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Forming Spirocyclohexadienone-Oxocarbenium Cation Species in the Biomimetic Synthesis of Amomols

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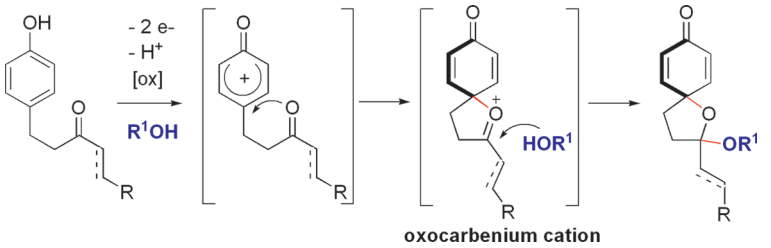

The oxidation of appropriate 2-(4-hydroxyphenyl)ethyl ketones gives direct access to amomols by means of the formation of a transient spirocyclohexadienone-oxocarbenium ion that is intermolecularly intercepted by an alcohol. Furthermore, homochiral amomols and other new analogues were synthesized for the first time and were biologically evaluated on *Plasmodium falciparum*.

Introduction

Biomimetic cascade reactions have been a source of inspiration for chemists due to their ability to generate complex scaffolds in a concise and efficient manner.[1] For the past few years, we have been involved in the synthesis of aculeatins, a family of antimalarial natural products extracted from *Amomum aculeatum* rhizomes, of which the most bioactive member is the aculeatin A (Scheme 1).[2] Our interest in optimizing the biological potency of aculeatins has induced us to develop short synthetic routes that encompass either stereodivergent, cascade, or tandem reaction strategies. Practical routes to the natural products and their congeners have thus emerged.[3] Recently, Kinghorn and co-workers have isolated two new members of this family, amomols A and B, from *Amomum aculeatum* leaves. The new substances show cytotoxicity against three cancer cell lines (Lu1, LNCaP, and MCF-7) with ED_{50} ranging from 0.5 to 0.9 μM.[4] The absolute configuration of the hydroxyl group at C-12 was assigned only on the basis of an ^{1}H NMR analysis of Mosher ester derivatives ($\Delta\delta_{R\text{-}S}$).[5] We became interested in testing the new natural products against malaria. This prompted us to explore a biomimetic synthesis of amomols and their derivatives that might also provide new insight into the cascade mechanism.

Our previous work[3e] demonstrated the direct production of aculeatins A and B in only one step through the oxidative conversion of phenol **1a** into a highly electrophilic phenoxnium cation **2a**[6] (Scheme 1). It is noteworthy that all syntheses of aculeatins reported to date use this oxidative strategy,[7] which was inspired by a biosynthetic hypothesis.[3a,7a] Since

(1) (a) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551–564. (b) de la Torre, M. C.; Sierra, M. A. *Angew. Chem., Int. Ed.* **2003**, *43*, 160–181. (c) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (d) Bulger, P. G.; Bagal, S. K.; Marquez, R. *Nat. Prod. Rep.* **2008**, *25*, 254–297.

(2) (a) Heilmann, J.; Mayr, S.; Brun, R.; Rali, T.; Sticher, O. *Helv. Chim. Acta* **2000**, *83*, 2939–2945. (b) Heilmann, J.; Brun, R.; Mayr, S.; Rali, T.; Sticher, O. *Phytochemistry* **2001**, *57*, 1281–1285.

(3) (a) Wong, Y.-S. *Chem. Commun.* **2002**, 686–687. (b) Peuchmaur, M.; Wong, Y.-S. *J. Org. Chem.* **2007**, *72*, 5374–5379. (c) Peuchmaur, M.; Wong, Y.-S. *Synlett* **2007**, 2902–2906. (d) Peuchmaur, M.; Saïdani, N.; Botté, C.; Maréchal, E.; Vial, H.; Wong, Y.-S. *J. Med. Chem.* **2008**, *51*, 4870–4873. (e) Traoré, M.; Ahmed-Ali, S.; Peuchmaur, M.; Wong, Y.-S. *Tetrahedron* **2010**, *66*, 5863–5872.

(4) Chin, Y.-W.; Salim, A. A.; Su, B.-N.; Mi, Q.; Chai, H.-B.; Riswan, S.; Kardono, L. B. S.; Ruskandi, A.; Farnsworth, N. R.; Swanson, S. M.; Kinghorn, A. D. *J. Nat. Prod.* **2008**, *71*, 390–395.

(5) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519. (b) Kelly, D. R. *Tetrahedron: Asymmetry* **1999**, *10*, 2927–2934. (c) Seco, J. M.; Quinoa, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915–2925.

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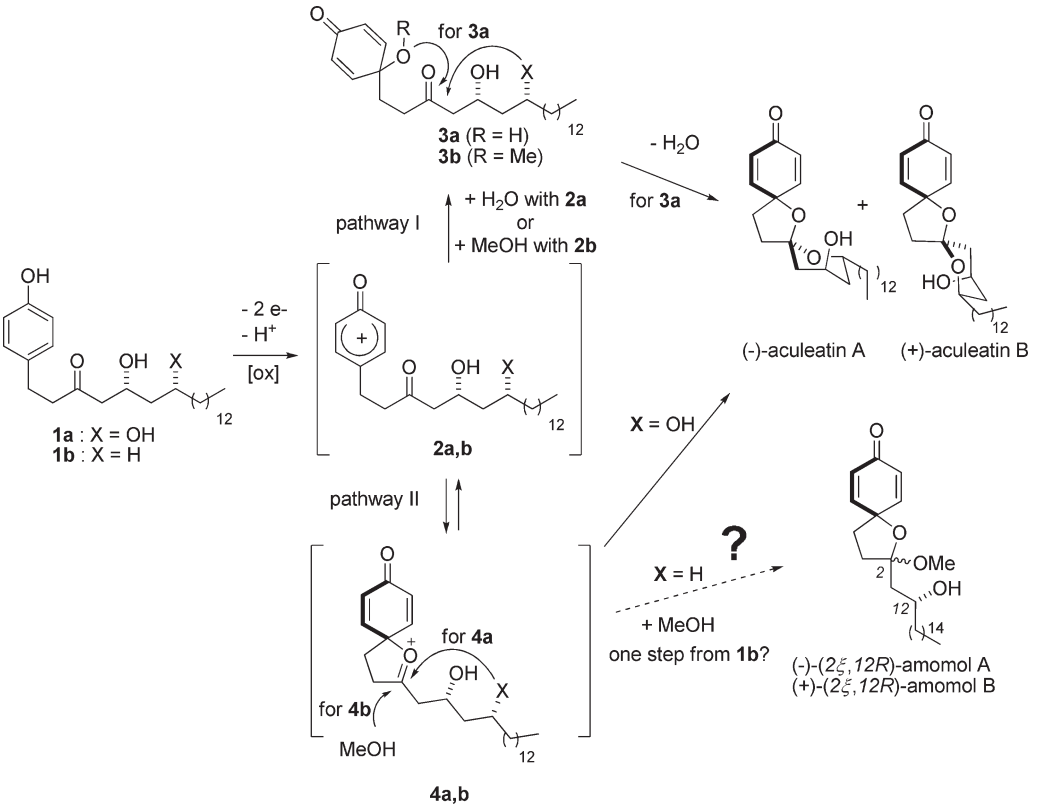
SCHEME 1. Plausible Biomimetic Pathways for the Synthesis of Aculeatins and Amomols



water was necessary to obtain good yields, two pathways, I and II, can be considered.

On one hand (pathway I), the phenoxonium cation **2a** can be first trapped by intermolecular addition of water, giving rise to the corresponding *p*-quinol **3a**, which then allows further ring formations to produce the aculeatins.[8] On the other hand (pathway II), a more straightforward cascade reaction can arise through the more kinetically favored intramolecular trapping of the phenoxonium cation **2a** by the γ-ketone. As a result, a highly electrophilic spirocyclohexadienone-oxocarbenium cation **4a** is formed, which then undergoes a final spiro-annulation to yield the aculeatins A and B. It turns out that phenoxonium cations display good propensity to be intercepted by other sp^2 or sp heteroatoms and carbon atoms.[9] In the context of aculeatin syntheses, we postulated that pathway II is involved in most cases,[3e] given that the cascade sequence usually proceeds at a fast rate. However, the actual intervention of a cationic species such as **4** remains to be established.

The foregoing considerations suggest that if pathway II were to operate, then the oxidation of phenol **1b** (X = H) should afford amomols A and B, through the intermolecular capture of a transient spirocyclohexadienone-oxocarbenium cation **4b** by a nucleophile such as methanol. By contrast, a mechanism according to pathway I would produce the *p*-quinol ether **3b**.

Results and Discussion

We selected 4-(4-hydroxyphenyl)-2-butanone **5** as a simpler model to test our hypothesis and to set up the best

(6) For reviews reporting phenoxonium cation as key transient reactant, see: (a) Tohma, H.; Kita, Y. *Topics in Current Chemistry*; Wirth, T., Ed.; Springer-Verlag: Berlin/Heidelberg, Germany, 2003; Vol. 224, p 209. (b) Rodriguez, S.; Wipf, P. *Synthesis* **2004**, 2767–2783. (c) Ciufolini, M. A.; Canesi, S.; Ousmer, M.; Braun, N. A. *Tetrahedron* **2006**, *62*, 5318–5337. (d) Quideau, S.; Pouysegu, L.; Deffieux, D. *Synlett* **2008**, 467–495. (e) Sabot, C.; Commare, B.; Duceppe, M.-A.; Nahi, S.; Guerard, K. C.; Canesi, S. *Synlett* **2008**, 3226–3230. (f) Pouysegu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235–2261. (g) Guerard, K. C.; Sabot, C.; Beaulieu, M.-A.; Giroux, M.-A.; Canesi, S. *Tetrahedron* **2010**, *66*, 5893–5901.

