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Regioselective Nucleophilic Additions to Cross-Conjugated Dienone System Bearing β-Fluorine: A Versatile Approach to Highly Substituted 2-Cyclopentenones

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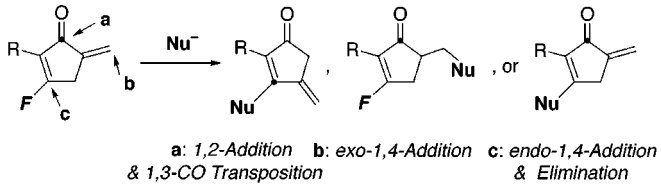
ABSTRACT



3-Fluoro-5-methylene-2-cyclopentenone is treated with appropriate nucleophiles and Lewis acids to undergo regioselective 1,2-addition, exocyclic 1,4-addition, and endocyclic 1,4-addition, leading to 3-substituted 4-methylene-2-cyclopentenones, 5-substituted 3-fluoro-2-cyclopentenones, and 3-substituted 5-methylene-2-cyclopentenones in good yields, respectively.

The cyclopentenone structure occurs in a number of biologically active compounds such as prostaglandins, pyrethroids, and steroids. Therefore, the preparation of related substructures is an area of considerable interest in synthetic organic chemistry.[1] Recently, we reported a facile synthesis of 5-alkylidene-3-fluoro-2-cyclopentenones via *fluorine-directed* Nazarov cyclizations of 2,2-difluorovinyl vinyl ketones, which are readily prepared from 2,2,2-trifluoroethyl *p*-toluenesulfonate.[2] One of the products, α-methylene cyclopentenone **1**, is an attractive synthetic intermediate for the preparation of cyclopentenone derivatives because of their highly functionalized structure, a cross-conjugated dienone system with a vinylic fluorine. There are three reaction sites to be attacked by nucleophiles in 1,2-addition, exocyclic 1,4-addition, and endocyclic 1,4-addition fashions in **1** (Scheme 1, paths **a**−**c**) which would allow their transformations into a variety of substituted 2-cyclopentenones. These considerations prompted us to investigate the regioselective additions of carbon and heteroatom nucleophiles to **1**.

While regioselective reactions of α,β-unsaturated carbonyl compounds with nucleophiles have been well investigated,[3] few examples of the selective additions to cross-conjugated dienones have been reported.[4] Herein we report that compound **1** selectively undergoes three types of addition

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(1) Waring, A. J. In *Comprehensive Organic Chemistry*; Stoddart, J. F., Ed.; Pergamon Press: Oxford, 1979; Vol. 1, p 1017.

(2) For fluorine-directed Nazarov cyclizations, see: Ichikawa, J.; Miyazaki, S.; Fujiwara, M.; Minami, T. *J. Org. Chem.* **1995**, *60*, 2320. Ichikawa, J.; Fujiwara, M.; Okauchi, T.; Minami, T. *Synlett* **1998**, 927.

(3) For a review, see: Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992.

(4) (a) Suzuki, M.; Mori, M.; Niwa, T.; Hirata, R.; Furuta, K.; Ishikawa, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 2376. (b) Siwapinyoyos, T.; Thebtaranonth, Y. *Tetrahedron Lett.* **1984**, *25*, 353. See also: (c) Westermann, J.; Neh, H.; Nickisch, K. *Chem. Ber.* **1996**, *129*, 963 and references therein.

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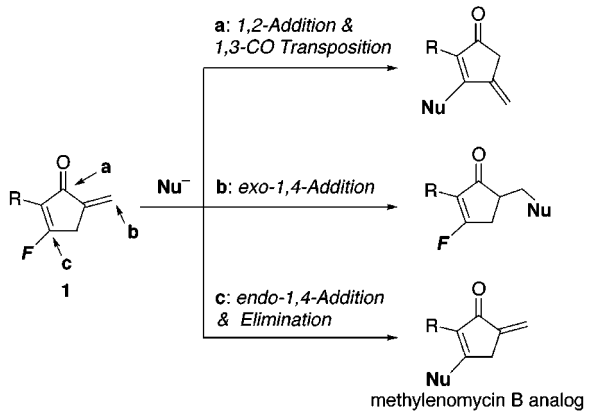
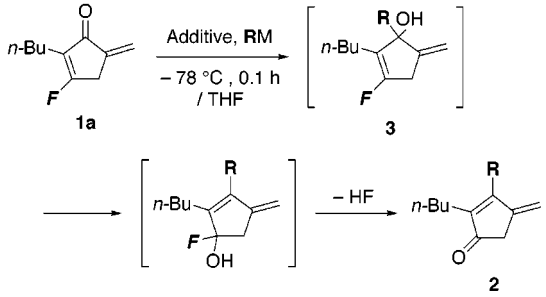
Scheme 1. Three Reaction Pathways of Nucleophilic Attack to **1**



