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Enantioselective Total Synthesis of the Potent Anti-inflammatory (+)-Myrrhanol A

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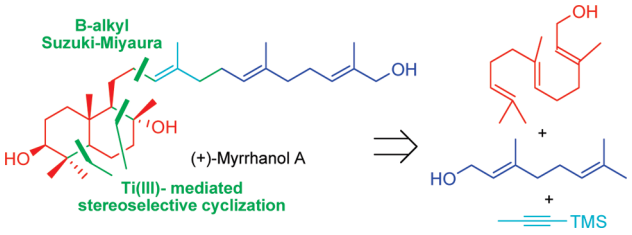
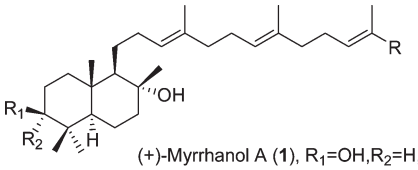


The first total synthesis of potent anti-inflammatory polypodanes (+)-myrrhanol A (**1**), (+)-myrrhanone A (**2**), (+)-myrrhanone B (**3**), and (+)-myrrhanol B (**4**) has been achieved. Key steps in our convergent, highly stereocontrolled route are a Ti(III)-mediated radical cyclization of a chiral monoepoxide to furnish a bicyclic synthon that combines stereospecifically with an acyclic vinyl iodide via an intermolecular B-alkyl Suzuki−Miyaura cross-coupling.

Introduction

(+)-Myrrhanol A (**1**), (+)-myrrhanone A (**2**), (+)-myrrhanone B (**3**), and (+)-myrrhanol B (**4**) are polypodane triterpenes isolated from guggul-gum resin.[1] Although most of the triterpenes contain a tetra- or pentacyclic skeleton as a result of cascade cyclizations and rearrangements of the acyclic precursors squalene (S) and 2,3-oxidosqualene (OS), these bicyclic polypodane triterpenes derive from incomplete cyclization of S or OS. Compounds **1**−**4** could be then encompassed in a group of triterpenes defined as "unusually cyclized triterpenes", characterized by deriving from cyclization proccesses different from those leading to tetra- and pentacyclic triterpenes. It is worth mentioning that there has been an increase in the description of this kind of natural compound in the past few years.[2]



(+)-Myrrhanol A (**1**), R_1=OH,R_2=H,R=CH_2OH
(+)-Myrrhanone A (**2**), R_1=R_2=O, R=CH_2OH
(+)-Myrrhanone B (**3**), R_1=R_2=O, R_1=COOH
(+)-Myrrhanol B (**4**), R_1=OH,R_2=H R=COOH

The resin from *B. mukul* is used in several alternative-medicine preparations including products prescribed or sold for the prevention of inflammation, lowering cholesterol, and reduction of plaque buildup in the arteries. In connection with this, myrrhanol A (**1**) and myrrhanone A (**2**) were shown to display a potent anti-inflammatory effect on exudative pouch fluid, angiogenesis, and granuloma weights in adjuvant-induced air-pouch granuloma of mice, their effects being more marked than those of hydrocortisone.[1]

Moreover, myrrhanol A (**1**), myrrhanone A (**2**), and myrrhanol B (**4**) were characterized as significant NO production inhibitors due to their inhibitory activities against

(1) (a) Kimura, I.; Yoshikawa, M.; Kobayashi, S.; Sugihara, Y.; Suzuki, M.; Oominami, H.; Murakami, T.; Matsuda, H.; Doiphode, V. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 985–989. (b) Matsuda, H.; Morikawa, T.; Ando, S.; Oominami, H.; Murakami, T.; Kimura, I.; Yoshikawa, M. *Bioorg. Med. Chem.* **2004**, *12*, 3037–3046.

(2) For reviews, see: (a) Domingo, V.; Arteaga, J. F.; Quilez , J. F.; Barrero, A. F. *Nat. Prod. Rep.* **2008**, *26*, 115–134. (b) Xu, R.; Fazio, G. C.; Matsuda, S. P. T. *Phytochemistry* **2004**, *65*, 261–291.

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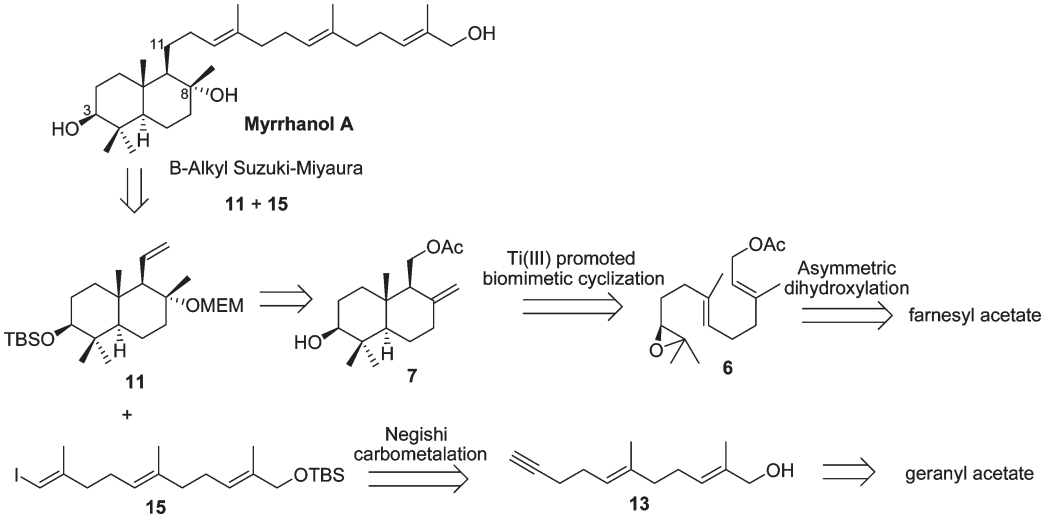
SCHEME 1. Retrosynthetic Analysis Based on a Ti(III)-Promoted Radical Cyclization and a B-Alkyl Suzuki−Miyaura Cross-Coupling

