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Fluoroallylboration−Olefination for the Synthesis of (*Z*)-4,4-Difluoropent-2-enoates and 5,5-Difluoro-5,6-dihydropyran-2-ones

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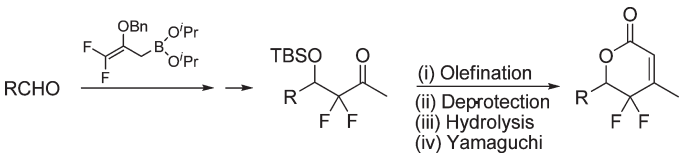
ABSTRACT



Horner−Wadsworth−Emmons (HWE) or Still−Gennari olefination of TBS-protected 3,3-difluoro-4-hydroxy-2-ones, derived from the difluoroallylboration of aldehydes, provides the *Z*-isomer of 4,4,-difluoropent-2-enoates. These, upon hydrolysis, followed by Yamaguchi cyclization, afford 5,5-difluoro-4-methyl-5,6-dihydro-α-pyrones in high yields.

The success of partially fluorinated analogues of natural and unnatural molecules in medicinal chemistry gave an impetus to synthetic fluoro-organic chemistry.[1] Often this chemistry blazes a path different from that of the nonfluorinated counterparts, making the synthesis of appropriately substituted fluorine-containing molecules a fascinating and challenging exercise.[2] As part of our projects on fluoroorganic synthesis via boranes,[3] we had recently reported the preparation of 3-(benzyloxy)-2,2-difluoro-but-3-en-1-ols (**1**), α,α-difluoro-*β*-hydroxy ketones (**2**), and the corresponding *cis*- and *trans*-1,3-diols via fluoroallylboration of aldehydes.[4] In continuation, we envisaged further applications of **1** for the preparation of *E*- and *Z*-4,4-difluoropent-2-enoates and 4-hydroxy- and 4-methyl-5,5-difluoro-5,6-dihydro-2-pyranones (Figure 1).

Sequential allylboration-ring-closing metathesis (RCM) is a demonstrated strategy for the preparation of α-pyrones,[5] including 6-fluoroalkyl analogues.[6] α-Pyrones are important constituents of natural products that have been exploited as end products[7] or intermediates[8] in synthetic and medicinal applications. The preparation of *gem*-difluorinated pyranone derivatives was envisaged as depicted in Scheme 1, via fluoroallylboration.[4]

(1) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.

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(6) Ramachandran, P. V.; Padiya, K. J.; Rauniyar, V.; Reddy, M. V.; Brown, H. C. *J. Fluorine Chem.* **2004**, *125*, 615.

(7) Examples of these include *β*-hydroxy-*δ*-lactones that are pharmacophores of LDL cholesterol-lowering statin drugs (e.g., Lovastatin, Merck: Mevacor),[7a] and oncorhyncolide.[7b] (a) Clive, D. L. J.; Murthy, K. S. K.; Wee, A. G. H.; Prasad, J. S.; Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Evans, C. F.; Haugen, R. D.; Heerze, L. D.; Barrie, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 3018. (b) Needham, J.; Andersen, R. J.; Kelly, M. T. *Tetrahedron Lett.* **1991**, *32*, 315.

(8) *β*-Methylpyranones are intermediates for the synthesis of 13-*cis*-retinoic acid,[8a] longifolene,[8b] Vitamin E,[8c] and Fumonisin B_2[8d] kavalactone derivatives: (a) Cahard, D.; Mammeri, M.; Poirier, J.-M.; Duhamel, L. *Tetrahedron Lett.* **2000**, *41*, 3619. (b) Lei, B.; Fallis, A. G. *J. Am. Chem. Soc.* **1990**, *112*, 4609. (c) Takano, S.; Shimazaki, Y.; Iwabuchi, Y.; Ogasawara, K. *Tetrahedron Lett.* **1990**, *31*, 3619. (d) Shi, Y.; Peng, L. F.; Kishi, Y. *J. Org. Chem.* **1997**, *62*, 5666.

