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Ti-Catalyzed Reformatsky-Type Coupling between α-Halo Ketones and Aldehydes

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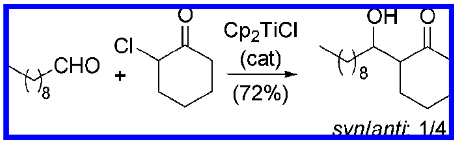
Received October 9, 2007



We describe the first Ti-catalyzed Reformatsky-type coupling between α-halo ketones and aldehydes. The reaction affords *β*-hydroxy ketones under mild, neutral conditions compatible with ketones and other electrophiles. The catalytic cycle possibly proceeds via bis(cyclopentadienyl)titanium enolates.

As long ago as 1887, Reformatsky reported the coupling between ethyl α-haloacetates and aldehydes or ketones promoted by zinc dust, thus establishing the basis of the Reformatsky reaction.[1] Currently, the Reformatsky reaction is considered in a broad sense as being the process that results from the insertion of a metal into a carbon−halogen bond activated by a carbonyl-, carbonyl-derived, or carbonyl-related group in a vicinal (or vinylogous) position, followed by coupling of the enolate thus formed with aldehydes, ketones, or other kinds of electrophile.[2a] In recent years, the Reformatsky reaction has been the subject of renewed interest, due largely to the replacement of heterogeneous zinc dust by homogeneous metals and metal derivatives, which have helped to improve the poor stereochemical control of the classic Reformatsky reaction and facilitated the development of metal-catalyzed versions of the process, among other advantages.[2,3] In this context, Little and co-workers introduced the use of Cp_2TiCl, a mild, homogeneous, single-electron-transfer reagent[4] to promote the Reformatsky-type reaction between α-halo esters and aldehydes.[5] This method proceeds at room temperature under mild conditions and affords good yields (78−95%) of *β*-hydroxy esters but requires stoichiometric proportions of Cp_2TiCl. Subsequently, Cozzi and co-workers developed a titanium-catalyzed version of the process, using $(CF_3CO)_2O$ as scavenger, which gives moderate yields of *β*-hydroxy esters.[6] Here we extend the Ti-based procedure to the Reformatsky-type coupling between α-halo ketones and aldehydes to obtain *β*-hydroxy ketones (aldol-like products) under neutral conditions. The reaction is catalyzed by substoichiometric proportions of the titanium complex, using Mn dust as stoichiometric reductant and a combination of Me_3SiCl and 2,4,6-collidine, developed in our laboratory, as titanocene-regenerating agent.[7]

Because Mn dust (unlike Zn) does not promote Reformatsky reactions,[5,6,8] we chose this metal to generate Cp_2TiCl for our experiments to avoid Zn-derived competing processes, which might generate misleading observations.[5,6,9] Thus, on the basis of our own experience with Ti-catalyzed reactions,[10] we anticipated the catalytic cycle depicted in Scheme 1.

According to our hypothesis, an α-halo ketone such as **1** would react with 2 equiv of $Cp_2Ti^{III}Cl$ to give a titanium(IV) enolate such as **2**, releasing 1 equiv of $Cp_2Ti^{IV}Cl_2$ (Scheme 1). Enolate **2** could subsequently react with an aldehyde (**3**) to give adduct **4**. Titanocene-regenerating agent **5**, presumably derived from the Me_3SiCl/collidine mixture used,[7a] would generate Cp_2TiCl_2 from **4**, releasing **6**, which after the final acidic quenching would give the desired *β*-hydroxy ketone **7**. Eventually the Mn present in the medium would reduce $Cp_2Ti^{IV}Cl_2$ to $Cp_2Ti^{III}Cl$, thus closing the catalytic cycle.

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(1) Reformatsky, S. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 1210−1212.

(2) For a recent review, see: (a) Ocampo, R.; Dolbier, W. R., Jr. *Tetrahedron* **2004**, *60*, 9325−9374. For recent reports on Reformatsky-type reactions catalyzed by SmI_2, [ClMn(salen)], low-valent Fe, and Co^I, see: (b) Lannou, M. I.; Hélion, F.; Namy, J. L. *Tetrahedron* **2003**, *59*, 10551−10565. (c) Orsini, F.; Lucci, E. M. *Tetrahedron Lett.* **2005**, *46*, 1909−1911. (d) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2951−2954. (e) Durandetti, M.; Périchon, J. *Synthesis* **2006**, 1542−1548. (f) Lombardo, M.; Gualandi, A.; Pasi, F.; Trombini, C. *Adv. Synth. Catal.* **2007**, *349*, 465−468.

