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The Thiopyran Route to Polypropionates: Enantioselective Synthesis of Membrenone B from Racemic Fragments

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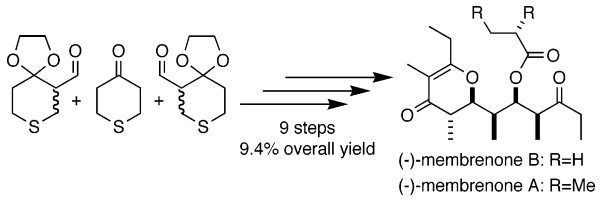

(6*S*,7*S*,8*S*,9*R*,10*S*)-(−)-Membrenone B was synthesized in nine steps (9.4% overall yield) beginning with two-directional aldol coupling of tetrahydro-4*H*-thiopyran-4-one with racemic 1,4-dioxa-8-thiaspiro[4.5]decane-6-carboxaldehyde. The first aldol reaction occurs with dynamic kinetic resolution to give a single adduct (>98% ee). The second aldol reaction is highly diastereoselective (three of eight possible adducts), and both major products are converted to membrenone B. The route also constitutes a formal synthesis of membrenone A.

An important aspect of marine chemical ecology[1] concerns predator−prey interactions. Opisthobranchs (commonly known as sea slugs) are soft-bodied marine molluscs often devoid of a protective shell, and their defense mechanism relies on the secretion of chemicals rendering them poisonous or at least extremely distasteful to potential predators.[2] In 1993, Ciavatta et al.[3] reported partial structures for membrenones A−C (**1**−**3**; Figure 1) isolated from the skin of the notaspidean *Pleurobranchus membranaceus*, a Mediterranean mollusc species. The scarcity of available material limited preliminary bioassays to membrenone A (**1**) that was shown to be a feeding deterrent to *Carassius auratus*.

In pioneering work conducted by Sampson and Perkins, the relative configurations of **1**−**3** were firmly established by stereoselective synthesis.[4] Considering all available data, a persuasive argument was presented[4c] that the natural products

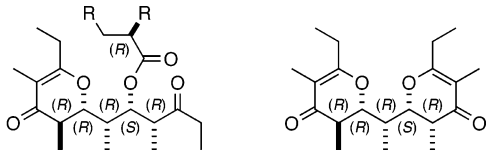

FIGURE 1. Structures and proposed absolute configurations for membrenones A−C.

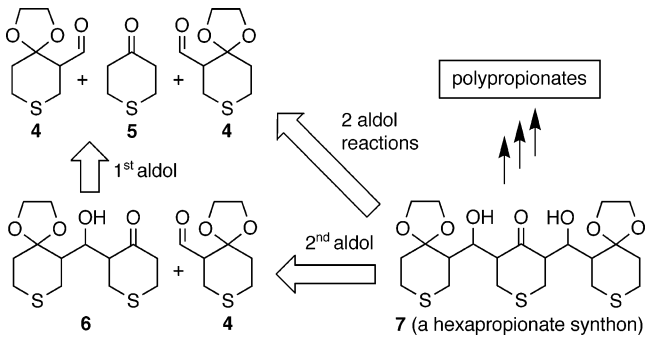

FIGURE 2. The thiopyran route to polypropionates.

1−**3** are the (+)-enantiomers with the absolute configurations indicated in Figure 1.[5] This assignment requires the conclusion that the originally reported[3] specific rotations for membrenones B (**2**) and C (**3**) are incorrect (wrong sign) and unfortunately cannot be substantiated because samples of natural material are no longer available. In this paper, we report a very concise synthesis of (−)-membrenone B (*ent*-**2**) from racemic fragments.[6]

The thiopyran route to polypropionates is an attractive strategy for the rapid assembly of stereochemically diverse hexapropionate synthons from simple precursors (Figure 2).[7−9] For example, we recently demonstrated that 11 of the 20 possible diastereomers of **7** could be selectively prepared in two or three steps from **4** and **5**.[8b] We chose the hexapropionate (−)-membrenone B (*ent*-**2**) as a synthetic target to test and illustrate this approach.

(1) Paul, V. J.; Puglisi, M. P.; Ritson-Williams, R. *Nat. Prod. Rep.* **2006**, *23*, 153−180.