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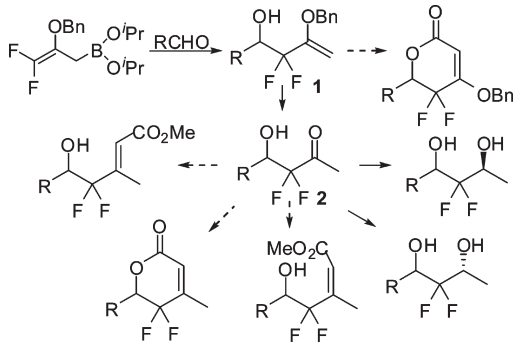
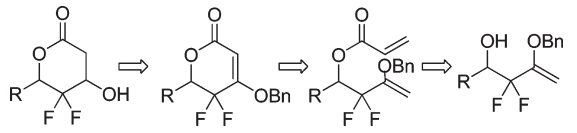


Figure 1. Fluoro-organic targets via difluoroallylboration.

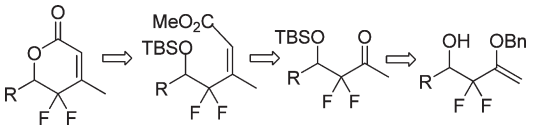
Scheme 1. Retrosynthetic Analysis for the Preparation of Difluoro-α-pyrones via Ring-Closing Metathesis



3-(Benzyloxy)-2,2-difluoro-1-phenylbut-3-en-1-ol (**1a**), obtained via the allylboration of benzaldehyde with diisopropyl 2-(benzyloxy)-3,3-difluoroallylboronate,[4] was converted to the corresponding acrylic ester. Attempted ring-closure of this ester via metathesis, under a variety of conditions using Grubb's first and second generation catalyst, was to no avail. A similar difficulty was reported by Qing[9] and Percy[10] and their co-workers during the preparation of 5,5-difluoro-5,6-dihydropyran-2-ones (α-pyrones), although Qing succeeded in achieving the RCM in the presence of Ti(O-*i*-Pr)$_4$.[11]

An alternative route to fluorinated α-pyrones was designed via an olefination−cyclization protocol (Scheme 2).[12] Wittig reactions[13] of fluorocarbonyls are reported to be faster[14,15] and there have been reports of reversal of selectivity in the olefination of α-fluorinated alkyl aryl ketones compared to the nonfluorinated ketones.[16] We examined

Scheme 2. Retrosynthetic Analysis for the Preparation of Difluoro-α-pyrones via Olefination−Cyclization



the Wittig, Still−Gennari, and Horner−Wadsworth−Emmons (HWE) olefinations of 4-(*tert*-butyldimethylsilyloxy)-3,3-difluoro-4-phenylbutan-2-one (**3a**) derived from **1a**. The difficulties and anomalies due to the presence of the difluoromethylene group and the successful preparation of a series of 6-substituted 5,5-difluoro-4-methyl-5,6-dihydropyran-2-ones are described herein.

The Wittig reaction of α,α-difluoro-β-hydroxy ketone **2a**, prepared by the debenzylation of the β-hydroxy enol benzyl ether **1a** with sodium in liquid ammonia[4] and (carbethoxymethylene)triphenylphosphorane in refluxing toluene, yielded 29% of the olefinic ester (**5a′**) in a 10:1 isomeric ratio in favor of the *Z*-isomer (vide infra). This is contrary to the formation of the *E*-isomer for the Wittig reaction of α-difluorocarbonyls reported by Kakinuma and co-workers,[16,17] whereas Tanaka and co-workers reported a 1:1 mixture of *E*- and *Z*-olefinic esters for the Wittig, Still−Gennari, and HWE reaction of α-difluoro cyclic ketones.[15] With the hope that the TBS-protected ketone might provide improved yields for the reaction, **2a** was converted to the corresponding silyl ether **3a**, followed by the Wittig reaction in refluxing toluene. A single isomer of the olefin (^{19}F NMR) was isolated in 35% yield,[18] identified as the *Z*-isomer (vide infra) of ethyl 5-(*tert*-butyldimethylsilyloxy)-4,4-difluoro-3-methyl-5-phenylpent-2-enoate (**4a′**).

To establish the stereochemistry of the above olefin and to prepare the corresponding α-pyrones, *Z*-stereospecific Still−Gennari olefination of **3a** was examined.[19] Thus, **3a** was treated with bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate and potassium bis(trimethylsilyl)-amide in the presence of 18-crown-6 in THF at −40 °C. The reaction was complete within 18 h (TLC) and the usual workup provided a much improved, 86% yield of the desired protected δ-hydroxy olefinic ester **4a** (Scheme 3). The ^{19}F NMR spectrum revealed the clean formation of a single stereoisomer. The *Z*-stereochemistry, similar to the results that have been reported for α-difluoro ketones,[16] was confirmed by the cyclization of this product to the α-pyrone **6a** (vide infra).

