JOC Notes

Iron-Catalyzed Cross-Coupling Reactions. A Scalable Synthesis of the Immunosuppressive Agent FTY720

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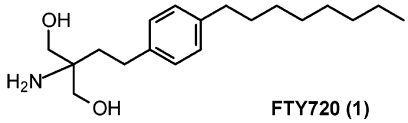
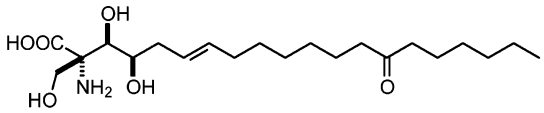
Abstract: A chemo- and regioselective cross-coupling reaction of the functionalized aryl triflate **5** with octylmagnesium bromide catalyzed by cheap, nontoxic, and environmentally benign $Fe(acac)_3$ sets the basis for a practical and scaleable synthesis of the octylbenzene derivative **6**, which serves as a key building block for the preparation of FTY720 (**1**). This 2-amino-1,3-propanediol derivative shows highly promising immunosuppressive properties and is currently in human clinical phase III trials.

Modern cross-coupling reactions are a domain of organopalladium and -nickel chemistry because catalysts based on these metals show an impressively wide scope and an excellent compatibility with many functional groups.[1,2] This exceptional application profile is apparent from a countless number of successful applications in academic as well as industrial settings and usually overcompensates the disadvantages resulting from the high costs of the palladium precursors, the concerns about the toxicity of nickel salts, the need for ancillary ligands, and the extended reaction times that are necessary in many cases.[1,2]

Encouraged by early reports of Kochi et al.,[3] our group recently started to explore the potential of iron catalysts as substitutes for palladium and nickel in certain cases. Gratifyingly, it was found that simple iron salts such as $Fe(acac)_3$ do not only allow activation of vinyl halides as originally disclosed[3,4] but also enable cross-coupling reactions of Grignard reagents with electron-deficient aryl chlorides and tosylates,[5−7] aryl triflates,[5,6] alkenyl triflates,[8] carboxylic acid chlorides,[8,9] and propargyl epoxides.[10,11] The reactions are particularly efficient for alkylmagnesium halides as the donors, whereas arylmagnesium halides are prone to undergo oxidative homodimerization as a parasitic side reaction.[5,12] Despite this present limitation, iron-catalyzed cross-couplings are distinguished by exceptionally fast reaction rates even at low temperatures and by the fact that they can be performed under "ligand-free" conditions using cheap, stable, nontoxic, and environmentally benign iron salts as substitutes for the expensive and/or physiologically suspicious noble metal catalysts usually employed. These advantages are substantiated by the scaleable synthesis of the potent immunosuppressive agent FTY720 (**1**)[13] outlined below.



FTY720 (1)



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FTY720, a simple mimic of the immunomodulating sphingosine myriocin (**2**),[14] appears to be unique among the immunosuppressive agents presently known for its ability to prevent lymphocytes from attacking trans-

(1) (a) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (b) *Cross-Coupling Reactions: A Practical Guide*; Miyaura, N., Ed.; Top. Curr. Chem.; Springer: Berlin, 2002; Vol. 219. (c) Knight, D. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3; pp 481−520. (d) *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*; Li, J. J., Gribble, G. W., Eds.; Elsevier: Oxford, 2000. (e) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002. (f) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: New York, 1995.

(2) Selected reviews: (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1. (c) Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669. (d) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (e) Beller, M.; Zapf, A.; Mägerlein, W. *Chem. Eng. Technol.* **2001**, *24*, 575. (f) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544. (g) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176 and literature cited therein.

(3) (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487. (b) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303. (c) Neumann, S. M.; Kochi, J. K. *J. Org. Chem.* **1975**, *40*, 599. (d) Smith, R. S.; Kochi, J. K. *J. Org. Chem.* **1976**, *41*, 502. (e) Kochi, J. K. *Acc. Chem. Res.* **1974**, *7*, 351.

