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**ARTICLE** *in* THE JOURNAL OF ORGANIC CHEMISTRY · NOVEMBER 2005

Impact Factor: 4.72 · DOI: 10.1021/jo0502910 · Source: PubMed



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VOLUME 70, NUMBER 21

JOC Articles

OCTOBER 14, 2005



# Exploiting Pd[II] and Ti[III] Chemistry To Obtain $\gamma$-Dioxygenated Terpenoids: Synthesis of Rostratone and Novel Approaches to Aphidicolin and Pyripyropene A

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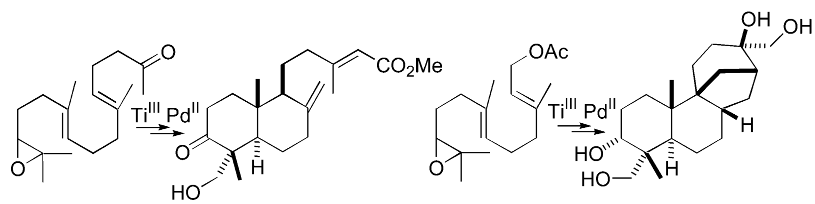
*Received February 15, 2005*




In nature there are several terpenoids with a characteristic $\gamma$-dioxygenated system on the A ring, and many of them show interesting pharmacological properties. We have developed a novel strategy for the synthesis of these terpenoids involving three stages: (a) the selective epoxidation of commercial polyenes, (b) titanium(III)-catalyzed cyclization of the epoxypolyprenes thus obtained, and (c) Pd-mediated remote functionalization of the equatorial methyl group attached at C-4 on ring A of the cyclic terpenoid thus formed. This strategy has proved to be useful for the synthesis of the natural labdane rostratone (**1**) and related terpenoids, as well as for advanced synthetic approaches toward the pharmacologically active products aphidicolin (**2**) and pyripyropene A (**3**).

## Introduction

Some organisms belonging to the kingdoms of plants and fungi are capable of synthesizing small quantities of highly functionalized terpenoids bearing a characteristic $\gamma$-dioxygenated system on the A ring (Figure 1), as occurs in the labdane diterpenoid **1** (rostratone) found in the plant *Nolana rostrata*,[1] in the antibiotic aphidicolin (**2**) excreted by *Cephalosporium aphidicola*,[2] and in the meroterpenoid pyripyropene A (**3**) isolated from the fungus *Aspergillus fumigatus*.[3] Many of these terpenoids possess interesting pharmacological properties. Aphidicolin, for example, shows marked activity against Herpes simplex,[4] and pyripyropene A has proved to be a powerful inhibitor of acyl-CoA:cholesterol acyltransferase (ACAT),[5] an enzyme related to atherosclerosis. These compounds have consequently attracted the attention of chemists, who have reported some procedures for synthesizing **2**[6] and **3**.[7] These syntheses, however, generally require numerous steps, including tedious protection and deprotection protocols, and eventually provide only low overall yields.

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10.1021/jo0502910 CCC: $30.25 © 2005 American Chemical Society
Published on Web 04/16/2005

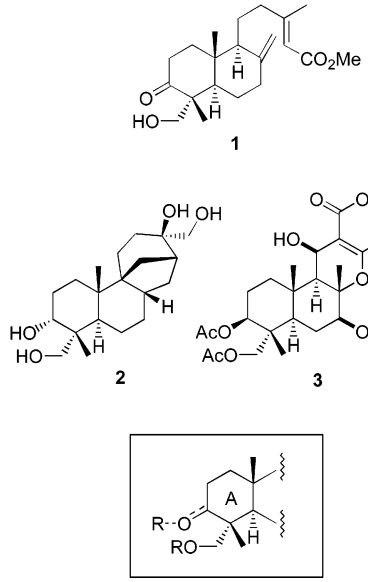
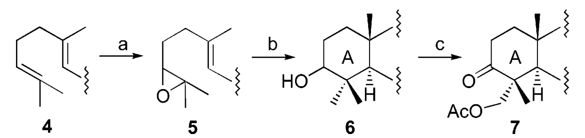


**FIGURE 1.** $\gamma$-Dioxygenated system of the ring A present in several bioactive terpenoids.

**SCHEME 1. Anticipated Synthesis of Terpenoids with the $\gamma$-Dioxygenated System on the A Ring**[a]



[a] Key: (a) selective epoxidation; (b) titanocene(III)-catalyzed cyclization; (c) oxidation and Pd-mediated remote functionalization.

A year ago we developed a novel method for the synthesis of complex terpenoids based on the titanocene(III)-catalyzed[8] radical cyclization of epoxypolyprenes (such as **5**) prepared from commercial polyenes.[9]

This method, which adheres to the principles of selectivity and atom- and step-economy required in contemporary chemistry,[10] provides 3$\beta$-hydroxy terpenoids (such as **6**) with two "unactivated" methyl groups at C-4 (Scheme 1).[9] With such derivatives in our hands we only needed to oxidize their equatorial methyl group to achieve the $\gamma$-dioxygenated system of compounds such as **7** (including **1**−**3**). The advantage of making this transformation by remote functionalization at the end of the synthetic sequence is that protecting groups would not be required during the building of the carbocyclic framework.

Organometallic chemistry affords mild and effective procedures to activate C−H bonds.[11] In particular, cyclopalladation reactions have proved to be capable of activating primary C−H bonds for the formation of C−I, C−O, and even C−C bonds.[12] Surprisingly, this kind of chemistry has been largely overlooked in the field of terpenoids.[13] In a preliminary communication we described how Pd$^{II}$-mediated C−H activation via palladacycles can be used for the remote functionalization of C-4 methyl groups of terpenoids obtained by titanocene(III)-catalyzed radical cyclization of epoxypolyenes.[14] Here we report on this procedure in full detail and its application to the synthesis of rostratone (**1**) and related labdanes and advanced approaches toward the pharmacologically active products aphidicolin (**2**) and pyripyropene A (**3**).

## Results and Discussion

First we explored the efficiency of palladium-mediated C−H activation reactions over a wide range of terpenoid skeletons to facilitate the completion of the sequence depicted in Scheme 1. We began the process by preparing a set of model ketones (commercial **8b** and **9b**−**14b**) with different cyclic skeletons containing five-, six-, and seven-membered rings (Figure 2) via the oxidation of alcohols **9a**−**14a** with Dess−Martin periodinane. These ketones were subsequently treated with hydroxylamine to form ketoximes **8c**−**14c** at yields ranging from 70% (**9c**) to 92% (**13c**).

Remote functionalization processes were then carried out as depicted in Scheme 2.[15] Reactions between ketoximes **10c**−**14c** and sodium tetrachloropalladate(II)/NaOAc gave palladacycle dimers **10f**−**14f** (in contrast to **8c** and **9c**, which decomposed after treatment with $Na_2PdCl_4$), which were then treated with pyridine and lead tetraacetate to obtain acetoxy oximes **10d**−**14d** in yields ranging from 72% to 100% (Table 1).

To check the possibility of activating C−H bonds of terpenoid (pseudo)axial methyl groups, we made further reactions with sodium tetrachloropalladate(II), this time using acetoxy oximes **10d**−**14d** as substrates. In this way we obtained moderate yields (42−55%) of acetates **15d** and **16d** (Figure 3) deriving from monocyclic oximes **10d** and **11d**, although the polycyclic substrates **12d**−**14d** remained unchanged. Presumably the stereochemical rigidity of these compounds prevents a suitable conformation to produce the required palladacycles.

Finally, the hydrolysis of oximes **10d**−**16d** with $TiCl_3$/$H_2O$ avoided any undesirable isomerization of the double

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(11) For a recent review into the potentials of organometallic chemistry for useful C−H bond activation procedures, see: Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507−514.

(12) (a) Carr, K.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1984**, 1227−1228. (b) Baldwin, J. E.; Nájera, C.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1985**, 126−127. (c) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856−11857. (d) Sezen, B.; Franz, R.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 13372−13373. (e) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300−2301. (f) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542−9543.

(13) We have only found two reports, both dealing with Pd-mediated primary C−H activation of pentacyclic triterpenoids; see: (a) Peakman, T. M.; Lo ten Haven, H.; Rullkotter, J.; Curiale, J. A. *Tetrahedron* **1991**, *47*, 3779−3786. (b) Bore, L.; Honda, T.; Gribble, G. W. *J. Org. Chem.* **2000**, *65*, 6278−6282.

(14) Justicia, J.; Oltra, J. E.; Cuerva, J. M. *Tetrahedron Lett.* **2004**, *45*, 4293−4296.

(15) Reactions between ketoximes **10c**−**14c** and sodium tetrachloropalladate(II)/NaOAc can be carried out either in MeOH or AcOH, but giving different yields. The best solvent for each substrate is that indicated in Table 1.