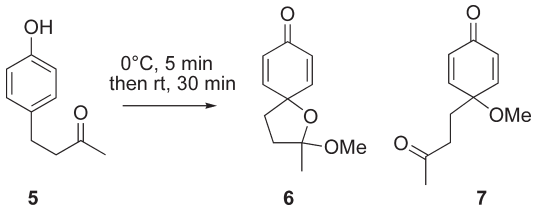
(7) For other synthetic approaches to aculeatins, see: (a) Baldwin, J. E.; Adlington, R. M.; Sham, V. W.-W.; Márquez, R.; Bulger, P. G. *Tetrahedron* **2005**, *61*, 2353–2363. (b) Falomir, E.; Álvarez-Bercedo, P.; Carda, M.; Marco, J. A. *Tetrahedron Lett*. **2005**, *46*, 8407–8410. (c) Álvarez-Bercedo, P.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2006**, *62*, 9641–9649. (d) Chandrasekhar, S.; Rambabu, Ch.; Shyamsunder, T. *Tetrahedron Lett*. **2007**, *48*, 4683–4685. (e) Ramana, C. V.; Srinivas, B. *J. Org. Chem*. **2008**, *73*, 3915–3918. (f) Suresh, V.; Selvam, J. J. P.; Rajesh, K.; Venkateswarlu, Y. *Tetrahedron: Asymmetry* **2008**, *19*, 1509–1513. (g) Zhen, Z.-B.; Gao, J.; Wu, Y. *J. Org. Chem*. **2008**, *73*, 7310–7316. (h) Kamal, A.; Reddy, P. V.; Prabhakar, S.; Balakrishna, M. *Tetrahedron: Asymmetry* **2009**, *20*, 2861–2865. (i) Malathong, V.; Rychnovsky, S. D. *Org. Lett*. **2009**, *11*, 4220–4223. (j) Harbindu, A.; Kumar, P. *Synthesis* **2010**, 1479–1484. (k) Ramana, C. V.; Pandey, S. K. *Tetrahedron* **2010**, *66*, 390–399. (l) Yadav, J. S.; Rao, K. V. R.; Ravindar, K.; Subba Reddy, B. V. *Synlett* **2010**, 51–54. (m) Yadav, J. S.; Thrimurtulu, N.; Venkatesh, M.; Prasad, A. R. *Synthesis* **2010**, 431–436.

(8) For a representative example, see ref 3c

(9) (a) Callinan, A.; Chen, Y.; Morrow, G. W.; Swenton, J. S. *Tetrahedron Lett*. **1990**, *31*, 4551–4552. (b) Swenton, J. S.; Carpenter, K.; Chen, Y.; Kerns, M. L.; Morrow, G. W. *J. Org. Chem*. **1993**, *58*, 3308–3316. (c) Swenton, J. S.; Callinan, A.; Chen, Y.; Rohde, J. J.; Kerns, M. L.; Morrow, G. W. *J. Org. Chem*. **1996**, *61*, 1267–1274. (d) Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem*. **1991**, *56*, 435–438. (e) Kita, Y.; Takada, T.; Gyoten, M.; Tohma, H.; Zenk, M. H.; Eichhorn, J. *J. Org. Chem*. **1996**, *61*, 5857–5864. (f) Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peters, E.-M. *Tetrahedron Lett*. **1998**, *39*, 4667–4670. (g) Braun, N. A.; Ousmer, M.; Bray, J. D.; Bouchu, D.; Peters, K.; Peters, E.-M.; Ciufolini, M. A. *J. Org. Chem*. **2000**, *65*, 4397–4408. (h) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc*. **2001**, *123*, 7534–7538. (i) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Org. Lett*. **2005**, *7*, 175–177. (j) Liang, H.; Ciufolini, M. A. *J. Org. Chem*. **2008**, *73*, 4299–4301. (k) Mendelsohn, B. A.; Ciufolini, M. A. *Org. Lett*. **2009**, *11*, 4736–4739. (l) Andrez, J.-C.; Giroux, M.-A.; Lucien, J.; Canesi, S. *Org. Lett*. **2010**, *12*, 4368–4371. (m) Beaulieu, M.-A.; Sabot, C.; Achache, N.; Guérard, K. C.; Canesi, S. *Chem.—Eur. J*. **2010**, *16*, 11224–11228.

conditions to obtain the amomol-like product **6** (Table 1). To our delight, when **5** was treated with $PhI(OAc)_2$ (PIDA) or $PhI(OCOCF_3)_2$ (PIFA) in methanol at 0 °C (entries 1 and 2),

TABLE 1. Conditions for the Preparation of Amomol-like Product 6



5 **6** **7**

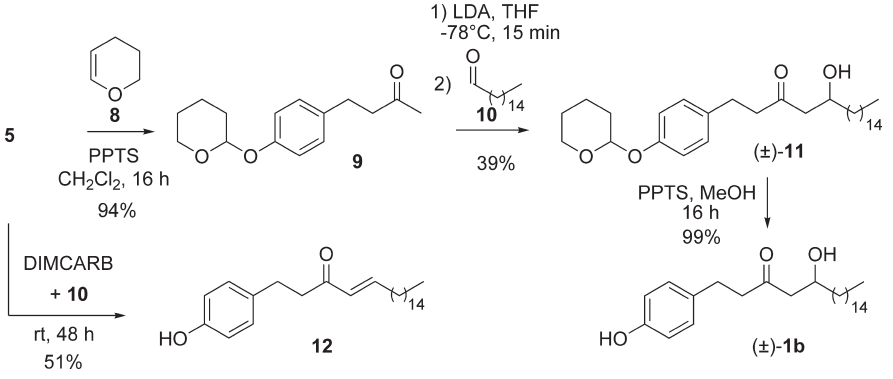
entry	reagent	conditions	**6** (%)[a]	**7** (%)[a]
1	PIDA	MeOH	35	25
2	PIFA	MeOH	39	44
3	PIDA	10 equiv of MeOH in CH_2Cl_2	68	8
4	PIDA	10 equiv of MeOH in acetone	34	8
5	PIDA	10 equiv of MeOH in CH_3CN	64	13
6	PIDA	10 equiv of MeOH in HFIP	75	0
7[b]	PIFA	10 equiv of MeOH in CH_2Cl_2		
8[b]	PIFA	10 equiv of MeOH in HFIP	5	

[a]Isolated yield. [b]Complex mixture.

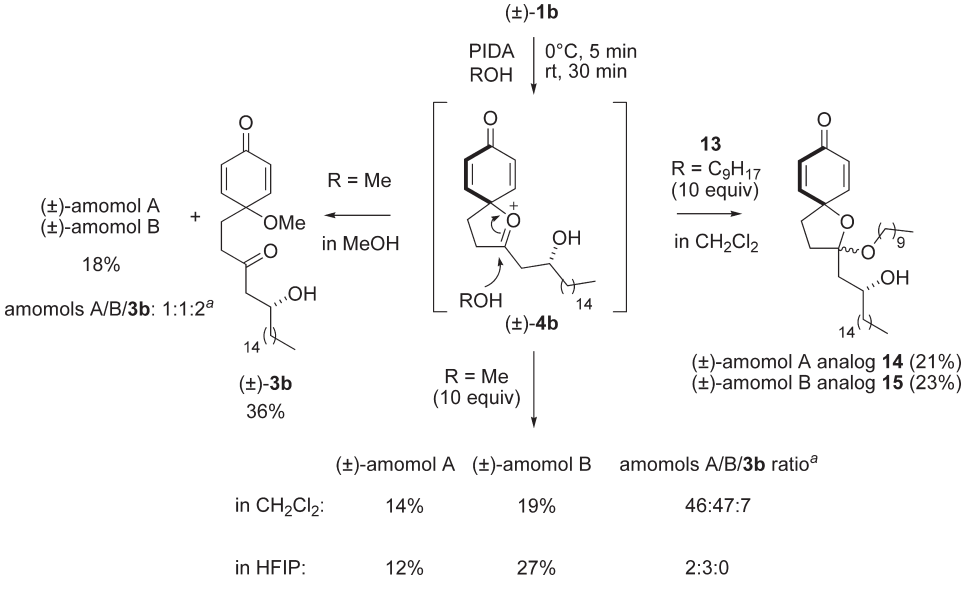
we observed the direct formation of the product **6**, albeit with the unwanted *p*-quinol ether **7** in about the same proportions. We postulated that a high concentration of the nucleophilic adduct (MeOH as solvent) may increase the competitive outcome for pathway I. Thus, we examined reactions with only 10 equiv of methanol using different solvents (entries 3−6). CH_2Cl_2 and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)[10] are among the best solvents (entries 3 and 6). Using PIDA as oxidant in CH_2Cl_2 (entry 3), we managed to isolate **6** in a yield of 68% along with a small amount of the *p*-quinol ether **7** (8%). Use of HFIP as a solvent gave a better yield of **6** (75%) with no trace of **7** (entry 6). Unexpectedly, when PIFA was used as oxidant (entries 7 and 8) in CH_2Cl_2 or HFIP, the reaction failed to yield any product, resulting mainly in the formation of complex mixtures.

