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Syntheses of β- and γ-fluorophenyl *cis*- and *trans*-α-methylene-γ-butyrolactones

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ABSTRACT

Preparation of a series of *cis*-γ-fluorophenyl-β-phenyl-α-methylene-γ-butyrolactones is reported via 'allylboration' of fluorobenzaldehydes with (*E*)-methyl 3-phenyl-2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)acrylate. The corresponding trans-γ-fluorophenyl lactones were prepared either (i) via 'allylboration' using the (*Z*)-reagents or (ii) via an indium triflate-mediated isomerization of the *cis*-products. The difficulty in isomerizing difluorinated *cis*-products confirms the probable intermediacy of carbocations. Finally, the synthesis of *cis*-β-fluorophenyl-γ-phenyl-α-methylene-γ-butyrolactones was achieved via an indium-catalyzed allylation–lactonization of aldehydes with (*Z*)-2-(bromomethyl)-3-(fluorophenyl)acrylates.

The transcription factor nuclear factor-kappa B (NF-κB) is receiving enormous attention since it regulates genes that influence the inflammatory response, cell growth, survival, chemoresistance, angiogenesis, invasion and metastasis.[1] In light of its diverse effects on multiple tumorigenic processes, NF-κB is an attractive target for inhibition in cancer cells. Naturally occurring compounds, such as parthenolide (Fig. 1), a sesquiterpene α-methylene-γ-butyrolactone (AMGBL) isolated from the herb feverfew have been shown to inhibit NF-κB.[2] The AMGBL framework is present in a large number of natural products and possesses a variety of biological properties.[3]

We had recently reported organoborane-mediated methodologies to construct a variety of AMGBL in a stereospecific manner (Scheme 1)[4] providing a unique opportunity to study their activity against various diseases related to NF-κB, including various cancers. These processes were exploited to tailor a series of α-methylene-γ-butyrolactones and conduct a structure activity relationship (SAR) on growth suppression of three human pancreatic cancer cell lines (Panc-1, MIA PaCa-2, and BxPc-3). This systematic study established a discernible relationship between the substitution pattern of AMGBL and their anti-proliferative activity and revealed that β,γ-diaryl-AMGBLs, particularly those with a *trans*-relationship exhibited a higher potency than parthenolide.[5] In view of the success of fluoroorganic molecules in medicinal chemistry[6] we were interested in the preparation of fluoroaryl

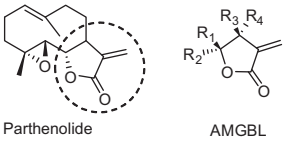
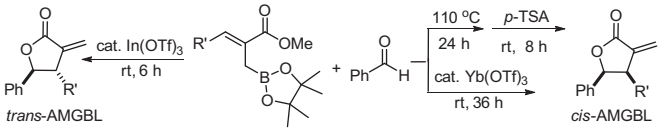


Figure 1. Bio-active AMGBLs.



Scheme 1. Preparation of *cis*- and *trans*-AMGBL

AMGBLs using our aforementioned protocols for examining their bio-activity. Also, we were interested in probing the effect of fluorine atoms during the isomerization for the preparation of *trans*-β,γ-diaryl AMGBLs. The results are presented herein.

We began our synthesis with the preparation of (*E*)-methyl 3-phenyl-2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-acrylate (**1**) as reported by us earlier via the Baylis–Hillman reaction or vinylalumination of benzaldehyde (Scheme 2).[4a] 'Allylborations' of *o*-, *m*-, and *p*-fluorobenzaldehydes (**2a**, **2b**, and **2c**, respectively) with **1** were carried out in refluxing toluene, when the reaction was complete within 40 h. Lactonization to the

