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Asymmetric synthesis of (*R*)- and (*S*)-2-trifluoromethylepinephrine ☆

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Abstract—An asymmetric synthesis of (*R*)- and (*S*)-2-trifluoromethylepinephrine (**1R** and **1S**) is presented. Trifluoromethylation involves nucleophilic aromatic substitution of halobenzene **4** most likely via a copper mediated CF_3 anion equivalent generated in situ. The asymmetric step involves conversion of 3,4-dimethoxy-2-trifluoromethylbenzaldehyde (**5**) to silyl cyanohydrin (**6R** and **6S**) using a chiral salen catalyst in the presence of titanium. **1R** and **1S** are potential alternatives to currently used vasoconstrictors in local anesthetic formulations.
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We are interested in the effects of trifluoromethylation of epinephrine, a phenethanolamine that functions as a vasoconstrictor in certain amide based local-anesthetic formulations and is known to degrade when the anesthetic is exposed to above ambient temperatures.[1] In general, fluorine modification of biologically relevant molecules and the structure–activity relationships of these analogues have generated considerable interest among chemists. The perturbation of a biological molecule with a CF_3 group is appealing to medicinal chemists due to its relatively small size, strong electronegativity, and lipophilic nature.[2] Recent trifluoromethylation methods involve nucleophilic attack of an aldehyde or ketone using CF_3 anion equivalents such as trifluoromethyl(trimethyl)silane,[3] trifluoroacetophenone,[4] and the TMS ether adduct of a trifluoroacetamide.[5]

Despite the challenges of synthesizing organofluorine compounds, the effects of fluorine substitution on the physicochemical properties of biologically significant compounds have been studied. Compounds that affect the central nervous system such as antidepressants, anorectic agents, and cardiostimulants have been modified by fluorine in the form of a CF_3 moiety, investigated for biological activity and used in medical applications.[6] Kirk and co-workers have synthesized mono- and difluoro analogues of phenethanolamines and demonstrated a correlation between adrenergic receptor affinity and the position of the fluorine atom on the benzene ring.[7,8]

In our search for CF_3 derivatives of epinephrine, we sought a regiospecific method of introducing the CF_3 group directly on the aromatic ring, a process that is not trivial. Gaseous sulfur tetrafluoride treatment of benzoic acid derivatives yielded a mixture of the corresponding CF_3 compounds and the acid fluoride.[9] In the presence of trifluoroacetic acid, xenon difluoride was also shown to trifluoromethylate aromatic compounds with limited regiospecificity.[10] Aniline was trifluoromethylated on the aromatic ring using *S*-(trifluoromethyl)dibenzothiophenium salts, however, substitution occurred at numerous positions and the trifluoromethylating agent had to be prepared.[11] To contrast, perfluoroalkyl metal compounds containing copper, generated in situ, were shown to readily convert halobenzene to α,α,α-trifluorotoluene.[12,13] This method is regiospecific and likely involves the in situ generation of $CuCF_3I$ anion using copper(I) iodide in the presence of sodium trifluoroacetate and NMP at elevated temperatures.[13] Herein, we describe the asymmetric synthesis of 2-trifluoromethylepinephrine (**1R** and **1S**).

3,4-Dimethoxy-2-iodobenzaldehyde (**4**) was generated by electrophilic aromatic substitution of isovanillin (**2**)

Keywords: Epinephrine; Trifluoromethylation; Asymmetric synthesis; Salen catalyst.

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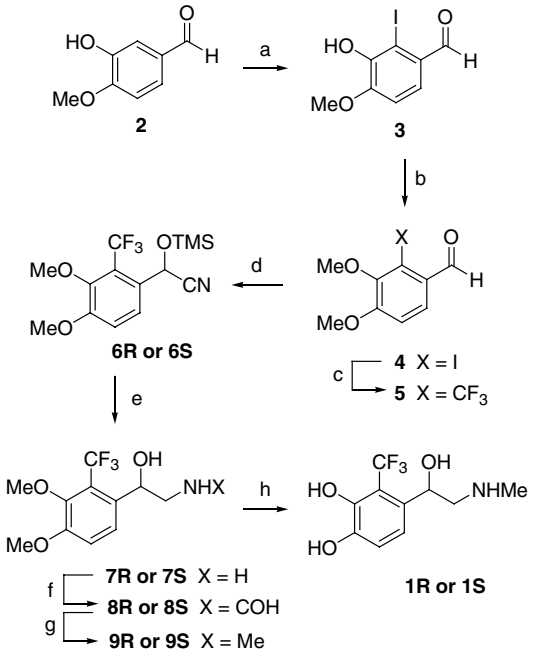
in pyridine with iodine monochloride to form **3** followed by methylation using dimethylsulfate (Scheme 1).[14] In a slight modification of a published procedure, introduction of the trifluoromethyl moiety to form 3,4-dimethoxy-2-trifluoromethylbenzaldehyde (**5**) was accomplished by heating an NMP solution of **4** with sodium trifluoroacetate in the presence of CuI.[14,15] Our findings support Markovich et al. observation that the reaction must be performed under extremely anhydrous conditions due to the undesired formation of veratraldehyde. Upon heating for 4 h, the reaction mixture was poured into water and the precipitate separated by centrifugation. Extraction of the mother liquor with hexane yielded **5** as a yellow oil in 25.1% yield.