(2) (a) Avila, C. In *Oceanography and Marine Biology−An Annual Review*; UCL Press: London, 1995; Vol. 33, pp 487−559. (b) Cimino, G.; Ciavatta, M. L.; Fontana, A.; Gavagnin, M. In *Bioactive Compounds from Natural Sources: Isolation Characterisation and Biological Properties*; Tringali, C., Ed.; Taylor & Francis Ltd: London, 2001; pp 577−637.

(3) Ciavatta, M. L.; Trivellone, E.; Villani, G.; Cimino, G. *Tetrahedron Lett.* **1993**, *34*, 6791−6794.

(4) (a) Perkins, M. V.; Sampson, R. A. *Tetrahedron Lett.* **1998**, *39*, 8367−8370. (b) Perkins, M. V.; Sampson, R. A. *Org. Lett.* **2001**, *3*, 123−126. (c) Sampson, R. A.; Perkins, M. V. *Org. Lett.* **2002**, *4*, 1655−1658.

(5) This assignment relies primarily on the circular dichroism (CD) data obtained from the synthetic (−)-enantiomers of **1**−**3** (i.e., *ent*-**1**−**3**) compared with those reported (ref 3) for the natural products and is consistent with the (*R*)-configuration for the 2-methylbutanoyl appendage in **1** as determined (ref 3) by Mosher's ester analysis of a product from $LiAlH_4$ reduction.

(6) For a previous synthesis of *ent*-**1** and *ent*-**2**, see ref 4c. For syntheses of **3** and (or) *ent*-**3**, see ref 4b and: (a) Marshall, J. A.; Ellis, K. C. *Org. Lett.* **2003**, *5*, 1729−1732. (b) Yadav, J. S.; Srinivas, R.; Sathaiah, K. *Tetrahedron Lett.* **2006**, *47*, 1603−1606.

(7) First aldol: (a) Ward, D. E.; Sales, M.; Man, C. C.; Shen, J.; Sasmal, P. K.; Guo, C. *J. Org. Chem.* **2002**, *67*, 1618−1629. (b) Ward, D. E.; Akinnusi, O. T.; Alarcon, I. Q.; Jheengut, V.; Shen, J.; Quail, J. W. *Tetrahedron: Asymmetry* **2004**, *15*, 2425−2430. (c) Ward, D. E.; Jheengut, V.; Akinnusi, O. T. *Org. Lett.* **2005**, *7*, 1181−1184.

(8) Second aldol: (a) Ward, D. E.; Guo, C.; Sasmal, P. K.; Man, C. C.; Sales, M. *Org. Lett.* **2000**, *2*, 1325−1328. (b) Ward, D. E.; Beye, G. E.; Sales, M.; Alarcon, I. Q.; Gillis, H. M.; Jheengut, V. *J. Org. Chem.* **2007**, *72*, 1667−1674.

(9) (a) Ward, D. E.; Gillis, H. M.; Akinnusi, O. T.; Rasheed, M. A.; Saravanan, K.; Sasmal, P. K. *Org. Lett.* **2006**, *8*, 2631−2634. (b) Ward, D. E.; Jheengut, V.; Beye, G. E. *J. Org. Chem.* **2006**, *71*, 8989−8992.

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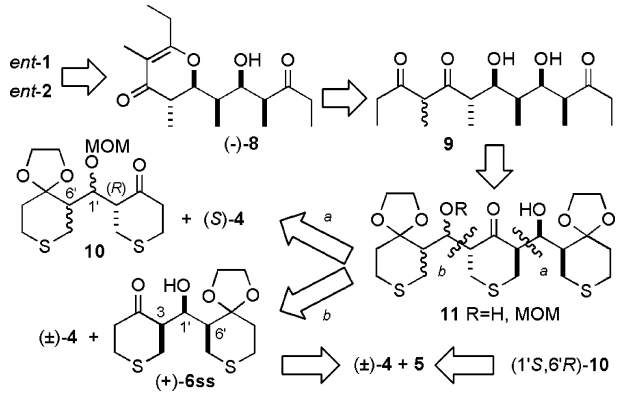
SCHEME 1. Retrosynthetic Analysis for *ent*-1 and *ent*-2