(4) (a) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199. (b) Cahiez, G.; Marquais, S. *Pure Appl. Chem.* **1996**, *68*, 53. (c) Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 1901. (d) Molander, G. A.; Rahn, B. J.; Shubert, D. C.; Bonde, S. E. *Tetrahedron Lett.* **1983**, *24*, 5449. (e) Fürstner, A.; Brunner, H. *Tetrahedron Lett.* **1996**, *37*, 7009. (f) Fakhfakh, M. A.; Franck, X.; Hocquemiller, R.; Figadère, B. *J. Organomet. Chem.* **2001**, *624*, 131. (g) Shinokubo, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, 2081.

(5) (a) Fürstner, A.; Leitner, A., Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (b) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 609.

(6) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 308.

(7) (a) Quintin, J.; Franck, X.; Hocquemiller, R.; Figadère, B. *Tetrahedron Lett.* **2002**, *43*, 3547. (b) Hocek, M.; Dvořáková, H. *J. Org. Chem.* **2003**, *68*, 5773.

(8) (a) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943. (b) Fürstner, A.; De Souza, D.; Parra-Rapado, L.; Jensen, J. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 5358.

(9) (a) Percival, W. C.; Wagner, R. B.; Cook, N. C. *J. Am. Chem. Soc.* **1953**, *75*, 3731. (b) Fiandanese, V.; Marchese, G.; Martina, V.; Ronzini, L. *Tetrahedron Lett.* **1984**, *25*, 4805. (c) Dell'Anna, M. M.; Mastrorilli, P.; Nobile, C. F.; Marchese, G.; Taurino, M. R. *J. Mol. Catal. A: Chem.* **2000**, *161*, 239. (d) Reddy, C. K.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1700. (e) Ritter, K.; Hanack, M. *Tetrahedron Lett.* **1985**, *26*, 1285. (f) Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Ronzini, L. *Tetrahedron Lett.* **1985**, *26*, 3595. (g) Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Ronzini, L. *Tetrahedron Lett.* **1987**, *28*, 2053.

(10) Fürstner, A.; Mendez, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5355.

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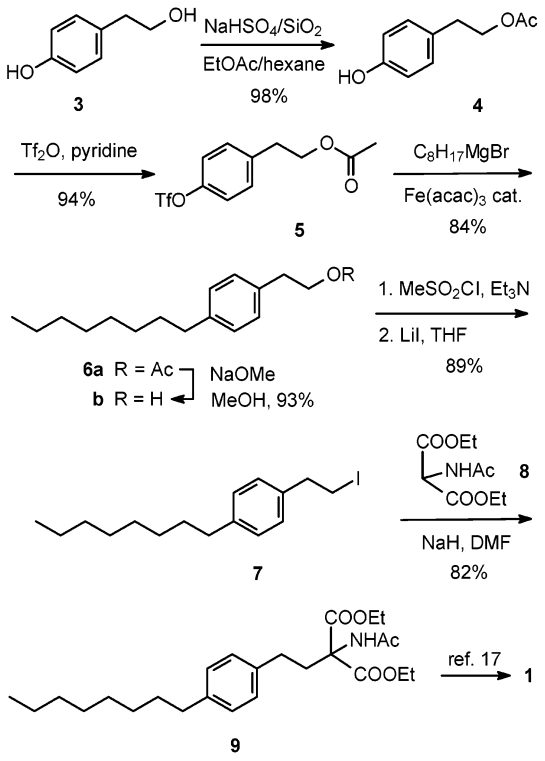
planted organs without changing the body's ability to respond to other immune challenges.[15] Importantly, the oral availability, efficacy, and safety of FTY720 have been proven in numerous investigations, especially when administered in combination with cyclosporine.[15] Due to these favorable properties, human trials have recently progressed into phase III clinical studies.[16]

The published syntheses of FTY720 start from building blocks as simple as octylbenzene, 4-octylbenzaldehyde, or 2-(4-octylphenyl)ethanol.[13,17,18] Since compounds of this type should be readily available by iron-catalyzed cross-coupling, we explored whether this methodology provides a practical and scaleable entry into this series of immunomodulating agents[19] and meets the selectivity issues associated with the use of highly reactive Grignard reagents as the nucleophiles.