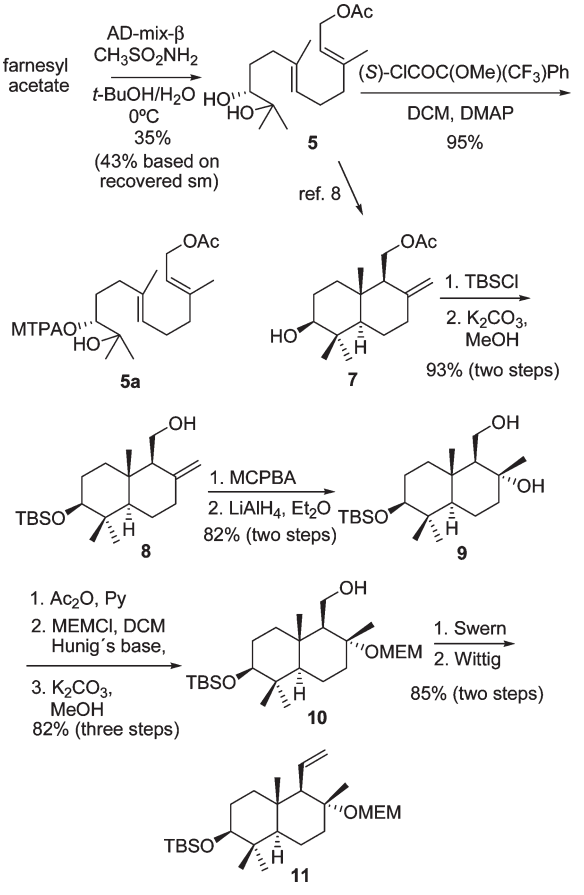


iNOS induction in LPS-activated macrophages, which substantiates the traditional effects of this herbal medicine for the treatment of inflammation.[1,3] The unusual triterpenoid structures of these compounds together with their potent biological activities prompted us to address their total synthesis.[4]

Results and Discussion

In designing a synthetic route toward (+)-myrrhanol A (**1**) we envisioned a convergent approach based on the coupling of a chiral synthon C16, namely, **11** with a polyprenated (*E*)-vinyl iodide, **15**, based on the retrosynthetic analysis outlined in Scheme 1. In our opinion, this approach will overcome the steric hindrance posed by C-11 in carbon−carbon coupling when the bicyclic synthon possesses 15 carbon atoms. In this regard, preliminary tests carried out in our laboratories proved the steric problems associated with the C15 + C15 coupling of related derivatives.

SCHEME 2. Synthesis of Bicyclic Synthon 11



The key steps involved a Ti(III)-mediated cyclization[5] of a chiral monoepoxide **6** and a B-alkyl Suzuki−Miyaura coupling of the synthons **11** and **15**.[6]

As shown in Scheme 2, the synthesis of the required boronate precursor **11** was projected in accordance with

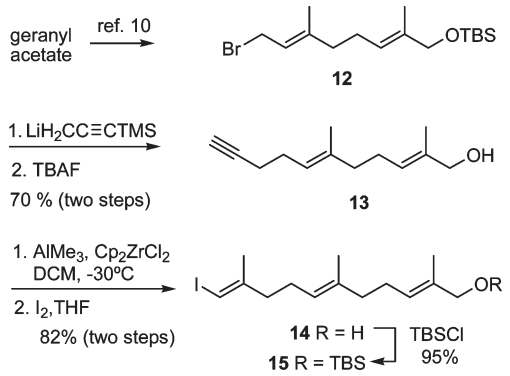
(3) Meselhy, M. R. *Phytochemistry* **2003**, *62*, 213–218.

(4) (a) Nishizawa, M.; Takao, H.; Kanoh, N.; Asoh, K.; Hatakeyama, S.; Yamada, H. *Tetrahedron Lett*. **1994**, *35*, 5693–5696. (b) Kinoshita, M.; Nakamura, D.; Fujiwara, N.; Akita, H. *J. Mol. Catal. B: Enzym*. **2003**, *22*, 161–172.