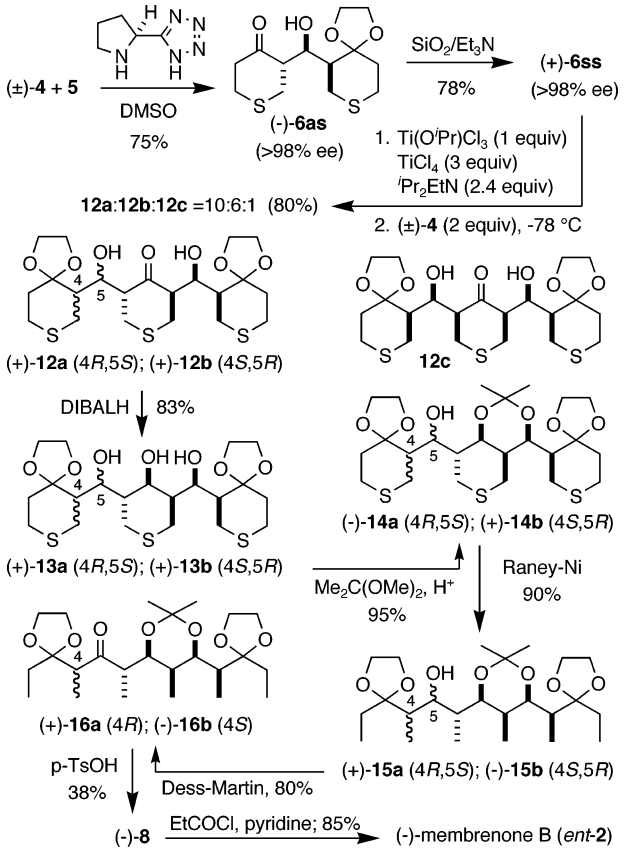


Both *ent*-**1** and *ent*-**2** are available by appropriate acylation of (−)-**8** (Scheme 1).[4c] From a retrosynthetic perspective, hydrolytic ring opening of the γ-dihydropyrone in **8** leads to **9** as a potential precursor. The dihydroxytrione **9** should be available by simple functional group manipulation of any of the four possible diastereomers of **11**[10] that, in turn, result from sequential two-directional aldol reactions of **5** with **4**.

The synthesis of **11** by coupling the chiral fragments **6** and **4** requires management of the issues of double stereodifferentiation and mutual kinetic enantioselection (MKE).[11] Previous work suggested that aldol reaction of (*S*)-**4**[7b] with any of the four diastereomers of the MOM derivatives **10** via their Ti(IV) enolates would produce **11** (R = MOM) with the desired absolute configuration (i.e., path *a*).[8b] Although routes to each of the diastereomers of **10** are available,[7] use of (1′*S*,6′*R*)-**10** would be particularly attractive because this isomer is easily prepared via the D-proline-catalyzed aldol reaction of **5** with (±)-**4** which proceeds with dynamic kinetic resolution (DKR).[7c] A more appealing and efficient approach would involve reaction of the Ti(IV) enolate of (+)-**6ss** with (±)-**4**, a process expected[8b] to occur with kinetic resolution (i.e., path *b*). Because (+)-**6ss** is also available via an organocatalyzed reaction of **5** with (±)-**4**,[9b] this route would allow the complete assembly of **11** (R = H) from achiral and racemic fragments.

Enantiomerically enriched (+)-**6ss** (>98% ee) was readily obtained on gram scale in 59% yield by organocatalyzed aldol reaction of (±)-**4** with **5** to give (−)-**6as** followed by isomerization (Scheme 2).[9b,12] Under carefully optimized conditions, aldol reaction of (±)-**4** with (±)-**6ss** via the Ti(IV) enolate gave a 10:3:1 mixture of (±)-**12a**, (±)-**12b**, and **12c**, respectively, in 80% yield.[8b] This result indicates the Ti(IV) enolate of (+)-**6ss** reacts 3−4 times faster with (*R*)-**4** than with (*S*)-**4** and implies that kinetic resolution will be modest in similar reactions where one component (i.e., **6ss** or **4**) is enantiopure and the other is racemic. In the event, reaction of (+)-**6ss** with (±)-**4** (2 equiv) under the same conditions gave an 11:6:1 mixture of (+)-**12a**, (+)-**12b**, and **12c**, respectively, in 80% yield. The slight erosion in the diastereoselectivity of the reaction using (+)-**6ss** compared to that with (±)-**6ss** suggests that racemization of **4** is slower than the aldol coupling under these conditions[13]