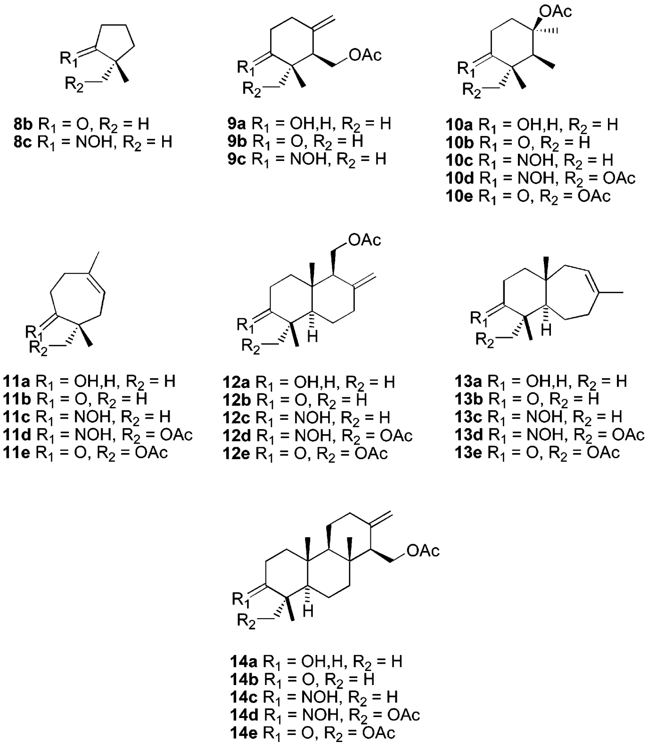



**FIGURE 2.** Chemical structure of the alcohols **9a**−**14a**, the model ketones **8b**−**14b**, the corresponding oximes, and the products derived from Pd-mediated remote functionalization.

**SCHEME 2. Remote Functionalization of Terpenoids via Dimeric Organopalladium Complexes**

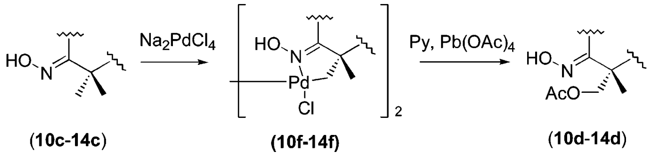



**TABLE 1. Yields of Products Obtained by Pd-Mediated Remote Functionalization of Oximes 10c−14c, 10d, and 11d**

| substrate | solvent[15] | acetoxy oxime (yield) | acetoxy ketone (yield) |
|---|---|---|---|
| **10c** | AcOH | **10d** (82%) | **10e** (82%) |
| **11c** | MeOH | **11d** (88%) | **11e** (85%) |
| **12c** | MeOH | **12d** (100%) | **12e** (85%) |
| **13c** | MeOH | **13d** (85%) | **13e** (85%) |
| **14c** | MeOH | **14d** (72%) | **14e** (85%) |
| **10d** | AcOH | **15d** (55%) | **15e** (83%) |
| **11d** | MeOH | **16d** (42%) | **16e** (85%) |

bonds, thus providing good yields of acetoxy ketones **10e**−**16e** (Table 1).

Once we were confident about the possibilities of the Pd-based method, we went on to try and synthesize the target molecule **1** (Scheme 3). As starting material we chose ethylene ketal **17**, which was easily prepared from commercially available farnesylacetone.[16] Bromonium-mediated epoxidation of **17**, followed by the titanium(III)-catalyzed cyclization of epoxypolyene **18** under anhydrous conditions, gave exocyclic alkene **19**[9a] (17% yield from farnesylacetone) with high degrees of regio- and stereo-selectivity. Further hydrolysis of ketal **19** with $CeCl_3/H_2O$ avoided undesired double-bond isomerization and provided an 85% yield of ketone **20**.[9a] Horner−Emmons olefination of **20** yielded **21a**, the methyl ester of the natural labdane **21b** found in both the Brazilian Copaiba tree and the Australian plant *Olearia teretifolia*.[17] The chemical synthesis of carboxylic acid **21b** has been achieved by Armstrong and Weiler through a 10-step sequence (4% overall yield) that ends with the saponification of ester **21a**.[18] Therefore, the titanocene(III)-based preparation of this ester (five steps, 11% overall yield) achieves a substantially improved formal synthesis of **21b**.

Dess−Martin oxidation of **21a** led to ketone **22a** (80% yield). Spectroscopic data of this ketone matched those reported for the methyl ester of 3-oxoanticopalic acid (**22b**), found in the needles of *Pinus strobus*.[19] To the best of our knowledge, this is the first total synthesis reported for **22a**, which confirms the structure proposed by Zinkel and Magee for the natural product **22b**.[19]

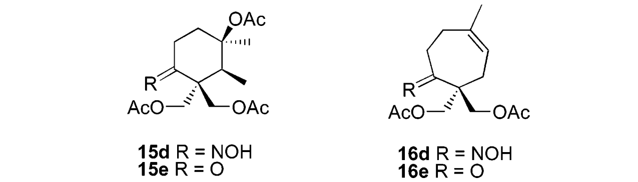
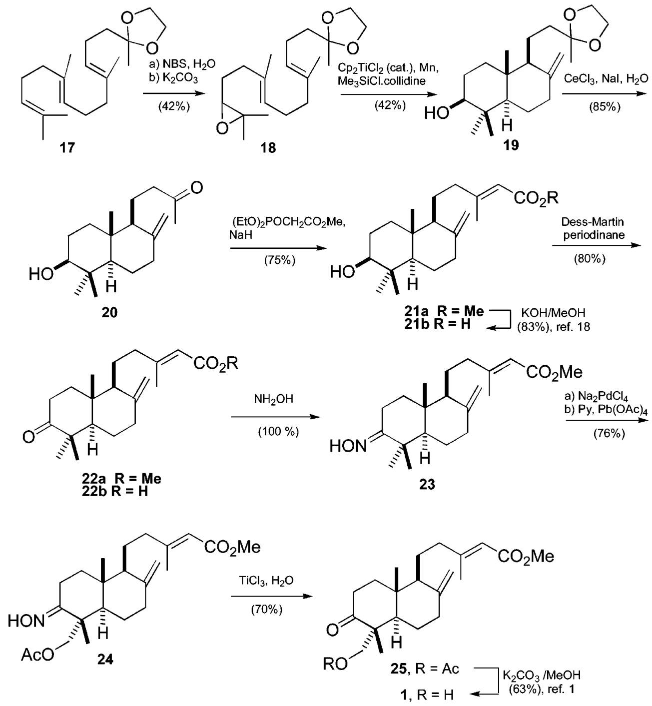



**FIGURE 3.** Chemical structure of products **15** and **16**.

**SCHEME 3. Formal Synthesis of Rostratone (1) and Related Labdanes 21b and Methyl 3-Oxoanticopalate (22a)**

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(19) Zinkel, D. F.; Magee, T. V. *Phytochemistry* **1987**, *26*, 769−774.

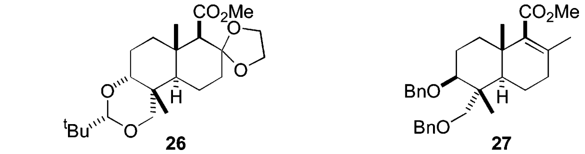
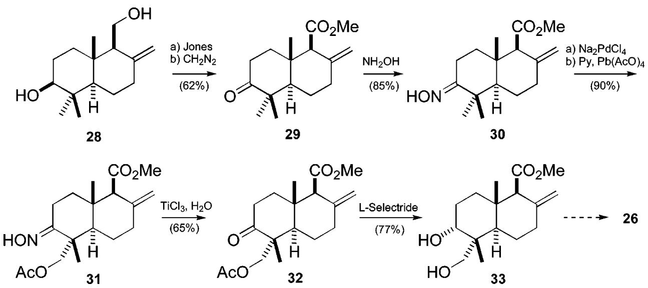
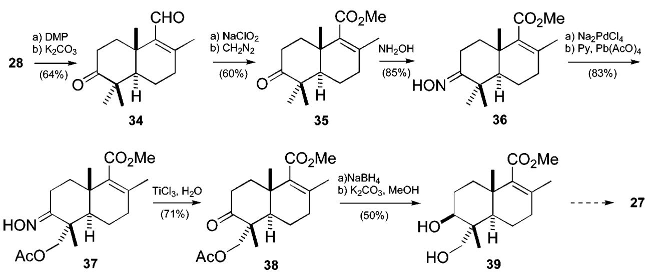


**FIGURE 4.** Chemical structure of synthons **26** and **27**.

**SCHEME 4. Advanced Approach toward Synthon 26**



**SCHEME 5. Advanced Approach toward Synthon 27**



Treatment of ketone **22a** with hydroxylamine led to the oxime **23** (60% yield from **20**) and finally the Pd-mediated remote functionalization of **23** and hydrolysis of oxime **24** afforded acetoxy ketone **25** (53% yield from **23**). The natural metabolite (**1**) from *N. rostrata* has been isolated and characterized by Garbarino et al. as its acetate (**25**).[1] Spectroscopic data of synthetic **25** matched those of the acetate reported by Garbarino and coworkers,[1] supporting the structure proposed for the natural product **1**. These authors also describe the selective saponification of the acetate group of **25** to give **1**, and therefore the sequence depicted in Scheme 3 may be regarded as the formal synthesis of **1**. To the best of our knowledge this is the first chemical synthesis of this ketone, which we have called rostratone.

