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Synthesis of aromatic compounds containing a 1,1-dialkyl-2-trifluoromethyl group, a bioisostere of the *tert*-alkyl moiety

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Abstract—1,1-Dialkyl-2-perfluoroalkyl compounds, which are potential metabolically stable bioisosteres of the *tert*-alkyl moiety, have been synthesized from the corresponding tertiary alcohols using titanium (IV) chloride—dimethylzinc or trimethylaluminium as the source of the methyl group. The synthetic methods proved to be versatile for synthesizing 1,1-dimethyl-2,2,2-trifluoroethyl compounds and analogs, including compounds containing aromatic and heterocyclic rings.

In structure–activity relationship studies, bulky alkyl groups, as exemplified by *tert*-butyls, are frequently critical for the biological activity,[1] however, they often are susceptible to rapid metabolic degradation such as ω-oxidation by P-450. In order to prevent this oxidative metabolism, we have designed and synthesized fluorinated analogs such as the 1,1-dimethyl-2,2,2-trifluoroethyl compounds which serve as metabolically stable bioisosteres (Fig. 1).

In our neurokinin-1 and TRPV1 antagonist programs, the 1,1-dimethyl-2,2,2-trifluoroethyl derivatives (**B** and **D**) showed significantly improved stability in human liver microsomes (HLM) while retaining the intrinsic activity of the *tert*-butyl derivatives (**A** and **C**), as shown in Figure 2. This report summarizes new synthetic methods for the preparation of 1,1-dimethyl-2,2,2-trifluoroethyl compounds and related analogs, discovered while prosecuting these two programs.[2]

The sometimes unstable *tert*-butyl group has often been replaced by the easily accessible and metabolically stable trifluoromethyl or trifluoromethoxy derivatives[3] as exemplified in Figure 2 for the TRPV1 antagonist program. However, in this case the modification to a trifluoromethyl group resulted in a decrease of activity, possibly due to the electron-withdrawing effect of the trifluoromethyl moiety. In our neurokinin-1 antagonist program,[2] we set out to address the issue of rapid metabolism, i.e. clearance in HLM, by the introduction of fluorine atoms directly on the *tert*-butyl moiety. Unfortunately, it was found that mono- or di-fluorination of alcohol **1** or aldehyde **4** by dimethylsulfur trifluoride (DAST)[4] resulted exclusively in the undesired compounds **3** and **6**, respectively, as shown in Figure 3. The formation of compound **3** and **6** can be explained by a migration of the phenyl group to the adjacent carbon followed by fluorination.[4]

Following this result, the preparation of 1,1-dimethyl-2,2,2-trifluoroethyl compounds was investigated. Methods for the trifluoromethylation[5] of carboxylic acid derivatives include direct fluorination using sulfur tetrafluoride (SF_4) or indirect fluorination via dithionic acid (or esters) using xenon difluoride/bromo trifluoride. However, neither of these reactions is practical on large scale. Consequently, our first attempt was the direct geminal dimethylation of trifluoromethylketone **7** using dimethyltitanium dichloride, as reported by Reetz,[6] but the reaction provided monomethylated **8a** instead as the major product without any desired **9a**, as shown in Figure 4. Since alcohol **8a** is considered to be an intermediate of **9a**, an additional step for the introduction of the second methyl group was necessary. Thus, our efforts shifted toward

Keywords: Bioisostere; *tert*-Butyl; Dimethyltitanium dichloride; Trimethylaluminium; 1,1-Dimethyl-2,2,2-trifluoroethyl.
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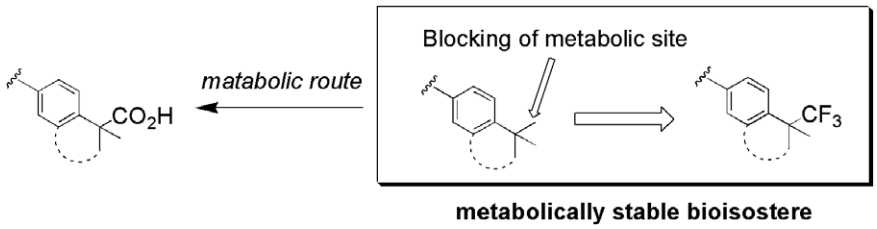


Figure 1.