SCHEME 2. Synthesis of (−)-Membrenone B (*ent*-2)



(i.e., no DKR).[11] The stereoselectivity of this aldol reaction is interesting. Only three of the eight possible adducts are produced, and it should be noted that (+)-**12a** and **12c** are derived from the reaction of (+)-**6ss** with (*R*)-**4**, whereas (+)-**12b** results from the reaction of (+)-**6ss** with (*S*)-**4**. These reactions occur with similar facility (i.e., MKE ≈ 3−4:1) thereby giving a mixture of products; however, both of the individual reactions are highly stereoselective. In any event, the two major adducts (94% of the products) have relative and absolute configurations appropriate for the synthesis of membrenones.

The diastereomers (+)-**12a** and (+)-**12b** were difficult to separate, and highly enriched samples were available only by repeated fractionation on silica gel.[14] Because the individual diastereomers were separately transformed into (−)-**8** with similar efficiencies, the mixture was used without separation (Scheme 2). Thus, the 11:6:1 mixture of aldol adducts (+)-**12a**, (+)-**12b**, and **12c**, respectively, was subjected to DIBALH reduction to give a 2.1:1 mixture of (+)-**13a** and (+)-**13b**, respectively, in good yield.[14] Each diol **13** gave the corresponding acetonide **14** with high diastereotopic group selectivity.[14,15] The resulting crude 2.8:1 mixture of (−)-**14a** and (+)-**14b** was desulfurized with Raney nickel to give a 2.8:1 mixture of (+)-**15a** and (−)-**15b** that in turn was oxidized to give a 2.8:1 mixture of (+)-**16a** and (−)-**16b**, respectively, in 72% yield

(10) The configurations at the undefined stereocenters in **11** are not relevant because those centers become trigonal in **8**.

(11) For a more complete discussion and references on this phenomenon, see ref 8b.

(12) The **ss** and **as** labels refer to the syn (**s**) or anti (**a**) relative configurations at C-3,1′ and C-1′,6′, respectively, in the diastereomers of **6** (and **10**).

(13) Consistent with that hypothesis, (*S*)-(−)-**4** (50% yield; ca. 20% optical purity) was recovered from the reaction.

(14) The racemic compounds have been described previously (ref 8a). For determination of the relative configurations for **12**, **13**, and **14**, see ref 8b.

(15) The alternative diastereomers would have a trans-fused tetrahydrothiopyrano[4,3-*d*]1,3-dioxin ring system with a large group in an axial orientation.

over the three steps. Brief exposure of the mixture of **16** to *p*-TsOH in CH_2Cl_2 gave the known (−)-**8** ([α]$_D$ −130, *c* 0.55, $CHCl_3$; lit.[4c] −114, *c* 0.48, $CHCl_3$) in moderate yield. Various alternative methods (e.g., Amberlyst, $FeCl_3$, $FeCl_3/SiO_2$, H_2SO_4/SiO_2) led to extensive decomposition.[16] Acylation of (−)-**8** with propanoyl chloride gave (−)-membrenone B (*ent*-**2**) with spectroscopic and chiroptical properties essentially identical to those previously reported.[4c]

In summary, the total synthesis of (6*S*,7*S*,8*S*,9*R*,10*S*)-(−)-membrenone B has been achieved in nine steps (9.4% overall yield) via two-directional aldol coupling of achiral ketone **5** with racemic aldehyde **4**. Remarkably, although the route involves coupling of chiral fragments, either (+)-**2**, (−)-*ent*-**2**, or (±)-**2** is selectively available from *identical* components simply by altering the catalyst used in the first aldol reaction. It is also noteworthy that the *entire* 17-carbon skeleton of **8** is derived from methyl acrylate as both **4** and **5** are directly and efficiently prepared from this simple precursor (e.g., 6.5% overall yield of (−)-**8** from methyl acrylate in 13 steps).[17] Because the conversion of (−)-**8** into *ent*-**1** by esterification with (*S*)-2-methylbutanoic acid is also known,[4c] our route constitutes a formal synthesis of (−)-membrenone A. Further applications of the thiopyran route to polypropionates are in progress and will be reported in due course.

