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Parallel Synthesis of Alkyl Tetrazole Derivatives Using Solid Support Chemistry

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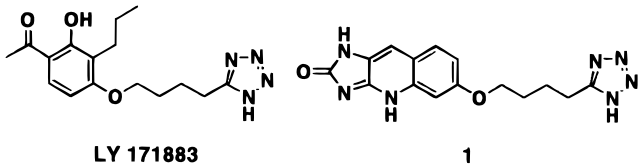
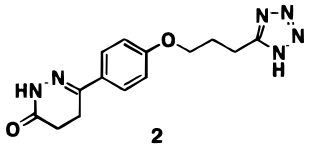
The synthesis of several ω-chloroalkyl tetrazoles and their subsequent attachment to a solid support is described. Using an in situ Finkelstein reaction, a variety of nucleophiles were alkylated and then cleaved from the resin to give pure alkyl tetrazole derivatives. A sample library of 5 × 6 demonstrates the general utility of this sequence.

The tetrazole group is a widely known and utilized bioisostere[1] for a carboxylate moiety. A C-alkylated tetrazole fragment has been incorporated into numerous biologically active compounds such as leukotriene antagonists (e.g., LY 171883),[2−5] inhibitors of cAMP phosphodiesterase (**1**),[6] antithrombotics (e.g., **2**),[7] and peroxisome proliferators.[8] Generally, these types of molecules are prepared through the alkylation of an appropriate nucleophile with a bromoalkyl nitrile followed by conversion of the cyano group to the corresponding tetrazole by employing either NaN_3 or Bu_3SnN_3.



LY 171883

1



2

As part of a structure−activity relationship study, we required a procedure to rapidly prepare and purify several analogues containing the alkyl tetrazole group. Preferably, such a method would be both efficient and convergent. The desired compounds fell into the general class shown in Figure 1, where the tetrazole would be attached to a hydrophobic moiety through an alkyl linking group. We wished to modulate both the linking group and the hydrophobic region by preparing a variety of tetrazole derivatives (**3**) and reacting them with different carbon and heteroatom centered nucleophiles (route A). We planned to protect the acidic N−H of an ω-haloalkyl tetrazole through attachment to a solid support. Subsequent cleavage from the resin would allow for the rapid parallel synthesis of pure desired alkyl tetrazole derivatives. The successful execution of this methodology will be discussed in this article.

The overall strategy (route A) contrasts to the existing routes to compounds such as LY 171883 where the tetrazole heterocycle is formed from the corresponding nitrile as the last step in the synthetic sequence (Figure 1; route B). In planning for the sequence outlined above, we found that the most electrophilic haloalkyl tetrazoles (iodo and bromo) are not known in the literature. Presumably during conversion of the precursor nitrile to the tetrazole, reactive alkyl halides would be converted to the corresponding alkyl azide. However, the smooth conversion of the less reactive chloroalkyl nitriles to chloroalkyl tetrazoles has been reported[9−11] by employing a mixture of $AlCl_3$ and NaN_3 in refluxing THF. Thus, we investigated the suitability of ω-chloroalkyl tetrazoles as alkylating agents and precursors for parallel synthesis. Using the protocol described above, we readily prepared five ω-chloroalkyl tetrazoles with a variety of alkyl linkers (see Table 1).

Before a strategy for attaching the tetrazoles to a solid support was considered, the alkylation of *p*-bromophenol was studied in solution to optimize reaction conditions. An ω-chloroalkyl tetrazole was first protected using trityl chloride to give a simple model system. No alkylation of *p*-bromophenol was observed upon heating with K_2CO_3. However, alkylation proceeded readily after an in situ Finkelstein reaction which converted the relatively unreactive chloroalkyl to the iodo derivative. Various solvents for the in situ Finkelstein reaction were studied including acetone, methyl ethyl ketone, acetonitrile, DMSO, and *N*-methylpyrrolidinone (NMP). We also compared NaI to KI and the effect of various temperatures (20, 40, and 60 °C) on the rate of reaction. From these studies, we found that the best conditions for the Finkelstein reaction were KI (1.5 equiv) in NMP at 60 °C. To complete the alkylation, K_2CO_3 (2 equiv) was added. Both the Finkelstein transhalogenation and the alkylation reactions occurred in one pot.

