(c 1.41, $CHCl_3$); FTIR (neat) 3057, 3017, 2927, 2853, 1600, 1572, 1493, 1453, 1420, 1249, 1085, 723, 689 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.74–7.15 (15 H, m), 6.99 (1 H, d, J = 8.4 Hz), 6.81–6.73 (2 H, m), 5.05 (1 H, dd, J = 9.7, 2.1 Hz), 4.91 (1 H, d, J = 11.0 Hz), 4.70, 4.63 (2 H, AB q, J = 11.7 Hz), 4.58 (1 H, d, M = 11.0 Hz), 4.56, 4.51 (2 H, AB q, J = 11.9 Hz), 3.77–3.53 (5 H, m), 2.50 (1 H, ddd, J = 12.5, 5.0, 2.1 Hz), 2.41 (6 H, s), (1 H, ddd, J = 12.5, 11.5, 9.7 Hz); HRFAB M + Na 561.2646.

4-Methoxyphenyl 3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside (25): 70% yield as a clear liquid; $[\alpha]^{25}_D$ −11.5° (c 0.47, $CHCl_3$); FTIR (neat) 3030, 2954, 2922, 2862, 1491, 1453, 1372, 1220, 1090, 830, 748, 700 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.37–7.27 (15 H, m), 7.00 (2 H, d, J = 9.1 Hz), 6.78 (2 H, d, J = 9.1 Hz), 4.99–4.52 (7 H, m), 3.81–3.56 (5 H, m), 3.77 (3 H, s), 2.51 (1 H, ddd, J = 12.6, 5.1, 1.7 Hz), 1.92 (1 H, ddd, J = 12.6, 10.5, 9.7 Hz); HRFAB M + Na 563.2388.

2,6-Dimethoxyphenyl 3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside (26): 10% yield as a clear liquid; $[\alpha]^{25}_D$ −35.0° (c 0.8); FTIR (neat) 2944, 2917, 2853, 1564, 1351, 1208, 1102, 1127, 789, 752 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.38–7.27 (15 H, m), 7.00 (1 H, t, J = 8.3 Hz), 6.54 (2 H, d, J = 8.3 Hz), 4.93 (1 H, d, J = 7.5 Hz), 4.88 (1 H, d, J = 11.0 Hz), 4.65 (2 H, AB q, J = 12.1 Hz), 4.61–4.53 (3 H, m), 3.78 (6 H, s), 3.76–3.51 (5 H, m), 2.65 (1 H, m), 1.96 (1 H, m); HRFAB M + Na 593.2515.

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Registry No. 1, 74372-90-0; 2, 4064-06-6; 3, 40246-33-1; 4, 135192-35-7; 5, 79384-22-8; 6, 81928-98-5; 7, 63598-36-7; 8, 135192-33-5; 8a, 135192-36-8; 9, 135192-34-6; 9a, 135225-04-6; 10, 135192-37-9; 11, 135192-38-0; 12, 135192-39-1; 13, 135192-40-4; 14, 135192-41-5; 15, 135192-42-6; 16, 135192-43-7; 17, 135192-44-8; 18, 135192-45-9; 19, 135192-46-0; 20, 135192-47-1; 21, 135192-48-2; 22, 124718-81-6; 23, 135192-49-3; 24, 135192-50-6; 25, 135192-51-7; 26, 135192-52-8; tribenzyl-D-glucal, 55628-54-1; 3,3-dimethyldioxirane, 74087-85-7; pentafluorophenyl chlorothionoformate, 135192-53-9; phenol, 108-95-2; 2,6-dimethylphenol, 576-26-1; 3,4-dimethylphenol, 95-65-8; 4-methoxyphenol, 150-76-5; 2,6-dimethoxyphenol, 91-10-1.

Supplementary Material Available: NMR spectra for compounds 4, 5, 8, 8a, 9, 9a, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 23, 24, 25, and 26 (22 pages). Ordering information is given on any current masthead page.

Synthesis of 2,3-Dimethoxy-5-iodobenzoic Acid

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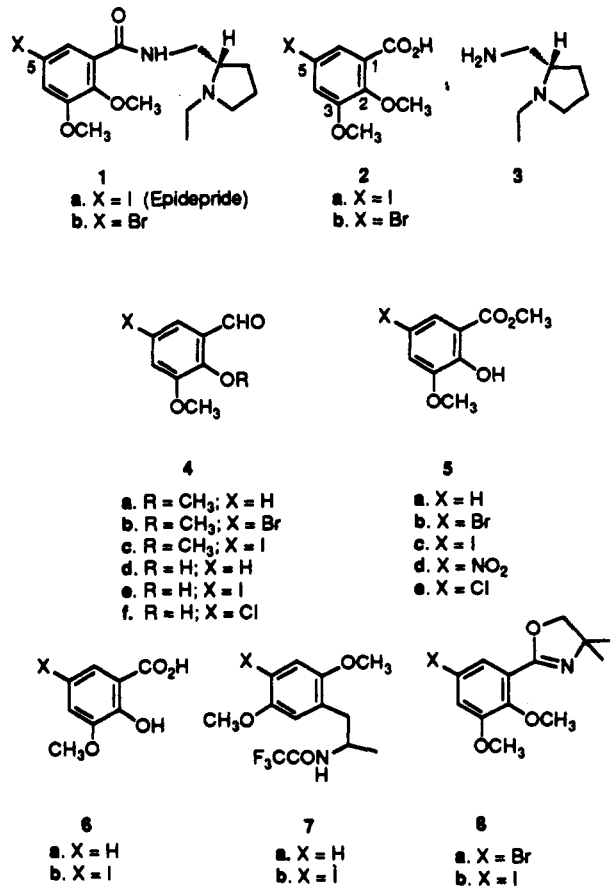
Methoxy-substituted benzamides containing 2-pyrrolidinylmethyl side chains are selective and biologically potent dopamine D_2 receptor antagonists, which when used clinically display minimal deleterious side effects.[1-3] Included in this class of neuroleptics is the 2,3-dimethoxy-5-iodobenzamide 1a (Chart I), also known as epidepride, which has recently been shown to possess high affinity in vitro binding properties.[4] The radioiodinated form of 1a serves as a superior in vivo dopamine D_2 receptor imaging agent.[5] Two syntheses of 1a have been reported, both in low yields (≤25%). The more recent synthesis[2] involved the anion-mediated conversion of the intact 5-bromobenzamide 1b to the 5-iodo 1a (25%). Improvement of this synthetic approach is limited by the unreactive nature of I_2 with the 5-lithio derivative of 1b and the propensity of the pyrrolidine fragment to undergo decomposition. The earlier route[6] to 1a (7%), which was patterned after previous syntheses of related benzamides,[1] employed coupling of the 5-iodobenzoic acid 2a[7] with (*S*)-2-(aminomethyl)-1-ethylpyrrolidine[8] (3). An improved synthesis of 1a by this convergent route is possible if an efficient

Chart I



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(2) Högberg, T.; Ström, P.; Hakan, H.; Ögren, S.-O. *Helv. Chim. Acta* **1990**, *73*, 417.