Experimental Section[18]

Aldol Reaction of (+)-6ss with (±)-4. The procedure was according to that reported for reaction of (±)-**6ss** with (±)-**4**.[8b] Ti(O^{i}Pr)Cl_3 (0.55 M in CH_2Cl_2, 1.7 mL, 0.93 mmol) was added dropwise via syringe to a stirred solution of (+)-**6ss** (284 mg, 0.93 mmol) in CH_2Cl_2 (25 mL) at −78 °C under argon. After 2 min, $TiCl_4$ (0.30 mL, 2.8 mmol) was added dropwise over 1 min, and the reaction mixture became a yellow slurry. After 2 min, ^{i}Pr$_2$EtN (0.39 mL, 2.2 mmol) was added dropwise via syringe (the yellow slurry dissolved and reaction mixture became black). After 1.5 h, (±)-**4** (351 mg, 1.9 mmol) was added neat via syringe. After 6 h, the reaction was quenched by addition of saturated aqueous NH_4Cl, diluted with water, and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC to give a 11:6:1 mixture (by ^{1}H NMR) of **12a**:**12b**:**12c**, respectively, as a white solid (368 mg, 80% combined yield). This mixture was used in the next step without further purification. Highly enriched samples of (+)-**12a** (contaminated with **12b**, ca. 90% purity; [α]$_D$ +73, *c* 0.9, $CHCl_3$) and (+)-**12b** ([α]$_D$ +71, *c* 0.7, $CHCl_3$) could be obtained by repeated fractionation of the mixture by PTLC (40% ethyl acetate in hexane, multiple elutions). Spectroscopic data for the purified samples were essentially identical to that reported for the racemic compounds.[8b,18] Fractionation of the products from a similar reaction (200 mg of (+)-**6ss**) provided (*S*)-(−)-**4** (ca. 50% yield; [α]$_D$ −27, *c* 1.0, C_6H_6; ca. 20% optical purity) and recovered (+)-**6ss** (ca. 10%).

(3*S*,4*S*,5*S*)-3-[(*S*)-(6*R*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(*R*)-(6*S*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4-hydroxy-2*H*-thiopyran ((+)-13a) and (3*S*,5*S*)-3,5-Bis[(*S*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4-hydroxy-2*H*-thiopyran ((+)-13b). DIBALH (1.0 M in toluene, 3.6 mL, 3.6 mmol) was added dropwise via syringe to a stirred solution of a 11:6:1 mixture (by ^{1}H NMR) of **12a**:**12b**:**12c**, respectively (270 mg, 0.55 mmol), in THF (10 mL) at −78 °C under Ar. After 3 h, excess DIBALH was quenched by dropwise addition of MeOH (1 mL), and the resulting mixture was allowed to reach room temperature over 15−30 min. A saturated aqueous solution of sodium potassium tartrate (10 mL) was slowly added (**Caution**: exothermic) to the well-stirred mixture. After 1 day, the mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (50−75% ethyl acetate in hexanes) to give a 2.1:1 mixture of **13a** and **13b**, respectively, as a white solid (226 mg, 83%). This mixture was used in the next step without further purification. Pure samples of (+)-**13a** ([α]$_D$ +24, *c* 1.0, $CHCl_3$) and (+)-**13b** ([α]$_D$ +46, *c* 2.1, CH_2Cl_2) were obtained by careful fractionation of the mixture and from similar reactions of single diastereomers of **12**. Spectroscopic data for the purified samples were essentially identical to that reported for the racemic compounds.[8a,18]

