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# Enantioselective Total Synthesis of Eicosanoid and Its Congener, Using Organocatalytic Cyclopropanation, and Catalytic Asymmetric Transfer Hydrogenation Reactions as Key Steps

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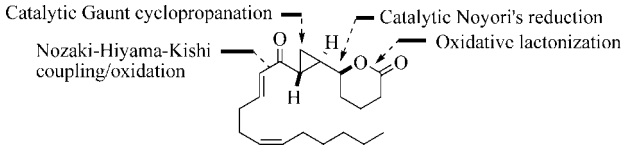



An enantioselective unified strategy for the syntheses of the oxylipin class of natural products was accomplished. Our strategy relies on three catalytic steps: (a) organocatalytic cyclopropanation, (b) the catalytic asymmetric transfer hydrogenation (CATHy) reaction, and (c) the Nozaki−Hiyama−Kishi reaction.

The *trans*-cyclopropane motif is a prevalent structural unit in a number of marine oxylipin family members, such as constanolactones **1a**,**b**, halicholactone **2**, solandelactones **3a**,**b**, and eicosanoid **4a**.[1] Primarily two subfamilies of oxylipins, constanolactones **1a**,**b** and solandelactones **3a**,**b** (Figure 1), have been identified based on the absolute configuration of the cyclopropane ring.

The solandelactones **3a**,**b** possess a (*R,R*)-cyclopropyl motif linked to saturated or unsaturated eight-membered lactone and a $C_{22}$ aliphatic carbon chain, whereas constanolactone **1a**,**b** possess a $\delta$-lactone, a dodecadiendiol side chain, and a (*S,S*)-cyclopropyl motif. The halicholactone **2** possesses a (*R,R*)-cyclopropyl motif as solandelactones but differs from it at $C_8$, $C_{12}$, and $C_{15}$. The intriguing biogenetic route proposed for constanolactone is via a 12-lipoxygenase pathway, which leads to intermediates such as arachidonic acid and an eicosanoid **4a**. Support for this pathway is provided by the isolation of **4a** from acetone powder of the Caribbean soft coral *Plexaura homomalla*.[2] The halicolactone is presumably derived from an eicosanoid with a $C_{20}$ carbon chain, while solandelactones might originate from docosanoid containing a $C_{22}$ carbon chain. The oxylipin family displays a moderate to low inhibitory activity against 5-lipoxygenase and also acts as inhibitors of farnesyltransferase, which is found in many types of cancer cells.[3] Due to significant

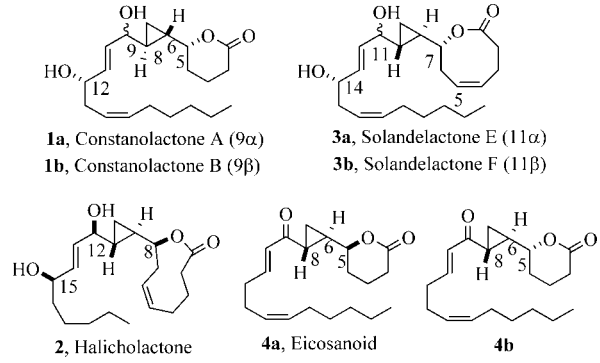
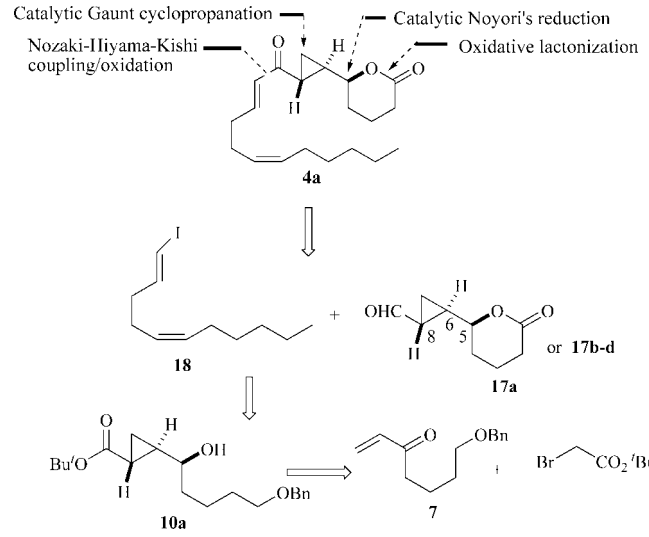