reactions: (1) 1,2-addition accompanied by spontaneous 1,3-carbonyl transposition (path **a**), (2) exocyclic 1,4-addition in the presence of a Lewis acid (path **b**), and (3) endocyclic 1,4-addition followed by elimination of a fluoride ion in the presence of a bulky Lewis acid or a protic acid (path **c**). These reactions provide a versatile approach to several types of substituted 2-cyclopentenones, including antibiotic methylenomycin B analogues.[5]

First, we examined the 1,2-addition reaction of **1** with alkylmetals (path **a**). Treatment of **1a** with MeMgBr or MeLi at −78 °C gave 2-butyl-3-methyl-4-methylene-2-cyclopentenone **2a** (R = Me)[6] in 31% and 61% yields, respectively (Scheme 2, Table 1, entries 1 and 2). These results show

Scheme 2. 1,2-Addition to **1a** Followed by 1,3-Carbonyl Transposition



that **1a** reacted with the nucleophile in 1,2-fashion to afford alcohol **3**, followed by rearrangement of the hydroxy group and successive elimination of hydrogen fluoride, which

(5) Haneishi, T.; Kitahara, N.; Takiguchi, Y.; Arai, M.; Sugawara, S. *J. Antibiot.* **1974**, *27*, 386. Haneishi, T.; Kitahara, N.; Takiguchi, Y.; Arai, M.; Sugawara, S. *J. Antibiot.* **1974**, *27*, 393. For the total synthesis of methylenomycin B, see: Mathew, J. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbiological Products*; Lukacs, G., Ed.; Springer-Verlag: Berlin, 1993; Vol. 2, p 435. Older, C. M.; Stryker, J. M. *Organometallics* **2000**, *19*, 3266 and references therein.

(6) All new compounds were fully characterized by ^{1}H, ^{19}F, and ^{13}C NMR, IR, MS, and combustion analysis (±0.3%) and/or HRMS.

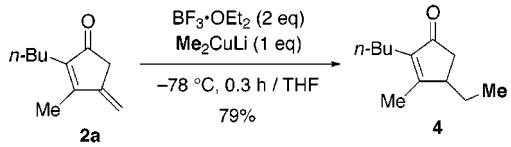
Table 1. Synthesis of 2,3-Disubstituted 4-Methylene-2-cyclopentenones **2**

entry	additive (equiv)	RM (equiv)	% yield
1[a]	—	MeMgBr (7)	31 (**2a**)
2	—	MeLi (2)	61 (**2a**)
3	CuI (1)	MeLi (2)	**87** (**2a**)
4	$CeCl_3$ (2)	MeLi (2)	74 (**2a**)
5	$CeCl_3$ (2)	*n*-BuLi (2)	**76** (**2b**)
6	CuI (1)	PhLi (2)	59 (**2c**)
7	$CeCl_3$ (2)	PhLi (2)	**79** (**2c**)

[a] The reaction was conducted for 1.3 h.

