Linker for the "Cyclization−Release" of Cyclic Molecules Prepared by Ring-Closing Metathesis



protocols have been developed to allow metathesis catalysts to be scavenged.[8] A polar isocyanide has been used to deactivate and facilitate the purification of metathesis products.[9] In addition, metathesis catalysts have been developed which are polymer- or ionic liquid-supported,[10] or functionalized with a heavy or light fluorous tag.[11]

In this paper, we describe the design and development of a fluorous-tagged linker for the parallel synthesis of cyclic small molecules using ring-closing metathesis as the key step. We also demonstrate that the linker may be used to prepare structurally diverse examples of nitrogen heterocycles, a class of molecules with highly varied biological function. The design features of the linker, **4**, are summarized in Scheme 1. The toluenesulfonyl group was incorporated to allow easy HPLC analysis after the functionalization step. The linker bears a perfluorooctyl chain such that, after use of excess reagents in the functionalization step, purification by fluorous-solid-phase extraction (F−SPE) would be possible.[12] The use of fluorous-tagged substrates in array chemistry can be highly effective as the products may be purified rapidly from excess reagents by F−SPE, a procedure which can be performed in parallel.[13] Thus, it was envisaged that the linker **4** would be appended with terminal alkene or alkyne substituent to yield a substrate (e.g., **6**) for a ring-closing metathesis cascade. In this paper, we describe the use of Fukuyama−Mitsunobu reactions[14] to prepare the cyclization precursors.

Most importantly, however, the linker was designed with a "cyclization−release"[15] strategy in mind: crucially, this strategy was expected to release only the required cyclic metathesis products from the fluorous tag. Furthermore, to facilitate removal of the metathesis catalyst from the required product, we planned to use a fluorous-tagged catalyst such as f-**3** (Figure 2).[11a] Initiation of each metathesis cascade was expected to occur at the terminal alkene (e.g., → **7**).[16] Ring-closing metathesis should

(3) (a) Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998**, *120*, 9084−9085.

(4) (a) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029−2032. (b) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653−5660.

(5) (a) Snider B. B.; Song F *Org. Lett.* **2001**, *3*, 1817−1820. (b) Wu, Y.; Esser, L.; De Brabander, J. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 4308−4310. (c) Smith, A. B., III; Zheng, J. *Synlett* **2001**, 1019−1023. (d) Furstner, A.; Dierkes, T.; Thiel, O. R.; Blanda, G. *Chem. Eur. J.* **2001**, *7*, 5286−5298. (e) Wu, Y.; Liao, X.; Wang, R.; Xie, X.-S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 3245−3253. (f) Smith, A. B., III; Zheng, J. *Tetrahedron* **2002**, *58*, 6455−6471.

(6) Gaul, C.; Njardarson, J. T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 6042−6043. (b) Reymond, S.; Cossy, J. *Eur. J. Org. Chem.* **2006**, 4800−4804.

(7) Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 166−168.

(8) (a) Ahn, Y. M.; Yang, K.; Georg, G. I. *Org. Lett.* **2001**, **3**,1411−1413. (b) Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 4137−4140.

(9) Galan, B. R.; Kalbarczyk, K. P.; Szczepankiewicz, S.; Keister, J. B.; Diver, S. T. *Org. Lett.* **2007**, *9*, 1203−1206.

(10) (a) Nguyen, S. T.; Trnka, T. M. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 1, pp 61−94. (b) Harned, A. M.; Probst, D. A.; Hanson, P. R. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 2, pp 361−402.

(11) (a) Matsugi, M.; Curran, D. P. *J. Org. Chem.* **2005**, *70*, 1636−1642. (b) Yao, Q.; Zhang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 74−75.

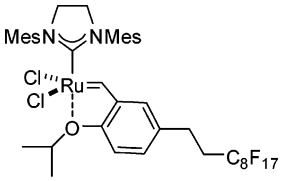
(12) (a) Luo, Z.; Zhang, Q.; Oderaotoshi, Y.; Curran, D. P. *Science* **2001**, *291*, 1766−1769. (b) Curran, D. P.; Luo, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9069−9072.