The synthesis of aphidicolin (**2**), reported by Corey et al.,[20] goes through an intermediate (**26**) closely related to the bicyclic synthon **27** employed by Nagamitsu et al.[7a] for the synthesis of pyripyropene A (**3**). This observation prompted us to develop a novel, divergent strategy for the chemical preparation of both intermediates **26** and **27** (Figure 4) starting from isodrimenediol (**28**), which is readily prepared by titanocene(III)-catalyzed cyclization of 10,11-epoxyfarnesyl acetate.[9a] From this diol the synthesis split into two branches, one directed toward **26** (Scheme 4) and the other toward **27** (Scheme 5). In the former, the exocyclic double bond of **28** remained after Jones oxidation and treatment with diazomethane, giving keto ester **29** (60% yield), which was easily transformed into oxime **30**. The Pd-mediated remote functionalization of **30** gave acetate **31**, which was hydrolyzed to acetoxy ketone **32** (50% yield from **29**). Finally, the stereoselective reduction of ketone provided diol **33** (77%). This $\gamma$-dihydroxylated sesquiterpenoid contains an exocyclic double bond that might undergo ozonolysis to the corresponding ketone, which after suitable protection should provide **26**. The transformation of **26** into aphidicolin (**2**) was solved by Corey et al. employing the Robinson spiroannulation process.[20]

In the synthetic branch toward pyripyropene A (Scheme 5), the exocyclic double bond was isomerized to a conjugated position after Dess–Martin oxidation of **28** and subsequent basic treatment, giving $\alpha,\beta$-unsaturated aldehyde **34** (65%). Further oxidation of this aldehyde, followed by esterification of the corresponding acid, furnished **35**. The palladium-mediated remote functionalization of **35**, via oxime **36**, furnished acetate **37**, which was hydrolyzed to obtain **38** (32% from **34**). Finally, borohydride reduction of **38** and selective saponification of the acetate group provided **39** (50%). Dibenzylation of **39** would presumably give **27**, thus completing the formal synthesis of pyripyropene A (**3**).

In summary, the results described here prove that Pd-mediated C–H activation is a suitable procedure for the remote functionalization of C-4 methyl groups of different terpenoid-like skeletons containing six- and seven-membered A rings. This procedure might facilitate the chemical preparation of terpenoids with a $\gamma$-dioxygenated system on the A ring, and in fact it has proved itself useful for the synthesis of the natural terpenoid rostratone (**1**) and related labdanes (**21b**, **22a**) and for synthetic approaches to aphidicolin (**2**) and pyripyropene A (**3**). At the moment we are attempting to complete the synthesis of both **2** and **3** using shorter and more efficient synthetic sequences than those reported to date.

## Experimental Section

**General.** For the reactions with titanocene all solvents and additives were thoroughly deoxygenated prior to use. Although all structures have been drawn as one enantiomer the synthesized compounds are racemic. Substances **9a**–**14a**,[9a,21] **17**,[16] **20**,[9a] and **28**[9a] were prepared according to known procedures. The following known compounds were isolated as pure samples and showed NMR spectra identical to those of the reported compounds: **8c**,[22] **11b**,[23] **21**,[17,18] **22**,[19] and **25**.[1]

**General Procedure for the Synthesis of Ketones (9b–14b) by Dess–Martin Oxidation.** A solution of alcohol (**9a**–**14a**) (1.0 mmol) and Dess–Martin periodinane (2.0 mmol) in wet $CH_2Cl_2$ (30 mL) was stirred at room temperature for 2 h. The mixture was diluted with *t*BuOMe, washed with 10% aqueous $Na_2S_2O_3$ and brine, and dried ($Na_2SO_4$), and the solvent was removed. The products were isolated by column chromatography of the residue on silica gel (hexane/*t*BuOMe) and characterized by spectroscopic techniques. The ketones obtained were isolated in the following yields: **9b** (70%), **10b** (88%), **11b** (76%), **12b** (94%), **13b** (72%), **14b** (91%).

**Ketone 9b.** Hexane/*t*BuOMe, 4:1; vitreous solid; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.01 (br s, 1H), 4.87 (br s, 1H), 4.15–4.05

(20) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 1742–1744.

(21) Barrero, A. F.; Cuerva, J. M.; Herrador, M. M.; Valdivia, M. V. *J. Org. Chem.* **2001**, *66*, 4074–4080.

(22) Conley, R. T.; Nowak, B. E. *J. Org. Chem.* **1962**, *27*, 3196–3201.

(23) For previous synthesis of karahanaenone (**11b**) see: Uneyama, K.; Date, T.; Torii, S. *J. Org. Chem.* **1985**, *50*, 3160–3163.

(m, 2H), 2.85−2.20 (m, 4H), 1.97 (s, 3H), 1.90−1.55 (m, 1H), 1.19 (s, 3H), 1.05 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 213.7 (C), 170.6 (C), 143.9 (C), 113.8 ($CH_2$), 63.6 ($CH_2$), 54.5 (CH), 37.7 ($CH_2$), 35.6 (C), 31.6 ($CH_2$), 27.1 ($CH_3$), 21.1 ($CH_3$), 20.8 ($CH_3$).[24]

**Ketone 10b.** Hexane/*t*BuOMe, 4:1; vitreous solid; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.05 (dt, $J$ = 14.6, 3.5 Hz, 1H), 2.59 (td, $J$ = 14.5, 5.4 Hz, 1H), 2.49 (td, $J$ = 14.5, 5.4 Hz, 1H), 2.03 (s, 3H), 1.66 (td, $J$ = 14.6, 4.3 Hz, 1H), 1.52 (s, 3H), 1.49−1.44 (m, 1H), 1.10 (s, 3H), 1.08 (s, 3H), 1.05 (d, $J$ = 3 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 214.9 (C), 170.1 (C), 82.5 (C), 50.9 (CH), 48.1 (C), 34.3 ($CH_2$), 34.2 ($CH_2$), 26.9 ($CH_3$), 24.6 ($CH_3$), 24.4 ($CH_3$), 21.6 ($CH_3$), 9.1 ($CH_3$).[24]

**Ketone 12b.** Hexane/*t*BuOMe, 7:3; white solid, mp 150−152 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.95 (br s, 1H), 4.63 (br s, 1H), 4.34 (dd, $J$ = 11.4, 4.1 Hz, 1H), 4.26 (dd, $J$ = 11.4, 8.5 Hz, 1H), 2.66 (td, $J$ = 12.9, 6.4 Hz, 1H), 2.50−2.38 (m, 2H), 2.15−2.05 (m, 3H), 2.04 (s, 3H), 1.88−1.48 (m, 4H), 1.12 (s, 3H), 1.05 (s, 3H), 0.96 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 216.1 (C), 171.3 (C), 145.5 (C), 108.4 ($CH_2$), 61.4 ($CH_2$), 55.1 (CH), 53.8 (CH), 47.9 (C), 38.6 (C), 37.5 ($CH_2$), 37.1 ($CH_2$), 34.6 ($CH_2$), 25.9 ($CH_3$), 24.6 ($CH_2$), 21.9 ($CH_3$), 21.1 ($CH_3$), 14.6 ($CH_3$); EIMS *m/z* 278 (3, $M^+$), 263 (1), 218 (100), 203 (30), 175 (50), 133 (65), 93 (55); HRFABMS calcd for $C_{17}H_{26}O_3Na$ *m/z* 301.1779, found *m/z* 301.1778.

**Ketone 13b.** (Hexane/*t*BuOMe, 4:1); vitreous solid; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.35 (t, $J$ = 6.3 Hz, 1H), 2.68 (m, 1H), 2.27 (dt, $J$ = 15.3, 4 Hz, 1H), 2.15−1.77 (m, 3H), 1.73 (s, 3H), 1.69−1.10 (m, 6H), 1.07 (s, 3H), 0.99 (s, 3H), 0.96 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 216.7 (C), 141.4 (C), 121.9 (CH), 59.5 (CH), 48.7 (C), 44.7 ($CH_2$), 40.9 ($CH_2$), 35.6 (C), 35.2 ($CH_2$), 34.3 ($CH_2$), 25.5 ($CH_3$), 25.4 ($CH_3$), 22.7 ($CH_2$), 21.7 ($CH_3$), 18.8 ($CH_3$); EIMS *m/z* 220 (25, $M^+$), 205 (20), 152 (100), 137 (90), 97 (95), 67 (80).[24]

**Ketone 14b.** Hexane/*t*BuOMe, 4:1; vitreous solid; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.86 (br s, 1H), 4.53 (br s, 1H), 4.33 (dd, $J$ = 11.1, 3.6 Hz, 1H), 4.18 (dd, $J$ = 11.1, 9 Hz, 1H), 2.56−2.39 (m, 4H), 2.01 (s, 3H), 2.00−1.09 (m, 11H), 1.08 (s, 3H), 1.02 (s, 3H), 0.90 (s, 3H), 0.78 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 217.6 (C), 171.4 (C), 146.2 (C), 107.6 ($CH_2$), 61.4 ($CH_2$), 58.9 (CH), 54.9 (CH), 54.9 (CH), 47.3 (C), 39.9 ($CH_2$), 39.4 ($CH_2$), 39.1 (C), 37.5 ($CH_2$), 37.3 (C), 34.1 ($CH_2$), 26.8 ($CH_3$), 23.3 ($CH_2$), 21.2 ($CH_3$), 21.0 ($CH_3$), 20.0 ($CH_2$), 16.2 ($CH_3$), 15.8 ($CH_3$); EIMS *m/z* 346 (5, $M^+$), 331 (3), 303 (3), 286 (90), 218 (45), 205 (100), 163 (45), 121 (55), 93 (60); HREIMS [$M^+$ − AcOH] calcd for $C_{20}H_{30}O$ *m/z* 286.2296, found *m/z* 286.2304.