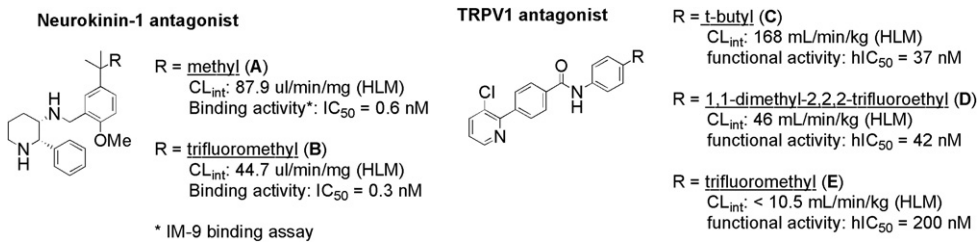


Figure 2.

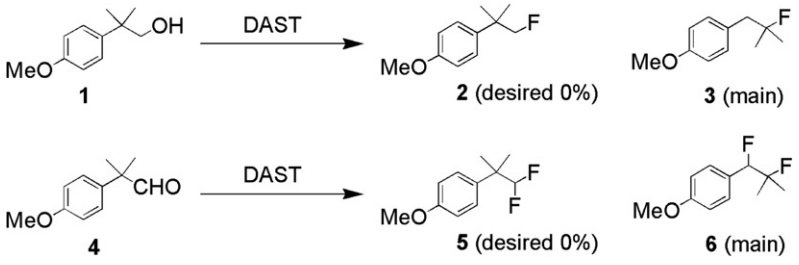


Figure 3.

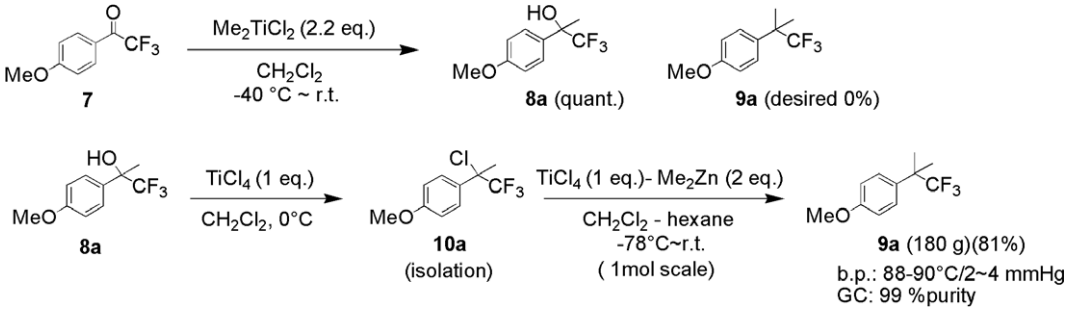
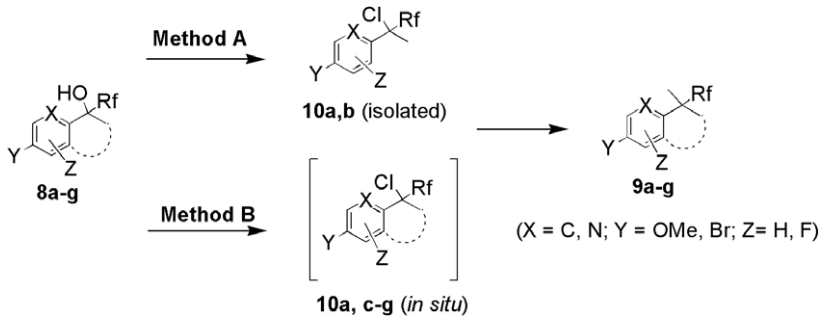


