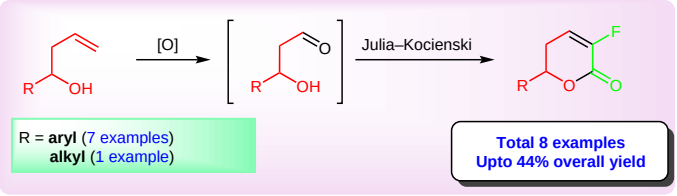
Synlett S. K. Mandal et al. Letter

Synthetic Studies Towards the Synthesis of 6-Substituted 3-Fluoro-5,6-dihydropyran-2-ones[1]

Samir K. Mandal[*a]
Apurba Sarkar[a]
Puskin Chakraborty[b]
Ashoke P. Chattopadhyay[c]

[a] Department of Chemistry, Saldiha College, Saldiha-722173, India
samirmandal2004@gmail.com
[b] Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur-700032, India
[c] Department of Chemistry, University of Kalyani, Kalyani-741235, India



Received: 26.06.2017
Accepted after revision: 11.07.2017
Published online: 17.08.2017
DOI: 10.1055/s-0036-1588534; Art ID: st-2017-d0518-l

Abstract The synthesis of 6-substituted 3-fluoro-5,6-dihydropyran-2-ones under mild conditions is described. The key step of the synthesis involves a Julia–Kocienski olefination.

Key words fluorosulfones, lactones, dihydropyranones, Julia–Kocienski olefination

6-Substituted α,β-unsaturated δ-lactones are pharmacologically important molecules that are used as antimalarial,[2] anticancer,[3] antitumor antibiotic,[4] and antifungal agents.[5] The activity of this class of naturally occurring lactones is due to the presence of the electrophilic α,β-unsaturated lactone moiety [e.g. (+)-boronolide and (–)-goniothalamin (Figure 1)],[6] but the ability to build in structural modifications is important.[7] Moreover, these lactone natural products can include complex polyketide[8] or polyacetoxylated[9] side chains in their structural features. This has encouraged the synthesis of analogues rather than synthesis of the conventional, more complex, naturally occurring molecules.[10]

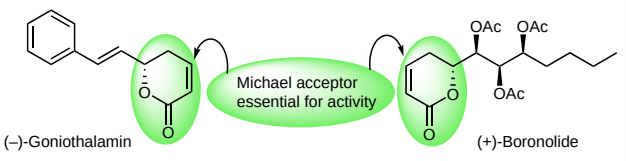


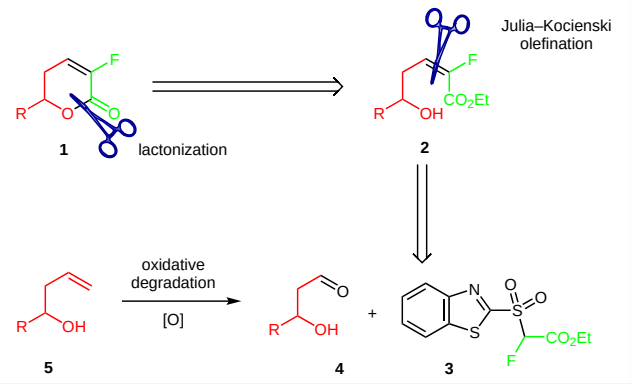
Figure 1 Active site of natural α,β-unsaturated δ-lactones

Incorporation of fluorine into organic molecules enhances their biological properties,[11] such as their metabolic stability, basicity, and binding affinity (with less toxicity),[12] through changes in the chemical, physical, and biological properties of the molecule.[13] Because it is similar in size to hydrogen and has strong electron-withdrawing properties, fluorine enhances the Michael-acceptor capabilities of conjugated double bonds of α-fluoro α,β-unsaturated carbonyl compounds.[9]