Having achieved the targeted TBS-protected olefinic ester, we turned our attention to the deprotection−cyclization to

(9) You, Z.-W.; Jiang, Z.-X.; Wang, B.-L.; Qing, F.-L. *J. Org. Chem.* **2006**, *71*, 7261.

(10) Audouard, C.; Fewcett, J.; Griffiths, G. A.; Percy, J. M.; Pintat, S.; Smith, C. A. *Org. Biomol. Chem.* **2004**, *2*, 528.

(11) You, Z.-W.; Wu, Y.-Y.; Qing, F.-L. *Tetrahedron Lett.* **2004**, *45*, 9479.

(12) For a similar reaction with non-fluorinated β-hydroxy carbonyls, see: Sabitha, G.; Sudhakar, K.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 8599.

(13) For a review, see: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Vedejs, E.; Peterson, M. J. *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; John Wiley & Sons, Inc.: New York, 1994; Vol. 21, pp 1−158.

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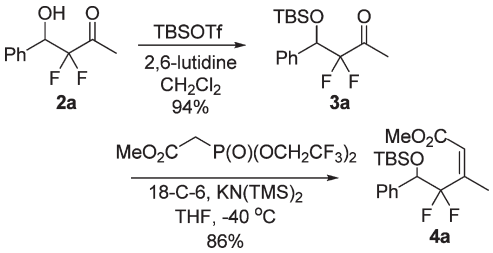
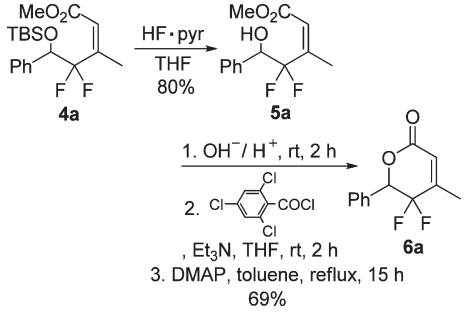
(19) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

Scheme 3. Preparation of *Z*-4,4-Difluoropent-2-enoate



Scheme 4. Preparation of δ,δ-Difluoro-α-pyrone



prepare the difluorinated pyrone. The standard deprotection of the TBS ether with TBAF resulted in poor yields of the hydroxy ester **5a**. Hydrolysis with a catalytic amount of *p*-TSA and cyclization[20] in refluxing toluene did not go to completion even after 2 days.

Deprotection of the TBS ether was then examined with HF−pyridine in THF, which yielded the δ-hydroxy ester **5a** in 80% yield (Scheme 4). Sodium hydroxide-mediated hydrolysis provided the crude δ-hydroxy acid, in quantitative yield, which was subjected to cyclization under Yamaguchi conditions[21] to achieve the targeted α-pyrone **6a** in 69% yield.

The successful synthesis of the difluoro-α-pyrone from **1a** was then extended to a series of 3-(benzyloxy)-2,2-difluorobut-3-en-1-ols (**1b**−**g**), after conversion to the corresponding α,α-difluoro β-hydroxy ketones (**2b**−**g**). Thus, the hydroxy ketones derived from benzaldehydes possessing electron-donating groups[22] at ortho-, para-, and meta-positions and aliphatic aldehydes, such as hydrocinnamaldehyde and cyclohexanecarboxaldehyde were olefinated to demonstrate the generality of the process for difluorinated α-pyrones.

The following benzyloxy alcohols **1** derived from the corresponding aldehydes [shown in brackets] were converted to the corresponding 5,5-difluoro-5,6-dihydropyran-2-ones in 20−39% overall yields in six steps: 3-(benzyloxy)-2,2-difluoro-1-(4-methoxyphenyl)-but-3-en-1-ol (**1b**) [4-methoxybenzaldehyde], 3-(benzyloxy)-2,2-difluoro-1-*p*-tolylbut-3-en-1-ol (**1c**) [*p*-tolualdehyde], and [3-(benzyloxy)-2,2-difluoro-1-(3-methoxyphenyl)-but-3-en-1-ol (**1d**) [3-methoxybenzaldehyde], as well as 3-(benzyloxy)-1-(2,6-dimethylphenyl)-2,2-difluorobut-3-en-1-ol (**1e**) [2,6-dimethylbenzaldehyde], 5-(benzyloxy)-4,