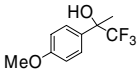
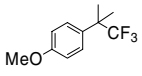
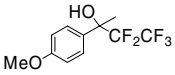
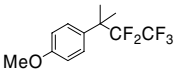
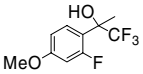
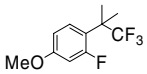
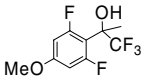
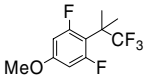
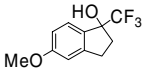
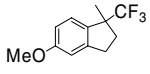
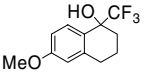
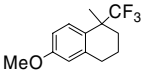
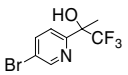
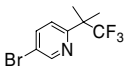
Figure 4.

the conversion of **8a** to **9a**. After several trials,[7] it was found that chlorination[8] of the tertiary alcohol **8a** using titanium (IV) chloride (1 equiv) at 0 °C followed by displacement with a methyl group using the titanium (IV) chloride (1 equiv)—dimethyl zinc (2 equiv) combination[7] at −78 °C produced the desired product **9a** in high combined yield (81%) for the two steps (*Method A*). This reaction has been run on a 1 mole scale to give 180 g of **9a**, reproducibly.

This method was applied to a variety of tertiary alcohol analogs **8b**–**g** in order to examine the scope and limitation of this approach, as shown in Table 1. While the methylation of non-cyclic analogs (entries **1** and **2**) by method A proceeded smoothly, for cyclic analogs elimination of hydrohalide or decomposition[9] of intermediates **8e** and **8f** took place (entries 5 and 6). In order to address this issue, a one-pot method (*Method B*) was found to be very effective in preventing the elimination reaction and instability during the isolation. In entries 5 and 6, chlorination of the cyclic tertiary alcohol using titanium (IV) chloride (2 equiv) at −78 °C followed by addition of dimethylzinc (2 equiv), all in one pot, afforded the desired products

Table 1. Methylation of tertiary alcohols using titanium (IV) chloride—dimethylzinc (Methods A and B)



Entry	Substrate	Product	Method (% yield)
1	 **8a**	 **9a**	A (95), B (51)
2	 **8b**	 **9b**	A (60)
3	 **8c**	 **9c**	B (34)
4	 **8d**	 **9d**	B (N.R.)
5	 **8e**	 **9e**	B (87)
6	 **8f**	 **9f**	B (92)
7	 **8g**	 **9g**	B (N.R.)

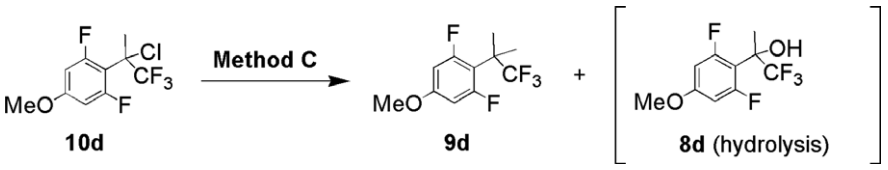
tert-Alcohol derivatives **8a–g** are prepared by trifluoromethylation of ketones using TMS-CF_3 or Grignard reaction via corresponding halide and 1,1,1-trifluoroacetone.

(**9e** and **9f**) in high yield.[6] Method B is superior to method A in terms of ease of operation as well as yield. Entries 4 and 7 show the limitations of this protocol, since neither case gave appreciable amount of expected product. Whether the failure of the reaction is due to the stronger electron-withdrawing nature of the aromatic ring, steric effects (entry 4), or in the case of entry 7 the presence of an intramolecular hydrogen bond, is unclear.