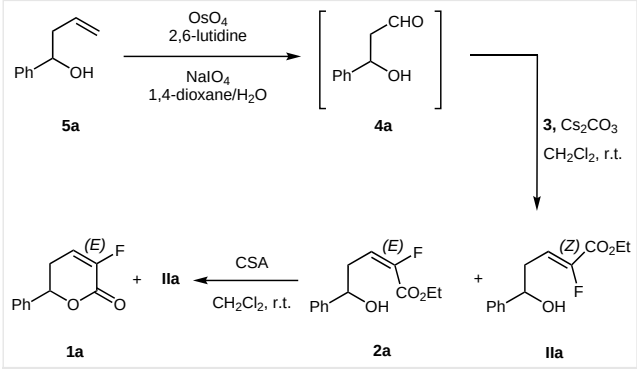
Introduction of fluorine can be achieved either by a building-block approach or by direct introduction.[14] Regio- and stereoselective fluorination is of topical interest in areas such as agrochemicals[15] and pharmaceuticals.[16] The Witting reaction, Horner–Wordsworth–Emmons reaction, the Julia reaction, and other reactions have been employed for this purpose.[17] The Julia–Kocienski olefination is a convenient method for the introduction of a fluorovinyl unit.[18] In line with our previous reports on the syntheses of various lactones,[19] we describe here the first synthesis of 6-substituted 3-fluoro-5,6-dihydropyran-2-one analogues by using a Julia–Kocienski olefination as a key step under mild conditions.

Several hetaryl sulfones have been used in the Julia–Kocienski olefination reaction. In particular, benzothiazole sulfones (BT-sulfones) have been widely used.[20,21] Therefore, BT-sulfone **3**[21a] was considered for our synthetic plan, and our retrosynthetic approach to the synthesis of lactone **1** is outlined in Scheme 1. Lactone **1** might be synthesized by the lactonization of **2**, which in turn might be synthesized by the condensation reaction of BT-sulfone **3** with a β-hydroxy aldehyde **4**. Aldehyde **4** should be readily accessible by oxidative cleavage of a homoallylic alcohol **5**.

In a preliminary study, homoallylic alcohol **5a**, prepared from benzaldehyde by a Reformatsky reaction, was treated with $RuCl_3$·$NaIO_4$ at room temperature in the presence of TBAI to yield aldehyde **4a** (Scheme 2).[22] Conversion of the alkene into an aldehyde in presence of the unprotected alcohol group occurred within 60 minutes (checked by TLC), and was confirmed by NMR spectroscopy of the condensation product. Because of the instability of β-hydroxy alde-



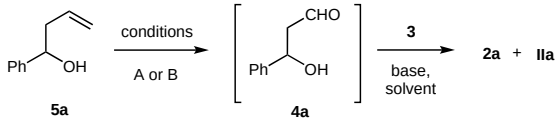
Scheme 1 Retrosynthetic analysis for the synthesis of 3-fluoro 6-substituted 5,6-dihydropyran-2-ones



Scheme 2 Synthesis of ethyl (2*Z*)-2-fluoro-5-hydroxy-5-phenylpent-2-enoate (**IIa**) and 3-fluoro-6-phenyl-5,6-dihydro-2*H*-pyran-2-one (**1a**)

hyde **4a**, the crude product was used directly in a condensation reaction with BT-sulfone **3**. Initially, the condensation was tested with DBU in CH_2Cl_2 at room temperature, but only trace amounts of the product were isolated (Table 1, entry 1). Changing the base with CH_2Cl_2 or THF as solvent (entries 2 and 3) only improved the yield to 23% with moderate stereoselectivity (*E*/*Z* = 1:1.5 or 1:1.2, respectively) and without any recovery of starting material. At this juncture, we realized it was necessary to develop either the oxidation conditions or the condensation reaction. A change in the phase-transfer catalyst to TBAB gave a similar result, as it slowed the oxidation process with residual starting material being isolated. Changing the reaction temperature had little effect on the yield or selectivity. To confirm the decomposition of β-hydroxy aldehyde **4a** under the reaction conditions (Conditions A), we examined other reported procedures.[22] We were pleased to find that OsO_4·$NaIO_4$ in the presence of 2,6-lutidine (Conditions B) provided an excellent oxidizing combination.[23] Several solvent systems, [1,4-dioxane–H_2O, *t*-BuOH–H_2O, and MeCN–H_2O (1:1)] were screened, but 1,4-dioxane–H_2O was found to be optimal. In terms of the yield and convenient separation, Cs_2CO_3 in CH_2Cl_2 at room temperature for the condensation with **3** (entry 4) was superior to Cs_2CO_3 in THF at room temperature (entry 3). The BT-sulfone remained unreacted when K_2CO_3 was used as the base (entry 5). Although stereoselectivity was low with the optimized conditions, the yield increased slightly when the reaction was performed under a nitrogen atmosphere (entry 6). The use of LDA at –20 °C led to a complex mixture (entry 7). The presence of additives or changes in the base showed little effect in improving the yield or selectivity (entries 8 and 9). Lactonization of **2a** in the presence of camphor-10-sulfonic acid (CSA) gave lactone **1a** in 33% overall yield (Scheme 2). We also attempted the conversion with the TBDMS-protected homoallyl alcohol **5a** under our optimized conditions, but obtained only a 24% overall yield of the desired lactone **1a**.