(3) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2568−2571.

(4) Bis(cyclopentadienyl)titanium(III) chloride (Nugent's reagent) can be generated in situ by stirring commercial Cp_2TiCl_2 with Zn or Mn dust in THF, where it exists as an equilibrium mixture of the monomer Cp_2TiCl and the dinuclear species $(Cp_2TiCl)_2$; see: (a) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986−997. (b) Enemærke, R. J.; Larsen, J.; Skrydstrup, T.; Daasbjerg, K. *J. Am. Chem. Soc.* **2004**, *126*, 7853−7864. (c) Daasbjerg, K.; Svith, H.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C.; Gansäuer, A.; Barchuck, A.; Keller, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 2041−2044. (d) Gansäuer, A.; Barchuk, A.; Keller, F.; Schmitt, M.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C.; Daasbjerg, K.; Svith, H. *J. Am. Chem. Soc.* **2007**, *129*, 1359−1371. For the sake of clarity, we represent this complex as Cp_2TiCl.

(5) Parrish, J. D.; Shelton, D. R.; Little, R. D. *Org. Lett.* **2003**, *5*, 3615−3617.

(6) Sgreccia, L.; Bandini, M.; Morganti, S.; Quintavalla, A.; Umani-Ronchi, A.; Cozzi, P. G. *J. Organomet. Chem.* **2007**, *692*, 3191−3197.

(7) For the Me_3SiCl/2,4,6-collidine combination as titanocene-regenerating agent, see: (a) Barrero, A. F.; Rosales, A.; Cuerva, J. M.; Oltra, J. E. *Org. Lett.* **2003**, *5*, 1935−1938. For pioneering work on collidine hydrochloride and other pyridine hydrochloride derivatives, see: (b) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849−12859.

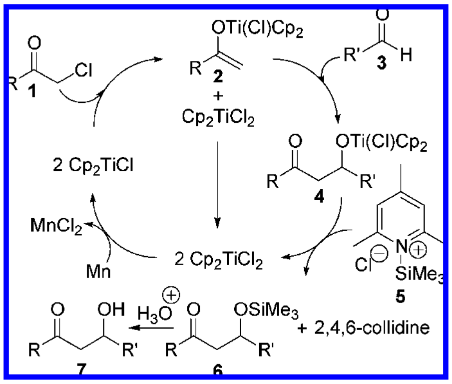
(8) In fact, after 6 h of stirring decanal (**8**) with **9** (2 equiv), Mn dust (8 equiv), 2,4,6-collidine (8 equiv), and Me_3SiCl (4 equiv) in the absence of Ti, an 81% yield of **8** was recovered unchanged and only a trace of coupling product **10** was detected. Comparison of this result with that presented in entry 1 of Table 1 (80% yield of **10** after the same reaction time) indicated that under our conditions the potential Reformatsky reaction promoted by Mn/Me_3SiCl would be substantially slower than the Ti-catalyzed process.

(9) It may be presumed that not only Cp_2TiCl but also Zn plays an important role in Zn/Cp_2TiCl_2-promoted Reformatsky reactions; see: (a) Ding, Y.; Zhao, Z.; Zhou, C. *Tetrahedron* **1997**, *53*, 2899−2906. (b) Chen, L.; Zhao, G.; Ding, Y. *Tetrahedron Lett.* **2003**, *44*, 2611−2614.

(10) (a) Rosales, A.; Oller-López, J. L.; Justicia, J.; Gansäuer, A.; Oltra, J. E.; Cuerva, J. M. *Chem. Commun.* **2004**, 2628−2629. (b) Justicia, J.; Rosales, A.; Buñuel, E. Oller-López, J. L.; Valdivia, M.; Haïdour, A.; Oltra, J. E.; Barrero, A. F.; Cárdenas, D. J.; Cuerva, J. M. *Chem. Eur. J.* **2004**, *10*, 1778−1788. (c) Justicia, J.; Oltra, J. E.; Cuerva, J. M. *J. Org. Chem.* **2004**, *69*, 5803−5806. (d) Justicia, J.; Oller-López, J. L.; Campaña, A. G.; Oltra, J. E.; Cuerva, J. M.; Buñuel, E.; Cárdenas, D. J. *J. Am. Chem. Soc.* **2005**, *127*, 14911−14921. (e) Estévez, R. E.; Oller-López, J. L.; Robles, R.; Melgarejo, C. R.; Gansäuer, A.; Cuerva, J. M.; Oltra, J. E. *Org. Lett.* **2006**, *8*, 5433−5436.