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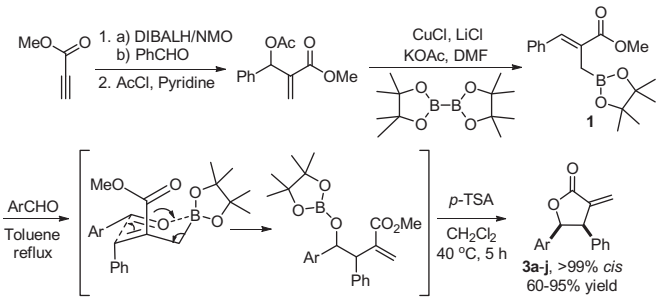
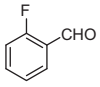
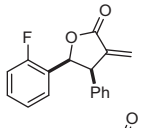
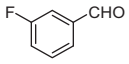
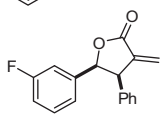
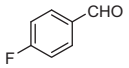
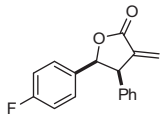
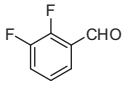
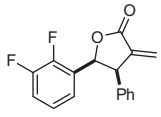
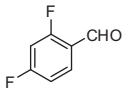
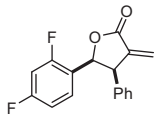
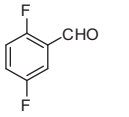
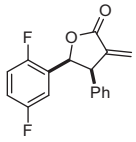
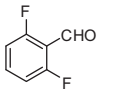
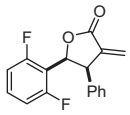
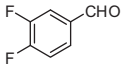
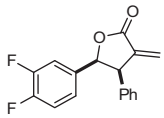
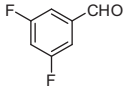
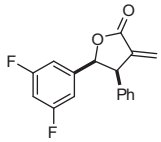
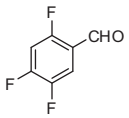
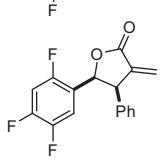


Scheme 2. Vinylalumination of benzaldehyde and formation of γ-fluorophenyl β-phenyl *cis*-AMGBL.

corresponding AMGBL was carried out with the intermediate *cis*-product by exchanging the solvent with dichloromethane, followed by the addition of *p*-toluenesulfonic acid (*p*-TSA) and warming to 40 °C. The lactonization was complete within 5 h (TLC) and workup provided the fluorinated *cis* lactones **3a**–**c** in 83–85% overall yields (Scheme 2) (Table 1).

The reaction was then extended to difluorobenzaldehydes. Thus, 2,3- (**2d**), 2,4- (**2e**), 2,5- (**2f**), 2,6- (**2g**), 3,4- (**2h**), and 3,5- (**2i**)—difluorobenzaldehydes were 'allylborated' with **1** and lactonized in the presence of *p*-TSA. Upon workup as above, all of the reactions, except the reaction of **2g** provided the corresponding *cis*-γ-difluorophenyl β-phenyl AMGBLs (**3**) in 76–87% yields (Table 1). 2,6-Difluorobenzaldehyde provided the lactone in only

Table 1
Preparation of *cis*-β-phenyl-γ-fluorophenyl-α-methylene-γ-lactones via 'allylboration'[a]

Entry	Aldehyde		AMGBL		Yield[b] %	dr[c]	
	2	Structure	**3**	Structure		*cis*	*trans*
1	**2a**		**3a**		85	>99	<1
2	**2b**		**3b**		84	>99	<1
3	**2c**		**3c**		83	>99	<1
4	**2d**		**3d**		82	>99	<1
5	**2e**		**3e**		85	>99	<1
6	**2f**		**3f**		87	>99	<1
7	**2g**		**3g**		60	>99	<1
8	**2h**		**3h**		95	>99	<1
9	**2i**		**3i**		76	>99	<1
10	**2j**		**3j**		90	>99	<1

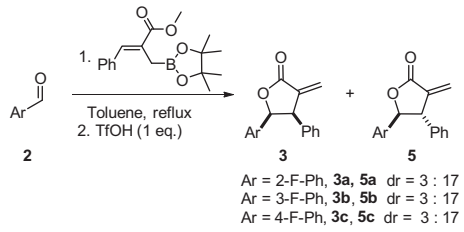
[a] Reactions were carried out in toluene at 110 °C for 40 h, followed by treatment with *p*-TSA in CH_2Cl_2 at rt for 5 h. See experimental in supplementary information.
[b] Isolated yield after chromatography.
[c] Determined by ^1H NMR of the crude reaction mixture.

60% yield. 2,3,5-Trifluorobenzaldehyde (**2j**) was also included in the series and the corresponding *cis*-lactone **3j** was obtained in 90% yield.

Having achieved the preparation of the *cis*-lactones, we progressed toward the preparation of the *trans*-lactones. The preparation of *trans*-β,γ-disubstituted α-methylene-γ-butyrolactones with the *cis*-product forming *E*-reagent **1** via isomerization of the reaction intermediate with catalytic amounts of Lewis acids, such as indium triflate has been described by us earlier.[4b] The reaction is believed to proceed via a carbocation mechanism, supported by the difficulty in isomerization of the intermediates derived from the reaction of benzaldehydes substituted with electron-withdrawing groups. In such cases, the isomerization was forced by using a strong Bronsted acid, such as trifluoromethanesulfonic acid.[4c] We were concerned about the isomerization of the intermediates derived from ring-fluorinated benzaldehydes since the introduction of fluorine atoms on the aromatic ring could destabilize the carbocation intermediate (Scheme 3).