The catalyst used for the asymmetric synthesis of **6** was formed via addition of titanium tetraisopropoxide to a CH_2Cl_2 solution of either (*R*,*R*) or (*S*,*S*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine [(*R*,*R*) or (*S*,*S*)-salen].[7] The solution was kept under an atmosphere of argon and stirred at room temperature for 1.5 h. Aldehyde **5** and TMSCN were added to the salen catalyst at −50 °C and stirred at that temperature for 5 days.[16] The solvent was removed in vacuo and the crude silyl cyanohydrin purified via flash column chromatography (75:25 hex/EtOAc). Solid β-aminoethanol **7R** [derived from (*S*,*S*)-salen] or **7S** [derived from (*R*,*R*)-salen] was formed via $LiAlH_4$ reduction of **6R** or **6S**, respectively, and analyzed for enantiomeric purity by chiral HPLC. The ee of crude **7** was determined to be 80% before recrystallization. Interestingly, an increase in ee of either **7R** or **7S** in the mother liquor was observed upon recrystallization from hex/EtOAc. Monomethylation of crude **7R** or **7S** using ethyl formate to form formamide **8R** or **8S**[17] followed by $LiAlH_4$ reduction yields 1-(3,4-dimethoxy-2-trifluoromethylphenyl)-2-methylaminoethanol (**9R** or **9S**, respectively) in >99% ee after recrystallization from hex/EtOAc.[18]

De-O-methylation of **9R** or **9S** with excess boron tribromide followed by MeOH quenching afforded the crude 2-trifluoromethylepinephrine (**1R** or **1S**).[19] The epinephrine derivatives were purified using reversed phase semi-preparative HPLC on an Adsorbosphere ODS column with a mobile phase of 95:5 water–acetonitrile (both components contained 0.1% TFA v/v), lyophilized and isolated as trifluoroacetate salts in >99% ee. Both **1R** and **1S** are light green, deliquescent solids that darken on exposure to atmosphere. We are currently investigating the receptor binding affinities and biological functional assays of these novel epinephrine derivatives.

^1H, ^{13}C, ^{19}F NMR, HRMS, and melting points (where applicable) for compounds **6R**, **6S**, **7R**, **7S**, **8R**, **8S**, **9R**, **9S**, **1R**, and **1S** are provided as supplementary material. The supplementary data is available online with the paper in ScienceDirect.



Scheme 1. Reagents and conditions: (a) ICl, pyridine, dioxane, 0 °C, then rt, 69.3%; (b) dimethylsulfate, K_2CO_3, acetone, reflux 6 h, 72.2%; (c) $NaOCOCF_3$, CuI, NMP, 175 °C, 4 h, 25.1%; (d) (*R*,*R*) or (*S*,*S*)-salen, Ti(*O*-*i*Pr)$_4$, CH_2Cl_2, TMSCN, −50 °C, 5 d, 76.6% for **6R**, 75.1% for **6S**; (e) $LiAlH_4$, diethylether, 0 °C, then rt, 52.8% for **7R**, 53.2% for **7S**; (f) ethyl formate, reflux 3 h; (g) $LiAlH_4$, THF, 0 °C, then reflux, 20.8% **9R** from **7R**, 21.2% **9S** from **7S**; (h) BBr_3, CH_2Cl_2, −78 °C, then rt, 60.0% for **1R**, 61.6% for **1S**.