Methylation using method B (entry 4 in Table 1) resulted in recovery of the starting material. Clearly, a more drastic set of conditions for the chlorination was needed. As expected, the reaction of **8d** with thionyl chloride (as the solvent) provided the desired chloride **10d**. However, the methylation of **10d** using method A (entry 1) led to a mixture of recovered starting material and alcohol **8d** in a ratio of 1:4. As shown in Table 2, other conditions (entries 2 and 8) also produced hydrolyzed product **8d** as the major product. It is assumed that **8d** is formed via halogen–metal exchange of **10d** followed by hydrolysis during the work-up without the insertion of the methyl group. However, investigation of alternate conditions resulted in the successful methylation of **10d**: when trimethylaluminium in cyclohexane was used as the source of the methyl group (entry 6), the desired **9d** was obtained cleanly (*Method C*).

The application of this method to 2-substituted heteroaryl derivatives using various reagents proved difficult to implement since halogenation of the

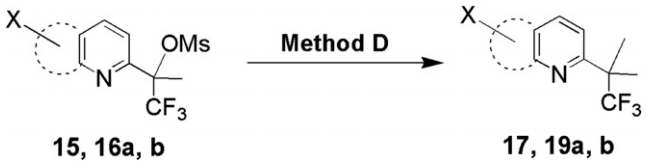
Table 2. Methylation of tertiary chlorides using trimethylaluminium (Method C)

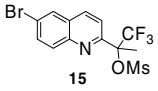
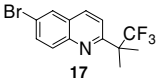
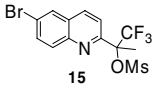
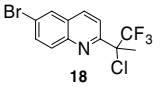
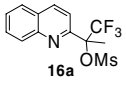
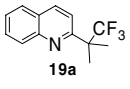
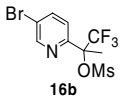
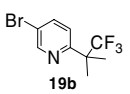
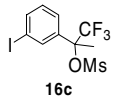
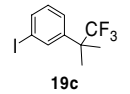


Entry	Lewis acid (2 equiv)	Me source (4 equiv)	Solvent	Products[e]		
				10d (chloride)	**9d** (desired)	**8d** (hydrolysis)
1[a]	$TiCl_4$	Me_2Zn	CH_2Cl_2	20	0	80
2[a]	$TiCl_4$	Me_3Al	CH_2Cl_2	0	0	90
3[a]	$AlCl_3$	Me_3Al	CH_2Cl_2	0	trace	10
4[a]	$BF_3{\cdot}Et_2O$	Me_3Al	CH_2Cl_2	100		
5[b]		Me_3Al	Toluene[g]	0	Major[f] (72)	5
6[b]		Me_3Al	Cyclohexane	0	95[f]	0
7[b,c]		MeMgBr	THF	50	20	30
8[d]		MeMgBr	HMPT	40	0	60

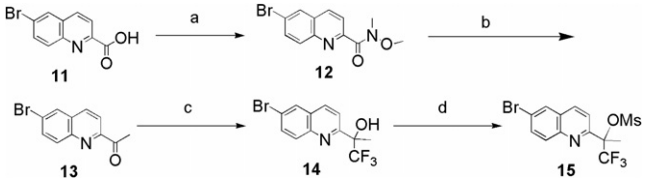
[a] Reaction condition; r.t. 16 h.
[b] Reaction condition; reflux, 16 h.
[c] LiBr (1.5 equiv) as an additive was added.
[d] Reaction condition; 110 °C, 4 h.
[e] The reaction was analyzed by ^1H NMR analysis of crude product.
[f] Isolated yield.
[g] Some toluene adducts were formed.

Table 3. Heteroaryl compounds



Entry	Substrate	Conditions			Product	Yield (%)
		Reagent (equiv)	Solvent[a]	Time (h) in rt		
1	 **15**	$AlMe_3$ (4)	Cyclohexane	1.5	 **17**	80
		$AlMe_3$(4)	CH_2Cl_2	1.5		88
		$AlMe_3$ (1.2)	Cyclohexane (suspension)	6		73% recovery[b]
		$AlMe_3$ (2.2)	Cyclohexane (suspension)	6		26% recovery[c]
		$AlMe_3$ (2)	CH_2Cl_2	1.5		86
2	 **15**	Me_2AlCl (4)	CH_2Cl_2	1.5	 **18**	95
3	 **16a**	Me_3Al (2)	CH_2Cl_2	1.5	 **19a**	91
4	 **16b**	Me_3Al (2)	CH_2Cl_2	1.5	 **19b**	65[d], 96[d]
5	 **16c**	Me_3Al (2)	Toluene	1.5	 **19c**	57