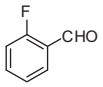
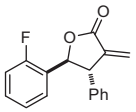
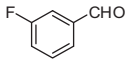
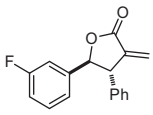
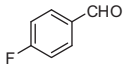
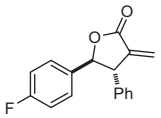
Indeed, attempted isomerization of the intermediate formed from the reaction of **1** and **2a** using the typical 0.2 equiv of indium triflate resulted in partial isomerization producing a 3:1 mixture of the lactone favoring the *cis*-isomer. Increasing the amount of the Lewis acid resulted in a low yield of the product lactone. Addition of a molar equiv of trifluoromethanesulfonic acid to the reaction mixture after the initial 'allylboration' (Scheme 4) resulted in the formation of a 17:3 mixture of the isomeric lactones favoring the *trans*-isomer. Fortunately, the diastereomers could be readily separated by silica gel column chromatography (Table 2). Similar results were obtained with fluorobenzaldehydes **2b** and **2c** as well. However, the isomerization became increasingly difficult with the increase in the number of fluorine atoms on the aromatic ring. For all of the difluorobenzaldehydes, only 30% of reaction intermediates were converted to the *trans*-isomer with 1 equiv of trifluoromethanesulfonic acid. Replacing toluene with more polar solvents, such as DMF and DMSO did not alter the result appreciably.

We then resorted to the direct synthesis of *trans*-γ-fluorophenyl β-phenyl AMGBLs using the isomer of the reagent, (*Z*)-ethyl 3-phenyl-2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)acrylate (**4**).[4a] The reagent **4** was prepared via the iodomethylboronate-mediated homologation[7] of the vinylaluminum reagent derived from the corresponding propiolate (Scheme 5).[8] Treatment of this reagent with all of the mono-, di- and trifluorinated benzaldehydes (**2a–j**), in the presence of indium triflate, provided *trans*-lactones

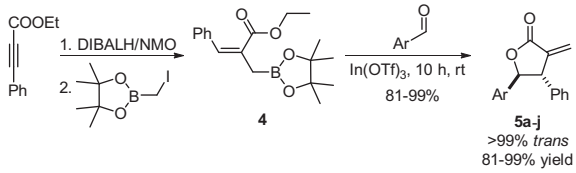


Scheme 4. 'Allylboration'–iosmerization–lactonization.

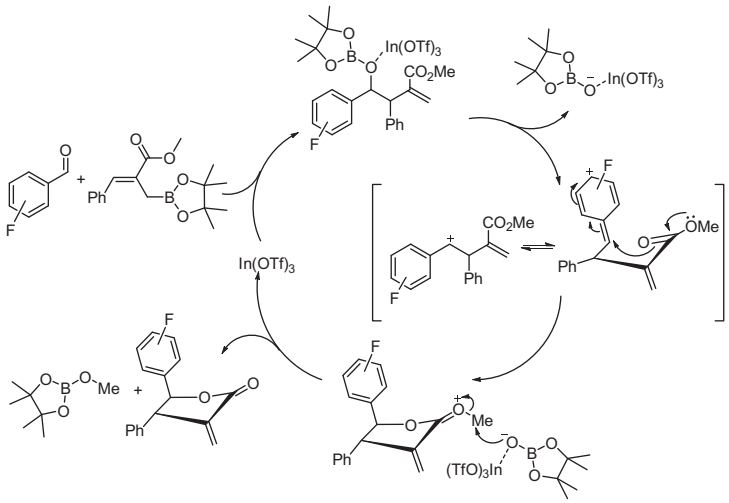
Table 2
Preparation of γ-fluorophenyl β-phenyl *trans*-α-methylene-γ-lactones via 'allylboration'–isomerization[a]

Entry	Aldehyde		AMGBL		Yield[b] %	dr[c]	
	2	Structure	**5**	Structure		*trans*	*cis*
1	**2a**		**5a**		85	85	15
2	**2b**		**5b**		85	85	15
3	**2c**		**5c**		86	85	15

[a] Reactions were carried out in toluene at 110 °C for 40 h, followed by treatment with triflic acid in CH_2Cl_2 at rt for 3 h. See experimental in supplementary information.
[b] Isolated yield after chromatography.
[c] Determined by ^1H NMR of the crude reaction mixture.