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(5) (a) Kessler, R. M.; Votaw, J. R.; de Paulis, T.; Schmidt, D.; Clanton, J. A.; Ansari, M. S.; Holdeman, K. P.; Pfeffer, R.; Manning, R. J. *Nuc. Med.* **1990**, *31*, 779. (b) Kessler, R. M.; Ansari, M. S.; Gillespie, D.; Schmidt, D.; de Paulis, T. Ibid. **1990**, *31*, 882. (c) Kessler, R. M.; de Paulis, T.; Ansari, S.; Gillispie, D.; Clanton, J.; Smith, H. E.; Ebert, M.; Manning, R. Ibid. **1989**, *30*, 803.

(6) de Paulis, T.; Clanton, J. A.; Schmidt, D.; Ansari, S.; Gillespie, D.; Kessler, R. M. 198th American Chemical Society National Meeting, Miami Beach, September 1989; American Chemical Society: Washington, DC, 1989; NUCL12. A two-step conversion of isoveratryl alcohol to 2a (9%) was disclosed during this presentation.

(7) The 2,3-dimethoxy-5-iodobenzoic acid 2a (or a corresponding ester of 2a) has not heretofore been reported in the literature.

(8) For a preparation of 3 in 97.5% enantiomeric excess (ee), see: Högberg, T.; Rämsby, S.; Ström, P. *Acta Chem. Scand.* **1989**, *43*, 660.

0022-3263/91/1956-5451$02.50/0

preparation of **2a** could be achieved. The simplicity of target **2a** and the noted lack of straightforward and reliable methods of aryl iodide preparations[9-11] prompted us to investigate its synthesis. We report in this note the effects of electrophilic iodination reaction conditions on aromatic precursors of **2a** and an efficient aryl anion mediated iodination route to **2a** resulting in a high-yield synthesis of epidepride.

Results and Discussion

Aromatic electron-donating substituents are capable of directing regiospecific electrophilic halogenations to positions either ortho or para to the activating group.[12] For example, the 2-methoxy moiety of 2,3-dimethoxybenzaldehyde (**4a**), which is ortho to both an electron-withdrawing carbonyl group and the activating 3-methoxy substituent, is capable of directing electrophilic bromination with Br_2 to the para position affording the 5-bromobenzaldehyde **4b** (62%).[13] Subsequent silver oxide oxidation of **4b** yields the 5-bromobenzoic acid **2b** (84%).[14] Synthesis of the 5-iodo analogue **2a** by a similar route was attempted. Allowing the aldehyde **4a** to react with I_2 in CCl_4 heated at reflux failed to produce the desired **4c**.[15] This result was not surprising since I_2 is considered less reactive than Br_2 in electrophilic aromatic substitution reactions.[16] A para activating group of greater electron-donating ability than methoxy[12] could compensate for the decreased reactivity of I_2. The commercial availability of 3-methoxysalicylaldehyde (**4d**) and the noted ease in which phenols are iodinated[11] led us to attempt iodination of **4d** with I_2 in refluxing CCl_4, both in the presence and in the absence of $NaHCO_3$. Under these conditions only recovered starting material was obtained.

With the assistance of mercuric oxide or copper(II) ion, iodination at the 5-position of **4d** has been achieved. Treatment of **4d** with I_2 and mercuric oxide in ethanol provided the 5-iodobenzaldehyde **4e**[17] (51%). Our efforts to improve this yield were unsuccessful. Furthermore, a control experiment in which the product **4e** was subjected to the same reaction conditions (I_2, HgO, and ethanol) resulted in decomposition of **4e** (ca. 35%) as revealed by the loss of the aldehyde moiety (^1H NMR). The modest yield of **4e** by the mercuric oxide procedure was apparently a consequence of product instability to the reaction conditions. When copper(II) ion was employed,[18] **4d** underwent iodination with I_2 to afford a 5-iodo copper(II) complex. Attempts to produce **4e** by the purported aqueous acid dissociation of the iodinated copper complex[18] did not afford useful amounts of product (**4e**, <5%). The formation of iodinating species more reactive than I_2 brought about by the addition of oxidizing metal reagents (HgO and Cu(II)) could account for the iodine substitutions on **4d**. Additionally, the low reactivity of **4d** with I_2 in the absence of an oxidizing agent could also be a function of a diminished directing effect of the phenol moiety as a consequence of the *o*-carbonyl group.[19] The need for metal reagents to facilitate I_2 reaction, the possible instability of the aldehyde moiety of **4d** to the mercuric reaction conditions, and the potential of altered reactivity of salicyl substrates as compared to phenols, which are devoid of *o*-carbonyl groups, directed our investigation to other iodination reaction conditions known to afford iodinating species more reactive than I_2 and nonaldehydic salicyl substrates.

Table I. Reactivity of Methyl 3-Methoxysalicylate (5a) to Various Direct Electrophilic Iodination Reaction Conditions

		reaction products and recovered starting material			
entry	reagents[a]	ester	5-substituent	yield,[b] %	method ref.
1[c]	NH_4I, $NOBF_4$, HOAc CF_3CO_2H, Ac_2O, O_2	**5a**	H	96	10
2[d]	I2, CF_3CO_2Ag, $CHCl_3$	**5a**	H	90	15
3	I_2, $AgNO_2$, CH_2Cl_2	**5d**	NO_2	75	21
		5a	H	10	
4[e]	I_2, Ag_2SO_4, CH_2Cl_2	**5c**	I	5[f]	22
		5a	H	90	
5	I_2, HgO, EtOH	**5c**	I	50[f]	17
		5a	H	0	
6	NaI, Chloramine-T, DMF	**5c**	I	53[f]	23
		5a	H	10	
7	NaI, NaOH, NaOCl, MeOH	**5c**	I	59[f]	11
		5e	Cl	13	
		5a	H	22	
8	ICl, HOAc	**5c**	I	8[f]	24
		5e	Cl	73	
		5a	H	6	

[a] Reaction conditions resulting in the formation of significant amounts (≥5%) of 5-substituted products are detailed in the Experimental Section. [b] Yields are isolated and unoptimized unless otherwise noted. [c] **5a** (1.10 mmol), NH_4I (1.1 mmol), HOAc (7.5 mL), CF_3CO_2H (1 mL), $NOBF_4$ (1.8 mol %), Ac_2O (0.5 mL), 20 °C (48 h). [d] **5a** (1.65 mmol), CF_3CO_2Ag (1.8 mmol), I_2 (1.81 mmol), $CHCl_3$ (25 mL), 40 °C (12 h). [e] **5a** (1.65 mmol), I_2 (1.81 mmol), Ag_2SO_4 (1.65 mmol) CH_2Cl_2 (10 mL), reflux (4 h). [f] Optimized yield.