Methylation of tertiary mesylates using aluminium reagents (Method D).
[a] All reactions were homogeneous solutions unless indicated.
[b] Mixture of **15** and **17** in a 98: <2 ratio.
[c] Mixture of **15** and **17** in a 94: <6 ratio.
[d] The conversion to **19b** was carried out in 64% and 96% yield including olefine derivative of 4.5% and 10%, respectively.



Scheme 1. Reagents: (a) N(Me)OMe-HCl, HBTU, TEA, DMF, 90%; (b) MeMgBr, THF, 95%; (c) TMS-CF3, AcOLi (cat), DMF, then dil HCl aq, THF, 96%; (d) NaH, methanesulfonyl chloride, THF, 96%.

tert-alcohol moiety was unsuccessful (entry 7 in Table 1). Recently, however, we have found a sequence that allows for the preparation of the 2-(1,1-dimethyl-2,2,2-trifluoroethyl)pyridine and quinoline moiety. This was accomplished by sequential *O*-mesylation of the tertiary alcohol derivatives followed by methylation. The typical *O*-mesyl derivative **15** was synthesized from the corresponding carboxylic acid **11** in four steps as shown in Scheme 1. Treatment of Weinreb amide[10] **12** with methylmagnesium halide afforded ketone **13**, which was converted to the mesylate **15** by the formation of the tertiary alcohol[11] using Ruppert's reagent (TMS-CF_3), followed by *O*-mesylation using sodium hydride.

The methylation of substrate **15** was then investigated using varying combinations of reagent and solvent, as detailed in Table 3. A positive result was obtained when **15** was treated with trimethylaluminium (2.0 equiv) in dichloromethane solution at 0 °C to ambient temperature, thus providing the expected 1,1-dimethyl-2, 2, 2-trifluoroethyl derivative **17** in high yield (*Method D*). Dichloromethane was superior over hydrocarbon solvents since it allows a homogeneous solution during the methylation step. Switching to dimethylaluminium chloride as the potential methyl source gave the chloride derivative **18** in 95% yield. This method can also be applied to aromatic compounds (entry 5), similarly to Method A.

The 1,1-dialkyl-2-perfluoroalkyl derivatives, which are potentially useful as metabolically stable bioisosteres of *tert*-alkyl compounds, can be synthesized from various tertiary alcohol derivatives using titanium chloride—dimethylzinc or trimethylaluminium. The one-pot (*Method B*) conversion of cyclic tertiary alcohols provides 1,1-dimethyl-2,2,2-trifluoroethyl analogs without by-products, while the methylation of heteroaryls using trimethylaluminium (*Method D*) is a convenient method that does not require low temperature or the preparation of a reagent.

Acknowledgments

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Appendix A. General procedure

*Method A: 1-methoxy-4-(2,2,2-trifluoro-1-chloro-1-methylethyl)benzene (**10a**)*. To a stirred solution of the alcohol **8a** (5.00 g, 22.7 mmol) in dry dichloromethane (50 ml) was added titanium (IV) chloride (2.37 ml ~ 4.09 g, 21.57 mmol) via a syringe with ice-cooling. The reaction mixture was stirred at the same temperature for 1.5 h. The mixture was poured into ice-water (150 g) and stirred for 15 min. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3×). The combined solution was washed with satd $NaHCO_3$ aqueous solution, brine, dried over anhydrous potassium carbonate, and concentrated in vacuo to give the crude product (5.31 g, 98%) as a yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$)δ 2.12 (3H, s), 3.83 (3H, s), 6.83–6.96 (2H, m), 7.52–7.63 (2H, m).