(α*S*,6*R*)-α-[(4*S*,4a*S*,8*R*,8a*R*)-4-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]-dec-6-yltetrahydro-2,2-dimethyl-4*H*,5*H*-thiopyrano[4,3-*d*]-1,3-dioxin-8-yl]-1,4-dioxa-8-thiaspiro[4.5]decane-6-methanol ((−)-14a) and (α*R*,6*S*)-α-[(4*S*,4a*S*,8*R*,8a*R*)-4-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yltetrahydro-2,2-dimethyl-4*H*,5*H*-thiopyrano[4,3-*d*]-1,3-dioxin-8-yl]-1,4-dioxa-8-thiaspiro[4.5]decane-6-methanol ((+)-14b). 2,2-Dimethoxypropane (1 mL, excess) and *p*-toluenesulfonic acid monohydrate (ca. 5 mg) were added to a stirred solution of a 2.1:1 mixture of triols **13a** and **13b**, respectively (105 mg, 0.21 mmol), in dichloromethane (3 mL) at room temperature. After 5 min, the reaction was complete by TLC analysis and the mixture was diluted with dichloromethane, washed sequentially with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give a crude 2.8:1 mixture (by ^{1}H NMR) of acetonides **14a** and **14b**, respectively, as a white solid (110 mg; >95% pure by ^{1}H NMR). This mixture was used in the next step without further purification. Pure samples of (−)-**14a** ([α]$_D$ −12, *c* 0.65, CH_2Cl_2) and (+)-**14b** ([α]$_D$ +19, *c* 0.56, CH_2Cl_2) were obtained from similar reactions of single diastereomers of **13**. Spectroscopic data for the purified samples were essentially identical to that reported for the racemic compounds.[8a,18]

(2*R*,3*S*,4*R*)-2-(2-Ethyl-1,3-dioxolan-2-yl)-4-{(4*R*,5*S*,6*R*)-6-[(*S*)-1-(2-ethyl-1,3-dioxolan-2-yl)ethyl]-2,2,5-trimethyl-1,3-dioxan-4-yl}pentan-3-ol ((+)-15a) and (2*S*,3*R*,4*R*)-2-(2-Ethyl-1,3-dioxolan-2-yl)-4-{(4*R*,5*S*,6*R*)-6-[(S)-1-(2-ethyl-1,3-dioxolan-2-yl)ethyl]-2,2,5-trimethyl-1,3-dioxan-4-yl}pentan-3-ol ((−)-15b). A suspension of freshly prepared W-2 Raney nickel (3 mL settled volume) in ethanol (1 mL) was added at once to a well-stirred solution of the above crude 2.8:1 mixture of (−)-**14a** and (+)-**14a** (110 mg) in methanol (5 mL). The reaction mixture was heated under reflux, and progress was monitored by TLC. If necessary, additional Raney nickel was added until reaction was complete (typically 3−4 h). The supernatant was filtered through a pad of Celite, and the residue was extracted by suspension in MeOH and heating under reflux for several minutes. This process was repeated with methanol and once with a 1:1 mixture of acetone and dichloromethane. The combined filtrates were concentrated to give a crude 2.8:1 mixture (by ^{1}H NMR) of **15a** and **15b**, respectively, as a clear oil (88 mg, >90% pure by ^{1}H NMR). This mixture was used in the next step without further purification. Pure samples of (−)-**15a** and (+)-**15b** were obtained after fractionation of the crude products from similar reactions of single diastereomers of **14**. For (+)-**15a**: [α]$_D$ +6, *c* 1.2, C_6H_6; IR ν_{max} 3479 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 4.17 (1H, dd, J = 1.5, 8 Hz), 4.16 (1H, s), 3.93 (1H, dd, J = 2, 6.5 Hz), 3.80 (1H, dd, J = 2, 9.5 Hz), 3.65−3.57 (4H, m), 3.53−3.43 (4H, m), 2.36 (1H, dq, J = 14, 7.5 Hz), 2.04 (1H, dq, J = 14, 7.5 Hz), 1.98−1.91 (3H, m), 1.84−1.72 (2H, m), 1.58 (1H, dq, J = 14, 7.5 Hz), 1.36 (3H, s), 1.30 (3H, s), 1.26 (3H, d, J = 7 Hz), 1.21 (3H, d, J = 7 Hz), 1.08 (3H, t, J = 7 Hz), 1.04 (3H, d, J = 7.5 Hz), 0.97 (3H, t, J = 7.5 Hz), 0.66 (3H, d, J = 7 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 115.2, 113.9, 99.7, 80.2, 74.9, 74.5, 65.7, 65.6, 65.5, 65.2, 42.7, 42.4, 38.6, 35.2, 30.4, 28.0, 26.6, 19.8, 12.6, 12.1, 8.9,

(16) The presence of elimination and retro-aldol products from **8** were detected (by ^{1}H NMR) in the crude reaction mixtures consistent with the previous synthesis (ref 4c).

(17) Ward, D. E.; Rasheed, M. A.; Gillis, H. M.; Beye, G. E.; Jheengut, V.; Achonduh, G. T. *Synthesis* **2007**, 1584−1586.