The methyl 3-methoxysalicylate (**5a**) was selected as an electrophilic iodination precursor for **2a** based on the increased stability of an ester relative to an aldehyde, the para-activating influence of a 2-hydroxyl moiety, and starting material accessibility.[20] As a test of substrate usefulness, **5a** was subjected to Br_2 and $NaHCO_3$ ($CHCl_3$, 20 °C),[13] which resulted in the rapid formation of the 5-bromo ester **5b** (78%). The facile bromine substitution led to the study shown in Table I of the effects of various modern and traditional direct electrophilic iodination reaction conditions upon **5a**. Three of the iodination pro-

(9) For reviews of the formation of aryl iodides by electrophilic substitution reactions, see: (a) Merkushev, E. B. *Synthesis* **1988**, 923. (b) Merkushev, E. B. *Russ. Chem. Rev.* **1984**, *53*, 343. (c) Roedig, A. *Methoden der Organishen Chemie (Houben-Weyl)*; J. Thieme Verlag: Stuttgart, 1960; 517f.

(10) Radner, F. *J. Org. Chem.* **1988**, *53*, 3548 and references cited therein.

(11) Edgar, K. J.; Falling, S. N. *J. Org. Chem.* **1990**, *55*, 5287 and references cited therein.

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(13) (a) Davies, W. *J. Chem. Soc.* **1923**, 1575. (b) Stork, G.; Conroy, H. *J. Am. Chem. Soc.* **1951**, *73*, 4743.

(14) Pettit, G. R.; Piatak, D. M. *J. Org. Chem.* **1960**, *25*, 721.

(15) (a) The formation of **4c** from **4a** has been described: Ghaffari, M. A.; van Lier, J. E. *J. Labelled Compds Radiopharm.* **1989**, *27*, 118. However, in our hands, **4c** could not be obtained by this procedure but could be made by the anion-mediated route shown in Scheme I. The spectroscopic and analytical data of **4c**, obtained by the route shown in Scheme I, are in disagreement with those presented by Ghaffari and van Lier.

(16) Pizey, J. S. *Synthetic Reagents*; Wiley: New York, 1970; Vol. 3, pp 227-276.

(17) Profft, E., Pannach, M. *Arch. Pharm.* **1966**, *299*, 633; *Chem. Abstr.* **1966**, *65*, 12131d.

(18) (a) Patil, J. N.; Sen, D. N. *Ind. J. Chem.* **1973**, *11*, 780. No yield was presented by Patil and Sen for the acid dissociation of the iodinated copper(II) complex; therefore, the efficiency of this sequence was evaluated.

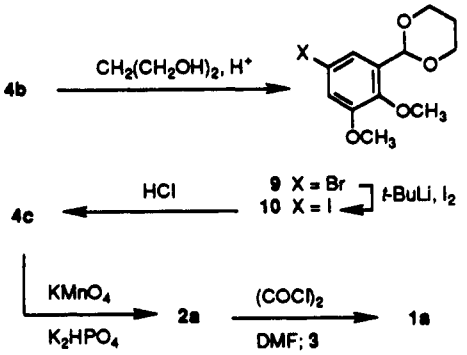
(19) Intramolecular hydrogen bonding between the phenol and the *o*-carbonyl groups in salicylic substrates has been noted to play a role in the altered chemical reactivity of these groups to various reaction conditions: Sadekov, I. D.; Minkin, V. I.; Luytskii, A. E. *Russ. Chem. Rev.* **1970**, *39*, 139.

(20) The acid **6a** was also considered a substrate for the iodination survey. At the outset of the study, we were unaware that differences in reactivity between the ester **5a** and the acid **6a** would be significant, as was the case when ICl was the iodinating reagent. The ester **5a** was considered a more convenient substrate to evaluate due to its enhanced solubility in a variety of solvents.

cedures (entries 1–3)[10,15,21] failed to yield the desired iodide **5c**, while the other methods (entries 4–8)[11,17,22–24] afforded **5c** in variable amounts.[25] Efforts to increase the yields of **5c** (entries 4–8) by elevating the amounts of reagents used and temperatures (35–60 °C) failed to provide increased yields of **5c** over those reported in Table I. The yield for conversion of **5a** to the iodo ester **5c** (entry 5, 50%) was similar to the result obtained for the transformation of **4d** to the iodo aldehyde **4e** (51%) under the same I_2–HgO conditions. Since starting materials were not recovered from either of these reactions and the control study in which the product **4e** when resubjected to the reaction conditions underwent partial decomposition, it was concluded that the salicyl moieties of both the esters and aldehydes, starting materials and products, were labile to the mercuric oxide conditions. Side products were also obtained from the electrophilic iodination survey (Table I), including the 5-nitro **5d** (entry 3) and the 5-chloro **5e** (entries 7–8) adducts.

The formation of the 5-nitro ester **5d** with I_2 and silver nitrite was not unexpected since these conditions have also been shown to effect nitration of amphetamine substrates.[26] In contrast, the NaI–sodium hypochlorite (NaOCl) and iodine monochloride (ICl)-induced chlorinations of **5a** are noteworthy. Although the actual iodinating agent(s) produced by the oxidation of NaI with NaOCl (entry 7) has yet to be identified,[11] it is possible that electrophilic Cl^+ (or its equivalent) is afforded in this process, resulting in the formation of **5e**. The chlorination result obtained with ICl (entry 8) was striking since salicyclic acid is known to efficiently undergo electrophilic iodination with ICl in acetic acid.[24] Several control reactions were performed to further investigate the ICl reactivity with salicyl substrates. Under the same ICl reaction conditions utilized for **5a**, the salicylic acid **6a** afforded the iodide **6b** (54%) and the salicylaldehyde **4d** yielded the chloride **4f** (61%). The conversion of **4d** to **4f** with ICl was also achieved in dichloromethane in the presence of $NaHCO_3$ (0 °C, 65%), therefore excluding solvent type as a critical factor for chlorinated product formation. Furthermore, in order to confirm the homogeneity of the ICl reagent,[27] the amphetamine substrate **7a** was converted to the iodoamphetamine **7b**.[28] Formation of the chlorides **4f** and **5e** vs the iodide **6b** seems to be a function of the absence or presence of a carboxylate proton in the starting material. This structural feature could influence both the effects on the mode of fission of the interhalogen ICl bond[29] and mechanistic changes as a function of pH,[30] providing iodinating species other than ICl such as the more reactive $[H_2OI]^+$ or HOI.[31] The desire for increased efficiency of iodine atom introduction at the 5-position of 3-methoxysalicyl substrates compared to the modest yields of **5c** formation (50–59%) obtained under the electrophilic aromatic substitution conditions of entries 5–7 prompted our investigation of an anion-based iodo–demetalation approach.