(13) Zhang, W.; Lu, Y.; Nagashima, T. *J. Comb. Chem.* **2005**, *7*, 893−897.

(14) (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373−4. (b) Olsen, C. A.; Witt, M.; Hansen, S. H.; Jaroszewski, J. W.; Franzyk, H. *Tetrahedron* **2005**, *61*, 6046−6055. (c) Rew, Y.; Goodman, M. *J. Org. Chem.* **2002**, *67*, 8820−8826.

(15) Moriggi, J.-D.; Brown, L. J.; Castro, J. L.; Brown, R. C. D. *Org. Biol. Chem* **2004**, *2*, 835−844.

(16) (a) Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484−2489.(b) Wallace, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912−1915.



f-3

FIGURE 2. Fluorous-tagged derivative of Grubbs−Hoveyda second-generation catalyst.

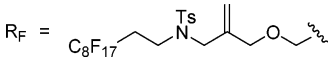


FIGURE 3. Definition of the fluorous-tagged substituent R_F.

then release only cyclized products from the fluorous-tagged linker (e.g., → **8** + **9**). Previously, Brown has shown that the efficiency of a solid-supported linker was greatly improved when the active catalyst was released directly back into solution.[15] Thus, we also designed the linker such that a subsequent ring-closing metathesis reaction (→ **10**) would release the catalytically active methylene complex efficiently.

Immediately after the reaction, the required cyclic products (e.g., **9**) would be contaminated with the remnant of the fluorous-tagged linker (**10**), the ruthenium-based catalyst, and any unreacted substrates (such as **6** or even **4**). It was envisaged that a F−SPE would allow effective removal of the fluorous-tagged components: the required product (e.g., **9**) would then be eluted in the organic fraction. The design of the linker should, therefore, allow (a) the efficient synthesis of the metathesis precursors (e.g., **6**); (b) the "cyclization−release" of the required cyclic metathesis products (e.g., **9**); (c) the purification of the required product from the remaining catalyst and the remnants of the linker (**10**); and (d) our approach to be applied in the parallel synthesis of libraries of cyclic small molecules.

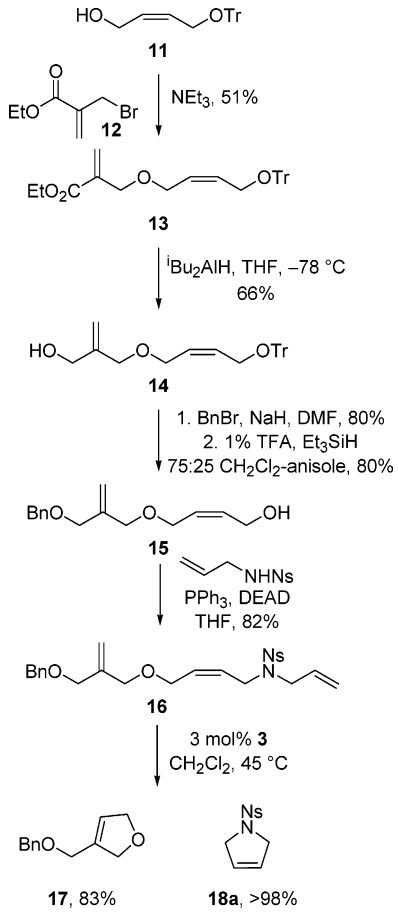
Results and Discussion

To validate the design of the fluorous-tagged linker **4**, we prepared the non-fluorous-tagged model **15** (Scheme 2). It was expected that reactions of **15** would test two features of the linker design: the "cyclization−release" of the required cyclic products, and the subsequent release of the active catalyst from the fluorous-tagged linker. Hence, alkylation of the alcohol[17] **11** using the allylic bromide[18] **12** gave the acrylate **13** which was reduced to yield the corresponding alcohol **14**. Benzylation and detritylation gave the alcohol **15**.