**General Procedure for Oxime Synthesis**: A mixture of ketone (**8b**−**14b**, 1 mmol), $NH_2OH{\cdot}HCl$ (2 mmol), and NaOAc (1 mmol) in MeOH (20 mL) was stirred at room temperature until the starting ketone was consumed. The solvent was then removed, and the residue was submitted to flash chromatography (hexane/*t*BuOMe), giving the corresponding oximes in the following yields: **8c** (75%), **9c** (70%), **10c** (89%), **11c** (80%), **12c** (88%), **13c** (92%), **14c** (91%).

**Oxime 9c.** Hexane.*t*BuOMe, 4:1; white solid, mp 142−144 °C; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.92 (br s, 1H), 4.77 (br s, 1H), 4.19 (dd, $J$ = 11.4, 5.1 Hz, 1H), 4.03 (dd, $J$ = 16.2, 6.3 Hz, 1H), 3.25 (dt, $J$ = 14.4, 4.5 Hz, 2H), 2.50−2.00 (m, 3H), 1.97 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 171.0 (C), 163.2 (C), 144.5 (C), 113.1 ($CH_2$), 62.9 ($CH_2$), 54.4 (CH), 40.5 (C), 29.9 ($CH_2$), 28.3 ($CH_3$), 22.9 ($CH_3$), 20.9 ($CH_3$), 20.8 ($CH_2$); HRFABMS calcd for $C_{12}H_{19}O_3NNa$ *m/z* 248.1263, found *m/z* 248.1261.

**Oxime 10c.** Hexane/*t*BuOMe, 4:1; white solid, mp 114−116 °C; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.50 (br s, 1H), 3.21 (dt, 1H), 2.93 (dt, 1H), 2.01 (s, 3H), 1.49 (s, 3H), 1.48−1.13 (m, 6H), 1.12 (s, 3H), 1.05 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 170.2 (C), 165.9 (C), 83.3 (C), 51.0 (CH), 40.9 (C), 33.8 ($CH_2$), 25.6 ($CH_3$), 25.1 ($CH_3$), 22.5 ($CH_3$), 22.4 ($CH_3$), 17.0 ($CH_2$), 9.1 ($CH_3$); EIMS *m/z* 227 (1, $M^+$), 212 (1), 167 (100), 153 (75), 111 (40); HRFABMS calcd for $C_{12}H_{21}O_3NNa$ *m/z* 250.1419, found *m/z* 250.1424.

**Oxime 11c.** Hexane/*t*BuOMe, 4:1; white solid, mp 109−111 °C; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.35 (t, $J$ = 6.6 Hz, 1H), 2.73 (t, $J$ = 6.6 Hz, 2H), 2.29 (t, $J$ = 6.6 Hz, 2H), 2.10 (d, $J$ = 6.9 Hz, 2H), 1.62 (s, 3H), 1.13 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 167.5 (C), 137.6 (C), 120.7 (CH), 43.3 (C), 38.6 ($CH_2$), 31.9 ($CH_2$), 27.1 ($CH_3$), 25.5 ($CH_3$), 21.4 ($CH_2$); EIMS *m/z* 167 (1, $M^+$), 152 (40), 126 (25), 108 (100), 76 (55); HREIMS calcd for $C_{10}H_{17}ON$ *m/z* 167.1310, found *m/z* 167.1314.

**Oxime 12c.** Hexane/*t*BuOMe, 4:1; white solid, mp 125−127 °C; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.87 (br s, 1H), 4.54 (br s, 1H), 4.27 (dd, $J$ = 11.4, 4.5 Hz, 1H), 4.20 (dd, $J$ = 11.4, 7.8 Hz, 1H), 3.25 (dt, $J$ = 18.3, 3.3 Hz, 2H), 2.44−2.38 (m, 1H), 1.99 (s, 3H), 1.92−1.16 (m, 7H), 1.14 (s, 3H), 1.03 (s, 3H), 0.87 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 171.0 (C), 166.2 (C), 146.0 (C), 108.0 ($CH_2$), 61.5 ($CH_2$), 55.2 (CH), 54.1 (CH), 40.8 (C), 38.9 (C), 37.2 ($CH_2$, two carbons), 26.9 ($CH_3$), 24.1 ($CH_2$), 23.3 ($CH_3$), 21.1 ($CH_3$), 17.6 ($CH_2$), 14.8 ($CH_3$); EIMS *m/z* 293 (8, $M^+$), 276 (25), 234 (97), 216 (100), 166 (55), 124 (65), 91 (80), 79 (75); HRFABMS calcd for $C_{17}H_{27}O_3NNa$ *m/z* 316.1888, found *m/z* 316.1889.

**Oxime 13c.** Hexane/*t*BuOMe, 4:1; white solid, mp 144−146 °C; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.53 (br s, 1H), 5.35 (t, $J$ = 6.6 Hz, 1H), 3.20 (dt, $J$ = 14.7, 3.9 Hz, 2H), 2.16−1.83 (m, 3H), 1.73 (s, 3H), 1.69−1.25 (m, 6H), 1.16 (s, 3H), 0.99 (s, 3H), 0.95 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 167.2 (C), 141.2 (C), 122.3 (CH), 59.9 (CH), 45.3 ($CH_2$), 41.7 (C), 40.9 ($CH_2$), 35.8 (C), 34.6 ($CH_2$), 26.4 ($CH_3$), 25.5 ($CH_3$), 23.2 ($CH_3$), 22.1 ($CH_2$), 19.0 ($CH_3$), 17.9 ($CH_2$); EIMS *m/z* 235 (40, $M^+$), 218 (75), 192 (20), 152 (60), 134 (70), 99 (85), 67 (100); HRFABMS calcd for $C_{15}H_{25}ONNa$ *m/z* 258.1833, found *m/z* 258.1831.

**Oxime 14c.** Hexane/*t*BuOMe, 4:1; white solid, mp 166−168 °C; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.84 (br s, 1H), 4.51 (br s, 1H), 4.31 (dd, $J$ = 11.1, 3.3 Hz, 1H), 4.17 (dd, $J$ = 11.1, 9.3 Hz, 1H), 2.98 (dt, $J$ = 15.3, 4.6 Hz, 2H), 2.41−2.21 (m, 4H), 2.00 (s, 3H), 1.90−1.17 (m, 9H), 1.14 (s, 3H), 1.04 (s, 3H), 0.90 (s, 3H), 0.76 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 171.5 (C), 166.9 (C), 146.4 (C), 107.4 ($CH_2$), 61.5 ($CH_2$), 59.2 (CH), 55.4 (CH), 55.0 (CH), 40.3 (C), 40.2 ($CH_2$), 39.4 ($CH_2$), 39.2 (C), 38.5 ($CH_2$), 37.6 (C), 37.5 ($CH_2$), 27.5 ($CH_3$), 23.1 ($CH_2$), 23.0 ($CH_3$), 21.2 ($CH_3$), 19.4 ($CH_2$), 16.1 ($CH_3$), 15.9 ($CH_3$); EIMS *m/z* 361 (1, $M^+$), 331 (7), 286 (90), 271 (15), 243 (10), 205 (100), 187 (17), 163 (35), 121 (55), 93 (65); HREIMS calcd for $C_{22}H_{35}O_3N$ *m/z* 361.2617, found *m/z* 361.2620.

**General Procedure for Pd^II-Mediated Remote Functionalization.** A mixture of oxime (**10c**−**14c**, **10d** and **11d**; 1 mmol), NaOAc (1.2 mmol), and $Na_2PdCl_4$ (1.2 mmol) in AcOH or MeOH (2−5 mL) (see Table 1) was stirred at room temperature for 48 h. The solvent was removed, and the residue diluted with $CH_2Cl_2$, filtered through a Celite pad, and concentrated. The residue obtained and Py (3.2 mmol) in THF (10 mL) were stirred at room temperature for 15 min. The reaction was then cooled to −78 °C, AcOH (66 mmol) and $Pb(OAc)_4$ (1.1 mmol) were added, and the resulting mixture allowed to warm to room temperature and stirred for 24 h. Subsequently, *t*BuOMe was added, and the mixture was washed with saturated $NaHCO_3$ and dried (anhydroud $Na_2SO_4$), and the solvent was removed. The residue was submitted to flash chromatography (hexane/*t*BuOMe) giving the corresponding acetoxy oximes in the following yields: **10d** (82%), **11d** (88%), **12d** (100%), **13d** (85%), **14d** (72%), **15d** (55%) and **16d** (42%). Oximes **14d**−**16d** were isolated contaminated with minor amounts of their hydrolysis products (**14e**−**16e**), so we decided to describe these products directly below.

**Acetoxy Oxime 10d.** Hexane/*t*BuOMe, 4:1; vitreous solid; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.27 (d, $J$ = 11.4 Hz, 1H), 4.00 (d, $J$ = 11.4 Hz, 1H), 3.17 (dt, $J$ = 15, 3.7 Hz, 1H), 2.89 (dt, $J$ = 14.5, 4 Hz, 1H), 2.02 (s, 3H), 2.01 (s, 3H), 1.98−1.75 (m, 3H), 1.53 (s, 3H), 1.09 (s, 3H), 1.01 (d, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 169.2 (C), 168.2 (C), 159.6 (C), 81.4

(24) We could not achieve good quality HRMS for ketones **9b**, **10b**, and **13b**.