Scheme I



Methodology known to convert the 5-bromooxazole **8a**, which is derived from **4b**,[13] to a variety of 5-substituted 2,3-dimethoxybenzoic acids[2] was employed in a manner where the aryl anion derived from the lithium-for-bromine exchange of **8a** was trapped with I_2. Treatment of **8a** with *tert*-butyllithium (–78 °C)[32] then I_2 (–78 → 20 °C) afforded, after acid hydrolysis of the oxazole protecting group, the desired 5-iodo acid **2a** (52%).[33] The aryl anion inducd formation of **2a** was improved by employing the dioxane containing bromide substrate **9** (Scheme I) rather than the oxazole **8a**. The aldehyde **4b**, which was obtained from **4d** (95%),[34] was protected with 1,3-propanediol to afford the 1,3-dioxane **9** (89%), which was allowed to react with *tert*-butyllithium (–78 °C) and then I_2 to provide the 5-iodo acetal **10**. Due to the labile nature of the protecting group, the acetal **10** was hydrolyzed directly to the 5-iodobenzaldehyde **4c** (**9** → **4c**, 85%). Oxidation of **4c** with potassium permanganate in the presence of *tert*-butyl alcohol and dipotassium hydrogen phosphate[35] afforded **2a** (86%). Conversion of **2a** to epidepride **1a** was effected by first forming the acid chloride (not shown) with oxalyl chloride followed by reaction with **3**[36] (100%).

In conclusion, a synthesis of the 5-iodobenzoic acid **2a** from the aldehyde **4d** was achieved in six steps (63%) by employing aryl anion mediated methodology for iodine atom introduction. The halogen exchange of the oxazole **8a** followed by deprotection was less efficient for **2a** production (52%). The attempted formation of **2a** by an

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(22) Sy, W.-W.; Lodge, B. A.; By, A. W. *Synth. Commun.* **1990**, *20*, 887.
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(24) Woollett, G. H.; Johnson, W. W. *Organic Syntheses*; Wiley: New York, 1943; *Collect. Vol. II*, p 343.
(25) Formation of the saponification product, 3-methoxy-5-iodosalicylic acid (**6b**), was not observed under the reaction conditions of entries 4–8.
(26) Sy, W.-W.; By, A. W. *Tetrahedron Lett.* **1985**, *26*, 1193.
(27) The propensity for ICl to form the potential chlorinating agents Cl_2 and ICl_3 has been noted: Buckles, R. E.; Bader, J. M. *Inorg. Synth.* **1967**, *9*, 130.
(28) Mathis, C. A.; Hoffman, A. J.; Nichols, D. E.; Shulgin, A. T. *J. Labeled Compds Radiopharm.* **1988**, *25*, 1255.
(29) (a) Reaction medium effects have been reported to play an important role in whether chlorination or iodination takes place with ICl: Brasted, R. C. In *Comprehensive Inorganic Chemistry: The Halogens*; Sneed, M. C., Maynard, J. L., Brasted, R. C., Eds.; D. Van Nostrand: New York, 1954; Vol. 3, Chapter 8. (b) In the absence of solvent, salicylic acid undergoes chlorination with ICl vapor; solvent and other reaction components influence the mode of interhalogen ICl bone fission, which is reflected by the formation of either chloride- or iodide-containing products: Bennett, F. W.; Sharpe, A. G. *J. Chem. Soc.* **1950**, 1383.
(30) Rao, M. D. P.; Padmanabha, J. *Ind. J. Chem.* **1981**, *20A*, 133.
(31) (a) $[H_2OI]^+$: Seevers, R. H.; Counsell, R. E. *Chem. Rev.* **1982**, *82*, 575 and references therein. (b) HOI: Covello, M. *Chim. Ther.* **1967**, *2*, 73.
(32) An increased yield of the iodide **8b** was obtained when *tert*-butyllithium was used instead of *n*-butyllithium. For a recent discussion of the benefits of utilizing *tert*-butyllithium, see: Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404 and references therein.
(33) An improved yield for the overall transformation of **8a** to **2a** was obtained when the intermediate **8b** was not isolated but hydrolyzed directly to the acid.
(34) The bromo benzaldehyde **4b** can also be prepared from **4d** (*o*-vanillin) in an overall yield of 95% (Cameron, D. W.; Deutscher, K. R.; Feutrill, G. I.; Hunt, D. E. *Aust. J. Chem.* **1982**, *35*, 1451) followed by methyl etherification of the phenol as described by Davies (1923) noted above. Utilizing these procedures, we also obtained **4b** in similar quantities.
(35) Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537.
(36) (a) The enantiomeric purity of **3** used in this preparation was >99.5% ee, which was prepared according to: Bishop, J. E.; Mathis, C. A.; Gerdes, J. M.; Whitney, J. M.; Eaton, A. M.; Mailman, R. B. *J. Med. Chem.* **1991**, *34*, 1612.

electrophilic iodination approach was limited by the decreased reactivity of salicyl-type phenol substrates and required the use of either oxidizing agents with I_2 or iodinating reagents more reactive than I_2. Under these conditions the placement of iodine atoms at the 5-positions of the aldehyde (**4d** → **4e**, 51%) and ester (**5a** → **5c**, 59%) salicyl substrates were less efficient processes compared to the anion-mediated halogen exchange of **9** → **4c** (85%). Though one could envisage the preparation of **2a** from **5a** via **5c** formation,[37] the overall yield for this conversion would be less than the six-step transformation of **4d** → **2a** (63%). The unusual ICl reactivity observed with 3-methoxysalicyl substrates exemplified the sometimes difficult task of preparing functionalized aryl iodides by electrophilic substitution. Finally, the coupling of **2a** to the amine **3** resulted in a significantly improved synthesis of the neuroleptic **1a**.