The allylic alcohol **15** was functionalized using a Fukuyama−Mitsunobu reaction to yield the sulfonamide **16**. Treatment of the triene **16** (2.1 mM in CH_2Cl_2) with 3 mol % Grubbs−Hoveyda second generation catalyst **3** for 4 h at 45 °C triggered the expected metathesis cascade, and the cyclic sulfonamide **18a** was obtained in >98% yield. In addition, a second ring-closing metathesis step yielded the required cyclic ether **17** in 83% yield, a process which must also release the active catalyst.

We next prepared the fluorous-tagged linker **4** which we had designed for the parallel synthesis of small molecules using a ring-closing metathesis reaction. Many of the intermediates in the preparation of the linker **4** were crystalline, which would

SCHEME 2. Synthesis of a Model Linker To Validate the "Cyclization−Release" Strategy



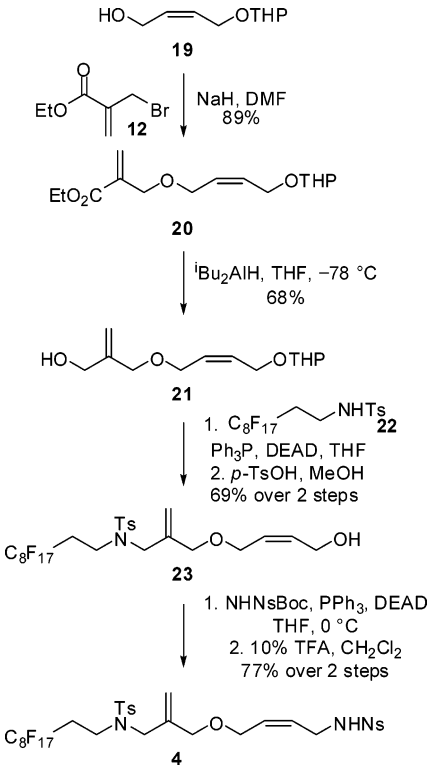
facilitate its synthesis on a large scale. Alkylation of the alcohol **19** using the allylic bromide **12** gave the acrylate **20**, which was reduced to yield the corresponding alcohol **21**. Reaction of the alcohol **21** with the fluorous-tagged toluenesulfonamide **22**, itself prepared by Fukuyama−Mitsunobu reaction, was followed by deprotection to give the crystalline fluorous-tagged alcohol **23**. Finally, the alcohol **23** was converted into the fluorous-tagged sulfonamide **4** (Scheme 3).

The fluorous-tagged linker **4** was functionalized by Fukuyama−Mitsunobu reaction with the unsaturated alcohols **24a**−**l** (Table 1; see the Supporting Information for the synthesis of novel substrates). A wide range of unsaturated substrates were investigated: the allylic alcohols **24a**,**b** (entries 1 and 2), the homoallylic alcohols **24c**,**d** (entries 3 and 4), the longer unsaturated alcohols **24e**,**f** (entries 5 and 6) and the propargylic alcohols **24g**−**i** (entries 7−9). In addition, the reactions of the chiral cyclic alcohols **24j**−**l**, each prepared from the corresponding *meso* diol (see the Supporting Information), were also studied (entries 10−12). In each case, the functionalized fluorous-tagged product was purified by F−SPE alone, and its purity was determined by analytical HPLC and 500 MHz ^{1}H NMR spectroscopy.