SCHEME 1



Commercial 2-(4-hydroxyphenyl)ethanol **3** was chosen as the starting material which was selectively protected as monoacetate **4** in almost quantitative yield on a multigram scale upon treatment with ethyl acetate in the presence of immobilized $NaHSO_4/SiO_2$ as a solid promoter (Scheme 1).[20] Because the phenolic −OH does not participate in this step, compound **4** can be directly converted into triflate **5** under standard conditions. Reaction of this product with octylmagnesium bromide in the presence of catalytic amounts of $Fe(acac)_3$ proceeds smoothly, delivering the expected cross-coupling product **6a** in high yield on a multigram scale. This reaction shows once again that the uncatalyzed attack of a Grignard reagent onto the ester group does not compete with the iron-catalyzed activation of the C−OTf bond.[21] Cleavage of the acetate followed by reaction of the resulting alcohol **6b** with methanesulfonyl chloride and LiI provided iodide **7**. Although the alkylation of this compound with commercial diethyl acetamidomalonate **8** had previously been described as a key step en route to **1**,[13,17a] we encountered difficulties in trying to reproduce the published procedure. In our hands, an almost quantitative elimination of HI with formation of the corresponding styrene derivative was observed when compound **7** was exposed to the sodium salt of **8** in EtOH.[22] Gratifyingly though, a simple switch to DMF as the reaction medium allowed us to perform the envisaged alkylation in 82% isolated yield. The resulting product **9** can be converted into FTY720 in three simple steps according to the literature[13,17,18] and therefore completes a highly efficient, practical, and flexible synthesis of this promising drug candidate.

(11) For further reports on iron-catalyzed reactions with different substrates, see: (a) Fabre, J.-L.; Julia, M.; Verpeaux, J.-N. *Tetrahedron Lett.* **1982**, *23*, 2469. (b) Alvarez, E.; Cuvigny, T.; Hervé du Penhoat, C.; Julia, M. *Tetrahedron* **1988**, *44*, 111. (c) Alvarez, E.; Cuvigny, T.; Hervé du Penhoat, C.; Julia, M. *Tetrahedron* **1988**, *44*, 119. (d) Brinker, U. H.; König, L. *Chem. Ber.* **1983**, *116*, 882. (e) Walborsky, H. M.; Banks, R. B. *J. Org. Chem.* **1981**, *46*, 5074. (f) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 6017. (g) Hojo, M.; Murakami, Y.; Aihara, H.; Sakuragi, R.; Baba, Y.; Hosomi, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 621. (h) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978. (i) Pasto, D. J.; Hennion, G. F.; Shults, R. H.; Waterhouse, A.; Chou, S.-K. *J. Org. Chem.* **1976**, *41*, 3496. (j) Hashmi, A. S. K.; Szeimies, G. *Chem. Ber.* **1994**, *127*, 1075. (k) Kauffmann, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 386. (l) Hölzer, B.; Hoffmann, R. W. *Chem. Commun.* **2003**, 732. (m) Nishii, Y.; Wakasugi, K.; Tanabe, Y. *Synlett* **1998**, 67.

(12) See, however, the highly efficient iron-catalyzed cross-coupling of arylmagnesium halides with alkyl halides disclosed recently: (a) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686−3687. (b) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297.

(13) Adachi, K.; Kohara, T.; Nakao, N.; Arita, M.; Chiba, K.; Mishina, T.; Sasaki, S.; Fujita, T. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 853.

(14) Fujita, T.; Inoue, K.; Yamamoto, S.; Ikumoto, T.; Sasaki, S.; Toyama, R.; Chiba, K.; Hoshino, Y.; Okumoto, T. *J. Antibiot.* **1994**, *47*, 208.