(C), 64.0 ($CH_2$), 42.2 (CH), 41.7 (C), 31.0 ($CH_2$), 23.1 ($CH_3$), 20.9 ($CH_3$), 19.1 ($CH_3$), 17.0 ($CH_3$), 15.3 ($CH_2$), 6.6 ($CH_3$); EIMS *m/z* 285 (1, $M^+$) 225 (35), 152 (100), 135 (55), 108 (30); HRFABMS calcd for $C_{14}H_{23}O_5NNa$ *m/z* 308.1473, found *m/z* 308.1480.

**Acetoxy Oxime 11d.** Hexane/*t*BuOMe, 4:1; vitreous solid; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.31 (t, $J = 6.3$ Hz, 1H), 4.11 (d, $J = 11$ Hz, 1H), 3.96 (d, $J = 11$ Hz, 1H), 2.87−2.62 (m, 3H), 2.38 (dd, $J = 15$, 6 Hz, 1H), 2.29 (br t, 2H), 2.04 (s, 3H), 1.62 (s, 3H), 1.15 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 171.1 (C), 164.5 (C), 138.2 (C), 119.3 (CH), 69.8 ($CH_2$), 46.7 (C), 33.1 ($CH_2$), 322 ($CH_2$), 25.5 ($CH_3$), 22.3 ($CH_3$), 21.8 ($CH_2$), 20.1 ($CH_3$); EIMS *m/z* 225 (1, $M^+$), 208 (1), 165 (50), 148 (100), 94 (35); HRFABMS calcd for $C_{12}H_{19}O_3NNa$ *m/z* 248.1262, found *m/z* 248.1266.

**Acetoxy Oxime 12d.** Hexane/*t*BuOMe, 4:1; vitreous solid; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 4.90 (br s, 1H), 4.58 (br s, 1H), 4.35−4.08 (m, 2H), 4.19 (d, $J = 11.1$ Hz, 1H), 4.03 (d, $J = 11.1$ Hz, 1H), 3.09 (dt, $J = 16.3$, 3.1 Hz, 1H), 2.44−2.35 (m, 1H), 2.25−2.05 (m, 1H), 2.04 (s, 3H), 2.01 (s, 3H), 2.00−1.10 (m, 7H), 1.02 (s, 3H), 0.85 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 172.1 (C), 171.0 (C), 162.0 (C), 145.5 (C), 108.2 ($CH_2$), 67.4 ($CH_2$), 61.4 ($CH_2$), 53.8 (CH), 47.9 (CH), 43.2 (C), 38.5 (C), 37.1 ($CH_2$), 35.5 ($CH_2$), 24.3 ($CH_2$), 21.1 ($CH_3$), 21.0 ($CH_3$), 19.7 ($CH_3$), 18.1 ($CH_2$), 14.7 ($CH_3$); EIMS *m/z* 351 (1, $M^+$), 336 (1), 317 (5), 276 (100), 264 (25), 216 (65), 201 (63), 173 (75), 133 (95), 91 (75); HRFABMS calcd for $C_{19}H_{29}O_5NNa$ *m/z* 374.1943, found *m/z* 374.1941.

**Acetoxy Oxime 13d.** Hexane/MeO*t*Bu, 4:1; vitreous solid; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.21 (br s, 1H), 5.35 (t, $J = 6.4$ Hz, 1H), 4.17 (d, $J = 11.1$ Hz, 1H), 4.10 (d, $J = 11.1$ Hz, 1H), 3.06 (dt, $J = 16$, 3 Hz, 2H), 2.26−2.14 (m, 2H), 2.05 (s, 3H), 1.72 (s, 3H), 1.70−1.10 (m, 7H), 0.97 (s, 3H), 0.93 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 171.2 (C), 163.2 (C), 141.4 (C), 122.1 (CH), 66.7 ($CH_2$), 51.9 (CH), 45.0 ($CH_2$), 44.2 (C), 39.4 ($CH_2$), 35.3 (C), 34.1 ($CH_2$), 25.4 ($CH_3$), 22.1 ($CH_2$), 21.1 ($CH_3$), 19.5 ($CH_3$), 19.0 ($CH_3$), 18.4 ($CH_2$); EIMS *m/z* 293 (10, $M^+$), 276 (5), 234 (15), 220 (65), 178 (18), 152 (98), 134 (60), 93 (55), 67 (70); HRFABMS calcd for $C_{17}H_{27}O_3NNa$ *m/z* 316.1888, found *m/z* 316.1882.

**General Procedure for Oxime Hydrolysis.** A mixture of $NH_4OAc$ (28 mmol), 20% HCl (0.5 mL), $H_2O$ (15 mL), and $TiCl_3$ (5 mmol) was added to a solution of acetoxy oxime (**10d**−**16d**, 1 mmol) in THF (20 mL), and the resulting mixture was stirred at room temperature until the starting oxime was consumed. The reaction was then diluted with *t*BuOMe, washed with saturated $NaHCO_3$, and dried over anhydroud $Na_2SO_4$, and the solvent was removed. The residue was submitted to flash chromatography (hexane/*t*BuOMe, 4:1) giving the corresponding acetoxy ketones in the following yields: **10e** (82%), **11e** (85%), **12e** (85%), **13e** (85%), **14e** (85%), **15e** (83%), **16e** (85%).

**Acetoxy Ketone 10e.** Hexane/*t*BuOMe, 4:1; white solid; mp 155−159 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 4.27 (d, $J = 11.1$ Hz, 1H), 3.87 (d, $J = 11.1$ Hz, 1H), 3.02 (ddd, $J = 14.4$, 5.5, 3.4 Hz, 1H), 2.49 (td, $J = 15.0$, 5.6 Hz, 1H), 2.27 (dt, $J = 15.8$, 4.0 Hz, 1H), 2.03 (s, 3H), 1.99 (s, 3H), 1.89 (q, $J = 7.0$ Hz, 1H), 1.74 (td, $J = 14.3$, 4.6 Hz, 1H), 1.58 (s, 3H), 1.07 (s, 3H), 1.04 (d, $J = 7.0$ Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 211.4 (C), 170.6 (C), 170.0 (C), 82.7 (C), 65.9 ($CH_2$), 50.9 (C), 43.7 (CH), 34.5 ($CH_2$), 33.2 ($CH_2$), 24.6 ($CH_3$), 22.3 ($CH_3$), 20.1 ($CH_3$), 17.5 ($CH_3$), 8.9 ($CH_3$); EIMS *m/z* 270 (1, $M^+$), 255 (1), 210 (5), 150 (15), 99 (100); HRFABMS calcd for $C_{14}H_{22}O_5Na$ *m/z* 293.1364, found *m/z* 293.1359.

**Acetoxy Ketone 11e.** Hexane/*t*BuOMe, 4:1; colorless oil; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.43 (br t, 1H), 4.11 (d, $J = 10.8$ Hz, 1H), 4.05 (d, $J = 10.8$ Hz, 1H), 2.80−2.75 (m, 1H), 2.75−2.65 (m, 1H), 2.53 (dd, $J = 15.8$, 5.7 Hz, 1H), 2.30−2.25 (m, 2H), 2.10 (dd, $J = 15.9$, 7.3 Hz, 1H), 2.02 (s, 3H), 1.67 (s, 3H), 1.09 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 214.5 (C), 170.8 (C), 137.4 (C), 120.6 (CH), 69.5 ($CH_2$), 53.5 (C), 38.5 ($CH_2$), 32.2 ($CH_2$), 31.8 ($CH_2$), 25.3 ($CH_3$), 20.9 ($CH_3$), 20.6 ($CH_3$); EIMS *m/z* 210 (10, $M^+$), 150 (50), 122 (52), 93 (100), 79 (35).[35]

**Acetoxy Ketone 12e.** Hexane/*t*BuOMe, 4:1; vitreous solid; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 4.95 (br s, 1H), 4.64 (br s, 1H), 4.37 (dd, $J = 11.5$, 4.0 Hz, 1H), 4.24 (dd, $J = 11.5$, 8.5 Hz, 1H), 4.16 (d, $J = 10.9$ Hz, 1H), 3.95 (d, $J = 10.9$ Hz, 1H), 2.64−2.43 (m, 3H), 2.03 (s, 6H), 1.85−1.15 (m, 7H), 0.98 (s, 3H), 0.95 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 212.7 (C), 171.2 (C), 170.7 (C), 145.1 (C), 108.8 ($CH_2$), 66.9 ($CH_2$), 61.3 ($CH_2$), 53.6 (CH), 50.6 (C), 47.6 (CH), 38.3 (C), 37.0 ($CH_2$), 35.8 ($CH_2$), 35.1 ($CH_2$), 24.4 ($CH_2$), 21.1 ($CH_3$), 20.9 ($CH_3$), 18.0 ($CH_3$), 15.0 ($CH_3$); EIMS *m/z* 336 (3, $M^+$), 276 (100), 234 (20), 216 (65), 201 (60), 161 (63), 133 (75), 91 (73); HRFABMS calcd for $C_{19}H_{28}O_5Na$ *m/z* 359.1834, found *m/z* 359.1834.