Attention was then turned to development of the solid-phase reaction. While attaching tetrazoles to a solid support has not been widely studied, we were encouraged by an

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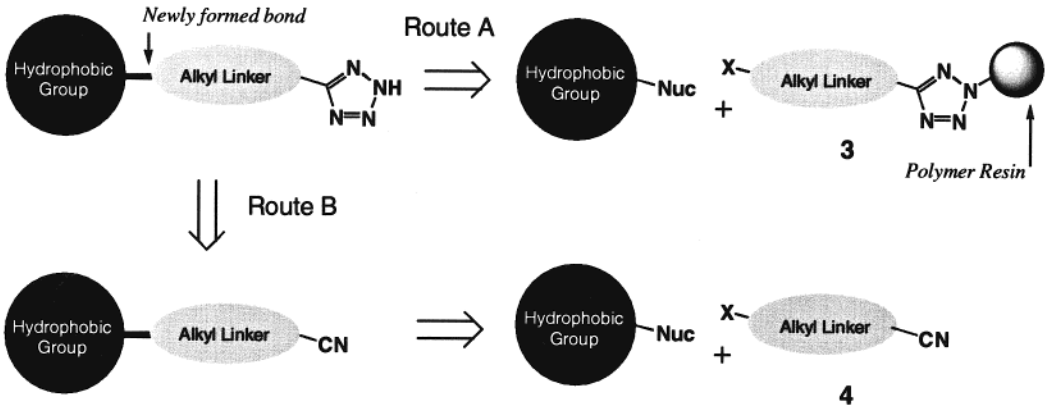
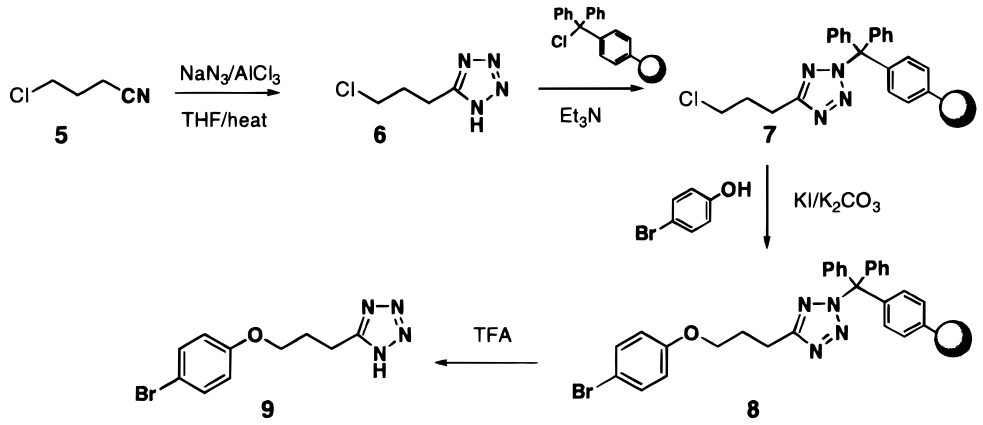


Figure 1.

Scheme 1



isolated literature example[12] in which a THP group was used as a linker to the Merrifield resin. We desired to develop an alternate procedure. In parallel with the model studies, a trityl resin was used for the chemistry on solid phase. Thus, commercially available trityl chloride resin (Novabiochem) was separately attached to each of the five ω-chloroalkyl tetrazoles. The millimoles of tetrazole per gram of resin were determined from weight gain (see Experimental Section). The resins were further characterized by solid-phase ^{13}C NMR.[13]

Having developed a procedure for attaching the alkyl tetrazoles to the solid support with good conversion, the model was extended further using *p*-bromophenol as a nucleophile (Scheme 1). Thus, the halide **6** was readily attached to the trityl resin, and *p*-bromophenol was subsequently alkylated to yield the phenolic ether **8**. Release from the resin was achieved by treating **8** with 5% TFA in CH_2Cl_2 to yield the desired product **9**. Compound **9** was shown to be pure by ^{1}H NMR and other analytical methods.

The reactions shown in Scheme 1 were translated to a 5 × 6 array using ω-chloro tetrazoles **6, 10, 11, 12,** and **13** and the nucleophiles **A, B, C, D, E,** and **F** that featured oxygen-, nitrogen-, sulfur-, and carbon-based reactive centers (Table 1). The products were cleaved from the support using 5% TFA/CH_2Cl_2 (room temperature/18 h). In the grid reported, the average yield was 71% with an average purity of >90%.