**FIGURE 1.** Oxylipin family.

**SCHEME 1. Retrosynthesis**

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(1) (a) Gerwick, W. H. *Chem. Rev.* **1993**, *93*, 1807. (b) Baertschi, S. W.; Brash, A. R.; Harris, T. M. *J. Am. Chem. Soc.* **1989**, *11*, 5003. (c) Niwa, H.; Wakamatsu, K.; Yamada, K. *Tetrahedron Lett.* **1989**, *30*, 4543. (d) Kigoshi, H.; Niwa, H.; Yamada, K.; Stouck, T. J.; Clardy, J. *Tetrahedron Lett.* **1991**, *32*, 2427. (e) Seo, Y.; Cho, K. W.; Rho, J.-R.; Kwon, B.-M.; Bok, S.-H.; Song, J.-I. *Tetrahedron Lett.* **1996**, *52*, 10583.

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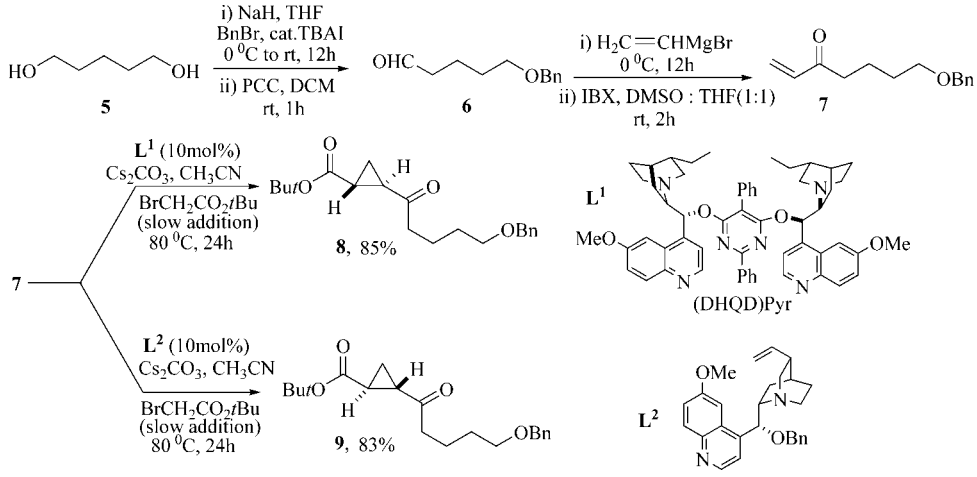
**SCHEME 2. Catalytic Cyclopropanation**