*1-Methoxy-4-(2,2,2-trifluoro-1,1-dimethylethyl)benzene (**9a**)*. To a stirred solution of titanium (IV) chloride (111 ml, 1.02 mol) in dry dichloromethane (200 ml) was added a solution of 1.0 M dimethylzinc in hexane (2050 ml, 2.05 mol) over a period of 1 h at −78 °C (inner temperature; −78 to −60 °C). After stirring for 20 min at the same temperature, to this mixture was added a solution of compound **10a** (243 g, 1.02 mol) in dry dichloromethane (150 ml) dropwise, keeping the inner temperature below −50 °C. After the cooling bath was removed the reaction temperature climbed rapidly to − 37 °C, and the mixture was cooled again to keep the temperature below −40 °C. Finally the temperature of the reaction mixture was raised to 0 °C and the reaction was quenched with water-saturated dichloromethane (150 ml), then water (200 ml), all the while cooling in a dry ice–methanol bath (inner temperature: −40 °C). After bringing the mixture to ambient temperature, additional water (1 L) was added and the mixture was stirred for 30 min. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic solution was washed with water, satd $NaHCO_3$ aqueous solution, brine, dried over sodium sulfate, and concentrated in vacuo to give the crude product, which was distilled to give the main fraction (180.9 g) at bp 88–90 °C/2 ~ 4 mm Hg. The main fraction solidified upon standing at room temperature; mp 52–52.2 °C (white solid). ^{1}H NMR (270 MHz, $CDCl_3$)δ 1.55 (6H, s), 3.81 (3H, s), 6.84–6.93 (2H, m), 7.35–7.45 (2H, m).

Method B: To a stirred solution of compound **8a** (1000 mg, 4.63 mmol) in dry dichloromethane (15 ml) was added titanium (IV) chloride (1.00 ml, 9.25 mmol) via a syringe at −78 °C (dark yellow–yellow solution). After 1.5 h at the same temperature, a 1.0 M dimethylzinc in hexane solution (18.5 ml, 18.5 mmol) was added dropwise at −78 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 3.5 h. The reaction mixture was poured into ice-water and stirred for 15 min. The aqueous layer was extracted with dichloromethane (3×) and the combined solution was washed with brine (1×), dried over sodium sulfate, and concentrated in vacuo to give the crude product.

The crude product was purified by column chromatography on silica gel (150 g) eluting with hexane–ethyl acetate (100:1) to give compound **9a** (515 mg, 51% yield) as a white solid.

^{1}H NMR (270 MHz, $CDCl_3$)δ 1.55 (6H, s), 3.81 (3H, s), 6.84–6.93 (2H, m), 7.35–7.45 (2H, m). *Anal. Calcd for* $C_{11}H_{13}F_3O$: C, 60.54; H, 6.00. Found: C, 60.58; H, 6.03.

*Method C: 2-(1-chloro-2,2,2-trifluoro-1-meyhylethyl)-1,3-difluoro-5-methoxybenzene (**10d**)*. A thionyl chloride (25 ml) solution of compound **8d** (8.7 g, 34.1 mmol) and pyridine (26 mg, 0.34 mmol) was stirred at 70 °C for 3 h. The reaction was concentrated in vacuo and diluted with water carefully. The product was extracted with hexane and the organic layer was dried over sodium sulfate, filtered, and concentrated to furnish compound **10d** (8.84 g, 94% yield) as a colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$)δ 2.24–2.29 (3H, m), 3.81 (3H, s), 6.44–6.54 (2H, m).

*1,3-Difluoro-5-methoxy-2-(2,2,2-trifluoro-1,1-dimethylethyl)benzene (**9d**)*. To a cyclohexane (100 ml) solution of compound **10 d** (8.84 g, 32.2 mmol) was added a 1.0 M hexane solution of trimethylaluminium (129 ml, 129 mmol) at room temperature and the mixture was stirred at reflux for 4 h. The reaction was quenched with a 2 M hydrochloride aqueous solution, extracted with hexane, followed by drying over sodium sulfate, filtration, and evaporation to furnish 7.9 g (97% yield) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (6H, s), 3.78 (3H, s), 6.39–6.49 (2H, m).