resulted in 1,3-carbonyl transposition leading to β-methylene cyclopentenone **2a**.[7,8] The rearrangement readily proceeded during workup due to the α-cation-stabilizing effect of fluorine[9,10] on the intermediary allylic cation. After screening of additives, cuprous iodide and cerium trichloride[11] were found to be effective for selective promotion of the 1,2-addition, raising the yield of **2a** up to 87% and 74%, respectively (entries 3 and 4). The reactions of **1a** with other alkyl and aryl anions were also conducted to afford **2b**,**c** (R = *n*-Bu, Ph)[6] in good yields (entries 5 and 7). Dienyl ketone **2** obtained above further underwent a regioselective 1,6-addition with nucleophiles in the presence of a Lewis acid. Treatment of **2a** with BF_3·OEt_2 and Me_2CuLi gave 2,3,4-trisubstituted 2-cyclopentenone **4**[6] in 79% yield (Scheme 3).[3,4c,12] Thus, the reaction sequence from **1** to **4** via **2** allows

Scheme 3. 1,6-Addition to **2a**



the synthesis of 2,3,4-trisubstituted 2-cyclopentenones with a variety of substitution patterns.

(7) Paleta, O.; Pelter, A.; Kebrle, J. *Tetrahedron Lett.* **1994**, *35*, 9259 and references therein. Tellier, F.; Sauvêtre, R. *J. Fluorine Chem.* **1996**, *76*, 181. Burdon, J.; Coe, P. L.; Haslock, I. b.; Powell, R. L. *Chem. Commun.* **1996**, 49 and references therein. See also: Yamazaki, T.; Hiraoka, S.; Sakamoto, J.; Kitazume, T. *Org. Lett.* **2001**, *3*, 743. For 1,3-carbonyl transposition, see: Larock, R. C. In *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 2nd ed.; VCH Publishers: New York, 1999; p 1201.

(8) For recent reports on the synthesis of alkylidene cyclopentenones, see: Herndon, J. W.; Zhu, J.; Sampedro, D. *Tetrahedron* **2000**, *56*, 4985 and references therein. Hashmi, A. S. K.; Bats, J. W.; Choi, J.-H.; Schwarz, L. *Tetrahedron Lett.* **1998**, *39*, 7491 and references therein.

(9) Chambers, R. D. *Fluorine in Organic Chemistry*; Antony Rowe: Chippenham, 1973; p 1. Smart, B. E. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Ed.; Plenum Press: New York, 1994; p 57. Allen, A. D.; Tidwell, T. T. In *Advances in Carbocation Chemistry*; Creary, X., Ed.; Jai Press: Greenwich, 1989; Vol. 1, p 1.

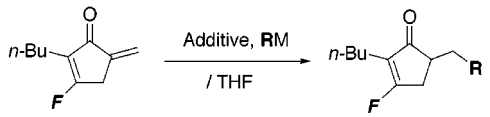
(10) For reports on cationic cyclizations where fluorine acts as an α-cation-stabilizing substituent, see: Johnson, W. S.; Daub, G. W.; Lyle, T. A.; Niwa, M. *J. Am. Chem. Soc.* **1980**, *102*, 7800. Johnson, W. S.; Lyle, T. A.; Daub, G. W. *J. Org. Chem.* **1982**, *47*, 161. Fish, P. V.; Johnson, W. S.; Jones, G. S.; Tham, F. S.; Kullnig, R. K. *J. Org. Chem.* **1994**, *59*, 6150 and references therein. Morikawa, T.; Kumadaki, I.; Shiro, M. *Chem. Pharm. Bull.* **1985**, *33*, 5144.

Table 2. Synthesis of 2,5-Disubstituted 3-Fluoro-2-cyclopentenones **5**

entry	additive (equiv)	RM (1 equiv)	conditions	% yield
1	–	Me_2CuLi	−78 °C, 1.5 h	
2	TMSOTf (1)	Me_2CuLi	−78 °C, 0.3 h	15 (**5a**)
3	TMSOTf (2)	Me_2CuLi	−78 °C, 0.2 h	83 (**5a**)
4	$BF_3{\cdot}OEt_2$ (2)	Me_2CuLi	−45 °C, 0.3 h	85 (**5a**)
5	$BF_3{\cdot}OEt_2$ (2)	$Me_2Cu(SCN)Li_2$	−45 °C, 0.3 h	**91** (**5a**)
6	$BF_3{\cdot}OEt_2$ (2)	n-$Bu_2Cu(SCN)Li_2$	−45 °C, 0.3 h	**83** (**5b**)
7	$BF_3{\cdot}OEt_2$ (2)	$Ph_2Cu(SCN)Li_2$	−45 °C, 0.3 h	**69** (**5c**)