Table 1 Screening for the Synthesis of Dihydropyranone **2a**

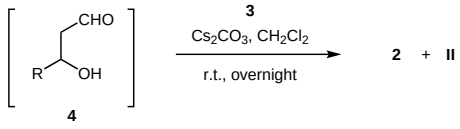


Entry	Oxidation conditions[a]	Base	Solvent	*E*/*Z*[b] (**2a**/**IIa**)	Yield[c] (%)
1	A	DBU	CH_2Cl_2	–	trace
2	A	Cs_2CO_3	CH_2Cl_2	1.5:1	20
3	A	Cs_2CO_3	THF	1.2:1	23
4	B	Cs_2CO_3	CH_2Cl_2	1.4:1	53
5	B	K_2CO_3	CH_2Cl_2	–	NR[d]
6	B[e]	Cs_2CO_3	CH_2Cl_2	1.4:1	62
7	B[f]	LDA	THF	complex mixture	–
8	B[g]	Cs_2CO_3	CH_2Cl_2	1.3:1	52
9	B[g]	DBU	CH_2Cl_2	1.4:1	48
10	B	DBU	toluene	1.1:1	–[h]

[a] Reaction conditions: A: $NaIO_4$ (5 equiv), $RuCl_3$ (1.0 mol%), TBAI (5.0 mol%), 10 M EtOAc–H_2O (1:5). B: $NaIO_4$ (4 equiv), 2,6-lutidine (2.0 equiv), OsO_4 (2.0 mol%), 10 M 1,4-dioxane–H_2O (3:1).
[b] Ratio determined from the ^{1}H NMR spectrum of the crude reaction mixture.
[c] Isolated yield of the mixture of *E*- and *Z*-isomers.
[d] No reaction.
[e] Under N_2.
[f] At –20 °C with 2.0 M LDA.
[g] Reaction in the presence of $MgBr_2$.
[h] The product was not isolated.

To evaluate the generality of the reaction, a series of β-hydroxy aldehydes containing either electron-rich or electron-deficient aryl rings **4a–h**, were prepared and treated with sulfone **3** under conditions B (Table 2).[24,25] The ratio of isomers was calculated by ^{1}H NMR analysis of the crude reaction mixture, which showed the alkene proton of the *E*-isomer (m) at a lower field than the *Z*-isomer (dt). The yields of the condensation products were moderate to good for the range of β-hydroxy aldehydes **4a–h**.

Table 2 Screening for Synthesis of Fluoro Esters **2a**

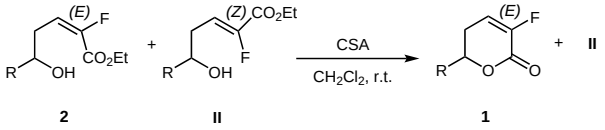


Entry	R	Products	Ratio *E*/*Z*[a] (**2a**/**IIa**)	Yield[b] (%)
1	Ph	**2a** + **IIa**	1.4:1	62
2	4-MeOC$_6$H$_4$	**2b** + **IIb**	2.4:1	67
3	3,4,5-(MeO)$_3$C$_6$H$_2$	**2c** + **IIc**	1.8:1	55
4	4-ClC$_6$H$_4$	**2d** + **IId**	2.8:1	68
5	4-FC$_6$H$_4$	**2e** + **IIe**	1:1.2	59
6	1-naphthyl	**2f** + **IIf**	1.3:1	67
7	(CH$_2$)$_2$Ph	**2g** + **IIg**	1.6:1	54
8	4-O$_2$NC$_6$H$_4$	**2h** + **IIh**	2.9:1	63

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture after the condensation reaction.
[b] Yield of the isolated mixture of the *E*- and *Z*-isomers.