10.1021/jo702189k CCC: $40.75

SCHEME 1. Anticipated Cycle for the Ti-Catalyzed Reformatsky-Type Coupling between α-Halo Ketones and Aldehydes

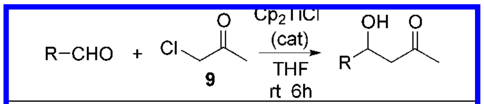


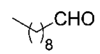
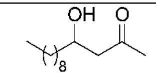
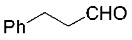
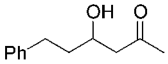
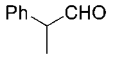
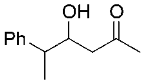
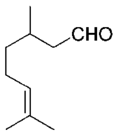
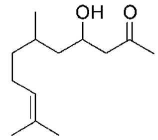
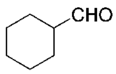
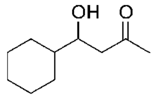
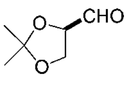
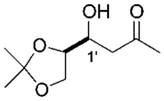
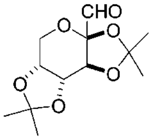
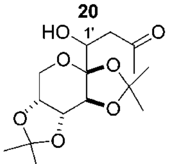
To check our hypothesis, we treated decanal (**8**) with chloroacetone (**9**) (2 equiv), a substoichiometric proportion of Cp_2TiCl_2 (0.2 equiv), Mn dust (8 equiv), 2,4,6-collidine (8 equiv),[11] and Me_3SiCl (4 equiv) in THF at rt. Thus, after 6 h of stirring we obtained an 80% yield (isolated product) of 4-hydroxytridecan-2-one (**10**) (Table 1). No formation of the corresponding conjugated alkenone (dehydration product) was detected under the mild conditions employed. This preliminary result in support of our hypothesis prompted us to study the Ti-catalyzed Reformatsky-type coupling between **9** and other aliphatic aldehydes (**11**, **13**, **15**, **17**, **19**, and **21**) under the same conditions (Table 1). Thus, we obtained the expected β-hydroxy ketones (**12**, **14**, **16**, **18**, **20**, and **22**) in yields (isolated products) ranging from a moderate 58% to a good 92%. Ti-catalyzed coupling between **9** and **13** gave a 7/3 mixture of Cram/anti-Cram addition products, showing moderate diastereofacial selectivity. Moreover, the Ti-catalyzed coupling of **9** with carbohydrate derivative **21** gave a 9/1 mixture of 1′*R* and 1′*S* epimers of **22**. In contrast, the Ti-catalyzed coupling between **9** and citronellal (**15**), the stereogenic center of which is farther than in **13**, showed no stereoselection. Neither was stereoselection observed for the Ti-catalyzed coupling of **9** with the glyceraldehyde derivative **19**.

Subsequently, we studied the Ti-catalyzed coupling between decanal (**8**) and different α-halo ketones (**23**, **25**, **26**, **28**, **30**, **31**, and **33**) (Table 2).

In this way, we obtained β-hydroxy ketones **24**, **27**, **29**, **32**, and **34** in yields (isolated products) ranging from an acceptable 61% to a high 94% (Table 2). It should be noted that chloro (**23** an **28**) and bromo ketones (**25** and **30**) gave similar results, suggesting that the nature of the halide atom is irrelevant for our process, at least as far as chlorides and bromides are concerned. Moreover, Ti-catalyzed coupling between 2-chlorocyclohexanone (**33**) and **8** gave mainly the 2*R**,1′*R** stereoisomer of **34**.[14] This stereoselectivity is similar to that reported for bis(cyclopentadienyl)titanium enolates.[15] Nevertheless, we observed no stereoselection for the Ti-catalyzed coupling of acyclic halo ketones **28**, **30**, and **31** with decanal (**8**) (Table 2).