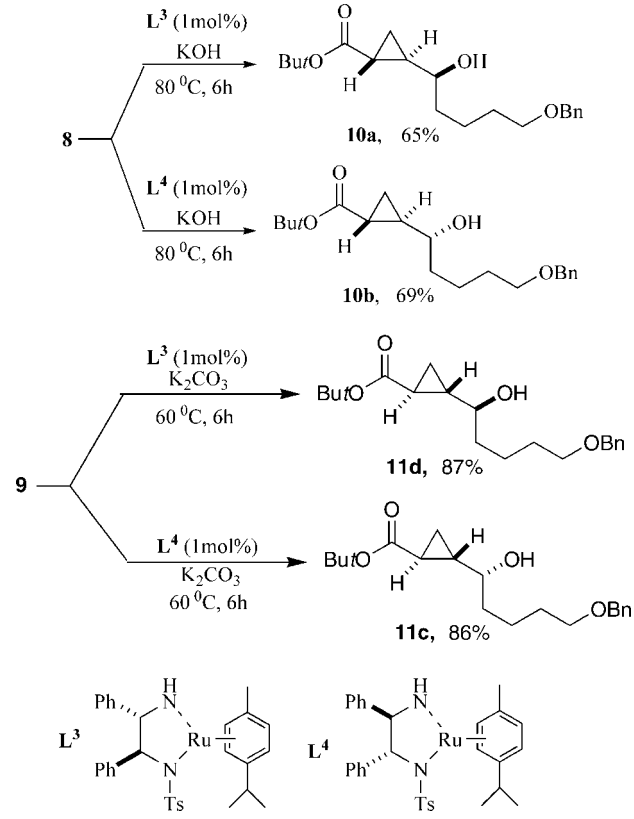

activity coupled with unique stereogenic variations within subfamilies of oxylipins, they have attracted the attention of synthetic organic chemists toward their synthesis.[4] The pioneering biomimetic synthesis initiated by White et al.[5] produced the first synthetic evidence of the intermediate of eicosanoid **4a**. Following this, the same group reported the syntheses of constanolactones **1a**,**b** and solandelactones **3a**,**b**.[6] Martin et al.[7] also successfully synthesized solandelactone **3a** and unambiguously assigned the absolute configuration. With our continued interest in developing catalytic enantioselective routes to strained small molecules,[8] we were attracted to the enantioselective total synthesis of eicosanoid **4a** and its congener **4b** (Figure 1).

Our strategy relies on three catalytic steps: (a) organocatalytic cyclopropanation, (b) the catalytic asymmetric transfer hydrogenation (CATHy) reaction, and (c) the Nozaki−Hiyama−Kishi reaction. Our retrosynthetic approach is shown in Scheme 1.

At the outset, we envisioned that all the members of the oxylipin family could be synthesized, in principle, by varying chirality inducing ligands of the above pivotal reactions with perfect stereocontrol and a predictable absolute stereochemistry. For the proposed unified synthetic strategy, the ideal advanced intermediate could be cyclopropyl $\delta$-lactone aldehydes **17a**−**d** and vinyl iodide **18**. We planned to exploit the enantioselective organocatalytic cyclopropanation protocol of Gaunt et al.[9] The synthesis began with the monoprotected pentanediol **5** as its benzyl ether, followed by oxidation to yield aldehyde **6.** Addition of vinylmagnesium bromide at 0 °C for 12 h afforded an allyl alcohol, which on further oxidation furnished vinyl ketone **7**. *tert*Butyl bromoacetate reacted with enone **7** in the presence of 10 mol % of **L**$^{1}$ $(DHQD)_2Pyr$ and $Cs_2CO_3$ as base upon heating furnished cyclopropane **8** in 85% isolated yield.

It was anticipated that the use of dimeric ligand **L**$^{1'}$ $(DHQ)_2Pyr$ would generate the enantiomer **9**. Nevertheless,

**SCHEME 3. Catalytic Asymmetric Transfer Hydrogenation Reaction**




subjecting *tert*-butyl bromoacetate and enone **7** in the presence of 10 mol % of **L**$^{1'}$ $(DHQ)_2Pyr$ under identical conditions led to the product **9** with decreased enantioselectivity. After considerable experimentation,[10] it was found that the benzyl ether of quinine ligand **L**$^{2}$ gave approximately equal magnitude of rotation as **8** but opposite in sign (Scheme 2). An effort to resolve the racemic cyclopropane product **8** on the chiral stationary phase (Chiralpak AD-H) was not successful. At this juncture, the enantioselectivity and relative configuration were assigned based upon analogy[9] and advanced further.