Thus a variety of different bond constructions (N−C, O−C, C−C, or S−C) are possible by simply changing the nature of the nucleophile in this reaction. Alkylation occurs readily on phenols, thiophenols, tetrazoles, phthalimides, and keto esters. All reactions were run exactly as detailed in the model reaction procedure in the Experimental Section. Although the experimental details are not reported in this paper, we additionally prepared 5-(2-chloroethyl)-1*H*-tetrazole and attached it to the solid support. Attempted alkylations using 5-(2-chloroethyl)-1*H*-tetrazole on the support were unsuccessful due to elimination to form the vinyl tetrazole, as determined by mass spectroscopy.

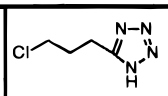
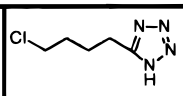
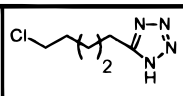
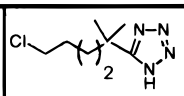
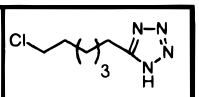
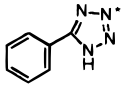
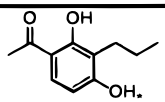
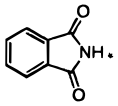
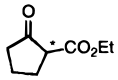
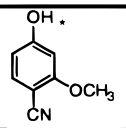
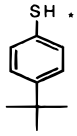
In summary, we have developed methodology to prepare ω-chloroalkyl tetrazoles and to attach them to a trityl chloride resin. We have optimized reaction conditions for an in situ Finkelstein reaction followed by an alkylation of several nucleophiles. This parallel synthesis methodology should permit the rapid preparation of a variety of pure alkyl tetrazole derivatives.

Experimental Section

The preparation of 5-(3-chloropropyl)-1*H*-tetrazole (**6**) and its attachment to a solid support is representative of the general experimental procedure.

5-(3-Chloropropyl)-1*H*-tetrazole (6). Under nitrogen, a mechanically stirred mixture of NaN_3 (50.7 g, 780 mmol) in THF (400 mL) was cooled to 0 °C, and solid $AlCl_3$ (23.5 g, 177 mmol) was added in portions (*caution—exothermic reaction*). After the addition was completed, 4-chlorobutyronitrile (18.4 g, 177 mmol) was added and the reaction was heated at reflux for 18 h. After cooling, the reaction was quenched with 5 N HCl (500 mL). *Due caution should be*

Table 1[a]

	 6	 10	 11	 12	 13
 A	6A 100%	10A 63%	11A 35%	12A 100%	13A 50%
 B	6B 57%	10B 34%	11B 24%	12B 64%	13B 40%
 C	6C 66%	10C 77%	11C 39%	12C 100%	13C 63%
 D	6D 100%	10D 68%	11D 61%	12D 100%	13D 81%
 E	6E 100%	10E 92%	11E 56%	12E 100%	13E 76%
 F	6F 100%	10F 74%	11F 66%	12F 88%	13F 54%

[a] Asterisk (*) indicates point of attachment.

exercised. Toxic HN_3 is formed. Wastes containing azide should be disposed of properly. The use of aqueous ceric ammonium nitrate as described by G. Lunn and E. B. Sansone, Destruction of Hazardous Chemicals in the Laboratory, 43−45, (Wiley Interscience) 1990, was employed. The product was extracted into EtOAc (2 × 300 mL), dried ($MgSO_4$), and concentrated. The residue was azeotroped with toluene and then triturated with hexane. The product solidified to give 17.9 g (69%), which could be recrystallized from hexane/EtOAc: mp 42−44 °C; ^{1}H NMR (DMSO-d_6) δ 2.16 (m, 2 H), 3.03 (t, 2 H), 3.30 (br s, 1 H), 3.73 (t, 2 H); MS (MH) *m*/*z* 147. Anal. Calcd for $C_4H_7ClN_4$: C, 32.78; H, 4.81; N, 38.22. Found: C, 32.52; H, 4.58; N, 37.94.