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(21) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(22) Attempts to debenzylate the benzyloxy alcohols **1**, prepared via the fluoroallylboration of benzaldehyde bearing electron-withdrawing groups, such as *p*-fluoro, *p*-chloro, and *p*-trifluoromethyl groups, resulted in dehalogenation along with debenzylation forming **2a**, **2a**, and **2c**, respectively. Debenyzlation of the benzyloxy alcohol derived from *p*-nitrobenzaldehyde resulted in the formation of the corresponding *p*-amino compound, 3,3-difluoro-4-hydroxy-4-(4-aminophenyl)butan-2-one.

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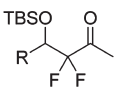
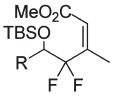
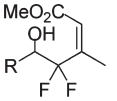
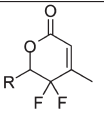
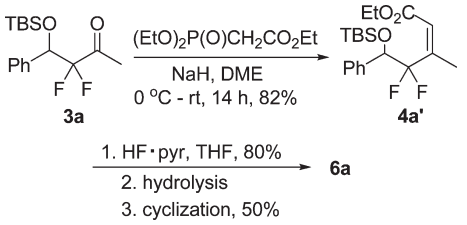
(25) A typical experimental procedure for the preparation of **6a** is as follows. **(a) Preparation of 4-(*tert*-butyldimethylsilyloxy)-3,3-difluoro-4-phenylbutan-2-one (3a):** 2,6-Lutidine (0.55 mL, 4.65 mmol) was added to a solution of 3,3-difluoro-4-hydroxy-4-phenylbutan-2-one (**2a**) (0.31 g, 1.55 mmol) in CH_2Cl_2 (6 mL) at 0 °C, followed by dropwise addition of TBDMSOTf (0.72 mL, 3.10 mmol), and the mixture was stirred at 0 °C for 3 h, and at RT for 3 h. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous NH_4Cl (8 mL). The organic layer was washed with brine, dried (anhyd. $MgSO_4$), filtered, and concentrated. The residue was purified by flash silica chromatography (hexane/EtOAc = 95/5) to yield **3a** as a colorless liquid (0.45 g, 94%). **(b) Preparation of *Z*-methyl 5-(*tert*-butyldimethylsilyloxy)-4,4-difluoro-3-methyl-5-phenylpent-2-enoate (4a):** To a solution of 18-crown-6 (0.85 g, 3.18 mmol) in THF (11 mL), at −78 °C, was added bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate (0.36 mL, 1.59 mmol) and a solution of $KN(TMS)_2$ (0.5 M in toluene, 4.12 mL, 2.06 mmol). The homogeneous mixture was stirred at that temperature for 15 min, followed by the addition of a solution of **3a** (0.50 g, 1.59 mmol) in THF (3 mL) and further stirring for 30 min and at −40 °C for 18 h. The reaction was allowed to warm to RT and quenched with sat. aqueous NH_4Cl (10 mL). The organics were extracted with Et_2O (3 × 20 mL) and the combined Et_2O layers were washed with sat. aq. $NaHCO_3$ solution, dried (anhyd. $MgSO_4$), filtered, and concentrated. The residue was purified by flash silica chromatography (hexane/EtOAc = 95/5) to provide **4a** as a colorless oil (0.51 g, 86%). **(c) Preparation of Z-methyl 4,4-difluoro-5-hydroxy-3-methyl-5-phenylpent-2-enoate (5a):** HF−pyridine complex (70%, 3.7 mL) was added to a solution of **4a** (0.14 g, 0.39 mmol) in THF (10 mL) at 0 °C, and the solution was stirred at RT for 18 h. The reaction was cautiously quenched with sat. aq. $NaHCO_3$ solution (9 mL) and extracted with EtOAc (3 × 10 mL). The combined extracts were washed with water and brine, dried (anhyd. $MgSO_4$), filtered, and concentrated. The residue was purified by flash silica chromatography (hexane/Et_2O = 1/1) to provide **5a** as a colorless oil (0.08 g, 80%). **(d) Preparation of 5,5-difluoro-4-methyl-6-phenyl-5,6-dihydro-2*H*-pyran-2-one (6a):** A mixture of **5a** (58 mg, 0.23 mmol) and 2 M NaOH solution (0.34 mL) in THF (1.9 mL) was stirred for 2 h at RT and the mixture was concentrated to provide a light yellow solid. This was acidified with aq. 2 M HCl and extracted with Et_2O (3 × 5 mL). The organic layer was washed with brine, dried (anhyd. $MgSO_4$), filtered, and concentrated to obtain the crude β-hydroxy acid as a light yellow oil (90 mg). 2,4,6-Trichlorobenzoyl chloride (0.07 mL, 0.41 mmol) was added to a mixture of the above β-hydroxy acid (90 mg, 0.37 mmol) and triethylamine (0.07 mL, 0.48 mmol) in THF (3.5 mL) and the mixture was stirred for 2 h at RT. After removal of triethylamine hydrochloride, the filtrate was diluted with toluene (25 mL) and added to a refluxing solution of 4-dimethylaminopyridine (0.18 g, 1.48 mmol) in toluene (35 mL) over a period 1.5 h. The reaction mixture was refluxed for 15 h, cooled to RT, then diluted with Et_2O, washed with 3% aq. HCl (2 × 15 mL), water, sat. aq. $NaHCO_3$ solution, and water, dried (anhyd. $MgSO_4$), filtered and concentrated. The residue was purified by flash silica chromatography (hexane/Et_2O = 1/1) to provide δ-lactone **6a** as a white solid (35 mg, 69%), mp 112−113 °C.