Next, we attempted exocyclic 1,4-addition of **1** (path **b**). Whereas no reaction was observed on treatment of **1a** with Me_2CuLi (Scheme 4, Table 2, entry 1), the addition of a

Scheme 4. Exocyclic 1,4-Addition to **1a**



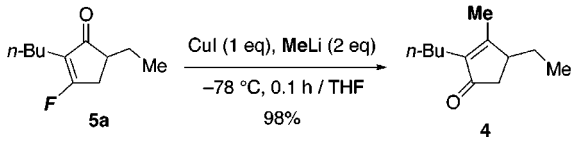
1a **5**

Lewis acid such as trimethylsilyl trifluoromethanesulfonate (TMSOTf) or boron trifluoride etherate ($BF_3{\cdot}OEt_2$) successfully promoted the desired reaction to give 2-butyl-5-ethyl-3-fluoro-2-cyclopentenone **5a** (R = Me)[6] (entries 3 and 4).[3,4c,12] Employing 2 equiv of the Lewis acid provided much better results than the use of 1 equiv (entries 2 and 3). Among the cuprates examined, higher order thiocyanocuprate cleanly promoted the reaction in the presence of $BF_3{\cdot}OEt_2$ to afford **5a**−**c** (R = Me, *n*-Bu, Ph)[6] in high yields (entries 5, 6, and 7). In all of these cases, the exocyclic 1,4-adducts **5** were obtained without contamination of endocyclic 1,4-addition products, presumably due to the high reactivity of the less hindered *exo*-methylene carbon in **1a** compared to that of the endocyclic β-carbon despite activation by the fluorine.[4,13]

Thus obtained exocyclic 1,4-adducts **5** were further transformed to 2,3,4-trisubstituted 2-cyclopentenones as shown in Scheme 5. On treatment of **5a** with MeLi and cuprous iodide, trisubstituted cyclopentenone **4** was obtained again in 98% yield through a similar reaction sequence to that from **1** to **2**, 1,2-addition followed by 1,3-carbonyl transposition.

Finally, we sought to effect the third pathway, the endocyclic 1,4-addition to **1** resulting in the construction of

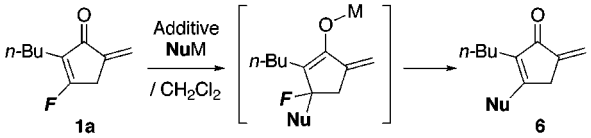
Scheme 5. 1,2-Addition to **5a** Followed by 1,3-Carbonyl Transposition



5a **4**

a methylenomycin B framework.[5,8] For this purpose the *endo*-type addition should be promoted in preference to the sterically favored exocyclic addition mentioned above. Aluminum tris(2,6-diphenylphenoxide) (ATPH), a bulky Lewis acid developed by Yamamoto and Maruoka,[14] was expected to prevent nucleophiles from attacking at the exocyclic β-carbon as well as at the carbonyl carbon of **1**. Eventually the substitution for the fluorine on the endocyclic β-carbon would proceed via an addition−elimination process.[13] Treatment of **1a** with ATPH in CH_2Cl_2, followed by addition of organolithium reagents at −78 °C, gave as expected 2,3-disubstituted 5-methylene-2-cyclopentenones **6a**,**b** (Nu = Me, Ph)[6] in moderate yields along with no *exo*-1,4- or 1,2-addition products (Scheme 6, Table 3, entries 1 and 2).