5-(4-Chlorobutyl)-1*H*-tetrazole (10). Recrystallized from 1,2-dichloroethane, 43%: mp 56−58 °C; ^{1}H NMR ($CDCl_3$) δ 1.88 (m, 2 H), 2.05 (m, 2 H), 3.17 (t, 2 H), 3.55 (t, 2 H); MS (MH) *m*/*z* 161. Anal. Calcd for $C_5H_9ClN_4$: C, 37.39; H, 5.65; N, 34.88. Found: C, 37.10; H, 5.57; N, 35.02.

5-(5-Chloropentyl)-1*H*-tetrazole (11). Recrystallized from 1,2-dichloroethane/hexane, 47%: mp 52−56 °C; ^{1}H NMR (DMSO-d_6) δ 1.40 (m, 2 H), 1.72 (m, 4 H), 2.88 (t, 2 H), 3.60 (m, 2 H); MS (MH) *m*/*z* 175. Anal. Calcd for $C_6H_{11}ClN_4$: C, 41.27; H, 6.35; N, 32.08. Found: C, 41.55; H, 6.30; N, 32.11.

5-(6-Chloro-2,2-dimethylhexyl)-1*H*-tetrazole (12). (6-Chloro-2,2-dimethylhexanenitrile is not commercially available but was readily prepared from available 6-bromo-2,2-dimethylhexanenitrile using 4 equiv $CaCl_2$ in DMF at 100 °C for 2 h).[15] Recrystallized from 1,2-dichloroethane, 33%: mp 119−121 °C; ^{1}H NMR (DMSO-d_6) δ 1.15 (m, 2 H), 1.34 (s, 6 H), 1.64 (m, 6 H), 3.32 (br s, 1 H), 3.57 (t, 3 H); MS (MH) *m*/*z* 203. Anal. Calcd for $C_8H_{15}ClN_4$: C, 47.41; H, 7.46; N, 27.64. Found: C, 47.62; H, 6.81; N, 27.52.

5-(6-Chlorohexyl)-1*H*-tetrazole (13). Obtained in 71% yield as a light tan oil: ^{1}H NMR ($CDCl_3$) δ 1.26 (m, 4 H), 2.55 (m, 2 H), 2.72 (m, 2 H), 2.91 (t, 2 H), 3.25 (t, 2 H); MS (MH) *m*/*z* 189. HRMS. Calcd for $C_7H_{14}ClN_4$: 189.0907. Found: 189.0900.

5-(3-Chloropropyl)-1*H*-tetrazole (6) on Trityl Resin (7). A mixture of trityl chloride resin (3.0 g, 5 mmol, Novabiochem, 1.66 mmol/g, batch #01-64-0074) was mixed with 5-(3-chloropropyl)-1*H*-tetrazole (2.2 g, 15 mmol), DMF (15 mL), and Et_3N. The slurry was gently shaken at room temperature for 60 h. The resin was collected by vacuum filtration and washed successively with DMF, water, DMF, THF, and Et_2O. The resin was dried in a vacuum oven without heat to give 4.17 g of solid: ^{13}C NMR ($CDCl_3$) δ 22.81, 30.41, 43.74. The resin contained 1.54 mmol/g of the chloroalkyl tetrazole based on a weight gain of 683 mg (93% of theory).

5-(4-Chlorobutyl)-1*H*-tetrazole (10) on Trityl Resin. ^{13}C NMR ($CDCl_3$) δ 24.64, 25.20, 31.65, 44.36. The resin contained 1.46 mmol/g of the chloroalkyl tetrazole based on weight gain.

5-(5-Chloropentyl)-1*H*-tetrazole (11) on Trityl Resin. ^{13}C NMR ($CDCl_3$) δ 25.13, 26.05, 27.09, 31.96, 44.69. The

resin contained 1.41 mmol/g of the chloroalkyl tetrazole based on weight gain.

5-(6-Chloro-2,2-dimethylhexyl)-1*H*-tetrazole (12) on Trityl Resin. ^{13}C NMR ($CDCl_3$) δ 21.56, 21.86, 25.46, 26.72, 27.05, 32.62, 34.55, 44.52. The resin contained 1.62 mmol/g of the chloroalkyl tetrazole based on weight gain.

5-(6-Chlorohexyl)-1*H*-tetrazole (13) on Trityl Resin. ^{13}C NMR ($CDCl_3$) δ 25.21, 26.26, 27.70, 28.02, 32.27, 44.79. The resin contained 1.28 mmol/g of the chloroalkyl tetrazole based on weight gain.