(5) For pioneering work in this field, see: (a) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc*. **1988**, *110*, 8561–8562. (b) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc*. **1989**, *111*, 4525–4527. (c) RajanBabu, T. V.; Nugent, W. A.; Beattie, M. S. *J. Am. Chem. Soc*. **1990**, *112*, 6408–6409. (d) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc*. 1994, *116*, 986−997. For reviews, see: (e) Gansäuer, A.; Bluhm, H. *Chem. Rev*. **2000**, *100*, 2771–2788. (f) Gansäuer, A.; Pierobon, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 207−220. (g) Gansäuer, A.; Rinker, B. *Tetrahedron* **2002**, *58*, 7017–7026. (h) Gansäuer, A.; Narayan, S. *Adv. Synth. Catal*. **2002**, *344*, 465–475. (i) Gansäuer, A.; Rinker, B. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 435−450. (j) Gansäuer, A.; Lauterbach, T.; Narayan, S. *Angew. Chem., Int. Ed*. **2003**, *42*, 5556–5573. (k) Cuerva, J. M.; Justicia, J.; Oller-Lopez, J. L.; Bazdi, B.; Oltra, J. E. *Mini-Rev. Org. Chem*. **2006**, *3*, 23–35. (l) Cuerva, J. M.; Justicia, J.; Oller-Lopez, J. L.; Oltra, J. E. *Top. Curr. Chem*. **2006**, *264*, 63–91. (m) Barrero, A. F.; Quilez del Moral, J. F.; Sanchez, E. M.; Arteaga, J. F. *Eur. J. Org. Chem*. **2006**, 1627–1641. For references of the catalytic version, see: (n) Gansäuer, A.; Bluhm, H. *Chem. Commun*. **1998**, 2143–2144. (o) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem., Int. Ed*. **1998**, *37*, 101–103. (p) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc*. **1998**, *120*, 12849–12859. (q) Barrero, A. F.; Rosales, A.; Cuerva, J. M.; Oltra, J. E. *Org. Lett*. **2003**, *5*, 1935–1938.

(6) (a) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457–2483. (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. *Angew. Chem., Int. Ed*. **2001**, *40*, 4544–4568.

SCHEME 3. Synthesis of Acyclic Synthon 15

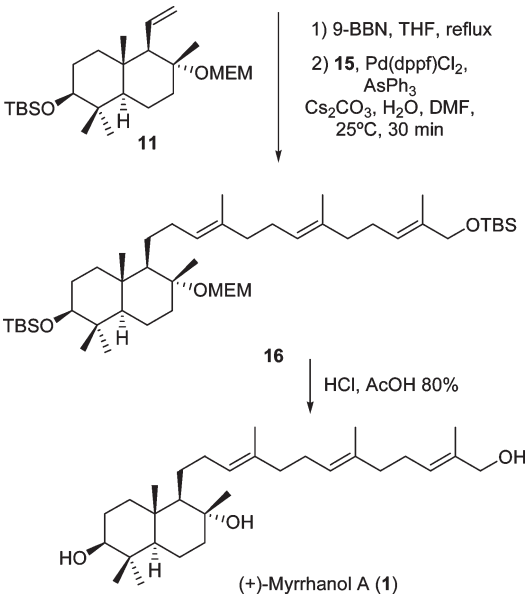


the absolute configuration found in the natural polypodanes, that is, 3*S*,5*R*,8*R*,9*R*,10*S* (myrrhanol A numbering).

The element of enantiocontrol in the synthesis was based on the Sharpless asymmetric terminal dihydroxylation[7] of *E*,*E*-farnesyl acetate to access enantioselectively key bicyclic **7**, already reported by us in our asymmetric synthesis of onocerane triterpenes.[8] This reaction proceeded with acceptable selectivity and efficiency to diol **5** in a 43% yield based on recovered starting material. The enantiopurity of this alcohol was established as 96% on the basis of the ^{1}H NMR spectrum of the corresponding (*S*)-Mosher ester **5a**.[9] Chiral diol **5** was efficiently converted into the isodrimenediol skeleton **7** via Ti(III)-mediated radical cyclization of the corresponding oxirane as previously described by us.[8] Protection of the 3-hydroxyl group of bicyclic **7** as its *tert*-butyldimethylsilylether and deprotection of the primary acetoxy group led to alcohol **8** in a 93% yield. Oxidation of the exocyclic double bond by MCPBA followed by reductive opening with $LiAlH_4$ of the oxirane ring generated the quaternary stereocenter at C-8 with the appropriate configuration, thus affording diol **9** in an 82% yield as the only diastereoisomer detected. The primary alcohol in **9** was selectively acetylated, whereas the tertiary hydroxyl group was protected as its MEM ether. At this point, the presence of orthogonal protecting groups at C-3, C-8, and C-11 positions provides the opportunity to extend the chain at C11 via a selective acetoxy-deprotection of the latter. Swern oxidation of the primary alcohol **10** and Wittig olefination of the corresponding sterically hindered aldehyde allowed us to achieve the required one-carbon homologation to afford the bicyclic synthon **11** in an 85% yield over two steps.