Scheme 6. Endocyclic 1,4-Addition to **1a** Followed by Elimination



1a **6**

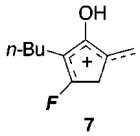
Furthermore, to achieve the endocyclic 1,4-addition we tried another device based on an electronic effect of fluorine: the reactions of **1a** with heteroatom nucleophiles such as alcohols and thiols in the presence of a protic acid. In contrast to the above-mentioned exocyclic 1,4-addition (Scheme 4, Table 2), the attack of nucleophiles would regioselectively occur on the fluorine-bearing carbon in the intermediary pentadienylic cation **7** (Figure 1) generated via

Table 3. Synthesis of 2,3-Disubstituted 5-Methylene-2-cyclopentenones **6**

entry	additive (equiv)	NuM (equiv)	conditions	% yield
1	ATPH (1.5)	MeLi (2)	−78 °C, 2 h	39 (**6a**)
2	ATPH (1.5)	PhLi (2)	−78 °C, 2 h	43 (**6b**)
3	TfOH (1)	MeOH (1)	rt, 0.1 h	82 (**6c**)
4	TfOH (1)	*c*-HexOH (1)	rt, 0.1 h	79 (**6d**)
5	TfOH (1)	$HC{\equiv}CCH_2OH$ (1)	rt, 0.1 h	85 (**6e**)
6	TfOH (1)	EtSH (1)	rt, 0.1 h	42 (**6f**)
7[a]	TfOH (1)	EtSH (1)	rt, 0.1 h	84 (**6f**)
8[a]	TfOH (2)	PhSH (1)	rt, 0.1 h	85 (**6g**)

[a] CH_2Cl_2−HFIP (1:1) was used as a solvent.

(11) Crimmins, M. T.; Dedopoulou, D. *Synth. Commun.* **1992**, *22*, 1953.
(12) For a review of organocopper reagents, see: Lipshutz, B. H. In *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; John Wiley & Sons: Chichester, 1994; p 283.
(13) We have reported that the fluorines on the β-carbon of α,β-unsaturated ketones are easily replaced by carbon and heteroatom nucleophiles via an addition−elimination process, see: Ichikawa, J.; Yokota, Y.; Kobayashi, M.; Minami, T. *Synlett* **1993**, 186. Ichikawa, J.; Kobayashi, M.; Yokota, Y.; Noda, Y.; Minami, T. *Tetrahedron* **1994**, *50*, 11637. Ichikawa, J.; Yokota, Y.; Kobayashi, M.; Amano, K.; Minami, T. *Synlett* **1996**, 243. Ichikawa, J.; Kobayashi, M.; Noda, Y.; Yokota, N.; Amano, K.; Minami, T. *J. Org. Chem.* **1996**, *61*, 2763. See also: Xiao, L.; Kitazume, T. *J. Fluorine Chem.* **1997**, *86*, 99.



7

Figure 1. Pentadienylic cation stabilized by α-fluorine.

protonation of **1a**, due to the α-cation-stabilizing effect of fluorine.[9,10] In the reaction of **1a** with alcohols, replacement of the fluorine was readily induced by TfOH at room temperature to afford 3-alkoxy-5-methylene-2-cyclopentenones **6c**−**e** (Nu = OMe, O*c*-Hex, $OCH_2C{\equiv}CH$)[6] in high yields (entries 3−5). Thiols also brought about a similar substitution successfully to give **6f**,**g** (Nu = SEt, SPh)[6] by the use of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as a cosolvent, presumably due to its high ionizing power, which facilitates the generation of carbocations (entries 7 and 8).[2,15]

In conclusion, we have accomplished 1,2-addition, exocyclic 1,4-addition, and endocyclic 1,4-addition to **1a**, 1,6-addition to **2a**, and 1,2-addition to **5a** with strict regioselectivity, leading to methylene cyclopentenones **2** and **6** and substituted cyclopentenones **4** and **5**. Thus, the combination of *fluorine-directed* Nazarov cyclizations[2] and the following transformations presented here furnishes an efficient route to a variety of highly substituted cyclopentenones, including cyclopentanoid antibiotic methylenomycin B analogues.

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http//pubs.acs.org.

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(14) Maruoka, K.; Shimada, I.; Imoto, H.; Yamamoto, H. *Synlett* **1994**, 519. For recent reports on ATPH, see: Saito, S.; Sone, T.; Murase, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 10216. Ooi, T.; Hokke, Y.; Tayama, E.; Maruoka, K. *Tetrahedron* **2001**, *57*, 135 and references therein.

(15) When **1a** was treated with TfOH in CH_2Cl_2−HFIP (1:1), a large low-field shift was observed in ^{19}F NMR (from 77.5 to 119.5 ppm relative to internal C_6F_6).