(15) See the following for leading references: (a) Mandala, S.; Hajdu, R.; Bergstrom, J.; Quackenbush, E.; Xie, J.; Milligan, J.; Thornton, R.; Shei, G.-J.; Card, D.; Keohane, C.; Rosenbach, M.; Hale, J.; Lynch, C. L.; Rupprecht, K.; Parsons, W.; Rosen, H. *Science* **2002**, *296*, 346. (b) Brinkmann, V.; Pinschewer, D. D.; Feng, L.; Chen, S. *Transplantation* **2001**, *72*, 764. (c) Brinkmann, V.; Davis, M. D.; Heise, C. E.; Albert, R.; Cottens, S.; Hof, R.; Bruns, C.; Prieschl, E.; Baumruker, T.; Hiestand, P.; Foster, C. A.; Zollinger, M.; Lynch, K. R. *J. Biol. Chem.* **2002**, *277*, 21453. (d) Chiba, K.; Yanagawa, Y.; Masubuchi, Y.; Kataoka, H.; Kawaguchi, T.; Ohtsuki, M.; Hoshino, Y. *J. Immunol.* **1998**, *160*, 5037. (e) Brinkmann, V.; Lynch, K. R. *Curr. Opin. Immunol.* **2002**, *14*, 569. (f) Schuurman, H.-J.; Menninger, K.; Audet, M.; Kunkler, A.; Maurer, C.; Vedrine, C.; Bernhard, M.; Gaschen, L.; Brinkmann, V.; Quesniaux, V. *Transplantation* **2002**, *74*, 951. (g) Nikolova, Z.; Hof, A.; Baumlin, Y.; Hof, R. P. *Transplant Immunol.* **2001**, *8*, 267 and literature cited therein.

(16) See: http://www.transplantationschweiz.ch/d/fty720/.

(17) (a) Kiuchi, M.; Adachi, K.; Kohara, T.; Minoguchi, M.; Hanano, T.; Aoki, Y.; Mishina, T.; Arita, M.; Nakao, N.; Ohtsuki, M.; Hoshino, Y.; Teshima, K.; Chiba, K.; Sasaki, S.; Fujita, T. *J. Med. Chem.* **2000**, *43*, 2946. (b) Durand, P.; Peralba, P.; Sierra, F.; Renaut, P. *Synthesis* **2000**, 505. (c) Kalita, B.; Barua, N. C.; Bezbarua, M.; Bez, G. *Synlett* **2001**, 1411. (d) See also: Hinterding, K.; Cottens, S.; Albert, R.; Zecri, F.; Buehlmayer, P.; Spanka, C.; Brinkmann, V.; Nussbaumer, P.; Ettmayer, P.; Hoegenauer, K.; Gray, N.; Pan, S. *Synthesis* **2003**, 1667.

(18) (a) EP 0627406 (Yoshitomi Pharmaceutical), 1994-12-07. (b) JP11310556 (Yoshitomi Pharmaceutical), 1999-11-09. (c) PCT/CN00/00046 (Hangzhou Zhongmei Huadong Pharmaceutical Co. Ltd.), 2000-11-03.

(19) For studies on other immunomodulators from this laboratory, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582. (b) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305. (c) Fürstner, A.; Grabowski, J.; Lehmann, C. W. *J. Org. Chem.* **1999**, *64*, 8275. (d) Fürstner, A.; Krause, H. *J. Org. Chem.* **1999**, *64*, 8281. (e) Fürstner, A.; Grabowski, J.; Lehmann, C. W.; Kataoka, T.; Nagai, K. *ChemBioChem* **2001**, *2*, 60. (f) Fürstner, A.; Grabowski, E. J. *ChemBioChem* **2001**, *2*, 706.

(20) Breton, G. W. *J. Org. Chem.* **1997**, *62*, 8952.

(21) Alcohol **6b** (ca. 20%) accompanying product **6a** originates from the work up and is not detected in the crude mixture, cf. Experimental Section.

(22) Similar difficulties are mentioned in ref 17b.

Experimental Section

General Methods. All reactions were carried out under Ar. The solvents were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O, DME (Mg−anthracene), CH_2Cl_2 (CaH_2), MeCN, Et_3N, pyridine, NMP, DMF (CaH_2), MeOH (Mg), hexane, and toluene (Na/K). Flash chromatography: Merck silica gel 60 (230−400 mesh). NMR: chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. Melting points are uncorrected. All commercially available compounds were used as received.