To extend the study with other phenolic precursors, we synthesized (±)-**1b** in three steps and the phenolic analogue **12** in one step[11] from **5** and hexadecanal **10**[12] (Scheme 2). The product **12** aims at proving that oxocarbenium cation species can also be generated through the bonding of the phenoxenium cation with the more electron rich carbonyl oxygen of an enone (vide infra).

SCHEME 2. Synthesis of Phenolic Precursors (±)-1b and 12



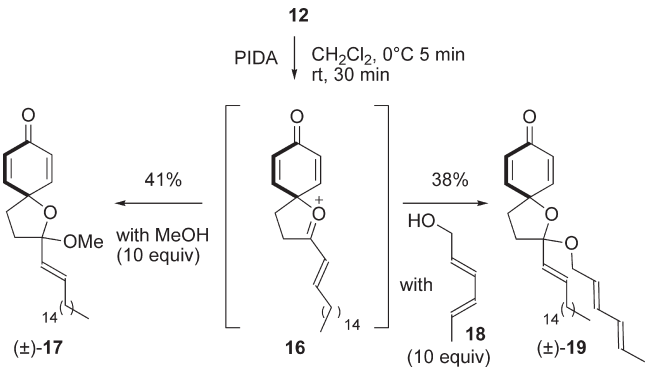
SCHEME 3. One-Step Synthesis of Amomols and New Derivatives from Phenol (±)-1b



	(±)-amomol A	(±)-amomol B	amomols A/B/**3b** ratio[a]
in CH_2Cl_2:	14%	19%	46:47:7
in HFIP:	12%	27%	2:3:0

[a]Ratio determined by ^1H NMR of the crude products.

SCHEME 4. 1,2-Selective Addition of Alcohols to Vinyl Oxocarbenium Cation 16 in CH_2Cl_2



When compound (±)-**1b** was treated with PIDA in methanol (Scheme 3), the *p*-quinol ether (±)-**3b** was obtained as the major product (36%), along with a mixture of amomols A and B (18%). These products were difficult to separate, necessitating multiple chromatographies that led to considerable material loss. Therefore, the final yields do not accurately reflect the true proportion of the various reaction products. A better indication of the product distribution was garnered through ^{1}H NMR analysis of the crude reaction mixtures, which indicated that amomols A and B and compound (±)-**3b** have formed in a ratio of ca. 1:1:2. Using CH_2Cl_2 as solvent with 10 equiv of methanol, (±)-amomols A and B were isolated in yields of 14% and 19%, respectively. The ratio of amomols A/B/**3b** analyzed by ^{1}H NMR was 46:47:7. Interestingly, with HFIP as solvent and with 10 equiv of methanol, a slight diastereoselectivity between amomols A and B was observed. The ratio of amomols A and B, evaluated by ^{1}H NMR, was found to be around 2:3 with no trace of *p*-quinol ether (±)-**3b**. Amomols A and B were isolated in yields of 12% and 27%, respectively. Likewise in the oxidation of **5** (see Table 1), the use of HFIP as solvent slightly improves the yields. However, because of the high cost of HFIP and because fighting malaria requires inexpensive syntheses of bioactive molecules, CH_2Cl_2 arises as a suitable solvent that performs well enough in the key oxidation reaction. Finally, to access two novel amomol analogues having an additional lipophilic side chain, (±)-**1b** was oxidized in CH_2Cl_2 with PIDA in the presence of 10 equiv of decanol **13** yielding (±)-amomols-like A **14** (21%) and B **15** (23%).

We also tested the ability of a carbonyl group of enone **12** to intercept the presumed phenoxonium cation obtained upon oxidation of the phenol. When compound **12** was oxidized with PIDA in CH_2Cl_2 containing 10 equiv of methanol, the amomol-like product (±)-**17** was indeed isolated in a yield of 41% (Scheme 4). This is consistent with the documented 1,2 regioselectivity in the addition of alcohols to vinyl oxocarbenium cations such as **16**.[13] However, these species can also behave as excellent dienophiles.[14] Thus, we examined the PIDA oxidation of **12** in CH_2Cl_2 containing 10 equiv of (2*E*,4*E*)-hexa-2,4-dien-1-ol **18**. The amomol-like structure (±)-**19** was obtained in a yield of 38%, indicating that the 1,2-addition of the alcohol to cation **16** proceeds faster than the [4 + 2] cycloaddition.

We also undertook the enantioselective synthesis of amomols A and B and their non-natural enantiomers to study the influence of their configurations on the antimalarial activity (Scheme 5). According to Nokami's procedure,[15] the reaction of (+)-**20** with hexadecanal (**10**) under acid catalysis provided the crotyl alcohol (−)-**21** in good yield (81%) and in high enantioselectivity (er > 95:5).[3b] Next, the hydroxyl group was converted into the tripropyl silyl ether to yield (+)-**22** (95%). This easily removable protecting group was amenable to clean TBAF deprotection without formation of the elimination product **12** during the later conversion of (−)-**28** into (−)-**1b**. The oxidative cleavage of (+)-**22** by the OsO_4/NMO/$NaIO_4$ procedure gave the aldehyde (−)-**23** in a moderate yield of 41%. Use of ozone in CH_2Cl_2 at −78 °C as an alternative procedure did not improve the yield. Treatment of (−)-**23** with the lithium salt of dimethyl methylphosphonate provided a *β*-hydroxyphosphonate **24** that was oxidized with Dess−Martin periodinane[16] to give the *β*-ketophosphonate (−)-**25** in an overall yield of 61%. The Horner−Wadsworth−Emmons coupling of *β*-ketophosphonate (−)-**25** and aldehyde **26** mediated by K_2CO_3 in ethanol gave enone (−)-**27** (79%). Hydrogenation of (−)-**27** induced simultaneous phenol debenzylation and enone reduction to afford product (−)-**28** (67%), from which the phenolic key intermediate (−)-**1b** was selectively obtained in a yield of 83% upon TBAF deprotection in THF at 25 °C over 30 min. Finally, (−)-**1b** was oxidized with PIDA in CH_2Cl_2 to give (−)-amomol A (15%) and (+)-amomol B (21%). Starting from the Nokami's reagent (−)-**20**, the non-natural enantiomers of (+)-amomol A and (−)-amomol B were similarly synthesized.

We have already reported that the cyclohexadienone moiety of aculeatins is required for antimalarial activity, given that the reduced analogue (±)-**29** of aculeatin A (Figure 1) is inactive. Furthermore, we have shown that products displaying two cyclohexadienone units, like (±)-**31** and **32**, show improved potency.[3d] The compounds thus synthesized were tested against the parasite *Plasmodium falciparum*, the causative agent of malaria, on a chloroquine sensitive strain 3D7.

In Figure 1, products are classified according to their efficiency, from least to most potent. Formerly synthesized molecules (±)-**30**,[3e] (±)-**29**, (±)-**31**, **32**,[3d] and homochiral natural and non-natural aculeatins A and B[3b] are represented with gray coloration. Amomols A and B proved to be potent antimalarial products, with IC_{50} ranging from 0.48 to 0.64 μM, very close to those of aculeatins. Similarly to aculeatins, the configuration of amomols does not have a strong impact on antimalarial efficiency, the configuration of natural (−)-amomol A being a little more efficient (0.48 μM). With amonol analogues, addition of a second lipophilic side chain like (±)-**14** and (±)-**15** or loss of spirocyclic

(10) Trifluoroethanol (TFE) was also examined as solvent in the oxidation of **5** with PIDA in the presence of 10 equiv of methanol. Amomols-like products including **6** were isolated as an inseparable mixture making characterization difficult.

(11) Mase, N.; Kitagawa, N.; Takabe, K. *Synlett* **2010**, 93–96.

(12) Gung, B. W.; Dickson, H. D.; Seggerson, S.; Bluhm, K. *Synth. Commun.* **2002**, *32*, 2733–2740.

(13) Lin, H.-C.; Yang, W.-B.; Gu, Y.-F.; Chen, C.-Y.; Wu, C.-Y.; Lin, C.-H. *Org. Lett.* **2003**, *5*, 1087–1089.

(14) Marmata, M.; Rashatasakhon, P. *Tetrahedron* **2003**, *59*, 2371–2395.

(15) Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168–9169.

(16) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.