Turning our attention to the synthesis of the synthon **15**, we started the linear sequence from the commercially available geranyl acetate (Scheme 3). Based on the work of Corey, allylic bromide **12** was obtained from geranyl acetate.[10]

SCHEME 4. Palladium-Catalyzed Cross-Coupling Reaction



Three carbons were then introduced via coupling with 1-trimethylsilyl propargyl lithium, which after deprotection gave **13** in a 70% overall yield. The *E*-vinyl iodide key intermediate **15** was then installed by a Negishi carbometalation.[11] This protocol proved to proceed with remarkably high regio- and stereoselectivity.

The target (+)-myrrhanol A was efficiently assembled as follows. Treatment of olefin **11** with 9-BBN in THF under reflux, followed by addition of $Pd(dppf)Cl_2$ and the geometrically pure vinyl iodide **15**, afforded the desired coupling product **16** in a 90% isolated yield as shown in Scheme 4. As expected, the alkene geometry of the acyclic partner was maintained in the Suzuki coupling product. Harsh conditions were necessary in the hydroboration reaction due to the sterically congested environment of the vinyl group in **11** (Scheme 4).

Concomitant deprotection of the three ethers present in **15** was achieved in only one step after treating this compound with a mixture of AcOH and HCl in THF to afford (+)-myrrhanol A (**1**). Considerable experimentation was needed to avoid both alkene isomerization and dehydration of the tertiary alcohol. MS and ^{1}H and ^{13}C NMR of our synthetic coincide completely with those of the natural product. The sign of the optical rotation $[\alpha]_D$ of both synthetic (+8.2°, *c* 1.0, MeOH) and natural myrrhanol A (+12.2°, *c* 1.0, MeOH) matched, thus confirming the absolute configuration of the natural compound.

Once the enantioselective synthesis of (+)-myrrhanol A was achieved, we decided to address the synthesis of its congeners (+)-myrrhanone A (**2**), (+)-myrrhanone B (**3**), and (+)-myrrhanol B (**4**) (Scheme 5), which although present in the resin of *B. mukul* in minor concentration also presented a significant NO production inhibitory activity. Thus, regioselective protection of the primary alcohol in **1** as its corresponding *tert*-butyldimethylsilylether and subsequent

(7) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M. *J. Org. Chem.* **1992**, *10*, 2768–2771.

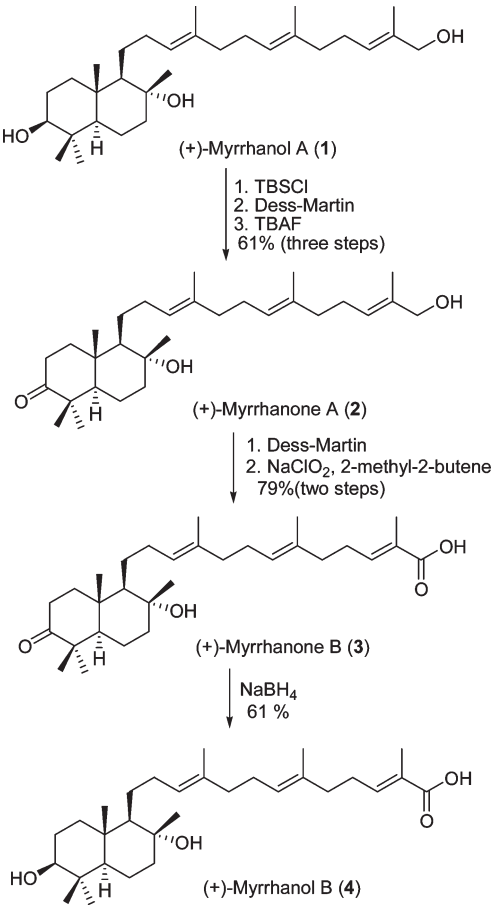
(8) For the preparation of racemic **7**: (a) Barrero, A. F.; Cuerva, J. M.; Herrador, M. M.; Valdivia, M. V. *J. Org. Chem.* **2001**, *66*, 4074–4078. (b) Justicia, J.; Rosales, A.; Bunuel, E.; Oller-Lopez, J. L.; Valdivia, M.; Haidour, A.; Oltra, J. E.; Barrero, A. F.; Cardenas, D. J.; Cuerva, J. M. *Chem.—Eur. J.* **2004**, *10*, 1778–1788. (c) Justicia, J.; Oltra, J. E.; Cuerva, J. M. *J. Org. Chem.* **2005**, *70*, 8265−8272. For the enantioselective preparation of **7**, see: Barrero, A. F.; Herrador, M. M.; Quilez del Moral, J. F.; Arteaga, P.; Arteaga, J. F.; Piedra, M.; Sanchez, E. M. *Org. Lett.* **2005**, *7*, 2301–2304.

(9) Zhang, J.; Corey, E. J. *Org. Lett.* **2001**, *3*, 3215–3216.

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

(11) Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639–6647.