*Method D: 1-(6-bromoquinolin-2-yl)-2,2,2-trifluoro-1-methylethyl methanesulfonate (**15**)*. To a stirred suspension of 60% sodium hydride (1.38 g, 34.5 mmol) in tetrahydrofuran (25 ml) was added a solution of compound **14** (5.52 g, 17.2 mmol) in tetrahydrofuran (20 ml) dropwise with ice-cooling (after the removal of ice-bath, hydrogen gas was generated). The reaction mixture was stirred at ambient temperature for 1 h, then 3 h at 40 °C, and to this was added dropwise a solution of methanesulfonyl chloride (3.95 g, 34.5 mmol) in tetrahydrofuran (30 ml) at ambient temperature. After 1h at same temperature, the mixture was heated at 40 °C for 2 h. The mixture was quenched with water (ca 50 ml; carefully), then satd $NaHCO_3$ solution, and extracted with ethyl acetate (3×). The combined solution was washed with brine, dried over sodium sulfate and concentrated in vacuo to give crude product, which was purified by column chromatography on silica gel (300 g) with hexane–ethyl acetate (5:1–3:1) to furnish the compound **15** (6.57 g, 96% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (3H, s), 3.24 (3H, s), 7.81–7.86 (2H, m), 7.96–8.05 (2H, m), 8.17 (1H, d, J = 8.8 Hz). MS (ESI): *m/z* 397, 399 $(M+H)^+$.

*6-Bromo-2-(2,2,2-trifluoro-1,1-dimethylethyl)quinoline (**17**)*. To a stirred solution of compound **15** (150 mg, 0.37 mmol) in dry dichloromethane (3 ml) was added dropwise a 2.0 M trimethylaluminium in hexane solution (377μl, 0.75 mmol) at ice-cooling. The reaction mixture was stirred at ambient temperature for 90 min. The mixture was quenched with satd $NaHCO_3$ (3 ml), then brine (1 ml). The mixture was filtered though a pad of celite and the filter cake was washed with ethyl acetate. The filtrate and washings were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give crude product (133 mg). The crude product was purified by column chromatography on packaged silica gel L size (120 g) with hexane only to furnish the compound **17** (103 mg, 86% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (6H, s), 7.66 (1H, d, J = 8.8 Hz), 7.75–7.80 (1H, m), 7.96–8.00 (2H, m), 8.06 (1H, d, J = 8.8 Hz). MS (ESI): *m/z* 318, 320 $(M+H)^+$.