The separation of the lactones **1a–h** from *Z*-isomers **IIa–h** by using CH_2Cl_2 as an eluent was next examined. Thus, a mixture of an *E*-isomer **2a–h** and a *Z*-isomer **IIa–h** collected after the condensation was lactonized[26] by treatment with CSA, and the lactone **1a–h** was collected in 24–44% overall yield (Table 3). Characterization of the lactone was carried out by HRMS, IR, and NMR analysis. The presence of fluorine was confirmed from the ^{13}C NMR spectra, which showed a high coupling constant ($^1J_{CF}$ = 257.0 Hz) for the vinylic carbon attached to the fluorine atom.

Table 3 Synthesized 6-Substituted 3-Fluoro-5,6-Dihydropyran-2-ones **1**



Entry	R	Yield[a] of **1** (%)	Overall yield[b] of **1** (%)
1	Ph	93	33
2	4-MeOC$_6$H$_4$	92	40
3	3,4,5-(MeO)$_3$C$_6$H$_2$	86	24
4	4-ClC$_6$H$_4$	90	44
5	4-FC$_6$H$_4$	92	24
6	1-naphthyl	94	32
7	(CH$_2$)$_2$Ph	89	26
8	4-O$_2$NC$_6$H$_4$	86	44

[a] Yield of the product isolated from the mixture of *E*- and *Z*-isomers with respect to the *E*-isomer.
[b] Yield with respect to the homoallylic alcohol.

In conclusion, a new methodology has been developed for constructing 6-substituted 3-fluoro-5,6-dihydropyran-2-ones by using a Julia–Kocienski olefination as the key step. Although the stereoselectivity is not high, the method has the advantages of using mild conditions and of being tolerant to various alcohol groups. Further studies are in progress to extend this protocol to the construction of fluorinated and non-fluorinated analogues of natural products.

Funding Information

This research project was funded by DST-SERB, India under the Start-Up Research Grant (Young Scientists)-CHEMICALSCIENCES [S.O #SB/FT/CS-192/2013].

Acknowledgment

S.K.M. and A.S. thank DST-SERB for Research Fellowships. S.K.M. also thanks Saldiha College, the University of Kalyani, Dr. Chattopadhyay, and Dr. Chakraborty for support.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588534.

References and Notes

(1) Presented at the NEHU (ETC-2016) and KU (NSCTC-VII-2016) conference: S. K. Mandal and A. P. Chattopadhyay, An Approach for the Synthesis of Fluorinated 6-Substituted 5,6-Dihydropyran-2-one Analogues. Also presented at the VB (RTCR-2017) conference: S. K. Mandal and A. Sarkar, Synthesis of Fluorinated 6-Substituted 5,6-Dihydropyran-2-one Analogues.
(2) (a) Cardona, W.; Quiñones, W.; Robledo, S.; Vélez, I.; Murga, J.; García-Fortanet, J.; Carda, M.; Cardona, D.; Echeverri, F. *Tetrahedron* **2006**, *62*, 4086. (b) Saeed, M.; Ilg, T.; Schick, M.; Abbas, M.; Voelter, W. *Tetrahedron Lett.* **2001**, *42*, 7401. (c) Davies-Coleman, M.; Rivett, D. *Phytochemistry* **1987**, *26*, 3047.
(3) Newlands, E. S.; Rustin, G. J. S.; Brampton, M. H. *Br. J. Cancer* **1996**, *74*, 648.
(4) Ohkuma, H.; Naruse, N.; Nishiyama, Y.; Tsuno, T.; Hoshino, Y.; Sawada, Y.; Konishi, M.; Oki, T. *J. Antibiot. (Tokyo)* **1992**, *45*, 1239.
(5) Teruya, T.; Simizu, S.; Kanoh, N.; Osada, H. *FEBS Lett.* **2005**, *579*, 2463.
(6) (a) Kumar, P.; Naidu, S. V. *J. Org. Chem.* **2006**, *71*, 3935. (b) de Fátima, A.; Kohn, L. K.; Antonio, M. A.; de Carvalho, J. E.; Pilli, R. A. *Bioorg. Med. Chem.* **2006**, *14*, 622.
(7) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2004**, *67*, 1216.
(8) Kudo, N.; Wolff, B.; Sekimoto, T.; Schreiner, E. P.; Yoneda, Y.; Yanagida, M.; Horinouchi, S.; Yoshida, M. *Exp. Cell Res.* **1998**, *242*, 540.
(9) Lin, J.; Qiu, X.-L.; Qing, F.-L. *Beilstein J. Org. Chem.* **2010**, *6*, 37.
(10) Bonazzi, S.; Eidam, O.; Güttinger, S.; Wach, J.-Y.; Zemp, I.; Kutay, U.; Gademann, K. *J. Am. Chem. Soc.* **2010**, *132*, 1432.