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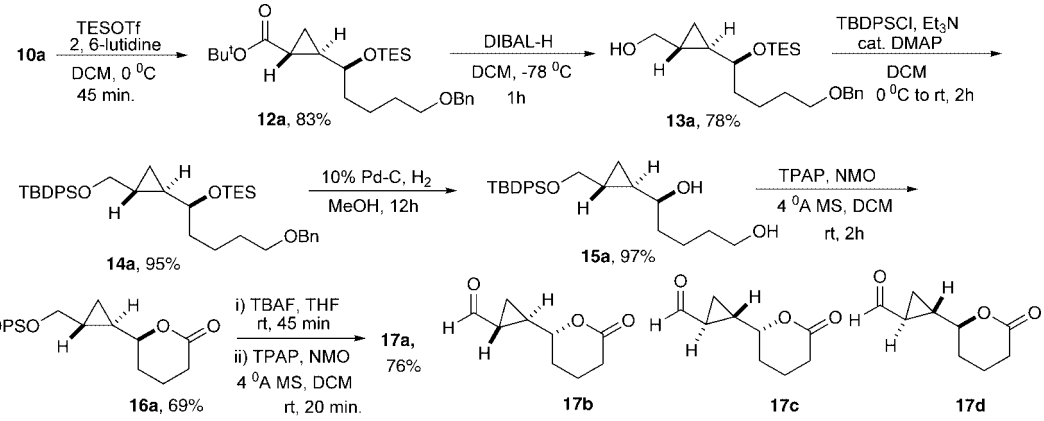
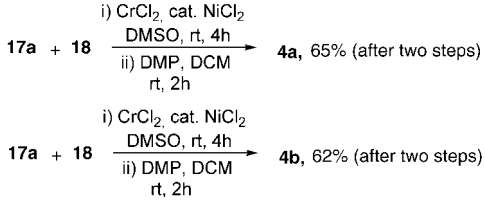
(9) Papageorgiou, C. D.; Cubillo de Dios, M. A.; Ley, S. V.; Gaunt, M. J. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 4641.

(10) The methoxy analogue of quinidine was found to be inferior to the benzyl analogue. Additionally, the benzyl analogue can be prepared easily in multigram quantities.

**SCHEME 4. Synthesis of Cyclopropyl δ-Lactone Aldehyde**




**SCHEME 5. Synthesis of Eicosanoid and Its Congener**




Next, we evaluated Noyori's[11a] catalytic asymmetric transfer hydrogenation reaction for the reduction of the keto group. The reduction of compound **8** by using 1 mol % of chiral Ru catalyst **L**$^{3}$ and 7 mol % of KOH in 2-propanol at 80 °C for 6 h proceeded cleanly to afford product **10a** in a 9:1 diastereomeric mixture.[12] The major diastereomer **10a** was isolated in 65% yield by column chromatography. Without KOH or with $K_2CO_3$ and below 60 °C, no product formation was observed.

Using **L**$^{4}$ as the ligand, under otherwise identical conditions, led to the alcohol **10b** with the same selectivity (9:1, dr)[11b] in 69% isolated yield. However, in the case of **9**, using **L**$^{3}$ as ligand under similar conditions, the product **11c** was obtained with decreased selectivity (8:2, dr). This problem was circumvented by using $K_2CO_3$ as the base and maintaining the reaction temperature at 60 °C. The isolated product **11c** showed excellent facial selectivity (9.5:0.5, dr)[12] in 87% yield. Similarly, employing **L**$^{4}$ as ligand, the diastereomer **11d** was successfully obtained with the same level of efficiency in 86% isolated yield (Scheme 3). The assignment of the stereochemistry of the newly formed hydroxyl group was based on Noyori's protocol,[11a] i.e., *S*,*S*-diamine-Ru catalyst induces the *S*-configuration (**10a** and **11c**),while *R*,*R*-diamine-Ru generates the *R*-configuration (**10b** and **11d**). The results indicate that the asymmetric reduction proceeded with good facial selectivity, as a result of reagent control with little or no influence due to the substrate.