References and notes

1. References on TRPV-1 antagonists BCTC (a) Valenzano, K. J.; Grant, E. R.; Wu, G.; Hachicha, M.; Schmid, L.; Tafesse, L.; Sun, Q.; Rotshteyn, Y.; Francis, J.; Limberis, J.; Malik, S.; Whittemore, E. R.; Hodges, D. *J. Pharmacol. Exp. Ther.* **2003**, *306*, 377; AMG 9810 (b) Gavva, N. R.; Tamir, R.; Qu, Y.; Klionsky, L.; Zhang, T. J.; Immke, D.; Wang, J.; Zhu, D.; Vanderah, T. W.; Porreca, F.; Doherty, E. M.; Norman, M. H.; Wild, K. D.; Bannon, A. W.; Louis, J-C.; Treanor, J. J. S. *J. Pharmacol. Exp. Ther.* **2005**, *313*, 474; *N*-(4-*tert*-Butylphenyl)-4-(3-methylpyridine-2-yl)benzamide (c) Park, H.-g.; Choi, J.-y.; Kim, M.-h.; Choi, S.-h.; Park, M.-k.; Lee, J.; Suh, Y.-G.; Cho, H.; Oh, U.; Kim, H.-D.; Joo, Y. H.; Shin, S. S.; Kim, J. K.; Jeong, Y. S.; Koh, H.-J.; Park, Y.-H.; Jew, S.-s. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 631; SC-0030 (d) Suh, Y.-G.; Lee, Y.-S.; Min, K.-H.; Park, O.-H.; Seung, H.-S.; Kim, H.-D.; Park, H.-G.; Choi, J.-Y.; Lee, J.; Kang, S.-W.; Oh, U.-t.; Koo, J.-y.; Joo, Y.-H.; Kim, S.-Y.; Kim, J. K.; Park, Y.-H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4389; (e) References regarding to NK-1 antagonists: Ito, F.; Kondo, H.; Shimada, K.; Nakane, M.; Lowe, J. A. III; Rosen, T.J.; Yang, B.V. WO 9221677 A1.
2. (a) Satake, K.; Shishido, Y.; Wakabayashi, H. WO 9708144 A1 (NK-1 antagonist in Pfizer); (b) Bakthavatchalam, R.; Blum, C. A.; Brielmann, H.; Darrow, J.W.; De Lombaert, S.; Yoon, T.; Zheng, X. WO 2004056774; (c) Park, H.-g.; Choi, J.-y.; Kim, M.-h.; Choi, S.-h.; Park, M.-k.; Lee, J.; Suh, Y.-G.; Cho, H.; Oh, U.; Kim, H.-D.; Joo, Y. H.; Shin, S. S.; Kim, J. K.; Jeong, Y. S.; Koh, H.-J.; Park, Y.-H.; Jew, S.-s. *Bioorg. Med. Chem. Lett* **2005**, *15*, 631.
3. (a) Trafts, K. W., Jr. In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; John Wiley and Sons: New York, 1965; p 556; (b) Macphee, J. A.; Panaye, A.; Dubois, J.-E. *Tetrahedron* **1978**, *34*, 1616.
4. Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.
5. (a) Hasek, W. R.; Smith, W. C.; Engelhardt, V. A. *J. Am. Chem. Soc* **1960**, *82*, 543; (b) Rozen, S.; Mishani, E. *J. Chem. Soc. Chem. Commun.* **1994**, 2081.
6. (a) Reetz, M. T.; Westermann, J.; Steinback, R. *J. Chem. Soc. Chem. Commun.* **1981**, 237; (b) Reetz, M. T.; Westermann, J. *J. Org. Chem.* **1983**, *48*, 254; (c) Reetz, M. T.; Westermann, J.; Steinback, R. Agnew. . *Chem. Int. Ed. Engel.* **1980**, *19*, 1; (d) Reetz, M. T.; Westermann, J.; Kyung, S.-h. *Chem. Ber.* **1985**, *118*, 1050.
7. At the beginning of the NK-1 project, the dimethylzinc reagent was only available commercially as a toluene solution. In the course of the methylation by

dimethylzinc in toluene, some toluene adducts were formed, but a 1:2 titanium chloride: dimethyl zinc mixture gave the dimethyl derivatives without toluene by-products. This problem has also been avoided through the use of hexane as the solvent Bonnet-Delpon, D.; Charpentier-Morize, M.; Jacquot, R. *J. Org. Chem.* **1988**, *53*, 759.

8. Franke, H.; Franke, H.; Krueger. H.-R.; Joppien, H.; Baumert, D.; Giles, D. P. DE 3602169.
9. The treatment of 5-methoxy-1-(trifluoromethyl)-2, 3-dihydro-1*H*-inden-1-ol (**12e**) with PBr_3 in dichloromethane (40 °C) gave the indene derivative in quantitative yield, while reaction with $TiCl_4$ (1 equiv) in dichloromethane (0 °C) resulted in decomposition during the workup.
10. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*(39), 3815.
11. (a) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393; (b) Mukaiyama, T.; Kawano, Y.; Fujisawa, H. *Chem. Lett.* **2005**, *34*, 1.