Model Reaction/General Parallel Synthesis Procedure. Into a 1 dram vial was placed 65 mg (0.1 mmol) of **7**, *p*-bromophenol (0.3 mmol) in 1.0 mL of NMP, 25 mg (0.15 mmol) of KI, and 28 mg (0.2 mmol) of anhydrous K_2CO_3 (Aldrich). The sealed vial was then placed in a 60 °C heating block and shaken for 48−60 h. The solids were collected by filtration and washed with NMP (1×), CH_2Cl_2 (3×), THF (1×), 50% aqueous THF (2×), THF (2×), and Et_2O (2×). Product **9** was cleaved from the support using 5% TFA/CH_2Cl_2 (room temperature/18 h). After concentration and vacuum-drying, 5-(3-(4-bromophenoxy)-propyl)-1*H*-tetrazole (**9**) was obtained in 78% yield: ^{1}H NMR ($CDCl_3$) δ 2.22 (m, 2 H), 3.18 (t, 2 H), 3.96 (t, 2 H), 6.64 (d, 2 H), 7.30 (d, 2 H); MS (MH) *m*/*z* 284.

Sample Library (5 × 6). Each product was characterized by ion spray MS, TLC (1/1 EtOAc/hexane with 1% HOAc), HPLC,[14] and ^{1}H NMR.

6A: quantitative yield; ^{1}H NMR ($CDCl_3$) δ 1.60 (t, 2 H), 3.10 (t, 2 H), 4.74 (t, 2 H), 7.02 (br s, 1 H), 7.45 (m, 3 H), 8.02 (m, 2 H); MS (MH) *m*/*z* 257; 86% purity by HPLC.

10A: 63% yield; ^{1}H NMR ($CDCl_3$) δ 1.92 (t, 2 H), 2.14 (t, 2 H), 3.08 (t, 2H), 4.68 (t, 2 H), 5.68 (br s, 1 H), 7.44 (m, 3 H), 8.02 (m, 2 H); MS (MH) *m*/*z* 271; 87% purity by HPLC.

11A: 35% yield; MS (MH) *m*/*z* 285; 89% purity by HPLC.

12A: quantitative yield; ^{1}H NMR ($CDCl_3$) δ 1.22 (m, 2 H), 1.47 (s, 6 H), 1.84 (m, 2 H), 2.01 (m, 2 H), 4.64 (t, 2 H), 4.90 (br s, 1 H), 7.43 (m, 3 H), 8.08 (m, 2 H); MS (MH) *m*/*z* 313; 86% purity by HPLC.

13A: 50% yield; ^{1}H NMR ($CDCl_3$) δ 1.43 (m, 4 H), 1.85 (t, 2 H), 2.08 (t, 3 H), 3.02 (t, 2 H), 4.63 (t, 2 H), 7.47 (m, 3 H), 8.10 (m, 2 H); MS (MH) *m*/*z* 299; 83% purity by HPLC.

6B: 57% yield; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.52 (m, 2 H), 2.38 (m, 2 H), 2.53 (s, 3 H), 2.60 (m, 2 H), 3.12 (t, 2 H), 4.14 (t, 2 H), 6.38 (d, 1 H), 7.56 (d, 1 H), 12.72 (s, 1 H); MS (MH) *m*/*z* 305; 97% purity by HPLC.

10B: 34% yield; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H), 1.43 (m, 2 H), 1.91 (m, 2 H), 2.03 (m, 2 H), 2.55 (s, 3 H), 2.58 (m, 2 H), 3.10 (t, 2 H), 4.06 (t, 2 H), 4.22 (br s, 1 H), 6.38 (d, 1 H), 7.55 (d, 1 H), 12.68 (s, 1 H); MS (MH) *m*/*z* 319; 100% purity by HPLC.

11B: 24% yield; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.47 (m, 2 H), 1.59 (m, 2 H), 1.89 (m, 4 H), 2.55 (s, 3 H), 2.59 (m, 2 H), 3.04 (t, 2 H), 3.98 (t, 2 H), 6.37 (d, 1 H), 7.57 (d, 1 H), 12.74 (s, 1 H); MS (MH) *m*/*z* 333; 100% purity by HPLC.