Having prepared the cyclopropyl alcohols **10a**, **10b**, **11c**, and **11d**, we next proceeded to synthesize eicosaniod **4a**. To this end, the secondary hydroxy group in **10a** was protected as TES-ether **12a**, and subsequent exposure to DIBAL-H in DCM at −78 °C yielded alcohol **13a**, which was protected as its TBDPS-ether **14a**. Hydrogenation over 10% Pd−C in MeOH under balloon pressure led to the deprotection of the TES and benzyl ether to furnish diol **15a**.[13a] It was proposed to selectively oxidize the primary alcohol and subject it to Yamaguchi lactonization[7b] to synthesize cyclopropyl δ-lactone **16a**. However, the Parikh−Doering[13b] oxidation proved problematic, showing a multitude of products on tlc. Consequently, we opted for the Ley[14] oxidation. To our delight, diol **15a** when subjected to Ley's conditions, afforded cleanly lactone **16a** by selective oxidation of the primary hydroxyl, hemiacetal formation, and further oxidation. Exposure of **16a** to TBAF in THF at rt and further oxidation using the Ley[14] protocol yielded aldehyde **17a** as a single isomer in 76% yield. The spectral and chirooptical data were in agreement with data reported in the literature.[5] Thus, the absolute configuration of the newly formed streogenic centers in **17a** was assigned as 5*S*, 6*R*, and 8*R*. Similarly, **17b**, **17c**, and **17d** were synthesized employing the same sequence of steps starting from **10b**, **11c**, and **11d**, respectively (Scheme 4). Since **17b** is a diastereomer of **17a**, the absolute configuration was assigned as 5*R*, 6*R*, 8*R*. Compound **17c** is an advanced intermediate used in the synthesis of constanolactone **1a**,**b**, and comparison of sign of rotation ($[\alpha]^{23}_{D}$ +78.0 (*c* 0.25, $CHCl_3$) {lit.[4c] $[\alpha]^{23}_{D}$ +73.0 (*c* 2.4, $CHCl_3$}) helped to assign its absolute configuration as 5*R*, 6*S*, and 8*S*.

Finally, the stage was set for the synthesis of eicosanoid **4a** by a Nozaki−Hiyama−Kishi coupling reaction of **17a** and **18**. The vinyliodo segment **18**was prepared by the Takai−Utimoto reaction.[15,5b]

Initially, we have evaluated a catalytic version of the Nozaki−Hiyama−Kishi coupling reaction.[16] The reaction of **17a** with **18**, using Mn (2 equiv), LiCl (2 equiv), TMSCl (1 equiv), 1 mol% of 4,4′-di-*tert*-butyldipyridyl-$CrCl_3$, and 0.2 mol % of 4,4′-di-*tert*-butyldipyridyl-$NiCl_2$ in DME at rt, for 4 h followed by workup afforded a mixture of alkenyl alcohols. This mixture on oxidation with the Dess−Martin periodinane yielded the target compound **4a** in 35% yield. Eventually, we selected a stoichiometric version of this same reaction to improve the yield of the final compound. The coupling of **17a** with **18**, using $CrCl_2$ in the presence of catalytic $NiCl_2$ in DMSO at rt, for 4 h followed by oxidation of crude product with Dess−Martin periodinane led to the target compound **4a** in 65% isolated yield.

(11) (a) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738. (b) To estimate the enantioselectivity, the **10b** was converted to (*S*)-methoxymandelate ester. The $^1$H NMR spectrum of corresponding ester showed >95% ee in coparision with (*S*)-methoxymandelate ester of racemic **10b** (please see the Supporting Information).

(12) (a) The diastereomeric ratio was estimated by the $^1$H NMR spectrum of crude product of **10** and **11**. (b) Reduction of **8** with $NaBH_4$ in MeOH led 1:1 mixture of **10a** and **10b**.

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(15) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

(16) Namba, K.; Wang, J.; Cui, S.; Kishi, Y. *Org. Lett.* **2005**, *7*, 5421.

The spectral and optical data of **4a** were in full agreement with that reported in the literature[5,4j] ($[\alpha]^{23}_D$ −30.0 (*c* 0.15, $CHCl_3$) {lit. $[\alpha]^{23}_D$ −27.4 (*c* 0.46, $CHCl_3$)}). The congener **4b** was synthesized in 62% yield from **17b** following the above-mentioned conditions (Scheme 5). The overall yield of the 11-step synthesis was 20% from **8** to **4a**.

In conclusion, we have succeeded in developing a catalytic enantioselective unified strategy for the synthesis of the oxylipin class of natural products. The salient features of this concise convergent synthesis are (i) the genesis of chirality through an organocatalytic reaction, (ii) the production of cyclopropanes as either enantiomer employing a catalytic quantity of quinine- or quinidine-based alkaloids, and (iii) the application of Noyori's CATHy reaction that could lead to the synthesis of C(5) epimeric alcohols, which in turn would facilitate the synthesis of every representative member of the oxylipin family. Further application of this strategy for the syntheses of halicholactones and solandelactones is underway.