Experimental Section

General Methods. Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl, and methylene chloride (CH_2Cl_2) was distilled from CaH_2 immediately prior to use. Solutions of *tert*-butyllithium were titrated.[38] Acetone was dried over potassium carbonate and distilled. *N,N*-Dimethylformamide (DMF) was distilled from calcium sulfate and stored over 4-Å molecular sieves. Chloroform ($CHCl_3$) was dried over anhydrous potassium carbonate and distilled from calcium sulfate. Purification of 1,3-propanediol was performed by drying over magnesium sulfate followed by distillation and then a second distillation from sodium and storage over 4-Å molecular sieves. Oxalyl chloride was distilled prior to use. Other solvents and reagents were used as received from commercial suppliers. All nonaqueous reactions were performed in oven-dried glassware under an atmosphere of argon, unless otherwise noted. Solutions of $NaHCO_3$, $NaHSO_3$, and NaOH noted in percent (%) were formulated by weight to weight ratios, HCl percent solutions were prepared by volume to volume ratios, and Clorox bleach was used as the 4% solution of NaOCl. Drying of the organic reaction solutions was effected with Na_2SO_4. Gravity column chromatography was performed with Kieselgel 60 (70–230 mesh, E. Merck) silica gel. The chromatography solvents employed were glass distilled, and solvent mixtures are reported as volume to volume ratios. Melting points were uncorrected and were obtained with a Mel-Temp apparatus.

The proton (300-MHz, TMS internal reference) NMR spectra were recorded in $CDCl_3$ unless otherwise noted. Infrared (IR) spectra were recorded as thin films either directly (neat) or as mineral oil composites (mulls).

Attempted Formation of 4c and 4e with I_2. A solution of 2,3-dimethoxybenzaldehyde (**4a**, 166 mg, 1 mmol) and iodine (258 mg, 1.01 mmol) in carbon tetrachloride (6 mL) was heated and stirred at reflux for 16 h. The reaction mixture was cooled and washed with dilute $NaHSO_3$ and then water. The organic portion was dried and filtered, and the solvent was removed in vacuo to afford a pale tan oil. Characterization of the oil by ^1H NMR spectroscopy revealed that only recovered starting material **4a** was obtained. A second reaction was performed utilizing the above conditions with the addition of $NaHCO_3$ (86 mg, 1.01 mmol) to the reaction mixture. Similar results were obtained according to ^1H NMR analysis. Treatment of 3-methoxysalicylaldehyde (**4d**) under the same conditions afforded only recovered starting material (^1H NMR).

Control Reaction of the Stability of 4e to Mecuric Oxide and I_2.[17] A solution of 5-iodo-3-methoxysalicylaldehyde (**4e**, 278 mg, 1.0 mmol) in ethanol (10 mL) was cooled to 0 °C then treated alternately with small portions of I_2 and HgO until 100 mol % of each reagent had been added (I_2 254 mg, 1.0 mmol; HgO 217 mg, 1.0 mmol). After the additions were complete, the reaction mixture was warmed to room temperature and stirred for 15 h. The mixture was filtered, and the filtrate was washed with saturated Na_2CO_3. The aqueous extract was acidified with 2 N H_3PO_4 to pH 4 and extracted with CH_2Cl_2. The organic portion was dried and filtered and the solvent removed under reduced pressure to afford a crude orange viscous oil that slowly crystallized. Recrystallization of the crude solid (ethanol) afforded recovered starting material **4e** (181 mg, 65%). The mother liquor was concentrated to afford a tan viscous multicomponent oil that when analyzed by ^1H NMR was devoid of an aldehyde signal (δ 10.99).

Attempted Formation of 4e with Copper(II) Ion.[18] A solution of 3-methoxysalicylaldehyde (**4d**, 10.0 g, 65.8 mmol) was dissolved in acetone (140 mL), and then 0.59 M $Cu(NH_3)_4SO_4$[39] (100 mL, 90 mol % based on **4d**) was added to the solution. The reaction mixture was stirred for 10 min (20 °C), and the solids were collected by filtration and washed with water then acetone. The copper(II) complex was isolated as an olive green solid after traces of the residual water and acetone were removed in vacuo (3 mmHg, 90 °C). The complex (1.0 g, 2.73 mmol) was dissolved in $CHCl_3$ (10 mL), and *N*-iodosuccinimide (1.23 g, 5.47 mmol) was added. The reaction mixture turned from green to red-brown and was allowed to stir at 20 °C (12 h). The solution was washed successively with 2 N HCl, 10% $NaHSO_3$, and water. The organic portion was dried and filtered and the solvent was removed under reduced pressure to afford a brown viscous oil. Purification of the oil by column chromatography (silica gel, CH_2Cl_2) yielded recovered **4d** (109 mg, 11%) and the iodoarene **4e** (33 mg, 2%). The balance of the organic materials was polymeric in nature and did not resemble either the desired product **4e** or starting material **4d** according to ^1H NMR analysis.

Methyl 5-Bromo-3-methoxysalicylate (5b). A solution of **5a** (1.0 g, 5.5 mmol) in $CHCl_3$ (10 mL) was treated with sodium bicarbonate (466 mg, 5.55 mmol). The mixture was cooled (0 °C), and bromine (888 mg, 5.55 mmol, 101 mol %) was added dropwise. The solution was allowed to warm to 20 °C and stirred for 48 h. The reaction mixture was quenched with saturated $NaHSO_3$ and washed with water. The organic portion was dried and filtered, and the solvent was removed in vacuo to provide a crude white solid. Purification of the crude material by column chromatography (silica gel, CH_2Cl_2) provided the bromo ester **5b** (1.12 g, 78%) as a white solid: mp 117–118 °C. ^1H NMR δ 10.84 (s, 1 H), 7.34 (d, 1 H, J = 2.34 Hz), 6.96 (d, 1 H, J = 2.16 Hz), 3.85 (s, 3 H), 3.70 (s, 3 H); IR (mull) 3080, 1660 cm^{-1}. Anal. Calcd for $C_9H_9BrO_4$: C, 41.41; H, 3.47. Found: C, 41.71; H, 3.42.

Electrophilic Iodination Survey with 5a (Table I). The ratio of reagents and reaction conditions used for entries 1, 2, and 4 are found in the Table I footnotes. The experimental details for the balance of the entries are described below.

Entry 3. Methyl 3-Methoxy-5-nitrosalicylate (5d). The ester **5a** (200 mg, 1.10 mmol) in CH_2Cl_2 (10 mL) was treated with I_2 (280 mg, 1.1 mmol) and silver nitrite (170 mg, 1.1 mmol). The reaction was stirred at 20 °C (48 h), and the resultant yellow precipitate was removed by filtration. The filtrate was washed successively with 10% $NaHSO_3$, saturated $NaHCO_3$, and water. The organic portion was dried and filtered, and the solvent was removed under reduced pressure to afford a crude yellow solid. Purification of the solid by column chromatography (silica, CH_2Cl_2) afforded the 5-nitro ester **5d** (187 mg, 75%) as a yellow solid: mp 136–138 °C; ^1H NMR δ 11.17 (br s, 1 H), 8.43 (d, 1 H, J = 2.61 Hz), 7.58 (d, 1 H, J = 2.58 Hz), 4.02 (s, 3 H), 3.98 (s, 3 H); IR (mull) 3090, 1670 cm^{-1}. Anal. Calcd for $C_9H_9O_6N$: C, 47.58; H, 3.99. Found: C, 47.42; H, 3.74. The balance of the material obtained from the chromatographic separation was **5a** (20 mg, 10%).