Table 1. Preparation of (*Z*)-4,4,-Difluoropent-2-enoates and 5,5-Difluoro-5,6-dihydropyran-2-ones

entry									
	no.	R	yield[a]	no.	yield[a]	no.	yield[a]	no.	yield[a]
1	**3a**	Ph	94	**4a**	86	**5a**	80	**6a**	69
2	**3b**	4-MeO-Ph	85	**4b**	81	**5b**	85	**6b**	74
3	**3c**	*p*-Tol	80	**4c**	77	**5c**	76	**6c**	73
4	**3d**	3-MeO-Ph	81	**4d**	83	**5d**	95	**6d**	64
5	**3e**	2,6-Me_2-Ph	88	**4e**	95	**5e**	87	**6e**	71
6	**3f**	$PhCH_2CH_2$	72	**4f**	86	**5f**	78	**6f**	78
7	**3g**	Chx	70	**4g**	74	**5g**	65	**6g**	75

[a] Isolated yield after column chromatography.

Scheme 5. HWE Reaction of α-Difluoroketone



4-difluoro-1-phenylhex-5-en-3-ol (**1f**) [hydrocinnamaldehyde], and 3-(benzyloxy)-1-cyclohexyl-2,2-difluorobut-3-en-1-ol (**1g**) [cyclohexanecarboxaldehyde]. The results are summarized in Table 1.

To expand the scope of the fluoroallylboration reaction, the *E*-specific Horner−Wadsworth−Emmons (HWE) reaction of **3a** was carried out with triethyl phosphonoacetate.[23] To our surprise, the reaction product **4a′**, a single stereoisomer of the olefinic ester, was similar to **4a** by ^{19}F NMR, revealing the formation of the *Z*-isomer (Scheme 5). Deprotection, hydrolysis, and cyclization afforded **6a** in 40% overall yield (three steps), confirming our observation, which was further corroborated in the case of **3f** as well. This is contrary to the *E*-isomer reported for the HWE reaction of 3-(*tert*-butyldimethylsilyloxy)-2,2-difluoro-4-phenylbutanal by Otaka and co-workers.[24] Kakinuma also had reported opposite stereoisomers for Still−Gennari and HWE reactions of α-difluoroalkyl aryl ketones.[16] We are further investigating this anomaly.

In summary, we have described the conversion of α, α-difluoro-β-hydroxybutan-2-ones, prepared via difluoroallylboration of aldehydes, to *Z*-4,4-difluoropent-2-enoates employing either Still−Gennari or Horner−Wadsworth−Emmons olefinations in high (74−95%) yields. The fluorinated *Z*-pentenoates were hydrolyzed to provide the corresponding δ-hydroxy acids and cyclized to 5, 5-difluoro-2-pyranones under Yamaguchi's lactonization conditions.[25] Explorations are underway to prepare the *E*-isomer of **4**.

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