## Experimental Section

**(1*R*,2*R*)-*tert*-Butyl-2-(5-(benzyloxy)pentanoyl)cyclopropane Carboxylate (8).** The catalyst $\mathbf{L^1}$ (0.85 g, 8.4 mmol, 0.1 equiv with respect to alkene) was added to a stirred solution of $Cs_2CO_3$ (3.7 g, 1.2 equiv) in MeCN (42 mL, 0.23 M) and heated to 80 °C. A solution of *tert*-butyl bromoacetate (1.82 g, 9.37mmol) and the alkene **7** (2.5 g, 11.41 mmol) in MeCN (42 mL) was added over 20 h by means of a syringe pump. The syringe was rinsed with MeCN (2 mL) and the reaction mixture was stirred for a further 4 h. The reaction mixture was filtered through a celite pad and rinsed with EtOAc (20 × 4 mL) and the resulting contents were concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc in hexane) to afford **8** (3.21 g, 85%) as a colorless liquid. $[\alpha]^{23}_D$ −126.1 (*c* 3.1, $CHCl_3$); IR (KBr) 2929, 2857, 1725, 1702, 1367, 1214, 1155, 1114 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.31−7.27 (5H, m), 4.46 (2H, s), 3.44 (2H, t, $J$ = 6.0 Hz), 2.62 (2H, t, $J$ = 6.7 Hz), 2.31 (1H, ddd, $J$ = 9.0, 6.0, 3.7 Hz), 2.07−1.99 (1H, m), 1.75−1.54 (4H, m), 1.39 (9H, s), 1.30 (2H, ddt, $J$ = 8.3, 6.0, 2.2 Hz); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 207.4, 171.0, 138.4, 128.2, 127.5, 127.4, 81.0, 72.8, 69.7, 43.3, 29.0, 28.6, 27.9, 24.9, 20.4, 16.7; MS (ES) *m*/*z* 355 (M + Na)$^+$; HRMS (ES) *m*/*z* 355.1889 (calcd for $C_{20}H_{28}O_4Na$ 355.1885).

**(1*R*,2*R*)-*tert*-Butyl-2-((*S*)-5-(benzyloxy)-1-hydroxypentyl)cyclopropane Carboxylate (10a).** To a solution of **8** (2.0 g, 6.02 mmol) in anhydrous 2-propanol (84 mL) under argon was added catalyst $\mathbf{L^3}$ (0.04 g, 0.065 mmol, 1.0 mol %), which was predissolved in $CH_2Cl_2$ (2 × 1 mL). To this reaction mixture was added KOH (25 mg, 7.5 mol %), and the resulting reaction mixture was heated to 80 °C for 6 h. After the reaction mixture was cooled to rt, the solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography (8% EtOAc in hexane) to give alcohol **10a** (1.3 g, 65%) as a colorless liquid. $[\alpha]^{23}_D$ −45.6 (*c* 0.8, $CHCl_3$); IR (KBr) 3431, 2923, 2854, 1718, 1366, 1153, 1099, 757 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.33−7.18 (5H, m), 4.46 (2H, s), 3.44 (2H, t, $J$ = 6.0 Hz), 3.05 (1H, q, $J$ = 12.8, 6.0 Hz), 1.88 (1H, OH, br s) 1.68−1.46 (8H, m), 1.43 (9H, s), 1.07 (1H, dt, $J$ = 9.0, 4.5 Hz), 0.73 (1H, dddd, $J$ = 10.5, 8.3, 6.0, 3.7 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 173.0, 138.4, 128.2, 127.5, 127.4, 80.2, 73.8, 72.8, 70.1, 36.7, 29.6, 28.2, 28.0, 22.1, 18.9, 12.3; MS (ES) *m*/*z* 357 (M + Na)$^+$; HRMS (ESI) *m*/*z* 357.2055 (calcd for $C_{20}H_{30}O_4Na$ 357.2041).

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**Supporting Information Available:** Detailed experimental procedures, characterization data, and copies of $^1H$, $^{13}C$, spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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