TABLE 1. Ti-Catalyzed Coupling between Chloroacetone (9) and Aliphatic Aldehydes 8, 11, 13, 15, 17, 19, and 21



Aldehyde	Product	Yield
 **8**	 **10**	80%
 **11**	 **12**	92%
 **13**	 **14**	69%[a]
 **15**	 **16**	91%[b]
 **17**	 **18**	68%
 **19**	 **20**	58%[b]
 **21**	 **22**	61%[c]

[a] Mixture of 4*R**,5*R** and 4*S**,5*R** diastereomers[12] in a ratio of 7/3. [b] 1/1 mixture of stereoisomers. [c] Mixture of 1′*R* and 1′*S* epimers[12] in a ratio of 9/1.

In contrast to the results described above for aliphatic aldehydes, aromatic aldehydes were not suitable substrates for our reaction, it being well-known that they are prone to undergo pinacolization reactions in the presence of Cp_2TiCl.[16] In fact, when we treated a mixture of benzaldehyde and chloroacetone under our conditions we did not detect any formation of 4-hydroxy-4-phenylbutan-2-one. Furthermore, other substrates, such as ketones (2-decanone, acetophenone), esters (ethyl benzoate, ethyl acetoacetate), and nitriles (benzyl cyanide), proved to be inert under our conditions. These observations

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[11] 2,4,6-Collidine can be recovered at the end of the experiment by simple acid−base extraction; see ref 7b.

[12] Stereochemical assignments were made by comparing NMR data with those previously described. For product **14**, see: (a) Heathcock, C. H.; Flippin, L. E. *J. Am. Chem. Soc.* **1983**, *105*, 1667−1668. For product **22**, see: (b) Izquierdo, I.; Plaza, M. T.; Robles, R.; Mota, A.; Franco, F. *Tetrahedron: Asymmetry* **2001**, *12*, 2749−2754.

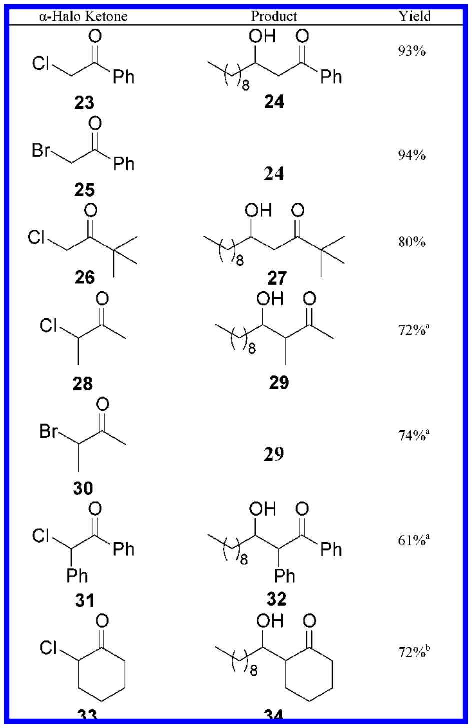
[13] Stereochemical assignments were made by comparing NMR data with those previously described for the closely related 2-(1-hydroxybutyl)-cyclohexanone; see: Le Roux, C.; Gaspard-Iloughmane, H.; Dubac, J.; Jaud, J.; Vignaux, P. *J. Org. Chem.* **1993**, *58*, 1835−1839.

[14] Stereoselectivity increased until a 8/1 ratio of 2*R**,1′*R** and 2*S**,1′*R** diastereomers when we carried out the reaction at −20 °C using 1.1 equiv of Cp_2TiCl.

[15] Murphy, P. J.; Procter, G.; Russell, A. T. *Tetrahedron Lett.* **1987**, *28*, 2037−2040.

[16] (a) Handa, Y.; Inanaga, J. *Tetrahedron Lett.* **1987**, *28*, 5717−5718. (b) Gansäuer, A. *Chem. Commun.* **1997**, 457−458. (c) Gansäuer, A.; Bauer, D. *J. Org. Chem.* **1998**, *63*, 2070−2071. (d) Hirao, T.; Hatano, B.; Asahara, M.; Muguruma, Y.; Ogawa, A. *Tetrahedron Lett.* **1998**, *39*, 5247−5248. (e) Dunlap, M. S.; Nicholas, K. M. *J. Organomet. Chem.* **2001**, *630*, 125−131.