SCHEME 5. Synthesis of (+)-Myrrhanone A (2), (+)-Myrrhanone B (3), and (+)-Myrrhanol B (4)



Dess−Martin oxidation at C3 provided after TBAF deprotection (+)-myrrhanone A (**2**) (Scheme 5). From myrrhanone A, the synthesis of (+)-myrrhanone B (**3**) requires the oxidation of the primary allylic alcohol to carboxylic acid. This transformation was uneventfully achieved using the Dess−Martin periodinane to afford the corresponding aldehyde, which was oxidized to the desired carboxylic acid **3** with sodium chlorite.[12] Finally, chemo- and stereoselective reduction of **3** afforded the target (+)-myrrhanol B (**4**).

Conclusion

In summary, we report a brief and convergent first total synthesis of the potent anti-inflammatory (+)-myrrhanol A and its also bioactive congeners (+)-myrrhanone A (**2**), (+)-myrrhanone B (**3**), and (+)-myrrhanol B (**4**), starting from commercially available geranyl and farnesyl acetate. The synthesis of these unusually cyclized triterpenes illustrates the versatility of the Ti(III)-mediated radical cyclization of asymmetric monoepoxides of polyprenes in the enantioselective synthesis of polycyclic natural structures. In our opinion, this radical approach complements conveniently the cationic version of these cyclizations used by Corey and others in the synthesis of polycyclic triterpenes.[13]

(12) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.
(13) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 8865–8869.

Experimental Section

(*R*,2*E*,6*E*)-10,11-Dihydroxy-3,7,11-trimethyldodeca-2,6-dienyl Acetate (5). To a mixture of *tert*-butanol (225 mL) and water (225 mL) were added 40.05 g of AD-mix-β (85.65 mmol $K_3Fe(CN)_6$, 85.65 mmol of K_2CO_3, 0.04 mmol of $[K_2OsO_2(OH)_4]$, and 0.3 mmol of $(DHQD)_2$-PHAL ligand (hydroquinidine 1,4-phthalazinediyl diether). The resulting mixture was stirred mechanically at 25 °C until two clear phases were obtained. Then, $CH_3SO_2NH_2$ (2.715 g, 28.50 mmol) was added, and the mixture was cooled to 0 °C. The resulting heterogeneous slurry was stirred vigorously at 0 °C, as farnesyl acetate (7.50 g, 28.50 mmol) was added at once. Stirring was continued at 0 °C for 24 h. At this time the oxidation was completed, and solid sodium sulphite (37.20 g) was added. The mixture was allowed to warm to room temperature and stirred until two clear phases were obtained. Ethyl acetate (150 mL) and water (45 mL) were added, and after separation of the layers, the aqueous phase was further extracted with ethyl acetate (3 × 100 mL). The combined organic extract was washed with a 2 N aqueous NaOH solution (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. This crude product was purified by flash chromatography (hexane/*t*-BuOMe, 1:3) to afford 1.5 g (5.71 mmol) of starting material and 2.97 g (9.9 mmol) of **5** as a clear colorless viscous oil. $[\alpha]^{20}_D$ = +12.1 (*c* 1.0, $CHCl_3$).[14] IR (film) 3446, 2971, 2930, 1735, 1717, 1437, 1365, 1229, 1159, 1074, 1022 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.31 (dt, J = 7.2, 1.2 Hz, 1H), 5.14 (dt, J = 6.8, 0.9 Hz, 1H), 4.56 (d, J = 6.8 Hz, 2H), 3.32 (dd, J = 10.5, 1.8 Hz, 1H), 2.40 (d, J = 4.5 Hz, 1H), 2.25−2.18 (m, 1H), 2.13−2.0 (m, 4H), 2.03 (s, 3H), 1.67 (s, 3H), 1.59 (s, 3H), 1.58−1.53 (m, 1H), 1.42−1.34 (m, 1H), 1.17 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 141.8, 135.2, 124.2, 118.4, 78.0, 72.9, 61.3, 39.3, 36.6, 29.5, 26.3, 25.9, 23.2, 20.9, 16.3, 15.8. HRFABMS: calcd for $C_{17}H_{30}O_4Na$ $[M+Na]^+$ 321.2042, found 321.2071.

(*S*)-MTPA Ester 5a. To a solution of **5** (9 mg, 0.03 mmol) in dry CH_2Cl_2 (1.2 mL) were added (*S*)-(+)-methoxy-α-(trifluoromethyl)phenylacetyl chloride (11 μL, 0.06 mmol) and DMAP (15 mg, 1.2 mmol). The resulting mixture was then stirred for 1 h at rt. The mixture was diluted with CH_2Cl_2 and then passed through a column of silica gel. The eluent was concentrated to give the desired (*S*)-MTPA ester **5a** (15 mg, 0.029 mmol) as a colorless oil. ^1H NMR (C_6D_6, 500 MHz), *R* enantiomer δ 7.82 (bd, J = 7.8 Hz, 2H), 7.09 (bt, J = 7.8 Hz, 2H), 7.02 (bt, J = 7.3 Hz, 1H), 5.40 (bt, J = 6.8 Hz, 1H), 5.08 (bt, J = 6.8 Hz, 1H), 5.00 (dd, J = 9.7, 2.4 Hz, 1H), 4.58 (d, J = 7.0 Hz, 2H); 3.51 (s, 3H), 2.02 (m, 2H), 1.94−1.84 (m, 4H), 1.66 (s, 3H), 1.55−1.40 (m, 2H), 1.46 (s, 3H), 1.38 (s, 3H), 0.98 (s, 3H), 0.89 (s, 3H); *S* enantiomer δ 3.44 (s, 3H).