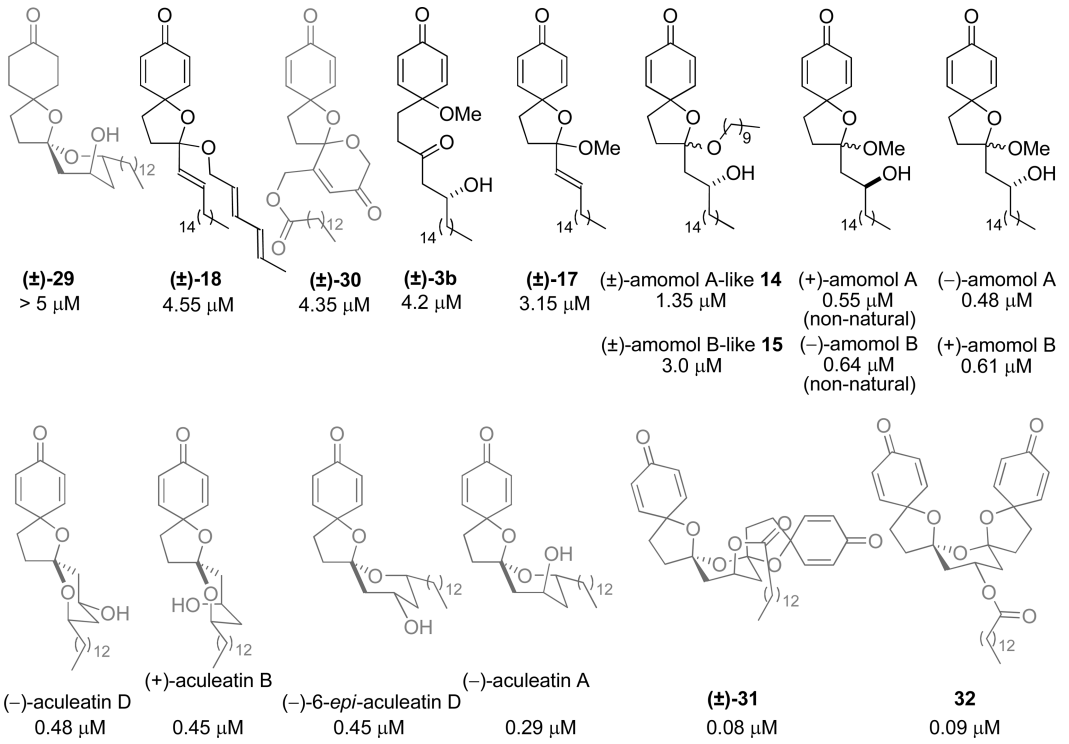
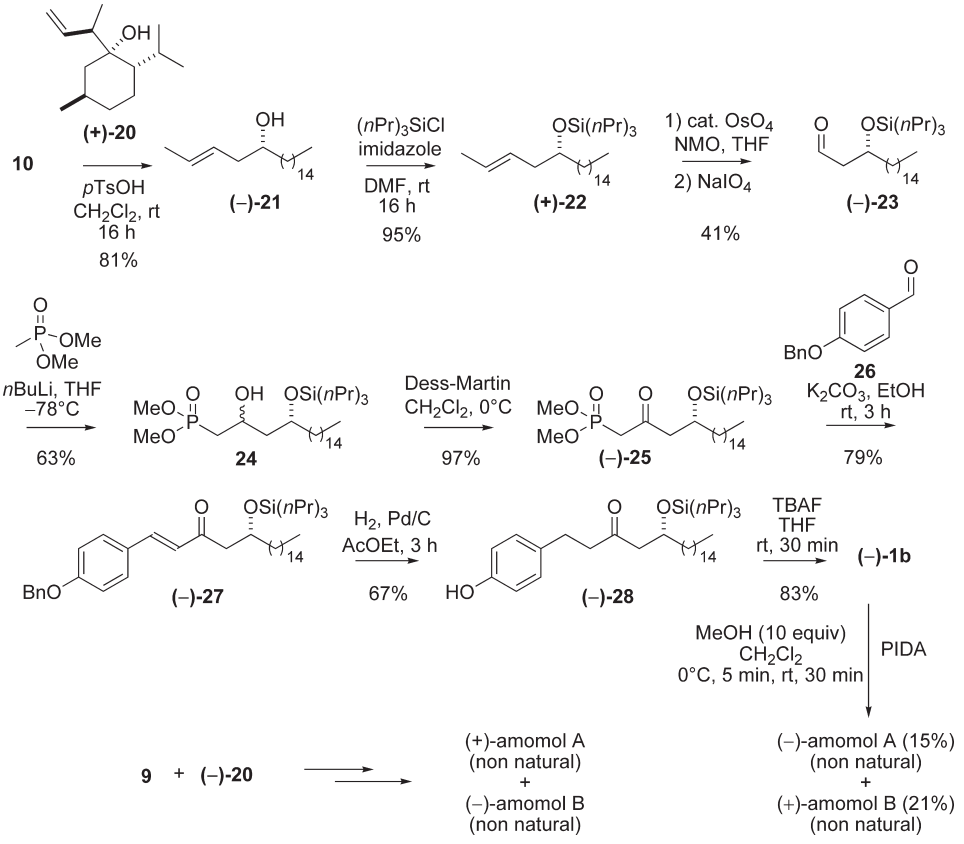


FIGURE 1. In vitro evaluation of amomols and their new analogues on *Plasmodium falciparum*.

SCHEME 5. Enantioselective Syntheses of Natural and Non-natural Amomols A and B



structure like (±)-**3b** are detrimental to the antimalarial activity. As a result, maximum antimalarial activity is observed in products having spirocyclohexadienone moieties and one lipophilic side chain.

Conclusions

We have shown that phenolic oxidation of the precursor **1b** yields amomols in only one step, presumably through to the formation of a transient spiro-oxocarbenium cation that subsequently reacts with methanol. This efficient biomimetic reaction allows two new bonds to be made with the trapping of an intermolecular alcohol. Moreover, we showed that this cascade sequence works equally well in combination with a more electron rich carbonyl oxygen of an enone. We made use of this straightforward process to obtain homochiral amomols and their new analogues in a modular manner. The resultant set of molecules has enabled us to get new insights on structure−activity relationships and has established amomols as potent antimalarial products. Taken together with our actual knowledge on aculeatins, the recent discovery of amomols constitutes indeed the "missing link" to an understanding of their biomimetic synthesis and to the identification of important functional groups involved in the antimalarial property.

Experimental Section

General Procedure for Phenolic Oxidation. Method A. To a stirred ice-cold solution of phenol (0.1 M) in the appropriate solvent was added alcohol (10 equiv) and PIDA (1.5 equiv). The mixture was stirred at 0 °C for 5 min and at room temperature for 30 min, after which time solid $NaHCO_3$ was added. The solid was removed by filtration and the solution was concentrated in vacuo to give a mixture that was purified by flash chromatography.

Method B. To a stirred ice-cold solution of phenol (0.1 M) in anhydrous methanol was added hypervalent iodine(III) reagent (1.5 equiv). The mixture was stirred at 0 °C for 5 min and at room temperature for 30 min, after which time solid $NaHCO_3$ was added. The solid was removed by filtration and the solution was concentrated in vacuo to give a mixture that was purified by flash chromatography.

(±)-2-Methoxy-2-methyl-1-oxaspiro[4.5]deca-6,9-dien-8-one (6). According to method A, and starting from 4-(4-hydroxyphenyl)butan-2-one (**5**) (115 mg, 0.70 mmol) and anhydrous MeOH (224 mg, 7.0 mmol) in CH_2Cl_2 (5 mL), the products were purified by flash chromatography on silica gel column chromatography, eluting with cyclohexane/EtOAc (75/25), to give (±)-**6** (94.0 mg, 0.48 mmol, 69%) along with **7** (11 mg, 0.057 mmol, 8%). R_f 0.23 (75/25 cyclohexane/EtOAc); IR ν_{max} (film, cm^{-1}) 3428, 2900, 1714, 1396, 1126; UV (MeOH) 220 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 3H), 1.94−2.04 (m, 2H), 2.21 (m, 1H), 2.36 (m, 1H), 3.26 (s, 3H), 6.05 (dd, J = 10.0, 1.8 Hz, 1H), 6.08 (dd, J = 10.0, 1.8 Hz, 1H), 6.75 (dd, J = 10.0, 3.0 Hz, 1H), 6.82 (dd, J = 10.0, 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4 (CH_3), 35.4 (CH_2), 39.1 (CH_2), 48.9 (CH_3), 78.7 (C), 109.7 (C), 126.9 (CH), 127.4 (CH), 149.2 (CH), 151.5 (CH), 185.5 (C); LMRS (ESI+) m/z (%) 217 $[M + Na]^+$ (38), 203 (100), 163 (75); HRMS (ESI+) m/z found 217.0838, $C_{11}H_{14}O_3Na$ requires 217.0835.

4-Methoxy-4-(3-oxobutyl)cyclohexa-2,5-dienone (7). According to method B with PIFA as oxidant (220 mg, 0.51 mmol) and starting from 4-(4-hydroxyphenyl)butan-2-one (**5**) (56 mg, 0.34 mmol) in anhydrous MeOH (2 mL), the products were purified by flash chromatography [silica gel eluting with cyclohexane/EtOAc (75/25)] to give **7** (30 mg, 0.15 mmol, 44%) and (±)-**6** (25.2 mg, 0.13 mmol, 39%). R_f 0.20 (75/25 cyclohexane/EtOAc); IR ν_{max} (film, cm^{-1}) 3500, 2900, 1750, 1110, 775; UV (MeOH) 227 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 2.04 (t, J = 7.6 Hz, 2H), 2.12 (s, 3H), 2.43 (t, J = 7.6 Hz, 2H), 3.21 (s, 3H), 6.38 (d, J = 10.2, Hz, 2H), 6.71 (d, J = 10.2, Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.5 (CH_3), 32.8 (CH_2), 37.6 (CH_2), 53.5 (CH_3), 75.3 (C), 131.9 (2 × CH), 150.7 (2 × CH), 185.1 (C), 207.3 (C); LRMS (ESI+) m/z (%) 217 $[M + Na]^+$ (100), 213 (25), 137 (49); HRMS (ESI+) m/z found 217.0835, $C_{11}H_{14}O_3Na$ requires 217.0835.