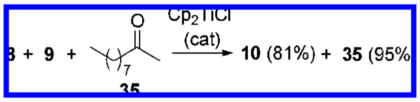
TABLE 2. Ti-Catalyzed Coupling between Decanal (8) and α-Halo Ketones 23, 25, 26, 28, 30, 31, and 33



α-Halo Ketone	Product	Yield
23	24	93%
25	24	94%
26	27	80%
28	29	72%[a]
30	29	74%[a]
31	32	61%[a]
33	34	72%[b]

[a] 1/1 mixture of stereoisomers. [b] Mixture of 2*R**,1′*R** and 2*S**,1′*R** diastereomers in a 4/1 ratio.[13]

SCHEME 2. Discrimination between Aldehyde 8 and Ketone 35 by the Ti-Catalyzed Coupling with α-Halo Ketone 9



suggested that our procedure might be chemospecific for aldehydes. Thus, when we treated an equimolar mixture of decanal (**8**) (1 equiv) and 2-decanone (**35**) (1 equiv) with chloroacetone (**9**) (2 equivs) and a substoichiometric proportion of Cp_2TiCl (0.2 equiv) we obtained an 81% yield of β-hydroxy ketone **10**, recovered 2-decanone unchanged, and (consequently) did not detect 4-hydroxy-4-methyldodecan-2-one (Scheme 2).

This discrimination between an aldehyde and a ketone is noteworthy, especially because this has not been reported for Reformatsky-type reactions catalyzed by other metals.[2b−f]

In conclusion, we describe here the first Ti-catalyzed Reformatsky-type coupling between α-halo ketones and aldehydes. The reaction affords medium-to-high yields of β-hydroxy ketones at room temperature under mild, neutral conditions compatible with ketones and other electrophiles. Stereochemical evidence supports the idea that the catalytic cycle proceeds via bis(cyclopentadienyl)titanium enolates. At the moment we are undertaking a more thorough investigation into this reaction mechanism and trying to develop an enantioselective version of the process.

Experimental Section

The following known compounds were isolated as pure samples and their NMR spectra matched those reported: **12**,[17] **14**,[12a] **18**,[18] and **22**.[12b]

General Procedure for Ti-Catalyzed Couplings between α-Halo Ketones and Aldehydes. Strictly deoxygenated THF (20 mL) was added to a mixture of commercial Cp_2TiCl_2 (0.2 mmol) and Mn dust (8 mmol) under an Ar atmosphere, and the suspension was stirred until it turned lime green (about 15 min). Subsequently, a solution of aldehyde (1 mmol), α-halo ketone (2 mmol), and 2,4,6-collidine (8 mmol) in THF (2 mL) and Me_3SiCl (4 mmol) were added, and the mixture was stirred for 6 h. A saturated solution of $KHSO_4$ (40 mL) was then added, and the mixture was extracted with EtOAc. The organic layer was washed with brine and dried (Na_2SO_4) and the solvent removed. The residue was submitted to flash chromatography (hexane/EtOAc), and isolated products were characterized by spectroscopic techniques. When water was used instead of the $KHSO_4$ solution, a β-trimethylsilanyloxy ketone was obtained (see product **36** in the Supporting Information).

Ti-Catalyzed Chemospecific Coupling of Chloroacetone with Decanal in the Presence of 2-Decanone. Strictly deoxygenated THF (20 mL) was added to a mixture of commercial Cp_2TiCl_2 (31 mg, 0.13 mmol) and Mn dust (282 mg, 3.84 mmol) under an Ar atmosphere, and the suspension was stirred until it turned lime green. Subsequently, a solution of decanal (100 mg, 0.64 mmol), 2-decanone (100 mg, 0.64 mmol), and chloroacetone (118 mg, 1.28 mmol) in THF (2 mL) followed by 2,4,6-collidine (542 mg, 4.48 mmol) and Me_3SiCl (278 mg, 2.56 mmol) were added, and the mixture was stirred for 6 h. A saturated solution of $KHSO_4$ (40 mL) was then added, and the mixture was extracted with EtOAc. The organic layer was washed with brine and dried (Na_2SO4) and the solvent removed. The residue was submitted to flash chromatography (hexane/EtOAc 4/1) giving β-hydroxy ketone **10** (101 mg, 81%) and 2-decanone (95 mg, 95%).