**Acetoxy Ketone 13e.** Hexane/*t*BuOMe, 4:1; white solid; mp 123−125 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.38 (br t, $J = 6.8$ Hz, 1H), 4.16 (d, $J = 10.9$ Hz, 1H), 4.03 (d, $J = 10.9$ Hz, 1H), 2.65 (ddd, $J = 16.6$, 7.1, 4.0 Hz, 1H), 2.36 (ddd, $J = 16.6$, 3.0, 2.5 Hz, 1H), 2.02 (s, 3H), 2.10−1.25 (m, 9H), 1.74 (s, 3H), 1.02 (s, 3H), 0.96 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 213.6 (C), 170.8 (C), 141.5 (C), 121.8 (CH), 66.4 ($CH_2$), 51.6 (CH), 44.7 ($CH_2$), 39.6 ($CH_2$), 35.6 ($CH_2$), 35.1 (C), 34.0 ($CH_2$), 25.4 ($CH_3$), 22.4 ($CH_2$), 21.0 ($CH_3$), 18.8 ($CH_3$), 17.8 ($CH_3$), (one quaternary-carbon signal was not observed); EIMS *m/z* 278 (40, $M^+$), 263 (1), 218 (20), 205 (25), 150 (55), 132 (70), 93 (100), 67 (97); HRFABMS calcd for $C_{17}H_{26}O_3Na$ *m/z* 301.1779, found *m/z* 301.1777.

**Acetoxy Ketone 14e.** Hexane/*t*BuOMe, 4:1; colorless oil; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 4.85 (br s, 1H), 4.52 (br s, 1H), 4.31 (dd, $J = 11.1$, 3.3 Hz, 1H), 4.17 (dd, $J = 11.1$, 9.3 Hz, 1H), 4.08−4.02 (m, 2H), 2.50−2.28 (m, 2H), 2.03 (s, 3H), 2.02 (s, 3H), 1.90−1.10 (m, 13H), 0.99 (s, 3H), 0.93 (s, 3H), 0.80 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 213.1 (C), 171.5 (C), 170.8 (C), 146.0 (C), 107.7 ($CH_2$), 67.7 ($CH_2$), 61.4 ($CH_2$), 58.5 (CH), 54.8 (CH), 50.1 (C), 47.9 (CH), 39.6 ($CH_2$), 39.1 (C), 37.9 ($CH_2$), 37.4 (C), 36.9 ($CH_2$), 35.1 ($CH_2$), 23.2 ($CH_2$), 21.2 ($CH_3$), 21.0 ($CH_3$), 19.9 ($CH_2$), 17.3 ($CH_3$), 15.9 ($CH_3$), 15.8 ($CH_3$); EIMS *m/z* 404 (8, $M^+$), 344 (30), 302 (15), 284 (27), 217 (40), 203 (100), 161 (55), 133 (85), 93 (97); HREIMS calcd for $C_{24}H_{36}O_5$ *m/z* 404.2563, found *m/z* 404.2568.

**Diacetoxy Ketone 15e.** Hexane/*t*BuOMe, 4:1; colorless oil; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.09 (d, $J = 11.4$ Hz, 1H), 4.67 (d, $J = 11.4$ Hz, 1H), 4.06 (d, $J = 11.4$ Hz, 1H), 3.96 (d, $J = 11.4$ Hz, 1H), 3.14 (dt, $J = 14.6$, 5.0 Hz, 1H), 2.76 (td, $J = 15.0$, 5.6, 1H), 2.25 (dt, $J = 15.0$, 4.0, 1H), 2.12 (s, 3H), 2.10−1.90 (m, 1H), 2.02 (s, 3H), 1.98 (s, 3H), 1.74 (dt, $J = 14.3$, 4.6 Hz, 1H), 1.61 (s, 3H), 1.12 (d, $J = 7.1$ Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 207.4 (C), 170.7 (C), 170.6 (C), 169.9 (C), 82.4 (C), 62.9 ($CH_2$), 62.7 ($CH_2$), 54.8 (C), 44.8 (CH), 34.9 ($CH_2$), 33.8 ($CH_2$), 24.5 ($CH_3$), 22.4 ($CH_3$), 21.0 ($CH_3$), 20.8 ($CH_3$), 8.9 ($CH_3$); EIMS *m/z* 328 (1, $M^+$), 268 (4), 208 (6), 195 (5), 166 (15), 148 (20), 99 (100); HRFABMS calcd for $C_{16}H_{24}O_7Na$ *m/z* 351.1419, found *m/z* 351.1427. The acidic hydrolysis of the oxime precursor produced minor amounts of a C-3 epimer.

**Diacetoxy Ketone 16e.** Hexane/*t*BuOMe, 4:1; colorless oil; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.41 (br t, 1H), 4.32 (d, $J = 11.3$ Hz, 2H), 4.10 (d, $J = 11.3$ Hz, 2H), 2.77 (t, $J = 6.6$ Hz, 2H), 2.37−2.30 (m, 4H), 2.03 (s, 6H), 1.69 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 211.4 (C), 170.7 (C), 138.8 (C), 119.3 (CH), 64.8 ($CH_2$), 56.6 (C), 38.6 ($CH_2$), 31.6 ($CH_2$), 27.3 ($CH_2$), 25.4 ($CH_3$), 20.9 ($CH_3$); EIMS *m/z* 268 (2, $M^+$), 208 (25), 166 (8), 148 (65), 120 (25), 106 (100), 79 (40); HREIMS [$M^+$ − AcOH] calcd for $C_{12}H_{16}O_3$ *m/z* 208.1099, found *m/z* 208.1104.

**Synthesis of 21a.** A mixture of NaH (61 mg, 2.6 mmol) and methyl diethylphosphonoacetate in THF (15 mL) was stirred at room temperature for 30 min. A solution of ketone **20** (74 mg, 0.25 mmol) in THF (5 mL) was added, and the mixture was stirred at 50 °C for 48 h. The mixture was then diluted with *t*BuOMe, washed with water, and dried over anhydrous $Na_2SO_4$, and the solvent was removed. The residue was submitted to flash chromatography (hexane/*t*BuOMe, 65:35) giving methyl esther **21a** (65 mg, 75%) as 9:1 mixture of

*E/Z* stereoisomers: vitreous solid; $^1$H NMR (300 MHz, $CDCl_3$) (major isomer) $\delta$ 5.62 (br s, 1H), 4.84 (br s, 1H), 4.49 (br s, 1H), 3.66 (s, 3H), 3.22 (dd, $J$ = 11.5, 4.2 Hz, 1H), 2.40−2.20 (m, 3H), 2.13 (s, 3H), 2.00−1.80 (m, 4H), 1.75−1.05 (m, 7H), 0.97 (s, 3H), 0.75 (s, 3H), 0.66 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) (major isomer) $\delta$ 160.9 (C), 147.7 (C), 122.7 (C), 115.1 (CH), 106.8 ($CH_2$), 78.8 (CH), 55.9 (CH), 54.7 ($CH_3$), 50.8 (CH), 43.3 (C), 39.8 ($CH_2$), 39.8 (C), 38.2 ($CH_2$), 37.1 ($CH_2$), 28.4 ($CH_3$), 28.0 ($CH_2$), 24.1 ($CH_2$), 21.7 ($CH_2$), 18.9 ($CH_3$), 15.5 ($CH_3$), 14.5 ($CH_3$); EIMS *m/z* 334 (1), 319 (10), 301 (15), 260 (15), 203 (18), 175 (20), 135 (100), 114 (90), 82 (50); HRFABMS calcd for $C_{21}H_{34}O_3Na$ *m/z* 357.2405, found *m/z* 357.2402.

**Synthesis of 22a.** Oxidation of alcohol **21a** with Dess−Martin periodinane (see general procedure described above) yielded ketone **22a** (80%) as a vitreous solid: hexane/*t*BuOMe, 4:1; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.63 (br s, 1H), 4.91 (br s, 1H), 4.56 (br s, 1H), 3.67 (s, 3H), 2.70−2.26 (m, 5H), 2.14 (s, 3H), 2.05−1.05 (m, 9H), 1.07 (s, 3H), 1.00 (s, 3H), 0.85 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 216.6 (C), 160.5 (C), 147.0 (C), 122.5 (C), 115.2 (CH), 107.7 ($CH_2$), 55.2 (CH), 55.2 ($CH_3$), 50.9 (CH), 47.8 (C), 39.7 ($CH_2$), 39.6 ($CH_2$), 39.4 (C), 37.9 ($CH_2$), 34.8 ($CH_2$), 26.2 ($CH_3$), 25.2 ($CH_2$), 22.1 ($CH_2$), 21.8 ($CH_3$), 19.0 ($CH_3$), 14.1 ($CH_3$).

**Preparation of Oxime 23.** Starting from ketone **22a** and following the general procedure described above for oxime synthesis, we obtained **23** (100%) as a vitreous solid: hexane/MeO*t*Bu, 85:15; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.62 (br s, 1H), 4.90 (br s, 1H), 4.53 (br s, 1H), 3.67 (s, 3H), 3.21 (dt, $J$ = 14.7, 3.6 Hz, 2H), 2.43−2.20 (m, 2H), 2.13 (s, 3H), 2.08−1.17 (m, 10H), 1.14 (s, 3H), 1.02 (s, 3H), 0.79 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 166.7 (C), 160.8 (C), 147.4 (C), 122.5 (C), 115.2 (CH), 107.3 ($CH_2$), 55.5 (CH), 55.5 ($CH_3$), 50.9 (CH), 40.8 (C), 39.7 ($CH_2$), 39.6 (C), 37.9 ($CH_2$), 37.4 ($CH_2$), 27.1 ($CH_3$), 24.6 ($CH_2$), 23.2 ($CH_3$), 21.9 ($CH_2$), 19.0 ($CH_3$), 17.7 ($CH_2$), 14.2 ($CH_3$); EIMS *m/z* 347 (2), 332 (5), 317 (8), 281 (20), 258 (40), 207 (100), 174 (35), 159 (42), 121 (55), 95 (70), 55 (90); HRFABMS calcd for $C_{21}H_{33}O_3NNa$ *m/z* 370.2358, found *m/z* 370.2360.