4-(4-(Tetrahydro-2*H*-pyran-2-yloxy)phenyl)butan-2-one (9). To a stirred solution of 4-(4-hydroxyphenyl)butan-2-one (**5**) (4 g, 24.39 mmol) in CH_2Cl_2 (50 mL) were added PPTS (612 mg, 2.44 mmol) and 3,4-dihydro-*2H*-pyran (**8**) (2.5 g, 29.76 mmol). The mixture was stirred for 16 h at room temperature. Then an aqueous solution of $NaHCO_3$ (30 mL) was added, followed by extraction with EtOAc (3 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The residue was subjected to silica gel column chromatography, eluting with cyclohexane/EtOAc (90/10), to give **9** (5.7 g, 22.98 mmol, 94%). R_f 0.18 (90/10 cyclohexane/EtOAc); IR ν_{max} (film, cm^{-1}) 2950, 1713, 1613, 1502; UV (MeOH) 274, 222 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 1.55−1.72 (m, 3H), 1.80−1.87 (m, 2H), 1.99 (m, 1H), 2.12 (s, 3H), 2.72 (m, 2H), 2.82 (m, 2H), 3.58 (m, 1H), 3.89 (m, 1H), 5.36 (t, J = 3.2 Hz, 1H), 6.96 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9 (CH_2), 25.3 (CH_2), 29.0 (CH_3), 30.2 (CH_2), 30.5 (CH_2), 45.5 (CH_2), 62.1 (CH_2), 96.5 (CH), 116.6 (2 × CH), 129.2 (2 × CH), 134.1 (C), 155.5 (C), 208.2 (C); HRMS (ESI+) m/z found 271.1310, $C_{15}H_{20}O_3Na$ requires 271.1310.

(±)-5-Hydroxy-1-(4-(tetrahydro-2*H*-pyran-2-yloxy)phenyl)-icosan-3-one (11). To a stirred ice-cold solution of diisopropylamine (918 mg, 9.09 mmol) in THF (10 mL) was added dropwise 2.5 M *n*-BuLi in hexane (9.09 mmol, 3.63 mL). The mixture was stirred at 0 °C for 15 min, and then cooled at −78 °C. Ketone **9** (1.88 g, 7.58 mmol) in THF (10 mL) was added dropwise, then the mixture was stirred for 15 min at −78 °C. Hexadecanal (**10**) (1.80 g, 7.58 mmol) was injected dropwise, then the mixture was stirred for 30 min and allowed to warm to room temperature over 1 h, after which time an aqueous solution of NH_4Cl (10 mL) was added, followed by extraction with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The residue was subjected to silica gel column chromatography, eluting with cyclohexane/EtOAc (90/10), to give (±)-**11** (1.45 g, 2.97 mmol, 39%). R_f 0.15 (90/10 cyclohexane/EtOAc); IR ν_{max} (film, cm^{-1}) 3346, 2909, 1707, 1514, 1351; UV (MeOH) 222 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.19−1.33 (m, 26H), 1.54−1.73 (m, 2H), 1.79−1.88 (m, 3H), 1.87−1.90 (m, 2H), 1.99 (m, 1H), 2.47 (dd, J = 17.5, 8.8 Hz, 1H), 2.56 (dd, J = 17.5, 3.0 Hz, 1H), 2.69−2.75 (m, 2H), 2.80−2.87 (m, 2H), 3.59 (m, 1H), 3.90 (m, 1H), 4.01 (m, 1H), 5.37 (t, J = 3.2 Hz, 1H), 6.96 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 19.0 (CH_2), 22.9 (CH_2), 25.4 (CH_2), 25.6 (CH_2), 28.9 (CH_2), 29.5 (CH_2), 29.8 (CH_2), 29.9 (8 × CH_2), 30.6 (CH_2), 32.1 (CH_2), 36.6 (CH_2), 45.5 (CH_2), 49.5 (CH_2), 62.3 (CH_2), 67.8 (CH_2), 96.6 (CH), 116.7 (2 × CH), 129.3 (2 × CH), 133.9 (C), 155.7 (C), 211.6 (C); HRMS (ESI+) m/z found 511.3763, $C_{31}H_{52}O_4Na$ requires 511.3763.

(±)-5-Hydroxy-1-(4-hydroxyphenyl)icosan-3-one (1b). To a stirred solution of (±)-**11** (650 mg, 1.29 mmol) in MeOH (20 mL) was added PPTS (80 mg, 0.26 mmol). The mixture was stirred overnight at room temperature. The solvent was removed in vaccuo and the residue was subjected to silica gel column chromatography, eluting with cyclohexane/EtOAc (80/20), to give (±)-**1b** (469.6 mg, 1.12 mmol, 99%). R_f 0.2 (75/25 cyclohexane/EtOAc); IR ν_{max} (film, cm^{-1}) 3375, 2915, 1689, 1516, 1459, 1260; UV (MeOH) 224 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.23−1.28 (m, 24H), 1.33−1.41 (m, 2H), 1.44−1.53 (m, 2H), 2.48 (dd, J = 17.5, 8.9 Hz, 1H), 2.57 (dd, J = 17.5, 2.9, 1H), 2.72 (m, 2H), 2.83 (m, 2H), 4.03 (m, 1H), 6.74 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 22.9 (CH_2), 25.7

(CH_2), 28.9 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 29.9 (7 × CH_2), 32.1 (CH_2), 36.4 (CH_2), 45.5 (CH_2), 49.4 (CH_2), 68.1 (CH), 115.6 (2 × CH), 129.6 (2 × CH), 133.0 (C), 154.6 (C), 212.1 (C); HRMS (ESI+) m/z found 427.3182, $C_{26}H_{44}O_3Na$ requires 427.3182.

(***E***)**-1-(4-Hydroxyphenyl)icos-4-en-3-one (12).** To a solution of 4-(4-hydroxyphenyl)butan-2-one (**5**) (1 g, 6.09 mmol) in DIMCARB (ration carbone dioxide/dimethylamine < 0.2/1, 6 mL) was added portionwise hexadecanal (**10**) (4.4 g, 18.33 mmol) (3 × 1 equiv, every 3 h) at room temperature. Stirring was continued for 48 h. The solvent mixture was acidified with 1 N HCl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fraction was dried with $MgSO_4$ then filtrated, and the solvent was removed in vacuo. The residue was subjected to silica gel column chromatography, eluting with cyclohexane/EtOAc (90/10), to give **12** (1.2 g, 3.11 mmol, 51%). R_f 0.23 (85/15 cyclohexane/EtOAc); IR ν_{max} (film, cm^{-1}) 3407, 2621, 1691, 1623, 1086; UV (MeOH) 278, 224 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.25−1.30 (m, 24H), 1.42 (m, 2H), 2.18 (m, 2H), 2.82−2.88 (m, 4H), 6.10 (d, J = 15.9 Hz, 1H), 6.75 (d, J = 8.5 Hz, 2H), 6.84 (dt, J = 15.9, 6.9 Hz, 1H), 7.03 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 22.9 (CH_2), 28.2 (CH_2), 29.4 (CH_2), 29.6 (2 × CH_2), 29.7 (CH_2), 29.9 (7 × CH_2), 31.1 (CH_2), 32.8 (CH_2), 42.1 (CH_2), 115.6 (2 × CH), 129.5 (2 × CH), 130.3 (CH), 133.0 (C), 148.9 (CH), 154.4 (C), 201.0 (C); HRMS (ESI+) m/z found 409.3078, $C_{26}H_{42}O_2Na$ requires 409.3087.

(±)-4-(5-Hydroxy-3-oxoicosyl)-4-methoxycyclohexa-2,5-dienone (3b). According to method B using PIDA as oxidant (64.4 mg, 0.17 mmol) and starting from (±)-**1b** (43.6 mg, 0.11 mmol) in MeOH (1.5 mL), the product (±)-**3b** (19.1 mg, 0.05 mmol, 36%) and a mixture of (±) amomols A and B (10.2 mg, 0.02 mmol, 18%) were obtained after flash chromatography [silica gel eluting with cyclohexane/EtOAc (90/10)]. R_f 0.19 (75/25 cyclohexane/EtOAc); IR ν_{max} (film, cm^{-1}) 3407, 2925, 1712, 1668, 1270; UV (MeOH) 225 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.23−1.28 (m, 24H), 1.29−1.52 (m, 3H), 1.67 (m, 1H), 2.04 (t, J = 7.6 Hz, 2H), 2.44 (t, J = 7.6 Hz, 2H), 2.51 (dd, J = 15.0, 6.0 Hz, 1H), 3.21 (s, 3H), 3.36 (m, 1H), 4.01 (m, 1H), 6.37 (d, J = 10.2 Hz, 2H), 6.71 (d, J = 10.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 22.9 (CH_2), 25.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 29.9 (7 × CH_2), 32.1 (CH_2), 32.6 (CH_2), 36.7 (CH_2), 37.8 (CH_2), 49.5 (CH_3), 53.4 (CH_2), 67.9 (CH), 75.2 (C), 132.0 (2 × CH), 150.6 (2 × CH), 185.3 (C), 210.3 (C); HRMS (ESI+) m/z found 457.3288, $C_{27}H_{46}O_4Na$ requires 457.3288.