(11) (a) Sham, H. L.; Wideburg, N. E.; Spanton, S. G.; Kohlbrenner, W. E.; Betebenner, D. A.; Kempf, D. J.; Norbeck, D. W.; Plattner, J. J.; Erickson, J. W. *J. Chem. Soc., Chem. Commun.* **1991**, 110. (b) Thaisrivongs, S.; Schostarez, H.; Pals, D. T.; Turner, S. R. *J. Med. Chem.* **1987**, *30*, 1837.

(12) (a) Kirsch, P. *Modern Fluoroorganic Chemistry. Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, **2004**. (b) Rivkin, A.; Yoshimura, F.; Gabarda, A. E.; Cho, Y. S.; Chou, T.-C.; Dong, H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 10913.

(13) (a) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3. (b) Lemal, D. M. *J. Org. Chem.* **2004**, *69*, 1. (c) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.

(14) (a) Ono, T.; Hayakawa, H.; Yasuda, N.; Uekusa, H.; Ohashi, Y. In *Current Fluoroorganic Chemistry: New Synthetic Directions, Technologies, Materials, and Biological Applications*; Soloshonok, V. A.; Mikami, K.; Yamazaki, T.; Welch, J. T.; Honek, J. F., Eds.; ACS Symposium Series 949: Washington, **2007**, Chap. 10 170. (b) Bégué, J.-P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992. (c) Alonso, D. A.; Fuensanta, M.; Gómez-Bengoa, E.; Nájera, C. *Adv. Synth. Catal.* **2008**, *350*, 1823. (d) Chevrie, D.; Lequeux, T.; Pommelet, J.-C. *Tetrahedron* **2002**, *58*, 4759. (e) Hara, S.; Yamamoto, K.; Yoshida, M.; Fukuhara, T.; Yoneda, N. *Tetrahedron Lett.* **1999**, *40*, 7815. (f) Chevrie, D.; Lequeux, T.; Demoute, J. P.; Pazenok, S. *Tetrahedron Lett.* **2003**, *44*, 8127. (g) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. *Chem. Rev.* **2015**, *115*, 9073. (h) Yanai, H.; Taguchi, T. *Eur. J. Org. Chem.* **2011**, 5939.

(15) Jeschke, P. *ChemBioChem* **2004**, *5*, 570.

(16) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley: Hoboken, **2008**.

(17) (a) Burton, D. J.; Yang, Z.-Y.; Qiu, W. *Chem. Rev.* **1996**, *96*, 1641. (b) Barros, M. E. S. B.; Freitas, J. C. R.; Oliveira, J. M.; da Cruz, C. H. B.; da Silva, P. B. N.; de Araújo, L. C. C.; Militão, G. C. G.; da Silva, T. G.; Oliveira, R. A.; Menezes, P. H. *Eur. J. Med. Chem.* **2014**, *76*, 291. (c) Oliveira, J. M.; Freitas, J. C. R.; Comasseto, J. V.; Menezes, P. H. *Tetrahedron* **2011**, *67*, 3003. (d) Nokami, J.; Anthony, L.; Sumida, S.-I. *Chem. Eur. J.* **2000**, *6*, 2909.

(18) (a) Kocienski, P. J.; Bell, A.; Blakemore, P. R. *Synlett* **2000**, 365. (b) Zajc, B.; Kumar, R. *Synthesis* **2010**, 1822. (c) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175.

(19) (a) Paira, M.; Banerjee, B.; Jana, S.; Mandal, S. K.; Roy, S. C. *Tetrahedron Lett.* **2007**, *48*, 3205. (b) Mandal, S. K.; Roy, S. C. *Tetrahedron Lett.* **2007**, *48*, 4131. (c) Mandal, S. K.; Roy, S. C. *Tetrahedron* **2008**, *64*, 11050. (d) Mandal, S. K.; Paira, M.; Roy, S. C. *J. Org. Chem.* **2008**, *73*, 3823. (e) Saha, S.; Mandal, S. K.; Roy, S. C. *Tetrahedron Lett.* **2011**, *52*, 3128.