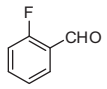
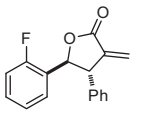
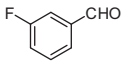
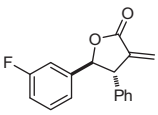
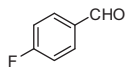
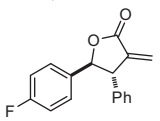
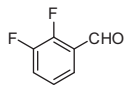
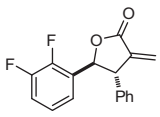
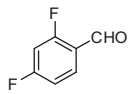
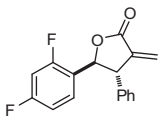
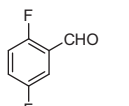
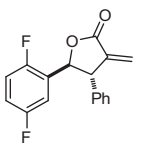
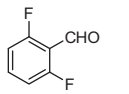
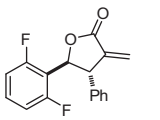
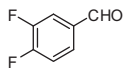
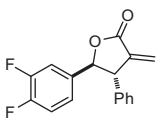
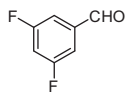
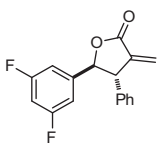
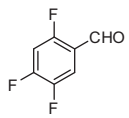
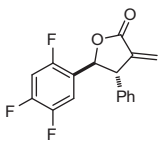


Scheme 5. Synthesis of γ-fluorophenyl, β-phenyl-*trans*-AMGBL.



Scheme 3. Proposed mechanism.

Table 3
Preparation of *trans*-β-phenyl-γ-fluorophenyl-α-methylene-γ-lactones via 'allylboration'[a]

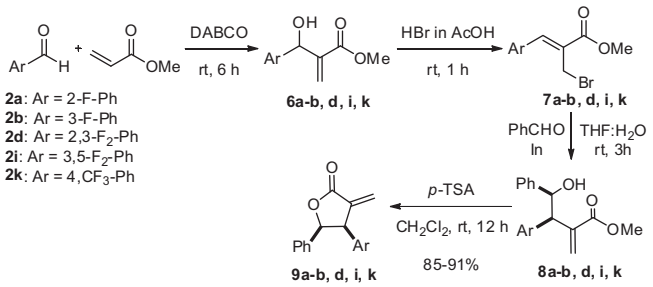
Entry	Aldehyde		AMGBL		Yield[b] %	dr[c]	
	2	Structure	**5**	Structure		*trans*	*cis*
1	**2a**		**5a**		94	>99	<1
2	**2b**		**5b**		96	>99	<1
3	**2c**		**5c**		95	>99	<1
4	**2d**		**5d**		97	>99	<1
5	**2e**		**5e**		93	>99	<1
6	**2f**		**5f**		98	>99	<1
7	**2g**		**5g**		81	>99	<1
8	**2h**		**5h**		91	>99	<1
9	**2i**		**5i**		99	>99	<1
10	**2j**		**5j**		98	>99	<1

[a] Reactions were carried out in toluene at rt for 10 h, followed by treatment with $In(OTf)_3$ in toluene at rt. See experimental in supplementary information.
[b] Isolated yield after chromatography.
[c] Determined by ^1H NMR of the crude reaction mixture.

(Scheme 5) in 91–98% yields within 10 h at room temperature (rt) (Table 3). Again, 2,6-difluorobenzaldehyde provided the lactone in a relatively lower (81%) yield (Table 3, entry 7).

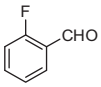
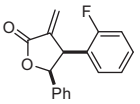
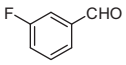
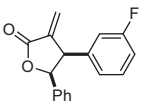
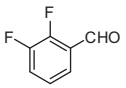
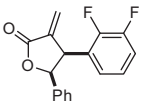
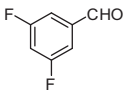
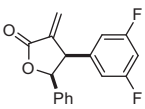
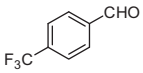
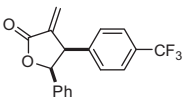
It must be noted that the isomerization of the product from reagent **1** occurs at 110 °C over 40 h, whereas no isomerization was observed with reagent **4** at rt over 10 h.

Having successfully synthesized both *cis*- and *trans*-γ-fluorophenyl-β-phenyl AMGBLs, we decided to include β-fluorophenyl-γ-phenyl AMGBLs also in the structure–activity relationship study.



Scheme 6. Synthesis of β-fluorophenyl γ-phenyl *cis*-AMGBL.