12B: 64% yield; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3 H), 1.42 (m, 2 H), 1.48 (s, 6 H), 1.76 (m, 2 H), 1.87 (m, 2 H), 2.55 (s, 3 H), 2.55 (m, 2 H), 3.42 (br m, 3 H), 3.97 (t, 2 H), 6.36 (d, 1 H), 7.54 (d, 1 H), 12.68 (s, 1 H); MS (MH) *m*/*z* 361; 100% purity by HPLC.

13B: 40% yield; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3 H), 1.49 (m, 6 H), 1.84 (m, 4 H), 2.52 (s, 3 H), 2.56 (m, 2 H), 3.08 (t, 2 H), 3.98 (t, 2 H), 6.38 (d, 1 H), 7.57 (d, 1 H), 12.72 (s, 1 H); MS (MH) *m*/*z* 347; 100% purity by HPLC.

6C: 66% yield; ^{1}H NMR (CD_3OD) δ 2.21 (m, 2 H), 3.03 (t, 2 H), 3.78 (t, 2 H), 7.82 (m, 4 H); MS (MH) *m*/*z* 258; 91% purity by HPLC.

10C: 77% yield; ^{1}H NMR ($CDCl_3$) δ 1.77 (m, 4 H), 3.07 (t, 2 H), 3.70 (t, 2 H), 5.05 (br s, 1 H), 7.65 (m, 2 H), 7.78 (m, 2 H); MS (MH) *m*/*z* 272; 97% purity by HPLC.

11C: 39% yield; ^{1}H NMR ($CDCl_3$) δ 1.37 (m, 2 H), 1.76 (m, 2 H), 1.97 (m, 2 H), 3.06 (t, 2 H), 3.74 (t, 2 H), 5.75 (br s, 1 H), 7.75 (m, 2 H), 7.84 (m, 2 H); MS (MH) *m*/*z* 286; 73% purity by HPLC.

12C: quantitative yield; ^{1}H NMR ($CDCl_3$) δ 1.14 (m, 2 H), 1.47 (s, 6 H), 1.70 (m, 2 H), 1.90 (m, 2 H), 3.75 (t, 2 H), 7.71 (m, 2 H). 7.85 (m, 2 H); MS (MH) *m*/*z* 314; 95% purity by HPLC.

13C: 63% yield; ^{1}H NMR ($CDCl_3$) δ 1.39 (m, 4 H), 1.66 (m, 2 H), 1.82 (m, 2 H), 3.04 (t, 2 H), 3.65 (t, 2 H), 5.41 (br s, 1 H), 7.70 (m, 2 H), 7.83 (m, 2 H); MS (MH) *m*/*z* 300; 95% purity by HPLC.

6D: quantitative yield; ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3 H), 1.88 (m, 2 H), 1.94 (m, 4 H), 2.42 (m, 4 H), 3.09 (t, 2 H), 4.20 (q, 2 H), 6.09 (br s, 1 H); MS (MH) *m*/*z* 267; 100% purity by HPLC.

10D: 68% yield; ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3 H), 1.33 (m, 2 H), 1.78 (m, 2 H), 1.97 (m, 4 H), 2.44 (m, 4 H), 3.08 (m, 2 H), 4.18 (q, 2 H); MS (MH) *m*/*z* 281; 100% purity by HPLC.

11D: 61% yield; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3 H), 1.37 (m, 2 H), 1.90 (m, 6 H), 2.31 (m, 2 H), 2.40 (m, 2 H), 2.50 (m, 2 H), 3.02 (t, 2 H), 4.17 (q, 2 H); MS (MH) *m*/*z* 295; 100% purity by HPLC.

12D: quantitative yield; ^{1}H NMR ($CDCl_3$) δ 1.19 (m, 2 H), 1.23 (t, 3 H), 1.45 (s, 6 H), 1.48 (m, 2 H), 1.84 (m, 8 H), 2.33 (m, 2 H), 4.14 (q, 2 H); MS (MH) *m*/*z* 323; 100% purity by HPLC.

13D: 81% yield; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3 H), 1.37 (m, 4 H), 1.79 (m, 4 H), 1.92 (m, 4 H), 2.38 (m, 4 H), 3.05 (t, 2 H), 4.13 (q, 2 H), 6.25 (br s, 1 H); MS (MH) *m*/*z* 309; 100% purity by HPLC.