(18) See the Supporting Information.

8.0, 7.5, 6.5; HRMS (CI, NH_3) *m*/*z* calcd for $C_{24}H_{44}O_7$ 445.3165 (M + H); found 445.3158. For (−)-**15b**: $[\alpha]_D$ −10, *c* 0.69, C_6H_6; IR ν_{max} 3524 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 4.16 (1H, br dd, J = 1.5, 6 Hz), 3.99 (1H, dd, J = 2, 6.5 Hz), 3.80 (1H, dd, J = 1.5, 9.5 Hz), 3.53−3.43 (8H, m), 2.93 (1H, s), 2.36 (1H, dq, J = 1.5, 7 Hz), 2.13 (1H, ddq, J = 6, 9.5, 7 Hz), 1.99 (1H, dq, J = 6.5, 7 Hz), 1.86−1.78 (2H, m), 1.77−1.70 (2H, ap q, J = 7.5 Hz), 1.62 (1H, dq, J = 14, 7.5 Hz), 1.45 (3H, s), 1.39 (3H, s), 1.26 (3H, d, J = 7 Hz), 1.21 (3H, d, J = 7 Hz), 1.11 (3H, d, J = 7 Hz), 1.07 (3H, d, J = 7 Hz), 0.98 (3H, t, J = 7.5 Hz), 0.95 (3H, t, J = 7.5 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 115.5, 114.0, 99.2, 77.3, 74.6, 72.9, 65.64, 65.60, 65.2, 65.0, 42.8, 42.1, 39.5, 35.2, 30.6, 28.3, 26.6, 20.1, 12.7, 11.5, 9.5, 8.7, 7.5, 6.5; HRMS (CI, NH_3) *m*/*z* calcd for $C_{24}H_{44}O_7$ 445.3165 (M + H); found 445. 3150.

(2*R*,4*S*)-2-(2-Ethyl-1,3-dioxolan-2-yl)-4-{(4*S*,5*S*,6*R*)-6-[(*S*)-1-(2-ethyl-1,3-dioxolan-2-yl)ethyl]-2,2,5-trimethyl-1,3-dioxan-4-yl}pentan-3-one ((+)-16a) and (2*S*,4*S*)-2-(2-Ethyl-1,3-dioxolan-2-yl)-4-{(4*S*,5*S*,6*R*)-6-[(*S*)-1-(2-ethyl-1,3-dioxolan-2-yl)ethyl]-2,2,5-trimethyl-1,3-dioxan-4-yl}pentan-3-one ((−)-16b). The Dess-Martin periodinane (170 mg, 0.40 mmol) was added to a stirred solution of the above crude 2.8:1 mixture of **15a** and **15b** (88 mg) in CH_2Cl_2 (3 mL). After 10 min, the mixture was diluted with ethyl acetate and washed sequentially with a 1:1 mixture of 10% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, water, and brine (20 mL). The aqueous washings were extracted with ethyl acetate, and the combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (20% ethyl acetate in hexane) to give a 2.8:1 mixture (by ^1H NMR) of **16a** and **16b**, respectively, as a white solid (68 mg, 72% from **13** over three steps). Pure samples of (+)-**16a** and (−)-**16b** were obtained from similar reactions of single diastereomers of **15**. For (+)-**16a**: $[\alpha]_D$ +140, *c* 1.6, C_6H_6; IR ν_{max} 1712 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 4.03 (1H, dd, J = 2, 10 Hz), 3.95 (1H, dd, J = 2, 6.5 Hz), 3.64 (1H, m), 3.53−3.42 (7H, m), 3.34 (1H, q, J = 7 Hz), 3.20 (1H, dq, J = 10.5, 7 Hz), 1.98 (1H, dq, J = 7, 6.5 Hz), 1.86−1.73 (4H, m), 1.55 (1H, dq, J = 14, 7 Hz), 1.40 (3H, s), 1.34 (3H, d, J = 7 Hz), 1.26 (3H, s), 1.23 (3H, d, J = 7 Hz), 1.13 (3H, d, J = 7 Hz), 1.05 (3H, d, J = 7 Hz), 0.96 (3H, t, J = 7.5 Hz), 0.90 (3H, t, J = 7.5 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 216.1, 113.9, 113.2, 99.3, 79.6, 74.3, 65.8, 65.7, 65.5, 65.2, 55.6, 49.7, 42.7, 34.3, 30.5, 27.9, 26.7, 19.7, 12.7, 12.6, 11.8, 7.6, 7.5, 6.3; HRMS (CI, NH_3) *m*/*z* calcd for $C_{24}H_{42}O_7$ 443.3009 (M + H); found 443.3009. For (−)-**16b**: $[\alpha]_D$ −34, *c* 0.24, C_6H_6; IR ν_{max} 1719 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.09 (1H, dd, J = 2, 10 Hz), 4.02−3.89 (8H, m), 3.87 (1H, dd, J = 2, 7 Hz), 3.08 (1H, q, J = 7 Hz), 2.97 (1H, dq, J = 9, 7 Hz), 1.89 (1H, dq, J = 5.5, 7 Hz), 1.80−1.66 (3H, m), 1.62−1.50 (2H, m), 1.36 (3H, s), 1.27 (3H, s), 1.15 (3H, d, J = 7 Hz), 0.97 (3H, d, J = 7 Hz), 0.92 (3H, m, J = 7 Hz), 0.90 (3H, d, J = 7 Hz), 0.89 (3H, t, J = 7 Hz), 0.88 (3H, t, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.7, 113.8, 112.4, 100.0, 75.6, 73.6, 65.8, 65.6, 65.4, 65.0, 52.5, 47.5, 41.9, 33.6, 30.0, 29.2, 26.0, 19.5, 12.5, 12.1, 12.0, 7.8, 7.1, 5.8; HRMS (CI, NH_3) *m*/*z* calcd for $C_{24}H_{42}O_7$ 443.3009 (M + H); found 443.3008.