Table 4
Preparation of *cis*-β-fluorophenyl-γ-phenyl-α-methylene-γ-lactones

Entry	Aldehyde		AMGBL		Yield[a] %
	2	Structure	**9**	Structure	
1	**2a**		**9a**		89
2	**2b**		**9b**		91
3	**2d**		**9d**		90
4	**2i**		**9i**		89
5	**2k**		**9k**		85

[a] Isolated yield of pure *cis*-diastereomer after chromatography from **8**.

Unfortunately, the synthesis of the latter AMGBLs demands the construction of the corresponding fluorophenyl-substituted reagent **1** for each fluoro-analog. To expedite their synthesis, we explored a simpler route. Among the various approaches for the synthesis of AMGBL's,[3,9] a common approach is the allylation of aldehydes using an in situ generated allylindium, followed by an acid catalyzed lactonization.[10] Accordingly, the allyl alcohol (**6**) from the Baylis–Hillman reaction of each of the fluorophenyl aldehydes and methyl acrylate was brominated using HBr in acetic acid to form **7** in 89–98% yields. The indium-mediated Barbier-type reaction of **7** with benzaldehyde provided the necessary *cis*-α-methylene-γ-hydroxyester **8** exclusively, which was lactonized in 85–91% yields in the presence of catalytic *p*-TSA (Scheme 6) (Table 4). Thus, we could achieve the synthesis of the required *cis*-β-fluorophenyl-γ-phenyl AMGBLs.

In conclusion, we have described the syntheses of a series of fluoro-analogs of *cis*- and *trans*-γ-fluorophenyl β-phenyl α-methylene-γ-butyrolactones.[11] While the *cis*-isomers could be readily synthesized with the *E*-reagent, the *trans*-isomers were synthesized either with the *Z*-reagent or via isomerization. However, the presence of fluorine atoms on the benzene ring destabilizes the intermediate carbocations, resulting in only partial isomerization. Finally, the synthesis of a series of *cis*-β-fluorophenyl-γ-phenyl-α-methylene-γ-butyrolactones was achieved via a Barbier type reaction. Examination of the biological properties of these novel fluorolactones is in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.07.106.

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11. *General procedure for the synthesis of cis-β-phenyl-γ-(fluorophenyl)-α-methylene-γ-butyrolactone* (**3**). The fluorinated benzaldehyde (5 mmol) was added to a solution of the substituted *E*-allylboronate **1** (1.81 g, 6 mmol), prepared as described earlier,[4c] in toluene and refluxed at 110 °C for 40 h. Upon completion of the reaction (TLC), the solvent was evaporated under vacuum and the crude mass was dissolved in CH_2Cl_2. *p*-TSA (20%) was added and refluxed at 40 °C for 5 h followed by the addition of 30% aq H_2O_2 (2 mL), methanol (2 mL) and pH 7 buffer and stirred overnight. The crude product was extracted with Et_2O and the combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified by silica gel chromatography (hexanes/ethyl acetate :: 95:5).
General procedure for the synthesis of trans-β-phenyl-γ-(fluorophenyl)-α-methylene-γ-butyrolactone (**5**): The fluorinated benzaldehyde (5 mmol) was added to a solution of the substituted *Z*-allylboronate, prepared as described before[4a] (1.9 g, 6 mmol) in toluene, followed by indium triflate (0.67 g, 0.12 mmol) and stirred at rt for 10 h. Upon completion of the reaction (TLC), the mixture was washed with water, extracted with Et_2O, the combined organics was dried over anhydrous Na_2SO_4, concentrated, and purified by flash column chromatography (silica gel, hexanes/ethyl acetate: 95:5) to obtain the product **5**.
General procedure for the preparation of methyl 3-(fluorophenyl)-4-hydroxy-2-methylene-4-phenylbutanoate (**8**). Benzaldehyde (3.0 mmol) was added to the solution of (*Z*)-methyl 2-(bromomethyl)-3-(fluorophenyl)acrylate (**7**)[10] (3 mmol) in THF (4.5 mL) and water (3 mL). In (3.6 mmol) was added to this solution. The reaction mixture was stirred at rt for 3 h. Upon completion (TLC), water (20 mL) was added to the reaction mixture and extracted using ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine, dried over anhyd Na_2SO_4, concentrated and purified by flash column chromatography to obtain **8**.
General procedure for the preparation of cis-β-(fluorophenyl)-γ-phenyl-a-methylene-γ-butyrolactone (**9**). *p*-Toluenesulfonic acid was (0.1 mmol) was added to a solution of **8** and stirred the content at rt for 12 h. Upon completion (TLC), water (10 mL) was added to the reaction mixture and extracted using dichloromethane (2 × 20 mL). The combined organics was washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified by flash column chromatography to obtain **9**.