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References and notes

1. Yagiela, J. A. Local anesthetics. In *Pharmacology and Therapeutics for Dentistry*, 4th ed.; Yagiela, J. A., Neidle, E. A., Dowd, F. J., Eds.; Mosby: St. Louis, 1998; pp 217–234; Hondrum, S. O.; Seng, G. F.; Rebert, N. W. *Anesthesia and Pain Control in Dentistry* **1993**, *2*, 198–202.
2. Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3–11.
3. Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613–7632; Prakash, G. K. S.; Mandal, M. *J. Fluorine Chem.* **2001**, *112*, 123–131.
4. Jablonski, L.; Billard, T.; Langlois, B. R. *Tetrahedron Lett.* **2003**, *44*, 1055–1057.
5. Billard, T.; Bruns, S.; Langlois, B. R. *Org. Lett.* **2000**, *2*, 2101–2103.
6. *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; *ACS Symposium Series 639*; American Chemical Society: Washington, DC, 1996.
7. Lu, S.-F.; Herbert, B.; Haufe, G.; Laue, K. W.; Padgett, W. L.; Oshunleti, O.; Daly, J. W.; Kirk, K. L. *J. Med. Chem.* **2000**, *43*, 1611–1619.

8. Chen, G. T.; King, M.; Gusovsky, F.; Creveling, C. R.; Daly, J. W.; Chen, B.-H.; Nie, J.-Y.; Kirk, K. L. *J. Med. Chem.* **1993**, *36*, 3947–3955.
9. Hasek, W. R.; Smith, W. C.; Engelhardt, V. A. *J. Am. Chem. Soc.* **1960**, *82*, 543–551; Dmowski, W.; Wiszniewski, W. *J. Fluorine Chem.* **1997**, *82*, 163–165.
10. Tanabe, Y.; Matsuo, N.; Ohno, N. *J. Org. Chem.* **1988**, *53*, 4582–4585.
11. Ono, T.; Umemoto, T. *J. Fluorine Chem.* **1996**, *80*, 163–166.
12. May, D. D. *Process for Trifluoromethylation of Aromatic Compounds*. U.S. Patent 5,233,104, 1993; Burton, D. J.; Wiemers, D. M.; Easdon, J. C. *Method of Preparation of Trifluoromethyl Copper and Trifluoromethyl Aromatics*. U.S. Patent 4,749,802, 1988.
13. Matsui, K.; Tobita, E.; Ando, M.; Kondo, K. *Chem. Lett.* **1981**, 1719–1720; Carr, G. E.; Chambers, R. D.; Holmes, T. F.; Parker, D. G. *J. Chem. Soc., Perkin Trans. 1* **1988**, 921–926; McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555–6666.
14. Markovich, K. M.; Tantishaiyakul, V.; Hamada, A.; Miller, D. D.; Romstedt, K. J.; Shams, G.; Shin, Y.; Fraundorfer, P. F.; Doyle, K.; Feller, D. R. *J. Med. Chem.* **1992**, *35*, 466–479.
15. General experimental procedure: To a 1000 mL three neck flask equipped with a stir bar, argon gas inlet adapter, thermometer to measure internal temperature, and a mineral oil bubbler, was added *N*-methyl-2-pyrrolidinone (360 mL) via a double ended cannula needle. The solvent was kept under streaming argon while 3,4-dimethoxy-2-iodo-benzaldehyde (**4**, 18.48 g, 63.3 mmol), CuI (24.11 g, 127 mmol), and sodium trifluoroacetate (34.43 g, 253 mmol) were quickly added. The flask was submerged in an oil bath preheated to 185 °C and heated to an internal temperature of 175 °C for 4 h with stirring. The contents of the flask were allowed to cool to rt and poured into a flask containing water (700 mL) with stirring for 0.5 h, which generated a light brown precipitate. The precipitate was removed by centrifugation (25 °C, 3700 rpm, 15 min) and the mother liquor was extracted with hexane (3×500 mL). The hexane extracts were combined and washed with an equal volume of water, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo to afford 3.72 g (15.9 mmol, 25.1%) of **5** as a yellow oil that was used without further purification.
16. In our attempt to optimize the asymmetric synthesis of **6R** and **6S**, we performed the addition of aldehyde **5** and TMSCN to the catalysts at an elevated temperature (rt) followed by stirring for 18 h. Reduction of the silyl cyanohydrins **6R** and **6S** yielded moderate to poor ee of β-aminoethanols **7R** and **7S**.