(±)-(Hydroxyheptadecyl)-2-nonyloxy-1-oxaspiro[4.5]deca-6,9-dien-8-on (14 and 15). According to method A and starting from (±)-**1b** (37 mg, 0.091 mmol) and decanol (**13**) (71 mg, 0.45 mmol) in CH_2Cl_2 (1.5 mL), the products (±)-**14** (10.6 mg, 0.019 mmol, 21%) and (±)-**15** (11.7 mg, 0.021 mmol, 23%) were obtained after flash chromatography [silica gel eluting with CH_2Cl_2/Et_2O (94/06)]. (±)-**14**: R_f 0.32 (96/4 CH_2Cl_2/Et_2O); IR ν_{max} (film, cm^{-1}) 3497, 2929, 1679, 1625; UV (MeOH) 225 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 6H), 1.23−1.40 (m, 40H), 1.41−1.54 (m, 4H), 1.69 (m, 1H), 2.05 (m, 1H), 2.10−2.20 (m, 2H), 2.32−2.44 (m, 2H), 3.56 (m, 2H), 3.83 (m, 1H), 6.12 (dd, J = 10.0, 2.0 Hz, 1H), 6.17 (dd, J = 10.0, 2.0 Hz, 1H), 6.78 (dd, J = 10.0, 3.0 Hz, 1H), 6.82 (dd, J = 10.0, 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (2 × CH_3), 22.9 (2 × CH_2), 25.7 (CH_2), 26.5 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 29.9 (10 × CH_2), 32.0 (2 × CH_2), 32.1 (2 × CH_2), 35.3 (CH_2), 37.0 (CH_2), 37.9 (CH_2), 41.8 (CH_2), 61.6 (CH_2), 69.3 (CH), 79.2 (C), 111.7 (C), 127.3 (CH), 128.0 (CH), 148.7 (CH), 150.6 (CH), 185.5 (C); HRMS (ESI+) m/z found 583.4697, $C_{36}H_{64}O_4Na$ requires 583.4697. (±)-**15**: R_f 0.30 (96/4 CH_2Cl_2/Et_2O); IR ν_{max} (film, cm^{-1}) 3497, 2929, 1679, 1625; UV (MeOH) 225 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 6H), 1.24−1.36 (m, 40H), 1.42 (m, 2H), 1.48−1.62 (m, 2H), 1.92−2.00 (m, 2H), 2.04 (m, 1H), 2.20−2.27 (m, 2H), 2.42 (m, 1H), 3.43 (m, 1H), 3.56 (m, 1H), 3.80 (m, 1H), 6.13 (dd, J = 10.0, 2.0 Hz, 1H), 6.16 (dd, J = 10.0, 2.0 Hz, 1H), 6.80 (dd, J = 10.0, 3.0 Hz, 1H), 6.85 (dd, J = 10.0, 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (2 × CH_3), 22.9 (2 × CH_2), 25.8 (CH_2), 26.5 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.8 (2 × CH_2), 29.9 (8 × CH_2), 30.3 (2 × CH_2), 32.1 (2 × CH_2), 35.5 (CH_2), 36.9 (CH_2), 38.0 (CH_2), 41.3 (CH_2), 61.3 (CH_2), 68.5 (CH), 78.9 (C), 111.8 (C), 127.6 (CH), 127.8 (CH), 148.5 (CH), 150.9 (CH), 185.5 (C); HRMS (ESI+) m/z found 583.4697, $C_{36}H_{64}O_4Na$ requires 583.4697.

(±)-[(*E*)-Heptadec-1-enyl]-2-methoxy-1-oxaspiro[4.5]deca-6,9-dien-8-one (17). According to method A and starting from **12** (105 mg, 0.27 mmol) and methanol (86 mg, 2.7 mmol) in CH_2Cl_2 (2.5 mL), the product (±)-**17** (46.8 mg, 0.11 mmol, 41%) was obtained after flash chromatography [silica gel eluting with cyclohexane/EtOAc (90/10)]. R_f 0.31 (85/15 cyclohexane/EtOAc); IR ν_{max} (film, cm^{-1}) 2920, 1680, 1631, 1463; UV (MeOH) 225 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.23−1.32 (m, 24H), 1.40 (m, 2H), 2.00−2.14 (m, 4H), 2.29 (m, 1H), 2.40 (m, 1H), 3.24 (s, 3H), 5.51 (dt, J = 15.6, 1.1 Hz, 1H), 5.93 (dt, J = 15.6, 6.7 Hz, 1H), 6.13 (dd, J = 10.0, 2.0 Hz, 1H), 6.16 (dd, J = 10.0, 2.0 Hz, 1H), 6.88 (dd, J = 10.0, 3.0 Hz, 1H), 6.91 (dd, J = 10.0, 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 22.9 (CH_2), 29.1 (CH_2), 29.4 (CH_2), 29.6 (2 × CH_2), 29.9 (6 × CH_2), 32.1 (2 × CH_2), 32.2 (CH_2), 35.3 (CH_2), 39.5 (CH_2), 49.8 (CH_3), 78.9 (C), 110.2 (C), 127.2 (CH), 127.5 (CH), 128.0 (CH), 134.5 (CH), 149.2 (CH), 151.5 (CH), 185.7 (C); HRMS (ESI+) m/z found 439.3179, $C_{27}H_{44}O_3Na$ requires 439.3183.

(±)-[(*E*)-Heptadec-1-enyl]-2-[(2*E*,4*E*)-hexa-2,4-dienyloxy]-1-oxaspiro[4.5]deca-6,9-dien-8-one (19). According to method A and starting from **12** (50 mg, 0.13 mmol) and (2*E*,4*E*)-hexa-2,4-dien-1-ol (**18**) (63.8 mg, 0.65 mmol) in CH_2Cl_2 (1.5 mL), the product (±)-**19** (21.5 mg, 0.05 mmol, 38%) was obtained after flash chromatography [silica gel, eluting with cyclohexane/EtOAc (90/10)]. R_f 0.17 (90/10 cyclohexane/EtOAc); IR ν_{max} (film, cm^{-1}) 2924, 1671, 1631, 1463; UV (MeOH) 226 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.22−1.33 (m, 24H), 1.39 (m, 2H), 1.76 (d, J = 6.6 Hz, 3H), 2.00−2.12 (m, 4H), 2.33−2.47 (m, 2H), 3.98 (dd, J = 12.6, 6.0 Hz, 1H), 4.05 (dd, J = 12.6, 6.3 Hz, 1H), 5.55 (d, J = 15.6 Hz, 1H), 5.63 (dt, J = 15.0, 6.3 Hz, 1H), 5.72 (dq, J = 14.8, 6.7 Hz, 1H), 5.93 (dt, J = 15.6, 6.8 Hz, 1H), 6.07 (m, 1H), 6.11−6.12 (m, 1H), 6.15 (m, 1H), 6.21 (m, 1H), 6.82 (dd, J = 10.0, 3. 0 Hz, 1H), 6.89 (dd, J = 10.0, 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 18.3 (CH_2), 22.9 (CH_2), 29.1 (CH_2), 29.4 (CH_2), 29.6 (2 × CH_2), 29.7 (CH_2), 29.8 (CH_2), 29.9 (5 × CH_2), 32.1 (CH_2), 32.2 (CH_2), 35.4 (CH_2), 39.6 (CH_2), 62.9 (CH_2), 79.0 (C), 110.1 (C), 127.1 (CH), 127.2 (CH), 127.6 (CH), 128.5 (CH), 130.1 (CH), 131.1 (CH), 132.6 (CH), 134.3 (CH), 149.2 (CH), 151.6 (CH), 185.8 (C); HRMS (ESI+) m/z found 505.3653, $C_{32}H_{50}O_3Na$ requires 505.3652.

(−)-(2*E*,5*R*)-Icos-2-en-5-ol [(−)-21]. To a stirred solution of hexadecanal (**10**) (2 g, 8.33 mmol) and (+)-(1*S*,2*S*,5*R*)-1-(1-methylallyl)-menthol (**20**) (3.5 g, 16.66 mmol) in CH_2Cl_2 (140 mL) was added *p*-TsOH (158 mg, 0.83 mmol). The mixture was stirred at room temperature overnight, after which time saturated aqueous $NaHCO_3$ (70 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 70 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The residue was subjected to silica gel column chromatography, eluting with cyclohexane/EtOAc (2/98), to give (−)-**21** (2 g, 6.76 mmol, 81%). $[\alpha]^{20}_D$ −0.6 (*c* 1.0, CH_3Cl); R_f 0.29 (95/5 cyclohexane/EtOAc); IR ν_{max} (film, cm^{-1}) 3442, 2956, 1645, 1130, 1094, 1020, 960; UV (MeOH) 276, 225, 208 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.24−1.31 (m, 24H), 1.40−1.47 (m, 4H), 1.69 (dd, J = 6.2, 0.6 Hz, 3H), 2.05 (m, 1H), 2.22 (m, 1H), 3.57 (m, 1H), 5.43 (m, 1H), 5.55 (dq,

J = 15.2, 6.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 18.2 (CH_3), 22.9 (CH_2), 25.9 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 29.9 (8 × CH_2), 32.1 (CH_2), 37.0 (CH_2), 40.9 (CH_2), 71.2 (CH), 127.4 (CH), 129.0 (CH); HRMS (ESI+) m/z found 319.2972, $C_{20}H_{40}ONa$ requires 319.2971. **(+)-(2*E*,5*S*)-Icos-2-en-5-ol [(+)-21]:** Starting from hexadecanal (**10**) and (−)-(1*R*,2*R*,5*S*)-1-(1-methylallyl)-menthol (**20**), the product (+)-**21** was similarly prepared. $[\alpha]^{20}_D$ +0.8 (c 1.0, CH_3Cl); HRMS (ESI+) m/z found 319.2974, $C_{20}H_{40}ONa$ requires 319.2971.