In general, the functionalization reactions proceeded efficiently within 1 h in THF with 4 equiv of the alcohol **24**, triphenylphosphine, and DEAD. The products of many Mitsunobu reactions[19a] are notoriously difficult to purify; however, by using a fluorous-tagged substrate, the excess reagents were efficiently removed in each case by F−SPE. The allylic alcohols **24b** (entry 2, Table 1) and **24j**−**l** (entries 10−12) underwent

(17) Hernández, A.-I.; Balzarini, J.; Karlsson, A.; Camarasa, M.-J.; Pérez-Pérez, M. J. *J. Med. Chem*, **2002**, *45*, 4254−4263.
(18) Villieras, J.; Rambaud, M. *Org. Synth.* **1988**, *66*, 220.

SCHEME 3. Preparation of the Fluorous-Tagged Linker 4 for the "Cyclization−Release" of Cyclic Small Molecules



clean S_N2 (rather than S_N2') substitution; with the allylic alcohols, **24j**−**l**, clean inversion of configuration was observed. However, a greater excess of the alcohols **24c**,**d** (10 equiv) was required to drive the functionalization step and, even under these conditions, the product contained some (5−9%) of unfunctionalized linker **4** (entries 3 and 4). Presumably, this observation stemmed from the propensity of the homoallylic systems to eliminate, reducing the efficiency of clean substitution.[19] In addition, we also noted the efficient functionalization of the fluorous-tagged allylic alcohol **23** with the sulfonamide **25** (entry 13).

In preliminary experiments, concentration of the crude products of some of the metathesis reactions prior to F−SPE, was found to lead to dimerization.[20] For example, the metathesis substrate derived from **24e** was metathesized (3 mol % f-**3**, CH_2Cl_2, 45 °C, 18 h), concentrated, and then purified by F−SPE and flash chromatography: the required product **18e** (18%) was obtained along with an inseparable mixture (23%) of cyclic dimers. Similarly, the metathesis of the substrate derived from **24h** was performed under an ethylene atmosphere and yielded the required product **18h** (30%) along with a dimer[21] (11%).

In order to avoid the dimerization of some products, a modified protocol was devised for use in subsequent experiments. Our results using this modified protocol are summarized in Table 2. In each case, the purity of the metathesis substrate, which had been purified by F−SPE alone, is specified. The "cyclization−cleavage" of the metathesis substrates (ca. 1 mM in CH_2Cl_2, 45 °C) was catalyzed by 3 mol % of the fluorous-tagged second-generation Grubbs−Hoveyda catalyst f-**3** (entries 1−8 and 10−13). The reactions were monitored by thin layer chromatography, and additional 3 mol% portions of catalyst were added as required. The crude reaction mixtures were diluted with 80:20 methanol−water, the dichloromethane removed by evaporation, and the remaining fluorophobic solutions were loaded directly onto F−SPE cartridges. The modified procedure avoided the formation of concentrated solutions of the metathesis products and the catalyst f-**3** prior to F−SPE purification. Following F−SPE, the organic fractions were analyzed by HPLC to give some insight into the efficiency of the cyclization process. Where analytically pure products had not been previously synthesized, the product of the metathesis reaction was purified by column chromatography.

The ring-closing metatheses of the allylic and homoallylic substrates, prepared from the allylic and homoallylic alcohols **24a**−**d**, yielded the corresponding *N*-sulfonyl dihydropyrroles **18a**,**b** and tetrahydropyridines **18c**,**d** (entries 1−4, Table 2). In these cases, HPLC analysis of the crude products after F−SPE alone showed that the cyclization process, with release of the products from the fluorous support, had proceeded efficiently. In the synthesis of **18a**, the fluorous-tagged dihydrofuran **10** was isolated from the fluorous fraction in 96% yield, demonstrating that the linker had functioned as proposed in Scheme 1. Furthermore, our approach enabled the synthesis of medium-ring and macrocyclic nitrogen heterocycles. The syntheses of the medium-ring heterocycles, **18e** and **18m**, proceeded rather efficiently (entries 5 and 13). Indeed, with the modified workup procedure, the dimerization of **18e** was not observed, and a higher yield of product was obtained. The macrocyclization to yield **18f** was less efficient, though the required product was, nonetheless, obtained in 24% yield (entry 6).