Entry 5. Methyl 5-Iodo-3-methoxysalicylate (5c). A mixture of **5a** (755 mg, 5.04 mmol), HgO (1.09 g, 5.04 mmol), and I_2 (1.28 g, 5.04 mmol) in ethanol (5 mL) was allowed to react and worked up according to the procedure noted above for the stability control reaction of **4e**. Purification of the crude reaction material by column chromatography (silica, ethyl acetate:hexane = 2:3) afforded **5c** (710 mg, 50%) as a yellow solid: mp 110–112 °C; ^1H NMR δ 10.94 (s 1 H), 7.70 (d, 1 H, J = 1.9 Hz), 7.19 (d, 1 H, J = 1.88 Hz), 3.91 (s, 3 H), 3.84 (s, 3 H); IR 3100, 1660 cm^{-1}. Anal. Calcd for $C_9H_9IO_4$: C, 35.09; H, 2.94. Found: C, 35.48; H, 2.86.

(37) Methylation of the phenol moiety of **5c** followed by saponification of the ester group could prove useful for the preparative formation of **2a**.

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Recovered starting material **5a** was not obtained nor was the formation of the corresponding carboxylic acid **6b** observed.

Entry 6. Sodium iodide (296 mg, 1.97 mmol) and **5a** (300 mg, 1.64 mmol) were placed in dry DMF (4 mL). Sodium *N*-chloro-*p*-toluenesulfonamide (Chloramine T, 450 mg, 1.98 mmol) was added to this reaction mixture. The solution was stirred at 20 °C (1 h), quenched with water (8 mL), and acidified to pH 3 with 5% HCl. The mixture was extracted with ethyl acetate, the organic portion was washed with saturated $Na_2S_2O_3$ and brine, then dried and filtered, and the solvent was removed in vacuo to afford a yellow solid. Purification of the solid by column chromatography (silica, CH_2Cl_2) yielded **5c** (269 mg, 53%) and a small portion of **5a** (30 mg, 10%).

Entry 7. Methyl 5-Chloro-3-methoxysalicylate (5e). A solution of **5a** (500 mg, 2.75 mmol), sodium iodide (412 mg, 2.75 mmol) and sodium hydroxide (110 mg, 2.75 mmol) in methanol (10 mL) was cooled to 0 °C, and then 4% sodium hypochlorite (Chlorox, 5.12 g) was added dropwise. After the addition was complete, the resultant tan, turbid solution was stirred at 0 °C (1 h) and quenched with 10% $Na_2S_2O_3$ (15 mL) and warmed to 20 °C. The solution was adjusted to pH 7 with 5% HCl and extracted with ether. The organic portion was dried and filtered, and the solvent was removed under reduced pressure to provide a gold oil. Purification of the oil by column chromatography (silica, ethyl acetate:hexane = 1:1.86) afforded the iodide **5c** (499 mg, 59%), recovered **5a** (109 mg, 22%), and the chloride **5e** (77 mg, 13%) as a pale yellow solid: mp 107–108 °C; ^{1}H NMR δ 10.90 (s, 1 H), 7.34 (d, 1 H, J = 2.46 Hz), 6.92 (d, 1 H, J = 2.43 Hz), 3.95 (s, 3 H), 3.91 (s, 3 H), 3.85 (s, 3 H); IR 3090, 1670 cm^{-1}. Anal. Calcd for $C_9H_9ClO_4$: C, 49.90; H, 4.19. Found: C, 49.98; H, 3.85.

Entry 8. Glacial acetic acid (20 mL) was charged with **5a** (500 mg, 2.75 mmol) and then with a solution of iodine monochloride (ICl, 666 mg, 4.1 mmol) in acetic acid (5 mL). The reaction mixture was stirred at 20 °C (1 h), after which a significant new component accompanied by starting material was noted by ^{1}H NMR and TLC. An additional amount of ICl was added (50 mol %), and the mixture was stirred 1 h (20 °C) and then warmed to 70 °C and stirred for an additional 1 h. The reaction mixture was cooled, diluted with water (50 mL), treated with Na_2SO_3 (2 g), and stirred for 15 min. The solution was extracted with CH_2Cl_2, and the organic portion was washed with 5% $NaHCO_3$ and water, dried, filtered, and concentrated under reduced pressure to afford a yellow solid. Purification of the solid by column chromatography (silica, CH_2Cl_2) yielded the chloride **5e** (433 mg, 73%), a small portion of the iodide **5c** (67 mg, 8%), and recovered **5a** (18 mg, 6%).

Iodine Monochloride Control Reactions. Preparation of 5-Chloro-3-methoxysalicylaldehyde (4f). 3-Methoxysalicylaldehyde (**4d**, 100 mg, 0.66 mmol) was allowed to react with ICl (161 mg, 0.98 mmol) in glacial acetic acid (10 mL) under conditions described above for ester **5a** to afford the chloro aldehyde **4f** (75 mg, 61%) as a tan solid: mp 114–116 °C; ^{1}H NMR δ 10.99 (s, 1 H), 9.86 (s, 1 H), 7.16 (d, 1 H, J = 1.5 Hz), 7.05 (d, 1 H, J = 1.5 Hz), 3.92 (s, 3 H); IR (mull) 3140, 1650 cm^{-1}. Anal. Calcd for $C_8H_7ClO_3$: C, 51.49; H, 3.78. Found: C, 51.32; H, 3.43.

The formation of **4f** was also achieved when a suspension **4d** (25 g, 0.164 mol), $NaHCO_3$ (36 g, 0.429 mol) and CH_2Cl_2 (200 mL) was allowed to react with ICl (40 g, 0.246 mol) at 0 °C (45 min). The reaction was quenched with $Na_2S_2O_4$, and then the mixture was washed with water. The organic portion was dried and filtered and the solvent removed under reduced pressure to afford a tan solid. Recrystallization of the solid from ethanol afforded 20.1 g of **4f** (65%).