Acetic Acid 2-(4-Hydroxyphenyl)ethyl Ester (4). A suspension of $NaHSO_4$ on silica (4 g)[20] and 2-(4-hydroxyphenyl)-ethanol **3** (11.1 g, 80 mmol) in EtOAc (100 mL) and hexane (200 mL) was refluxed for 22 h. After that reaction time, additional $NaHSO_4$ on silica (1 g) was added and reflux was continued for 4 h. For workup, the solid material was filtered off and carefully rinsed with Et_2O (200 mL), the combined filtrates were evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 10:1 → 4:1) to give acetate **4** as a colorless solid (14.2 g, 98%).[20] Mp = 57−58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, J = 8.6, 2H), 6.77 (d, J = 8.6, 2H), 5.56 (s, OH), 4.24 (t, J = 7.1, 2H), 2.86 (t, J = 7.1, 2H), 2.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 154.4, 130.0, 129.6, 115.4, 65.3, 34.1, 21.0. MS m/z (rel intensity): 180 (M^+, <1), 120 (100), 107 (68), 91 (12), 77 (18), 65 (4), 51 (4), 43 (38).

Acetic Acid 2-[4-(Trifluoromethanesulfonyloxy)phenyl]-ethyl Ester (5). A solution of triflic anhydride (26.7 g, 95 mmol) in CH_2Cl_2 (30 mL) was added over a period of 1 h to a solution of phenol **4** (14.2 g, 79 mmol) in CH_2Cl_2 (150 mL) and pyridine (30 g) at 0 °C. After the addition was complete, stirring was continued for 1 h at ambient temperature. For workup, the reaction was quenched with aq satd $NaHCO_3$, the aqueous layer was repeatedly extracted with *tert*-butyl methyl ether, the combined organic layers were dried over Na_2SO_4 and evaporated, and the residue was dried in vacuo (10^{-3} Torr) to give analytically pure triflate **5** as a colorless syrup (23.2 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, J = 8.7, 2H), 7.22 (d, J = 8.7, 2H), 4.28 (t, J = 6.8, 2H), 2.97 (t, J = 6.8, 2H), 2.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 148.3, 138.5, 130.6, 121.6, 118.7, 64.2, 34.3, 20.8. MS m/z (rel intensity): 252 (41), 119 (100), 107 (9), 91 (21), 69 (13), 51 (4). Anal. Calcd for $C_{11}H_{11}F_3O_5S$: C, 42.31; H, 3.55. Found: C, 42.36; H, 3.46.

Acetic Acid 2-(4-Octylphenyl)ethyl Ester (6a). A solution of octylmagnesium bromide (0.63 M in THF, 45 mL) was added over a period of 50 min to a solution of triflate **5** (7.23 g, 23.2 mmol) and $Fe(acac)_3$ (818 mg, 2.32 mmol) in THF (150 mL) and NMP (13.6 mL), causing an immediate color change from red to dark brown/black and a slight increase of the reaction temperature. After the solution was stirred for 30 min, additional octylmagnesium bromide (20 mL), $Fe(acac)_3$ (400 mg, 1.13 mmol), and NMP (4.5 mL) were added, and stirring was continued for another 30 min. The reaction was then quenched with aq HCl (1 M), the aqueous phase was repeatedly extracted with *tert*-butyl methyl ether, the combined organic layers were dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 50:1 → 30:1) to give product **6a** as a colorless syrup (4.08 g, 64%).[17a] A second fraction contains 2-(4-octylphenyl)ethanol **6b** (1.1 g, 20%) formed as a byproduct during the workup. Spectroscopic data of compound **6a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11 (s, 4H), 4.26 (t, J = 7.2, 2H), 2.90 (t, J = 7.6, 2H), 2.60 (t, J = 7.6, 2H), 2.03 (s, 3H), 1.60 (m, 2H), 1.4−1.2 (m, 10H), 0.88 (t, J = 6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 141.1, 134.8, 128.7, 128.5, 65.0, 35.5, 34.6, 31.8, 31.5, 29.4, 29.3, 29.2, 22.6, 20.9, 14.0. MS: m/z (rel intensity): 216 (100), 159 (2), 145 (2), 130 (4), 117 (99), 105 (9), 91 (7), 57 (4), 43 (21).