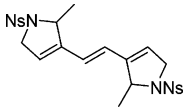
The metatheses of the propargylic substrates were more problematic (entries 7−9, Table 2). The metatheses of the substrates prepared from the propargylic alcohols **24g**,**h** were performed under an ethylene atmosphere,[22] and rather poor yields of the required products **18g**,**h** were observed (entries 7−8). With the substrate derived from **24i** (entry 9), the method was more successful with second generation Grubbs-Hoveyda catalyst **3**: at the end of the reaction, the catalyst was effectively removed using a water-soluble phosphine, $P(CH_2OH)_3$,[8b] and a 78% yield of the diene **18i** was obtained.

The metathesis cascades of the substrates derived from **24j**−**l** gave the chiral heterocyclic products **18j**−**l** (entries 10−11 and 12a).[23] The enantiomerically enriched product **18j**, whose two

(19) (a) Hughes, D. L. *Org. React.* **42**, 375−376. (b) Dias, L. C.; Diaz, G.; Ferriera, A. A.; Meira, P. R.R.; Ferreria, E. *Synthesis* **2003**, *4*, 603−622. (c) Mulzer, J.; Angermann, A.; Schubert, B.; Seilz, C. *J. Org. Chem.* **1986**, *51*, 5294−5299.

(20) For examples of ring-expanding metathesis reactions, see: (a) Lee, C. W.; Choi, T.-L.; Grubbs, R. H. *J. Am. Chem. Soc.* **2002**, *124*, 3224−3225. (b) Zheng, X.; Jones, C. W; Weck M. *J. Am. Chem. Soc.* **2007**, *129*, 1105−12. (c) Zhang, W.; Moore, J. S; *Angew. Chem., Int. Ed.* **2006**, *45*, 4416−4439.

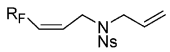
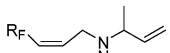
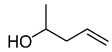
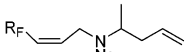
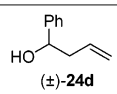
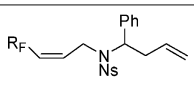
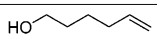
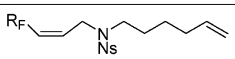
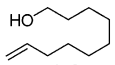
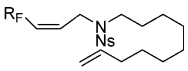
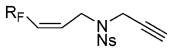
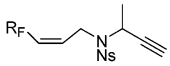
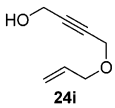
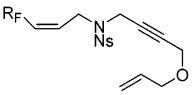
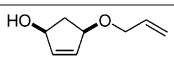
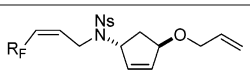
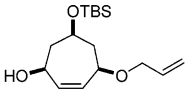
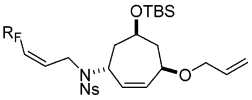
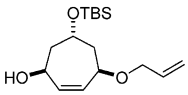
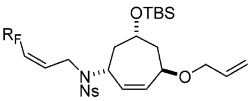
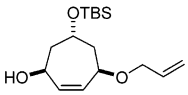
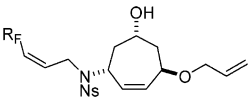
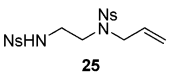
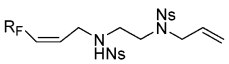
(21) The structure of the dimeric product obtained after concentration of the crude reaction mixture, and purification by F−SPE and column chromatography is



(22) For mechanistic study of the effect of ethylene on ring-closing enyne metathesis, see: Lloyd-Jones, G. C.; Margue, R. G.; de Vries, J. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 7442−7447.

(23) For similar metathesis cascade reactions conducted in solution phase, see: (a) Choi, T.-L.; R. H. Grubbs, *Chem. Commun.* **2001**, 2648−2649. (b) Dochnahl, M.; Schulz, S. R.; Blechert, S. *Synlett* **2007**, *16*, 2599−2601. (c) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H *J. Am. Chem. Soc.* **1996**, *118*, 6634−6640.