Synthesis of 5-Iodo-3-methoxysalicylic Acid (6b). The acid **6a** (100 mg, 0.6 mmol) and ICl (146 mg, 0.89 mmol) were allowed to react in glacial acetic acid (10 mL) according to the procedure noted for ester **5a**. The crude material obtained after workup was recrystallized ($CHCl_3$) to afford the 5-iodo acid **6b** (95 mg, 54%) as a white solid: mp 216–218 °C dec; ^{1}H NMR (acetone-d_6) δ 7.77 (d, 1 H, J = 1.2 Hz), 7.43 (d, 1 H, J = 1.2 Hz) 3.89 (s, 3 H); IR (mull) 3090, 1647 cm^{-1}. Anal. Calcd for $C_8H_7IO_4$: C, 32.68; H, 2.40. Found: C, 32.71; H, 2.68.

Formation of 1-(2,5-Dimethoxy-4-iodophenyl)-2-(trifluoroacetamido)propane (7b).[28] The amphetamine **7a** (160 mg, 0.55 mmol) in glacial acetic acid (2.5 mL) was treated with ICl (89 mg, 0.55 mmol) in glacial acetic acid (2.5 mL). The solution was stirred at 60 °C (1 h) then cooled and quenched with $NaHSO_3$, diluted with water, and extracted with CH_2Cl_2. The organic portion was washed with 5% $NaHCO_3$ and water, dried, and filtered and the solvent removed in vacuo to afford the iodoamphetamine **7b** (190 mg, 83%).

2-(2,3-Dimethoxy-5-iodophenyl)-4,5-dihydro-4,4-dimethyloxazole (8b) and 2,3-Dimethoxy-5-iodobenzoic Acid (2a). The oxazole **8a**[2] (209 mg, 0.65 mmol) was dissolved in THF (5 mL), and the solution was cooled to −78 °C then treated dropwise with 1.5 M *tert*-butyllithium (1.4 mmol, 954 μL). After the addition was complete the mixture was stirred at −78 °C for 20 min. The resultant aryllithium species was allowed to react with iodine (507 mg, 2.0 mmol) in THF (5 mL), and the solution was stirred at −78 °C for 1 h, warmed to −45 °C, and stirred 1.5 h followed by warming to room temperature. The reaction mixture was quenched with water (15 mL), and the solvent was removed under reduced pressure. The resultant crude mixture was diluted with $CHCl_3$ and washed with 10% $NaHSO_3$ (10 mL). The aqueous phase was made basic with 10% K_2CO_3 and extracted with $CHCl_3$. The organic portions were combined, dried, filtered and the solvent removed in vacuo to provide a tan crude oil. The iodide **8b** could be isolated by column chromatography (silica gel; EtOAc:hexane = 3:1): ^{1}H NMR δ 7.63 (δ d, 1 H, J = 2.1 Hz), 7.23 (d, 1 H, J = 2.1 Hz), 4.09 (s, 2 H), 3.88 (s, 3 H), 3.83 (s, 1 H), 1.36 (s, 6 H). Anal. Calcd for $C_{13}H_{16}INO_3$: C, 43.10; H, 4.40. Found: C, 43.23; H, 4.47.

Routinely, **8b** was not isolated but hydrolyzed directly to acid. The crude reaction product was treated with 1 N HCl (10 mL) and heated at reflux (2.5 h). The solution was cooled and then extracted with ethyl acetate. The organic portion was dried and filtered, and the solvent was removed under reduced pressure to afford a tan oil. Purification of the oil by column chromatography (silica, 1:9 MeOH–CH_2Cl_2) afforded the iodo acid **2a** (106 mg, 52%) as a white solid: mp 128–130 °C; ^{1}H NMR δ 11.20 (br s, 1 H), 8.03 (d, 1 H, J = 2.37 Hz), 7.38 (d, 1 H, J = 2.03 hz), 4.05 (s, 3 H), 3.90 (s, 1 H); IR (mull) 3120, 1730 cm^{-1}. Anal. Calcd for $C_9H_9IO_4$: C, 35.09; H, 2.95. Found: C, 35.15; H, 2.61.

5-Bromo-2,3-dimethoxy-1-(1,3-dioxan-2-yl)benzene (9). A solution of the aldehyde **4b**[34] (3.0 g, 12.2 mmol), 1,3-propanediol (1.02 g, 13.0 mmol), and *p*-toluenesulfonic acid (228 mg, 1.2 mmol) in benzene (150 mL) was heated at reflux (24 h) and azeotrope water removed by a Dean-Stark collector. The reaction mixture was cooled (20 °C) and washed with 5% NaOH and then water. The organic portion was dried and filtered and the solvent removed under reduced pressure to yield acetal **9** (3.2 g, 89%) as a yellow oil: ^{1}H NMR δ 7.35 (d, 1 H, J = 2.5 Hz), 6.92 (d, 1 H, J = 2.4 Hz), 5.73 (s, 1 H), 4.21 (m, 2 H), 3.97 (m, 2 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 2.8–2.12 (br m, 1 H), 1.41 (m, 1 H). Anal. Calcd for $C_{12}H_{15}O_4Br$: C, 47.54; H, 4.99. Found: C, 47.59, H, 4.83.

2,3-Dimethoxy-1-(1,3-dioxan-2-yl)-5-iodobenzene (10) and 2,3-Dimethoxy-5-iodobenzaldehyde (4c). A solution of the bromo acetal **9** (4.0 g 13.2 mmol) in THF (15 mL) was cooled to −78 °C, and then 1.7 M *tert*-butyllithium (29.7 mmol, 17.5 mL) was added (dropwise). After the addition was complete the pale yellow reaction mixture was stirred at −78 °C for 45 min. The resultant aryllithium species was allowed to react with a solution of iodine (10.06 g, 39.6 mmol) in THF (15 mL). The reaction was stirred at −78 °C for 45 min then warmed to 0 °C and stirred for 30 min. The mixture was warmed to room temperature and quenched with water. The solvent was removed under reduced pressure, and the resulting yellow residue was dissolved in ether (50 mL) and washed with saturated $Na_2S_2O_3$ (50 mL). The organic layer was dried and filtered, and the solvent was removed in vacuo to afford a yellow semisolid. ^{1}H NMR analysis of the residue revealed a 1:1.28 mixture of the iodo acetal **10** and iodo aldehyde **4c**. The iodo acetal could be isolated by column chromatography (gravity, silica gel, CH_2Cl_2): ^{1}H NMR δ 7.49 (d, 1 H, J = 2.0 Hz), 7.12 (d, 1 H, J = 2.0 Hz), 5.73 (s, 1 H), 4.21 (m, 2 H), 3.97 (m, 2 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 2.8–2.12 (br m, 1 H), 1.41 (dp, 1 H, J = 1.24, 13.5 Hz). Anal. Calcd for $C_{12}H_{15}O_4I$: C, 41.16; H, 4.32. Found: C, 41.43; H, 4.03. Routinely, the acetal–aldehyde mixture was not separated but subjected to 5% HCl (20 mL) in THF (20 mL) and heated at 60 °C (24 h) to remove the acetal-protecting group. The solvent was evaporated under reduced pressure, and the remaining aqueous portion was extracted with ether. The ether layer was washed with 1 N NaOH, dried, filtered,

and concentrated to afford a tan solid that was recrystallized from ethanol to provide the iodobenzaldehyde **4c** (3.20 g, 85%) as a white solid: mp 100–101 °C; ^{1}H NMR δ 10.28 (s, 1 H), 7.70 (d, 1 H, J = 2.02 Hz), 7.36 (d, 1 H, J = 2.0 Hz), 3.95 (s, 3 H), 3.88 (s 3 H); IR (mull) 1670 cm^{-1}. Anal. Calcd for $C_9H_9IO_3$: C, 37.01; H, 3.11. Found: C, 37.38; H, 3.05.