**Synthesis of Acetoxy Oxime 24.** Palladium-mediated remote functionalization of oxime **23** (see general procedure) gave acetoxy oxime **24** (76%) as a vitreous solid. NMR spectra indicated that, after flash chromatography, oxime **24** was contaminated by some proportion of its hydrolysis product (**25**). Therefore, this contaminated oxime was used in the next hydrolysis step without further purification.

**Synthesis of Ketone 25.** Standard oxime hydrolysis of compound **24** gave acetoxy ketone **25** (70%) as a vitreous solid. Spectroscopic data matched those reported in ref 1.

**Preparation of Keto Ester 29.** A sample of Jones' reagent (1 mL) was added to a solution of diol **28** (275 mg, 1.15 mmol) in acetone (35 mL) and stirred at room temperature for 1 h. The solvent was then removed, and the residue was dissolved in *t*BuOMe, washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated. The residue was stirred with a saturated solution of $CH_2N_2$ in $Et_2O$ (5 mL) for 30 min. The solvent was removed, and the residue was submitted to flash chromatograpy (hexane/*t*BuOMe, 7:3) giving **29** (187 mg, 62%) as a white solid: mp 119−121 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.87 (s, 1H), 4.67 (s, 1H), 3.62 (s, 3H), 2.68 (s, 1H), 2.66 (m, 1H), 2.43 (dt, $J$ = 15, 3.3 Hz, 1H), 2.27 (ddq, $J$ = 15, 3.3, 1.5 Hz, 1H), 2.04 (m, 1H), 1.77 (m, 1H), 1.65−1.44 (m, 4H), 1.22 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 215.5 (C), 171.6 (C), 142.6 (C), 109.6 ($CH_2$), 61.9 (CH), 54.6 (CH), 51.3 ($CH_3$), 47.8 (C), 38.7 (C), 37.3 ($CH_2$), 35.5 ($CH_2$), 34.6 ($CH_2$), 25.7 ($CH_3$), 23.9 ($CH_2$), 22.0 ($CH_3$), 13.7 ($CH_3$); EIMS *m/z* 264 (80), 232 (40), 189 (30), 147 (70), 123 (85), 91 (100); HRFABMS calcd for $C_{16}H_{24}O_3Na$ *m/z* 287.1623, found *m/z* 287.1623.

**Preparation of Oxime 30.** This oxime was obtained from ketone **29** following the general procedure for oxime synthesis (85% yield): white solid (hexane/*t*BuOMe, 1:1) mp 179−181 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.86 (s, 1H), 4.66 (s, 1H), 3.62 (s, 3H), 3.26 (dt, $J$ = 15, 3.6 Hz, 1H), 2.75 (s, 1H), 2.43 (dq, $J$ = 13.5, 2 Hz, 1H), 2.04 (td, $J$ = 14.4, 4.8 Hz, 2H), 1.80−1.65 (m, 3H), 1.65−1.22 (m, 3H), 1.18 (s, 3H), 1.15 (s, 3H), 1.05 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 171.8 (C), 166.1 (C), 142.9 (C), 109.2 ($CH_2$), 62.2 (CH), 54.8 (CH), 51.1 ($CH_3$), 40.8 (C), 38.9 (C), 37.1 ($CH_2$), 35.7 ($CH_2$), 26.8 ($CH_3$), 23.5 ($CH_2$), 23.4 ($CH_3$), 17.6 ($CH_2$), 13.9 ($CH_3$); EIMS *m/z* 279 (10), 262 (15), 220 (15), 166 (30), 119 (40), 91 (100); HREIMS calcd for $C_{16}H_{25}NO_3$ *m/z* 279.1912, found *m/z* 279.1912.

**Synthesis of Acetoxy Oxime 31.** The palladium-mediated remote functionalization of oxime **30** (see general procedure) gave acetoxy oxime **31** (90%) as a vitreous solid: hexane/*t*BuOMe, 7:3; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.86 (br s, 1H), 4.67 (br s, 1H), 4.12 (d, $J$ = 11.2 Hz, 1H), 4.02 (d, $J$ = 11.2 Hz, 1H), 3.64 (s, 3H), 3.09 (ddd, $J$ = 16.5, 5.1, 2.6 Hz, 2H), 2.82 (s, 1H), 2.44−2.40 (m, 2H), 2.03 (s, 3H), 1.72−1.32 (m, 6H), 1.14 (s, 3H), 1.03 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 171.6 (C), 171.0 (C), 166.8 (C), 142.5 (C), 109.4 ($CH_2$), 67.4 ($CH_2$), 62.1 (CH), 51.1 ($CH_3$), 47.6 (CH), 43.1 (C), 38.6 (C), 35.7 ($CH_2$), 35.6 ($CH_2$), 23.6 ($CH_2$), 21.0 ($CH_3$), 19.8 ($CH_3$), 18.1 ($CH_2$), 13.9 ($CH_3$); EIMS *m/z* 337 (70), 321 (10), 277 (85), 260 (88), 218 (55), 186 (75), 134 (77), 91 (100), 79 (65); HRFABMS calcd for $C_{18}H_{27}O_5NNa$ *m/z* 360.1786, found *m/z* 360.1787.

**Synthesis of Acetoxy Ketone 32.** Standard hydrolysis of oxime **31** gave acetoxy ketone **32** (65%) as a vitreous solid: hexane/*t*BuOMe, 7:3; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.91 (br s, 1H), 4.71 (br s, 1H), 4.11 (d, $J$ = 10.8 Hz, 1H), 3.94 (d, $J$ = 10.8 Hz, 1H), 3.67 (s, 3H), 2.88 (br s, 1H), 2.65−2.53 (m, 1H), 2.48−2.34 (m, 2H), 2.01 (s, 3H), 1.90−1.73 (m, 2H), 1.69−1.40 (m, 4H), 1.24 (s, 3H), 0.99 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 212.4 (C), 171.5 (C), 170.0 (C), 142.2 (C), 109.9 ($CH_2$), 69.9 ($CH_2$), 61.9 (CH), 51.2 ($CH_3$), 50.5 (C), 47.1 (CH), 38.3 (C), 35.7 ($CH_2$), 35.4 ($CH_2$), 35.0 ($CH_2$), 23.9 ($CH_2$), 20.9 ($CH_3$), 18.1 ($CH_3$), 13.8 ($CH_3$); EIMS *m/z* 322 (15, $M^+$), 290 (10), 250 (45), 230 (80), 203 (55), 161 (65), 133 (100), 91 (98), 55 (70); HRFABMS calcd for $C_{18}H_{26}O_5Na$ *m/z* 345.1677, found *m/z* 345.1674.

**Obtention of $\gamma$-Dihydroxylated Synthon 33.** L-Selectride (0.32 mL, 0.32 mmol) was added to a solution of ketone **32** (9 mg, 0.032 mmol) in THF (3 mL) at −78 °C; the resulting mixture was stirred for 22 h, extracted with *t*BuOMe, washed with 2 N HCl, and dried over anhydrous $Na_2SO_4$; and the solvent was removed. The residue was submitted to flash chromatography (hexane/*t*BuOMe, 1:1) giving diol **33** (7 mg, 77%) as a white solid: mp 203−205 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.84 (s, 1H), 4.66 (s, 1H), 3.70 (br t, $J$ = 2.0 Hz, 1H), 3.65 (s, 3H), 3.48 (d, $J$ = 11.4 Hz, 1H), 3.39 (d, $J$ = 11.4 Hz, 1H), 2.96 (br s, 1H), 2.41 (ddd, $J$ = 15.0, 3.5, 2.1 Hz, 1H), 2.22−1.80 (m, 8H), 1.10 (s, 3H), 0.70 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 177.1 (C), 143.6 (C), 108.7 ($CH_2$), 76.8 (CH), 71.2 ($CH_2$), 62.8 (CH), 51.1 ($CH_3$), 41.4 (CH), 40.6 (C), 38.8 (C), 36.0 ($CH_2$), 31.3 ($CH_2$), 26.8 ($CH_2$), 22.7 ($CH_2$), 18.0 ($CH_3$), 14.5 ($CH_3$); EIMS *m/z* 282 (10, $M^+$), 251 (35), 235 (100), 191 (45), 173 (40), 147 (42), 91 (55); HRFABMS calcd for $C_{16}H_{26}O_4Na$ *m/z* 305.1728, found *m/z* 305.1725.