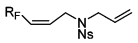
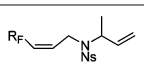
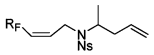
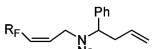
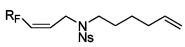
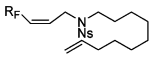
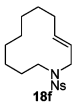
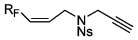
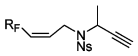
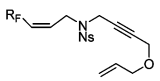
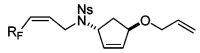
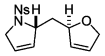
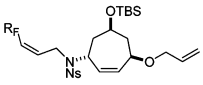
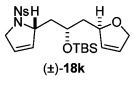
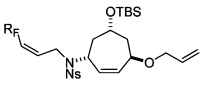
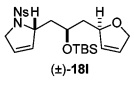
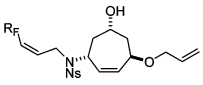
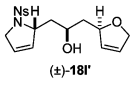
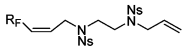
TABLE 1. Functionalization of the Fluorous-Tagged Linkers 4 and 23 (See Figure 3 for the Definition of the Fluorous-Tagged Substituent R_F)*

entry	substrate	linker	method	functionalized linker	yield / % (purity[a] / %)
1	 **24a**	**4**	A1		>98 (>98)
2	 (±)-**24b**	**4**	A1		83 (97)
3	 (±)-**24c**	**4**	A2		>98 (84[b])
4	 (±)-**24d**	**4**	A2		>98 (86[b])
5	 **24e**	**4**	A1		89 (>98)
6	 **24f**	**4**	A1		82 (90)
7	 **24g**	**4**	A1		96 (95)
8	 (±)-**24h**	**4**	A1		>98 (>98)
9	 **24i**	**4**	A1		97 (95)
10	 (+)-**24j**	**4**	A1		94 (96)
11	 (±)-**24k**	**4**	A1		82 (87)
12a	 (±)-**24l**	**4**	A1		>98 (89)
12b	 (±)-**24l**	**4**	A1 then B		>98 (89)[c] 70 (95)
13	 **25**	**23**	A3		94 (96)

*Methods: A1: (i) linker **4** (0.025 M), alcohol **24** (4 equiv), DEAD (4 equiv), PPh_3 (4 equiv), THF, 0 °C, 1 h; (ii) F-SPE; A2: (i) linker **4** (0.025 M), alcohol **24** (10 equiv), DEAD (4 equiv), PPh_3 (4 equiv), THF, 0 °C, 1 h; (ii) F-SPE; A3: (i) linker **23** (0.025 M), sulfonamide **23** (4 equiv), DEAD (4 equiv), PPh_3 (4 equiv), THF, 0 °C, 1 h; (ii) F−SPE; B: TBAF, THF; F−SPE. [a] Yield of product purified by F−SPE only. The purity of the compound is shown in parentheses and was determined by analytical HPLC. [b] HPLC analysis revealed that the linker **4** was present (entry 3: 9%; entry 4: 5%). [c] Yield and purity after method A1.

five-membered rings were formed in the cascade, was obtained in >98% yield (entry 10, Table 2). The metathesis cascades of the substrates derived from the cycloheptenols **24k**,**l** resulted in moderate yields of the products **18k**,**l** (entries 11 and 12a). The metathesis of the unsilylated substrate derived from **24l** was slightly lower yielding than the silylated substrate and gave the product **18l′** in 50% yield (compare entries 12a and 12b).