(+)-(2*E*,5*R*)-(Icos-2-en-5-yloxy)tripropylsilane [(+)-22]. To a stirred solution of (−)-**21** (2 g, 6.76 mmol) in DMF (40 mL) were successively added imidazole (2.8 g, 40.56 mmol) and chlorotripropylsilane (3.9 g, 20.28 mmol). The mixture was stirred at room temperature overnight, after which time saturated aqueous NH_4Cl (20 mL) was added, and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The residue was subjected to silica gel column chromatography, eluting with cyclohexane, to give (+)-**22** (2.9 g, 6.41 mmol, 95%). $[\alpha]^{20}_D$ +5 (c 1.0, CH_3Cl); R_f 0.28 (cyclohexane); IR ν_{max} (film, cm^{-1}) 2950, 1202, 1052, 963; UV (MeOH) 226 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.54−0.61 (m, 6H), 0.88 (t, J = 6.8 Hz, 3H), 0.96 (t, J = 7.2 Hz, 9H), 1.24−1.30 (m, 24H), 1.31−1.43 (m, 10H), 1.64 (dd, J = 6.2, 0.6 Hz, 3H), 2.05−2.17 (m, 2H), 3.62 (m, 1H), 5.35−5.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4 (CH_3), 17.1 (3 × CH_2), 17.5 (3 × CH_2), 18.2 (CH_3), 18.9 (3 × CH_3), 23.0 (CH_2), 25.7 (CH_2), 29.7 (CH_2), 30.1 (9 × CH_2), 32.3 (CH_2), 37.2 (CH_2), 41.1 (CH_2), 72.8 (CH), 127.1 (CH), 128.3 (CH); HRMS (ESI+) m/z found 475.4306. $C_{29}H_{60}ONaSi$ requires 475.4306. **(−)-(2*E*,5*S*)-(Icos-2-en-5-yloxy)tripropylsilane [(−)-22]:** Starting from (+)-**21**, the product (−)-**22** was similarly prepared. $[\alpha]^{20}_D$ −4 (c 1.0, CH_3Cl); HRMS (ESI+) m/z found 475.4306, $C_{29}H_{60}ONaSi$ requires 475.4306.

(−)-(*R*)-3-(Tripropylsilyloxy)octadecanal [(−)-23]. To a stirred solution of (+)-**22** (1.1 g, 2.43 mmol) and NMO (569 mg, 4.86 mmol) in THF (12 mL) was added a solution of OsO_4 (4 wt % in H_2O, 1.3 g, 0.24 mmol). The mixture was stirred for 2 h at room temperature, after which time saturated aqueous $NaHSO_3$ (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The resulting colorless oil was diluted in EtOAc/MeOH/THF/H_2O (2/2/1/1) (30 mL), the $NaIO_4$ (3.1 g, 14.6 mmol) was added, and the mixture was stirred for 30 min, after which time saturated aqueous $NaHCO_3$ (15 mL) was added and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The residue was subjected to silica gel column chromatography, eluting with cyclohexane/EtOAc (95/5), to give (−)-**23** (439.4 mg, 1.0 mmol, 41%). $[\alpha]^{20}_D$ −5.2 (c 1.0, CH_3Cl); R_f 0.36 (95/5 cyclohexane/EtOAc); IR ν_{max} (film, cm^{-1}) 2955, 1733; UV (MeOH) 209 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.54−0.65 (m, 6H), 0.88 (t, J = 6.8 Hz, 3H), 0.96 (t, J = 7.2 Hz, 9H), 1.22−1.36 (m, 24H), 1.36−1.50 (m, 10H), 2.50 (dd, J = 5.9, 2.5 Hz, 2H), 4.18 (m, 1H), 9.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 17.0 (3 × CH_2), 17.2 (3 × CH_2), 18.7 (3 × CH_3), 22.9 (CH_2), 25.4 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 29.9 (8 × CH_2), 32.2 (CH_2), 38.2 (CH_2), 51.1 (CH_2), 68.4 (CH), 202.6 (C); HRMS (ESI+) m/z found 463.3941, $C_{27}H_{56}O_2NaSi$ requires 463.3942. **(+)-(*S*)-3-(Tripropylsilyloxy)octadecanal [(−)-23]:** Starting from (+)-**22**, the product (−)-**23** was similarly prepared. $[\alpha]^{20}_D$ +4.7 (c 1.0, CH_3Cl); HRMS (ESI+) m/z found 463.3942, $C_{27}H_{56}O_2NaSi$ requires 463.3942.

(4*R*)-Dimethyl (2-Hydroxy-4-tripropylsilyloxy)nonadecylphosphonate (24). A stirred solution of dimethyl methylphosphonate (599 mg, 4.83 mmol) in dry THF (8 mL) was cooled at −78 °C and treated dropwise with *n*-BuLi 2.5 M in hexane (1.9 mL, 4.83 mmol). The reaction mixture was stirred at −78 °C for 10 min, after which time a solution of (−)-**23** (710 mg, 1.61 mmol) in dry THF (4 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h, and then allowed to warm to room temperature over 1 h, before hydrolysis with aqueous NH_4Cl (10 mL), followed by extraction with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The residue was subjected to silica gel column chromatography, eluting with cyclohexane/EtOAc (60/40), to give **24** (570.6 mg, 1.01 mmol, 63%). R_f 0.14 (50/50 cyclohexane/EtOAc); IR ν_{max} (film, cm^{-1}) 3389, 2950, 1468, 1330, 1224, 106; UV (MeOH) 227 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.56−0.66 (m, 6H), 0.88 (t, J = 6.8 Hz, 3H), 0.96 (t, J = 7.2 Hz, 9H), 1.21−1.33 (m, 26H), 1.33−1.45 (m, 6H), 1.45−1.55 (m, 2H), 1.60−1.75 (m, 2H), 1.90−2.05 (m, 2H), 3.74 (s, 3H), 3.77 (s, 3H), 3.98 (m, 1H), 4.10−4.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, an asterisk (*) indicates the diastereomer pick) δ 14.2 (CH_3), 16.9 (3 × CH_2), 17.0, 17.2* (3 × CH_2), 18.6 (3 × CH_3), 22.8 (CH_2), 24.9, 25.5* (CH_2), 29.5 (CH_2), 29.7 (CH_2), 29.8 (6 × CH_2), 32.0 (CH_2), 32.7, 32.9* (CH_2), 34.0, 34.2* (CH_2), 36.9, 37.7* (CH_2), 43.2, 43.3* (CH_2), 44.0, 44.1* (CH_2), 52.2, 52.3* (CH_3), 52.4, 52.5* (CH_3), 63.6, 65.8* (CH), 70.8, 72.3* (CH); HRMS (ESI+) m/z found 587.4227, $C_{30}H_{65}O_5NaSiP$ requires 587.4231. **(4*S*)-Dimethyl (2-hydroxy-4-tripropylsilyloxy)nonadecylphosphonate (24):** HRMS (ESI+) m/z found 587.4229, $C_{30}H_{65}O_5NaSiP$ requires 587.4231.

(−)-(*R*)-Dimethyl 2-Oxo-4-(tripropylsilyloxy)nonadecylphosphonate [(−)-25]. To a stirred ice-cold solution of (−)-**24** (215 mg, 0.38 mmol) in dry CH_2Cl_2 (6 mL) was added Dess−Martin's reagent (242 mg, 0.57 mmol). The reaction mixture was allowed to warm to room temperature and further stirred for 30 min, before hydrolysis with 1 N NaOH (5 mL), followed by extraction with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The residue was subjected to silica gel column chromatography, eluting with cyclohexane/EtOAc (40/60), to give (−)-**25** (210 mg, 0.37 mmol, 97%). $[\alpha]^{20}_D$ −18.1 (c 1.0, CH_3Cl); R_f 0.28 (50/50 cyclohexane/EtOAc); IR ν_{max} (film, cm^{-1}) 2924, 1698, 1216; UV (MeOH) 227 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (m, 6H), 0.88 (t, J = 6.8 Hz, 3H), 0.95 (t, J = 7.2 Hz, 9H), 1.24−1.30 (s, 26H), 1.30−1.40 (m, 6H), 1.40−1.48 (m, 2H), 2.69 (dd, J = 15.8, 5.3 Hz, 1H), 2.75 (dd, J = 15.8, 6.7 Hz, 1H), 3.10 (m, 1H), 3.16 (m, 1H), 3.77 (d, J = 2.5 Hz, 3H), 3.80 (d, J = 2.5 Hz, 3H), 4.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 16.8 (3 × CH_2), 16.9 (3 × CH_2), 18.4 (3 × CH_3), 22.7 (CH_2), 24.9 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.7 (8 × CH_2), 31.9 (CH_2), 37.6 (CH_2), 41.9, 43.2 (CH_2), 51.2 (CH_2), 52.7, 52.8 (CH_3), 52.8, 52.9 (CH_3), 68.8 (CH), 200.9, 201.0 (C); HRMS (ESI+) m/z found 585.4074, $C_{30}H_{63}O_5NaSiP$ requires 585.4075. **(+)-(*S*)-dimethyl 2-oxo-4-(tripropylsilyloxy)-nonadecylphosphonate [(+)-25]:** $[\alpha]^{20}_D$ +17.8 (c 1.0, CH_3Cl); HRMS (ESI+) m/z found 585.4075, $C_{30}H_{63}O_5NaSiP$ requires 585.4075.