17. We observed *s-cis* and *s-trans* isomers of both **8R** and **8S** by ^{1}H NMR, most likely due to slow rotation around the CO–N bond. The ratio of *s-cis* to *s-trans* for each enantiomer was ~4:1 using the benzylic proton as the integration indicator. The detection of monosubstituted formamide isomers by NMR is noted in: Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. In *Tables of Spectral Data for Structure Determination of Organic Compounds*, 2nd ed.; Fresenius, W., Huber, J. F. K., Pungor, E., Rechnitz, G. A., Simon, W., West, T. S., Eds.; Springer: Berlin, 1989; p H155.
18. The separation of enantiomers via recrystallization is a phenomenon that has been previously observed. See: Oi, R.; Sharpless, K. B. *Org. Synth.* **1995**, *73*, 1.
19. General experimental procedure for **1R**: To a 25 mL round bottom flask equipped with a stir bar was added (*R*)-1-(3,4-dimethoxy-2-trifluoromethylphenyl)-2-methylaminoethanol (**9R**, 190 mg, 0.68 mmol) in CH_2Cl_2 (1.5 mL) with stirring under an atmosphere of argon. The solution was cooled to −78 °C followed by the slow addition of boron tribromide (1 M in CH_2Cl_2, 2.5 mL, 2.5 mmol) via a glass syringe. The solution was warmed to room temperature, stirred overnight, cooled to −78 °C, and quenched with methanol (3 mL, 74 mmol). A referee noted the possibility of solvolysis with racemization upon boron tribromide demethylation of **9R**. We have performed the quenching of the boron tribromide de-O-methylation reaction using water and observed partial inversion of configuration of the carbon containing the benzylic alcohol. This inversion, however, was prevented upon quenching the de-O-methylation reaction in methanol. When using methanol we observed a small amount of benzylic methyl ether formation, as evident by LCMS (APCI) analysis, in addition to optically pure **1R**. Upon warming the methanolic solution, the epinephrine derivative was purified using reversed phase semi-preparative HPLC yielding 149 mg (0.41 mmol, 60.0%) of a light green solid. The ee of **1R** and **1S** was determined by HPLC analysis with UV detection at 290 nm on a Cyclobond I 2000 RSP chiral column (4.6×250 mm) using aqueous $(NH_4)H_2PO_4$ (pH = 4, 100 mM) at a flow of 1 mL/min. The absolute configuration of **1R** and **1S** was determined by comparison of the elution order of authentic (*R*)-epinephrine and racemic epinephrine using identical chiral HPLC conditions.
^{1}H NMR for **1R** trifluoroacetate salt (300 MHz, D_2O, δ) 7.12 (d, 1H, $J = 8.5$ Hz), 7.04 (d, 1H, $J = 8.5$ Hz), 5.30 (d, 1H, $J = 7.2$ Hz), 3.20–3.07 (m, 2H), 2.73 (s, 3H). ^{13}C NMR (75.6 MHz, D_2O, δ) 163.1 (q, $J = 35$ Hz, trifluoroacetate), 145.5, 143.7, 130.3, 124.8 (q, $J = 275$ Hz), 119.2, 118.6, 116.5 (q, $J = 291$ Hz, trifluoroacetate), 114.4 (q, $J = 29$ Hz), 64.9, 55.1, 33.0. ^{19}F NMR (282.8 MHz, D_2O, δ) −53.0, −75.4 (trifluoroacetate). LCMS (APCI) m/z: $[M+H]^+$ 252. HRMS (ESI) calcd for $[M+H]^+$ $C_{10}H_{13}F_3NO_3$, 252.0848; Found 252.0849. t_R **1R** = 4.6 min. $[\alpha]_D^{25}$ −33.8 (*c* 2.1, H_2O), mp = 61–63 °C.
^{1}H NMR for **1S** trifluoroacetate salt (300 MHz, D_2O, δ) 7.17 (d, 1H, $J = 8.5$ Hz), 7.10 (d, 1H, $J = 8.5$ Hz), 5.33 (dd, 1H, $J = 2.2$, 9.1 Hz), 3.24–3.11 (m, 2H), 2.74 (s, 3H). ^{13}C NMR (75.6 MHz, D_2O, δ) 163.2 (q, $J = 34$ Hz, trifluoroacetate), 145.5, 143.7, 130.3, 124.6 (q, $J = 275$ Hz), 119.3, 118.6, 116.6 (q, $J = 292$ Hz, trifluoroacetate), 114.4 (q, $J = 29$ Hz), 65.0, 54.8, 33.0. ^{19}F NMR (282.8 MHz, D_2O, δ) −53.2, −5.4 (trifluoroacetate). LCMS (APCI) m/z: $[M+H]^+$ 252. HRMS (ESI) calcd for $[M+H]^+$ $C_{10}H_{13}F_3NO_3$, 252.0848; Found 252.0852. t_R **1S** = 4.8 min. $[\alpha]_D^{25}$ +32.9 (*c* 2.2, H_2O), mp = 61–66 °C.