(2*S*,3*S*)-6-Ethyl-2,3-dihydro-2-[(1*R*,2*R*,3*S*)-2-hydroxy-1,3-dimethyl-4-oxohexyl]-3,5-dimethyl-4*H*-pyran-4-one ((−)-8). *p*-Toluenesulfonic acid monohydrate (10 mg, 0.05 mmol) was added to a stirred solution of a 2.8:1 mixture of **16a** and **16b** (11.8 mg, 0.027 mmol) in CH_2Cl_2 (1 mL) at room temperature. After 10 min, the mixture was diluted with CH_2Cl_2, washed sequentially with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated, and fractionated by PTLC (30% ethyl acetate in hexanes) to give (−)-**8** as a colorless oil (3 mg, 38%): $[\alpha]_D$ −130, *c* 0.55, $CHCl_3$; lit.[4c] −114, *c* 0.48, $CHCl_3$. Spectroscopic data for (−)-**8** were essentially identical to that reported by Sampson and Perkins.[4c,18]

(6*S*,7*S*,8*S*,9*R*,10*S*)-Membrenone B ((−)-*ent*-2). The procedure was according to Sampson and Perkins.[4c] Pyridine (7 μL, 0.09 mmol) and propionyl chloride (8 μL, 0.09 mmol) were sequentially added to a stirred solution of (−)-**8** (5.1 mg, 0.02 mmol) in dry CH_2Cl_2 (1 mL) at room temperature under argon. After 1.5 h, the reaction was diluted with CH_2Cl_2 and washed sequentially with aqueous citric acid (2 M) and saturated aqueous $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by PTLC (30% ethyl acetate in hexanes) to give (−)-*ent*-**2** as a white solid (5.4 mg, 89%). Spectroscopic and chiroptical data for (−)-*ent*-**8** were essentially identical to that previously reported:[3,4c] $[\alpha]_D$ −50, *c* 0.46, $CHCl_3$ (lit.[4c] −44, *c* 0.68, $CHCl_3$); CD curve (1.1 mM in $CHCl_3$) $[\theta]_{301}$ +7300, $[\theta]_{269}$ −17000, $[\theta]_{269}/[\theta]_{301}$=2.3 (lit.[4c] 1 mM in $CHCl_3$: $[\theta]_{300}$ +6613, $[\theta]_{267}$ −15,438, $[\theta]_{267}/[\theta]_{300}$=2.3).

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Supporting Information Available: Spectroscopic data for *ent*-**2**, **8**, **13a/b**, and **14a/b**; ^1H and ^{13}C NMR spectra for all reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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