(2*S*,4a*S*,5*S*)-Decahydro-2-hydroxy-1,1,4a-trimethyl-6-methylenenaphthalen-5-yl)methyl Acetate (7). A mixture of Cp_2TiCl_2 (276 mg, 1.11 mmol) and Mn dust (2438 mg, 44.32 mmol) in strictly deoxygenated THF (70 mL) and Ar atmosphere was stirred at rt until the red solution turned green. Then, a solution of 1550 mg (5.54 mmol) of epoxide **4** and 2,4,6-collidine (5.1 mL, 38.78 mmol) and Me_3SiCl (2.8 mL, 22.16 mmol) were added. The reaction mixture was stirred for 2 h (TLC monitoring), quenched with 1 N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in THF (20 mL) and stirred with Bu_4NF (6.7 mL, 6.67 mmol) for 3 h. Then, THF was removed, and the mixture was diluted with *t*-BuOMe, washed with brine, and dried over anhydrous Na_2SO_4 and the solvent was removed. The resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 1:1) to afford 732 mg (47%) of **7**.[9]

(14) Vidari, G; Dapiaggi, A.; Zanoni, G.; Gaslaschelli, L. *Tetrahedron Lett*. **1993**, *34*, 6485–6488.

(2*E*,6*E*,10*E*)-11-Iodo-2,6,10-trimethylundeca-2,6,10-trien-1-ol (14). To a solution of zirconocene dichloride (125 mg, 428 mmol) in CH_2Cl_2 (3.4 mL) at rt under an argon atmosphere was added dropwise a solution of trimethylaluminum in heptane (2 M in heptane, 2.6 mL, 5.14 mmol). After 15 min, the solution was cooled to 0 °C, and a solution of alkyne **13** (325 mg, 1.69 mmol) dissolved in CH_2Cl_2 (3.4 mL) was added to the above lemon yellow solution. The reaction mixture was stirred at 0 °C for 6 h and then cooled to −30 °C. Iodine (869 mg, 3.42 mmol) was added as a solution in 2 mL of THF. The resulting brown slurry was warmed to 0 °C and poured slowly with stirring into an iced saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ether (3 × 20 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ and dried over Na_2SO_4. Concentration followed by flash chromatography on silica gel with 1:2 hexane/ether as eluent provided the desired product **14** as a colorless oil (464 mg, 1.39 mmol, 82%). IR 3419, 2919, 2850, 1644, 1442 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 5.86 (s, 1 H), 5.37 (t, J = 6.9 Hz, 1H), 5.07 (t, J = 6.9 Hz, 1H), 3.99 (s, 2H), 2.22 (t, J = 7.9 Hz, 2H), 2.10 (m, 4H), 2.01 (t, J = 7.2 Hz, 2H), 1.83 (s, 3H), 1.66 (s, 3H), 1.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.5, 136.4, 135.5, 126.6, 123.9, 75.1, 69.3, 39.6, 39.4, 28.2, 26.3, 24.1, 16.1, 13.7. HRFABMS: calcd for $C_{14}H_{23}IONa$ $[M+Na]^+$ 357.0691, found 357.0698.

Compound 16. To olefin **11** (240 mg, 0.527 mmol) was added a solution of 9-BBN (3.16 mL, 0.5 M in THF), and the solution was stirred at reflux for 4 h. This solution was transferred by cannula to another flask containing a mixture of vinyl iodide **15** (292 mg, 0.652 mmol), Pd(dppf)Cl_2, CH_2Cl_2 (53 mg, 0.065 mmol), $AsPh_3$ (29 mg, 0.097 mmol), Cs_2CO_3 (664 mg, 2.04 mmol), and water (0.375 mL, 15 mmol) in DMF (7.5 mL). After 30 min, the brown reaction mixture was diluted with water and extracted three times with *t*-BuOMe. The organic layer was washed with water and brine and dried over Na_2SO_4. Concentration followed by silica gel flash-chromatography (hexane/*t*-BuOMe, 12:1) yielded 368 mg (90%) of **16**. $[\alpha]^{20}_D$ = +1.5 (*c* 1.0, CH_2Cl_2); IR (film) 2952, 2930, 2856, 1598, 1448, 1253, 1101, 1067, 1039, 835, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.38 (t, J = 7.0 Hz, 1H), 5.14 (t, J = 7.2 Hz, 1H), 5.11 (t, J = 7.1 Hz, 1H), 4.86 (t, J = 7.7 Hz, 1H), 4.73 (t, J = 7.7 Hz, 1H), 3.99 (s, 2H), 3.74−3.62 (m, 2H), 3.54 (t, J = 4.8 Hz, 2H), 3.38 (s, 3H), 3.19 (dd, J = 11.2, 4.5 Hz, 1H), 2.14−1.90 (m, 10H), 1.70−0.84 (m, 12H), 1.60 (s, 3H), 1.59 (s, 6H), 1.18 (s, 3H), 0.90 (s, 9H), 0.88 (s, 12H), 0.80 (s, 3H), 0.71 (s, 3H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.7, 134.4, 134.2, 125.2, 124.4, 124.4, 88.8, 80.2, 79.3, 71.9, 68.7, 66.4, 59.2, 58.9, 54.9, 40.1, 39.7, 39.4, 39.3, 38.6, 38.0, 31.4, 28.5, 27.5, 26.7, 26.2, 26.1, 26.0 (3C), 25.9 (3C), 20.7, 19.9, 18.4, 18.1, 16.1, 16.0, 15.9, 15.8, 13.4, −3.8, −4.9, −5.3 (2C). HRFABMS: calcd for $C_{46}H_{88}O_5Si_2Na$ $[M + Na]^+$ 799.6067, found 799.6054.