Compound 10: colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 4.10−3.95 (m, 1H), 2.60 (dd, $J = 13.2$, 6.0 Hz, 1H), 2.50 (dd, $J = 13.2$, 2.1 Hz, 1H), 2.15 (s, 3H), 1.60−1.20 (m, 16H), 0.85 (t, $J = 5.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 210.3 (C), 67.7 (CH), 50.1 (CH_2), 36.6 (CH_2), 32.1 (CH_2), 31.0 (CH_3), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 25.6 (CH_2), 22.9 (CH_2), 14.3 (CH_3), (one carbon signal was not observed); IR (film) 3391, 1637 cm^{-1}; FABHRMS calcd for $C_{13}H_{26}O_2Na$ *m/z* 237.1830, found *m/z* 237.1832.

Compound 16: colorless oil; 1:1 mixture of stereoisomers; ^1H NMR (400 MHz, $CDCl_3$) δ 5.05 (t, $J = 7.2$ Hz, 1H), 4.16−4.04 (m, 1H), 3.00 (brs, 1H, OH), 2.62−2.42 (m, 2H), 2.14 (s, 3H), 2.00−1.86 (m, 2H), 1.64 (s, 3H), 1.56 (s, 3H), 1.40−1.00 (m, 5H), 0.87 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 210.1 (C), 131.3 (C), 124.9 (CH), 124.8 (CH), 65.9 (CH), 65.4 (CH), 50.9 (CH_2), 50.4 (CH_2), 44.0 (CH_2), 43.9 (CH_2), 37.0 (CH_2), 36.8 (CH_2), 30.9 (CH_3), 29.2 (CH), 28.8 (CH), 25.8 (CH_3), 25.6 (CH_2), 25.5 (CH_3), 20.2 (CH_3), 19.2 (CH_3), 17.8 (CH_3), 17.8 (CH_2) (some carbon signals were not observed); IR (film) 3426, 1636 cm^{-1}; FABHRMS calcd for $C_{13}H_{24}O_2Na$ *m/z* 235.1674, found *m/z* 235.1673.

Compound 20: colorless oil; 1:1 mixture of stereoisomers; ^1H NMR (400 MHz, $CDCl_3$) δ 4.12−4.08 (m, 1.5H, isomer a), 4.01 (t, $J = 8.0$ Hz, 0.5H, isomer a), 3.98−3.90 (m, 1.5H, isomer b), 3.84 (dd, $J = 8$, 6 Hz, 0.5H, isomer b), 3.14 (brs, 0.5H, OH, isomer a), 2.84 (dd, $J = 17.4$, 2.0 Hz, 0.5H, isomer a), 2.75 (brs, 0.5H, OH, isomer b), 2.70 (dd, $J = 17.4$, 8.2 Hz, 0.5H, isomer b), 2.60 (dd, $J = 17.4$, 8.2 Hz, 0.5H, isomer a), 2.57 (dd, $J = 17.4$, 3.0 Hz, 0.5H, isomer b), 2.20 (s, 3H), 1.44 (s, 1.5H, isomer a), 1.39 (s, 1.5H, isomer b), 1.35 (s, 1.5H, isomer a), 1.33 (s, 1.5H, isomer b); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 209.8 (C), 208.2(C), 109.7 (C), 109.6 (C), 77.8 (CH), 77.6 (CH), 69.2 (CH), 67.9 (CH), 67.1 (CH_2), 65.7 (CH_2), 46.6 (CH_2), 46.4 (CH_2), 31.0 (CH_3), 30.9 (CH_3), 26.8 (CH_3), 26.5 (CH_3), 25.3 (CH_3), 25.2 (CH_3); IR (film) 3428,

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1637 cm^{-1}; FABHRMS calcd for $C_9H_{16}O_4Na$ *m*/*z* 211.0946, found *m*/*z* 211.0946.

Compound 24: white solid; mp 97−98 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.5 Hz, 2H), 7.56 (t, *J* = 8.5 Hz, 1H), 7.45 (t, *J* = 8.5 Hz, 2H), 4.20 (m, 1H), 3.29 (brs, 1H, OH), 3.14 (dd, *J* = 17.6, 2.8 Hz, 1H), 3.03 (dd, *J* = 17.6, 8.8 Hz, 1H), 1.62−1.25 (m, 16H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 201.0 (C), 136.8 (C), 133.5 (CH), 128.7 (CH), 128.1 (CH), 67.8 (CH), 45.1 (CH_2), 36.6 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 25.6 (CH_2), 22.7 (CH_2), 14.2 (CH_3) (one carbon signal was not observed); IR (KBr) 3378, 1679 cm^{-1}; FABHRMS calcd for $C_{18}H_{28}O_2Na$ *m*/*z* 299.1987, found *m*/*z* 299.1987.