2-(4-Octylphenyl)ethanol (6b). A solution of acetate **6a** (11.62 g, 42 mmol) and NaOMe (227 mg, 4.2 mmol) in MeOH (300 mL) was stirred for 8 h at ambient temperature. The solvent was evaporated, and the residue was purified by flash chromatography (10:1 → 4:1) to give alcohol **6b** as a colorless syrup (9.15 g, 93%).[17a] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (s, 4H), 3.83 (t, J = 6.5, 2H), 2.83 (t, J = 6.6, 2H), 2.57 (t + br s, J = 7.6, 2H+OH), 1.59 (m, 2H), 1.4−1.2 (m, 10H), 0.88 (t, J = 6.5, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.1, 135.4, 128.9, 128.6, 63.7, 38.7, 35.5, 31.9, 31.5, 29.4, 29.3, 29.2, 22.6, 14.1. MS: m/z (rel intensity) 234 (M^+, 17), 203 (18), 135 (25), 117 (23), 105 (100), 91 (33), 77 (10), 57 (12).

2-(4-Octylphenyl)-1-iodoethane (7). A solution of methanesulfonyl chloride (2.51 g, 22 mmol) in CH_2Cl_2 (20 mL) was added over 10 min to a solution of alcohol **6b** (4.10 g, 17.5 mmol) and Et_3N (2.83 g, 28 mmol) in CH_2Cl_2 (80 mL). After being stirred for 1 h, the reaction was quenched with aq satd $NaHCO_3$, the organic phase was dried (Na_2SO_4) and evaporated, and the crude mesylate was dissolved in THF (120 mL). LiI (7.1 g, 53 mmol) was added, and the resulting mixture was stirred for 4 h at ambient temperature. After evaporation of all volatile components, the residue was suspended in hexane and the suspension was vigorously stirred for 5 min. The solid material was filtered off through a short pad of silica, the filtrate was evaporated, and the residue was dried in vacuo (10^{-3} Torr) to give analytically pure iodide **7** as a colorless oil (5.37 g, 89%).[17a] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14−7.05 (m, 4H), 3.32 (t, J = 7.9, 2H), 3.14 (t, J = 7.9), 2H), 2.56 (t, J = 7.7, 2H), 1.59 (m, 2H), 1.38−1.18 (m, 10H), 0.87 (t, J = 6.9, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.6, 137.9, 128.6, 128.1, 40.1, 35.6, 31.9, 31.4, 29.5, 29.4, 29.3, 22.7, 14.1, 5.8. MS: m/z (rel intensity) 344 (M^+, 7), 245 (8), 217 (100), 119 (50), 105 (7), 91 (10), 57 (5), 43 (5).

Diethyl 2-Acetamido-2-[2-(4-octylphenyl)ethyl]malonate (9). Diethyl 2-acetamidomalonate **8** (1.95 g, 9 mmol) was added in portions to a solution of NaH (215 mg, 9 mmol) in DMF, and the resulting mixture was stirred for 30 min until the evolution of H_2 ceased. Iodide **7** (514 mg, 1.5 mmol) was then introduced, and stirring was continued for 1 h at 50−60 °C (bath temperature). The reaction was quenched with water, the aqueous phase was repeatedly extracted with *tert*-butyl methyl ether, the combined organic layers were dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (hexanes, then hexanes/EtOAc, 1:1) to give product **9** as a colorless solid (534 mg, 82%). Mp = 58−59 °C (51−53 °C).[17a] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10−7.01 (m, 4H), 6.76 (s, 1H), 4.20 (m, 4H), 2.68 (t, J = 8.0, 2H), 2.55 (t, J = 7.7, 2H), 2.45 (t, J = 8.0, 2H), 1 97 (s, 3H), 1.57 (m, 2H), 1.35−1.20 (m, 10H), 1.24 (t, J = 7.2, 6H), 0.88 (t, J = 7.0, 3H). ^{13}C NMR: (75 MHz, $CDCl_3$): δ 169.0, 168.1, 140.7, 137.6, 128.36, 128.27, 66.4, 62.5, 35.5, 33.3, 31.9, 31.6, 29.7, 29.4, 29.3, 29.2, 22.9, 22.6, 14.1, 14.0. MS: m/z (rel intensity) 433 (M^+, <1), 388 (2), 318(2), 301 (2), 244 (2), 217 (93), 171 (100), 143 (15), 105 (14), 91 (5), 57 (5), 43 (14).

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