(−)-(1*E*,5*R*)-1-[4-(Benzyloxy)phenyl]-5-(tripropylsilyloxy)isos-1-en-3-one [(−)-27]. To a stirred solution of (−)-**25** (323 mg, 0.57 mmol) in EtOH (5 mL) were added successively 4-(benzyloxy)-benzaldehyde (**26**) (121 mg, 0.57 mmol) and K_2CO_3 (157 mg, 1.14 mmol). The reaction mixture was stirred at room temperature for 3 h, after which time aqueous NH_4Cl (5 mL) was added, and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The residue was subjected to silica gel column chromatography, eluting with cyclohexane/EtOAc (90/10), to give (−)-**27** (292 mg, 0.46 mmol, 79%). $[\alpha]^{20}_D$ −8.2 (c 1.0, CH_3Cl); R_f 0.67 (90/10 cyclohexane/EtOAc); IR ν_{max} (film, cm^{-1}) 2929, 1685, 1654, 1605, 1512, 1171; UV (MeOH) 323, 278 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (m, 6H), 0.88 (t, J = 6.8 Hz, 3H), 0.92 (t, J = 7.2 Hz, 9H), 1.23−1.30 (m, 26H), 1.30−1.38 (m, 6H), 1.46−1.52 (m, 2H), 2.64 (dd, J = 14.7, 5.2 Hz, 1H), 2.84 (dd, J = 14.7, 7.0 Hz, 1H), 4.25 (m, 1H), 5.07

(s, 2H), 6.64 (d, J = 16.1 Hz, 1H), 6.97 (d, J = 8.7 Hz, 2H), 7.32 (m, 1H), 7.35−7.43 (m, 4H), 7.45−7.52 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 17.1 (3 × CH_2), 17.2 (3 × CH_2), 18.7 (3 × CH_3), 22.9 (CH_2), 25.4 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 29.9 (8 × CH_2), 32.1 (CH_2), 38.3 (CH_2), 48.6 (CH_2), 69.8 (CH), 70.2 (CH_2), 115.4 (2 × CH), 125.4 (CH), 127.6 (2 × CH), 127.7 (C), 128.3 (CH), 128.8 (2 × CH), 130.2 (2 × CH), 136.6 (C), 142.7 (CH), 160.9 (C, C33), 199.4 (C, C3); HRMS (ESI+) m/z found 671.4823, $C_{42}H_{68}O_3NaSi$ requires 671.4830. **(+)-(1*E*,5*S*)-1-[4-(benzyloxy)phenyl]-5-(tripropylsilyloxy)isos-1-en-3-one [(+)-27]:** $[\alpha]^{20}_D$ +7.4 (c 1.0, CH_3Cl); HRMS (ESI+) m/z found 671.4823, $C_{42}H_{68}O_3NaSi$ requires 671.4830.

(−)-(*R*)-1-(4-Hydroxyphenyl)-5-(tripropylsilyloxy)isocan-3-one [(−)-28]. To a stirred solution of (−)-**27** (393.4 mg, 0.61 mmol) in EtOAc (8 mL) was added 10% Pd/C (55.2 mg, 0.06 mmol). The reaction mixture was stirred at room temperature under H_2 atmosphere for 3 h, after which time the reaction mixture was filtrated on Celite and the solution was concentrated in vacuo. The residue was subjected to silica gel column chromatography, eluting with cyclohexane/EtOAc (90/10), to give (−)-**28** (230.4 mg, 0.41 mmol, 67%). $[\alpha]^{20}_D$ −12.8 (c 1.0, CH_3Cl); R_f 0.25 (90/10 cyclohexane/EtOAc); IR ν_{max} (film, cm^{-1}) 3993, 2924, 1702, 1605, 1512, 1047; UV (MeOH) 224, 278 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.56 (m, 6H), 0.88 (t, J = 6.8 Hz, 3H), 0.95 (t, J = 7.2 Hz, 9H), 1.23−1.28 (m, 22H), 1.29−1.37 (m, 10H), 1.38−1.44 (m, 2H), 2.44 (dd, J = 15.1, 4.9 Hz, 1H), 2.58 (dd, J = 15.1, 7.2 Hz, 1H), 2.73 (m, 2H), 2.79 (m, 2H), 4.16 (m, 1H), 6.75 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 17.0 (3 × CH_2), 17.2 (3 × CH_2), 18.7 (3 × CH_3), 22.9 (CH_2), 25.3 (CH_2), 28.8 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 29.9 (8 × CH_2), 32.1 (CH_2), 38.0 (CH_2), 46.7 (CH_2), 50.5 (CH_2), 69.4 (CH), 115.6 (2 × CH), 129.5 (2 × CH), 132.9 (C), 154.4 (C), 210.6 (C); HRMS (ESI+) m/z found 583.4515, $C_{35}H_{64}O_3SiNa$ requires 583.4522. **(+)-(*S*)-1-(4-hydroxyphenyl)-5-(tripropylsilyloxy)isocan-3-one [(+)-28]:** $[\alpha]^{20}_D$ +11.7 (c 1.0, CH_3Cl); HRMS (ESI+) m/z found 583.4516, $C_{35}H_{64}O_3SiNa$ requires 583.4522.

(−)-(*R*)-5-hydroxy-1-(4-hydroxyphenyl)icosan-3-one [(−)-1b]. To a stirred solution of (−)-**9** (102.8 mg, 0.18 mmol) in THF (3 mL) was added a solution of 1 M TBAF in THF (0.2 mL). The reaction mixture was stirred at room temperature for 30 min, after which time the mixture was concentrated in vacuo. The residue was subjected to silica gel column chromatography, eluting with cyclohexane/EtOAc (25/75), to give (−)-**1b** (59.5 mg, 0.15 mmol, 83%). $[\alpha]^{20}_D$ −18.8 (c 1.0, CH_3Cl); HRMS (ESI+) m/z found 427.3181, $C_{26}H_{44}O_3Na$ requires 427.3182. **(+)-(*S*)-5-hydroxy-1-(4-hydroxyphenyl)icosan-3-one [(+)-1b]:** $[\alpha]^{20}_D$ +19.2 (c 1.0, CH_3Cl); HRMS (ESI+) m/z found 427.3184, $C_{26}H_{44}O_3Na$ requires 427.3182.

(−)-Amomol A and (+)-Amomol B. According to method A, and starting from (−)-**1b** (48.4 mg, 0.12 mmol), (−)-amomol A (natural) (7.8 mg, 0.018 mmol, 15%) and (+)-amomol B = (natural) (10.8 mg, 0.025 mmol, 21%) were isolated by flash chromatography (elution with CH_2Cl_2/Et_2O). **Amomol A:** $[\alpha]^{20}_D$ −11.1 (c 0.6, CH_3Cl); R_f 0.36 (75/25 cyclohexane/EtOAc); IR ν_{max} (film, cm^{-1}) 2915, 1671, 1636, 1560, 1167; UV (MeOH) 230 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 6.8 Hz, 3H), 1.22−1.34 (m, 24H), 1.35−1.47 (m, 3H), 1.52 (m, 1H), 1.69 (dd, J = 14.7, 1.8 Hz, 1H), 2.07 (m, 1H), 2.13 (m, 1H), 2.15 (m, 1H), 2.34 (m, 1H), 2.39 (m, 1H), 3.35 (s, 3H), 3.85 (m, 1H), 6.12 (dd, J = 10.0, 2.0 Hz, 1H), 6.17 (dd, J = 10.0, 2.0 Hz, 1H), 6.78 (dd, J = 10.0, 3.0 Hz, 1H), 6.84 (dd, J = 10.0, 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 22.9 (CH_2), 25.7 (CH_2), 29.6 (CH_2), 29.9 (9 × CH_2), 32.1 (CH_2), 35.1 (CH_2), 37.0 (CH_2), 38.0 (CH_2), 40.9 (CH_2), 49.2 (CH_3), 69.3 (CH), 79.3 (C), 111.8 (C), 127.3 (CH), 127.9 (CH), 148.6 (CH), 150.6 (CH), 185.5 (C); HRMS (ESI+) m/z found 457.3285, $C_{27}H_{46}O_4Na$ requires 457.3288. **(+)-Amomol B:** $[\alpha]^{20}_D$ +8.9 (c 0.6, CH_3Cl); R_f 0.36 (75/25 cyclohexane/EtOAc); IR ν_{max} (film, cm^{-1}) 2915, 1671, 1636, 1560, 1167; UV (MeOH) 230 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.22−1.35 (m, 25H), 1.43 (m, 2H), 1.53 (m, 1H), 1.96 (m, 2H), 2.06 (m, 1H), 2.24 (m, 2H), 2.42 (m, 1H), 3.31 (s, 3H), 3.79 (m, 1H), 6.13 (dd, J = 10.0, 2.0 Hz, 1H), 6.17 (dd, J = 10.0, 2.0 Hz, 1H), 6.81 (dd, J = 10.0, 3.0 Hz, 1H), 6.85 (dd, J = 10.0, 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 22.9 (CH_2), 25.8 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 29.9 (8 × CH_2), 32.1 (CH_2), 35.3 (CH_2), 36.9 (CH_2), 38.0 (CH_2), 40.3 (CH_2), 48.8 (CH_3), 68.4 (CH), 78.9 (C), 111.8 (C), 127.6 (CH), 127.7 (CH), 148.4 (CH), 150.8 (CH), 185.5 (C); HRMS (ESI+) m/z found 457.3286, $C_{27}H_{46}O_4Na$ requires 457.3288.

(+)-Amomol A and (−)-Amomol B (non-natural). According to method A and starting from (+)-**1b** (53.6 mg, 0.133 mmol), (+)-amomol A (6.0 mg, 0.014 mmol, 11%) and (−)-amomol B (14.2 mg, 0.033 mmol, 25%) were isolated after flash chromatography (elution with CH_2Cl_2/Et_2O). **(+)-Amomol A:** $[\alpha]^{20}_D$ +10.9 (c 0.4, CH_3Cl); HRMS (ESI+) m/z found 457.3288, $C_{27}H_{46}O_4Na$ requires 457.3288. **(−)-Amomol B:** $[\alpha]^{20}_D$ −8.2 (c 0.5, CH_3Cl); HRMS (ESI+) m/z found 457.3286, $C_{27}H_{46}O_4Na$ requires 457.3288.

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Supporting Information Available: NMR spectra of all new compounds and details on biological assay. This material is available free of charge via the Internet at http://pubs.acs.org.