6E: quantitative yield; ^{1}H NMR ($CDCl_3$) δ 2.30 (m, 2 H), 3.36 (t, 2 H), 4.15 (s, 3 H), 4.18 (t, 2 H), 6.97 (d, 1 H), 7.20 (d, 1 H), 7.36 (dd, 1 H); MS (MH) *m*/*z* 260; 89% purity by HPLC.

10E: 92% yield; ^{1}H NMR ($CDCl_3$) δ 1.78 (m, 2 H), 2.09 (m, 2 H), 3.23 (t, 2 H), 4.06 (s, 3 H), 4.19 (t, 2 H), 5.83 (br s, 1 H), 6.95 (d, 1 H), 7.17 (d, 1 H), 7.35 (dd, 1 H); MS (MH) *m*/*z* 274; 93% purity by HPLC.

11E: 56% yield; ^{1}H NMR ($CDCl_3$) δ 1.56 (m, 2 H), 1.88 (m, 4 H), 3.10 (t, 2 H), 3.76 (br s, 1 H), 3.91 (s, 3 H), 4.05 (t, 2 H), 6.88 (d, 1 H), 7.12 (d, 1 H), 7.25 (d, 1 H); MS (MH) *m*/*z* 288; 89% purity by HPLC.

12E: quantitative yield; ^{1}H NMR ($CDCl_3$) δ 1.44 (m, 2 H), 1.50 (s, 6 H), 1.74 (m, 2 H), 1.91 (m, 2 H), 3.90 (s, 3

H), 4.04 (t, 2 H), 6.88 (d, 1 H), 7.14 (d, 1 H), 7.27 (dd, 1 H), 8.23 (br s, 1 H); MS (MH) *m*/*z* 316; 86% purity by HPLC.

13E: 76% yield; ^{1}H NMR ($CDCl_3$) δ 1.48 (m, 4 H), 1.86 (m, 4 H), 3.05 (t, 2 H), 3.88 (s, 3 H), 4.07 (t, 2 H), 6.45 (br s, 1 H), 6.88 (d, 1 H), 7.09 (d, 1 H), 7.27 (dd, 1 H); MS (MH) *m*/*z* 302; 73% purity by HPLC.

6F: 74% yield; ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9 H), 2.15 (m, 2 H), 2.94 (t, 2 H), 3.17 (t, 2 H), 7.23 (m, 4 H); MS (MH) *m*/*z* 277; 100% purity by HPLC.

10F: 33% yield; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9 H), 1.74 (m, 2 H), 1.98 (m, 2 H), 2.92 (t, 2 H), 3.03 (t, 2 H), 7.25 (m, 4 H); MS (MH) *m*/*z* 291; 100% purity by HPLC.

11F: 66% yield; MS (MH) *m*/*z* 305; 100% purity by HPLC.

12F: 88% yield; ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 9 H), 1.28 (m, 2 H), 1.46 (s, 6 H), 1.58 (m, 2 H), 1.76 (m, 2 H), 2.82 (t, 2 H), 6.58 (br s, 1 H), 7.22 (m, 4 H); MS (MH) *m*/*z* 333; 92% purity by HPLC.

13F: 54% yield; ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 9 H), 1.31 (m, 2 H), 1.43 (m, 2 H), 1.62 (m, 2 H), 1.85 (m, 2 H), 2.85 (t, 2 H), 3.04 (t, 2 H), 7.26 (m, 4 H); MS (MH) *m*/*z* 319; 100% purity by HPLC.

References and Notes

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(13) ^{13}C NMR spectra were obtained by adding $CDCl_3$ to 100 mg of resin, allowing it to swell, and then collecting data for 30 000 transients on a Bruker AC250 NMR over 5 h (Larry Spangle, Lilly P. Chem. Dept).
(14) HPLC was performed using a Waters symmetry C-18 column (4.6 × 50 mm, 3.5 μm particle size (#WAT200625)) using a gradient starting with 90% A(0.1% TFA/water)/10% B (0.1% TFA/CH_3CN) to 10% A/ 90% B over 7.5 min. Both 218λ and 254λ were monitored. Purity was determined at 218λ since absorption was much stronger at this wavelength.
(15) Nissan Chemical Industries, Ltd. Japanese patent 57197231 (1983). CAN 98:178727.

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