Formation of 2a from 4c. The aldehyde **4c** (200 mg, 0.685 mmol) was dissolved in *tert*-butyl alcohol (5 mL), and 1.25 M dipotassium hydrogen phosphate (2.7 mL) and 1.0 M potassium permanganate (4.1 mL) were added. The reaction mixture was stirred at 20 °C (30 min) and then quenched with saturated Na_2SO_3. The resulting solution was adjusted to pH 3 with concd HCl then extracted with $CHCl_3$. The organic portion was extracted with 1 N NaOH. The aqueous basic layer was acidified to pH 3 with 1 N H_3PO_4 then extracted with $CHCl_3$. The chloroform layer was dried and filtered, and the solvent was removed under reduced pressure to yield the acid **2a** (180 mg, 86%).

(*S*)-2,3-Dimethoxy-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-5-iodobenzamide (1a, Epidepride). The benzoic acid **2a** (600 mg, 1.95 mmol) was dissolved in CH_2Cl_2 (10 mL), and to this solution was added DMF (2 drops) and oxalyl chloride (0.425 mL, 4.87 mmol). The mixture was stirred at room temperature (1 h), and the solvent was removed in vacuo affording the corresponding acid chloride as a pale yellow residue (not characterized). The residue was dissolved in CH_2Cl_2 (10 mL), and the aminopyrrolidine **3**[36] (623 mg, 4.87 mmol) in CH_2Cl_2 (5 mL) was added to this solution. The reaction mixture was allowed to stir for 1 h (20 °C), and the solvent was removed under reduced pressure. The crude product was redissolved in CH_2Cl_2 (20 mL) and washed with 1 N NaOH (20 mL), and the phases were separated. The organic portion was dried and filtered, and the solvent was removed in vacuo to afford a yellow oil that was purified by column chromatography (silica gel; 1:9 MeOH–CH_2Cl_2) to yield epidepride **1a** (810 mg, 100%) as a yellow oil: ^{1}H NMR δ 8.30 (br s, 1 H), 8.03 (d, 1 H, J = 1.62 Hz), 7.28 (d, 1 H, J = 1.62 Hz), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.77 (ddd, 1 H, J = 13.6, 7.0, 3.2 Hz), 3.33 (dt, 1 H, J = 14.0, 3.8), 3.32 (br t, 1 H, J = 7.2 Hz), 2.89 (dq, 1 H, J = 11.8, 7.4 Hz), 2.62 (br m, 1 H), 2.19 (m, 1 H), 1.77–1.63 (m, 5 H), 1.15 (t, 3 H, J = 7.2 Hz); IR (neat) 3330, 1640 cm^{-1}. Anal. Calcd for $C_{16}H_{23}IN_2O_3$: C, 45.95; H, 5.45. Found: C, 46.17; H, 5.56.

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Registry No. **1a**, 107188-87-4; **2a**, 134419-42-4; **3**, 22795-99-9; **4a**, 86-51-1; **4b**, 71295-21-1; **4c**, 7396-66-9; **4d**, 148-53-8; **4e**, 7359-14-0; **4f**, 7740-05-8; **5a**, 6342-70-7; **5b**, 134419-43-5; **5c**, 134419-44-6; **5d**, 134419-45-7; **5e**, 134419-46-8; **6a**, 877-22-5; **6b**, 134419-47-9; **7a**, 79315-43-8; **7b**, 111381-04-5; **8a**, 107189-00-4; **8b**, 134528-76-0; **9**, 134419-48-0; **10**, 134419-49-1.

Unique Catalysis by Eu(dppm)$_3$: Catalytic Molecular Recognition in Aldol and Michael Reactions†

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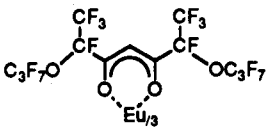
Development of efficient catalysis of C–C bond formations is the current subject of intensive activities.[1] For aldol-type reactions of carbonyl compounds with enol silyl ethers in particular, several catalysts including chiral ones have been developed.[2] It occurred to us that Eu(dppm)$_3$, tris[di(perfluoro-2-propoxypropionyl)methanato]europium(III) (**1**), originally developed by Ishikawa et al. as a chiral NMR shift reagent,[3] ought to be a superb catalyst for certain C–C bond-forming reactions[4] because of the stronger Lewis acidity due to the highly fluorinated ligand. Disclosed herein are the preliminary observations on the unique catalysis by Eu(dppm)$_3$ in the aldol and Michael reactions.



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In order to define the scope of the Eu catalysis, we first attempted reactions of various carbonyl/enol silyl ether pairs in the presence of 2.5 mol % of (+)-Eu(dppm)$_3$ in the range of −78 to 25 °C. We found that the Eu(III) catalyst was effective only for the reactions of aldehydes or α,β-unsaturated ketones with ketene silyl acetals (KSA) but totally ineffective for any pairs of ketone/KSA and aldehyde/ketone-derived enol silyl ether.[5] Thus, the Eu catalysis provides remarkable levels of chemoselectivity for both carbonyl and enol silyl ether partners.[6]

In addition, the Eu catalysis shows high levels of aldehyde discrimination in the competitive aldol reactions with KSA (Table I). First, the Eu catalyst can differentiate the steric difference in aldehydes to much higher extents than those observed with a stoichiometric use of $TiCl_4$ even at lower temperature (entries 1 and 2). Second, the Eu catalyst can uniquely recognize the delicate difference in electronic effect involved in benzaldehydes. Interestingly enough, *p*-nitrobenzaldehyde ($\sigma_{p\text{-}NO_2}$ = +0.78)[7] is *less* reactive than benzaldehyde in the Eu-catalyzed process (eq 1). More significantly, the Eu catalyst shows the remarkable preference for *o*-methoxybenz-

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