**Synthesis of Keto Aldehyde 34.** Dess−Martin periodinane (1.20 g, 3.0 mmol) was added to a solution of diol **28** (237 mg, 0.99 mmol) in $CH_2Cl_2$ (25 mL), and the mixture was stirred at room temperature for 4 h. Then *t*BuOMe was added, and the solution was washed with a 1:1 mixture of aqueous 10% $Na_2S_2O_3$ and saturated $NaHCO_3$, and brine. The organic layer was dried (anhydrous $Na_2SO_4$), and the solvent was removed. The residue was dissolved in 0.5 M methanolic $K_2CO_3$ (20 mL) at 0 °C and stirred for 3 h. The mixture was then diluted with *t*BuOMe and washed with 2 N HCl and brine. The organic layer was dried (anhyd. $Na_2SO_4$), and the solvent was removed. Flash chromatography (hexane/*t*BuOMe, 7:3) of the residue provided keto aldehyde **34** (148 mg, 64%) as a vitreous solid: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.99 (s, 1H), 2.73 (q, $J$ = 6.4 Hz, 1H), 2.43 (dd, $J$ = 8, 7 Hz, 2H), 2.27 (dd, $J$ = 8, 4.2 Hz, 2H), 2.04 (s, 3H), 1.68−1.40 (m, 3H), 1.32−1.20 (m, 1H), 1.12 (s, 3H), 1.03 (s, 3H), 0.99 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 217.3 (C), 191.6 (CH), 156.1 (C), 141.7 (C), 51.2 (CH), 47.0 (C), 38.1 (C), 36.4 ($CH_2$), 34.5 ($CH_2$), 34.1 ($CH_2$), 27.3 ($CH_3$), 20.8 ($CH_3$), 19.3 ($CH_3$), 19.2 ($CH_2$), 18.9 ($CH_3$); EIMS *m/z* 234 (100), 206 (40), 149 (50), 123 (80), 91 (85); HRFABMS calcd for $C_{15}H_{22}O_2Na$ *m/z* 257.1517, found *m/z* 257.1521.

**Synthesis of Keto Ester 35.** A mixture of $NaClO_2$ (422 mg, 4.72 mmol) and $NaH_2PO_4 \cdot H_2O$ (305 mg, 3.54 mmol) was added to a solution of **34** (138 mg, 0.59 mmol) in a mixture of *t*BuOH/$H_2O$/2-methyl-2-butene (4.5:1.6:1 ratio, 20 mL). The solution was stirred at room temperature for 20 h before being extracted with *t*BuOMe, washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated. The residue was stirred with a saturated solution of $CH_2N_2$ in $Et_2O$ (5 mL) for 30 min. The solvent was removed and the residue submitted to flash chromatograpy (hexane/MeO*t*Bu, 3:1) giving **35** (90 mg, 60%) as a vitreous solid: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.68 (s, 3H), 2.59−2.47 (m, 2H), 2.41 (t, $J$ = 5.3 Hz, 1H), 2.09 (t, $J$ = 6.8 Hz, 4H), 1.77−1.60 (m, 2H), 1.61 (s, 3H), 1.24 (s, 3H), 1.06 (s, 3H), 1.02 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 216.4 (C), 170.3 (C), 136.2 (C), 134.0 (C), 51.2 ($CH_3$), 50.1 (CH), 47.2 (C), 38.2 (C), 34.9 ($CH_2$), 34.2 ($CH_2$), 32.0 ($CH_2$), 26.5 ($CH_3$), 22.2 ($CH_3$), 21.9 ($CH_3$), 19.5 ($CH_3$), 18.2 ($CH_2$); EIMS *m/z* 264 (45), 217 (55), 182 (70), 147 (75), 91 (100), 79 (70); HRFABMS calcd for $C_{16}H_{24}O_3Na$ *m/z* 287.1623, found *m/z* 287.1626.

**Preparation of Oxime 36.** Starting from ketone **35** and following the general procedure described above, we obtained oxime **36** (85% yield) as a white solid: hexane/*t*BuOMe, 1:1; mp 151−153 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.69 (s, 3H), 3.10 (ddd, $J$ = 16.0, 5.3, 3.3 Hz, 1H), 2.27−2.05 (m, 4H), 1.60 (s, 3H), 1.55−1.30 (m, 4H), 1.26 (s, 3H), 1.15 (s, 3H), 1.07 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 170.5 (C), 165.9 (C), 137.1 (C), 133.5 (C), 51.2 ($CH_3$), 50.4 (CH), 40.1 (C), 36.6 (C), 34.6 ($CH_2$), 32.2 ($CH_2$), 27.49 ($CH_3$), 23.27 ($CH_3$), 20.93 ($CH_3$), 19.97 ($CH_3$), 19.06 ($CH_2$), 17.52 ($CH_2$); EIMS *m/z* 279 (1), 262 (35), 222 (15), 158 (50), 119 (60), 91 (100); HREIMS calcd for $C_{16}H_{25}NO_3$ *m/z* 279.1912, found *m/z* 279.1912.

**Synthesis of Acetoxy Oxime 37.** The palladium-mediated remote functionalization of oxime **36** (see general procedure) gave acetoxy oxime **37** (83%) as a vitreous solid: hexane/*t*BuOMe, 7:3; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.50 (br s, 1H), 4.07 (br s, 2H), 3.72 (s, 3H), 2.90 (dq, $J$ = 17.5, 2.7 Hz, 2H), 2.47−2.35 (m, 1H), 2.12−2.02 (m, 2H), 2.01 (s, 3H), 1.80−1.67 (m, 2H), 1.66 (s, 3H), 1.22 (s, 3H), 1.08 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 171.1 (C), 170.5 (C), 161.9 (C), 136.6 (C), 133.9 (C), 68.6 ($CH_2$), 51.2 ($CH_3$), 43.6 (CH), 42.7 (C), 36.3 (C), 33.3 ($CH_2$), 32.0 ($CH_2$), 21.0 ($CH_3$), 20.8 ($CH_3$), 19.7 ($CH_3$), 19.5 ($CH_3$), 19.1 ($CH_2$), 18.6 ($CH_2$); EIMS *m/z* 337 (35), 306 (20), 278 (18), 260 (40), 215 (20), 189 (25), 153 (100), 121 (30), 91 (55); HRFABMS calcd for $C_{18}H_{27}O_5NNa$ *m/z* 360.1786, found *m/z* 360.1785.

**Synthesis of Acetoxy Ketone 38.** Standard hydrolysis of oxime **37** gave acetoxy ketone **38** (71%) as a vitreous solid: hexane/*t*BuOMe, 7:3; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.06−4.02 (m, 2H), 3.74 (s, 3H), 2.61−2.40 (m, 2H), 2.18−2.00 (m, 3H), 1.99 (s, 3H), 1.85−1.75 (m, 4H), 1.65 (s, 3H), 1.28 (s, 3H), 1.01 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 213.5 (C), 170.7 (C), 170.3 (C), 136.1 (C), 134.5 (C), 67.7 ($CH_2$), 51.3 ($CH_3$), 50.1 (C), 43.3 (CH), 36.1 (C), 35.2 ($CH_2$), 33.9 ($CH_2$), 31.8 ($CH_2$), 21.0 ($CH_3$), 20.9 ($CH_3$), 19.7 ($CH_3$), 19.3 ($CH_2$), 17.4 ($CH_3$); EIMS *m/z* 322 (50, $M^+$), 291 (50), 262 (35), 215 (100), 187 (45), 175 (80), 147 (75), 91 (83); HRFABMS calcd for $C_{18}H_{26}O_5Na$ *m/z* 345.1677, found *m/z* 345.1674.

**Obtention of $\gamma$-Dihydroxylated Synthon 39.** A sample of $NaBH_4$ (26 mg, 0.81 mmol) was added to a solution of **38** (26 mg, 0.081 mmol) in DME (5 mL) and stirred at 0 °C for 1 h. The mixture was then diluted with *t*BuOMe, washed with 2 N HCl, and dried (anhydrous $Na_2SO_4$), and the solvent was removed. The residue was dissolved in 0.5 M methanolic $K_2CO_3$ (20 mL) at 0 °C and stirred for 2 h. The mixture was then diluted with *t*BuOMe and washed with 2 N HCl and brine. The organic layer was dried (anhydrous $Na_2SO_4$), and the solvent was removed. Flash chromatography (hexane/*t*BuOMe, 1:4) of the residue provided diol **39** (11 mg, 50%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.73 (d, $J$ = 10.3 Hz, 1H), 3.71 (s, 3H), 3.68 (dd, $J$ = 11.4, 4.6 Hz, 1H), 3.42 (d, $J$ = 10.3 Hz, 1H), 2.11−2.04 (m, 2H), 1.75−1.10 (m, 7H), 1.59 (s, 3H), 1.23 (s, 3H), 0.92 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 170.58 (C), 137.9 (C), 132.9 (C), 76.6 (CH), 71.8 ($CH_2$), 51.1 ($CH_3$), 44.5 (CH), 41.8 (C), 36.4 (C), 34.6 ($CH_2$), 31.9 ($CH_2$), 27.1 ($CH_2$), 20.9 ($CH_3$), 20.8 ($CH_3$), 18.4 ($CH_2$), 11.1 ($CH_3$); EIMS *m/z* 282 (10, $M^+$), 251 (35), 235 (100), 191 (45), 173 (40), 147 (42), 91 (55); HRFABMS calcd for $C_{16}H_{26}O_4Na$ *m/z* 305.1728, found *m/z* 305.1725.

**Acknowledgment.** The authors acknowledge the Spanish “Junta de Andalucía” for financial support (research group FQM339), Dr. A. F. Barrero for his collaboration in the early stage of the work, and our English colleague Dr. J. Trout for revising our text. J.J. thanks the Spanish Ministry of Science and Technology for a grant enabling him to pursue these studies.

**Supporting Information Available:** $^1$H or $^{13}$C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0502910