TABLE 2. "Cyclization−Release" of Heterocyclic Products by Ring-Closing Metathesis (See Figure 3 for the Definition of the Fluorous-Tagged Substituent R_F)*

entry	substrate	substrate purity[a] /%	method	catalyst (mol%)	time/hr	product	yield/% (% mass of product, and HPLC purity after F-SPE)[b]
1		>98	C1	f-**3** (3)	6	 **18a**	*c,d* (89,91)
2		97	C1	f-**3** (2 × 3)[e]	72	 (±)-**18b**	65 (83,93)
3		84	C1	f-**3** (3)	18	 (±)-**18c**	*c* (>98,80)
4		86	C1	f-**3** (3)	27	 (±)-**18d**	66 (91,86)
5		>98	C1	f-**3** (3)	18	 **18e**	*c* (77,83)
6		90	C1	f-**3** (2 × 3)[e]	72	 **18f**	24 (40,69)
7		95	C1[f]	f-**3** (3)	48	 **18g**	10 (31,61)
8		>98	C1[f]	f-**3** (2 × 3)[e]	42	 (±)-**18h**	*c* (43, 83)
9		95	C2	**3** (3)	7	 **18i**	78[g] (*h*)
10		96	C1	f-**3** (3)	18	 (+)-**18j**	*c* (>98,98)
11		87	C1	f-**3** (3 × 3)[e]	72	 (±)-**18k**	43 (71,78)
12a		89	C1	f-**3** (3)	48	 (±)-**18l**	63 (80,55)
12b		95	C1	f-**3** (3)	120	 (±)-**18l'**	50 (63,85)
13		96	C1	f-**3** (3)	18	 **18m**	*c* (73,98)

*Methods: C1: (i) substrate (ca. 1 mM), catalyst f-**3**, CH_2Cl_2, 45 °C; (ii) add 80:20 methanol−water then remove CH_2Cl_2 by evaporation; (iii) F−SPE; C2: (i) substrate (ca. 1 mM), catalyst **3**, CH_2Cl_2, 45 °C; (ii) Et_3N (86 equiv), $P(CH_2OH)_3$ (86 equiv) then silica (iii) filter through a Celite pad; (iv) column chromatography. [a] See Table 1 for the determination of the purity of the functionalized linkers. [b] Yield of product purified by F−SPE and column chromatography. The numbers in parentheses are the percentage mass recovery and the purity, determined by analytical HPLC, after F−SPE alone. [c] The products obtained after F−SPE were analyzed by HPLC after F−SPE and compared with analytically pure samples prepared separately. [d] The fluorous-tagged metathesis product **10** was isolated in 96% yield. [e] The reaction was monitored by thin layer chromatography, and the catalyst was added in 3 mol % portions as required. [f] The reaction was performed under an ethylene atmosphere. [g] With f-**3**, the organic fraction was noticably brown following F−SPE: on concentration, the required product **18i** was observed to decompose (TLC) and was obtained in 17% yield. [h] Not applicable.

Conclusions

We have described the development of a novel fluorous-tagged linker for application in the parallel synthesis of libraries of cyclic small molecules using ring-closing metathesis. To demonstrate its synthetic scope, the fluorous-tagged linker was functionalized with a wide range of unsaturated alcohols using the Fukuyama−Mitsunobu reaction; in each case, F−SPE was used to purify the functionalized linker from the excess reagents. The design of the linker was such that "cyclization−release" of cyclic products, triggered using a light-fluorous tagged derivative of the Grubbs−Hoveyda second-generation catalyst, was coupled with the regeneration of the active catalyst. After metathesis, F−SPE was used to separate the released cyclic compounds from the fluorous-tagged linker and catalyst.

Our investigations have demonstrated the efficiency and generality of a fluorous-tagged linker strategy in the synthesis of heterocycles using ring-closing metathesis. The rapid synthesis of a wide range of small- and medium-ring and macrocyclic heterocycles, and the facile purification steps involved, provides a strong foundation for the synthesis of more complex molecules using the same strategy. Indeed, the application of a fluorous-tagged linker in the diversity-oriented synthesis of more complex, natural product-like molecules will be described in due course.