Compound 27: colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 3.94−3.88 (m, 1H), 3.12 (brs, 1H, OH), 2.60 (dd, *J* = 17.8, 2.4 Hz, 1H), 2.45 (dd, *J* = 17.8, 9.1 Hz, 1H), 1.48−1.16 (m, 16H), 1.06 (s, 9H), 0.80 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$; DEPT) δ 218.0 (C), 68.0 (CH), 44.5 (C), 43.2 (CH_2), 36.6 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 26.4 (CH_3), 25.7 (CH_2), 22.8 (CH_2), 14.2 (CH_3), (two carbon signals were not observed); IR (film) 3433, 1638 cm^{-1}; FABHRMS calcd for $C_{16}H_{32}O_2Na$ *m*/*z* 279.2300, found *m*/*z* 279.2301.

Compound 29: colorless oil; roughly 1:1 mixture of *syn/anti* stereoisomers; ^1H NMR (400 MHz, $CDCl_3$) δ 3.90 (m, 0.5H, syn isomer), 3.64 (m, 0.5H, anti isomer), 2.85−2.70 (m, 1H, OH), 2.58 (quint, *J* = 7.3 Hz, 0.5H, anti isomer), 2.53 (dq, *J* = 7.3, 3.3 Hz, 0.5H, syn isomer), 2.23 (s, 3H), 1.53−1.16 (m, 14H), 1.10 (d, *J* = 7.3, 1.5H, syn isomer), 1.08 (d, *J* = 7.3 Hz, 1.5H, anti isomer), 0.85 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 213.9 (C), 213.8 (C), 76.8 (CH), 70.1 (CH), 52.3 (CH), 51.0 (CH), 34.6 (CH_2), 34.1 (CH_2), 31.9 (CH_2), 29.7 (CH_3), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_3), 26.0 (CH_2), 25.5 (CH_2), 22.6 (CH_2), 14.0 (CH_3), 13.7 (CH_3), 10.2 (CH_3) (some carbon signals were not observed); IR (film) 3414, 1698, 1635 cm^{-1}; FABHRMS calcd for $C_{14}H_{28}O_2Na$ *m*/*z* 251.1987, found *m*/*z* 251.1988.

Compound 32: colorless oil; 1:1 mixture of stereoisomers; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98−7.90 (m, 2H), 7.50−7.44 (m, 1H), 7.42−7.18 (m, 7H), 4.57 (d, *J* = 8.5 Hz, 0.5H, isomer a), 4.54 (d, *J* = 5.4 Hz, 0.5H, isomer b), 4.38−4.28 (m, 1H), 2.90 (brs, 1H, OH) 1.42−1.16 (m, 16H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 201.2 (C), 201.0 (C), 137.0 (C), 136.7 (C), 136.5 (C), 135.2 (C), 133.4 (CH), 133.3 (CH), 129.8 (CH), 129.2 (CH), 129.1 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 127.8 (CH), 127.7 (CH), 73.8 (CH), 72.6 (CH), 60.9 (CH), 58.8 (CH), 34.8 (CH_2), 33.8 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 26.1 (CH_2), 25.7 (CH_2), 22.8 (CH_2), 14.3 (CH_3) (some carbon signals were not observed); IR (film) 3430, 1637 cm^{-1}; FABHRMS calcd for $C_{24}H_{32}O_2Na$ *m*/*z* 375.2300, found *m*/*z* 375.2298.

Compound 34:[19] colorless oil; mixture of syn/anti stereoisomers; ^1H NMR (400 MHz, $CDCl_3$) δ 4.15 (m, 0.5H, syn isomer), 3.72 (m, 0.5H, anti isomer), 3.41 (d, *J* = 4.0, 0.5H, OH, anti isomer), 2.45−1.21 (m, 25H), 0.83 (t, *J* = 6.0 Hz, 3H); IR (film) 3464, 1701 cm^{-1}.

Acknowledgment. We thank the Spanish MEC (project CTQ2005-08402/BQU, grant to R.E.E.) and the "Junta de Andalucía" (group FQM339, grant to M.P.) for financial support. We also thank our English colleague Dr. J. Trout for revising our English text.

Supporting Information Available: Reformatsky-type reactions promoted by stoichiometric proportions of Cp_2TiCl. Copies of NMR spectra for all products reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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