(20) (a) Li, B.; Masuda, S.; Minato, D.; Zhou, D.; Sugimoto, K.; Nemoto, H.; Matsuya, Y. *Tetrahedron* **2014**, *70*, 3981. (b) Calata, C.; Pfund, E.; Lequeux, T. *Tetrahedron* **2011**, *67*, 1398. (c) Ghosh, A. K.; Banerjee, S.; Sinha, S.; Kang, S. B.; Zajc, B. *J. Org. Chem.* **2009**, *74*, 3689. (d) Zajc, B.; Kake, S. *Org. Lett.* **2006**, *8*, 4457.

(21) (a) Mandal, S. K.; Ghosh, A. K. Kumar R.; Zajc, B. *Org. Biomol. Chem.* **2012**, *10*, 3164. (b) Chowdhury, M.; Mandal, S. K.; Banerjee, S.; Zajc, B. *Molecules* **2014**, *19*, 4418. (c) Ayeni, D. O.; Mandal, S. K.; Zajc, B. *Tetrahedron Lett.* **2013**, *54*, 6008.

(22) Yuasa, Y.; Shibuya, S.; Yuasa, Y. *Synth. Commun.* **2003**, *33*, 3947.

(23) Lee, K.; Kim, H.; Hong, J. *Org. Lett.* **2009**, *11*, 5202.

(24) **3-Hydroxy-3-phenylpropanal (4a); Typical Oxidation Procedure**

To a solution of 1-phenylbut-3-en-1-ol (**5a**; 150 mg, 1.01 mmol) in 3:1 1,4-dioxane/H_2O (10 mL) at r.t. were successively added 2.5% OsO_4 in *t*-BuOH (0.18 mL; 0.022 mmol) and 2,6-lutidine (0.24 mL, 2.02 mmol). $NaIO_4$ (864 mg, 4.04 mmol) was then added in portions over 30 min, and the mixture was stirred at r.t. for 2 h. The reaction was quenched by addition of H_2O (10 mL), and the mixture was diluted with Et_2O (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The organic layers were combined, washed with H_2O (2 × 25 mL) and brine (25 mL), then dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude product, which was used directly in the condensation reaction.

(25) **Ethyl (2*E*)-2-Fluoro-5-hydroxy-5-phenylpent-2-enoate (2a) and Ethyl (2*Z*)-2-Fluoro-5-hydroxy-5-phenylpent-2-enoate (IIa); Typical Condensation Procedure**

Cs_2CO_3 (780 mg, 2.4 mmol) was added to a stirred solution of the crude **4a** and sulfone **3** (366 mg, 1.2 mmol) in CH_2Cl_2 (10 mL) at r.t., and the mixture was stirred overnight. The solids were removed by filtration, and the solvent was removed in vacuo. The crude product was purified by column chromatography [silica gel (100–200 mesh) EtOAc/PE (4:1)] to give a mixture of **2a** and **IIa**; yield: 147 mg (62%)

(26) **3-Fluoro-6-phenyl-5,6-dihydro-2*H*-pyran-2-one (1a): Typical Lactonization Procedure**

The mixture of **2a** and **IIa** obtained from the condensation reaction was treated with CSA (5 mg, 2 mol%) in CH_2Cl_2 (10 mL) at r.t. overnight. The resulting mixture was concentrated and purified by column chromatography [silica gel (100–200 mesh), CH_2Cl_2] to give a white solid; yield: 63 mg (33% overall); mp 82 °C.

IR (KBr) 1743, 1674, 1164, 769 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.66–2.74 (m, 1 H), 2.83–2.93 (m, 1 H), 5.54 (dd, *J* = 4.0, 12.0 Hz, 1 H), 6.36–6.40 (m, 1 H), 7.36–7.48 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.6 (d, $^3J_{CF}$ = 4.0 Hz), 80.0, 118.0 (d, $^2J_{CF}$ = 13.0 Hz), 126.1 (2 C), 128.9 (2 C), 129.1, 137.4, 147.6 (d, $^1J_{CF}$ = 258.0 Hz), 158.9 (d, $^2J_{CF}$ = 31.0 Hz). HRMS: *m*/*z* [M + H] calcd for $C_{11}H_{10}FO_2$: 193.0665; found: 193.0668.