Experimental Section

(2*R*,2′*R*)-2-(2′,5′-Dihydrofuran-2′-ylmethyl)-1-(2″-nitrobenzenesulfonyl)-2,5-dihydro-1*H*-pyrrole 18j. Diethyl azodicarboxylate (37 μL, 0.234 mmol, 4 equiv) was added to a stirred solution of the fluorous-tagged sulfonamide **4** (55 mg, 0.058 mmol), triphenylphosphine (61 mg, 0.234 mmol, 4 equiv) and the alcohol **24j** (33 mg, 0.234 mmol, 4 equiv) in THF (2 mL, 25 mM) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 1 h. The solvent was removed under reduced pressure to give a crude product which was purified by F−SPE to give a crude product (58 mg, 94% by mass; 96% purity by analytical HPLC). The catalyst f-**3** (1.5 mg, 3 mol %) was added to a stirred solution of the metathesis precursor (56 mg, 0.053 mmol) in dichloromethane (ca. 1 mM) at 45 °C and the reaction mixture heated at 45 °C. Heating was continued until completion was indicated by TLC. The reaction mixture was allowed to cool to room temperature and 80:20 MeOH−H_2O (equivalent volume to the dichloromethane used) was added. The dichloromethane was removed under reduced pressure to give the crude product, as a solution in MeOH−H_2O, which was purified by F−SPE to give the crude *bicycle* **18j** (18 mg, >98% by mass; 98% purity by analytical HPLC) as a colorless oil: R_f 0.32 (50:50 petrol−EtOAc); $[\alpha]_D^{20}$+12.4 (*c* 1.0, $CHCl_3$); IR (film) 3087, 3021, 2912, 2852, 1585 and 1543; ^{1}H NMR (300 MHz) 7.94−7.89 (1 H, m, H-3″), 7.74−7.60 (3 H, m, H-4″, H-5″ and H-6″), 5.97 (1 H, ddd, *J* 6.4, 4.4 and 2.1, H-4′), 5.87 (1 H, ddd, *J* 6.4, 3.6 and 1.5, H-4), 5.80 (1 H, ddd, *J* 6.4, 3.6, 2.3, H-3), 5.70 (1 H, ddd, *J* 6.4, 3.8 and 1.8, H-3′), 5.02−4.93 (1 H, m, H-2), 4.97−4.78 (1 H, m, H-2′), 4.61−4.56 (2 H, m, H-5), 4.32 (1 H, ddd, *J* 14.8, 4.4 and 2.3, H-5′$_A$), 4.19 (1 H, app ddt, *J* 14.8, 5.1 and 2.1, H-5′$_B$), 2.24 (1 H, dt, *J* 14.1 and 3.6, methylene H_A) and 1.82 (1 H, dt, *J* 14.1 and 8.5); δ_C (75 MHz, $CDCl_3$) 133.9, 132.4, 132.0, 131.5, 130.3, 130.1, 126.8, 124.6, 123.7, 121.0 (C-3, C-4, C-3′, C-4′, Ar), 84.0 (C-2′), 75.3 (C-5′), 66.7 (C-2), 55.8 (C-5) and 42.8 (methylene); *m*/*z* (ES) 359.0 ([M + Na]$^+$, 52), 253.0 (100), 186.0 (79) (found [M + Na]$^+$, 359.0684 $C_{15}H_{16}N_2O_5S$ requires [M + Na]$^+$, 359.0672).

Acknowledgment. We thank EPSRC and the Wellcome Trust for funding and James Titchmarsh for HPLC analyses.

Supporting Information Available: Details of all experimental procedures including syntheses of the HPLC standards and the cyclic unsaturated alcohols **24j**,**k**, ^{1}H NMR spectra and HPLC chromatograms for the functionalized fluorous linkers, ^{1}H and ^{13}C NMR spectra of all purified compounds, HPLC chromatograms of the heterocyclic compounds directly after F-SPE purification, and 500 MHz ^{1}H NMR spectra and HPLC data acquired during the synthesis of the heterocycle **18j** from the alcohol **24j**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7026273