(+)-Myrrhanol A (1). To a solution of **12** (211 mg, 0.271 mmol) and 80% aqueous AcOH (4.2 mL) in THF (2.8 mL) was gradually added 2 M HCl (0.7 mL) at room temperature for 30 min, and the whole mixture was stirred for 3.5 h at the same temperature. The reaction mixture was diluted with brine and extracted with *t*-BuOMe. The organic layer was washed with 7% aqueous $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (hexane/*t*-BuOMe, 1:2) to give (+)-myrrhanol A (**1**) (99 mg, 80%). Colorless oil, $[\alpha]^{25}_D$ = +8.2 (*c* 1.0, MeOH); IR(film) 3429, 2928, 1640, 1448, 1364, 1037 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.39 (t, J = 7.0 Hz, 1H), 5.16 (t, J = 7.1 Hz, 1H), 5.11 (t, J = 7.0 Hz, 1H), 3.99 (s, 2H), 3.21 (dd, J = 11.4, 4.6 Hz, 1H), 2.15−1.86 (m, 10H), 1.83 (bd, J = 11.6 Hz, 1H), 1.73−1.08 (m, 9H), 1.65 (s, 3H), 1.60 (s, 3H), 1.55 (s, 3H), 1.12 (s, 3H), 1.02 (t, J = 3.7 Hz, 1H), 0.98 (s, 3H), 0.89 (bd, J = 11.2 Hz, 1H), 0.79 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.1, 134.7, 134.6, 126.0, 125.0, 124.5, 78.7, 73.9, 68.9, 61.2, 55.0, 44.4, 39.6, 39.3, 38.81 (2C), 37.8, 31.3, 28.1, 27.1, 26.5, 26.1, 25.1, 23.7, 20.2, 16.2, 16.0, 15.5, 15.3, 13.7. HRFABMS: calcd for $C_{30}H_{52}O_3Na$ $[M + Na]^+$ 483.3813, found 483.3825.

(+)-Myrrhanone A (2). To a stirred solution of (+)-myrrhanol A (73 mg, 0.159 mmol) in DMF (3 mL) were added imidazole (16 mg, 0.238 mmol) and TBSCl (36 mg, 0.238 mmol) at rt. The reaction progress was monitored by TLC, and after consumption of the starting product (20 min), the mixture was diluted with *t*-BuOMe and water and extracted with *t*-BuOMe. The combined organic layer was washed with 2 N HCl and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude was dissolved in dry CH_2Cl_2 (4.1 mL) under Ar, and Dess−Martin reagent (118 mg, 0.278 mmol) was added. After 2 h at rt the reaction was quenched with a saturated solution of $Na_2S_2O_3$−$NaHCO_3$ that was added slowly to the mixture. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude was dissolved in THF (2 mL) and stirred with TBAF 1 M (0.25 mL, 0.25 mmol) for 30 min (TLC monitoring). Then, THF was removed, the mixture was diluted with *t*-BuOMe, washed with brine, and dried over anhydrous Na_2SO_4, and the solvent removed. The resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 1:1) to afford 45 mg (61% over three steps) of (+)-myrrhanone A (**2**). Colorless oil, $[\alpha]^{25}_D$ = +6.9 (*c* 1.0, MeOH); IR (film) 3406, 2935, 2862, 1702, 1456, 1385, 1078, 1006 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.31 (t, J = 7.0 Hz, 1H), 5.08 (t, J = 7.2 Hz, 1H), 5.04 (t, J = 6.8 Hz, 1H), 3.9 (s, 2H), 2.51 (ddd, J = 16.0, 11.7, 7.0 Hz, 1H), 2.32 (ddd, J = 16.0, 6.3, 3.4 Hz, 1H), 2.08−1.80 (m, 11H), 1.58−1.21 (m, 8H), 1.58 (s, 3H), 1.52 (s, 6H), 1.11 (s, 3H), 1.04 (t, J = 3.9 Hz, 1H), 1.02 (s, 3H), 0.94 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.9, 135.4, 134.7, 134.6, 125.9, 124.8, 124.5, 73.7, 68.9, 60.3, 55.1, 47.5, 43.8, 39.6, 39.3, 38.6, 38.3, 33.9, 31.1, 26.5, 26.3, 26.1, 25.7, 23.6, 21.4, 21.3, 16.2, 16.0, 14.81, 13.7. HRFABMS: calcd for $C_{30}H_{50}O_3Na$ $[M + Na]^+$ 481.3657, found 481.3667.

(+)-Myrrhanone B (3). To a mixture of (+)-myrrhanone A (37 mg, 0.080 mmol) in CH_2Cl_2 (2 mL) under Ar was added Dess−Martin reagent (67 mg, 0.16 mmol). After 2 h at rt the reaction was quenched with a saturated solution of $Na_2S_2O_3$−$NaHCO_3$ that was added slowly to the mixture, and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Filtration on silica gel (hexane/*t*-BuOMe 1:2) afforded the allylic aldehyde, which was dissolved in 2 mL of *tert*-butyl alcohol and 1 mL of 2-methyl-2-butene. A solution of sodium chlorite (29 mg, 0.32 mmol) and sodium dihydrogenphosphate (33 mg, 0.24 mmol) in 0.5 mL of water was added dropwise over a 10 min period. The pale yellow reaction mixture was stirred at room temperature overnight. Volatile components were then removed under vacuum. The residue was dissolved in 30 mL of water and extracted with two 15 mL portions of hexane. The aqueous layer was acidified to pH 3 with HCl and extracted with three 20 mL portions of ether. The combined ether layers were washed with 50 mL of cold water, dried, and concentrated. The resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 2:1) to give 30 mg (79% overall yield) of (+)-myrrhanone B (**3**). Colorless oil, $[\alpha]^{25}_D$ = +7.1 (*c* 1.0, MeOH); IR (film) 3423, 2936, 1687, 1643, 1457, 1385 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.76 (bt, J = 7.3 Hz, 1H), 5.06 (t, J = 7.0 Hz, 1H), 5.04 (t, J = 6.8 Hz, 1H), 2.53 (ddd, J = 16.0, 11.7, 7.0 Hz, 1H), 2.33 (ddd, J = 16.0, 6.4, 3.5 Hz, 1H), 2.24 (q, J = 7.1 Hz, 2H), 2.05−1.76 (m, 9H), 1.76 (s, 3H), 1.57−1.14 (m, 8H), 1.54 (s, 3H), 1.52 (s, 3H), 1.16 (s, 3H), 1.08 (t, J = 3.9 Hz, 1H), 1.04 (s, 3H), 0.96 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.6, 171.4, 134.6, 144.1, 133.4, 126.9, 125.4, 125.1, 74.4, 60.4, 55.1, 47.4, 43.6, 39.3, 38.6, 38.2, 37.9, 33.9, 31.3, 26.8, 26.2, 25.9, 25.7, 23.5, 21.3 (2 C), 16.0, 15.7, 14.7, 12.0. HRFABMS: calcd for $C_{30}H_{48}O_4Na$ $[M + Na]^+$ 495.3450, found 495.3441.

(+)-Myrrhanol B (4). To a solution of (+)-myrrhanone B (10 mg, 0.021 mmol) in dry MeOH was added $NaBH_4$, and the mixture was stirred for 2 h. The reaction was quenched with acetone and concentrated under reduced pressure. The residue was dissolved in 10 mL of water, and this was acidified to pH 3 with HCl and extracted with three 10 mL portions of EtOAc, washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting crude was purified by HPLC (hexane/*t*-BuOMe, 1:1) to afford 6 mg (60%) of (+)-myrrhanol B (**4**). Colorless oil, $[\alpha]^{28}_D = +6.2$ (*c* 1.0, MeOH); IR (film) 3453, 2930, 2862, 1709, 1650, 1456, 1385, 1080, 1006 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.70 (bt, J = 7.2 Hz, 1H), 5.04 (t, J = 7.0 Hz, 1H), 5.02 (t, J = 7.1 Hz, 1H), 3.18 (dd, J = 11.6, 4.6 Hz, 1H), 2.21 (q, J = 6.8 Hz, 2H), 2.08−1.72 (m, 9H), 1.74 (bs, 3H), 1.64−1.02 (m, 9H), 1.53 (s, 3H), 1.51 (s, 3H), 1.10 (s, 3H), 0.98 (t, J = 3.8 Hz, 1H), 0.92 (s, 3H), 0.84 (bd, J = 11.9 Hz, 1H), 0.73 (s, 3H), 0.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 143.6, 137.0, 133.2, 126.9, 125.5, 125.4, 78.8, 75.1, 61.4, 55.0, 44.3, 39.3, 38.8 (2C), 37.9, 37.8, 31.6, 28.1, 27.1, 26.5, 25.7, 25.6, 23.6, 20.2, 16.0, 15.7, 15.5, 15.3, 12.1. HRFABMS calcd for $C_{30}H_5O_4Na$ $[M + Na]^+$ 497.3607, found 497.3625.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **6**, **8**−**11**, **13**, **15**, and ^1H and ^{13}C NMR spectra of **1-11**, and **13-16**. This material is available free of charge at http://pubs.acs.org.This material is available free of charge via the Internet at http://pubs.acs.org.